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High Grade Meningiomas: Current Therapy Based on Tumor Biology

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Abstract

Atypical (WHO grade II) and malignant meningiomas (WHO Grade III) are a rare subset of primary intracranial tumors. Due to the high recurrence rate after surgical resection and radiotherapy, there has been a recent interest in exploring other systemic treatment options for these refractory tumors. Recent advances in molecular sequencing of tumors have elucidated new pathways and drug targets currently being studied. This article provides a thorough overview of novel investigational therapeutics, including targeted therapy, immunotherapy, and new technological modalities for atypical and malignant meningiomas. There is encouraging preclinical evidence regarding the efficacy of the emerging treatments discussed in this chapter. Several clinical trials are currently recruiting patients to translate targeted molecular therapy for recurrent and high-grade meningiomas.

Keywords: targeted therapy, molecular biology, progression free survival, overall survival, meningioma, genomics, angiogenesis, immunotherapy, outcomes

1. Introduction

Meningiomas (MN) are a type of central nervous system (CNS) tumors that arise from the leptomeningeal arachnoid covering the encephalon and the spinal cord, more specifically, from the arachnoid cap cells [1]. In adults, MN accounts for approximately 37.6% of all primary brain tumors, and corresponds to the most common intracranial tumor in adults over 35 years [1, 2]. According to Ostrom et al., incidence of MN in the United States (US) is 8.83 per 100,000 per year [3]. Around 90% of all MN cases are diagnosed intracranially, with the rest arising from the spinal arachnoid [4]. The median age at diagnosis for MN is 65 years [4] with the majority of patients being in the range of 55–74 [4]. Cases in the pediatric population are extremely rare, corresponding only to 0.4–4.6% of all pediatric tumors [2]. There is a female predominance in case proportion, with a female:male ratio of 3:1 for all MN, and 9:1 for spinal cord MNs [2, 5]. MNs are characterized for being slow in growth and often not infiltrative, with an insidious development of symptoms. Clinical presentation of MN might vary from patient to patient, with tumor localization being the main determining factor of clinical features. Signs and symptoms might include headaches because of increased intracranial pressure,

focal neurological deficits (mainly cranial nerve focalization), and seizures. In the case of MN developing in the frontal lobe, personality changes, altered mental status and mood disturbances might appear [6].

According to the World Health Organization (WHO), MN is classified in three subtypes: common type or WHO grade I, atypical/intermediate type or WHO grade II and the anaplastic/malignant type or WHO grade III. These high-grade tumors might develop *de novo* or as a transformation from a lower grade MN [7]. Approximately 70% of cases are WHO grade I, 28% are WHO grade II and only around 3% are classified as WHO grade III. According to a cohort of 992 patients with MN, the proportion of atypical and anaplastic MN was higher in males than females ($p = 0.003$) [4]. The more aggressive behavior in grade II and III MN is represented by a worse prognosis in terms of overall survival (OS) and recurrence risk after surgical resection (SR). In a cohort of 102 patients with grade II and III MN, 5-year OS (5-yOS) was 97.5% and 67.4% respectively, with a median OS (mOS) of 167 months and 72 months respectively [8]. These results showed a marked increase in survival over the last decades, arguably because of the introduction of better surgical techniques, radiation therapy and some forms of chemotherapy, as previous research showed a 5-yOS of 75% for grade II MN and 32% for grade III MN [9]. Tumor recurrence has been found to be considerably increased in high grade MN, with a 50% and 80% 5-year recurrence for grade II and grade III MN respectively, and only 5–10% for grade I MN [10, 11].

As high-grade MN continue to be a difficult to treat condition, with high recurrence and low response rates, molecular insights into precision medicine have been investigated in the last two decades. With a better understanding of the cellular and molecular pathways underlying MN pathophysiology, recurrence and malignancy, newer therapies have been considered as possible candidates for the treatment of these conditions. Some agents include newer systemic chemotherapeutic agents like trabectedin, inhibitors of the Epidermal Growth Factor Receptor (EGFR) like erlotinib and gefitinib, inhibitors of the Platelet-Derived Growth Factor Receptor (PDGFR), inhibitors of mTOR, especially from the complex 1 (mTORC1) as well as its upstream and downstream elements (AKT/PI3K and MEK). The biological process of angiogenesis is also under research, with ongoing trials with anti-angiogenic agents from the Tyrosine Kinase Inhibitors (TKIs) targeting the Vascular Endothelial Growth Factor (VEGF) pathway, as well as antibody agents like bevacizumab. As it is expected, immunotherapy with checkpoint inhibitors is also under current investigation, with anti-PD1 and anti-PD-L1 monoclonal antibodies being tested in clinical trials. In this chapter we are going to cover the molecular biology of MNs, especially in the cases of grade II and grade III MN. We will also discuss the current knowledge in systemic treatments as well as therapies in clinical trials and possible candidates that are being tested *in vitro*.

2. Molecular biology

Advancements in understanding the pathophysiology and molecular biology of MNs are critical for improving risk evaluation and prognosis. Similarly, to design novel treatments aimed at blocking canonical pathways involved in carcinogenesis and disease evolution. As molecular analyzes of meningiomas continue to evolve, several cytogenetic, genomic, epigenetic, and expression alterations associated with tumor aggressiveness and proclivity for recurrence have been identified as potential biomarkers to enhance risk stratification [12]. Recently, several seminal studies evaluating the genomics of intracranial meningiomas have rapidly changed the understanding of the disease. The importance of NF2 (neurofibromin 2), TRAF7

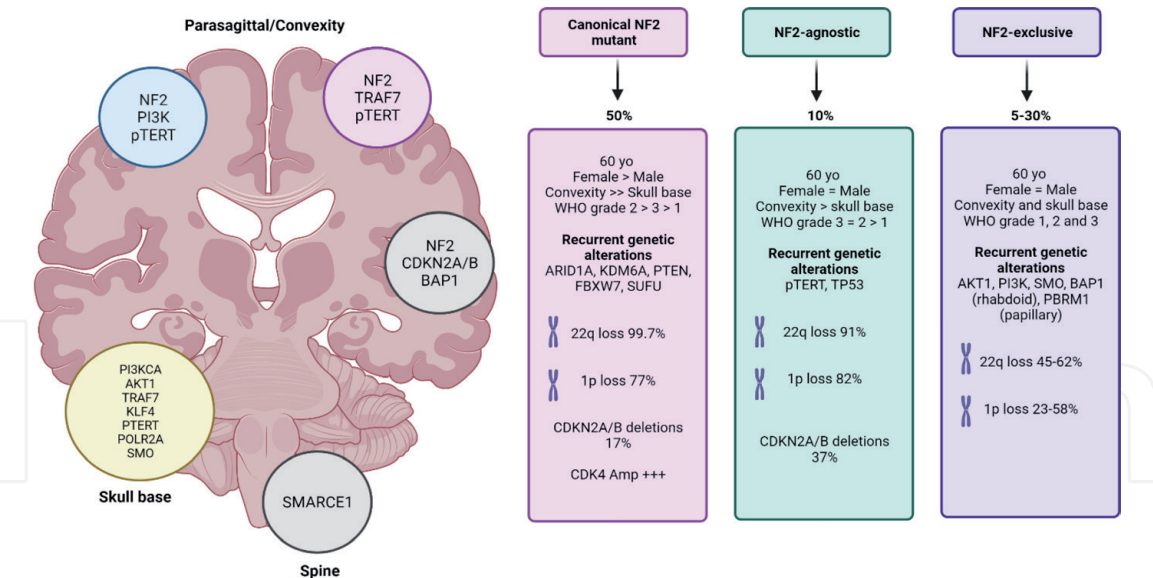


Figure 1.
Main cytogenetic and recurrent genetic alterations in recurrent and high-grade meningiomas according to the WHO classification and anatomical location.

(tumor necrosis factor [TNF] receptor-associated factor 7), KLF4 (Kruppel-like factor-4), AKT1, SMO (smoothened), PIK3CA (phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha), and POLR2 (RNA polymerase II subunit A) demonstrates that there are at least six distinct mutational classes of meningiomas. In addition, six methylation classes of meningioma have been appreciated, enabling improved prognosis prediction compared with traditional WHO grades. Genomic studies have shed light on the nature of recurrent meningioma, distinct intracranial locations and mutational patterns, and a potential embryonic cancer stem cell-like origin [13–16] (**Figure 1**).

2.1 Cytogenetics and genomics

A large number of meningiomas possess a normal karyotype, with an overall low incidence of genomic alterations (including somatic copy number alterations—SCNA, rearrangements, and low mutational burden) [17–19]. However, these disruptions increase following tumor grade, the number of recurrences, and biological aggressiveness. More than half of all identified genomic alterations involve the NF2, which underlies inherited Neurofibromatosis syndrome. Indeed, the most significant SCNA in meningioma is chromosome 22 monosomy, which is present in ~56% of cases and leads to losing the genomic locus containing NF2 (22q12.2) [20, 21]. Among grade I meningiomas, those carrying NF2 alterations are more likely to progress than those with a normal karyotype. In addition, the frequency of NF2 aberrations increases with tumor grade.

Loss of heterozygosity on chromosome 1p is present in 16% of MNs [22]. Characterization of the smallest region of overlapping deletion on this chromosome spans ~3.7 megabases and identified 59 genes, 17 of which have putative tumor-suppressive functions based on gene ontology. The protein methyltransferase and tumor suppressor RIZ1, is located on chromosome 1p, and studies implicate its loss of expression in meningioma progression [23]. Loss of the CDKN2A/CDKN2B locus on chromosome 9q is common in grade II meningiomas that transition to anaplastic lesions [24]. Additionally, a study showed that the levels of p16 and p15, the proteins encoded by CDKN2A and CDKN2B, may hold prognostic significance and/or represent a promising therapeutic target [25]. Recently, Nassiri et al. described

four consensus molecular groups of MN by combining DNA somatic copy-number aberrations, DNA somatic point mutations, DNA methylation, and messenger RNA abundance in a unified analysis [26]. These molecular groups predicted clinical outcomes compared with existing classification schemes. Each molecular group showed distinctive and prototypical biology (immunogenic, benign NF2 wild-type, hypermetabolic and proliferative) that informed therapeutic options. Proteogenomic characterization reinforced the robustness of defined molecular groups and uncovered highly abundant and group-specific protein targets [26].

2.2 NF2-related meningiomas

Globally, meningiomas have a low mutation rate (~3.5 mutations per megabase) compared to other cancers [25]. Various efforts to genotype the disease using NGS have identified NF2 mutations as the predominant alteration in spontaneous and Neurofibromatosis syndrome-associated tumors [24], at a frequency of ~40% in low grade and nearly 80% in high-grade tumors [27]. MNs related to alterations in NF2 were more common in the cerebral convexities and posterior skull base than those found in other anatomic locations, and up to 13% were associated with other co-mutations, including single mutations in CREBBP, PIK3CA (R108H), PIK3R1, BRCA1, and SMARCB1 [27]. Unfortunately, within NF2 mutated meningiomas, none of these identified mutations can predict the chance of recurrence, which can vary widely.

TERT promoter mutations have recently been reported in ~6% of all MNs, with ~80% of these also harboring alterations (mutations or deletions) at the NF2 locus [28]. Similar to overall mutational burden, TERT mutations increase with tumor grade. In grade I MN, TERT C228T and C250T mutations are linked with transformation to higher grades [28], prompting many neuro-oncologists to consider standardized testing for TERT promoter mutations. Further studies demonstrate that the presence of C228T and C250T correlates with increased TERT mRNA and functional increases in telomerase activity [29]. In grade II or III tumors, univariate analysis revealed a significant association with decreased PFS (progression-free survival; median 12.5 vs. 26 months, $p = 0.004$) and OS (overall survival; mean 26 vs. 46 months, $p = 0.009$) [30]. In vitro studies demonstrated that TERT mutated meningioma cells show decreased TERT activity in response to YK-4-279, a small molecule inhibitor of ETS transcription factor, suggesting a novel potential strategy for targeting this subgroup of tumors. In addition to individual TERT promoter mutations, recent efforts using targeted sequencing approaches identified an additional TERT promoter in the known hotspot G124A, which like other TERT mutations, seems to correlate with poor prognosis [31].

2.3 Non-NF2 meningioma

Non-NF2 mutated meningiomas, which generally have a benign behavior, are usually chromosomally stable, and often located in the anterior, medial, or skull base regions, possess a distinct mutational landscape [27]. Recent high throughput sequencing studies suggest an average of only 1.56 (SD \pm 1.07) genomic alterations (GAs) per non-NF2 mutated tumor [31]. The pro-apoptotic E3 ubiquitin ligase, tumor necrosis factor receptor-associated factor 7 (TRAF7) is mutated ~25% of all meningiomas [31]. Such alterations occur in the C-terminal WD40 protein interaction domain, suggesting they may alter protein-protein interactions with MAPK and NF- κ B family members [32]. While TRAF7 mutation is mutually exclusive with NF2 mutations, it is almost always correlated with PI3K and activating E17K mutation in AKT1, with the K409Q alteration of KLF4 [33].

AKT1, also referred to as protein kinase B, is a well-known oncogene. AKT activation relies on the PI3K pathway and is recognized as a critical node in the mTOR pathway. The E17 hotspot is the most characterized of AKT1 mutations and leads to constitutive activation of the protein. Mutations in AKT1 have also been shown to confer resistance to allosteric kinase inhibitors *in vitro* and are oncogenic in many solid tumors. Specifically, the E17K mutation is found in 7–12% of grade I meningiomas [34], is enriched in the meningothelial subtype [17], and is predictive of decreased PFS in olfactory groove tumors [35]. Altering the same signaling pathway PIK3CA mutations are also found in ~7% of non-NF2 tumors and are mutually exclusive with AKT1 mutation [36]. Targeted sequencing of this gene revealed novel non-synonymous mutations, A3140T and A3140G, which are reported as pathogenic, and C112T, which is also predicted to be pathogenic [31]. Indeed, increased PI3K signaling is related to aggressive behavior, especially within high-grade meningiomas [37], suggesting that therapeutics targeted toward this pathway may be a potential option.

Sequencing of 71 meningiomas genes recently identified two novel missense mutations in FGFR3, T932C, and G1376C, both of which were predicted to be pathogenic [31]. Identifying these mutations in patients with skull base low-grade tumors was associated with a good prognosis, given the absence of recurrence and the requirement of IMRT. KLF4 gene encodes a protein that belongs to the Kruppel family of transcription factors. The encoded zinc finger protein is required to control the G1-to-S transition of the cell cycle following DNA damage by mediating the tumor suppressor gene p53. In addition, KLF4 is involved in the differentiation of epithelial cells and may also function in skin, skeletal, and kidney development [38]. In meningiomas, KLF4 is thought to act as a tumor suppressor gene, expressed in low-grade tumors and downregulated in anaplastic tumors. At the genomic level, KLF4 is mutated in ~12% of grade I meningiomas, virtually all of which are of the secretory sub-type and harbor TRAF7 mutations [39]. All identified KLF4 mutations result in a K409Q substitution within the DNA binding domain, which likely alters several protein functions [40].

SMO (Smoothened, Frizzled Class Receptor) gene encoded a G protein-coupled receptor that interacts with the patched protein, a receptor for hedgehog proteins. Mutations in SMO, which result in L412F or W535L substitutions, lead to functional activation of Hedgehog signaling in meningioma [17, 41]. These mutations are present in ~5.5% of grade I meningiomas and are mutually exclusive with TRAF7, KLF4, and AKT1 mutations [27]. Meningiomas with the L412F mutation are more likely to recur (XX) and are enriched at the midline, perhaps due to the role that Hedgehog signaling plays in hemisphere separation during development [36]. Mutations in the Hedgehog family member SUFU are also found at low frequencies in sporadic meningiomas, and their germinal counterpart is also present in familial meningiomatosis [42]. Additional hedgehog family germline mutations occur in SMARCE1 and SMARCB1, though these carry less risk of recurrence than familial NF2 mutations [43, 44].

