doi: 10.2176/jns-nmc.2022-0114

Neurol Med Chir (Tokyo) 62, 347-360, 2022

Online July 22, 2022

Advances in Molecular Biological and Translational Studies in World Health Organization Grades 2 and 3 Meningiomas: A Literature Review

Atsushi OKANO,[1] Satoru MIYAWAKI,[1] Yu TERANISHI,[1]
Kenta OHARA,[1] Hiroki HONGO,[1] Yu SAKAI,[1]
Daiichiro ISHIGAMI,[1] Hirofumi NAKATOMI,[1,2] and Nobuhito SAITO[1]

[1]*Department of Neurosurgery, Faculty of Medicine, The University of Tokyo, Tokyo, Japan*
[2]*Department of Neurosurgery, Kyorin University, Tokyo, Japan*

Abstract

The treatment of World Health Organization (WHO) grades 2 and 3 meningiomas remains difficult and controversial. The pathogenesis of high-grade meningiomas was expected to be elucidated to improve treatment strategies. The molecular biology of meningiomas has been clarified in recent years. High-grade meningiomas have been linked to *NF2* mutations and 22q deletion. *CDKN2A/B* homozygous deletion and *TERT* promoter mutations are independent prognostic factors for WHO grade 3 meningiomas. In addition to 22q loss, 1p, 14p, and 9q loss have been linked to high-grade meningiomas. Meningiomas enriched in copy number alterations may be biologically invasive. Furthermore, several new comprehensive classifications of meningiomas have been proposed based on these molecular biological features, including DNA methylation status. The new classifications may have implications for treatment strategies for refractory aggressive meningiomas because they provide a more accurate prognosis compared to the conventional WHO classification. Although several systemic therapies, including molecular targeted therapies, may be effective in treating refractory aggressive meningiomas, these drugs are being tested. Systemic drug therapy for meningioma is expected to be developed in the future. Thus, this review aims to discuss the distinct genomic alterations observed in WHO grade 2 and 3 meningiomas, as well as their diagnostic and therapeutic implications and systemic drug therapies for high-grade meningiomas.

Keywords: genomic alteration, copy number alteration, mRNA expression, DNA methylation, systemic medical therapy

Introduction

Meningiomas in adults are the most common primary intracranial tumors.[1)] Approximately 80%, 15%-20%, and 1%-3% of meningiomas are benign (World Health Organization [WHO] grade 1), atypical (WHO grade 2), and malignant (WHO grade 3), respectively.[1-7)] Recurrence occurs in 3%-20%, 30%-40%, and 50%-58% of grades 1, 2, and 3 meningiomas, respectively.[8-12)] High-grade meningiomas often become refractory to standard surgical and radiation therapy and are therefore difficult to manage. Chemotherapy and other systemic medical therapies are reserved as salvage therapy in these patients. These therapies, however, have had only limited success and have shown little clinical benefit.[13,14)] Thus, the molecular biological characteristics of these high-grade meningiomas should be clarified. Systemic medical therapies are also expected to be developed to combat them. The *World Health Organization Classification of Tumors of the Central Nervous System*, fifth edition, published in 2021, described these genetic characteristics.[15)] The WHO 2021 classification introduced significant changes that advance the role of molecular diagnostics of central nervous system tumors. *TERT* promoter (*TERTp*) mutation and homozygous *CDKN2A/B* deletion have been included as independent criteria for WHO grade 3 meningiomas[15)] (Table 1). Novel molecular classifications based on multimolecular omics analysis have been recently reported and appear to have clinical application.[16,17)]

Received April 8, 2022; Accepted May 10, 2022

Table 1 2021 WHO classification of meningiomas

WHO grade	Subtype	Criteria
Grade 1	Meningothelial Fibrous Transitional Psammomatous Angiomatous Microcystic Secretory Lymphoplasmacyte-rich Metaplastic	
Grade 2	Atypical Chordoid Clear cell	4-19 mitotic figures in 10 consecutive HPF of each 0.16 mm^2 or Unequivocal brain invasion (not only perivascular spread or indentation of brain without pial breach) or Specific morphological subtype (chordoid or clear cell) or At least three of the following 1. Increased cellularity 2. Small cells with high N:C ratio 3. Prominent nucleoli 4. Sheeting (uninterrupted pattern-less or sheet-like growth) 5. Foci of spontaneous (non-iatrogenic) necrosis
Grade 3	Anaplastic Rhabdoid Papillary	20 or more mitotic figures in 10 consecutive HPF of each 0.16 mm^2 (at least 12.5/mm^2) or Frank anaplasia (sarcoma-, carcinoma-, or melanoma-like appearance) or *TERT* promoter mutation or Homozygous deletion of *CDKN2A* and/or *CDKN2B*

HPF high power field.

This article aims to review the distinct genomic alterations observed in WHO grade 2 and 3 meningiomas and discuss their diagnostic and therapeutic implications, as well as systemic drug therapies for high-grade meningiomas.[15,18,19]

Genomic Alterations and mRNA Expressions (Table 2)

NF2 gene encodes the tumor suppressor protein merlin, a negative regulator of mTORC1.[20,21] The rate of *NF2* mutations in low-grade meningiomas is ~40%, whereas, the rate of *NF2* mutations in high-grade meningiomas is significantly higher at 80%.[22] The incidence of non-*NF2* mutations is <5% in 20% of high-grade meningiomas without *NF2* mutations, compared to 35% in grade 1 non-*NF2* meningiomas. This significantly lower incidence suggests that high-grade meningiomas have a different genetic basis.[23]

Homozygous deletion of the *CDKN2A/B* gene located at 9p21 has been frequently observed in anaplastic meningiomas.[18,24-29] *CDKN2A/B* homozygous deletion was found in about 4.9% of meningiomas of all WHO grades and subtypes. Atypical meningiomas made up 27% of the cases with *CDKN2A/B* homozygous deletion, while anaplastic meningiomas made up 73%. In particular, *CDKN2A/B* homozygous deletion, in particular, was able to identify patients with poor prognosis among WHO grade 2 and 3 cases.[18] Consequently, *CDKN2A/B* homozygous deletion has been added as an independent criterion for WHO grade 3 meningiomas in the 2021 WHO classification.[15]

TERTp mutations occur at specific hotspots known as C228T and C250T in meningiomas.[19,30,31] *TERTp* mutations occur in 4.7%, 7.9%, and 15.4% of WHO grades 1, 2, and 3 meningiomas, respectively.[30] *TERTp* mutations are associ-

Table 2 Main genomic alterations in WHO grades 2 and 3 meningioma

Gene	Locus	Product	Frequency	Histology	Pathway
NF2[18-21]	22q12.2	Merlin	40%-80%	Atypical, anaplastic	PI3K/AKT/mTOR and hippo
CDKN2A/2B[16, 22-27]	9p.21.34	p16(INK4A)/p15(INK4B)	<5%	Atypical, anaplastic	Cell cycle regulation
TERTp[17, 28, 29]	5p15.33	TERT	5%-15%	Atypical, anaplastic	Telomerase activity
BAP1[32]	3p21.1	Ubiquitin carboxy-terminal hydrase 1	<1%	Rhabdoid	DNA repair
PBRM1[35]	3p21.1	Subunit of PBAF complex	2.8%	Papillary	Chromatin remodeling
DMD[39]	Xp21.1	Dystrophin	NA	Atypical, anaplastic	Cytoskeleton
SMARCB1[40, 41]	22p11.23	Subunit of SWI/SNF complex	5%	Atypical, anaplastic	Chromatin remodeling
SMARCE1[20, 42, 43]	17q21.2	Subunit of SWI/SNF complex	3%-4%	Clear cell	Chromatin remodeling
SMARCA4[20, 42, 43]	19p13.2	Subunit of SWI/SNF complex	NA	Atypical, anaplastic	Chromatin remodeling
ARID1A[45]	1p36.11	Subunit of SWI/SNF complex	12% in grade 3	Anaplastic	Chromatin remodeling
PIK3CA[40, 46-48]	3p26.32	Catalytic subunit of kinase, PI3K	3%-7%	Grades 1-3	PI3K/AKT/mTOR

ated with increased TERT expression and telomerase activity but not with telomere length.[32,33] The recurrence rate in WHO grade 1 and 2 cases with *TERTp* mutation is higher than in WHO grade 3 cases without *TERTp* mutation. This suggests that *TERTp* mutation is a prognostic factor independent of WHO grade.[30] Therefore, the presence of *TERTp* mutation has been added as an independent criterion for WHO grade 3 meningiomas in the WHO classification 2021.[15] Furthermore, *TERTp* mutations are associated with tumor progression and poor outcome of *de novo* high-grade meningiomas after following adjuvant radiotherapy.[34]

