EANO guideline on molecular testing of meningiomas for targeted therapy selection

Felix Sahm, Luca Bertero, Sebastian Brandner, David Capper, Roland Goldbrunner, Michael D Jenkinson, Michel Kalamarides, Katrin Lamszus, Nathalie L Albert, Maximilian J Mair, Anna S Berghoff, Christian Mawrin, Hans-Georg Wirsching, Sybren L.N. Maas, David R. Raleigh, Guido Reifenberger, Leonille Schweizer, Abigail K. Suwala, Ghazaleh Tabatabai, Emeline Tabouret, Susan Short, Patrick Y. Wen, Michael Weller, Emilie Le Rhun, Pieter Wesseling, Martin van den Bent, Matthias Preusser

FS, AKS: Dept. of Neuropathology, University Hospital Heidelberg, Heidelberg Gemany and CCU Neuropathology, German Cancer Research Center (DKFZ), German Consortium for Translational Cancer Research (DKTK), Heidelberg, Germany

LB: Pathology Unit, Department of Medical Sciences, University of Turin, Turin, Italy

SB: Department of Neurodegenerative Disease, UCL Queen Square Institute of Neurology and Division of Neuropathology, University College London Hospitals NHS Foundation Trust, London, WC1N3BG, UK

DC: Department of Neuropathology, Charité - Universitätsmedizin Berlin, Corporate Member of Freie Universität Berlin and Humboldt-Universität zu Berlin, Berlin, Germany; German Cancer Consortium (DKTK), partner site Berlin and German Cancer Research Center (DKFZ), Heidelberg, Germany.

RG: Dept. of Neurosurgery, University Hospital Cologne, Cologne, Germany

MDJ: Department of Neurosurgery, University of Liverpool and Walton Centre, Liverpool, UK

MK: Department of Neurosurgery, Pitie-Salpetriere Hospital, AP-HP Sorbonne Université, Paris, France.

KL: Department of Neurosurgery, University Medical Center Hamburg-Eppendorf, Hamburg, Germany

NLA, MJM: Department of Nuclear Medicine, LMU Hospital, LMU Munich, Munich, Germany

MJM, ASB, MP: Division of Oncology, Department of Medicine I, Medical University of Vienna, Vienna, Austria

CM: Department of Neuropathology, University Hospital Magdeburg, Magdeburg, Germany

HGW, MW: Department of Neurology, Brain Tumor Center & Clinical Neuroscience Center, University Hospital and University of Zurich, Zurich, Switzerland

SLNM: Department of Pathology, Leiden University Medical Center, Leiden, Netherlands and Department of Pathology, Erasmus MC Cancer Institute, University Medical Center Rotterdam, Rotterdam, The Netherlands

DRR: Departments of Radiation Oncology, Neurological Surgery, and Pathology, University of California, San Francisco, San Francisco, CA, USA

GR: Institute of Neuropathology, Medical Faculty, Heinrich Heine University and University Hospital Düsseldorf, and German Cancer Consortium (DKTK), partner site Essen/Düsseldorf, Düsseldorf. Germany

LS: Institute of Neurology (Edinger Institute), University Hospital Frankfurt, Goethe University, Frankfurt am Main, Germany and German Cancer Consortium (DKTK), Partner Site Frankfurt/Mainz, German Cancer Research Center (DKFZ), Heidelberg, Germany and Frankfurt Cancer Institute (FCI), Frankfurt am Main, Germany.

GT: Department of Neurology & Interdisciplinary Neuro-Oncology, University Hospital Tübingen, Center for Neuro-Oncology, Comprehensive Cancer Center Tübingen-Stuttgart, DKTK partner site Tübingen, University of Tübingen

ET: Aix-Marseille Univ, APHM, CNRS, INP, Inst Neurophysiopathol, GlioME Team, plateforme PETRA, CHU Timone, Service de Neurooncologie, Marseille, France

SCS: Department of Oncology and Leeds Institute of Medical Research at St James's Hospital, Leeds, UK

PYW: Center For Neuro-Oncology, Dana-Farber Cancer Institute

ELR: Department of Medical Oncology and Hematology, Brain Tumor Center, University Hospital and University of Zurich, Zurich, Switzerland

PW: Dept. of Pathology, Amsterdam University Medical Centers/VUmc, Amsterdam, The Netherlands, and Princess Máxima Center for Pediatric Oncology, Utrecht, The Netherlands

MvdB: The Brain Tumor Center at Erasmus MC Cancer Institute, Erasmus MC, Rotterdam, The Netherlands

Corresponding author:

Matthias Preusser, MD

Division of Oncology, Department of Medicine I

Medical University of Vienna, Vienna, Austria

Waehringer Guertel 18-20, 1090 Vienna, Austria

Phone: +43 (0)1 40400 44450

Email: matthias.preusser@meduniwien.ac.at

Abstract

Meningiomas are the most common primary intracranial tumors of adults. For meningiomas that progress or recur despite surgical resection and radiotherapy, additional treatment options are limited due to lack of proven efficacy. Meningiomas show recurring molecular aberrations, which may serve as predictive markers for systemic pharmacotherapies with targeted drugs or immunotherapy, radiotherapy or radioligand therapy. Here, we review the evidence for a predictive role of a wide range of molecular alterations and markers including *NF2*, *AKT1*, *SMO*, *SMARCE1*, *PIK3CA*, *CDKN2A*/B, *CDK4/6*, *TERT*, *TRAF7*, *BAP1*, *KLF4*, *ARID1*/2, *SUFU*, PD-L1, SSTR2A, PR/ER, mTOR, *VEGFR*, *PDGFR*, as well as homologous recombination deficiency (HRD), genomic copy number variations, DNA methylation classes and combined gene expression profiles. In our assessment based on the established ESMO ESCAT (European Society for Medical Oncology Scale for Clinical Actionability of molecular Targets) evidence level criteria, no molecular target reached ESCAT I ("ready for clinical use") classification and only mTOR pathway activation and NF2 alterations reached ESCAT II ("investigational") classification, respectively. Our evaluations may guide targeted therapy selection in clinical practice and clinical trial efforts and highlight areas for which additional research is warranted.

Key words: meningioma, targeted therapy, predictive marker

Introduction

Meningiomas are the most common intracranial tumors of adults and constitute approximately 40% of all primary Central Nervous System (CNS) tumors. [1] Most meningiomas are benign, with around 75-80% of cases being classified as CNS World Health Organization (WHO) grade 1 according to the 5th edition of the WHO Classification of CNS Tumors (CNS5). [2] 20-25% of meningiomas show histopathological or molecular features indicating higher risk of recurrence and are classified as CNS WHO grade 2 (15-20% of cases) or 3 (1-5% of patients).

According to international guidelines and established clinical practice, surgical resection is recommended for most meningiomas at diagnosis. [3] Postoperative radiotherapy may be considered based on extent of resection and histological grade. For progressive or recurrent meningioma, local therapies (i.e. further surgical resection or salvage radiotherapy) are commonly recommended. Other treatment options including various systemic therapies and targeted radionuclide therapy have been investigated, but none are established as management standard. [3–6]

Extensive molecular profiling efforts of meningiomas have led to the identification of multiple recurring aberrations and patterns on the genetic, epigenetic, transcriptomic and protein level. [7,8] These alterations can be relevant to identify early signs of progression in otherwise benign appearing meningiomas. Some of these molecular features may represent suitable targets for treatment with specific inhibitors, immunotherapies or radioligands. Indeed, some clinical trials indicate potential clinical activity with some of these precision medicine approaches in meningiomas. [5,6] Despite the fact that no approved targeted treatments are available for this tumor type, meningiomas may show potential targets for off-label targeted therapies in molecular screening efforts performed in the clinical routine. [9] However, evidence-based evaluations of the clinical utility as treatment targets of the various molecular alterations typically found in meningiomas are widely missing so far.

In this guideline, we review the molecular alterations with potential therapeutic implications in meningiomas, similar to a prior European Association of Neuro-Oncology (EANO) guideline on glial, glioneuronal, and neuronal CNS tumors. [10] This guideline will facilitate research efforts aiming at advancing precision medicine approaches for meningiomas. Furthermore, we hope to support decision making in routine clinical practice, as modern molecular profiling methods often reveal potential treatment targets in meningiomas that may lead to therapeutic considerations by

treating physicians or in tumor boards. [9] To this end, we provide integrated and concise recommendations on testing for each individual alteration/marker based on evidence level evaluations in the main text of this paper. Detailed discussions and literature reviews for most targets (excluding those with few available data) are provided in the supplement accompanying this publication.

Molecular testing: how to test

Multiple types of molecular markers are relevant for the diagnosis and treatment of meningiomas, and thus, a wide range of testing methods/assays can be used, mandating a careful selection of the most appropriate tool for the specific question and setting. Since the general recommendations about molecular testing of CNS neoplasms and the characteristics of each assay type are valid independent of the tumor type, readers can refer to the recently published EANO guidelines concerning the molecular diagnostic assessment of glial and glioneuronal tumors for a comprehensive review of this topic.[10]

Specifically for meningioma, the intra-tumoral heterogeneity needs to be accounted for when selecting areas for DNA/RNA extraction. For example, *TERT* promoter mutations or *CDKN2A/B* deletions can be restricted to more aggressive subclones, and methylation subgroup allocation can vary within a tumor. [11,12] Identification of these areas should be guided by morphology (cell density, prominent nuclei, high nucleus/cytoplasm ratio, mitotic count), supported by immunohistochemistry (Ki-67, pHH3). This selection is suggested on the understanding that the more aggressive areas will determine the outcome. Morphological evaluation, and tissue size *per se*, may be limited in frozen material, hence FFPE tissue is typically more amenable to assess heterogeneity and select areas for DNA/RNA extraction. Of note, fibroblastic meningiomas often show limited detectable antibody binding, possibly due to their spindle-shaped cytology. [13] Further detail on testing for individual markers is provided in the supplement.

How to report findings

According to a recently published guideline of EANO on the use of molecular tools, [14] the report of the results of molecular testing should include information on the exact type of test(s) performed, and on the origin (pathology number) and nature (formalin-fixed, paraffin-embedded [FFPE] versus snap frozen) of the sample used for analysis. Furthermore, information should be provided on how representative the sample is for the tumor of interest, highlighting indications for heterogeneity or low tumor cell content where applicable. The report of next generation

sequencing (NGS) data should include the list of the genes or othweise determined target regions that were interrogated by the test or a reference where to fing this information. Also, details of the identified alterations should be provided according to international standards as released by the Human Genome Variation Society (https://varnomen.hgvs.org/), including transcript identification (or genomic location with reference genome version), nucleotide and amino acid exchange, read depth at the respective position, and variant allele frequencies (VAF). [15] Similarly, the genes/regions covered by (targeted or whole transcriptome) RNA sequencing should be reported, as well as the applied bioinformatics pipeline and the number of fusion reads. Also, the significance and functional plausibility (e.g., retention of the kinase domain in a tyrosine kinase receptor) should be checked before reporting the presence of a gene fusion.[14,16]

The report of the results of methylome profiling should (in addition to information on the amount of DNA input and the estimated tumor cell content/fraction of the extracted DNA) encompass information on quality of bisulphite conversion, classifier version(s) used, highest scoring methylation category/categories with the respective calibrated score(s), and sub-classification with score(s) if applicable. DNA methylome profiling by array-based analyses can also identify specific genomic alterations. However, in case the presence of gene fusions and/or particular mutations are suggested for which therapeutic approaches are considered, ultimate proof is warranted by orthogonal methodology (e.g., sequencing). [14]

Integrated inspection of morphology, NGS and/or methylation data is essential to assess the molecular data in context of tumor cell content. Typically, this is not a similar challenge in meningioma tissue as e.g. in diffuse glioma. Yet, low fractions of canonical, presumably early mutations (*NF2, AKT1, TRAF7, SMO*) or low amplitudes of CNVs, especially 22q deletion, may indicate low tumor cell content in the extracted area and possibly explain lower methylation scores.