POLR2A (RNA Polymerase II Subunit A) catalyzes the transcription of DNA into RNA using the four ribonucleoside triphosphates as substrates. In addition, POLR2A is the largest and catalytic component of RNA polymerase II which synthesizes mRNA precursors and many functional non-coding RNAs. POLR2A encodes RPB1 (DNA-directed RNA polymerase II subunit), a gene found altered in about 6% of meningiomas [42]. From another perspective, inactivating somatic and germline mutations or gene deletions in the BAP1 tumor suppressor gene are explicitly found within high-grade rhabdoid meningioma [45]. Also, the loss of BAP1 is correlated with tumor aggressiveness and decreased time to progression. Alterations in the SWI/SNF pathway, specifically mutations in ARID1A, were

recently found in 12% of high-grade meningiomas. Other components of this canonical pathway, including SMARCB1, SMARCA4, and PBRM1, are altered in up to 15% of patients with non-NF2-dependent meningiomas [46].

3. Epigenetics

Through whole-genome analysis, global DNA methylation profiling has demonstrated that higher methylation levels are associated with increased tumor aggressiveness and risk of recurrence. DNA methylation is an epigenetic change hypothesized to contribute to genomic instability by silencing genes involved with DNA repair and control of cell cycling. Evidence suggests that methylation status may predict tumor behavior more accurately than the current WHO classification, thus, DNA methylation status has been proposed as an alternative classification system for MNs [47]. The most important genes involved in the DNA methylation of MNs are tissue inhibitors of metalloproteinase 3 (TIMP3), cyclin-dependent kinase inhibitor 2A (CDKN2A), and tumor protein 73 (TP73), which are hypermethylated in at least 10% of cases [48]. TIMP3 hypermethylation results in transcriptional downregulation and inhibits its tumor suppressor properties [49]. In addition, TIMP3 is frequently hypermethylated in higher-grade MNs (40–60%) and is related to a decrease in relapse-free time and increased biological aggressiveness [50]. Notably, TIMP3 is found on chromosome 22q12, and almost all cases with gene hypermethylation had a concurrent allelic loss of 22q. About 60–80% of high-grade meningiomas carry TP73 promoter methylation, a rare event not common in grade I tumors, suggesting its potential use as a marker for high-grade lesions [51].

Recently, several studies highlighted the importance of global methylation profiles in the molecular subclassification of meningiomas [52]. Olar et al. demonstrated that unsupervised clustering of DNA methylation data classified meningiomas into two distinct subgroups associated with recurrence-free survival. A statistically significant association between DNA methylation subclasses and tumor recurrence was maintained after adjusting for clinical factors, such as WHO grade and Simpson grade [41]. Similarly, Sahm et al. identified two major groups and six subgroups of meningiomas based on unsupervised clustering of DNA methylation data, with significantly different genomic makeup and clinical behaviors. Interestingly, most non-NF2 meningiomas clustered together into a single benign subgroup [53]. These initial efforts suggest that epigenetic signatures may have solid clinical associations with tumor recurrence, to a more significant extent than can be correlated with mutational genetic analysis and could be used clinically to stratify patients. An additional manifestation of the importance of epigenetic changes in meningioma clinical behavior was recently shown, describing an increased risk of recurrence in tumors that show a loss of histone H3K27 trimethylation [54].

3.1 Protein expression

Classically, the identification of meningiomas using immunohistochemistry has been done using the expression of the progesterone receptor (PR) and the epithelial membrane antigen (EMA). However, over the last few years, it has been found that the specificity of PR for the diagnosis of high-grade meningiomas is low, especially when trying to differentiate between clear cell, fibrous, and microcystic subtypes. Likewise, EMA expression correctly identifies ~90% of grade I meningiomas, but only 75% of grade III, with even lower specificity rates for secretory and microcystic subtypes [55]. Due to these markers' poor performance, the expression of somatostatin receptor 2A (SSTR2A) in combination with EMA was included, a profile

that provides a sensitivity of 100% and specificity of 95%, regardless of tumor grade. Likewise, recent work suggests that the absence of Sox10 and STAT6 [56, 57] are superior approaches to distinguishing meningioma from schwannoma, solitary fibrous tumor, and synovial sarcoma.

In addition, marking for lymphocyte infiltration can contribute to the grading of meningiomas and the prediction of response to some interventions. Most low-grade meningiomas possess a high percentage of CD-3+ T-lymphocytes but relatively few CD20+ B cells; however, across tumor grades, these populations are greatly enriched compared to those seen in peripheral blood mononuclear cells (PBMC) [58]. Flow cytometry analysis reveals evidence of class switching in B cells, an increased percentage of CD8+ cells compared to CD4+ T cells, and a prevalence of CD45RO+/CD45RA– effector cells compared to naive T cells [59]. This information allows predicting that tumor-infiltrating immune cells have had exposure to various tumor antigens despite low BMR. Among high-grade meningiomas and particularly anaplastic tumors, there is a reduction in the count of CD4+, CD8+, and PD-1+ T cells, and an increase in the number of FoxP3+ T-regulatory cells (Tregs) [60]. This immune cell phenotype, also observed in other tumor types, is associated with tumor-mediated evasion of the immune system.

Du et al. report high levels of PD-L1 mRNA, which correlated to protein expression levels, in ~40% of grade I, 60% of grade II, and 77–88% of grade III meningiomas [59]. Nevertheless, Everson et al. only identified PD-L1 expression in 25% of grade III cases, with no expression detected in grade I or II cases [25]. The controversy has been amplified since PD-L1 does not predict outcomes. However, in the future, the expression of TIM-3 and LAG-3 could be helpful to consider the use of agonist monoclonal antibodies [58]. Another potential biomarkers that could

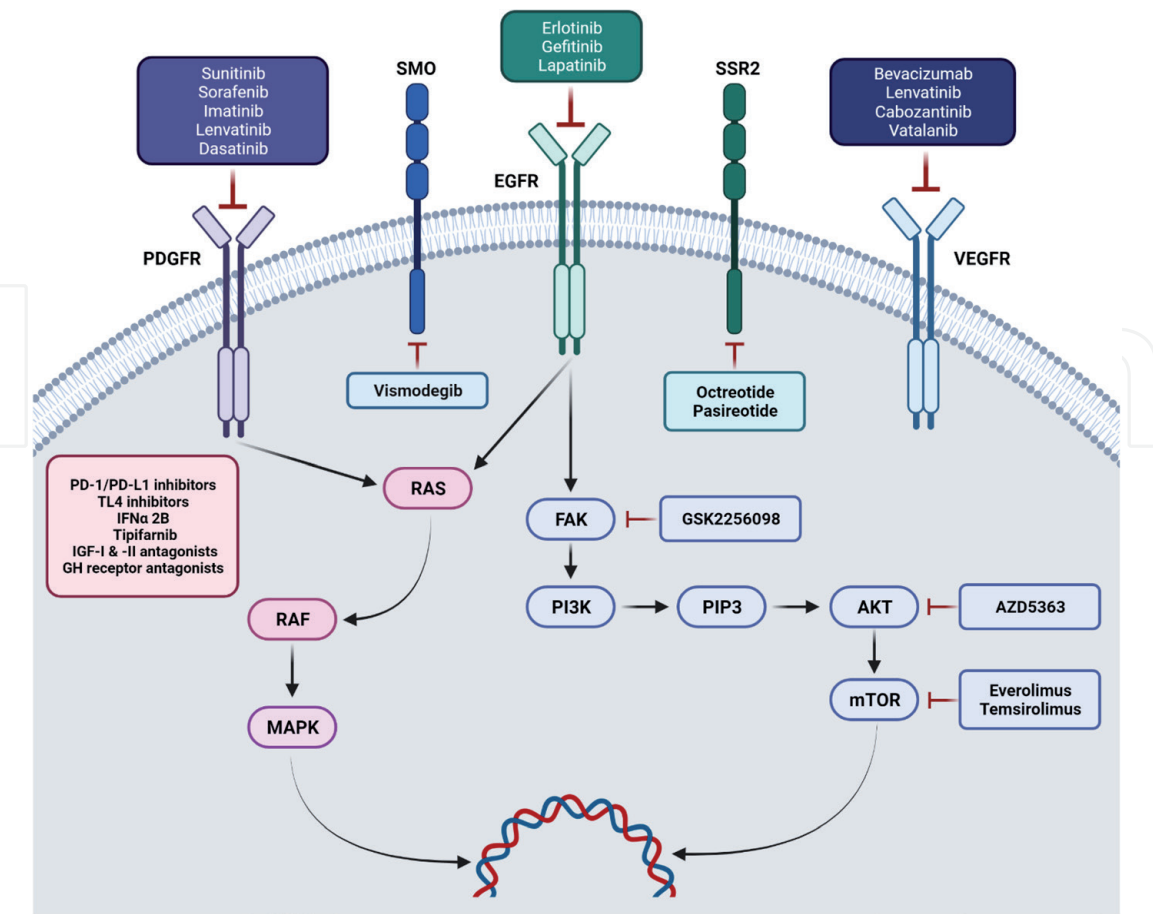


Figure 2.
Signaling pathways and potential targets implicated in high-grade meningiomas.

predict the response to targeted therapies are EGFR expression, which is present in up to 90% of meningiomas [25]. Furthermore, the expression of TOP2A (35% of the samples) is associated with a higher tumor grade and could be useful to assess the usefulness of anthracyclines or trabectedin. Likewise, TOP1 over-expression is observed in 29% of meningiomas and correlates with sensitivity to irinotecan and topotecan, while elevated levels of PDGFR and c-MET are observed in more than 20% of cases [25] (**Figure 2**).

4. Medical treatment for meningioma

The classical first-line treatment for all MNs is surgery. However, high grade meningiomas have a high recurrence rate; up to 60% of tumors may recur after 15 years of complete resection [12, 61]. Unfortunately, at the moment there are no standard effective treatments determined because of lack of existent evidence [12]. The use of systemic treatments as standard care remains experimental and is reserved for cases of recurrent/progressive disease not suitable for surgery or radiotherapy [62]. Hereafter we are going to present some of the systemic strategies currently in used and under study. A summary of the main therapies that have shown some benefit in MN treatment can be seen in **Table 1**, and a summary of current active clinical trials is shown in **Table 2**.

4.1 Chemotherapy

It is known that chemotherapy is poorly effective as adjuvant treatment after surgery and radiotherapy. Some clinical trials and case series have shown a minimal or no impact in patients' outcomes. However, some agents are being tested in several clinical trials [63].

Hydroxyurea is a ribonucleotide reductase inhibitor that was initially developed to treat myeloproliferative disorders and chronic myelogenous leukemia [64]. It induces apoptosis in meningioma cells, arresting meningioma cells in the S-phase of the cell cycle [63]. In pre-clinical trials from Schrell et al., they demonstrated that hydroxyurea prevent recurrence for 24 months in patients who had complete resection [65, 66]. However, clinical trials, failed to provide similar results showing that 50% of the patients achieve stable disease, a median PFS of 44–176 weeks and acceptable toxicity [63, 65–71]. Other retrospective studies with small sample sizes, have shown a median PFS of 10–80 weeks [64]. Weston et al. also found that hydroxyurea may prevent progression, but does not reduce tumor size and causes significant side effects [72]. It is important to emphasize that in these trials many patients did not received radiotherapy or that radiotherapy was administered concurrently, making data interpretation difficult [73]. In addition, a retrospective study of 60 patients from Chamberlain et al. reported a disease progression in 65% of the patients and a median PFS of 4 months in patients treated with hydroxyurea after recurrence (Chamberlain and Johnston, 2011). Finally, some studies suggest hydroxyurea may have outcomes equivalent to those when radiation therapy was used [74].

Additionally, some studies reported reduction of hydroxyurea efficacy when other concomitant therapies are administrated [64]. In a study by Reardon et al., hydroxyurea and imatinib were used to treat patients with recurrent refractory meningiomas, a good tolerance was reported; however, the combination did not affect survival [75]. Other authors suggest that chemotherapy should be based on expression of drug resistance genes, in patients whose mRNA analysis predicted sensitivity to chemotherapy. In these cases, a concomitant treatment with mitoxantrone and hydroxyurea reported long-term efficacy [61]. Currently, some investigators are

Type of agent	Medication	Mechanism of action
Chemotherapy	Temozolomide	Alkylating agent
	Irinotecan	Topoisomerase 1 inhibitor
	Hydroxyurea	Ribonucleotide reductase inhibitor
	Trabectedin	Mechanism unclear
Plant-derived agents	AKBA	Induction of apoptosis and antiinflammatory
	Curcumin	Interaction with multiple cell signaling proteins
EGFR antagonists	Gefitinib	EGFR antagonist
	Erlotinib	EGFR antagonist
	Monoclonal antibodies	Humanized antibodies to EGFR
PDGFR antagonists	Imatinib	PDGFR antagonist
	Satinib	PDGFR inhibitors
	Nilotinib	PDGFR inhibitors
mTOR inhibitors	Temsirolimus	mTOR inhibitor
	Vistusertib	mTOR inhibitor
	Everolimus	mTOR inhibitor
VEGFR antagonists	Bevacizumab	Humanized monoclonal antibody to VEGFR
	Cediranib	VEGFR antagonist
Combination antagonists	Sorafenib	VEGFR and PDGFR antagonist
	Sunitinib	VEGFR and PDGFR antagonist
	Vatalanib	VEGFR and PDGFR antagonist
Hormonal agents	Megestrol Mifepristone	Progesterone receptor partial agonist Progesterone receptor competitive antagonist
	Tamoxifen	Estrogen receptor antagonist
	Octreotide Pasireotide	Somatostatin mimetic Somatostatin mimetic
	Pegvisomant	Growth hormone receptor antagonist
	Lutathera	Somatostatin receptor affinity and radiation β- emission
	Fenretinide	Synthetic retinoid induces apoptosis
Immunomodulators	IFNα 2B	Antiproliferative and antiangiogenic
	Nivolumab Pembrolizumab Aveoumab Sintilimab	PD-1 receptor and ligand inhibitors
	Trametinib	Inhibits MEK1 and MEK2
	Alpelisib	PI3K inhibitor
	Ipililumab	CTLA-4 blockade
Oncolytic virus	Adenovirus	Antineoplastic effect against the malignant meningioma and significant tumor regression
	Herpes virus	Replication of adenovirus and oncolysis at high dose and at a lower dose meningioma cells killing
Farnesyl transferase inhibitors	Tipifarnib	Farnesyl transferase inhibitor

Type of agent	Medication	Mechanism of action
Possible adjunctive agents	Calcium channel blockers	Reduction of intracellular calcium concentrations
	Statins	MAPK pathway inhibition
	Antiretrovirals	Protein downregulation
RNAi		Antisense abrogation of mRNA strands

Table 1.
A summary of different agents with promising evidence in the treatment of high-grade meningioma.