Somatic mutations in *BAP1* have been identified in a rare subset of aggressive meningiomas with rhabdoid morphology.[35] *BAP1* codes a BRCA1-associated protein and is essential for DNA repair. Its inactivation is oncogenic.[36] Cases with germline *BAP1* mutations also exist in the subset of cases with somatic *BAP1* mutations. This indicates that such meningiomas can occur as part of the BAP1 cancer predisposition syndrome. Furthermore, immunohistochemistry-based negative nuclear staining for BAP1 reveals the absence of BAP1 expression.[37] Therefore, immunohistochemistry can help predict the prognosis of meningiomas with rhabdoid features.[37]

Biallelic inactivation of *PBRM1* in papillary meningiomas was recently reported.[38] BAF180 protein, a subunit of the polybromo-associated BAF complex chromatin remodeling complex, is encoded by *PBRM1*. *PBRM1* mutations, which is a tumor suppressor gene, have been found in clear cell renal cell carcinoma, papillary renal cell carcinoma, and bladder carcinoma.[36] PBRM1 mutations significantly increase cell proliferation and migration.[39] BAF180 protein is required for centromeric cohesion, and cells lacking *PBRM1* have DNA damage and dynamic chromosome instability.[40] *PBRM1* mutations can overlap with *BAP1* mutations, and their prognostic role in meningiomas remains unknown.[38]

Mutations in the *DMD* gene, which codes for dystrophin, have also been linked to progressive/high-grade meningiomas.[41] *DMD* inactivation was found in 32% of progressive meningiomas, either through genomic deletion or loss of protein expression. Furthermore, the presence of DMD inactivation in advanced or high-grade meningiomas reduces overall and progression-free survival.[41] Importantly, somatic *DMD* mutations and *TERTp* mutations are mutually independent in predicting unfavorable outcomes.[41]

Mutations in SWI/SNF chromatin remodeling complex members have been found in high-grade meningiomas.[42,43] *SMARCB1* is also found on 22q, and mutations in this gene may be found in cases with *NF2* mutations. Other SWI/SNF complex members, e.g., *SMARCE1*, *SMARCA4*, and *ARID1A*, have also been shown to be mutated on multiple occasions.[22,44,45] *SWI/SNF* gene mutations are more frequently detected in anaplastic (16%) meningiomas than in benign and atypical meningiomas (<5%).[46] *ARID1A* mutations were found in 19.1%, 16.8%, and 15.8% of WHO grades 1, 2, and 3 meningiomas, respectively, and the presence of an *ARID1A* mutation was associated with a 7.4-fold mortality risk.[47]

PIK3CA mutations are most commonly found in WHO grade 1 meningioma, which accounts for 4%-7% of all meningioma cases.[42,48] The presence of *PIK3CA* mutations in high-grade meningiomas was first reported in 2006.[49] *PIK3CA* mutations are found in 3.7% of anaplastic meningiomas[50] and are relatively rare in high-grade meningiomas. Moreover, *PIK3CA* mutations are found in meningiomas without additional copy number alterations or somatic mutations. This suggests that *PIK3CA* may have played a role in the tumorigenesis of malignant meningioma.

Only 0.6% of meningiomas have mutations in mismatch repair genes (MMR), e.g., *MSH2*, *MSH6*, *SETD2*, and *POLE*, but interest exists in studying these mutations in aggressive meningiomas.[51] Firstly, these mutations can be targets for immunotherapy because MMR mutations are often associated with neoantigens. Pembrolizumab, a PD-1 inhibitor, has been approved for solid tumors with MMR muta-

tions.[52] These drugs may also be effective in meningiomas with MMR mutations. Secondly, MMR mutation frequency is rare in high-grade meningiomas despite genetic instability. Thus, other driver events may be involved in high-grade meningioma development.

NF2 mutations have been linked to chromatin remodeling genes like *SUZ12*, *KDM5D*, *KDM6A*, *SETD6*, *KMT2C*, *KMT2D*, or *CREBBP* as well as DNA damage response genes like *ATM*, *ATR*, or *BAP1* in chordoid meningiomas.[53] Importantly, these mutations are independent prognostic factors for chordoid meningioma's aggressive course.

Although many factors have been identified through transcriptome analysis, the current study focused on the *FOXM1* gene, which is of particular importance. *FOXM1* was identified as a key transcription factor for tumor growth and a marker of poor clinical outcome.[17,54-56] *FOXM1* is a promitotic transcription factor necessary for cell proliferation during development.[57,58] *FOXM1* expression in meningioma has previously been reported to be high in invasive tumors.[59] Furthermore, meningiomas with a poor prognosis had a high somatic mutation burden. The FOXM1-wnt signaling pathway was associated with a mitotic gene expression program, poor clinical outcome, and primary meningioma growth. To summarize, *FOXM1* activity promotes meningioma proliferation and tumor growth by collaborating with the dysregulated FOXM1-wnt signaling pathway.[54]

Unlike WHO grade 1 meningioma, the association between tumor location and genetic genomic alterations in high-grade meningiomas is not reported in detail. Thus, further studies are needed.

Copy Number Alterations

Genomic instability is linked to tumor aggressiveness, and karyotypic abnormalities are noted to gradually increase as meningiomas become more aggressive.[60,61] The most noticeable difference between grades 2 and 3 meningiomas is an increase in copy number alterations (CNAs) when compared to grade 1 meningiomas. Loss of chromosomes 1p, 4p, 6q, 9q, 10, 14q, and 22q or gain of chromosomes 1q, 9q, 12q, 15q, 17q, 19, 20, and 5 have also been described.[22,27,55,61-64] CNAs become more common as the WHO grade of meningioma rises. The number of CNAs is strongly associated with the risk of recurrence in atypical meningiomas after gross total resection.[60] These results suggest that meningiomas with a high number of CNAs may have a biologically aggressive behavior.[22]

Grades 2 and 3 meningiomas are strongly linked to deletion or loss of genetic locus on chromosome 22q that contains the NF2 gene.[4,22] The rate of loss of heterozygosity for 22q increases with the grade, from 50% in WHO grade 1 meningioma to 75%-85% in WHO grade 3 meningioma.[65,66] Other tumor suppressor genes found on chromosome 22q include *SMARCB1*, *CHEK2*, and *CLH22*. Loss of 22q loss results in a state of genetic instability that is prone to somatic mutations. This results in a genetically diverse and aggressive tumor phenotype.

After 22q loss, the second most common copy number in meningiomas is 1p loss which is associated with higher WHO grade.[46,55,67-69] 1p loss is found in 40%-76% and 70%-100% of WHO grades 2 and 3 meningiomas, respectively, and is especially common in recurrent and high-grade tumors.[61] Interestingly, 1p loss is an independent marker of meningioma recurrence and progression.[70,71] However, 1p loss is observed at a significantly lower frequency in grade 3 rhabdoid meningiomas, a particularly aggressive subtype, compared to other high-grade subtypes.[22] Recently, 1p36 loss was reported as the prognostic marker of regrowth after gamma knife surgery for WHO grade 1 meningiomas.[72] However, genetic alterations associated with radiation therapy efficacy in high-grade meningiomas have not been identified.

The loss of chromosomes 14q, 9p, and 6q are major additional alterations found in high-grade meningiomas.[46,55,69] 14q loss is detected in 40%-57% and 55%-100% of WHO grades 2 and 3 meningiomas, respectively, especially in high-grade tumors.[71] Loss of both 1p and 14q has been associated with early tumor recurrence and is a prognostic factor independent of WHO grade.[73] 9p loss is a common finding in WHO grade 3 meningiomas. *CDKN2A/B* deletions on 9p are especially linked to tumor recurrence. As aforementioned, these genes have recently been studied as biomarkers of poor prognosis.[18,74,75] Other chromosome abnormalities have been reported, as summarized in Table 3.

Epigenetic Alteration

H3K27 me3 was referred to in the WHO 2021 classification. Lack of H3K27 me3 staining in meningioma cells has been linked to faster progression, establishing its role as an adjunct prognostic marker.[76,77] This provides important prognostic information, particularly in WHO grade 2 or borderline cases between WHO grades 1 and 2.[76,78] In another large cohort study including 1,268 cases, lack of H3K27 me3 staining was found in 4.7% of meningiomas and was noted to be more common in females, in convexity or falx.[79] The WHO grading system also revealed a significant difference in trimethylation loss: 3.1%, 10.4%, and 17.7% in grades 1, 2, and 3, respectively. Anaplastic (16.7%) and rhabdoid (20.0%) meningioma had the highest rate of trimethylation loss, followed by atypical and chordoid meningiomas (9.9% and 14.3%). Furthermore, significantly more cases were noted with a MIB1 labeling index (LI) of ≥6.9% in 18.3% of cases where H3K27 me3 staining was missing. The combination of H3K27 me3 loss and MIB1 LI has been reported to be a poor prognostic marker for meningiomas.[79] The importance of H3K27 me3 loss in IHC has been highlighted.