Immunohistochemistry (IHC) data should include description of potential heterogeneity, which controls were used and evaluated, and optimally information on the applied clone.[17]

Attributing pathogenic significance to findings

Estimating and attributing the pathogenetic significance to a detected variant or, more broadly, to a molecular alteration is a complex task requiring the integration of multiple layers of information. Useful data include the germline frequency of the variant, the specific position within the gene sequence, the existence of already known variants at the same location and the predicted impact

on protein structure and function. [15,18] For instance, a variant with a relatively high germline frequency is unlikely to be pathogenetic, while an exon-located missense variant resulting in a different amino acid or nonsense variants are more likely to be pathogenetic.

Evaluation of these features should result in the classification of potential pathogenetic significance. Concerning somatic variants in cancer, a 5-tier system has been proposed, [15] similarly to what has been established since longer time for germline variants. [19] This scoring system is based on the standardized evaluation of the previously mentioned features and results in the following 5 categories: benign, likely benign, variant of uncertain significance (VUS), likely oncogenic and oncogenic.

Multiple databases have been created to collect data about the identified variants in different tumor types and to provide information regarding their frequency and potential pathogenicity, but coverage in terms of the analyzed neoplasms and genes varies since most frequent tumors are more represented. Moreover, changes in diagnostic classifications can limit the longitudinal value of collected data, although this pitfall is less relevant for meningiomas since, overall, is a well characterized diagnostic entity since long time. In addition to general databases, gene-specific repositories are also available; for example, concerning meningiomas, a database of *NF2* variants is available (https://databases.lovd.nl/shared/genes/NF2).

Finally, the use of deep learning-based approaches is expected to improve the pathogenetic classification of newly detected variants in terms of clinical relevance, required resource and consistency.[20]

Attributing clinical significance to findings

Meningiomas display a variety of recurring molecular aberrations. In order to grade the evidence for the relevance of these potential targets for targeted therapy, we are applying here the widely accepted European Society for Medical Oncology (ESMO) Scale for Clinical Actionability of molecular Targets (ESCAT), [21] which was also used in the prior EANO guideline on molecular testing. [10] The ESCAT defines six levels of clinical evidence for molecular targets according to the implications for patient management (**Table 1**). While ESCAT was primarily developed for assessment of genomic alterations, we apply it here in a broader sense and use it also for grading of potential biomarkers defined by protein expression or assessed with other methods such as immunohistochemistry or molecular imaging.

Molecular testing: when to test

In meningioma, surgical resection and radiotherapy are established treatment options recommended at initial diagnosis and recurrence. [3] Systemic pharmacotherapy and targeted radionuclide therapy are currently regarded as experimental and are to be considered only after exhaustion of surgical resections and radiotherapy options. [5] Therefore, outside of clinical trials in the first line setting, molecular testing intended for selection of targeted therapy is not recommended at initial diagnosis, but is potentially more relevant at recurrence and consideration of such a therapy line. However, information of risk of recurrence based on molecular markers and subgroups (*TERT*, *CDKN2A/B*, DNA methylation) may already be advisable at initial diagnosis and, depending on assay, already reveal predictive information discussed here. Guidance on the selection of molecular testing for prognostic markers in meningiomas and their integration into grading has recently been provided by the cIMPACT-NOW consortium. [22] As recommended for glial tumors, molecular testing should be performed on the most recent tumor tissue sample whenever possible, as molecular alterations may change as tumors progress. [10] Furthermore, the development of newer methodologies over time may also justify deferring analysis until clinically indicated, as novel techniques may be able to investigate multiple targets with a single test saving time and laboratory costs. Novel technology may also alleviate the current limitation of molecular testing due to cost, both of single analyses and of equipment in general. Concerning the testing strategy, high-throughput profiling for diagnostic markers may in parallel yield information on multiple of the potential targets discussed here. The gradual deterioration of nucleic acid in FFPE material over time can reduce the quality of test results at a later stage, and therefore this has to be considered in the testing strategy.

Molecular targets

Mammalian target of rapamycin (mTOR) pathway activation

The serine/threonine kinase mammalian target of rapamycin (mTOR) is a key regulator of a signaling axis involved in control of cell growth, cell cycle progression, and protein synthesis. Activating mutations in *mTOR* or inactivating mutations in *TSC1* or *TSC2* can be detected by NGS panels, whole-exome sequencing (WES) or whole genome sequencing (WGS). mTOR inhibitors are established and approved treatments for several tumor types. While mTOR pathway upregulation in meningiomas via these activating mutations is rare, upregulation of this pathway via inactivation of NF2 is very common in these tumors and thus a potential target for therapeutic

intervention. [5,23–25] However, high-level evidence for the efficacy of this therapeutic approach is still lacking (as detailed in the supplemental information), rendering mTOR pathway activation an **ESCAT IIB** target.

Neurofibromin 2 (merlin, schwannomin; NF2)

NF2 non-synonymous inactivating mutations are the most common molecular alterations in meningioma, especially at the convexity, found in up to 60% of sporadic cases. [26] Loss of heterozygosity of chromosome arm 22q, on which *NF2* is located, is the most frequent chromosomal aberration in meningiomas and is part of a two-step inactivation of NF2. [27] *NF2* encodes merlin, a cytoskeletal protein involved in contact inhibition, directly and indirectly regulating the activity of several protein kinases such as RTK, FAK and PI3K/Akt converging on mTOR, and activating the Hippo pathway. *NF2* copy number loss may be tested by comparative genome hybridization (CGH) arrays, reverse-type quantitative polymerase chain reaction (RT-qPCR), methylation sequencing or other quantitative DNA analyses. Detection of *NF2* sequence variants requires DNA sequencing technology, in particular NGS.

Based on limited clinical trial results, NF2 alterations are considered a predictive biomarker for patient treatment (**ESCAT IIB**), [21] opening interesting perspectives, but lacking the basis for strong recommendation. To date, most clinical trials employing *NF2* loss as a molecular target have been performed in recurrent or progressive, mostly heavily pretreated meningioma patients without a control arm. The mTOR inhibitor everolimus in combination with octreotide led to reduced growth rates as compared to the period prior to study enrollment in a small phase 2 clinical trial. [28] The ErbB2/EGFR inhibitor lapatinib likewise led to slowed tumor growth in another small phase 2 clinical trial. [29,30] The FAK inhibitor GSK2256098 yielded stable disease in 8 of 24 higher grade *NF2*-altered meningiomas in an uncontrolled phase 2 clinical trial. [31] A prospective phase 2 platform trial has documented a radiographic responses rate in 28% (5 of 18 patients) in evaluable meningiomas associated with NF2-related schwannomatosis. [32] These encouraging results warrant further evaluation in randomized clinical trials.

Phosphatidylinositol 3-kinase, catalytic subunit alpha (PIK3CA)

The PI3K/AKT/mTOR pathway impacts diverse cellular activities such as cell growth, proliferation, differentiation, motility, and cellular survival and is altered in a large proportion of cancers. [33] *PIK3CA* variants are mostly encountered in WHO grade 1 and at a lower frequency in WHO grade 2 meningioma and are strongly enriched in the benign DNA methylation classes ben-1, ben-2 and

ben-3. [34] Depending on the series, *PIK3CA* variants have been identified in approximately 1-5% of meningiomas[35–37] and typically occur in non-NF2 altered meningiomas. Among non-NF2 meningiomas, they are detected mutually exclusive to variants in *AKT1* and *SMO* (and mostly exclusive to *KLF4*) but may frequently co-occur with *TRAF7* mutations. [36] *PIK3CA*-mutated tumors are typically encountered in the skull base. [36] *PIK3CA* mutations are usually detected with DNA sequencing panels. For other indications, *PIK3CA* inhibitors have already been approved (details in supplemental text). Preclinical data showed an additive inhibitory effect of the combination of the PI3K inhibitor alpelisib and MEK inhibitor trametinib on meningioma cell lines and primary cultures, reversing the AKT activation. [38] Currently, the safety of combining alpelisib with trametinib is being investigated in a phase 1 clinical trial involving patients with progressive refractory meningioma (registered under NCT03631953). *PIK3CA* alteration represents an **ESCAT IIIA** target.

BRCA1-associated protein 1 (BAP1)

BAP1 is a member of the Polycomb group family, counteracting Polycomb Repressive Complex 1 (PRC1)-mediated histone ubiquitylation. It remodels chromatin and maintains a functional epigenetic landscape. *BAP1* mutations are enriched in malignant, including rhabdoid meningiomas, but represent under 1% of mutations across all meningiomas. *BAP1* germline mutations are associated with multiple types of malignancies, including mesothelioma, uveal melanoma, renal cell carcinoma and, infrequently (1-4%), malignant meningiomas. Testing for BAP1 alterations can be achieved by immunostaining, detecting loss of protein expression, or more comprehensively with next-generation sequencing methods. [39–42] Treatment options have been evaluated in more common BAP1-associated malignancies and involve histone deacetylase (HDAC) inhibitors, [43] enhancer of zeste homolog 2 (EZH2) inhibitors, [44] platinum agents, [45] poly-(ADP-ribose) polymerase (PARP) inhibitors, [46,47] and immunotherapy[48,49] (ESCAT IIA). However, in meningioma, controlled trials for *BAP1*-mutant meningiomas have not been conducted (**ESCAT IIIA**).

Programmed death ligand 1 (PD-L1)

Immune checkpoint inhibitors targeting PD-L1 and its receptor PD-1 have shown meaningful clinical benefit and are approved for treatment of several extra-CNS tumor types. For some of these tumor types, treatment indication per approval is dependent on demonstration of PD-L1 expression using a validated test. [50] There is limited evidence for clinical efficacy of PD-1/PD-L1

inhibitors in meningioma and lack of data on the predictive role of PD-L1 expression for immune checkpoint inhibitor activity. A small phase II trial investigating pembrolizumab in recurrent and progressive grade 2 and 3 meningiomas met its primary PFS endpoint, but did not find a significant correlation between PD-L1 expression and outcome. [51] Another phase II study on nivolumab in meningiomas recurring after surgery and radiation therapy failed to meet its primary endpoint of PFS-6. [52] In conclusion, PD-L1 testing as a basis for immune checkpoint inhibitor therapy is not recommended in the clinical routine and should only be considered in the context of clinical trials or well-annotated compassionate use programs and prospective registries once standard treatment options are exhausted **(ESCAT IIIB)**.

Somatostatin receptor (SSTR)

SSTRs are established targets for drug and radioligand therapies in endocrine cancers. In meningioma, SSTRs are widely expressed in meningiomas, particularly the SSTR2 subtype is found in approximately 80-95% of cases.[53]

SSTR2 represents an **ESCAT IIIA** target in meningiomas. There is proven efficacy of the radioligand [^{177}Lu]Lu-DOTATATE in SSTR2-positive (as determined by PET) neuroendocrine tumors based on randomized clinical trials. [54,55] Furthermore, retrospective series and an interim analysis of a prospective single-arm study suggest potential efficacy for SSTR2-targeted radionuclide therapy in meningioma. [56–59] To date there are no conclusive data on the efficacy of SSTR2-targeted radionuclide therapy from prospective controlled clinical trials in meningioma. The European Organisation for Research and Treatment of Cancer (EORTC) is activating the first randomized clinical trial to investigate the efficacy of [177Lu]Lu-DOTATATE in SSTR2-positive meningiomas (LUMEN-1, NCT06326190).

The somatostatin analogue lanreotide has been proven to be efficacious in enteropancreatic neuroendocrine tumors showing SSTR positivity (as determined by scintigraphy). [60] Another trial showed efficacy in controlling tumor growth in patients with metastatic neuroendocrine midgut tumors, but did not use SSTR status as inclusion criterion. [61] The efficacy of somatostatin analogues in meningiomas has been investigated in some studies, but remains unknown due to methodological limitations.[62,28,63]

At present, SSTR testing by immunohistochemistry or PET as a basis for targeted treatment are not recommended in the clinical routine for meningiomas and should only be considered in the

context of clinical trials or well-annotated compassionate use programs and prospective registries once standard treatment options are exhausted (**ESCAT IIIA**).