ClinicalTrials.gov Identifier	Status	Intervention	Arms	Outcomes
NCT03071874	Active, not recruiting	AZD2014 a dual mTORC1/mTORC2 inhibitor	Experimental: AZD2014	PFS OS Radiographic response rate Duration of radiographic response Frequency of adverse events
NCT02648997	Recruiting	Nivolumab 240 mg every 2 weeks Nivolumab 480 mg once every 4 weeks	Experimental: Cohort 1 (original cohort): Nivolumab Monotherapy	PFS Median PFS Median OS Objective radiologic response rate Adverse events
		Ipilimumab 1 mg/kg every 3 weeks Nivolumab 480 mg once every 4 weeks Nivolumab 3 mg/kg every 3 weeks External Beam RT	Experimental: Cohort 2: Nivolumab in Combination with Ipilimumab	PFS Median PFS Median OS Objective radiologic response rate Adverse events
NCT03279692	Active, not recruiting	Pembrolizumab	Experimental: Pembrolizumab	PFS OS Toxicity Intracranial response
NCT04997317	Recruiting	177Lu-DOTA-JR11 (Phase 0); Cycle 1 and Cycle 2 (cross-over) 177Lu-DOTATOC (Phase 0); Cycle 1 and Cycle 2 (cross-over), Cycle 3 and 4	Active Comparator: Phase 0: Group A	Change in Tumor-to-dose limiting organ dose ratio T-to-bone marrow Change in Tumor-to-dose limiting organ dose ratio T-to-kidney Assessment of treatment safety (phase I/II) by number of AEs graded according to CTCAE v5.0
		177Lu-DOTA-JR11 (Phase 0); Cycle 1 and Cycle 2 (cross-over) 177Lu-DOTATOC (Phase 0); Cycle 1 and Cycle 2 (cross-over), Cycle 3 and 4	Active Comparator: Phase 0: Group B	
		177Lu-DOTA-JR11 (Phase I/II)	Active Comparator: Phase I/II	
NCT03971461	Recruiting	Lutathera	Experimental: Lutathera	PFS at 6 months Objective response rate OS at 12 months PFS OS

ClinicalTrials.gov Identifier	Status	Intervention	Arms	Outcomes
NCT04082520	Recruiting	Gallium Ga 68-DOTATATE Lutetium Lu 177 Dotatate Magnetic Resonance Imaging Positron Emission Tomography Quality-of-Life Assessment Questionnaire Administration	Treatment (gallium Ga 68-DOTATATE PET/MRI, Lutathera)	PFS at 6 months OS PFS Adverse events incidence Change in quality of life Local control Duration of local control Objective response to treatment Response rate by volumetric analysis
NCT03016091	Recruiting	Pembrolizumab	Experimental: Arm 1 IV Pembrolizumab	PFS at 6 months PFS at 12 months OS
NCT03604978	Recruiting	Ipilimumab Nivolumab Stereotactic Radiosurgery	Patients receive nivolumab	Maximum tolerated combination of radiosurgery and nivolumab plus or minus ipilimumab Incidence of adverse event profile Objective response rate Objective radiological response PFS OS Changes of peripheral T-cells
NCT02333565	Unknown	Everolimus Octreotide	Experimental: Combinaison everolimus and octreotide	PFS rate
NCT04501705	Recruiting	Apatinib mesylate	Experimental: test group	PFS-6% ORR OS
NCT03267836	Recruiting	Avelumab Proton surgery	Experimental: Avelumab + proton therapy	Immunogenicity Safety of therapy Pathologic response PFS OS
NCT04728568	Recruiting	Sintilimab	Experimental: Sintilimab	PFS at 6 months OS
NCT03631953	Recruiting	Trametinib Alpelisib	Experimental: Alpelisib in combination with Trametinib administered	Dose Limiting Toxicity (DLT) rate of combination Alpelisib and Trametinib
NCT00904735	Unknown	Hydroxyurea Imatinib mesylate	Experimental: Arm I Patients receive hydroxyurea and imatinib	PFS Survival Response rate according to MacDonald criteria Toxicity as assessed by NCI CTCAE v. 3.0
		Hydroxyurea	Experimental: Arm II Patients receive hydroxyurea	

Table 2.
A summary of currently ongoing clinical trials that assess the effectiveness and safety of different systemic therapies in high-grade meningiomas.

looking for the role of hydroxyurea as an adjunct to other therapies, such as calcium channel blockers, as calcium channel antagonists have an inhibitory effect on meningioma growth in culture [76]. For this matter, Ragel et al. reported that calcium channel antagonists can block stimulatory effects of growth factors on meningioma cell cultures and increase hydroxyurea effectiveness [77]. Evidence of hydroxyurea treatment in patients with high grade meningioma varies widely across patients. Demonstrating that this treatment is generally well-tolerated but evidence in tumor control is not conclusive to establish a standard treatment in high-grade MNs.

Trabectedin it is an alkylating agent used in soft tissue sarcomas. It inhibits transcription, its mechanism is not completely understood but some studies reported decreased cell proliferation, induction of apoptosis and inhibition of transcription factor binding by binding to the minor groove of the DNA helix [78]. In the randomized phase II clinical trial NCT02234050 by EORTC Brain Tumor Group (EORTC-1320-BTG), treatment with trabectedin in grade II/III meningiomas did not improve PFS or OS and it was associated with significantly higher toxicity as compared to local standard care. A median PFS of 4.17 months was reported in the local standard care arm and of 2.43 months in the trabectedin arm (hazard ratio [HR] for progression, 1.42; 80% CI, 1.00–2.03; $p = 0.204$). Also, the median OS was 10.61 months in the local standard care arm and was 11.37 months in the trabectedin arm (HR for death, 0.98; 95% CI, 0.54–1.76; $p = 0.94$). In 44.4% of the local standard care arm patients occurred adverse events (4 serious adverse events, 0 lethal events) and 59% of the trabectedin arm presented adverse events (57 serious adverse events and 2 toxic deaths) [79]. Trabectedin did not improve PFS and OS and was associated with significantly higher toxicity. Evidence is not conclusive to establish a standard treatment in high grade meningiomas. However, the data future clinical trials are needed.

Temozolomide another alkylating agent, used as standard care in management of glioma. It does not prolong PFS in clinical trials of recurrent meningioma [80]. It is believed that the no effect on meningioma could be due to intact activity of the DNA repair enzyme O6-methylguanine DNA methyltransferase (MGMT) [63, 81, 82].

Chamberlain et al. reported a median time tumor progression of 4.6 years and median OS of 5.3 years in patients treated with cyclophosphamide, doxorubicin, and vincristine. They also reported high toxicity and very low response. However, without a control group the results are difficult to interpret [83]. Some small case series also reported results by administering cyclophosphamide, adriamycin, vincristine, ifosfamide/mesna or adriamycin/dacarbazine, but the evidence is limited [84]. In some in vitro and in vivo animal studies, was reported that irinotecan has an anti-meningioma effect. However, it did not show benefits in phase II clinical trials [81, 82, 85].

Finally, some preclinical studies evaluated the response of Plant-Derived Chemotherapeutic Agents. Curic et al. described antitumorigenic properties from curcumin (from the spice plant *Curcuma longa*) [86]. Additionally, Park et al. reported a cytotoxic effect of acetyl-11-keto-beta-boswellic acid (substance isolated from the *Boswellia serrata*), by inhibition of microsomal prostaglandin E synthase-1 and the serine protease cathepsin G [87]. Overall, traditional chemotherapy has demonstrated limited clinical efficacy in treating meningiomas. Additionally, it may lead to complications as immunosuppression, myelosuppression, gastrointestinal distress, organ damage, and fatigue [88].

5. Targeted therapy

Unlike other solid tumors, MN presents with a low mutation rate of approximately 3.5 mutations per megabase [25]. However, the case of high-grade MNs

has been evaluated recently. Bi et al. analyzed 39 samples of high-grade MN and found an average of 23 (range 1–223) nonsynonymous coding alterations. This number of alterations is similar to that of craniopharyngioma and thyroid cancer, but considerably lower than other aggressive tumors like head and neck carcinoma, colorectal carcinoma and melanoma [34]. Because of its relatively low mutational burden, very few potential molecular targets have been identified. Interestingly, Bi et al. found that non-NF2 driver mutations in high-grade MN was considerably lower than in low grade MN, which reduces the number of possible targets than can be addressed. In the other hand, NF2 is usually altered in high-grade MN (80% of cases) more frequently than in low grade MN (40%). Most of genetic and regulatory alterations that have been described in high grade MN occur downstream to a disrupted NF2 protein. Some of the pathways altered might involve Rac1/Cdc42, Ras/JNK and the master regulator AP-1 [89]. Furthermore, one of the main pathways associated with NF2 is the mTOR signaling cascade. NF2 naturally acts as a repressor of the mTORC1 and mTORC2, and when it is mutated, unregulated activation of this pathway occurs. Based on this, mTOR and some of its upstream/downstream effectors (Akt/PI3K) have been identified as potential targets. Other pathways regulated by receptor tyrosine kinases (RTKs) like EGFR, PDGFR and VEGFR (angiogenesis) are also being studied.

6. Epidermal Growth Factor Receptor (EGFR) inhibitors

The EGFR pathway has been demonstrated to play a role in the tumorigenesis of a great proportion of meningioma cases. Torp et al. demonstrated that EGFR expression is not detectable in healthy and injured adult human meninges, but is expressed in cases of meningioma [90]. Arnli et al. also showed that EGFR was absent in healthy meninges but present in MN [91]. Narla et al. analyzed 79 samples of MN using immunohistochemistry, to detect EGFR expression. They found that EGFR was expressed in all different grades of MN, but its expression was considerably higher in grade I MN (82.93%), than grade II MN (35.71%) and grade III MN (20%) ($p < 0.0001$) [92]. When analyzed as a general population, the expression of EGFR in MN ranges between 50% and 89% [93]. Even though EGFR is a potentially targetable molecule, its significance in meningioma might not be prognostic [94]. Caltabiano et al. analyzed MN samples using immunohistochemistry and FISH. They found that the expression of EGFR was not associated with outcomes like OS and PFS. Interestingly, they also found that progression from low grade MN to higher grades was associated with an increase in the level of EGFR expression (not the proportion of expression) [95].

Similar results were published by Wernicke et al. who found in a cohort of 89 MN samples that EGFR expression was more common in grade I MN than in other grades. They also showed that the staining percentage (SP) of immunoreactive cells was associated with histopathologic subtypes ($p = 0.029$), with anaplastic MN having the highest average SP [96]. EGFR expression in MN is also accompanied by a demonstrated receptor activation [93]. In the cell line IOMM-Lee, EGFR was found to play a role in radiation-induced progression of MN. Furthermore, EGFR is involved in the regulation of certain intracellular pathways including the MAPK, the PI3K/Akt and phospholipase C pathways, which have been seen to be activated in meningioma [37, 97].

In 2010, results from a phase II trial of erlotinib and gefitinib for the treatment of MN were published. Erlotinib is an orally available, reversible TKI directed against EGFR. Its use has been approved in different neoplastic disorders including non-small cell lung cancer (NSCLC) and pancreatic cancer [98]. Gefitinib is a first-generation

EGFR-TKI also approved for the treatment of locally advanced and advanced NSCLC [99]. In 2010, a clinical trial enrolled patients with recurrent histologically confirmed MN that were treated with no more than 2 chemotherapy regimens.

The study evaluated 25 patients with a median age of 57 years. From this cohort, 16 patients received gefitinib and 9 received erlotinib. Nine patients had atypical MN and 8 had anaplastic MN. PFS and OS were assessed at 6 and 12 months. For patients with low-grade histology, PFS-6 was 25%, PFS12 was 13%, OS-6 was 63% and OS12 50%. In the other hand, high-grade meningiomas seemed to respond a little better with a PFS6 of 29%, PFS-12 18%, OS6 71% and OS-12 65%. When statistical analysis was done no significant difference between low-grade and high-grade MN was seen [100]. Survival outcomes were not significantly better than that of standard treatment.

In 2020 Ferluga et al. found that STAT1 is overexpressed and present a constitutive phosphorylation in MN. They also found that this overactivation was not associated with the JAK-STAT pathway but instead it was induced by the constitutive phosphorylation of EGFR. They even demonstrated that STAT1 knockdown models presented a significant reduction of cellular proliferation as well as a deactivation of AKT and ERK1/2. The most interesting finding of this study was that the researchers used BM-1 cells and exposed them to three different EGFR inhibitors, two from second generation (canertinib and afatinib) and one first generation (erlotinib). After exposure to canertinib and afatinib, a decrease in about 60% of STAT1 expression was seen as well as an almost complete elimination of phosphorylated forms of STAT1, this effect was not seen after exposure to erlotinib.

Lapatinib is a dual EGFR/ErbB2 inhibitor currently approved for the treatment of advanced breast cancer with ErbB2 (HER2) expression [101]. There is preclinical evidence of lapatinib efficacy in decreasing tumoral growth in NF2-related Schwannomas. Ammoun et al. demonstrated that when NF2 is mutated or lost, there is an upregulation of different RTKs in Schwannoma, with EGFR and HER2 being two of the highest expressed [102]. Similar results have been seen in NF2-related MN. When the researchers added lapatinib at 5 and 10 μ M concentrations to cultures of Schwannoma cells derived from patients' samples, they found that lapatinib successfully induced inhibition of the intracellular pathways downstream HER2, including ERK 1/2 and Akt. They also showed that after 24 h of exposure to lapatinib, cell viability decreased in a dose-dependent manner, with statistically significant differences between both concentrations of lapatinib to baseline, and from lapatinib 5 μ M to lapatinib 10 μ M [102].

The same group of researchers also tested lapatinib during a phase II clinical trial, with good results in terms of volumetric response, progression-free survival and safety profile [103]. Six years after this trial, the authors did a retrospective analysis of patients presenting with NF2-related meningiomas from the same cohort of patients with Schwannoma. Eight patients fulfilled criteria for analysis. After two months under treatment with lapatinib, the best volumetric response achieved was 26.1%. It is important to mention that in the group that was receiving lapatinib, two tumors increased in volume by more than 20%. Results from this analysis were confusing, with no clear benefit of lapatinib, however, the sample was extremely small, and the analysis was retrospective. This study might influence the development of future, prospective, larger clinical trials specifically for patients with MN [104].

In 2001, Crombet et al. published their results on the efficacy of a mouse anti-human neutralizing monoclonal antibody against EGFR (ior egf/r3). They performed a phase I clinical trial using this antibody in 9 patients with high-grade brain tumors that persisted or relapsed after surgery. Only one of the patients had MN (hemangiopericytic). The patient had 48 years old and a Karnofsky Performance

Score of 90. She received four doses of 160 mg of antibody. At the end of the study, no objective response was seen in any of the patients, however the remained with stable disease until 6 months after the last antibody dose [105]. Even though EGFR inhibition has revolutionized cancer care in neoplasms with high incidence like NSCLC and colorectal cancer, these effects have not been seen in brain tumors, even when EGFR upregulation has been proved. Further studies must be performed with newer and more effective EGFR inhibitors, including monoclonal antibodies.

7. Platelet-Derived Growth Factor Receptor (PDGFR) inhibitors

PDGFR is another RTK whose expression is critical during development, as well as in the growth and differentiation of certain cell lineages. Its role in multiple chronic diseases have been studied, and it is considered a possible target in conditions like cancer, fibrosis, neurological disorders and atherosclerosis. The PDGF/PDGFR axis promotes cell proliferation, survival and migration primarily in cells of mesenchymal origin [106]. The ligands for PDGFR are four different polypeptide chains (PDGF-A, PDGF-B, PDGF-C and PDGF-D) which can be organized in an array of dimers that behave as functional growth factors (PDGF-AA, PDGF-BB, PDGF-AB, PDGF-CC and PDGF-DD [107]. These ligands have two different receptors, PDGFR α and PDGFR β . The different ligands bind to the receptors with a differential specificity. PDGF-A, -B and -C will bind strongly to PDGFR α while the others will bind to PDGFR β [106].