Table 3 Main copy number alterations in WHO grades 2 and 3 meningioma

Alteration	Chromosome	Related genes	Frequency in grade 2	Frequency in grade 3
Loss	22q[4, 20, 63, 64]	*NF2, SMARCB1, CHEK2,* and *CLH22*	75%–85%	75%–85%
	1p[44, 53, 65-67]	*TP73, CDKN2C, RAD54,* and *EPB41, GADD45A*, and *ALPL*	40%–76%	70%–100% (except for rhabdoid)
	14q[44, 53, 67]	*NDRG2, MEG3*, and *AKT1*	40%–57%	55%–100%
	9p[16, 71, 72]	*CDKN2A/B*	32%	38%
	6q[53]	*CTGF*	33%	53%–63%
	18q[53]	*MADH2, MADH4, APM-1*, and *DCC*	43%	47%–75%
	10p[53]		29%	47%
	10q[53]	*PTEN* and *DMBT1*	29%	58%–63%
	11p[20]		NA	21%–50%
	7p[20]		NA	38%
	4p[53]		19%	21%–38%
	6p[53]		14%	26%
	4q[53]		NA	26%
	18p[53, 62]	*DAL-1* and *bcl-2*	NA	NA
	X[53]		NA	26%
Gain	20q[20, 53]		48%	58%
	15q[53]		43%	42%
	17q[20, 53]	*STAT3* and *RPS6K*	33%	63%
	12q[20, 53]	*CDK4* and *MDM2*	43%	42%
	5p[20, 53]		38%	NA
	5q[20, 53]		38%	NA
	1q[53]		33%	42%
	9q[53]		33%	37%
	20p[20, 53]		33%	32%
	2q[53]		29%	26%
	3[53]		29%	NA
	2p[53]		24%	32%
	12p[20, 53]		24%	NA
	16p[53]		24%	32%
	17p[53]		24%	47%
	8q[53]		19%	26%
	11q[53]		24%	21%
	21q[20, 53]		NA	32%
	13q[53]		NA	26%
	7q[20, 53]		NA	21%
	16q[53]		NA	21%

NA not available.

Global DNA Methylation Profiling

Meningiomas are classified into six groups, according to Sahm et al., based on global DNA methylation profiling using a genome-wide methylation array.[27] Higher methylation levels have been linked to a higher risk of tumor aggressiveness and recurrence according to this classification.[27] DNA methylation is a type of epigenetic change that has been linked to genomic instability by silencing genes involved in DNA repair and cell cycle regulation. This group reported that DNA methylation-based classification can be used to diagnose other types of tumors.[80,81]

Integrative Molecular Classifications of Meningiomas (Tables 4 and 5)

Meningioma integrative molecular classifications have recently been proposed.[16,17,82] A combined model score based on WHO grading, CNAs, and global DNA methylation classification has been developed[16] (Table 4). Patients were classified as having low (0-2), intermediate (3-5), and high (>5) integrated risk in that model. Although both methylation classification and the classification by CNAs have been independently proven to be better predictors than WHO grade alone, this integrated score consistently outperforms each component.[16] In another study, an integrated molecular analysis of CNAs, DNA somatic mutations, global DNA methylation status, and transcriptome revealed four consensus molecular groups[17] (Table 5). These molecular groups outperformed traditional classification in predicting clinical outcomes. Furthermore, each group exhibited distinctive and prototypical biology (MG1, immunogenic; MG2, benign *NF2* wild-type; MG3, hypermetabolic; and MG4 proliferative), making them potential therapeutic targets.[17] MG1 group demonstrated large immune infiltration and was enriched by pathways involved in immune regulation and signaling. The MG2 subset's transcriptome is enriched for vascular and angiogenic pathways. The pathways converging the metabolism of several macromolecules were specifically enriched in MG3 tumors. MG4 group was enriched in pathways involved in cell cycle regulation and several important and complementary transcription factor networks related to proliferation, e.g., MYC, CDKs, and kinesins.[17] Meningioma classification based on molecular biological features is being proposed. These classifications, along with those for other gliomas, have the potential to change the way diagnostic meningioma samples are processed.

Table 4 Integrative molecular classification of meningiomas 1

Components of classification		Score
WHO grading	Grade 1	0
	Grade 2	1
	Grade 3	2
DNA copy number alterations Losses chromosome 1p, 6q, and 14q	None present	0
	1-2 present	2
	3 present	3
Global DNA methylation status	Benign	0
	Intermediate	2
	Malignant	4
Classifications		Total score
Low risk		0-2
Intermediate risk		3-5
High risk		6-10
Outcome		
Low > intermediate > high		

Systemic Medical Therapies (Table 6)

Molecular targeted therapies

Neurosurgeons face therapeutic challenges when dealing with aggressive high-grade meningiomas that do not respond to surgeries and radiation therapy. Advances in understanding intracellular signaling pathways and microenvironment in meningiomas have led to the promise of molecular targeted therapies for meningiomas.[83] *NF2* mutations and 22q loss are most frequently observed in recurrent high-grade meningiomas and are potential therapeutic targets. GSK2256098, a FAK inhibitor that is supposed to be active when merlin expression is defective, is currently being studied in an umbrella clinical trial that is specifically targeting meningiomas with *NF2* mutations.[84] *BAP1*

Table 5 Integrative molecular classification of meningiomas 2

	DNA somatic point mutations	DNA copy number alterations	Messenger RNA abundance (transcriptome)	Global DNA methylation status
MG1 Immunogenic	*NF2* and *SMARCB1*	22q loss	Immunogenic	Differences in genome-wide DNA methylation patterns between groups
MG2 Benign NF2 wild-type	*AKT1, KLF4, SMO, POLR2A*, and *TRAF7*	5, 12, and 20 gain	Vascular/angiogenesis	
MG3 Hypermetabolic	*NF2, TERTp*, and *CREBBP*	1p, 6, 14p, 18, and 22q loss	Hypermetabolic	
MG4 Proliferative	*NF2, TERTp, CREBBP*, and *CHD2*	1p, 6, 10, 14q, 18, 22q loss, and 1q gain	Proliferative	
Outcome				
MG1 > MG2 > MG3 > MG				

Table 6 Systemic medical therapies for meningiomas

Classification	Drugs	Mechanism	Phase	Case	Result	Study
Molecular-targeted therapy	GSK2256098	FAK inhibitor	Phase II	Recurrent or progressive cases with *NF2* mutations	Improving PFS6 rate PFS6 rate of >41.5%	Brastianos et al. 2020 NCT02523014
	Tazemetostat	EZH2 inhibitor	Phase II	*BAP1* mutation (Rhabdoid)	Ongoing	NCT02860286
	Ribociclib	CDK4/6 inhibitor	Phase II	Grades 2 and 3 with *CDKN2A/B* deletion	Ongoing	NCT02933736 Tien et al. 2019
	Vistusertib (AZD2014)	mTORC1/C2 inhibitor	Phase II	Recurrent grades 2 and 3 with *NF2* mutation	Ongoing	NCT03071874
	Vistusertib (AZD2014)	mTORC1/C2 inhibitor	Phase II	Progressive cases with *NF2* mutation	Ongoing	NCT02831257
	Everolimus + octreotide	mTOR inhibitor + Somatostatin agonist	Phase II	Refractory aggressive/progressive cases	Improving PFS6 rate PFS6 rate of 55%	Graillon et al. 2020 CEVOREM trial
	Everolimus + bevacizumab	mTOR inhibitor + Anti-VEGF	Phase II	Recurrent/progressive cases	Improving PFS6 rate PFS6 rate of 69%	Shih et al. 2016
	Alpelisib + trametinib	PI3K inhibitor + MEK inhibitor	Phase II	Progressive refractory cases with *PIK3CA* mutation	Ongoing	NCT03631953
	Vismodegib	Hedgehog pathway targeting	Phase II	Recurrent/progressive cases with *SMO/PTCH1* mutation	Ongoing	NCT02523014 Alliance clinical trial
	Afuresertib	AKT1 inhibitor	Case report	Grade 1 with *AKT1* mutation	Potential	Weller et al. 2017
	Bevacizumab	Anti-VEGF monoclonal antibody	Phase II	Grades 2 and 3	PFS6 rate of 43.8%	Nayak et al. 2012
	Bevacizumab	Anti-VEGF monoclonal antibody	Phase II	Grades 1-3	PFS6 rate of 77% in grade 2 46% in grade 3	Grimm et al. 2015
	Bevacizumab	Anti-VEGF monoclonal antibody	Case series	Grades 2 and 3 previous treated with RT	78.9% of edema improvement	Furuse et al. 2016
	Vatalanib (PTK787)	VEGF and PDGF receptors inhibitor	Phase II	Recurrent or progressive cases	Response rate of 0% PFS6 rate of 64.3% in grade 2 37.5% in grade 3	Raizer et al. 2014
	Sunitinib	Multitarget tyrosine kinase inhibitor	Phase II	Recurrent grades 2 and 3	Response rate of 6% PFS6 rate of 42%	Kaley et al. 2015
	Erlotinib or gefitinib	EGF receptor inhibitor	Phase II	Recurrent cases	No significant efficacy PFS6 rate of 29% in grades 2 and 3	Norden et al. 2010
	Imatinib	PDGF receptor inhibitor	Phase II	Recurrent cases	No significant efficacy PFS6 rate of 0% in grades 2 and 3	Wen et al. 2009
	Cabozantinib	Multitarget tyrosine kinase inhibitor	Case report	Recurrent cases	Potential	Kotecha et al. 2021
	Apatinib	VEGF receptor inhibitor	Case series	Recurrent anaplastic case	Potential	Wang et al. 2020