AKT1

The *AKT1* gene is located on chromosome 14q32.33 and represents an oncogene that encodes protein kinase B alpha, beta, and gamma. Specific point mutations in *AKT1* (p.E17K) induce a conformational change in the protein, altering its localization from the cytoplasm to the plasma membrane, resulting in the constitutive activation of the AKT1 kinase and in the down-stream activation of the mTOR and ERK1/2 signaling pathways. *AKT1* p.E17K mutations are found in 10% of meningiomas, typically in CNS WHO grade 1 anterior or middle skull base location, *NF2*-wildtype meningothelial or transitional meningiomas. [64–66] *AKT1* mutations were not detected in radiation-induced meningiomas. [67,68] There are several pharmacological AKT1 inhibitors, notably AZD5363 (capivasertib), which is approved for breast cancer patients with hormone receptor positive, HER2-negative locally advanced or metastatic breast cancer with one or more biomarker alterations (*PIK3CA*, *AKT1* or *PTEN*). [69] Capivasertib showed activity across several tumor types harbouring *AKT1* p.E17K mutations in a multihistology basket study. [70] Capivasertib has also shown activity in a single patient with *AKT1* p.E17K-mutant metastatic meningioma. [71] Overall, AKT1 represents an **ESCAT IIIA** target in meningioma.

Smoothened (SMO)

Smoothened (SMO) is a G protein-coupled receptor encoded by the *SMO* gene and contributing to the hedgehog signaling cascade. *SMO* mutations are a rare oncogenic event in meningiomas, occurring in about 5% of cases and associated with a skull base location, meningothelial histology and CNS WHO grade 1 tumors. [64,65] Recurrent *SMO* mutations (p.W535L and p.L412F) have been identified in meningiomas and are mutually exclusive with alterations in *NF2, AKT1, PIK3CA, TRAF7, KLF4* and *POLR2A*. SMO antagonists are approved for treatment of basal cell carcinoma, a neoplasm characterized by alterations in the hedgehog pathway, usually consisting of *PTCH1* mutations and, more rarely, secondary to *SMO* alterations. [72,73] Data regarding treatment of *SMO*-mutant meningiomas are lacking. Vismodegib was administered in a *SMO*-mutant meningioma within the NCI-MATCH ECOG-ACRIN Trial (EAY131) Subprotocol T achieving a partial response. [74] According to current evidence, an **ESCAT IIIA** can be assigned, but novel data is expected in the coming months thanks to an ongoing phase II, multi-arm trial (NCT02523014), which is evaluating the efficacy of vismodegib for treatment of *SMO*-mutant

meningiomas. Enrollment in a clinical trial with SMO antagonists should be considered in progressing/recurrent *SMO*-mutant meningiomas if conventional treatments including surgery and/or radiotherapy have been exhausted and clinical conditions allow further therapies.

Cyclin-dependent kinases and inhibitors (CDKN2A/B, CDK4, CDK6)

The cyclin-dependent kinase inhibitor genes 2A (*CDKN2A*) and 2B (*CDKN2B*), as well as the cyclin-dependent kinase genes 4 (*CDK4*) and 6 (*CDK6*) encode regulators of the cell cycle and are frequently aberrant in various types of cancers. In meningiomas, homozygous *CDKN2A/B* deletions are found in ~5-7% of cases and associated with poor outcome. [75,76] Testing methods include CGH microarrays, copy number analyses from DNA methylation arrays, NGS, WES, WGS, or fluorescent in-situ hybridization (FISH).

The CDK4/6 inhibitors palbociclib, ribociclib, and abemaciclib showed preclinical efficacy; however, clinical efficacy remains unclear as only single-arm clinical trials have been completed or are planned in adult patients with meningioma (**ESCAT IVA**). Assessing homozygous *CDKN2A/B* deletion in meningiomas is currently only recommended for grading purposes or in the context of clinical trials.

Suppressor of fused homolog (SUFU)

Suppressor of fused homolog (SUFU) is a negative regulator of the hedgehog signaling pathway. [77] In the presence of hedgehog stimulation, activated GLI proteins are produced from the SUFU-GLI complex promoting the transcription of target genes. *SUFU* alterations are associated with development disorders and tumor predisposition. [78,79] In the latter setting, SUFU exerts an onco-suppressor function, thus alterations resulting in a loss of function are observed. Initially, the association between germline pathogenetic *SUFU* variants and medulloblastoma were investigated and these alterations are a rare cause, compared to *PTCH1* mutations, of nevoid basal cell carcinoma syndrome (NBCCS) (also known as Gorlin syndrome). [80,81] Concerning meningiomas, *SUFU* mutations were initially reported in familial cases, [82–84] but further cases demonstrated their occurrence also in sporadic cases with a frequency of up to 5%.[85–87] *SUFU* mutations were associated with a concurrent *NF2* alteration, a convexity location, CNS WHO grade 3 and recurrent tumor. These findings are of interest considering that Smoothened (SMO) alterations, another protein of the hedgehog signaling cascade, are associated with an *NF2*-intact status, skull base location and WHO grade 1. [88,89] Most of the observed *SUFU* alterations are gene mutations, but focal exon deletions and gene rearrangements have also been reported.

Based on these findings, *SUFU* alterations in routine diagnostics can be tested using a DNA NGS panel targeting the most frequently altered genes in meningiomas. [86] In terms of therapeutic relevance, SUFU protein is a downstream effector of SMO in the hedgehog pathway, thus SMO targeting is not effective. [90,91] Further downstream inhibition of GLI proteins has been evaluated in preclinical models, [92–102] but specific data about meningioma is lacking (**ESCAT IVA)**. Molecular profiling should be proposed if clinically required or if a familial predisposition is suspected. In the latter setting, compliance with local regulations in terms of germline testing is warranted. If a SUFU alteration is detected, treatment should be proposed in the context of a clinical trial if available.

Platelet-derived growth factor receptors (PDGFR-alpha/beta)

PDGFRs are established targets in a variety of systemic cancers. [103] Early studies raised the possibility that platelet-derived growth factor (PDGF) may be involved in meningioma growth. The PDGF ligands AA and BB and PDGF receptor-beta are present in most meningiomas regardless of grade, [104,105] which raised the possibility of an autocrine loop. [106] Administration of PDGF-BB to meningioma cells in culture stimulated growth while anti-PDGF-BB antibodies inhibited tumor cell growth. [106] These findings suggested that PDGFR inhibition may have therapeutic value in patients with meningiomas. However, trials with agents such as imatinib mesylate which inhibit PDGFR-alpha and -beta did not show any activity. [107] Other trials with multikinase inhibitors that targeted PDGFR, such as sunitinib, showed modest activity, [108] but this may be due primarily to its inhibition of VEGFR. More recent molecular analysis of meningiomas did not find evidence of PDGFR amplification or mutations. [109,110] Therefore, testing for PDGFR alterations is discouraged in routine clinical practice and use of PDGFR inhibitors should only be considered in the context of clinical trials (**ESCAT IVA**).

Progesterone receptor (PR) and estrogen receptor (ER)

The steroid hormone receptors PR and ER are established targets for antihormonal treatment in breast cancer. [111,112] Overall, 76% of meningiomas express PR and 6% express ER. While some evidence for therapeutic actionability is available from preclinical studies, conclusive data indicating clinically relevant efficacy are lacking. A phase III trial failed to show an effect of the progesterone receptor inhibitor mifepristone on failure-free or overall survival of unresectable meningioma. [113] Therefore, testing for PR or ER expression as a basis for antihormonal treatment is discouraged for the clinical routine and should only be considered in the context of clinical trials

(ESCAT IVA). In contrast, progestin is known to increase the risk for meningioma and associated with enrichment of PIK3CA mutations.[114,115]

SWI/SNF related, matrix associated, actin dependent regulator of chromatin E1 (SMARCE1)

SMARCE1 is a subunit of the chromatin-remodeling SWI/SNF (or BAF) complex. SMARCE1 loss drives development of clear cell meningiomas and is a biomarker for this diagnosis.[116,117] Genes encoding mSWI/SNF complexes are mutated in over 20% of human cancers.[118] They have in common the disruption of members of the functional complex, comprising SMARCA4/2, ARID1A/B, SMARCB1 and SMARCE1 subunits.[119,120] Treatment of SMARCE1-deficient meningioma cells with small molecule inhibitors degrading bromodomain containing 9 (BRD9), a non-canonical barrier-to-autointegration factor (BAF) component, leads to their selective growth inhibition, although clinical evidence is missing.[121] SMARCE1 is an **ESCAT IVA** target.

Krüppel-like factor 4 (KLF4)

Krüppel-like factor 4 (KLF4) is a transcription factor involved in a variety of cellular signaling pathways.[122–127] *KLF4* mutations have a high rate of co-occurrence with *TRAF7* mutations. Detection of mutations in *KLF4/TRAF7* are the molecular hallmark of secretory meningiomas.[128] In unselected meningioma groups, *KLF4*-mutated tumors are detected in about 6-9%.[64,129] Among non-*NF2* meningiomas, *KLF4* mutations can be found in up to 38%.[130] The *KLF* mutation is a typical hotspot mutation, affecting codon 409 which results in a lysine to glutamine exchange (p.K409Q).[125,128] *KLF4* status may be assessed together with other relevant genes, especially *TRAF7* and *NF2,* through NGS panel sequencing.[129] There is only one preclinical study available, showing potential activity of the mTOR inhibitor temsirolimus in *KLF4* (p.K409Q)-mutated meningioma.[125] KLF4 represents an **ESCAT IVA** target.

Telomerase reverse transcriptase (TERT)

TERT hotspot mutations have been detected in 5-6% of all meningiomas and is generally associated with an aggressive clinical course.[131,132] *TERT* promoter mutations are an independent criterion for CNS WHO grade 3 meningioma regardless of histology type. Preclinical and clinical studies using *TERT* as a therapeutic target in meningiomas are missing so far (**ESCAT V**). Testing for *TERT* promoter mutations in meningiomas is recommended for grading and prognostic purposes.

Vascular Endothelial Growth Factor (VEGF) and Vascular Endothelial Growth Factor Receptors (VEGFR)

Vascular endothelial growth factor (VEGF) and vascular endothelial growth factor receptors (VEGFR) are well established targets in cancer. [133] VEGF and its receptors are frequently expressed in meningiomas and are likely to be important for tumor growth and production of peritumoral edema. [134,135] Several retrospective studies have shown possible benefit of bevacizumab in slowing tumor growth in recurrent meningiomas**.** [136–141] **An uncontrolled multicenter phase 2 trial of bevacizumab in 42 patients with recurrent meningiomas showed that it was well-tolerated. Bevacizumab did not produce any radiographic responses but progression-free survival at 6 months (PFS-6) was 87% for grade 1 meningiomas, 77% for grade 2 meningiomas, and 46% for grade 3 meningiomas,** [142] **which appears superior to historical benchmarks of 29% for grade I meningiomas and 26%** for WHO grade 2/3 meningiomas. [4] **Bevacizumab has also been combined with everolimus in a small uncontrolled** prospective study in 18 patients with progressive, refractory meningioma. A best response of stable disease (SD) was observed in 15 patients (88 %) and 6 patients had SD for more than twelve months. Median PFS was 22 months (95 % CI 4.5-26.8).[143]

Some VEGFR inhibitors have also shown possible benefit in uncontrolled studies in patients with recurrent meningioma. In a phase 2 trial of the VEGFR, platelet-derived growth factor receptor (PDGFR) and c-kit inhibitor sunitinib in 36 heavily pretreated CNS WHO grade 2 and 3 meningioma patients, PFS-6 was 42%**,**[108] **compared to the historic PFS-6 benchmark of 26% for grade 2 and 3 meningiomas**. [4] Expression of VEGFR2 on tumor cells was associated with PFS, showing a median PFS of 1.4 months in VEGFR2-negative patients versus 6.4 months in VEGFR2-positive patients (P = .005). There have also been case reports suggesting benefit from other multitarget VEGFR inhibitors such as cabozantinib**.**[144]

While testing for VEGF or VEGFR is not recommended as molecular predictive biomarker (**ESCAT X**), use of bevacizumab and VEGFR inhibitors such as sunitinib can be considered for patients with refractory recurrent meningiomas, although more definitive clinical trials evaluating these agents are needed.