It has been demonstrated that MN expresses different forms of PDGF ligands, namely PDGF-AA and PDGF-BB, and expresses considerable levels of PDGFR β . It has been shown that the PDGF/PDGFR axis might play a key role in the tumorigenesis of MN. Black et al. proved that PDGFR β in MN cells derived from patients are susceptible to the stimulation with PDGF-BB ligands, with a shown increased in the activation of MAPK [21] and c-fos, a critical part of the master regulator AP-1, and a recognized proto-oncogene [108, 109]. Unlike EGFR expression, PDGFR levels appear to be higher in atypical and anaplastic MN than in grade I MN. In those MN that express PDGFR and the aforementioned PDGF ligands, there is an autocrine loop that supports maintenance and cell growth [109]. Todo et al. demonstrated that there is a considerable decrease in meningioma cells proliferation when these cells are given a neutralizing antibody against PDGF-BB. They saw a similar but less potent behavior when an anti-PDGF-AA antibody, also suggesting that the PDGF-BB pathway is the most important for meningioma maintenance [110].

Imatinib, a potent PDGF inhibitor currently used in different conditions (mainly chronic myeloid leukemia), has also been proven in MN patients. Imatinib possess a very low IC₅₀ of 0.1 μ M, this is especially important in MN as the blood-brain-barrier might decrease the flux of imatinib and other drug particles into the brain. In the NABTC 01–08 study, 23 patients with MN were enrolled, with 13 patients bearing low grade tumors, five with atypical MN and five with anaplastic MN. Response was only evaluated in 19 patients from whom 10 patients experienced disease progression. The rest of the patients remained disease stable. Median PFS was only 2 months, with a PFS₆ of 29.4%. When analyzed separately, PFS for grade I MN was 3 months and PFS₆ was as high as 45%. In the case of high-grade MN, PFS was 2 months but PFS₆ was 0%.

The current landscape of PDGF inhibition is somewhat promising. Other agents like sunitinib, MLN518, dasatinib, AMN 107, pazopanib, sorafenib, CP673451 and CHIR 265 have been studied [111]. Furthermore, combination therapies using imatinib and other different agents like hydroxyurea [112], which has showed some benefit in the treatment of glioblastoma in a Phase I/II trial [113].

8. mTOR inhibitors

The mTORC1 (mammalian target of rapamycin complex 1) pathway has been reported to interact with merlin as a negative regulator of cell growth control [114]. mTOR is a serine/threonine kinase involved in cell signaling controlling transcription, actin cytoskeleton organization, translational activation, and metabolism in response to environmental cues [9]. The protein exists in two distinct multiprotein complexes. The rapamycin-sensitive complex mTORC1 regulates cell growth and proliferation in response to growth factors and metabolic conditions, whereas the rapamycin-insensitive mTORC2 regulates locally restricted growth processes within a cell and is involved in cell migration. Merlin was shown to enhance the kinase activity of mTORC2 [115].

Previously, Pachou et al. [116] found that mTORC1 is activated in the majority of MNs (7–10%) and that systemic mTORC1 inhibition can impair meningioma tumor formation in vivo. In addition, Akt is well known to be an upstream element of mTORC1 and to be activated in meningioma cells by platelet-derived growth factor [117]. PDGF also induces phosphorylation of p70S6K, the expression of which was reported to be increased in malignant MNs [118].

Several groups analyzed the biological effects of everolimus and temsirolimus on meningioma cell viability. They could clearly show that both inhibitors were effective in reducing meningioma cell viability and proliferation [114]. Moreover, evidence was found that the NF2 gene status may affect the response to both inhibitors but differentially activated mTOR pathways could not explain this result in isogenic meningioma cell lines with and without merlin expression [119]. Further, octreotide was shown to augment the inhibitory effect on the mTOR pathway in meningioma cell lines because mTOR inhibition increases the hyperphosphorylation of AKT which thereby increases cell proliferation [120].

In 2020, Graillon et al. reported the results of the CEVOREM trial, a phase II open label study that evaluated the combination of everolimus and octreotide in 20 high-grade MNs patients. Furthermore, four patients harbored NF2 germline mutation [121]. The overall PFS6 was 55% (95% CI 31.3–73.5%), and 6- and 12-month OS rates were 90% (95% CI 65.6–97.4%) and 75% (95% CI 50.0–88.7%), respectively. A decrease >50% was observed in the growth rate at 3 months in 78% of tumors. In addition, the median tumor growth rate decreased from 16.6%/3 months before inclusion to 0.02%/3 months at 3 months ($p < 0.0002$) and 0.48%/3 months at 6 months after treatment ($p < 0.0003$) [120].

In a small trial, everolimus has also been studied in conjunction with bevacizumab without finding any objective tumor response but showing a slight increase in PFS for those with high-grade MNs (NCT00972335) [122]. In this study, 88% of the 18 patients showed SD for a median duration of 10 months (2–29 months). Nevertheless, overall median PFS was 22 months (95% CI 4.5–26.8), higher for patients with WHO grade II and III than grade I tumors (22.0 months vs. 17.5 months). Four patients discontinued treatment due to toxicity (proteinuria, 2; colitis, 1, thrombocytopenia, 1), but another grade 3 toxicity was uncommon, and no patient had grade 4 toxicity. The interesting improvement in higher histological grade MNs could be due to their increased vasculature and the increased dependence on the mTOR pathway of these lesions [122].

There is currently a phase 0, single group assignment, trial for everolimus in NF2 mutant MNs and vestibular schwannomas (NCT01880749). There are two single group assignment phase II trials of another mTOR inhibitor, AZD2014; NCT03071874 for recurrent grade II/III MNs and NCT02831257 for NF2 patients with MNs. These trials will help determine the efficacy of mTOR inhibition in patients with these challenging lesions. Besides, a case report of a female patient

with metastatic meningotheliomatous meningioma involving the brain and the lung was treated with the pan-AKT inhibitor, AZD5363 for AKT1E17K mutation, showed a favorable and durable response [123]. Ex vivo cultured meningioma cells revealed sensitivity to the drug as shown by pan-AKT accumulation on immunoblots. The patient has been treated for more than a year with a response which warrants further research [123].

9. Anti-angiogenesis

Angiogenesis depends on the balance between angiogenic and anti-angiogenic regulators [124]. Among the former, VEGF has been demonstrated to play an essential role in stimulating angiogenesis by promoting the migration, proliferation, and tube formation of endothelial cells. VEGF upregulation has been shown in MNs, suggesting its role as a pro-angiogenic factor responsible for edema formation in these tumors [125–127].

Neoangiogenesis in MNs is regulated by the balance between concentrations of both VEGF and semaphorin 3A (SEMA3A) in the tumor's microenvironment rather than by VEGF alone [125]. Accordingly, neo-angiogenesis would be blocked or stimulated depending on the prevalence of VEGF or SEMA3A with a high ratio between VEGF and SEMA3A as a negative predictor of recurrences [125]. Additionally, VEGF expression in MNs seems to be enhanced by hypoxia-inducible factor 1- α [128] and EGF [129], and reduced by dexamethasone.

Caveolin-1 (cav-1), which is a 20-KDa protein mainly expressed by fibroblasts, endothelial cells, myocytes, and adipocytes, seems to be involved in the oncogenesis and progression of several neoplasms, including MNs [130]. Similar to what has been reported in several solid tumors, a significant correlation has been shown between tumor-cell-derived cav-1 and microvascular density (MVD) in MNs [131], suggesting that this protein behaves as a pro-angiogenic factor. Consistent with this hypothesis, cav-1 has been shown to regulate endothelial cell growth and differentiation and to stimulate capillary tubule formation in vitro [132]. Moreover, VEGF-mediated pathological angiogenesis is strikingly reduced in cav-1 knock-out mice [133]. On the other hand, the association between cav-1 expression and MVD may also be related to factors regulating both the MNs neo-angiogenesis and cav-1 expression. Indeed, cav-1 may function as a pro-tumorigenic factor that can stimulate cell proliferation, following its tyrosine-14 phosphorylation by Src kinase [134].

Endothelin-1 (ET-1) has been demonstrated to play a role in the mechanism of meningioma tumorigenesis via the ETA receptor [135]. ET-1 expression/upregulation may contribute to meningioma growth by inducing the formation of new blood vessels. Indeed, a significant correlation has been shown between the expression of ET-1 and that of VEGF or MVD in MNs, in agreement with its proangiogenic action in these tumors.

Following these biological considerations, several angiogenesis inhibitors, such as bevacizumab, sunitinib, and vatalanib, have been evaluated in phase II trials with promising results [136]. The efficacy and safety of bevacizumab were evaluated in grades II and III MNs, finding a PFS6 of 43.8%. In addition, a review of 22 additional case reports for a total of 92 patients revealed a PFS of 16.8 months with 6 months PFS of 73% in those exposed to bevacizumab [137]. A phase II trial designed for all grades recurrent MNs that included 15 patients (15, 22, and 13 grade I, II, and III, respectively) showed stability of the disease in 100% of benign tumors and 82–85% among those with high-grade injuries. In addition, the PFS6, the median PFS, and OS, were 87%, 22.5 months, and 35.6 months for patients with grade I tumors, while this distribution was 77%, 15.3 months, and not reached for

grade II, and 46%, 3.7 months, and 12.4 months for grade III, respectively [138]. There is an ongoing phase II trial evaluating bevacizumab in recurrent and progressive MNs (NCT01125046).

Kaley et al. reported a prospective, multicenter single-arm phase 2 trial that investigated the efficacy of sunitinib, a tyrosine kinase inhibitor that inhibits VEGF and PDGF receptors, which are over-expressed in MNs [139]. Thirty-six patients with grade II and III recurrent or progressive MNs were enrolled. They were heavily pre-treated (median five recurrences) and received sunitinib at 50 mg per day for days 1–28 of a 42-day cycle. The PFS6 was 42%, the median PFS was 5.2 months (95% CI 2.8–8.3), and the median overall survival was 24.6 months (16.5–38.4). Adverse events included four (8%) intratumoral hemorrhages, of which one was fatal, one (2%) grade 4 thrombotic microangiopathy, and one (2%) grade 3 gastrointestinal perforation. MRI perfusion in the exploratory group indicated that sunitinib is an active agent, and expression of VEGFR2 predicted PFS with a median of 1.4 months in VEGFR2-negative patients versus 6.4 months in VEGFR2-positive patients ($p = 0.005$) [139]. More recently, Cardona et al. reported a PFS of 9.1 months (95% CI 6.8–16.8) in a cohort of patients with high-grade MNs treated with sunitinib [140].

10. Hormonal therapy

Evidence suggests that meningioma growth could be hormone dependent because of the female predominance specially after puberty and reproductive years. Additionally, that 30% of the meningiomas are estrogen receptor positive and 70% are progesterone receptor positive [76]. It is also known, that high grade meningiomas express more estrogen receptors whereas benign meningiomas express more progesterone receptors [141]. It is also important to add, that approximately 90% of meningiomas express somatostatin receptors [142]. Therefore, hormonal therapies have been utilized in high grade meningioma treatment.

Due to estrogen receptors low expression, treatment with tamoxifen (estrogen receptor antagonist) has not shown effective results. Additionally, there is not any reports of androgen receptor antagonists in meningiomas [143]. In 1993 Goodwin et al. in a retrospective case series of 21 patients with meningioma treated with tamoxifen, they reported response in only 1 patient and disease progression in 10 patients [144]. Additionally, in a case study from Markwalder et al. a small group of patients with inoperable meningiomas that received tamoxifen were studied and only two patients show radiographical partial response [145].

Currently, due to the lack of evidence of anti-estrogenic agents' effect on meningioma no recommendation is available. Mifepristone is a progesterone receptor inhibitor. In a study published in 1991 by Wolfsberger et al., they used mifepristone as treatment of unresectable meningioma patients, they reported that five patients showed reduction of tumor size on neuroimaging and visual field improvement; in addition, three patients experienced headache relief and improvement in extraocular muscle function. No toxicities were reported [141]. Other study by Lamberts et al. reported stable disease in three patients, tumor size reduction in other three patients and no toxicities were reported [146]. These studies were limited because of the small sample size and tumor stage wasn't described in any of them. Therefore, more studies are needed to conclude the effect of mifepristone in high grade meningiomas. Other trial by Ji et al. reported a median PFS of 10 months and a median OS of 31 months in the mifepristone arm of patients with recurrent meningioma [147]. Additionally, in 2006 Grunberg et al. reported a reduction of less than 10% of the tumor area without clinical improvement in eight patients with unresectable meningioma who received mifepristone [148].

Megestrol acetate is an oral progesterone agonist that was used in a small trial. However no response was observed in high grade meningiomas [76]. So far there is no evidence that supports the use of progesterone receptor inhibitors in high grade meningiomas.

Somatostatin is important in regulation and proliferation of normal cells and tumor cells. It is known that meningiomas report the highest frequency of somatostatin receptor expression in brain tumors, especially the sst2A subtype. It is also reported that somatostatin inhibits meningioma growth in vitro in most studies, but increases meningioma proliferation in some [76].

Chamberlan et al. reported that 31% of patients demonstrated a partial radiographic response and 44% achieved PFS at 6 months with minimal toxicity in patients treated with octreotide (a somatostatin agonist). Furthermore, one-third of patients showed stable disease after treatment [149]. Therefore, somatostatin analogs are recommended for systemic treatment of unresectable or radiorefractory relapsed meningiomas [150]. The phase II CEVOREM trial explored the efficacy of the combination of everolimus (an mTOR inhibitor) and octreotide in high grade meningiomas treatment. The trial reported that the 6-month progression-free survival rate was 55% and the 6-month overall survival was 90% and 12-month survival rate was 90%. Additionally, a decrease of more than 50% was observed in the growth rate at 3 months in 78% of the tumors. That happens because, octreotide suppressed AKT activation during everolimus treatment and synergistically reduced expression of downstream proteins [121]. The previous results suggest that the combination of everolimus and octreotide could be a very good option to treat high grade meningiomas, however more studies are needed. In other phase II trial by Johnson et al. only 2 of 12 high grade cases experience long progression-free intervals, but at the end all patients experienced disease progression with median time of 17 weeks; a median survival 2.7 years was reported and octreotide was well-tolerated [151]. Additionally, an in-vitro study by Graillon et al. reported a significant anti-proliferative effects octreotide, but no apoptotic response [152].

Parasoreotide (SOM230C) is an intramuscularly long-acting somatostatin analogue. In the phase II trial by Norden et al., they reported that pasireotide has limited activity in recurrent meningiomas, a PFS-6 of 17% and median PFS of 15 weeks were reported. Furthermore, expression of somatostatin receptor was predictive of favorable response. However the findings in this trial require further investigation [153]. These findings are promising, nevertheless, larger randomized studies should be conducted to make a solid conclusion.

Growth hormone is secreted by the pituitary gland, and it induces production of insulin-like growth factor-I (IGF-I-), these hormones influence normal growth and metabolism [73]. There is existent evidence that reports abundant growth hormone receptors expression in meningioma cells. There is also reported that inhibition of these receptors represents a decreased meningioma cell proliferation [154]. McCutcheon et al. reported that administration of pegvisomant reduces meningioma growth and in some cases causes tumor regression. Pegvisomant blocks growth hormone receptors and induces downregulation of the GH/IGF-I axis [155]. In other study, Puduvalli et al. reported that fenretinide, a synthetic retinoid, induced apoptosis in meningioma primary cells tested, it also increases levels of the death receptor DR5 and causes mitochondrial membrane depolarization. They also reported eradication of IGF-I proliferation in the meningioma cells [156].