Table 6 Systemic medical therapies for meningiomas (continued)

Classification	Drugs	Mechanism	Phase	Case	Result	Study
SSTR2A agonist	Octreotide	Somatostatin agonist	Phase II	Recurrent cases with overexpression of SR	Limited efficacy	Chamberlain et al. 2007
	Octreotide	Somatostatin agonist	Phase II	Recurrent cases with overexpression of SR	No significant efficacy	Johnson et al. 2011
	Octreotide	Somatostatin agonist	Phase II	Recurrent grade 2 or 3 with positive octreotide SPECT	No significant efficacy PFS6 rate of 44.4% in grades 2 and 3	Simo et al. 2014
	Pasireotide LAR	Somatostatin agonist	Phase II	Recurrent cases with SR overexpression	Limited efficacy PFS6 rate of 17% in grades 2 and 3	Norden et al. 2015
PRRT	^{90}Y-DOTATOC		Phase II	SR-positive progressive cases	PFS6 rate of 78.6% in grade 1 PFS6 rate of 14.3% in grades 2 and 3	Bartolomei et al. 2009
	^{90}Y-DOTATOC		Phase II	SR-positive progressive or recurrent cases	PFS6 rate of 100% in grade 1 PFS6 rate of 0% in grades 2 and 3	Geyster-Gillieron et al. 2015
	^{90}Y-DOTATOC and Lutathera (^{177}Lu-DOTATATE)		Phase II	SR-positive progressive WHO grade 1	SD of 65.6%, PD of 34.4%	Marincek et al. 2015
	Lutathera (^{177}Lu-DOTATATE)		Phase II	Progressive grades 1-3	Ongoing	NCT03971461
	Cu-64SARTATE and Cu-67SARTATE		Phase II	Refractory grades 1-3	Ongoing	NCT03936426
Hydroxyurea	Hydroxyurea		Phase II	Recurrent grade 1 or 2	No significant efficacy	Loven et al. 2004
	Hydroxyurea		Phase II	Recurrent grade 1	Limited efficacy	Weston et al. 2006
Immunotherapy	Nivolumab/Ipilimumab	PD-1/CTLA4 blocking antibody	Phase II	Recurrent grades 2 or 3	No significant efficacy PFS6 rate of 42.4% in grades 2 and 3	Bi et al. 2021 NCT02648997
	Pembrolizomab	PD-1 blocking antibody	Phase II	Refractory grades 2 or 3	Ongoing	NCT03016091
	Pembrolizomab	PD-1 blocking antibody	Phase II	Recurrent grades 2 or 3	PFS6 rate of 48% in grades 2 and 3 Median PFS of 7.6 months	Brastianos et al. 2022 NCT03279692
	Nivolumab/ipilimumab	PD-1/CTLA4 blocking antibody	Phase II	Recurrent grades 2 or 3	Ongoing	NCT03604978
	Avelumab	PD-L1	Phase II	Recurrent, radiation refractory cases	Ongoing	NCT03267836
Progesterone receptor antagonist	Mifepristone	Progesterone receptor antagonist	Phase III	Unresectable grades 1 or 2	No significant efficacy	Ji et al. 2015
Trabectedin	Trabectedin	Antisarcomatous drug	Phase II	Recurrent grades 2 or 3	No significant efficacy	Preusser et al. 2019 EORTC-1320-BTG

PFS6 6 months progression-free survival, SSTR2A somatostatin receptor 2A, PRRT peptide receptor radionuclide therapy, SD stable disease, and PD progression disease.

mutations are potential targets for the BAP1 inhibitor, tazemetostat.[37,46] Ribociclib, a CDK 4/6 inhibitor, has been tested in vitro and is currently being tested in recurrent WHO grades 2 and 3 meningiomas with *CDKN2A/B* homozygous deletion.[52,85]

The PI3K/AKT/mTOR pathway has recently been shown to be overactivated in the majority of meningiomas with *NF2* mutations.[86,87] Merlin functions as a negative regulator of mTORC1, and its loss is important for *NF2*-dependent tumorigenesis.[20,21] These results suggest that mTORC1 may be a promising therapeutic target. Vistusertib (AZD2014), a dual mTORC1-mTORC2 inhibitor, is currently in clinical trials.[88]

The function of somatostatin receptor 2A (SSTR2A) in meningioma is unknown. However, they are present in almost all meningiomas and are strongly present in 70% of cases.[89] SSTR2A activation by somatostatin agonist, octreotide, leads to inhibiting meningioma cell proliferation via PI3K/AKT/mTOR pathway inhibition.[88] Somatostatin agonists were found to be ineffective in the majority of aggressive meningiomas in multiple clinical trials.[89-91] The CEVOREM study, which combined an mTOR inhibitor, everolimus, and a somatostatin agonist, octreotide, for refractory and progressive meningiomas, revealed a radiographic response in four of 20 patients at 3 months and encouraged PFS at 6 and 12 months of 58.2% and 38%, respectively, with a median follow-up of 12.3 months.[89] Therefore, additional studies are needed to assess the efficacy of everolimus and octreotide in a randomized trial. A phase II clinical trial with everolimus plus antivascular endothelial growth factor (VEGF) drug, bevacizumab, for the treatment of recurrent or progressive meningioma revealed that stable disease was achieved in 15 of 17 patients.[92] Furthermore, one of the advantages of everolimus is that it is an oral medication. In vitro data on primary meningioma cell lines have demonstrated caspase-induced cell death mediated by the MEK inhibitor, trametinib. Therefore, alpelisib, a PI3K inhibitor, in combination with trametinib may be effective in meningioma treatment. This combination therapy is currently being studied.[52]

In the case of *AKT1* inhibitor, the *AKT1* inhibitor afuresertib (AZD5363) is effective. Afuresertib was used to treat a WHO grade 1 meningioma with *AKT1* mutation, which resulted in long-term treated disease control.[85] According to this study, the *AKT1* mutation could be a potential therapeutic target.

SMO mutations cause the sonic hedgehog signaling pathway to be overexpressed. *SMO* mutations are more common in the anterior skull base of meningiomas.[93,94] A phase II clinical trial with vismodegib, which is an SMO receptor antagonist, is currently ongoing.

Anti-VEGF drugs remain the most commonly used drugs in aggressive meningiomas today. When compared to WHO grade 1 meningiomas, it is secreted twofold in atypical meningiomas and tenfold in anaplastic meningiomas.[95-97] Bevacizumab was found to have the most significant tumor growth inhibition effect in recurrent WHO grades 2 and 3 meningiomas and anti-edematous activity in 2016.[98] PFS6 rates in grades 2 and 3 meningiomas ranged from 43.8% to 77% in several prospective studies.[99,100] Another study found that bevacizumab showed a significant reduction in volume and peritumoral edema in meningiomas that had been previously treated with radiation therapy. These findings suggest that bevacizumab has an important role in postradiation changes and radiation necrosis.[101] Future studies should look for more predictors to further determine efficacy. Other anti-angiogenic agents, e.g., vatalanib, an inhibitor of VEGF and platelet-derived growth factor (PDGF) receptors, and sunitinib, a multitargeted tyrosine kinase inhibitor, have shown limited efficacy with response rates of 0% and 6%, respectively.[102,103] In a phase II trial, erlotinib or gefitinib, an EGF receptor inhibitor and PDGF receptor inhibitor, were investigated. However, no statistically significant changes were noted in PFS or OS.[104,105] Two new VEGF targeting drugs, cabozantinib and apatinib, have been reported to be active.[106,107]