AT-rich binding domain protein 1A (ARID1A)

AT-rich binding domain protein 1A (ARID1A) has multiple biological roles and is involved in diverse processes including DNA damage repair, maintenance of genomic integrity, cell cycle regulation, epithelial–mesenchymal transition, and steroid receptor response and functions as a tumor suppressor. The *ARID1A* gene is mutated in nearly half of ovarian clear cell carcinomas and around one-third of endometrial and ovarian carcinomas of the endometrioid type. [145] *ARID1A* gene alterations have been described in 5.4% of meningiomas, with a higher prevalence in recurrent tumors and an association with adverse prognosis. [87,146] Experimental strategies at inducing synthetic lethality in ARID1A-deficient cancers including inhibitors of PARP, EZH2, BET, ataxia telangiectasia and Rad3-related protein (ATR), and HDAC are under investigation. [145] Furthermore, the high prevalence of *ARID1A* mutations in mismatch repair deficient cancers suggests that it has the potential to be a biomarker predicting sensitivity to immune checkpoint inhibition. [145] However, no preclinical or clinical data on targeted therapy of *ARID1A* mutant meningiomas exist and HRD testing is discouraged outside of specifically designed clinical trials (**ESCAT X**).

Homologous recombination deficiency (HRD)

Homologous recombination deficiency (HRD) is a well-established predictive factor for the magnitude of response to PARP inhibitor therapy in ovarian cancer. [147,148] An association of HRD-like signatures with radiation-associated meningiomas and with the malignant methylation class has been reported. [149] There are no preclinical or clinical data on the activity of PARP inhibitors in meningioma, and HRD testing is discouraged outside of specifically designed clinical trials (**ESCAT X**).

TNF receptor associated factor 7 (TRAF7)

The TNF receptor associated factor 7 (*TRAF7*) gene is a tumor suppressor gene located on chromosome 16p13.3. The frequency of missense mutations in *TRAF7* across meningiomas is 20-25% and these mutations typically affect CNS WHO grade 1 tumors, with preferential location in the base of the skull and an association with brain invasion. [64] Otherwise these mutations are rare, but may be found in intraneural perineuriomas and mesotheliomas. In meningioma, *TRAF7* mutations are commonly detected by gene panel sequencing and mutually exclusive with *NF2* mutations, but may co-occur with mutations in *KLF4* or *AKT1*. [150] Somatic *TRAF7* mutations have also been identified in normal appearing leptomeninges. [151] They are not found in radiation-

associated meningiomas[65] nor in the pediatric population. [152] Germ-line mutations of *TRAF7* cause congenital heart defects. [153] *TRAF7*-mutant meningioma primary cultures lack cilia, and *TRAF7* knockdown causes cardiac, craniofacial, and ciliary defects in Xenopus and zebrafish, suggesting a mechanistic convergence for *TRAF7*-driven meningiomas and developmental heart defects. [154] The consequences of *TRAF7* mutations are thought to include disruption of the catalytic activity of the E3 ubiquitin ligase interaction with the MAPK pathway and RAS GTPases, resulting in altered actin dynamics and promoting anchorage-independent growth. [155] At present, *TRAF7* mutations must be considered a non-druggable alteration (**ESCAT X**).

Other molecular markers / signatures

Moving beyond molecular markers that affect a single gene or locus, specific markers or a combination thereof can have prognostic or predictive value in meningioma patients. Since the 1960s, the occurrence of copy-number variations (CNV) has been studied in meningioma. [156] Heterozygous loss of chromosome 22q that harbors the *NF2* gene, is present in more than half of meningiomas and is an important part of two-step inactivation of NF2 activity. [34,157] In meningioma, specific CNVs are associated with increased risk for progression and therefore several models to utilize CNVs for risk prediction have been proposed. [158,159] So far, the most consistent marker is the loss of chromosome 1p. [34,157,160,161] Models that include multiple CNVs and other (molecular) information attribute points to losses in chromosomes 1p/6q/14q, WHO grade and epigenetic status (integrated risk score) [34] or 1p, 3p, 4p/q, 6p/q, 10p/q, 14q, 18p/q, 19p/q, *CDKN2A/B* and mitotic count (integrated grade).[157]

More recently, meningioma molecular fingerprinting was expanded to the level of whole genome analyses. [34,37,109,162–165] First, epigenetic profiling identified three meningioma methylation families termed benign, intermediate and malignant. [37] These methylation classes can be subdivided into methylation classes ben-1, ben-2, ben-3, int-A, int-B and mal. Other epigenetic subclassification systems have been proposed, with varying overlap. [166–168] The recent cIMPACT-NOW update 8 provides recommendations on their integration into diagnostics. [22] Each methylation family and class is associated with specific clinical outcomes and molecular alterations. To further investigate the biological and clinical relevance of overarching meningioma molecular families, epigenetic profiling was expanded with (single cell) RNA sequencing and CNV-analysis either stepwise[163,164] or in an integrated prognostic model. [109] Extracting the common divider between molecular groups defined by either epigenetics, transcriptomics, CNV-profiles and NF2-status identified three

prognostic molecular subtypes: low risk NF2-altered and NF2-wildtype groups and a high(er) risk NF2-altered group.[165]

Taken together, CNVs and advanced molecular based risk prediction models can have a value in risk attribution to meningioma patients. They are however (currently) not targetable and their clinical value needs to be further investigated for possible inclusion in future guidelines.

Predictive markers of radiotherapy

DNA methylation profiling, RNA sequencing, copy number variants, DNA sequencing, targeted gene expression profiling, and histological features provide robust prognostic information for postoperative meningioma outcomes, either alone or in integrated models.[34,37,109,157,162–164,169–175] These myriad approaches for meningioma molecular classification demonstrate biological concordance across unsupervised systems, but concordance across unsupervised and supervised systems that incorporate or were trained on clinical endpoints is poor. Both unsupervised and supervised approaches for meningioma molecular classification remain prognostic for clinical outcomes in patients who were treated with postoperative radiotherapy,[164,176] including in patients who were treated with postoperative radiotherapy on prospective clinical trials.[161,173] Prediction of postoperative radiotherapy responses remains an active area of investigation. Some unsupervised approaches appear unable or have not been tested to predict radiotherapy responses,[164] but targeted gene expression profiling has recently been proposed as a robust system for distinguishing meningiomas that benefit from postoperative radiotherapy from meningiomas where radiotherapy appears to offer no benefit.[173] Having been tested for analytical and clinical validity in more than 2000 meningiomas from 13 medical centers across 3 continents, including in patients who were treated with postoperative radiotherapy on prospective clinical trials,[173] this 34-gene expression biomarker is a promising candidate for implementation in routine clinical decision making but requires prospective multicenter validation in randomized clinical trials (ESCAT assessment not applicable, as it was developed for drug treatments). Likewise, a very recent study has proposed a combined DNA methylation- and RNA expression-based risk assessment that identifies radiation-resistant meningiomas.[177] Collectively, these studies both suggest that molecular high-throughput data may reveal patterns that are able to stratify for cases with differential response to radiotherapy. However, since both studies yielded and validated different marker sets, there is so far no integrated interpretation and recommendation on these approaches feasible.

Conclusions and future outlook

Meningiomas harbor a number of recurring molecular alterations that may be amenable for targeted therapy. So far, sufficient data from prospective clinical trials are missing to justify clear recommendations for molecularly targeted therapy in routine practice. However, ongoing efforts aim at translating personalized treatment with specific inhibitors, immunotherapies, radioligand therapies and radiotherapy based on molecular analysis of meningioma samples into clinical use. The evidence-based evaluation of molecular targets presented here may support decision making in molecular tumor boards aiming to identify potential treatments for patients with meningiomas guide and are intended to facilitate clinical studies.

Acknowldegements

The authors are grateful to Lynn Gottmann (Division of Oncology, Medical University of Vienna) for support with referencing. This work was supported by the European Society for Medical Oncology (ESMO) by means of a Translational Research Fellowship awarded to Maximilian J. Mair.

Author contributions

All authors contributed with text paragraphs, literature review and evidence level assessment for chapters assigned to them by FS and MP. FS and MP compiled all submitted chapters into a manuscript draft, which was circulated for review to all co-authors. FS and MP incorporated all feedback and the final manuscript version was approved by all authors.

Conflict of interest

FS is co-founder and shareholder of Heidelberg Epignostix GmbH and received research support from Illumina and honoraria from Bayer and Illumina.

LB has received honoraria for lectures from Servier

MJM has received research funding from Bristol-Myers Squibb and travel support from Pierre Fabre.

MP has received honoraria for lectures, consultation or advisory board participation from the following for-profit companies: Bayer, Bristol-Myers Squibb, Novartis, Gerson Lehrman Group (GLG), CMC Contrast, GlaxoSmithKline, Mundipharma, Roche, BMJ Journals, MedMedia, Astra Zeneca, AbbVie, Lilly, Medahead, Daiichi Sankyo, Sanofi, Merck Sharp & Dome, Tocagen, Adastra, Gan & Lee Pharmaceuticals, Janssen, Servier, Miltenyi, Böhringer-Ingelheim, Telix, Medscape, OncLive.

G.R. no conflicts of interest.

MDJ has received honoraria for lectures, consultation or advisory board participation from Servier, myTomorrows, GlaxoSmithKline, Integra.

MW has received research grants from Novartis, Quercis and Versameb, and honoraria for lectures or advisory board participation or consulting from Anheart, Bayer, Curevac, Medac, Neurosense, Novartis, Novocure, Orbus, Pfizer, Philogen, Roche and Servier.

ELR has received a research grants from Bristol Meyers Squibb (BMS), and honoraria for lectures or advisory board participation or consulting from Bayer, Biodexa / Sitoxi, Janssen, Leo Pharma, Pierre Fabre, Roche, Seattle Genetics and Servier.

SCS has received honoraria for lectures, consultation or advisory board participation from Servier, Roche, Miltenyi, Chimerix, CeCaVa,MedAc and research grant support from Apollomics.

LS – no conflict of interest.

NLA has received honoraria for lectures, consultation or advisory board participation from Novartis / Advanced Accelerator Applications, Telix Pharmaceuticals, Servier and OncLive and research funding from Novocure and Telix Pharmaceuticals.

Anna Sophie Berghoff has research support from Daiichi Sankyo, Roche and honoraria for lectures, consultation or advisory board participation from Roche Bristol-Meyers Squibb, Merck, Daiichi Sankyo, AstraZeneca, CeCaVa, Seagen, Alexion, Servier as well as travel support from Roche, Amgen and AbbVie.

G.R. no conflicts of interest.

SB: no conflict of interest.

PW: no conflict of interest

HGW: no conflict of interest.

References

1. Ostrom QT, Price M, Neff C, et al. CBTRUS Statistical Report: Primary Brain and Other Central Nervous System Tumors Diagnosed in the United States in 2016-2020. *Neuro Oncol*. 2023;25(12 Suppl 2):iv1-iv99. doi:10.1093/neuonc/noad149

2. Louis DN, Perry A, Wesseling P, et al. The 2021 WHO Classification of Tumors of the Central Nervous System: a summary. *Neuro Oncol*. 2021;23(8):1231-1251. doi:10.1093/neuonc/noab106

3. Goldbrunner R, Stavrinou P, Jenkinson MD, et al. EANO guideline on the diagnosis and management of meningiomas. *Neuro Oncol*. 2021;23(11):1821-1834. doi:10.1093/neuonc/noab150

4. Kaley T, Barani I, Chamberlain M, et al. Historical benchmarks for medical therapy trials in surgery- and radiation-refractory meningioma: a RANO review. *Neuro Oncol*. 2014;16(6):829-840. doi:10.1093/neuonc/not330

5. Mair MJ, Berghoff AS, Brastianos PK, Preusser M. Emerging systemic treatment options in meningioma. *J Neurooncol*. 2022;161(2):245-258. doi:10.1007/s11060-022-04148-8

6. Wang JZ, Landry AP, Raleigh DR, et al. Meningioma: International Consortium on Meningiomas (ICOM) consensus review on scientific advances & treatment paradigms for clinicians, researchers, and patients. *Neuro Oncol*. Published online May 2, 2024:noae082. doi:10.1093/neuonc/noae082

7. Preusser M, Brastianos PK, Mawrin C. Advances in meningioma genetics: novel therapeutic opportunities. *Nat Rev Neurol*. 2018;14(2):106-115. doi:10.1038/nrneurol.2017.168

8. Wang JZ, Nassiri F, Aldape K, von Deimling A, Sahm F. The Epigenetic Landscape of Meningiomas. *Adv Exp Med Biol*. 2023;1416:175-188. doi:10.1007/978-3-031-29750-2_13