Finally, insulin-like growth factor-II acts like IGF-I. In multiple studies have reported that the invasiveness of meningiomas is correlated to levels of IGF-II expression [157]. However, several studies are needed to establish IGF-II blockade could be an option to treat patients with meningiomas. These results provide

preliminary evidence, but further studies are needed to explore these options as treatment against meningioma.

11. Interferons

Existent evidence, shows that recombinant interferon- α (INF- α) is a biologic agent able to inhibit DNA synthesis, it binds to the interferon-a/b receptor and is involved in cell resistance to viral infection [64]. In 1991 in vitro studies also reported that interferon-alpha inhibits tumor cells growth [158].

In 1997 Kaba et al., reported a minor reduction of tumor size in one patient and a stable disease that lasted up to 14 months in four of six patients with recurrent unresectable meningioma who received INF- α 2b [159]. Other study in 2001, reported a stable disease that lasted up to eight years in nine of twelve patients treated with INF- α [160]. In 2008 Chamberlain and Glantz, reported in a phase II study that 26 of 35 patients that received treatment with INF- α demonstrated stable disease after the first 3 cycles and that 9 patients developed progressive disease. Additionally, a PFS rate was 54% at 6 months and 31% at 12 months were reported, median time to tumor progression was 7 months and median survival was 8 months. Furthermore, no patient demonstrated neuroradiographic complete or partial response, fatigue, anemia and leukopenia were the most common toxicities but overall, the drug was safe. A limitation from this study is that it was conducted only in patients with refractory grade I meningiomas [161]. Currently, these options are used as therapy for recurrent meningiomas or progression following surgery and radiation. It is also used for meningiomas that no respond to standard treatment options. Nevertheless, evidence that supports the use of interferons for meningiomas is poor.

12. Oncolytic virus

Oncolytic viruses are biologic anti-tumor agents that selectively kill tumor cells leaving non tumoral cells intact [63]. A lot of oncolytic viruses have been investigated in different clinical trials, however no clinical trials have been conducted in meningiomas [162].

There are a few preclinical trials conducted in meningioma models. In 2005 Grill et al. evaluated the efficacy of conditionally replicating adenovirus (Ad) for oncolysis of meningiomas of 12 patients. Four different Ads were constructed and tested on meningioma cells and spheroids: Ad with an E1ACR2 deletion (Ad.d24), Ad with complete E1 region (Ad.E1+), Ad encoding the luciferase marker gene (Ad.Luc) and Ad encoding the luciferase gene in the E3 region (Ad.E1Luc). They demonstrated replication of adenovirus and oncolysis in primary cell cultures of meningioma cells at high dose (greater than 50 plaque-forming units per cell). Additionally, they also reported that at a lower dose (5 plaque-forming units per cell), Ad.d24 kills meningioma cells more efficiently than Ad.E1+ in benign, atypical, and malignant meningiomas [163].

Herpes virus it has a large dsDNA with more than 30 kb making the virus encoding for nonessential genes, this feature allows for genetic manipulation. Additionally, herpesviruses have a good safety profile, because they replicate in the nucleus without causing insertional mutagenesis [164].

In 1992, Market et al. added thymidine kinase-negative herpes simplex-I mutant virus, d/sptk, to meningioma cell cultures. They reported an antineoplastic effect against the malignant meningioma and significant tumor regressions [165]. In the study from Yazaki et al., reported that mutant herpes simplex virus (termed G207)

can replicate and kill cells from human malignant meningiomas in cell culture. They also reported tumor growth reduction in nude mice harboring human malignant meningioma [166]. Additionally, it is reported that efficacy of oncolytic herpes simplex viruses (HSV) as single agent is unsatisfactory; so in 2006 Liu et al. demonstrated that oncolytic HSV encoding dnFGFR enhances antitumor efficacy [167]. In 2016 Nigim et al., reported that G47 Δ , an oncolytic HSV derived from G207, was able to replicate and kill several human primary meningioma cultures in vitro. They also reported that this treatment prolonged survival, with 20% of mice surviving more than 160 days. Furthermore, a lack of signs of encephalitis associated with G47 Δ treatment was reported [168]. In 2018, they also reported that the mechanism of action of oHSV enables killing NF2 intact and mutant meningiomas and meningiomas that harbor other mutations [63].

Several studies have demonstrated the ability of oncolytic viruses to recruit T cells and induce immune responses against virus and tumor. Furthermore, some studies have demonstrated that oncolytic viruses combined with other cancer therapies, create synergistic effects in brain cancer treatment. Although many questions remain to be answered to fully exploit the therapeutic potential of oncolytic viruses against meningiomas [169].

13. Immune checkpoint inhibitors

Several studies have aimed to characterize the interactions between MNs and the immune system. Specifically, studies of the immune microenvironment in MNs have revealed that NY-ESO-1, PD-L1, PD-L2, B7-H3, and CTLA-4 are expressed in MNs and may be at least partly responsible for the suppression of the anti-tumor immune response [170, 171]. PD-L1 is expressed in MNs, and expression levels are higher for higher-grade tumors [172]. The expression of these proteins has been associated with tumor progression, recurrence, and poor survival outcomes. Fang et al. extensively characterized the immune infiltrate in MNs and found that the immune cells infiltrating MNs are mainly antigen-experienced T cells and B cells [58]. In their study, B cells were activated and underwent immunoglobulin class switching, somatic hypermutation, and clonal expansion. T-cells demonstrated evidence of antigen exposure and increased expression of PD-1 and TIM-3, which can be a sign of an exhausted phenotype. Tumor-infiltrating lymphocytes in MNs are mainly T-cells. Interestingly in anaplastic MNs, the number of CD4 and CD8 T-cells is low. At the same time, the proportion of Tregs is increased [59]. These data support the notion that an immunosuppressive microenvironment in MNs may contribute to tumor progression.

In a mouse model of meningioma, infusion of anti-PD1 antibody avelumab plus highly-active NK cells (HaNK) led to increased survival, showing the importance of innate NK cell activity [173]. Currently there are two case reports on PD-L1 checkpoint inhibition for recurrent MNs [174, 175]. The cases report disease-free recurrence for >2 years in one patient and > 6 months in another patient, with both having reductions in tumor volume, cerebral edema, and patient-reported symptoms following nivolumab treatment. Based on the existing evidence on PD-L1 expression in recurrent MNs, five clinical trials are enrolling patients with to receive anti-PD1 antibodies nivolumab, avelumab, or pembrolizumab. An ongoing phase II trial is designed to compare nivolumab alone to combination therapy with the anti-CTLA-4 antibody ipilimumab (NCT02648997). A phase Ib trial will investigate the preoperative use of avelumab in combination with hypo-fractionated proton radiotherapy for 3 months to evaluate its effect on the size of unresected MNs (NCT03267836). The other trials are recruiting patients with recurrent MNs to receive adjuvant immunotherapy as PD1 blockade.

14. CAR-T cell therapy

Chimeric Antigen Receptor (CAR) T cell therapies are a novel therapeutic approach to cancer. The standard treatment consists in the leukapheresis of autologous peripheral blood mononuclear cells from the patient bearing the tumor. After successful leukapheresis, T cell isolation is performed. T cells are then grown in culture and are further transduced with a lentiviral vector carrying an integrative plasmid that encodes the CAR, which is essentially a fusion protein containing a single-chain variable fragment derived from a full antibody, plus a transmembrane domain and different array of intracellular co-receptor and co-stimulatory domains that will trigger the intracellular signaling necessary for T cell activation [176].

CAR-T cell therapies were initially approved in 2017 (axi-cel and tisa-cel) for the treatment of relapsed/refractory diffuse large B cell lymphoma and relapsed/refractory B-cell acute lymphoblastic leukemia [177]. Unfortunately, the landscape of CAR-T cell therapies in solid tumors has not been promising, mainly due to different resistance from typical features of the tumor microenvironment like high acidity, immune effector exhaustion induction and the extracellular matrix. Different workaround strategies have been explored to address these problems and currently, highly engineered cells and very complex therapies (CAR-Ts in combination with checkpoint inhibition, or small molecules, or chemotherapy, or immunomodulators) are under study in different clinical trials [178].

Brain tumors have not been an exception in CAR-T development, with glioblastoma being the most attacked condition. Tang et al. reported a case of a patient with an anaplastic MN that underwent three surgical resections and had an Ommaya device implanted. IHC from her tumor sample showed a high expression of B7-H3, also known as CD276 ([179], p. 3). The researchers prepared CAR-Ts from autologous PBMCs, and during CAR-T development patient recur and CAR-Ts were administered in three doses via the Ommaya device. A fourth surgical treatment was performed as patient was progressing quickly, and unfortunately the patient died one day after surgery. Post-mortem analysis of the tumor sample showed that CAR-T indeed penetrated the tumor and successfully targeted some cells expressing B7-H3, however, as not all the tumor was expressing this molecule, antigen loss and selection of other cells with a different transcriptome occurred [180]. Even though results were not as expected, this case marks an important step toward the development of cell therapies of different natures, to treat brain tumors, especially those of high recurrency and aggressiveness.

15. Conclusions

Treatment in MN has remained similar since some decades ago. Major improvements in survival are achieved mainly by surgery and radiation therapy. Most cases of MN will respond to these conventional therapies, however, transformation of low-grade MN to high-grade MN, or de novo high-grade MN are highly recurrent and impose a very low survivability. For these tumors, surgery and radiation therapy are less than enough. With the era of genomic analysis and a better understanding of the genetic basis of cancer, different molecular targets and new therapeutic approaches have been studied for high-grade MN treatment. In this review we went through the main critical advancements in evidence that suggests that molecular targeting might be the future of high-grade MN treatment. To the date, all these molecular approaches are still under study, a conventional management is still the mainstay, but we hope in the following years, new evidence of the clinical relevance of these therapies is available and introduction of them into the therapeutic arsenal could be a true.

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References

- [1] Kalamarides M, Stemmer-Rachamimov AO, Niwa-Kawakita M, Chareyre F, Taranchon E, Han ZY, et al. Identification of a progenitor cell of origin capable of generating diverse meningioma histological subtypes. *Oncogene*. 2011;**30**:2333-2344. DOI: 10.1038/onc.2010.609
- [2] Huntoon K, Toland AMS, Dahiya S. Meningioma: A review of clinicopathological and molecular aspects. *Frontiers in Oncology*. 2020;**10**:1-14. DOI: 10.3389/fonc.2020.579599
- [3] Ostrom QT, Cioffi G, Gittleman H, Patil N, Waite K, Kruchko C, et al. CBTRUS statistical report: Primary brain and other central nervous system tumors diagnosed in the United States in 2012-2016. *Neuro-Oncology*. 2019;**21**: V1-V100. DOI: 10.1093/neuonc/noz150
- [4] Holleczeck B, Zampella D, Urbschat S, Sahm F, von Deimling A, Oertel J, et al. Incidence, mortality and outcome of meningiomas: A population-based study from Germany. *Cancer Epidemiology*. 2019;**62**:101562. DOI: 10.1016/j.canep.2019.07.001
- [5] Wen PY, Huse JT. 2016 World Health Organization Classification of central nervous system tumors. *Continuum: Lifelong Learning in Neurology*. 2017;**23**:1531-1547. DOI: 10.1212/CON.0000000000000536
- [6] Magill ST, Young JS, Chae R, Aghi MK, Theodosopoulos PV, McDermott MW. Relationship between tumor location, size, and WHO grade in meningioma. *Neurosurgical Focus*. 2018;**44**:E4. DOI: 10.3171/2018.1.FOCUS17752
- [7] Moliterno J, Cope WP, Vartanian ED, Reiner AS, Kellen R, Ogilvie SQ, et al. Survival in patients treated for anaplastic meningioma. *Journal of Neurosurgery*. 2015;**123**:23-30. DOI: 10.3171/2014.10.JNS14502
- [8] Wang YC, Chuang CC, Wei KC, Chang CN, Lee ST, Wu CT, et al. Long term surgical outcome and prognostic factors of atypical and malignant meningiomas. *Scientific Reports*. 2016;**6**:35743. DOI: 10.1038/srep35743
- [9] Perry A, Scheithauer BW, Stafford SL, Lohse CM, Wollan PC. "Malignancy" in meningiomas: A clinicopathologic study of 116 patients, with grading implications. *Cancer*. 1999;**85**:2046-2056. DOI: 10.1002/(SICI)1097-0142(19990501)85:9<2046::AID-CNCR23>3.0.CO;2-M
- [10] Brodbelt AR, Barclay ME, Greenberg D, Williams M, Jenkinson MD, Karabatsou K. The outcome of patients with surgically treated meningioma in England: 1999-2013. A cancer registry data analysis. *British Journal of Neurosurgery*. 2019;**33**:641-647. DOI: 10.1080/02688697.2019.1661965
- [11] Negroni C, Hilton DA, Ercolano E, Adams CL, Kurian KM, Baiz D, et al. GATA-4, a potential novel therapeutic target for high-grade meningioma, regulates miR-497, a potential novel circulating biomarker for high-grade meningioma. *eBioMedicine*. 2020;**59**:102941. DOI: 10.1016/j.ebiom.2020.102941
- [12] Al-Rashed M, Foshay K, Abedalthagafi M. Recent advances in meningioma immunogenetics. *Frontiers in Oncology*. 2020;**9**:1472. DOI: 10.3389/fonc.2019.01472
- [13] Louis DN, Perry A, Reifenberger G, von Deimling A, Figarella-Branger D, Cavenee WK, et al. The 2016 World Health Organization classification of tumors of the central nervous system:

A summary. *Acta Neuropathologica*. 2016;**131**:803-820. DOI: 10.1007/s00401-016-1545-1

[14] Pham MH, Zada G, Mosich GM, Chen TC, Giannotta SL, Wang K, et al. Molecular genetics of meningiomas: A systematic review of the current literature and potential basis for future treatment paradigms. *Neurosurgical Focus*. 2011;**30**:E7. DOI: 10.3171/2011.2.FOCUS1117

[15] Preusser M, Brastianos PK, Mawrin C. Advances in meningioma genetics: Novel therapeutic opportunities. *Nature Reviews. Neurology*. 2018;**14**: 106-115. DOI: 10.1038/nrneurol.2017.168

[16] Ragel BT, Jensen RL. Aberrant signaling pathways in meningiomas. *Journal of Neuro-Oncology*. 2010;**99**:315-324. DOI: 10.1007/s11060-010-0381-8

[17] Bi WL, Greenwald NF, Abedalthagafi M, Wala J, Gibson WJ, Agarwalla PK, et al. Genomic landscape of high-grade meningiomas. *NPJ Genomic Medicine*. 2017;**2**:15. DOI: 10.1038/s41525-017-0014-7

[18] Lerner C, Ketter R, Linsler S, Henn W, Oertel J, Urbschat S. Establishment of a molecular cytogenetic analysis for native tumor tissue of meningiomas-suitable for clinical application. *Molecular Cytogenetics*. 2014;**7**:12. DOI: 10.1186/1755-8166-7-12

[19] Williams EA, Santagata S, Wakimoto H, Shankar GM, Barker FG, Sharaf R, et al. Distinct genomic subclasses of high-grade/progressive meningiomas: NF2-associated, NF2-exclusive, and NF2-agnostic. *Acta Neuropathologica Communications*. 2020;**8**:171. DOI: 10.1186/s40478-020-01040-2

[20] Barbera S, Miguel TS, Gil-Benso R, Muñoz-Hidalgo L, Roldan P, Gonzalez-Darder J, et al. Genetic changes with prognostic value in

histologically benign meningiomas. *Clinical Neuropathology*. 2013;**32**: 311-317. DOI: 10.5414/NP300580

[21] Rutledge MH, Sarrazin J, Rangaratnam S, Phelan CM, Twist E, Merel P, et al. Evidence for the complete inactivation of the NF2 gene in the majority of sporadic meningiomas. *Nature Genetics*. 1994;**6**:180-184. DOI: 10.1038/ng0294-180

[22] Sulman EP, White PS, Brodeur GM. Genomic annotation of the meningioma tumor suppressor locus on chromosome 1p34. *Oncogene*. 2004;**23**:1014-1020. DOI: 10.1038/sj.onc.1206623

[23] Liu ZY, Wang JY, Liu HH, Ma XM, Wang CL, Zhang XP, et al. Retinoblastoma protein-interacting zinc-finger gene 1 (RIZ1) dysregulation in human malignant meningiomas. *Oncogene*. 2013;**32**:1216-1222. DOI: 10.1038/onc.2012.155

[24] Goutagny S, Yang HW, Zucman-Rossi J, Chan J, Dreyfuss JM, Park PJ, et al. Genomic profiling reveals alternative genetic pathways of meningioma malignant progression dependent on the underlying NF2 status. *Clinical Cancer Research*. 2010;**16**:4155-4164. DOI: 10.1158/1078-0432.CCR-10-0891

[25] Everson RG, Hashimoto Y, Freeman JL, Hodges TR, Huse J, Zhou S, et al. Multiplatform profiling of meningioma provides molecular insight and prioritization of drug targets for rational clinical trial design. *Journal of Neuro-Oncology*. 2018;**139**:469-478. DOI: 10.1007/s11060-018-2891-8

[26] Nassiri F, Liu J, Patil V, Mamatjan Y, Wang JZ, Hugh-White R, et al. A clinically applicable integrative molecular classification of meningiomas. *Nature*. 2021;**597**:119-125. DOI: 10.1038/s41586-021-03850-3

[27] Clark VE, Erson-Omay EZ, Serin A, Yin J, Cotney J, Ozduman K, et al.