SSTR2A-targeted drug

Several clinical trials have found that low somatostatin agonists have low activity against aggressive meningiomas.[89-91] In contrast, the use of somatostatin analog has been shown to slow tumor growth in WHO grade 1 skull base meningiomas.[108,109] Peptide receptor radionuclide therapy (PRRT) for recurrent meningiomas was proposed based on high SSTR expression. This treatment is designed to specifically target the tumors that express and internalize SSTR2A. Several retrospective studies have been conducted using various agents, e.g., ^{90}Y-DOTATOC or ^{177}Lu-DOTATATE, Lutathera.[110-114] These findings concluded that PRRT has a promising effect on WHO grades 1 and 2 meningiomas, but is less useful in aggressive WHO grades 2 and 3 meningiomas.[115] A possible reason is that in aggressive WHO grades 2 and 3 meningiomas, SSTR2A expression is lower than in WHO grade 1 and meningiomas.[116] Thus, PRRT could be less effective for this group. However, SSTR1 and SSTR5 expressions are higher than in WHO grades 1 and 2 meningiomas.[116] A broader affinity of substances used for PPRT has the potential to improve the efficacy.[116] New drugs in the USA, Copper 64 labeled sartate and ^{177}Lu-DOTA-Tyr3-octreotate, are being investigated.[117]

Hydroxyurea

Hydroxyurea was the first drug proposed for the treatment of meningiomas;[118,119] it is an oral inhibitor of ribonucleotide reductase. Several clinical trials have been conducted,[120-122] wherein their findings suggest that hydroxyurea may have potential but uncertain activity in low-grade meningiomas, whereas no significant effect has been reported in WHO grades 2 and 3 meningiomas.

Immunotherapy

The immune system's role in the progression of meningioma has long been suspected.[123,124] According to studies,[125-127] the immune microenvironment may have an impact on high-grade meningioma. According to some studies, programmed death-ligand 1 (PD-L1) expression is increased in high-grade meningiomas.[128,129] However, a phase II clinical trial of PD-1 blocking antibody, nivolumab, in recurrent high-grade meningiomas showed no improvement in PFS6.[130] Most recently, another PD-1 blocking antibody, pembrolizumab, in recurrent high-grade meningiomas showed promising efficacy.[131] Several studies are being done with anti-CTLA4, pembrolizumab, either alone or with the combination of radiation therapy and anti-PD1, PD-L1, or CTLA4 agents.[132] Since meningiomas express different potential immunotherapy targets, e.g., PD-L2, CTLA-4, and B7-H3, it has been suggested that the combination of immunotherapy with radiotherapy or targeted therapy may improve the local immune response.[126]

Progesterone receptor antagonist (mifepristone)

Progesterone receptor (PR) expression is found in 70% of meningiomas.[133] PR is strongly expressed in low-grade meningiomas, while the PR expression is reduced in high-grade meningiomas.[134,135] Although PR was expected to be a potential therapeutic target for growth inhibition, a randomized double-blind placebo-controlled phase III trial concluded that the PR antagonist, mifepristone, lacked efficacy.[136]

Trabectedin

Trabectedin binds to the minor groove of the DNA double helix. It affects several transcription factors and DNA repair mechanisms and has immunomodulatory and antangiogenic.[137,138] It is currently approved for advanced soft tissue sarcoma and ovarian cancer.[139] Trabectedin suppressed meningioma cells from WHO grades 2 and 3 meningiomas through multiple mechanisms, and a favorable response was observed in a patient with recurrent anaplastic meningioma treated with trabectedin.[140] However, in the EORTC Brain Tumor Group's randomized phase II trial (EORTC-1320-BTG), trabectedin did not improve overall survival in recurrent WHO grades 2 and 3 meningiomas.[141]

Conclusion

Meningiomas' molecular biological characteristics have been clarified. Furthermore, several new comprehensive classifications of meningiomas based on these molecular biological features have been proposed. These classifications are expected to provide a more accurate prognosis than the traditional WHO classification and to influence treatment strategies for refractory aggressive meningiomas. Future systemic drug therapy research, including molecular targeted therapies, is also expected to be developed.

Ethical Approval and Informed Consent

No informed consent was required in this study because no humans were directly involved.

Conflicts of Interest Disclosure

None

References

1) Ostrom Q T, Cioffi G, Gittleman H, et al.: CBTRUS statistical report: primary brain and other central nervous system tumors diagnosed in the United States in 2012-2016. *Neuro Oncol* 21: v1-v100, 2019
2) Bulleid L S, James Z, Lammie A, Hayhurst C, Leach P A: The effect of the revised WHO classification on the incidence of grade II meningioma. *Br J Neurosurg* 34: 584-586, 2020
3) Louis D N, Ohgaki H, Wiestler O D, et al.: The 2007 WHO classification of tumours of the central nervous system. *Acta Neuropathol* 114: 97-109, 2007
4) Louis D N, Perry A, Reifenberger G, et al.: The 2016 World Health Organization Classification of Tumors of the central nervous system: a summary. *Acta Neuropathol* 131: 803-820, 2016
5) Perry A: Unmasking the secrets of meningioma: a slow but rewarding journey. *Surg Neurol* 61: 171-173, 2004
6) Rogers L, Gilbert M, Vogelbaum M A: Intracranial meningiomas of atypical (WHO grade II) histology. *J Neurooncol* 99: 393-405, 2010
7) Oya S, Ikawa F, Ichihara N, et al.: Nation-wide brain tumor registry-based study of intracranial meningioma in Japan: analysis of surgery-related risks. *Neurol Med Chir (Tokyo)* 61: 98-106, 2021
8) Jääskeläinen J, Haltia M, Servo A: Atypical and anaplastic meningiomas: radiology, surgery, radiotherapy, and outcome. *Surg Neurol* 25: 233-242, 1986
9) Kolles H, Niedermayer I, Schmitt C, et al.: Triple approach for diagnosis and grading of meningiomas: histology, morphometry of Ki-67/Feulgen stainings, and cytogenetics. *Acta Neurochir* 137: 174-181, 1995
10) Maier H, Ofner D, Hittmair A, Kitz K, Budka H: Classic, atypical, and anaplastic meningioma: three histopathological subtypes of clinical relevance. *J Neurosurg* 77: 616-623, 1992
11) Perry A, Stafford S L, Scheithauer B W, Suman V J, Lohse C M: Meningioma grading: an analysis of histologic parameters. *Am J Surg Pathol* 21: 1455-1465, 1997
12) Chiba K, Sugawara T, Kobayashi D, Sato A, Murota Y, Maehara T: Atypical histological features as risk factors for recurrence in newly diagnosed WHO Grade I meningioma. *Neurol Med Chir (Tokyo)* 61: 647-651, 2021
13) Simó M, Argyriou A A, Macià M, et al.: Recurrent high-grade meningioma: a phase II trial with somatostatin analogue therapy. *Cancer Chemother Pharmacol* 73: 919-923, 2014
14) Chamberlain M C: The role of chemotherapy and targeted therapy in the treatment of intracranial meningioma. *Curr Opin Oncol* 24: 666-671, 2012
15) Louis D N, Perry A, Wesseling P, et al.: The 2021 WHO Classification of Tumors of the central nervous system: a summary. *Neuro Oncol* 23: 1231-1251, 2021