9. Luger AL, König S, Samp PF, et al. Molecular matched targeted therapies for primary brain tumors-a single center retrospective analysis. *J Neurooncol*. 2022;159(2):243-259. doi:10.1007/s11060-022-04049-w

10. Capper D, Reifenberger G, French PJ, et al. EANO guideline on rational molecular testing of gliomas, glioneuronal, and neuronal tumors in adults for targeted therapy selection. *Neuro Oncol*. 2023;25(5):813-826. doi:10.1093/neuonc/noad008

11. Sahm F, Schrimpf D, Stichel D, et al. DNA methylation-based classification and grading system for meningioma: a multicentre, retrospective analysis. *Lancet Oncol*. 2017;18(5):682-694. doi:10.1016/S1470-2045(17)30155-9

12. Vasudevan HN, Choudhury A, Hilz S, et al. Intratumor and informatic heterogeneity influence meningioma molecular classification. *Acta Neuropathol*. 2022;144(3):579-583. doi:10.1007/s00401-022-02455-y

13. 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. *J Neuropathol Exp Neurol*. 2017;76(4):289-298. doi:10.1093/jnen/nlx008

14. Sahm F, Brandner S, Bertero L, et al. Molecular diagnostic tools for the World Health Organization (WHO) 2021 classification of gliomas, glioneuronal and neuronal tumors; an EANO guideline. *Neuro Oncol*. 2023;25(10):1731-1749. doi:10.1093/neuonc/noad100

15. Horak P, Griffith M, Danos AM, et al. Standards for the classification of pathogenicity of somatic variants in cancer (oncogenicity): Joint recommendations of Clinical Genome Resource (ClinGen), Cancer Genomics Consortium (CGC), and Variant Interpretation for Cancer Consortium (VICC). *Genet Med*. 2022;24(5):986-998. doi:10.1016/j.gim.2022.01.001

16. Heyer EE, Deveson IW, Wooi D, et al. Diagnosis of fusion genes using targeted RNA sequencing. *Nat Commun*. 2019;10(1):1388. doi:10.1038/s41467-019-09374-9

17. Sahm F, Aldape KA, Brastianos PK, et al. cIMPACT-NOW Update 8: Clarifications on WHO grading and molecular risk parameters for meningiomas. *(in submission)*. Published online 2024.

18. Li MM, Datto M, Duncavage EJ, et al. Standards and Guidelines for the Interpretation and Reporting of Sequence Variants in Cancer: A Joint Consensus Recommendation of the Association for Molecular Pathology, American Society of Clinical Oncology, and College of American Pathologists. *J Mol Diagn*. 2017;19(1):4-23. doi:10.1016/j.jmoldx.2016.10.002

19. Richards S, Aziz N, Bale S, et al. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. *Genet Med*. 2015;17(5):405-424. doi:10.1038/gim.2015.30

20. Li Q, Ren Z, Cao K, Li MM, Wang K, Zhou Y. CancerVar: An artificial intelligence–empowered platform for clinical interpretation of somatic mutations in cancer. *Science Advances*. 2022;8(18):eabj1624. doi:10.1126/sciadv.abj1624

21. Mateo J, Chakravarty D, Dienstmann R, et al. A framework to rank genomic alterations as targets for cancer precision medicine: the ESMO Scale for Clinical Actionability of molecular Targets (ESCAT). *Ann Oncol*. 2018;29(9):1895-1902. doi:10.1093/annonc/mdy263

22. Sahm F, Aldape KD, Brastianos PK, et al. cIMPACT-NOW Update 8: Clarifications on molecular risk parameters and recommendations for WHO grading of meningiomas. *Neuro Oncol*. Published online August 30, 2024:noae170. doi:10.1093/neuonc/noae170

23. Pachow D, Wick W, Gutmann DH, Mawrin C. The mTOR signaling pathway as a treatment target for intracranial neoplasms. *Neuro Oncol*. 2015;17(2):189-199. doi:10.1093/neuonc/nou164

24. Pinker B, Barciszewska AM. mTOR Signaling and Potential Therapeutic Targeting in Meningioma. *Int J Mol Sci*. 2022;23(4). doi:10.3390/ijms23041978

25. Graillon T, Tabouret E, Salgues B, et al. Innovative treatments for meningiomas. *Rev Neurol (Paris)*. 2023;179(5):449-463. doi:10.1016/j.neurol.2023.03.006

26. Papi L, De Vitis LR, Vitelli F, et al. Somatic mutations in the neurofibromatosis type 2 gene in sporadic meningiomas. *Hum Genet*. 1995;95(3):347-351. doi:10.1007/BF00225206

27. Ruttledge MH, Sarrazin J, Rangaratnam S, et al. Evidence for the complete inactivation of the NF2 gene in the majority of sporadic meningiomas. *Nat Genet*. 1994;6(2):180-184. doi:10.1038/ng0294-180

28. Graillon T, Sanson M, Campello C, et al. Everolimus and Octreotide for Patients with Recurrent Meningioma: Results from the Phase II CEVOREM Trial. *Clin Cancer Res*. 2020;26(3):552-557. doi:10.1158/1078-0432.CCR-19-2109

29. Osorio DS, Hu J, Mitchell C, et al. Effect of lapatinib on meningioma growth in adults with neurofibromatosis type 2. *J Neurooncol*. 2018;139(3):749-755. doi:10.1007/s11060-018-2922-5

30. Karajannis MA, Legault G, Hagiwara M, et al. Phase II trial of lapatinib in adult and pediatric patients with neurofibromatosis type 2 and progressive vestibular schwannomas. *Neuro Oncol*. 2012;14(9):1163-1170. doi:10.1093/neuonc/nos146

31. Brastianos PK, Twohy EL, Gerstner ER, et al. Alliance A071401: Phase II Trial of Focal Adhesion Kinase Inhibition in Meningiomas With Somatic *NF2* Mutations. *J Clin Oncol*. 2023;41(3):618-628. doi:10.1200/JCO.21.02371

32. Plotkin SR, Yohay KH, Nghiemphu PL, et al. Brigatinib in NF2-Related Schwannomatosis with Progressive Tumors. *N Engl J Med*. 2024;390(24):2284-2294. doi:10.1056/NEJMoa2400985

33. Fruman DA, Chiu H, Hopkins BD, Bagrodia S, Cantley LC, Abraham RT. The PI3K Pathway in Human Disease. *Cell*. 2017;170(4):605-635. doi:10.1016/j.cell.2017.07.029

34. Maas SLN, Stichel D, Hielscher T, et al. Integrated Molecular-Morphologic Meningioma Classification: A Multicenter Retrospective Analysis, Retrospectively and Prospectively Validated. *J Clin Oncol*. 2021;39(34):3839-3852. doi:10.1200/JCO.21.00784

35. Berghoff AS, Hielscher T, Ricken G, et al. Prognostic impact of genetic alterations and methylation classes in meningioma. *Brain Pathol*. 2022;32(2):e12970. doi:10.1111/bpa.12970

36. Abedalthagafi M, Bi WL, Aizer AA, et al. Oncogenic PI3K mutations are as common as AKT1 and SMO mutations in meningioma. *Neuro Oncol*. 2016;18(5):649-655. doi:10.1093/neuonc/nov316

37. Sahm F, Schrimpf D, Stichel D, et al. DNA methylation-based classification and grading system for meningioma: a multicentre, retrospective analysis. *Lancet Oncol*. 2017;18(5):682-694. doi:10.1016/S1470-2045(17)30155-9

38. Mondielli G, Mougel G, Darriet F, et al. Co-Targeting MAP Kinase and Pi3K-Akt-mTOR Pathways in Meningioma: Preclinical Study of Alpelisib and Trametinib. *Cancers (Basel)*. 2022;14(18). doi:10.3390/cancers14184448

39. van de Nes JAP, Nelles J, Kreis S, et al. Comparing the Prognostic Value of BAP1 Mutation Pattern, Chromosome 3 Status, and BAP1 Immunohistochemistry in Uveal Melanoma. *Am J Surg Pathol*. 2016;40(6):796-805. doi:10.1097/PAS.0000000000000645

40. Koopmans AE, Verdijk RM, Brouwer RWW, et al. Clinical significance of immunohistochemistry for detection of BAP1 mutations in uveal melanoma. *Mod Pathol*. 2014;27(10):1321-1330. doi:10.1038/modpathol.2014.43

41. Righi L, Duregon E, Vatrano S, et al. BRCA1-Associated Protein 1 (BAP1) Immunohistochemical Expression as a Diagnostic Tool in Malignant Pleural Mesothelioma Classification: A Large Retrospective Study. *J Thorac Oncol*. 2016;11(11):2006-2017. doi:10.1016/j.jtho.2016.06.020

42. Shankar GM, Santagata S. BAP1 mutations in high-grade meningioma: implications for patient care. *Neuro Oncol*. 2017;19(11):1447-1456. doi:10.1093/neuonc/nox094

43. Krug LM, Kindler HL, Calvert H, et al. Vorinostat in patients with advanced malignant pleural mesothelioma who have progressed on previous chemotherapy (VANTAGE-014): a phase 3, double-blind, randomised, placebo-controlled trial. *Lancet Oncol*. 2015;16(4):447-456. doi:10.1016/S1470-2045(15)70056-2

44. Zauderer MG, Szlosarek PW, Le Moulec S, et al. EZH2 inhibitor tazemetostat in patients with relapsed or refractory, BAP1-inactivated malignant pleural mesothelioma: a multicentre, open-label, phase 2 study. *Lancet Oncol*. 2022;23(6):758-767. doi:10.1016/S1470-2045(22)00277-7

45. Hassan R, Morrow B, Thomas A, et al. Inherited predisposition to malignant mesothelioma and overall survival following platinum chemotherapy. *Proc Natl Acad Sci U S A*. 2019;116(18):9008-9013. doi:10.1073/pnas.1821510116

46. George TJ, DeRemer DL, Parekh HD, et al. Phase II trial of the PARP inhibitor, niraparib, in BAP1 and other DNA damage response (DDR) pathway deficient neoplasms including cholangiocarcinoma. *J Clin Oncol*. 2020;38(4, Suppl).

47. Hassan R, Mian I, Wagner C, et al. Phase II study of olaparib in malignant mesothelioma (MM) to correlate efficacy with germline and somatic mutations in DNA repair genes. *J Clin Oncol*. 2020;38(15, Suppl).

48. Dual Checkpoint Blockade Takes Aim at Relapsed Mesothelioma. *Cancer Discov*. 2017;7(8):OF7. doi:10.1158/2159-8290.CD-NB2017-087

49. Alley EW, Lopez J, Santoro A, et al. Clinical safety and activity of pembrolizumab in patients with malignant pleural mesothelioma (KEYNOTE-028): preliminary results from a non-randomised, open-label, phase 1b trial. *Lancet Oncol*. 2017;18(5):623-630. doi:10.1016/S1470-2045(17)30169-9

50. Vranic S, Gatalica Z. PD-L1 testing by immunohistochemistry in immuno-oncology. *Biomol Biomed*. 2023;23(1):15-25. doi:10.17305/bjbms.2022.7953

51. Brastianos PK, Kim AE, Giobbie-Hurder A, et al. Phase 2 study of pembrolizumab in patients with recurrent and residual high-grade meningiomas. *Nat Commun*. 2022;13(1):1325. doi:10.1038/s41467-022-29052-7

52. Bi WL, Nayak L, Meredith DM, et al. Activity of PD-1 blockade with nivolumab among patients with recurrent atypical/anaplastic meningioma: phase II trial results. *Neuro Oncol*. 2022;24(1):101-113. doi:10.1093/neuonc/noab118

53. Agopiantz M, Carnot M, Denis C, Martin E, Gauchotte G. Hormone Receptor Expression in Meningiomas: A Systematic Review. *Cancers*. 2023;15(3):980. doi:10.3390/cancers15030980

54. Strosberg J, El-Haddad G, Wolin E, et al. Phase 3 Trial of (177)Lu-Dotatate for Midgut Neuroendocrine Tumors. *N Engl J Med*. 2017;376(2):125-135. doi:10.1056/NEJMoa1607427