- Genomic analysis of non-NF2 meningiomas reveals mutations in TRAF7, KLF4, AKT1, and SMO. *Science*. 2013;**339**:1077-1080. DOI: 10.1126/science.1233009
- [28] Sahm F, Schrimpf D, Olar A, Koelsche C, Reuss D, Bissel J, et al. TERT promoter mutations and risk of recurrence in meningioma. *Journal of the National Cancer Institute*. 2016;**108**:djv377. DOI: 10.1093/jnci/djv377
- [29] Spiegl-Kreinecker S, Lötsch D, Neumayer K, Kastler L, Gojo J, Pirker C, et al. *TERT* promoter mutations are associated with poor prognosis and cell immortalization in meningioma. *Neuro-Oncology*. 2018;**20**:1584-1593. DOI: 10.1093/neuonc/noy104
- [30] Biczok A, Kraus T, Suchorska B, Terpolilli NA, Thorsteinsdottir J, Giese A, et al. TERT promoter mutation is associated with worse prognosis in WHO grade II and III meningiomas. *Journal of Neuro-Oncology*. 2018;**139**: 671-678. DOI: 10.1007/s11060-018-2912-7
- [31] AlSahlawi A, Aljelaify R, Magrashi A, AlSaeed M, Almutairi A, Alqubaishi F, et al. New insights into the genomic landscape of meningiomas identified FGFR3 in a subset of patients with favorable prognoses. *Oncotarget*. 2019;**10**:5549-5559. DOI: 10.18632/oncotarget.27178
- [32] Yuzawa S, Nishihara H, Tanaka S. Genetic landscape of meningioma. *Brain Tumor Pathology*. 2016;**33**:237-247. DOI: 10.1007/s10014-016-0271-7
- [33] Zotti T, Scudiero I, Vito P, Stilo R. The emerging role of TRAF7 in tumor development: TRAF7 in tumor development. *Journal of Cellular Physiology*. 2017;**232**:1233-1238. DOI: 10.1002/jcp.25676
- [34] Brastianos PK, Horowitz PM, Santagata S, Jones RT, McKenna A, Getz G, et al. Genomic sequencing of meningiomas identifies oncogenic SMO and AKT1 mutations. *Nature Genetics*. 2013;**45**:285-289. DOI: 10.1038/ng.2526
- [35] 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-Oncology*. 2017;**14**:now276. DOI: 10.1093/neuonc/now276
- [36] Abedalthagafi M, Bi WL, Aizer AA, Merrill PH, Brewster R, Agarwalla PK, et al. Oncogenic PI3K mutations are as common as *AKT1* and *SMO* mutations in meningioma. *Neuro-Oncology*. 2016;**18**:649-655. DOI: 10.1093/neuonc/nov316
- [37] Mawrin C, Sasse T, Kirches E, Kropf S, Schneider T, Grimm C, et al. Different activation of mitogen-activated protein kinase and Akt signaling is associated with aggressive phenotype of human meningiomas. *Clinical Cancer Research*. 2005;**11**:4074-4082. DOI: 10.1158/1078-0432.CCR-04-2550
- [38] Tang H, Zhu H, Wang X, Hua L, Li J, Xie Q, et al. KLF4 is a tumor suppressor in anaplastic meningioma stem-like cells and human meningiomas. *Journal of Molecular Cell Biology*. 2017;**9**:315-324. DOI: 10.1093/jmcb/mjx023
- [39] Reuss DE, Piro RM, Jones DTW, Simon M, Ketter R, Kool M, et al. Secretory meningiomas are defined by combined KLF4 K409Q and TRAF7 mutations. *Acta Neuropathologica*. 2013;**125**:351-358. DOI: 10.1007/s00401-013-1093-x
- [40] Schuetz A, Nana D, Rose C, Zocher G, Milanovic M, Koenigsmann J, et al. The structure of the Klf4 DNA-binding domain links to self-renewal and macrophage differentiation. *Cellular and Molecular Life Sciences*.

2011;**68**:3121-3131. DOI: 10.1007/s00018-010-0618-x

[41] Proctor DT, Ramachandran S, Lama S, Sutherland GR. Towards molecular classification of meningioma: Evolving treatment and diagnostic paradigms. *World Neurosurgery*. 2018;**119**:366-373. DOI: 10.1016/j.wneu.2018.08.019

[42] Clark VE, Harmanci AS, Bai H, Youngblood MW, Lee TI, Baranoski JF, et al. Recurrent somatic mutations in POLR2A define a distinct subset of meningiomas. *Nature Genetics*. 2016;**48**:1253-1259. DOI: 10.1038/ng.3651

[43] Gerkes EH, Fock JM, den Dunnen WFA, van Belzen MJ, van der Lans CA, Hoving EW, et al. A heritable form of SMARCE1-related meningiomas with important implications for follow-up and family screening. *Neurogenetics*. 2016;**17**:83-89. DOI: 10.1007/s10048-015-0472-y

[44] Smith MJ, Wallace AJ, Bennett C, Hasselblatt M, Elert-Dobkowska E, Evans LT, et al. Germline SMARCE1 mutations predispose to both spinal and cranial clear cell meningiomas. *The Journal of Pathology*. 2014;**234**:436-440. DOI: 10.1002/path.4427

[45] Shankar GM, Abedalthagafi M, Vaubel RA, Merrill PH, Nayyar N, Gill CM, et al. Germline and somatic BAP1 mutations in high-grade rhabdoid meningiomas. *Neuro-Oncology*. 2016;**19**(4):535-545. DOI: 10.1093/neuonc/now235

[46] Collord G, Tarpey P, Kurbatova N, Martincorena I, Moran S, Castro M, et al. An integrated genomic analysis of anaplastic meningioma identifies prognostic molecular signatures. *Scientific Reports*. 2018;**8**:13537. DOI: 10.1038/s41598-018-31659-0

[47] Gao F, Shi L, Russin J, Zeng L, Chang X, He S, et al. DNA methylation

in the malignant transformation of meningiomas. *PLoS One*. 2013;**8**:e54114. DOI: 10.1371/journal.pone.0054114

[48] Bello MJ, Amiñoso C, Lopez-Marin I, Arjona D, Gonzalez-Gomez P, Alonso ME, et al. DNA methylation of multiple promoter-associated CpG islands in meningiomas: Relationship with the allelic status at 1p and 22q. *Acta Neuropathologica*. 2004;**108**:413-421. DOI: 10.1007/s00401-004-0911-6

[49] He S, Pham MH, Pease M, Zada G, Giannotta SL, Wang K, et al. A review of epigenetic and gene expression alterations associated with intracranial meningiomas. *Neurosurgical Focus*. 2013;**35**:E5. DOI: 10.3171/2013.10.FOCUS13360

[50] Barski D, Wolter M, Reifemberger G, Riemenschneider MJ. Hypermethylation and transcriptional downregulation of the TIMP3 gene is associated with allelic loss on 22q12.3 and malignancy in meningiomas. *Brain Pathology*. 2010;**20**:623-631. DOI: 10.1111/j.1750-3639.2009.00340.x

[51] Nakane Y, Natsume A, Wakabayashi T, Oi S, Ito M, Inao S, et al. Malignant transformation-related genes in meningiomas: Allelic loss on 1p36 and methylation status of p73 and RASSF1A. *Journal of Neurosurgery*. 2007;**107**:398-404. DOI: 10.3171/JNS-07/08/0398

[52] Olar A, Wani KM, Wilson CD, Zadeh G, DeMonte F, Jones DTW, et al. Global epigenetic profiling identifies methylation subgroups associated with recurrence-free survival in meningioma. *Acta Neuropathologica*. 2017;**133**:431-444. DOI: 10.1007/s00401-017-1678-x

[53] Sahm F, Schrimpf D, Stichel D, Jones DTW, Hielscher T, Schefzyk S, et al. DNA methylation-based classification and grading system for meningioma: A multicentre, retrospective analysis. *The Lancet Oncology*. 2017;**18**:682-694. DOI: 10.1016/S1470-2045(17)30155-9

- [54] Katz LM, Hielscher T, Liechty B, Silverman J, Zagzag D, Sen R, et al. Loss of histone H3K27me3 identifies a subset of meningiomas with increased risk of recurrence. *Acta Neuropathologica*. 2018;**135**:955-963. DOI: 10.1007/s00401-018-1844-9
- [55] Boulagnon-Rombi C, Fleury C, Fichel C, Lefour S, Marchal Bressenot A, Gauchotte G. Immunohistochemical approach to the differential diagnosis of meningiomas and their mimics. *Journal of Neuropathology and Experimental Neurology*. 2017;**76**:289-298. DOI: 10.1093/jnen/nlx008
- [56] Berghoff AS, Kresl P, Bienkowski M, Koelsche C, Rajky U, Hainfellner JA, et al. Validation of nuclear STAT6 immunostaining as a diagnostic marker of meningeal solitary fibrous tumor (SFT)/hemangiopericytoma. *Clinical Neuropathology*. 2017;**36**:56-59. DOI: 10.5414/NP300993
- [57] Ng J, Celebre A, Munoz DG, Keith JL, Karamchandani JR. Sox10 is superior to S100 in the diagnosis of meningioma. *Applied Immunohistochemistry & Molecular Morphology*. 2015;**23**:215-219. DOI: 10.1097/PAI.0000000000000072
- [58] Fang L, Lowther DE, Meizlish ML, Anderson RCE, Bruce JN, Devine L, et al. The immune cell infiltrate populating meningiomas is composed of mature, antigen-experienced T and B cells. *Neuro-Oncology*. 2013;**15**:1479-1490. DOI: 10.1093/neuonc/not110
- [59] Du Z, Abedalthagafi M, Aizer AA, McHenry AR, Sun HH, Bray M-A, et al. Increased expression of the immune modulatory molecule PD-L1 (CD274) in anaplastic meningioma. *Oncotarget*. 2015;**6**:4704-4716. DOI: 10.18632/oncotarget.3082
- [60] Zou W. Regulatory T cells, tumour immunity and immunotherapy. *Nature Reviews. Immunology*. 2006;**6**:295-307. DOI: 10.1038/nri1806
- [61] Apra C, Peyre M, Kalamarides M. Current treatment options for meningioma. *Expert Review of Neurotherapeutics*. 2018;**18**:241-249. DOI: 10.1080/14737175.2018.1429920
- [62] Maggio I, Franceschi E, Tosoni A, Nunno VD, Gatto L, Lodi R, et al. Meningioma: Not always a benign tumor. A review of advances in the treatment of meningiomas. *CNS Oncology*. 2021;**10**:CNS72. DOI: 10.2217/cns-2021-0003
- [63] Nigim F, Wakimoto H, Kasper E, Ackermans L, Temel Y. Emerging medical treatments for meningioma in the molecular era. *Biomedicine*. 2018;**6**:86. DOI: 10.3390/biomedicines6030086
- [64] Karsy M, Guan J, Cohen A, Colman H, Jensen RL. Medical management of meningiomas. *Neurosurgery Clinics of North America*. 2016;**27**:249-260. DOI: 10.1016/j.nec.2015.11.002
- [65] Schrell UMH, Rittig MG, Anders M, Kiesewetter F, Marschalek R, Koch UH, 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. *Journal of Neurosurgery*. 1997;**86**:845-852. DOI: 10.3171/jns.1997.86.5.0845
- [66] Schrell UMH, Rittig MG, Anders M, Koch UH, Marschalek R, Kiesewetter F, et al. Hydroxyurea for treatment of unresectable and recurrent meningiomas. II. Decrease in the size of meningiomas in patients treated with hydroxyurea. *Journal of Neurosurgery*. 1997;**86**:840-844. DOI: 10.3171/jns.1997.86.5.0840
- [67] Hahn BM, Schrell UMH, Sauer R, Fahlbusch R, Ganslandt O, Grabenbauer GG. Prolonged oral hydroxyurea and concurrent 3d-conformal radiation in patients with