16) Maas S L N, Stichel D, Hielscher T, et al.: Integrated molecular-morphologic meningioma classification: A multicenter retrospective analysis, retrospectively and prospectively validated. *J Clin Oncol* 39: 3839-3852, 2021
17) Nassiri F, Liu J, Patil V, et al.: A clinically applicable integrative molecular classification of meningiomas. *Nature* 597: 119-125, 2021
18) Sievers P, Hielscher T, Schrimpf D, et al.: CDKN2A/B homozygous deletion is associated with early recurrence in meningiomas. *Acta Neuropathol* 140: 409-413, 2020
19) Sahm F, Schrimpf D, Olar A, et al.: Tert promoter mutations and risk of recurrence in meningioma. *J Natl Cancer Inst* 108: 2016
20) James M F, Han S, Polizzano C, et al.: NF2/merlin is a novel negative regulator of mTOR complex 1, and activation of mTORC1 is associated with meningioma and schwannoma growth. *Mol Cell Biol* 29: 4250-4261, 2009
21) López-Lago M A, Okada T, Murillo M M, Socci N, Giancotti F G: Loss of the tumor suppressor gene NF2, encoding merlin, constitutively activates integrin-dependent mTORC1 signaling. *Mol Cell Biol* 29: 4235-4249, 2009
22) Bi W L, Greenwald N F, Abedalthagafi M, et al.: Genomic landscape of high-grade meningiomas. *NPJ Genom Med* 2: 2017
23) Pawloski J A, Fadel H A, Huang Y W, Lee I Y: Genomic biomarkers of meningioma: A focused review. *Int J Mol Sci* 22: 2021
24) Perry A, Banerjee R, Lohse C M, Kleinschmidt-DeMasters B K, Scheithauer B W: A role for chromosome 9p21 deletions in the malignant progression of meningiomas and the prognosis of anaplastic meningiomas. *Brain Pathol* 12: 183-190, 2002
25) Boström J, Meyer-Puttlitz B, Wolter M, et al.: Alterations of the tumor suppressor genes CDKN2A (p16(INK4a)), p14(ARF), CDKN2B (p15(INK4b)), and CDKN2C (p18(INK4c)) in atypical and anaplastic meningiomas. *Am J Pathol* 159: 661-669, 2001
26) Goutagny S, Yang H W, Zucman-Rossi J, et al.: Genomic profiling reveals alternative genetic pathways of meningioma malignant progression dependent on the underlying NF2 status. *Clin Cancer Res* 16: 4155-4164, 2010
27) Sahm F, Schrimpf D, Stichel D, et al.: DNA methylation-based classification and grading system for meningioma: a multicentre, retrospective analysis. *Lancet Oncol* 18: 682-694, 2017
28) Guyot A, Duchesne M, Robert S, et al.: Analysis of CDKN2A gene alterations in recurrent and non-recurrent meningioma. *J Neurooncol* 145: 449-459, 2019
29) Peyre M, Stemmer-Rachamimov A, Clermont-Taranchon E, et al.: Meningioma progression in mice triggered by Nf2 and Cdkn2ab inactivation. *Oncogene* 32: 4264-4272, 2013
30) Mirian C, Duun-Henriksen A K, Juratli T, et al.: Poor prognosis associated with tert gene alterations in meningioma is independent of the WHO classification: an individual patient data meta-analysis. *J Neurol Neurosurg Psychiatry* 91: 378-387, 2020
31) Maier A D, Stenman A, Svahn F, et al.: Tert promoter mutations in primary and secondary WHO grade III meningioma. *Brain Pathol* 31: 61-69, 2021
32) Stögbauer L, Stummer W, Senner V, Brokinkel B: Telomerase activity, tert expression, hTERT promoter alterations, and alternative lengthening of the telomeres (ALT) in meningiomas - a systematic review. *Neurosurg Rev* 43: 903-910, 2020
33) Paramasivam N, Hübschmann D, Toprak U H, et al.: Mutational patterns and regulatory networks in epigenetic subgroups of meningioma. *Acta Neuropathol* 138: 295-308, 2019
34) Deng J, Sun S, Chen J, et al.: Tert alterations predict tumor progression in de novo high-grade meningiomas following adjuvant radiotherapy. *Front Oncol* 11: 747592, 2021
35) Shankar G M, Santagata S: BAP1 mutations in high-grade meningioma: implications for patient care. *Neuro Oncol* 19: 1447-1456, 2017
36) Carbone M, Harbour J W, Brugarolas J, et al.: Biological mechanisms and clinical significance of BAP1 mutations in human cancer. *Cancer Discov* 10: 1103-1120, 2020
37) Shankar G M, Abedalthagafi M, Vaubel R A, et al.: Germline and somatic BAP1 mutations in high-grade rhabdoid meningiomas. *Neuro Oncol* 19: 535-545, 2017
38) Williams E A, Wakimoto H, Shankar G M, et al.: Frequent inactivating mutations of the PBAF complex gene PBRM1 in meningioma with papillary features. *Acta Neuropathol* 140: 89-93, 2020
39) Wang H, Qu Y, Dai B, et al.: PBRM1 regulates proliferation and the cell cycle in renal cell carcinoma through a chemokine/chemokine receptor interaction pathway. *PLOS ONE* 12: e0180862, 2017
40) Miao D, Margolis C A, Gao W, et al.: Genomic correlates of response to immune checkpoint therapies in clear cell renal cell carcinoma. *Science* 359: 801-806, 2018
41) Juratli T A, McCabe D, Nayyar N, et al.: DMD genomic deletions characterize a subset of progressive/higher-grade meningiomas with poor outcome. *Acta Neuropathol* 136: 779-792, 2018
42) Youngblood M W, Duran D, Montejo J D, et al.: Correlations between genomic subgroup and clinical features in a cohort of more than 3000 meningiomas. *J Neurosurg* 133: 1-10, 2019. doi: 10.3171/2019.8.JNS191266
43) Jungwirth G, Warta R, Beynon C, et al.: Intraventricular meningiomas frequently harbor NF2 mutations but lack common genetic alterations in TRAF7, AKT1, SMO, KLF4, PIK3CA, and tert. *Acta Neuropathol Commun* 7: 140, 2019
44) Abedalthagafi M S, Bi W L, Merrill P H, et al.: ARID1A and tert promoter mutations in dedifferentiated meningioma. *Cancer Genet* 208: 345-350, 2015
45) Tauziede-Espariat A, Parfait B, Besnard A, et al.: Loss of SMARCE1 expression is a specific diagnostic marker of clear cell meningioma: a comprehensive immunophenotypical and molecular analysis. *Brain Pathol* 28: 466-474, 2018
46) Collord G, Tarpey P, Kurbatova N, et al.: An integrated genomic analysis of anaplastic meningioma identifies prognostic molecular signatures. *Sci Rep* 8: 13537, 2018
47) Gill C M, Loewenstern J, Rutland J W, et al.: SWI/SNF chromatin remodeling complex alterations in meningioma. *J Cancer Res Clin Oncol* 147: 3431-3440, 2021
48) Yuzawa S, Nishihara H, Tanaka S: Genetic landscape of meningioma. *Brain Tumor Pathol* 33: 237-247, 2016
49) Pang J C, Chung N Y, Chan N H, Poon W S, Thomas T, Ng H K: Rare mutation of PIK3CA in meningiomas. *Acta Neuropathol* 111: 284-285, 2006
50) Birzu C, Peyre M, Sahm F: Molecular alterations in meningioma: prognostic and therapeutic perspectives. *Curr Opin Oncol* 32: 613-622, 2020
51) Dunn I F, Du Z, Touat M, et al.: Mismatch repair deficiency in high-grade meningioma: a rare but recurrent event associated with dramatic immune activation and clinical response to PD-1 blockade. *JCO Precis Oncol* 2018: 2018
52) Kim L: A narrative review of targeted therapies in meningioma. *Chin Clin Oncol* 9: 76, 2020
53) Georgescu M M, Nanda A, Li Y, et al.: Mutation status and epi-