55. Strosberg JR, Caplin ME, Kunz PL, et al. (177)Lu-Dotatate plus long-acting octreotide versus high-dose long-acting octreotide in patients with midgut neuroendocrine tumours (NETTER-1): final overall survival and long-term safety results from an open-label, randomised, controlled, phase 3 trial. *Lancet Oncol*. 2021;22(12):1752-1763. doi:10.1016/S1470-2045(21)00572-6

56. Mirian C, Duun-Henriksen AK, Maier A, et al. Somatostatin Receptor-Targeted Radiopeptide Therapy in Treatment-Refractory Meningioma: Individual Patient Data Meta-analysis. *J Nucl Med*. 2021;62(4):507-513. doi:10.2967/jnumed.120.249607

57. Minczeles NS, Bos EM, de Leeuw RC, et al. Efficacy and safety of peptide receptor radionuclide therapy with [(177)Lu]Lu-DOTA-TATE in 15 patients with progressive treatment-refractory meningioma. *Eur J Nucl Med Mol Imaging*. 2023;50(4):1195-1204. doi:10.1007/s00259-022-06044-9

58. Kurz SC, Zan E, Cordova C, et al. Evaluation of the SSTR2-targeted Radiopharmaceutical 177Lu-DOTATATE and SSTR2-specific 68Ga-DOTATATE PET as Imaging Biomarker in Patients with Intracranial Meningioma. *Clin Cancer Res*. 2024;30(4):680-686. doi:10.1158/1078-0432.CCR-23-2533

59. Seystahl K, Stoecklein V, Schüller U, et al. Somatostatin receptor-targeted radionuclide therapy for progressive meningioma: benefit linked to 68Ga-DOTATATE/-TOC uptake. *Neuro Oncol*. 2016;18(11):1538-1547. doi:10.1093/neuonc/now060

60. Caplin ME, Pavel M, Ćwikła JB, et al. Lanreotide in metastatic enteropancreatic neuroendocrine tumors. *N Engl J Med*. 2014;371(3):224-233. doi:10.1056/NEJMoa1316158

61. Rinke A, Müller HH, Schade-Brittinger C, et al. Placebo-controlled, double-blind, prospective, randomized study on the effect of octreotide LAR in the control of tumor growth in patients with metastatic neuroendocrine midgut tumors: a report from the

PROMID Study Group. *J Clin Oncol*. 2009;27(28):4656-4663. doi:10.1200/JCO.2009.22.8510

62. Norden AD, Ligon KL, Hammond SN, et al. Phase II study of monthly pasireotide LAR (SOM230C) for recurrent or progressive meningioma. *Neurology*. 2015;84(3):280-286. doi:10.1212/WNL.0000000000001153

63. Jensen LR, Maier AD, Lomstein A, et al. Somatostatin analogues in treatment-refractory meningioma: a systematic review with meta-analysis of individual patient data. *Neurosurg Rev*. 2022;45(5):3067-3081. doi:10.1007/s10143-022-01849-6

64. Clark VE, Erson-Omay EZ, Serin A, et al. Genomic analysis of non-NF2 meningiomas reveals mutations in TRAF7, KLF4, AKT1, and SMO. *Science*. 2013;339(6123):1077-1080. doi:10.1126/science.1233009

65. Brastianos PK, Horowitz PM, Santagata S, et al. Genomic sequencing of meningiomas identifies oncogenic SMO and AKT1 mutations. *Nat Genet*. 2013;45(3):285-289. doi:10.1038/ng.2526

66. Sahm F, Bissel J, Koelsche C, et al. AKT1E17K mutations cluster with meningothelial and transitional meningiomas and can be detected by SFRP1 immunohistochemistry. *Acta Neuropathol*. 2013;126(5):757-762. doi:10.1007/s00401-013-1187-5

67. Bleeker FE, Felicioni L, Buttitta F, et al. AKT1(E17K) in human solid tumours. *Oncogene*. 2008;27(42):5648-5650. doi:10.1038/onc.2008.170

68. Carpten JD, Faber AL, Horn C, et al. A transforming mutation in the pleckstrin homology domain of AKT1 in cancer. *Nature*. 2007;448(7152):439-444. doi:10.1038/nature05933

69. Turner NC, Oliveira M, Howell SJ, et al. Capivasertib in Hormone Receptor-Positive Advanced Breast Cancer. *N Engl J Med*. 2023;388(22):2058-2070. doi:10.1056/NEJMoa2214131

70. Hyman DM, Smyth LM, Donoghue MTA, et al. AKT Inhibition in Solid Tumors With AKT1 Mutations. *J Clin Oncol*. 2017;35(20):2251-2259. doi:10.1200/JCO.2017.73.0143

71. Weller M, Roth P, Sahm F, et al. Durable Control of Metastatic AKT1-Mutant WHO Grade 1 Meningothelial Meningioma by the AKT Inhibitor, AZD5363. *J Natl Cancer Inst*. 2017;109(3):1-4. doi:10.1093/jnci/djw320

72. Sekulic A, Migden MR, Oro AE, et al. Efficacy and safety of vismodegib in advanced basal-cell carcinoma. *N Engl J Med*. 2012;366(23):2171-2179. doi:10.1056/NEJMoa1113713

73. Sekulic A, Migden MR, Lewis K, et al. Pivotal ERIVANCE basal cell carcinoma (BCC) study: 12-month update of efficacy and safety of vismodegib in advanced BCC. *J Am Acad Dermatol*. 2015;72(6):1021-1026.e8. doi:10.1016/j.jaad.2015.03.021

74. Tsao AS, Song Z, Ho AL, et al. Phase II study of vismodegib in patients with SMO or PTCH1 mutated tumors: Results from NCI-MATCH ECOG-ACRIN Trial (EAY131) Subprotocol T. *J Clin Oncol*. 2022;40.

75. Sievers P, Hielscher T, Schrimpf D, et al. CDKN2A/B homozygous deletion is associated with early recurrence in meningiomas. *Acta Neuropathol*. 2020;140(3):409-413. doi:10.1007/s00401-020-02188-w

76. Wang JZ, Patil V, Liu J, et al. Increased mRNA expression of CDKN2A is a transcriptomic marker of clinically aggressive meningiomas. *Acta Neuropathol*. 2023;146(1):145-162. doi:10.1007/s00401-023-02571-3

77. Jing J, Wu Z, Wang J, et al. Hedgehog signaling in tissue homeostasis, cancers, and targeted therapies. *Signal Transduct Target Ther*. 2023;8(1):315. doi:10.1038/s41392-023-01559-5

78. Dubourg C, Carré W, Hamdi-Rozé H, et al. Mutational Spectrum in Holoprosencephaly Shows That FGF is a New Major Signaling Pathway. *Hum Mutat*. 2016;37(12):1329-1339. doi:10.1002/humu.23038

79. De Mori R, Romani M, D'Arrigo S, et al. Hypomorphic Recessive Variants in SUFU Impair the Sonic Hedgehog Pathway and Cause Joubert Syndrome with Cranio-facial and Skeletal Defects. *Am J Hum Genet*. 2017;101(4):552-563. doi:10.1016/j.ajhg.2017.08.017

80. Pastorino L, Ghiorzo P, Nasti S, et al. Identification of a SUFU germline mutation in a family with Gorlin syndrome. *Am J Med Genet A*. 2009;149A(7):1539-1543. doi:10.1002/ajmg.a.32944

81. Chen Y, Zhang H, Zhao Y, Ma J. Congenital medulloblastoma in two brothers with SUFU-mutated Gorlin-Goltz syndrome: Case reports and literature review. *Front Oncol*. 2022;12:988798. doi:10.3389/fonc.2022.988798

82. Kijima C, Miyashita T, Suzuki M, Oka H, Fujii K. Two cases of nevoid basal cell carcinoma syndrome associated with meningioma caused by a PTCH1 or SUFU germline mutation. *Fam Cancer*. 2012;11(4):565-570. doi:10.1007/s10689-012-9548-0

83. Aavikko M, Li SP, Saarinen S, et al. Loss of SUFU function in familial multiple meningioma. *Am J Hum Genet*. 2012;91(3):520-526. doi:10.1016/j.ajhg.2012.07.015

84. Askaner G, Lei U, Bertelsen B, Venzo A, Wadt K. Novel SUFU Frameshift Variant Leading to Meningioma in Three Generations in a Family with Gorlin Syndrome. *Case Rep Genet*. 2019;2019:9650184. doi:10.1155/2019/9650184

85. Clark VE, Harmancı AS, Bai H, et al. Recurrent somatic mutations in POLR2A define a distinct subset of meningiomas. *Nat Genet*. 2016;48(10):1253-1259. doi:10.1038/ng.3651

86. Mawrin C, Koch R, Waldt N, et al. A new amplicon-based gene panel for next generation sequencing characterization of meningiomas. *Brain Pathology*. 2022;32(2):e13046. doi:10.1111/bpa.13046

87. Williams EA, Santagata S, Wakimoto H, et al. Distinct genomic subclasses of high-grade/progressive meningiomas: NF2-associated, NF2-exclusive, and NF2-agnostic. *Acta Neuropathol Commun*. 2020;8(1):171. doi:10.1186/s40478-020-01040-2

88. Clark VE, Erson-Omay EZ, Serin A, et al. Genomic Analysis of Non-NF2 Meningiomas Reveals Mutations in TRAF7, KLF4, AKT1, and SMO. *Science*. 2013;339(6123):1077-1080. doi:10.1126/science.1233009

89. Brastianos PK, Horowitz PM, Santagata S, et al. Genomic sequencing of meningiomas identifies oncogenic SMO and AKT1 mutations. *Nature Genetics*. 2013;45(3):285-289. doi:10.1038/ng.2526

90. Kool M, Jones DTW, Jäger N, et al. Genome sequencing of SHH medulloblastoma predicts genotype-related response to smoothened inhibition. *Cancer Cell*. 2014;25(3):393-405. doi:10.1016/j.ccr.2014.02.004

91. Robinson GW, Orr BA, Wu G, et al. Vismodegib Exerts Targeted Efficacy Against Recurrent Sonic Hedgehog-Subgroup Medulloblastoma: Results From Phase II Pediatric Brain Tumor Consortium Studies PBTC-025B and PBTC-032. *J Clin Oncol*. 2015;33(24):2646-2654. doi:10.1200/JCO.2014.60.1591

92. Lospinoso Severini L, Ghirga F, Bufalieri F, Quaglio D, Infante P, Di Marcotullio L. The SHH/GLI signaling pathway: a therapeutic target for medulloblastoma. *Expert Opin Ther Targets*. 2020;24(11):1159-1181. doi:10.1080/14728222.2020.1823967

93. Lauth M, Bergström A, Shimokawa T, Toftgård R. Inhibition of GLI-mediated transcription and tumor cell growth by small-molecule antagonists. *Proc Natl Acad Sci U S A*. 2007;104(20):8455-8460. doi:10.1073/pnas.0609699104

94. Wickström M, Dyberg C, Shimokawa T, et al. Targeting the hedgehog signal transduction pathway at the level of GLI inhibits neuroblastoma cell growth in vitro and in vivo. *Int J Cancer*. 2013;132(7):1516-1524. doi:10.1002/ijc.27820

95. Kim J, Aftab BT, Tang JY, et al. Itraconazole and arsenic trioxide inhibit Hedgehog pathway activation and tumor growth associated with acquired resistance to smoothened antagonists. *Cancer Cell*. 2013;23(1):23-34. doi:10.1016/j.ccr.2012.11.017

96. Beauchamp EM, Ringer L, Bulut G, et al. Arsenic trioxide inhibits human cancer cell growth and tumor development in mice by blocking Hedgehog/GLI pathway. *J Clin Invest*. 2011;121(1):148-160. doi:10.1172/JCI42874

97. Li XY, Zhou LF, Gao LJ, et al. Cynanbungeigenin C and D, a pair of novel epimers from Cynanchum bungei, suppress hedgehog pathway-dependent medulloblastoma by blocking signaling at the level of Gli. *Cancer Lett*. 2018;420:195-207. doi:10.1016/j.canlet.2018.02.005

98. Infante P, Mori M, Alfonsi R, et al. Gli1/DNA interaction is a druggable target for Hedgehog-dependent tumors. *EMBO J*. 2015;34(2):200-217. doi:10.15252/embj.201489213

99. Berardozzi S, Bernardi F, Infante P, et al. Synergistic inhibition of the Hedgehog pathway by newly designed Smo and Gli antagonists bearing the isoflavone scaffold. *Eur J Med Chem*. 2018;156:554-562. doi:10.1016/j.ejmech.2018.07.017

100. Hyman JM, Firestone AJ, Heine VM, et al. Small-molecule inhibitors reveal multiple strategies for Hedgehog pathway blockade. *Proc Natl Acad Sci U S A*. 2009;106(33):14132-14137. doi:10.1073/pnas.0907134106

101. Manetti F, Stecca B, Santini R, et al. Pharmacophore-Based Virtual Screening for Identification of Negative Modulators of GLI1 as Potential Anticancer Agents. *ACS Med Chem Lett*. 2020;11(5):832-838. doi:10.1021/acsmedchemlett.9b00639

102. Maresca L, Crivaro E, Migliorini F, et al. Targeting GLI1 and GLI2 with small molecule inhibitors to suppress GLI-dependent transcription and tumor growth. *Pharmacol Res*. 2023;195:106858. doi:10.1016/j.phrs.2023.106858

103. Zou X, Tang XY, Qu ZY, et al. Targeting the PDGF/PDGFR signaling pathway for cancer therapy: A review. *Int J Biol Macromol*. 2022;202:539-557. doi:10.1016/j.ijbiomac.2022.01.113

104. Hermanson M, Funa K, Hartman M, et al. Platelet-derived growth factor and its receptors in human glioma tissue: expression of messenger RNA and protein suggests the presence of autocrine and paracrine loops. *Cancer Res*. 1992;52(11):3213-3219.