- p>progressive or recurrent meningioma: Results of a pilot study.
- Journal of Neuro-Oncology*
- . 2005;
- 74**
- :157-165. DOI: 10.1007/s11060-004-2337-3
- [68] Loven D, Hardoff R, Bar Sever Z, Steinmetz AP, Gornish M, Rappaport ZH, et al. Non-resectable slow-growing meningiomas treated by hydroxyurea. *Journal of Neuro-Oncology*. 2004;**67**:221-226. DOI: 10.1023/B:NEON.0000021827.85754.8e
- [69] Mason WP, Gentili F, Macdonald DR, Hariharan S, Cruz CR, Abrey LE. Stabilization of disease progression by hydroxyurea in patients with recurrent or unresectable meningiomas. *Journal of Neurosurgery*. 2002;**97**:341-346. DOI: 10.3171/jns.2002.97.2.0341
- [70] Newton H, Scott S, Volpi C. Hydroxyurea chemotherapy for meningiomas: Enlarged cohort with extended follow-up. *British Journal of Neurosurgery*. 2004;**18**:495-499. DOI: 10.1080/02688690400012392
- [71] Rosenthal MA, Ashley DL, Cher L. Treatment of high risk or recurrent meningiomas with hydroxyurea. *Journal of Clinical Neuroscience*. 2002;**9**: 156-158. DOI: 10.1054/jocn.2001.1019
- [72] Weston G, Martin A, Mufti G, Strong A, Gleeson M. Hydroxyurea treatment of meningiomas: A pilot study. *Skull Base*. 2006;**16**:157-160. DOI: 10.1055/s-2006-949518
- [73] Moazzam AA, Wagle N, Zada G. Recent developments in chemotherapy for meningiomas: A review. *Neurosurgical Focus*. 2013;**35**:E18. DOI: 10.3171/2013.10.FOCUS13341
- [74] Kim J, Kim KH, Kim YZ. The clinical outcome of hydroxyurea chemotherapy after incomplete resection of atypical meningiomas. *Brain Tumor Research and Treatment*. 2017;**5**:77. DOI: 10.14791/btrt.2017.5.2.77
- [75] Reardon DA, Norden AD, Desjardins A, Vredenburgh JJ, Herndon JE, Coan A, et al. Phase II study of Gleevec® plus hydroxyurea (HU) in adults with progressive or recurrent meningioma. *Journal of Neuro-Oncology*. 2012;**106**:409-415. DOI: 10.1007/s11060-011-0687-1
- [76] Chamberlain MC. The role of chemotherapy and targeted therapy in the treatment of intracranial meningioma. *Current Opinion in Oncology*. 2012;**24**:666-671. DOI: 10.1097/CCO.0b013e328356364d
- [77] Ragel BT, Couldwell WT, Wurster RD, Jensen RL. Chronic suppressive therapy with calcium channel antagonists for refractory meningiomas. *Neurosurgical Focus*. 2007;**23**:E10. DOI: 10.3171/FOC-07/10/E10
- [78] Preusser M, Spiegl-Kreinecker S, Lötsch D, Wöhrer A, Schmook M, Dieckmann K, et al. Trabectedin has promising antineoplastic activity in high-grade meningioma: Trabectedin in meningioma. *Cancer*. 2012;**118**: 5038-5049. DOI: 10.1002/cncr.27460
- [79] Preusser M, Silvani A, Le Rhun E, Soffietti R, Lombardi G, Sepulveda J, et al. PL3.2 Trabectedin for recurrent WHO grade II or III meningioma: A randomized phase II study of the EORTC Brain Tumor Group (EORTC-1320-BTG). *Neuro-Oncology*. 2019;**21**: iii2-iii3. DOI: 10.1093/neuonc/noz126.005
- [80] Gupta S, Bi WL, Dunn IF. Medical management of meningioma in the era of precision medicine. *Neurosurgical Focus*. 2018;**44**:E3. DOI: 10.3171/2018.1.FOCUS17754
- [81] Shao Z, Liu L, Zheng Y, Tu S, Pan Y, Yan S, et al. Molecular mechanism and approach in progression of meningioma. *Frontiers in Oncology*. 2020;**10**:538845. DOI: 10.3389/fonc.2020.538845

- [82] Wilson TA, Huang L, Ramanathan D, Lopez-Gonzalez M, Pillai P, De Los Reyes K, et al. Review of atypical and anaplastic meningiomas: Classification, molecular biology, and management. *Frontiers in Oncology*. 2020;**10**:565582. DOI: 10.3389/fonc.2020.565582
- [83] Chamberlain MC. Adjuvant combined modality therapy for malignant meningiomas. *Journal of Neurosurgery*. 1996;**84**:733-736. DOI: 10.3171/jns.1996.84.5.0733
- [84] Chamberlain MC. Intracerebral meningiomas. *Current Treatment Options in Neurology*. 2004;**6**:297-305. DOI: 10.1007/s11940-004-0029-0
- [85] Chamberlain MC, Tsao-Wei DD, Groshen S. Salvage chemotherapy With CPT-11 for recurrent meningioma. *Journal of Neuro-Oncology*. 2006;**78**:271-276. DOI: 10.1007/s11060-005-9093-x
- [86] Curic S, Wu Y, Shan B, Schaaf C, Utpadel D, Lange M, et al. Curcumin acts anti-proliferative and pro-apoptotic in human meningiomas. *Journal of Neuro-Oncology*. 2013;**113**:385-396. DOI: 10.1007/s11060-013-1148-9
- [87] Park YS, Lee JH, Bondar J, Harwalkar JA, Safayhi H, Golubic M. Cytotoxic action of acetyl-11-keto- β -boswellic acid (AKBA) on meningioma cells. *Planta Medica*. 2002;**68**:397-401. DOI: 10.1055/s-2002-32090
- [88] König M, Osnes T, Bruland Ø, Sundby Hall K, Bratland Å, Meling TR. The role of adjuvant treatment in craniofacial malignancy: A critical review. *Frontiers in Oncology*. 2020;**10**:1402. DOI: 10.3389/fonc.2020.01402
- [89] Dai J, Ma Y, Chu S, Le N, Cao J, Wang Y. Identification of key genes and pathways in meningioma by bioinformatics analysis. *Oncology Letters*. 2018;**15**:8245-8252. DOI: 10.3892/ol.2018.8376
- [90] Torp SH, Helseth E, Dalen A, Unsgaard G. Expression of epidermal growth factor receptor in human meningiomas and meningeal tissue. *APMIS*. 1992;**100**:797-802. DOI: 10.1111/j.1699-0463.1992.tb04002.x
- [91] Arnli MB, Backer-Grøndahl T, Ytterhus B, Granli US, Lydersen S, Gulati S, et al. Expression and clinical value of EGFR in human meningiomas. *PeerJ*. 2017;**2017**:215-222. DOI: 10.7717/peerj.3140
- [92] Narla S, Uppin MS, Saradhi MV, Sahu BP, Purohit AK, Sundaram C. Assessment of expression of epidermal growth factor receptor and p53 in meningiomas. *Neurology India*. 2014;**62**:37-41. DOI: 10.4103/0028-3886.128276
- [93] Bujko M, Kober P, Tysarowski A, Matyja E, Mandat T, Bonicki W, et al. EGFR, PIK3CA, KRAS and BRAF mutations in meningiomas. *Oncology Letters*. 2014;**7**:2019-2022. DOI: 10.3892/ol.2014.2042
- [94] Burnett BA, Womeldorff MR, Jensen R. Meningioma: Signaling pathways and tumor growth. In: *Handbook of Clinical Neurology*. Amsterdam: Elsevier; 2020. pp. 137-150. DOI: 10.1016/B978-0-12-804280-9.00009-3
- [95] Caltabiano R, Barbagallo GMV, Castaing M, Cassenti A, Senetta R, Cassoni P, et al. Prognostic value of EGFR expression in de novo and progressed atypical and anaplastic meningiomas: An immunohistochemical and fluorescence in situ hybridization pilot study. *Journal of Neurosurgical Sciences*. 2013;**57**:139-151
- [96] Wernicke AG, Dicker AP, Whiton M, Ivanidze J, Hyslop T,

- Hammond EH, et al. Assessment of Epidermal Growth Factor Receptor (EGFR) expression in human meningioma. *Radiation Oncology*. 2010;**5**:46. DOI: 10.1186/1748-717X-5-46
- [97] Johnson M, Toms S. Mitogenic signal transduction pathways in meningiomas: Novel targets for meningioma chemotherapy? *Journal of Neuropathology and Experimental Neurology*. 2005;**64**:1029-1036. DOI: 10.1097/01.jnen.0000189834.63951.81
- [98] Tang PA, Tsao MS, Moore MJ. A review of erlotinib and its clinical use. *Expert Opinion on Pharmacotherapy*. 2006;**7**:177-193. DOI: 10.1517/14656566.7.2.177
- [99] Dhillon S. Gefitinib: A review of its use in adults with advanced non-small cell lung cancer. *Targeted Oncology*. 2015;**10**:153-170. DOI: 10.1007/s11523-015-0358-9
- [100] Norden AD, Raizer JJ, Abrey LE, Lamborn KR, Lassman AB, Chang SM, et al. Phase II trials of erlotinib or gefitinib in patients with recurrent meningioma. *Journal of Neuro-Oncology*. 2010;**96**:211-217. DOI: 10.1007/s11060-009-9948-7
- [101] Opdam FL, Guchelaar H-J, Beijnen JH, Schellens JHM. Lapatinib for advanced or metastatic breast cancer. *The Oncologist*. 2012;**17**:536-542. DOI: 10.1634/theoncologist.2011-0461
- [102] Ammoun S, Cunliffe CH, Allen JC, Chiriboga L, Giancotti FG, Zagzag D, et al. ErbB/HER receptor activation and preclinical efficacy of lapatinib in vestibular schwannoma. *Neuro-Oncology*. 2010;**12**:834-843. DOI: 10.1093/neuonc/noq012
- [103] Karajannis MA, Legault G, Hagiwara M, Ballas MS, Brown K, Nusbaum AO, et al. Phase II trial of lapatinib in adult and pediatric patients with neurofibromatosis type 2 and progressive vestibular schwannomas. *Neuro-Oncology*. 2012;**14**:1163-1170. DOI: 10.1093/neuonc/nos146
- [104] Osorio DS, Hu J, Mitchell C, Allen JC, Stanek J, Hagiwara M, et al. Effect of lapatinib on meningioma growth in adults with neurofibromatosis type 2. *Journal of Neuro-Oncology*. 2018;**139**:749-755. DOI: 10.1007/s11060-018-2922-5
- [105] Crombet T, Torres O, Rodríguez V, Menéndez A, Stevenson A, Ramos M, et al. Phase I clinical evaluation of a neutralizing monoclonal antibody against epidermal growth factor receptor in advanced brain tumor patients: Preliminary study. *Hybridoma*. 2001;**20**:131-136. DOI: 10.1089/02724570152057634
- [106] Papadopoulos N, Lennartsson J. The PDGF/PDGFR pathway as a drug target. *Molecular Aspects of Medicine*. 2018;**62**:75-88. DOI: 10.1016/j.mam.2017.11.007
- [107] Fredriksson L, Li H, Eriksson U. The PDGF family: Four gene products form five dimeric isoforms. *Cytokine & Growth Factor Reviews*. 2004;**15**:197-204. DOI: 10.1016/j.cytogfr.2004.03.007
- [108] Black PM, Carroll R, Glowacka D, Riley K, Dashner K. Platelet-derived growth factor expression and stimulation in human meningiomas. *Journal of Neurosurgery*. 1994;**81**:388-393. DOI: 10.3171/jns.1994.81.3.0388
- [109] Candelieri GA, Glorieux FH, Prud'homme J, St-Arnaud R. Increased expression of the c-fos proto-oncogene in bone from patients with fibrous dysplasia. *The New England Journal of Medicine*. 1995;**332**:1546-1551. DOI: 10.1056/NEJM199506083322304
- [110] Todo T, Adams EF, Fahlbusch R, Dingermann T, Werner H. Autocrine growth stimulation of human

- meningioma cells by platelet-derived growth factor. *Journal of Neurosurgery*. 1996;**84**:852-858; discussion 858-859. DOI: 10.3171/jns.1996.84.5.0852
- [111] Norden AD, Drappatz J, Wen PY. Targeted drug therapy for meningiomas. *Neurosurgical Focus*. 2007;**23**:E12. DOI: 10.3171/FOC-07/10/E12
- [112] Reardon DA, Egorin MJ, Quinn JA, Rich JN, Gururangan I, Vredenburgh JJ, et al. Phase II study of imatinib mesylate plus hydroxyurea in adults with recurrent glioblastoma multiforme. *Journal of Clinical Oncology*. 2005;**23**: 9359-9368. DOI: 10.1200/JCO.2005.03.2185
- [113] Wen PY, Yung WKA, Lamborn KR, Dahia PL, Wang Y, Peng B, et al. Phase I/II study of imatinib mesylate for recurrent malignant gliomas: North American brain tumor consortium study 99-08. *Clinical Cancer Research*. 2006;**12**:4899-4907. DOI: 10.1158/1078-0432.CCR-06-0773
- [114] James MF, Han S, Polizzano C, Plotkin SR, Manning BD, Stemmer-Rachamimov AO, et al. NF2/merlin is a novel negative regulator of mTOR complex 1, and activation of mTORC1 is associated with meningioma and schwannoma growth. *Molecular and Cellular Biology*. 2009;**29**:4250-4261. DOI: 10.1128/MCB.01581-08
- [115] Ryskalin L, Lazzeri G, Flaibani M, Biagioni F, Gambardella S, Frati A, et al. mTOR-dependent cell proliferation in the brain. *BioMed Research International*. 2017;**2017**:7082696. DOI: 10.1155/2017/7082696
- [116] Pachow D, Andrae N, Kliese N, Angenstein F, Stork O, Wilisch-Neumann A, et al. mTORC1 inhibitors suppress meningioma growth in mouse models. *Clinical Cancer Research*. 2013;**19**:1180. DOI: 10.1158/1078-0432.CCR-12-1904
- [117] Johnson MD, Okedli E, Woodard A, Toms SA, Allen GS. Evidence for phosphatidylinositol 3-kinase-Akt-p7S6K pathway activation and transduction of mitogenic signals by platelet-derived growth factor in meningioma cells. *Journal of Neurosurgery*. 2002;**97**:668-675. DOI: 10.3171/jns.2002.97.3.0668
- [118] Cai DX, James CD, Scheithauer BW, Couch FJ, Perry A. PS6K amplification characterizes a small subset of anaplastic meningiomas. *American Journal of Clinical Pathology*. 2001;**115**:213-218. DOI: 10.1309/FVNU-7UBY-DXE3-77MT
- [119] Corona AM, Di L, Shah AH, Crespo R, Eichberg DG, Lu VM, et al. Current experimental therapies for atypical and malignant meningiomas. *Journal of Neuro-Oncology*. 2021;**153**:203-210. DOI: 10.1007/s11060-021-03759-x
- [120] Graillon T, Defilles C, Mohamed A, Lisbonis C, Germanetti A-L, Chinot O, et al. Combined treatment by octreotide and everolimus: Octreotide enhances inhibitory effect of everolimus in aggressive meningiomas. *Journal of Neuro-Oncology*. 2015;**124**:33-43. DOI: 10.1007/s11060-015-1812-3
- [121] Graillon T, Sanson M, Campello C, Idbaih A, Peyre M, Peyrière H, et al. Everolimus and octreotide for patients with recurrent meningioma: Results from the Phase II CEVOREM Trial. *Clinical Cancer Research*. 2020;**26**: 552-557. DOI: 10.1158/1078-0432.CCR-19-2109
- [122] Shih KC, Chowdhary S, Rosenblatt P, Weir AB, Shepard GC, Williams JT, et al. A phase II trial of bevacizumab and everolimus as treatment for patients with refractory, progressive intracranial meningioma. *Journal of Neuro-Oncology*. 2016;**129**: 281-288. DOI: 10.1007/s11060-016-2172-3