thelial differentiation stratify recurrence risk in chordoid meningioma-A multicenter study with high prognostic relevance. *Cancers (Basel)* 12: 2020
54) Vasudevan H N, Braunstein S E, Phillips J J, et al.: Comprehensive molecular profiling identifies FOXM1 as a key transcription factor for meningioma proliferation. *Cell Rep* 22: 3672-3683, 2018
55) Harmancı A S, Youngblood M W, Clark V E, et al.: Integrated genomic analyses of de novo pathways underlying atypical meningiomas. *Nat Commun* 8: 14433, 2017
56) Lin P, Buxton J A, Acheson A, et al.: Antiangiogenic gene therapy targeting the endothelium-specific receptor tyrosine kinase Tie2. *Proc Natl Acad Sci U S A* 95: 8829-8834, 1998
57) Fu Z, Malureanu L, Huang J, et al.: Plk1-dependent phosphorylation of FoxM1 regulates a transcriptional programme required for mitotic progression. *Nat Cell Biol* 10: 1076-1082, 2008
58) Korver W, Schilham M W, Moerer P, et al.: Uncoupling of S phase and mitosis in cardiomyocytes and hepatocytes lacking the winged-helix transcription factor Trident. *Curr Biol* 8: 1327-1330, 1998
59) Laurendeau I, Ferrer M, Garrido D, et al.: Gene expression profiling of the hedgehog signaling pathway in human meningiomas. *Mol Med* 16: 262-270, 2010
60) Aizer A A, Abedalthagafi M, Bi W L, et al.: A prognostic cytogenetic scoring system to guide the adjuvant management of patients with atypical meningioma. *Neuro Oncol* 18: 269-274, 2016
61) Weber R G, Boström J, Wolter M, et al.: Analysis of genomic alterations in benign, atypical, and anaplastic meningiomas: toward a genetic model of meningioma progression. *Proc Natl Acad Sci U S A* 94: 14719-14724, 1997
62) Leone P E, Bello M J, de Campos J M, et al.: NF2 gene mutations and allelic status of 1p, 14q and 22q in sporadic meningiomas. *Oncogene* 18: 2231-2239, 1999
63) Lee Y, Liu J, Patel S, et al.: Genomic landscape of meningiomas. *Brain Pathol* 20: 751-762, 2010
64) Perry A, Cai D X, Scheithauer B W, et al.: Merlin, DAL-1, and progesterone receptor expression in clinicopathologic subsets of meningioma: a correlative immunohistochemical study of 175 cases. *J Neuropathol Exp Neurol* 59: 872-879, 2000
65) Suppiah S, Nassiri F, Bi W L, et al.: Molecular and translational advances in meningiomas. *Neuro Oncol* 21: i4-i17, 2019
66) Peyre M, Kalamarides M: Molecular genetics of meningiomas: building the roadmap towards personalized therapy. *Neurochirurgie* 64: 22-28, 2018
67) Bi W L, Prabhu V C, Dunn I F: High-grade meningiomas: biology and implications. *Neurosurg Focus* 44: E2, 2018
68) Driver J, Hoffman S E, Tavakol S, et al.: A molecularly integrated grade for meningioma. *Neuro Oncol* 24: 796-808, 2022. doi: 10.1093/neuonc/noab213
69) Pérez-Magán E, Rodríguez de Lope A, Ribalta T, et al.: Differential expression profiling analyses identifies downregulation of 1p, 6q, and 14q genes and overexpression of 6p histone cluster 1 genes as markers of recurrence in meningiomas. *Neuro Oncol* 12: 1278-1290, 2010
70) Linsler S, Kraemer D, Driess C, et al.: Molecular biological determinations of meningioma progression and recurrence. *PLOS ONE* 9: e94987, 2014
71) Lamszus K: Meningioma pathology, genetics, and biology. *J Neuropathol Exp Neurol* 63: 275-286, 2004
72) Damen P J J, Bulthuis V J, Hanssens P E J, et al.: WHO grade I meningiomas that show regrowth after gamma knife radiosurgery often show 1p36 loss. *Sci Rep* 11: 16432, 2021
73) Cai D X, Banerjee R, Scheithauer B W, Lohse C M, Kleinschmidt-Demasters B K, Perry A: Chromosome 1p and 14q FISH analysis in clinicopathologic subsets of meningioma: diagnostic and prognostic implications. *J Neuropathol Exp Neurol* 60: 628-636, 2001
74) Williams E A, Santagata S, Wakimoto H, et al.: Distinct genomic subclasses of high-grade/progressive meningiomas: NF2-associated, NF2-exclusive, and NF2-agnostic. *Acta Neuropathol Commun* 8: 171, 2020
75) Barresi V, Simbolo M, Fioravanzo A, et al.: Molecular Profiling of 22 Primary Atypical meningiomas Shows the Prognostic Significance of 18q Heterozygous Loss and CDKN2A/B Homozygous Deletion on Recurrence-Free Survival. *Cancers (Basel)* 13: 2021
76) Katz L M, Hielscher T, Liechty B, et al.: Loss of histone H3K27 me3 identifies a subset of meningiomas with increased risk of recurrence. *Acta Neuropathol* 135: 955-963, 2018
77) Gauchotte G, Peyre M, Pouget C, et al.: Prognostic value of histopathological features and loss of H3K27me3 immunolabeling in anaplastic meningioma: A multicenter retrospective study. *J Neuropathol Exp Neurol* 79: 754-762, 2020
78) Nassiri F, Wang J Z, Singh O, et al.: Loss of H3K27me3 in meningiomas. *Neuro Oncol* 23: 1282-1291, 2021
79) Behling F, Fodi C, Gepfner-Tuma I, et al.: H3K27me3 loss indicates an increased risk of recurrence in the Tübingen meningioma cohort. *Neuro Oncol* 23: 1273-1281, 2021
80) Capper D, Jones D T W, Sill M, et al.: DNA methylation-based classification of central nervous system tumours. *Nature* 555: 469-474, 2018
81) Koelsche C, Schrimpf D, Stichel D, et al.: Sarcoma classification by DNA methylation profiling. *Nat Commun* 12: 498, 2021
82) Nassiri F, Mamatjan Y, Suppiah S, et al.: DNA methylation profiling to predict recurrence risk in meningioma: development and validation of a nomogram to optimize clinical management. *Neuro Oncol* 21: 901-910, 2019
83) Graillon T, Tabouret E, Chinot O: Chemotherapy and targeted therapies for meningiomas: what is the evidence? *Curr Opin Neurol* 34: 857-867, 2021
84) Brastianos P K, Twohy E, Gerstner E R, et al.: Alliance A071401: Phase II trial of FAK inhibition in meningiomas with somatic NF2 mutations. *J Clin Oncol* 38: 2502, 2020
85) Tien A C, Li J, Bao X, et al.: A Phase 0 trial of ribociclib in recurrent glioblastoma patients incorporating a tumor pharmacodynamic- and pharmacokinetic-guided expansion cohort. *Clin Cancer Res* 25: 5777-5786, 2019
86) Pachow D, Andrae N, Kliese N, et al.: mTORC1 inhibitors suppress meningioma growth in mouse models. *Clin Cancer Res* 19: 1180-1189, 2013
87) Johnson M D, Okedli E, Woodard A, Toms S A, Allen G S: Evidence for phosphatidylinositol 3-kinase-Akt-p7S6K pathway activation and transduction of mitogenic signals by platelet-derived growth factor in meningioma cells. *J Neurosurg* 97: 668-675, 2002
88) Graillon T, Defilles C, Mohamed A, et al.: Combined treatment by octreotide and everolimus: octreotide enhances inhibitory effect of everolimus in aggressive meningiomas. *J Neurooncol* 124: 33-43, 2015
89) Graillon T, Sanson M, Campello C, et al.: Everolimus and octreotide for patients with recurrent meningioma: results from the Phase II CEVOREM trial. *Clin Cancer Res* 26: 552-557, 2020
90) Chamberlain M C, Glantz M J, Fadul C E: Recurrent men-