105. Kirsch M, Wilson JC, Black P. Platelet-derived growth factor in human brain tumors. *J Neurooncol*. 1997;35(3):289-301. doi:10.1023/a:1005872718547

106. Todo T, Adams EF, Fahlbusch R, Dingermann T, Werner H. Autocrine growth stimulation of human meningioma cells by platelet-derived growth factor. *J Neurosurg*. 1996;84(5):852-859. doi:10.3171/jns.1996.84.5.0852

107. Wen PY, Yung WKA, Lamborn KR, et al. Phase II study of imatinib mesylate for recurrent meningiomas (North American Brain Tumor Consortium study 01-08). *Neuro Oncol*. 2009;11(6):853-860. doi:10.1215/15228517-2009-010

108. Kaley TJ, Wen P, Schiff D, et al. Phase II trial of sunitinib for recurrent and progressive atypical and anaplastic meningioma. *Neuro Oncol*. 2015;17(1):116-121. doi:10.1093/neuonc/nou148

109. Nassiri F, Liu J, Patil V, et al. A clinically applicable integrative molecular classification of meningiomas. *Nature*. 2021;597(7874):119-125. doi:10.1038/s41586-021-03850-3

110. Bi WL, Greenwald NF, Abedalthagafi M, et al. Genomic landscape of high-grade meningiomas. *npj Genomic Medicine*. 2017;2(1):15. doi:10.1038/s41525-017-0014-7

111. Loibl S, André F, Bachelot T, et al. Early breast cancer: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up. *Ann Oncol*. 2024;35(2):159-182. doi:10.1016/j.annonc.2023.11.016

112. Gennari A, André F, Barrios CH, et al. ESMO Clinical Practice Guideline for the diagnosis, staging and treatment of patients with metastatic breast cancer. *Ann Oncol*. 2021;32(12):1475-1495. doi:10.1016/j.annonc.2021.09.019

113. Ji Y, Rankin C, Grunberg S, et al. Double-Blind Phase III Randomized Trial of the Antiprogestin Agent Mifepristone in the Treatment of Unresectable Meningioma: SWOG S9005. *J Clin Oncol*. 2015;33(34):4093-4098. doi:10.1200/JCO.2015.61.6490

114. Peyre M, Gaillard S, de Marcellus C, et al. Progestin-associated shift of meningioma mutational landscape. *Ann Oncol*. 2018;29(3):681-686. doi:10.1093/annonc/mdx763

115. Nguyen P, Roland N, Neumann A, et al. Prolonged use of nomegestrol acetate and risk of intracranial meningioma: a population-based cohort study. *Lancet Reg Health Eur*. 2024;42:100928. doi:10.1016/j.lanepe.2024.100928

116. Tauziede-Espariat A, Parfait B, Besnard A, et al. Loss of SMARCE1 expression is a specific diagnostic marker of clear cell meningioma: a comprehensive immunophenotypical and molecular analysis. *Brain Pathol*. 2018;28(4):466-474. doi:10.1111/bpa.12524

117. Sievers P, Sill M, Blume C, et al. Clear cell meningiomas are defined by a highly distinct DNA methylation profile and mutations in SMARCE1. *Acta Neuropathol*. 2021;141(2):281-290. doi:10.1007/s00401-020-02247-2

118. Kadoch C, Hargreaves DC, Hodges C, et al. Proteomic and bioinformatic analysis of mammalian SWI/SNF complexes identifies extensive roles in human malignancy. *Nat Genet*. 2013;45(6):592-601. doi:10.1038/ng.2628

119. Mashtalir N, D'Avino AR, Michel BC, et al. Modular Organization and Assembly of SWI/SNF Family Chromatin Remodeling Complexes. *Cell*. 2018;175(5):1272-1288.e20. doi:10.1016/j.cell.2018.09.032

120. Mashtalir N, Suzuki H, Farrell DP, et al. A Structural Model of the Endogenous Human BAF Complex Informs Disease Mechanisms. *Cell*. 2020;183(3):802-817.e24. doi:10.1016/j.cell.2020.09.051

121. St Pierre R, Collings CK, Samé Guerra DD, et al. SMARCE1 deficiency generates a targetable mSWI/SNF dependency in clear cell meningioma. *Nat Genet*. 2022;54(6):861-873. doi:10.1038/s41588-022-01077-0

122. Takahashi K, Yamanaka S. Induction of pluripotent stem cells from mouse embryonic and adult fibroblast cultures by defined factors. *Cell*. 2006;126(4):663-676. doi:10.1016/j.cell.2006.07.024

123. Wang Y, Yang C, Gu Q, et al. KLF4 Promotes Angiogenesis by Activating VEGF Signaling in Human Retinal Microvascular Endothelial Cells. *PLoS One*. 2015;10(6):e0130341. doi:10.1371/journal.pone.0130341

124. Rowland BD, Bernards R, Peeper DS. The KLF4 tumour suppressor is a transcriptional repressor of p53 that acts as a context-dependent oncogene. *Nat Cell Biol*. 2005;7(11):1074-1082. doi:10.1038/ncb1314

125. von Spreckelsen N, Waldt N, Poetschke R, et al. KLF4(K409Q)-mutated meningiomas show enhanced hypoxia signaling and respond to mTORC1 inhibitor treatment. *Acta Neuropathol Commun*. 2020;8(1):41. doi:10.1186/s40478-020-00912-x

126. von Spreckelsen N, Waldt N, Timmer M, et al. Clinical Characteristics and Magnetic Resonance Imaging-Based Prediction of the KLF4(K409Q) Mutation in Meningioma. *World Neurosurg*. 2021;154:e665-e670. doi:10.1016/j.wneu.2021.07.119

127. Tsytsykova AV, Wiley G, Li C, et al. Mutated KLF4(K409Q) in meningioma binds STRs and activates FGF3 gene expression. *iScience*. 2022;25(8):104839. doi:10.1016/j.isci.2022.104839

128. Reuss DE, Piro RM, Jones DTW, et al. Secretory meningiomas are defined by combined KLF4 K409Q and TRAF7 mutations. *Acta Neuropathol*. 2013;125(3):351-358. doi:10.1007/s00401-013-1093-x

129. Mawrin C, Koch R, Waldt N, et al. A new amplicon-based gene panel for next generation sequencing characterization of meningiomas. *Brain Pathol*. 2022;32(2):e13046. doi:10.1111/bpa.13046

130. Youngblood MW, Miyagishima DF, Jin L, et al. Associations of meningioma molecular subgroup and tumor recurrence. *Neuro Oncol*. 2021;23(5):783-794. doi:10.1093/neuonc/noaa226

131. Sahm F, Schrimpf D, Olar A, et al. TERT Promoter Mutations and Risk of Recurrence in Meningioma. *Journal of the National Cancer Institute*. 2016;108(5):1-4. doi:10.1093/jnci/djv377

132. Spiegl-Kreinecker S, Lötsch D, Neumayer K, et al. TERT promoter mutations are associated with poor prognosis and cell immortalization in meningioma. *Neuro Oncol*. 2018;20(12):1584-1593. doi:10.1093/neuonc/noy104

133. Pérez-Gutiérrez L, Ferrara N. Biology and therapeutic targeting of vascular endothelial growth factor A. *Nat Rev Mol Cell Biol*. 2023;24(11):816-834. doi:10.1038/s41580-023-00631-w

134. Preusser M, Hassler M, Birner P, et al. Microvascularization and expression of VEGF and its receptors in recurring meningiomas: pathobiological data in favor of anti-angiogenic therapy approaches. *Clin Neuropathol*. 2012;31(5):352-360. doi:10.5414/NP300488

135. Fiani B, Jarrah R, Bhandarkar AR, et al. Peritumoral edema in meningiomas: pathophysiology, predictors, and principles for treatment. *Clin Transl Oncol*. 2023;25(4):866-872. doi:10.1007/s12094-022-03009-0

136. Dasanu CA, Alvarez-Argote J, Limonadi FM, Codreanu I. Bevacizumab in refractory higher-grade and atypical meningioma: the current state of affairs. *Expert Opin Biol Ther*. 2019;19(2):99-104. doi:10.1080/14712598.2019.1559292

137. Alanin MC, Klausen C, Caye-Thomasen P, et al. Effect of bevacizumab on intracranial meningiomas in patients with neurofibromatosis type 2 - a retrospective case series. *Int J Neurosci*. 2016;126(11):1002-1006. doi:10.3109/00207454.2015.1092443

138. Nunes FP, Merker VL, Jennings D, et al. Bevacizumab treatment for meningiomas in NF2: a retrospective analysis of 15 patients. *PLoS One*. 2013;8(3):e59941. doi:10.1371/journal.pone.0059941

139. Nayak L, Iwamoto FM, Rudnick JD, et al. Atypical and anaplastic meningiomas treated with bevacizumab. *J Neurooncol*. 2012;109(1):187-193. doi:10.1007/s11060-012-0886-4

140. Alexander AY, Onyedimma C, Bhandarkar AR, et al. The role of bevacizumab for treatment-refractory intracranial meningiomas: a single institution's experience and a systematic review of the literature. *Acta Neurochir*. 2022;164(11):3011-3023. doi:10.1007/s00701-022-05348-x

141. Franke AJ, Skelton WPIV, Woody LE, et al. Role of bevacizumab for treatment-refractory meningiomas: A systematic analysis and literature review. *Surg Neurol Int*. 2018;9:133. doi:10.4103/sni.sni_264_17

142. Erratum: This is a corrigendum to: Kumthekar et al, A multi-institutional phase II trial of bevacizumab for recurrent and refractory meningioma, Neuro-Oncology Advances, Volume 4, Issue 1, January-December 2022, vdac123, https://doi.org/10.1093/noajnl/vdac123. *Neurooncol Adv*. 2023;5(1):vdad103. doi:10.1093/noajnl/vdad103

143. Shih KC, Chowdhary S, Rosenblatt P, et al. A phase II trial of bevacizumab and everolimus as treatment for patients with refractory, progressive intracranial meningioma. *J Neurooncol*. 2016;129(2):281-288. doi:10.1007/s11060-016-2172-3

144. Kotecha R, Tonse R, Appel H, et al. Regression of Intracranial Meningiomas Following Treatment with Cabozantinib. *Surg Neurol Int*. 2021;28(2):1537-1543. doi:10.3390/curroncol28020145

145. Li JJ, Lee CS. The Role of the AT-Rich Interaction Domain 1A Gene (ARID1A) in Human Carcinogenesis. *Genes*. 2024;15(1):5. doi:10.3390/genes15010005

146. Chaluts D, Dullea JT, Ali M, et al. ARID1A mutation associated with recurrence and shorter progression-free survival in atypical meningiomas. *J Cancer Res Clin Oncol*. 2023;149(8):5165-5172. doi:10.1007/s00432-022-04442-y