- [123] Weller M, Roth P, Sahm F, Burghardt I, Schuknecht B, Rushing EJ, et al. Durable control of metastatic AKT1-mutant WHO Grade 1 meningothelial meningioma by the AKT inhibitor, AZD5363. *Journal of the National Cancer Institute*. 2017;**109**. DOI: 10.1093/jnci/djw320
- [124] Pistolesi S, Boldrini L, Gisfredi S, De Ieso K, Camacci T, Caniglia M, et al. Angiogenesis in intracranial meningiomas: Immunohistochemical and molecular study. *Neuropathology and Applied Neurobiology*. 2004;**30**: 118-125. DOI: 10.1046/j.0305-1846.2003.00516.x
- [125] Barresi V, Tuccari G. Increased ratio of vascular endothelial growth factor to semaphorin3A is a negative prognostic factor in human meningiomas. *Neuropathology: Official Journal of the Japanese Society of Neuropathology*. 2010;**30**:537-546. DOI: 10.1111/j.1440-1789.2010.01105.x
- [126] Barresi V, Tuccari G. Evaluation of neo-angiogenesis in a case of chordoid meningioma. *Journal of Neuro-Oncology*. 2009;**95**:445-447. DOI: 10.1007/s11060-009-9942-0
- [127] Guevara P, Escobar-Arriaga E, Saavedra-Perez D, Martinez-Rumayor A, Flores-Estrada D, Rembao D, et al. Angiogenesis and expression of estrogen and progesterone receptors as predictive factors for recurrence of meningioma. *Journal of Neuro-Oncology*. 2010;**98**:379-384. DOI: 10.1007/s11060-009-0086-z
- [128] Jensen RL, Soleau S, Bhayani MK, Christiansen D. Expression of hypoxia inducible factor-1 alpha and correlation with preoperative embolization of meningiomas. *Journal of Neurosurgery*. 2002;**97**:658-667. DOI: 10.3171/jns.2002.97.3.0658
- [129] Tsai JC, Hsiao YY, Teng LJ, Shun CT, Chen CT, Goldman CK, et al. Regulation of vascular endothelial growth factor secretion in human meningioma cells. *Journal of the Formosan Medical Association = Taiwan yi zhi*. 1999;**98**:111-117
- [130] Barresi V, Cerasoli S, Paioli G, Vitarelli E, Giuffrè G, Guiducci G, et al. Caveolin-1 in meningiomas: Expression and clinico-pathological correlations. *Acta Neuropathologica*. 2006;**112**:617-626. DOI: 10.1007/s00401-006-0097-1
- [131] Barresi V, Cerasoli S, Tuccari G. Correlative evidence that tumor cell-derived caveolin-1 mediates angiogenesis in meningiomas. *Neuropathology: Official Journal of the Japanese Society of Neuropathology*. 2008;**28**:472-478. DOI: 10.1111/j.1440-1789.2008.00902.x
- [132] Massimino ML, Griffoni C, Spisni E, Toni M, Tomasi V. Involvement of caveolae and caveolae-like domains in signalling, cell survival and angiogenesis. *Cellular Signalling*. 2002;**14**:93-98. DOI: 10.1016/s0898-6568(01)00232-7
- [133] Chang S-H, Feng D, Nagy JA, Sciuto TE, Dvorak AM, Dvorak HF. Vascular permeability and pathological angiogenesis in caveolin-1-null mice. *The American Journal of Pathology*. 2009;**175**:1768-1776. DOI: 10.2353/ajpath.2009.090171
- [134] Li S, Seitz R, Lisanti MP. Phosphorylation of caveolin by src tyrosine kinases. The alpha-isoform of caveolin is selectively phosphorylated by v-Src in vivo. *The Journal of Biological Chemistry*. 1996;**271**:3863-3868
- [135] Knowles J, Loizidou M, Taylor I. Endothelin-1 and angiogenesis in cancer. *Current Vascular Pharmacology*. 2005;**3**:309-314. DOI: 10.2174/157016105774329462

- [136] Kim L. A narrative review of targeted therapies in meningioma. *Chinese Clinical Oncology*. 2020;**9**: 76-76. DOI: 10.21037/cco-2020-mbt-01
- [137] Lou E, Sumrall AL, Turner S, Peters KB, Desjardins A, Vredenburgh JJ, et al. Bevacizumab therapy for adults with recurrent/progressive meningioma: A retrospective series. *Journal of Neuro-Oncology*. 2012;**109**:63-70. DOI: 10.1007/s11060-012-0861-0
- [138] Grimm SA, Kumthekar P, Chamberlain MC, Schiff D, Wen PY, Iwamoto FM, et al. Phase II trial of bevacizumab in patients with surgery and radiation refractory progressive meningioma. *Journal of Clinical Oncology*. 2015;**33**:2055-2055. DOI: 10.1200/jco.2015.33.15_suppl.2055
- [139] Kaley TJ, Wen P, Schiff D, Ligon K, Haidar S, Karimi S, et al. Phase II trial of sunitinib for recurrent and progressive atypical and anaplastic meningioma. *Neuro-Oncology*. 2015;**17**:116-121. DOI: 10.1093/neuonc/nou148
- [140] Cardona AF, Ruiz-Patiño A, Zatarain-Barrón ZL, Hakim F, Jiménez E, Mejía JA, et al. Systemic management of malignant meningiomas: A comparative survival and molecular marker analysis between Octreotide in combination with Everolimus and Sunitinib. *PLoS One*. 2019;**14**:e0217340. DOI: 10.1371/journal.pone.0217340
- [141] Wolfsberger S, Doostkam S, Boecher-Schwarz H-G, Roessler K, van Trotsenburg M, Hainfellner JA, et al. Progesterone-receptor index in meningiomas: Correlation with clinico-pathological parameters and review of the literature. *Neurosurgical Review*. 2004;**27**:238-245. DOI: 10.1007/s10143-004-0340-y
- [142] Arena S, Barbieri F, Thellung S, Pirani P, Corsaro A, Villa V, et al. Expression of somatostatin receptor mRNA in human meningiomas and their implication in in vitro antiproliferative activity. *Journal of Neuro-Oncology*. 2004;**66**:155-166. DOI: 10.1023/B:N EON.0000013498.19981.55
- [143] Zhao L, Zhao W, Hou Y, Wen C, Wang J, Wu P, et al. An overview of managements in meningiomas. *Frontiers in Oncology*. 2020;**10**:1523. DOI: 10.3389/fonc.2020.01523
- [144] Goodwin JW, Crowley J, Eyre HJ, Stafford B, Jaekle KA, Townsend JJ. A phase II evaluation of tamoxifen in unresectable or refractory meningiomas: A southwest oncology group study. *Journal of Neuro-Oncology*. 1993;**15**:75-77. DOI: 10.1007/BF01050266
- [145] Markwalder T-M, Seiler RW, Zava DT. Antiestrogenic therapy of meningiomas—A pilot study. *Surgical Neurology*. 1985;**24**:245-249. DOI: 10.1016/0090-3019(85)90030-8
- [146] Lamberts SW, Tanghe HL, Avezaat CJ, Braakman R, Wijngaarde R, Koper JW, et al. Mifepristone (RU 486) treatment of meningiomas. *Journal of Neurology, Neurosurgery, and Psychiatry*. 1992;**55**:486-490. DOI: 10.1136/jnnp.55.6.486
- [147] Ji Y, Rankin C, Grunberg S, Sherrod AE, Ahmadi J, Townsend JJ, et al. Double-blind phase III randomized trial of the antiprogesterone agent mifepristone in the treatment of unresectable meningioma: SWOG S9005. *Journal of Clinical Oncology*. 2015;**33**:4093-4098. DOI: 10.1200/JCO.2015.61.6490
- [148] Grunberg SM, Weiss MH, Russell CA, Spitz IM, Ahmadi J, Sadun A, et al. Long-term administration of mifepristone (RU486): Clinical tolerance during extended treatment of meningioma.

Cancer Investigation. 2006;**24**:727-733.
 DOI: 10.1080/07357900601062339

- [149] Chamberlain MC, Glantz MJ, Fadul CE. Recurrent meningioma: Salvage therapy with long-acting somatostatin analogue. *Neurology*. 2007;**69**:969-973. DOI: 10.1212/01.wnl.0000271382.62776.b7
- [150] Foiani G, Guelfi G, Chiaradia E, Mancini F, Trivelli C, Vitellozzi G, et al. Somatostatin receptor 2 expression in canine meningioma. *Journal of Comparative Pathology*. 2019;**166**:59-68. DOI: 10.1016/j.jcpa.2018.11.002
- [151] Johnson DR, Kimmel DW, Burch PA, Cascino TL, Giannini C, Wu W, et al. Phase II study of subcutaneous octreotide in adults with recurrent or progressive meningioma and meningeal hemangiopericytoma. *Neuro-Oncology*. 2011;**13**:530-535. DOI: 10.1093/neuonc/nor044
- [152] Graillon T, Romano D, Defilles C, Saveanu A, Mohamed A, Figarella-Branger D, et al. Octreotide therapy in meningiomas: In vitro study, clinical correlation, and literature review. *Journal of Neurosurgery*. 2017;**127**:660-669. DOI: 10.3171/2016.8.JNS16995
- [153] Norden AD, Ligon KL, Hammond SN, Muzikansky A, Reardon DA, Kaley TJ, et al. Phase II study of monthly pasireotide LAR (SOM230C) for recurrent or progressive meningioma. *Neurology*. 2015;**84**:280-286. DOI: 10.1212/WNL.0000000000001153
- [154] Friend KE, Radinsky R, McCutcheon IE. Growth hormone receptor expression and function in meningiomas: Effect of a specific receptor antagonist. *Journal of Neurosurgery*. 1999;**91**:93-99. DOI: 10.3171/jns.1999.91.1.0093
- [155] McCutcheon IE, Flyvbjerg A, Hill H, Li J, Bennett WF, Scarlett JA,

- et al. Antitumor activity of the growth hormone receptor antagonist pegvisomant against human meningiomas in nude mice. *Journal of Neurosurgery*. 2001;**94**:487-492. DOI: 10.3171/jns.2001.94.3.0487
- [156] Puduvalli VK, Li JT, Chen L, McCutcheon IE. Induction of apoptosis in primary meningioma cultures by fenretinide. *Cancer Research*. 2005;**65**:1547-1553. DOI: 10.1158/0008-5472.CAN-04-0786
- [157] Nordqvist AC, Peyrard M, Pettersson H, Mathiesen T, Collins VP, Dumanski JP, et al. A high ratio of insulin-like growth factor II/insulin-like growth factor binding protein 2 messenger RNA as a marker for anaplasia in meningiomas. *Cancer Research*. 1997;**57**:2611-2614
- [158] Koper JW, Zwarthoff EC, Hagemeyer A, Braakman R, Avezaat CJJ, Bergström M, et al. Inhibition of the growth of cultured human meningioma cells by recombinant interferon- α . *European Journal of Cancer & Clinical Oncology*. 1991;**27**:416-419. DOI: 10.1016/0277-5379(91)90375-N
- [159] Kaba SE, DeMonte F, Bruner JM, Kyritsis AP, Jaeckle KA, Levin V, et al. The treatment of recurrent unresectable and malignant meningiomas with interferon alpha-2B. *Neurosurgery*. 1997;**40**:271-275. DOI:10.1097/00006123-199702000-00007
- [160] Muhr C, Gudjonsson O, Lilja A, Hartman M, Zhang ZJ, Långström B. Meningioma treated with interferon-alpha, evaluated with [(11)C]-L-methionine positron emission tomography. *Clinical Cancer Research: An Official Journal of the American Association for Cancer Research*. 2001;**7**:2269-2276
- [161] Chamberlain MC, Glantz MJ. Interferon- α for recurrent World Health Organization grade 1 intracranial

meningiomas. *Cancer*. 2008;**113**: 2146-2151. DOI: 10.1002/cncr.23803

[162] Ning J, Wakimoto H. Oncolytic herpes simplex virus-based strategies: Toward a breakthrough in glioblastoma therapy. *Frontiers in Microbiology*. 2014;**5**. DOI: 10.3389/fmicb.2014.00303

[163] Grill J, Lamfers MLM, van Beusechem VW, van der Valk P, Huisman A, Sminia P, et al. Oncolytic virotherapy of meningiomas in vitro with replication-competent adenovirus. *Neurosurgery*. 2005;**56**:146-154. DOI: 10.1227/01.NEU.0000146207.55774.69

[164] Aldrak N, Alsaab S, Algethami A, Bhare D, Wakimoto H, Shah K, et al. Oncolytic Herpes simplex virus-based therapies for cancer. *Cell*. 2021;**10**: 1541. DOI: 10.3390/cells10061541

[165] Markert JM, Coen DM, Malick A, Mineta T, Martuza RL. Expanded spectrum of viral therapy in the treatment of nervous system tumors. *Journal of Neurosurgery*. 1992;**77**:590-594. DOI: 10.3171/jns.1992.77.4.0590

[166] Yazaki T, Manz HJ, Rabkin SD, Martuza RL. Treatment of human malignant meningiomas by G207, a replication-competent multimitated herpes simplex virus 1. *Cancer Research*. 1995;**55**:4752-4756

[167] Liu T-C, Zhang T, Fukuhara H, Kuroda T, Todo T, Canron X, et al. Dominant-negative fibroblast growth factor receptor expression enhances antitumoral potency of oncolytic Herpes simplex virus in neural tumors. *Clinical Cancer Research*. 2006;**12**: 6791-6799. DOI: 10.1158/1078-0432.CCR-06-0263

[168] Nigim F, Esaki S, Hood M, Lelic N, James MF, Ramesh V, et al. A new patient-derived orthotopic malignant meningioma model treated with oncolytic herpes simplex virus.

Neuro-Oncology. 2016;**18**:1278-1287. DOI: 10.1093/neuonc/now031

[169] de Sostoa J, Dutoit V, Migliorini D. Oncolytic viruses as a platform for the treatment of malignant brain tumors. *International Journal of Molecular Sciences*. 2020;**21**:7449. DOI: 10.3390/ijms21207449

[170] Deng J, Ma M, Wang D, Zhu H, Hua L, Sun S, et al. Expression and clinical significance of immune checkpoint regulator B7-H3 (CD276) in human meningioma. *World Neurosurgery*. 2020;**135**:e12-e18. DOI: 10.1016/j.wneu.2019.10.044

[171] Proctor DT, Patel Z, Lama S, Resch L, van Marle G, Sutherland GR. Identification of PD-L2, B7-H3 and CTLA-4 immune checkpoint proteins in genetic subtypes of meningioma. *OncoImmunology*. 2019;**8**:e1512943. DOI: 10.1080/2162402X.2018.1512943

[172] Han SJ, Reis G, Kohanbash G, Shrivastav S, Magill ST, Molinaro AM, et al. Expression and prognostic impact of immune modulatory molecule PD-L1 in meningioma. *Journal of Neuro-Oncology*. 2016;**130**:543-552. DOI: 10.1007/s11060-016-2256-0

[173] Giles AJ, Hao S, Padget M, Song H, Zhang W, Lynes J, et al. Efficient ADCC killing of meningioma by avelumab and a high-affinity natural killer cell line, haNK. *JCI Insight*. 2019;**4**:e130688. DOI: 10.1172/jci.insight.130688

[174] Dunn IF, Du Z, Touat M, Sisti MB, Wen PY, Umeton R, 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 Precision Oncology*. 2018;1-12. DOI: 10.1200/PO.18.00190

[175] Gelerstein E, Berger A, Jonas-Kimchi T, Strauss I, Kanner AA, Blumenthal DT, et al. Regression of

intracranial meningioma following treatment with nivolumab: Case report and review of the literature. *Journal of Clinical Neuroscience*. 2017;**37**:51-53. DOI: 10.1016/j.jocn.2016.11.011

[176] June CH, Sadelain M. Chimeric antigen receptor therapy. *The New England Journal of Medicine*. 2018;**379**:64-73. DOI: 10.1056/NEJMr1706169

[177] Zheng P-P, Kros JM, Li J. Approved CAR T cell therapies: Ice bucket challenges on glaring safety risks and long-term impacts. *Drug Discovery Today*. 2018;**23**:1175-1182. DOI: 10.1016/j.drudis.2018.02.012

[178] Marofi F, Motavalli R, Safonov VA, Thangavelu L, Yumashev AV, Alexander M, et al. CAR T cells in solid tumors: Challenges and opportunities. *Stem Cell Research & Therapy*. 2021; **12**:81. DOI: 10.1186/s13287-020-02128-1

[179] Yang S, Wei W, Zhao Q. B7-H3, a checkpoint molecule, as a target for cancer immunotherapy. *International Journal of Biological Sciences*. 2020;**16**:1767-1773. DOI: 10.7150/ijbs.41105

[180] Tang X, Liu F, Liu Z, Cao Y, Zhang Z, Wang Y, et al. Bioactivity and safety of B7-H3-targeted chimeric antigen receptor T cells against anaplastic meningioma. *Clinical & Translational Immunology*. 2020; **9**:e1137-e1137. DOI: 10.1002/cti2.1137