ingioma: salvage therapy with long-acting somatostatin analogue. *Neurology* 69: 969-973, 2007
91) Norden A D, Ligon K L, Hammond S N, et al.: Phase II study of monthly pasireotide LAR (SOM230C) for recurrent or progressive meningioma. *Neurology* 84: 280-286, 2015
92) Shih K C, Chowdhary S, Rosenblatt P, et al.: A phase II trial of bevacizumab and everolimus as treatment for patients with refractory, progressive intracranial meningioma. *J Neurooncol* 129: 281-288, 2016
93) Brastianos P K, Horowitz P M, Santagata S, et al.: Genomic sequencing of meningiomas identifies oncogenic SMO and AKT1 mutations. *Nat Genet* 45: 285-289, 2013
94) Boetto J, Bielle F, Sanson M, Peyre M, Kalamarides M: SMO mutation status defines a distinct and frequent molecular subgroup in olfactory groove meningiomas. *Neuro Oncol* 19: 345-351, 2017
95) Lamszus K, Lengler U, Schmidt N O, Stavrou D, Ergün S, Westphal M: Vascular endothelial growth factor, hepatocyte growth factor/scatter factor, basic fibroblast growth factor, and placenta growth factor in human meningiomas and their relation to angiogenesis and malignancy. *Neurosurgery* 46: 938-947; discussion 947-938, 2000
96) Nassehi D, Dyrbye H, Andresen M, et al.: Vascular endothelial growth factor A protein level and gene expression in intracranial meningiomas with brain edema. *APMIS* 119: 831-843, 2011
97) Goldman C K, Bharara S, Palmer C A, et al.: Brain edema in meningiomas is associated with increased vascular endothelial growth factor expression. *Neurosurgery* 40: 1269-1277, 1997
98) Furtner J, Schöpf V, Seystahl K, et al.: Kinetics of tumor size and peritumoral brain edema before, during, and after systemic therapy in recurrent WHO grade II or III meningioma. *Neuro Oncol* 18: 401-407, 2016
99) Grimm S A, Kumthekar P, Chamberlain M C, et al.: Phase II trial of bevacizumab in patients with surgery and radiation refractory progressive meningioma. *J Clin Oncol* 33: 2055, 2015
100) Nayak L, Iwamoto F M, Rudnick J D, et al.: Atypical and anaplastic meningiomas treated with bevacizumab. *J Neurooncol* 109: 187-193, 2012
101) Furuse M, Nonoguchi N, Kawabata S, et al.: Intratumoral and peritumoral post-irradiation changes, but not viable tumor tissue, may respond to bevacizumab in previously irradiated meningiomas. *Radiat Oncol* 10: 156, 2015
102) Raizer J J, Grimm S A, Rademaker A, et al.: A phase II trial of PTK787/ZK 222584 in recurrent or progressive radiation and surgery refractory meningiomas. *J Neurooncol* 117: 93-101, 2014
103) Kaley T J, Wen P, Schiff D, et al.: Phase II trial of sunitinib for recurrent and progressive atypical and anaplastic meningioma. *Neuro Oncol* 17: 116-121, 2015
104) Norden A D, Raizer J J, Abrey L E, et al.: Phase II trials of erlotinib or gefitinib in patients with recurrent meningioma. *J Neurooncol* 96: 211-217, 2010
105) Wen P Y, Yung W K, Lamborn K R, et al.: Phase II study of imatinib mesylate for recurrent meningiomas (North American Brain Tumor Consortium study 01-08). *Neuro Oncol* 11: 853-860, 2009
106) Kotecha R, Tonse R, Appel H, et al.: Regression of intracranial meningiomas following treatment with cabozantinib. *Curr Oncol* 28: 1537-1543, 2021
107) Wang Y, Li W, Jing N, et al.: Apatinib in recurrent anaplastic meningioma: a retrospective case series and systematic literature review. *Cancer Biol Ther* 21: 583-589, 2020
108) Graillon T, Romano D, Defilles C, et al.: Pasireotide is more effective than octreotide, alone or combined with everolimus on human meningioma in vitro. *Oncotarget* 8: 55361-55373, 2017
109) Schulz C, Mathieu R, Kunz U, Mauer U M: Treatment of unresectable skull base meningiomas with somatostatin analogs. *Neurosurg Focus* 30: E11, 2011
110) Seystahl K, Stoecklein V, Schüller U, et al.: Somatostatin receptor-targeted radionuclide therapy for progressive meningioma: benefit linked to 68Ga-DOTATATE/-TOC uptake. *Neuro Oncol* 18: 1538-1547, 2016
111) Gerster-Gilliéron K, Forrer F, Maecke H, Mueller-Brand J, Merlo A, Cordier D: 90Y-DOTATOC as a therapeutic option for complex recurrent or progressive meningiomas. *J Nucl Med* 56: 1748-1751, 2015
112) Marincek N, Radojewski P, Dumont R A, et al.: Somatostatin receptor-targeted radiopeptide therapy with 90Y-DOTATOC and 177Lu-DOTATOC in progressive meningioma: long-term results of a phase II clinical trial. *J Nucl Med* 56: 171-176, 2015
113) van Essen M, Krenning E P, Kooij P P, et al.: Effects of therapy with [177Lu-DOTA0, Tyr3]octreotate in patients with paraganglioma, meningioma, small cell lung carcinoma, and melanoma. *J Nucl Med* 47: 1599-1606, 2006
114) Bartolomei M, Bodei L, De Cicco C, et al.: Peptide receptor radionuclide therapy with (90)Y-DOTATOC in recurrent meningioma. *Eur J Nucl Med Mol Imaging* 36: 1407-1416, 2009
115) Mirian C, Duun-Henriksen A K, Maier A, et al.: Somatostatin receptor-targeted radiopeptide therapy in treatment-refractory meningioma: individual patient data meta-analysis. *J Nucl Med* 62: 507-513, 2021
116) Behling F, Fodi C, Skardelly M, et al.: Differences in the expression of SSTR1-5 in meningiomas and its therapeutic potential. *Neurosurg Rev* 45: 467-478, 2022
117) Zahid A, Johnson D R, Kizilbash S H: Efficacy of (177)Lu-Dotatate therapy in the treatment of recurrent meningioma. *Mayo Clin Proc Innov Qual Outcomes* 5: 236-240, 2021
118) Schrell U M, Rittig M G, Anders M, et al.: Hydroxyurea for treatment of unresectable and recurrent meningiomas. I. Inhibition of primary human meningioma cells in culture and in meningioma transplants by induction of the apoptotic pathway. *J Neurosurg* 86: 845-852, 1997
119) Newton H B, Slivka M A, Stevens C: Hydroxyurea chemotherapy for unresectable or residual meningioma. *J Neurooncol* 49: 165-170, 2000
120) Rosenthal M A, Ashley D L, Cher L: Treatment of high risk or recurrent meningiomas with hydroxyurea. *J Clin Neurosci* 9: 156-158, 2002
121) Loven D, Hardoff R, Sever Z B, et al.: Non-resectable slow-growing meningiomas treated by hydroxyurea. *J Neurooncol* 67: 221-226, 2004
122) Weston G J, Martin A J, Mufti G J, Strong A J, Gleeson M J: Hydroxyurea treatment of meningiomas: a pilot study. *Skull Base [et al]* 16: 157-160, 2006
123) Koper J W, Zwarthoff E C, Hagemeijer A, et al.: Inhibition of the growth of cultured human meningioma cells by recombinant interferon-alpha. *Eur J Cancer* 27: 416-419, 1991
124) Wöber-Bingöl C, Wöber C, Marosi C, Prayer D: Interferon-alfa-2b for meningioma. *Lancet* 345: 331, 1995
125) Choudhury A, Raleigh D R: Preclinical models of meningioma: cell culture and animal systems. *Handb Clin Neurol* 169: 131-136, 2020
126) Proctor D T, Patel Z, Lama S, Resch L, van Marle G, Sutherland G R: Identification of PD-L2, B7-H3 and CTLA-4 immune checkpoint proteins in genetic subtypes of men-

ingioma. *Oncoimmunology* 8: e1512943, 2019
127) Li Y D, Veliceasa D, Lamano J B, et al.: Systemic and local immunosuppression in patients with high-grade meningiomas. *Cancer Immunol Immunother* 68: 999-1009, 2019
128) Du Z, Abedalthagafi M, Aizer A A, et al.: Increased expression of the immune modulatory molecule PD-L1 (CD274) in anaplastic meningioma. *Oncotarget* 6: 4704-4716, 2015
129) Karimi S, Mansouri S, Mamatjan Y, et al.: Programmed death ligand-1 (PD-L1) expression in meningioma; prognostic significance and its association with hypoxia and NFkB2 expression. *Sci Rep* 10: 14115, 2020
130) Bi W L, Nayak L, Meredith D M, et al.: Activity of PD-1 blockade with Nivolumab among patients with recurrent atypical/anaplastic meningioma: Phase II trial results. *Neuro Oncol* 24: 101-113, 2022. doi: 10.1093/neuonc/noab118
131) Brastianos P K, Kim A E, Giobbie-Hurder A, et al.: Phase 2 study of pembrolizumab in patients with recurrent and residual high-grade meningiomas. *Nat Commun* 13: 1325, 2022
132) Karimi S, Mansouri S, Nassiri F, et al.: Clinical significance of checkpoint regulator "Programmed death ligand-1 (PD-L1)" expression in meningioma: review of the current status. *J Neurooncol* 151: 443-449, 2021
133) Wahab M, Al-Azzawi F: Meningioma and hormonal influences. *Climacteric* 6: 285-292, 2003
134) Hsu D W, Efird J T, Hedley-Whyte E T: Progesterone and estrogen receptors in meningiomas: prognostic considerations. *J Neurosurg* 86: 113-120, 1997
135) Bozzetti C, Camisa R, Nizzoli R, et al.: Estrogen and progesterone receptors in human meningiomas: biochemical and immunocytochemical evaluation. *Surg Neurol* 43: 230-233, ; discussion 234, 1995
136) Ji Y, Rankin C, Grunberg S, et al.: Double-blind Phase III randomized trial of the antiprogestin agent mifepristone in the treatment of unresectable meningioma: SWOG S9005. *J Clin Oncol* 33: 4093-4098, 2015
137) Germano G, Frapolli R, Belgiovine C, et al.: Role of macrophage targeting in the antitumor activity of trabectedin. *Cancer Cell* 23: 249-262, 2013
138) Jimenez P C, Wilke D V, Branco P C, et al.: Enriching cancer pharmacology with drugs of marine origin. *Br J Pharmacol* 177: 3-27, 2020
139) Huygh G, Clement P M, Dumez H, et al.: Ecteinascidin-743: evidence of activity in advanced, pretreated soft tissue and bone sarcoma patients. *Sarcoma* 2006: 56282, 2006
140) Preusser M, Spiegl-Kreinecker S, Lötsch D, et al.: Trabectedin has promising antineoplastic activity in high-grade meningioma. *Cancer* 118: 5038-5049, 2012
141) Preusser M, Silvani A, Le Rhun E, et al.: Trabectedin for recurrent WHO grade 2 or 3 meningioma: a randomized phase 2 study of the EORTC Brain Tumor Group (EORTC-1320-BTG). *Neuro Oncol* 24: 755-767, 2022. doi: 10.1093/neuonc/noab243

Corresponding author: Satoru Miyawaki, M.D., Ph.D.
Department of Neurosurgery, Faculty of Medicine, The University of Tokyo, 7-3-1 Hongo, Bunkyo-ku, Tokyo 113-8655, Japan.
e-mail: smiya-nsu@m.u-tokyo.ac.jp