147. Miller RE, Leary A, Scott CL, et al. ESMO recommendations on predictive biomarker testing for homologous recombination deficiency and PARP inhibitor benefit in ovarian cancer. *Ann Oncol*. 2020;31(12):1606-1622. doi:10.1016/j.annonc.2020.08.2102

148. González-Martín A, Harter P, Leary A, et al. Newly diagnosed and relapsed epithelial ovarian cancer: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up. *Ann Oncol*. 2023;34(10):833-848. doi:10.1016/j.annonc.2023.07.011

149. Paramasivam N, Hübschmann D, Toprak UH, et al. Mutational patterns and regulatory networks in epigenetic subgroups of meningioma. *Acta Neuropathol*. 2019;138(2):295-308. doi:10.1007/s00401-019-02008-w

150. Dogan H, Blume C, Patel A, et al. Single-cell DNA sequencing reveals order of mutational acquisition in TRAF7/AKT1 and TRAF7/KLF4 mutant meningiomas. *Acta Neuropathol*. 2022;144(4):799-802. doi:10.1007/s00401-022-02485-6

151. Boetto J, Plu I, Ducos Y, et al. Normal meninges harbor oncogenic somatic mutations in meningioma-driver genes. *Acta Neuropathol*. 2023;146(6):833-835. doi:10.1007/s00401-023-02635-4

152. Kirches E, Sahm F, Korshunov A, et al. Molecular profiling of pediatric meningiomas shows tumor characteristics distinct from adult meningiomas. *Acta Neuropathol*. 2021;142(5):873-886. doi:10.1007/s00401-021-02351-x

153. Castilla-Vallmanya L, Selmer KK, Dimartino C, et al. Phenotypic spectrum and transcriptomic profile associated with germline variants in TRAF7. *Genet Med*. 2020;22(7):1215-1226. doi:10.1038/s41436-020-0792-7

154. Mishra-Gorur K, Barak T, Kaulen LD, et al. Pleiotropic role of TRAF7 in skull-base meningiomas and congenital heart disease. *Proc Natl Acad Sci U S A*. 2023;120(16):e2214997120. doi:10.1073/pnas.2214997120

155. Najm P, Zhao P, Steklov M, et al. Loss-of-Function Mutations in TRAF7 and KLF4 Cooperatively Activate RAS-Like GTPase Signaling and Promote Meningioma Development. *Cancer Res*. 2021;81(16):4218-4229. doi:10.1158/0008-5472.CAN-20-3669

156. Zang KD, Singer H. Chromosomal consitution of meningiomas. *Nature*. 1967;216(5110):84-85. doi:10.1038/216084a0

157. Driver J, Hoffman SE, Tavakol S, et al. A molecularly integrated grade for meningioma. *Neuro Oncol*. 2021;24(5):796-808. doi:10.1093/neuonc/noab213

158. Magill ST, Vasudevan HN, Seo K, et al. Multiplatform genomic profiling and magnetic resonance imaging identify mechanisms underlying intratumor heterogeneity in meningioma. *Nat Commun*. 2020;11(1):4803. doi:10.1038/s41467-020-18582-7

159. Domingues PH, Sousa P, Otero Á, et al. Proposal for a new risk stratification classification for meningioma based on patient age, WHO tumor grade, size, localization, and karyotype. *Neuro Oncol*. 2014;16(5):735-747. doi:10.1093/neuonc/not325

160. Ketter R, Urbschat S, Henn W, et al. Application of oncogenetic trees mixtures as a biostatistical model of the clonal cytogenetic evolution of meningiomas. *Int J Cancer*. 2007;121(7):1473-1480. doi:10.1002/ijc.22855

161. Maas SLN, Sievers P, Weber DC, et al. Independent prognostic impact of DNA methylation class and chromosome 1p loss in WHO grade 2 and 3 meningioma undergoing adjuvant high-dose radiotherapy: comprehensive molecular analysis of EORTC 22042-26042. *Acta Neuropathol*. 2023;146(6):837-840. doi:10.1007/s00401-023-02642-5

162. Nassiri F, Mamatjan Y, Suppiah S, et al. DNA methylation profiling to predict recurrence risk in meningioma: development and validation of a nomogram to optimize clinical management. *Neuro Oncol*. 2019;21(7):901-910. doi:10.1093/neuonc/noz061

163. Choudhury A, Magill ST, Eaton CD, et al. Meningioma DNA methylation groups identify biological drivers and therapeutic vulnerabilities. *Nat Genet*. 2022;54(5):649-659. doi:10.1038/s41588-022-01061-8

164. Choudhury A, Chen WC, Lucas CHG, et al. Hypermitotic meningiomas harbor DNA methylation subgroups with distinct biological and clinical features. *Neuro Oncol*. 2023;25(3):520-530. doi:10.1093/neuonc/noac224

165. Bayley JC, Hadley CC, Harmanci AO, Harmanci AS, Klisch TJ, Patel AJ. Multiple approaches converge on three biological subtypes of meningioma and extract new insights from published studies. *Sci Adv*. 2022;8(5):eabm6247. doi:10.1126/sciadv.abm6247

166. Nassiri F, Liu J, Patil V, et al. A clinically applicable integrative molecular classification of meningiomas. *Nature*. 2021;597(7874):119-125. doi:10.1038/s41586-021-03850-3

167. Bayley JC, Hadley CC, Harmanci AO, Harmanci AS, Klisch TJ, Patel AJ. Multiple approaches converge on three biological subtypes of meningioma and extract new insights from published studies. *Sci Adv*. 2022;8(5):eabm6247. doi:10.1126/sciadv.abm6247

168. Choudhury A, Magill ST, Eaton CD, et al. Meningioma DNA methylation groups identify biological drivers and therapeutic vulnerabilities. *Nat Genet*. 2022;54(5):649-659. doi:10.1038/s41588-022-01061-8

169. Olar A, Wani KM, Wilson CD, et al. Global epigenetic profiling identifies methylation subgroups associated with recurrence-free survival in meningioma. *Acta Neuropathologica*. 2017;133(3):431-444. doi:10.1007/s00401-017-1678-x

170. Olar A, Goodman LD, Wani KM, et al. A gene expression signature predicts recurrence-free survival in meningioma. *Oncotarget*. 2018;9(22):16087-16098. doi:10.18632/oncotarget.24498

171. Chen WC, Vasudevan HN, Choudhury A, et al. A Prognostic Gene-Expression Signature and Risk Score for Meningioma Recurrence After Resection. *Neurosurgery*. 2021;88(1). https://journals.lww.com/neurosurgery/fulltext/2021/01000/a_prognostic_gene_expression_signature_and_risk.22.aspx

172. Chen WC, Magill ST, Wu A, et al. Histopathological features predictive of local control of atypical meningioma after surgery and adjuvant radiotherapy. *J Neurosurg*. Published online 2018:1-8. doi:10.3171/2017.9.JNS171609

173. Chen WC, Choudhury A, Youngblood MW, et al. Targeted gene expression profiling predicts meningioma outcomes and radiotherapy responses. *Nat Med*. 2023;29(12):3067-3076. doi:10.1038/s41591-023-02586-z

174. Youngblood MW, Duran D, Montejo JD, et al. Correlations between genomic subgroup and clinical features in a cohort of more than 3000 meningiomas. *J Neurosurg*. 2019;133(5):1345-1354. doi:10.3171/2019.8.JNS191266

175. Patel AJ, Wan YW, Al-Ouran R, et al. Molecular profiling predicts meningioma recurrence and reveals loss of DREAM complex repression in aggressive tumors. *Proc Natl Acad Sci U S A*. 2019;116(43):21715-21726. doi:10.1073/pnas.1912858116

176. Vaubel RA, Kumar R, Weiskittel TM, et al. Genomic markers of recurrence risk in atypical meningioma following gross total resection. *Neurooncol Adv*. 2023;5(1):vdad004. doi:10.1093/noajnl/vdad004

177. Wang JZ, Patil V, Landry AP, et al. Molecular classification to refine surgical and radiotherapeutic decision-making in meningioma. *Nat Med*. Published online August 21, 2024. doi:10.1038/s41591-024-03167-4

Figure captions

Figure 1. Overview on frequency and ESCAT score of molecular targets found in meningiomas. Numbers as found in literature. ARID1A = AT-rich binding domain protein 1A; BAP1 = BRCA1-associated protein 1; CDK4/6 = cyclin-dependent kinase 4/6; CDKN2A/B cyclin-dependent kinase inhibitor 2A/B; ESCAT = European Society for Medical Oncology Clinical Actionability of molecular Targets; KLF4 = Krüppel-like factor 4; mTOR = mammalian target of rapamycin; NF2 = neurofibromin 2/schwannomin; PD-L1 = programmed cell death ligand 1; PDGFR = platelet-derived growth factor receptor; PIK3CA = Phosphatidylinositol 3-kinase, catalytic subunit alpha; SMARCE1 = SWI/SNF related, matrix associated, actin dependent regulator of chromatin E1; SMO = smoothened; SSTR = somatostatin receptor; SUFU = suppressor of fused homolog; TERT = telomerase reverse transcriptase; TRAF7 = TNF receptor associated factor 7; VEGF(R) = vascular endothelial growth factor (receptor).

Tables

Table 1. European Society for Medical Oncology (ESMO) Scale for Clinical Actionability of molecular Targets (ESCAT). [21] Reprinted with permission.

	ESCAT evidence tier	Required level of evidence	Clinical value class	Clinical implication
Ready for routine use	I: Alteration-drug match is associated with improved outcome in clinical trials	IA: prospective, randomized clinical trials show the alteration-drug match in a specific tumor type results in a clinically meaningful improvement of a survival endpoint IB: prospective, non-randomized clinical trials show that the alteration-drug match in a specific tumor type, results in clinically meaningful benefit as defined by ESMO MCBS 1.1 C: clinical trials across tumor types or basket clinical trials show clinical benefits associated with the alteration-drug match, with similar benefits observed across tumor types	Drug administered to patients with the specific molecular alteration has led to improved clinical outcome in prospective clinical trial(s)	Access to the treatment should be considered standard of care
Investigational	II: alteration-drug match is associated with antitumor activity, but the	IIA: retrospective studies show patients with the specific alteration in a specific tumor type experience clinically meaningful benefit with the	Drug administered to a molecularly defined patient population is likely to result	Treatment to be considered "preferable" in the context of evidence collection either as a

	magnitude of benefit is unknown	matched drug compared with alteration-negative patients IIB: prospective clinical trial(s) show the alteration-drug match in a specific tumor type results in increased responsiveness when treated with a matched drug, however, no data currently available on survival endpoints	in clinical benefit in a given tumor type, but additional data are needed	prospective registry or as a prospective clinical trial
Hypothetical target	III: alteration-drug match suspected to improve outcome based on clinical trial data in other tumor type(s) or with similar molecular alteration	IIIA: clinical benefit demonstrated in patients with the specific alteration (as tiers I and II above) but in a different tumor type. Limited/ absence of clinical evidence available for the patient-specific cancer type or broadly across cancer types IIIB: an alteration that has a similar predicted functional impact as an already studied tier I abnormality in the same gene or pathway, but does not have associated supportive clinical data	Drug previously shown to benefit the molecularly defined subset in another tumor type (or with a different mutation in the same gene), efficacy, therefore, is anticipated for but not proved	Clinical trials to be discussed with patients
	IV: preclinical evidence of actionability	IVA: evidence that the alteration or a functionally similar alteration influences drug sensitivity in preclinical in vitro or in vivo models	Actionability is predicted based on preclinical studies, no conclusive	Treatment should “only be considered” in the context of early clinical trials. Lack of clinical data

		IVB: actionability predicted in silico	clinical data are available	should be stressed to patients
Combination development	V: alteration-drug match is associated with objective response, but without clinically meaningful benefit	Prospective studies show that targeted therapy is associated with objective responses, but this does not lead to improved outcome	Drug is active but does not prolong PFS or OS, probably in part due to mechanisms of adaptation	Clinical trials assessing drug combination strategies could be considered
	X: lack of evidence for actionability	No evidence that the genomic alteration is therapeutically actionable	There is no evidence, clinical or preclinical, that a genomic alteration is a potential therapeutic target	The finding should not be taken into account for clinical decision

Figure 1