

## European Association of Neuro-Oncology guideline on molecular testing of meningiomas for targeted therapy selection

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### 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 a 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, VEGF(R), PDGFR, as well as homologous recombination deficiency, 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.

### Keywords

meningioma | predictive marker | targeted therapy

Meningiomas are the most common intracranial tumors of adults and constitute approximately 40% of all primary central nervous system (CNS) tumors.<sup>1</sup> 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).<sup>2</sup> 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.<sup>3</sup> Postoperative radiotherapy may be considered based on the extent of resection and histological grade. For progressive or recurrent meningioma, local

therapies (ie, 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 standards.<sup>3-6</sup>

Extensive molecular profiling efforts of meningiomas have led to the identification of multiple recurring aberrations and patterns on the genetic, epigenetic, transcriptomic, and protein levels.<sup>7,8</sup> These alterations can be relevant to identifying 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.<sup>5,6</sup> 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.<sup>9</sup> 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.<sup>10</sup> 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.<sup>9</sup> 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.<sup>10</sup>

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.<sup>11,12</sup> Identification of these areas

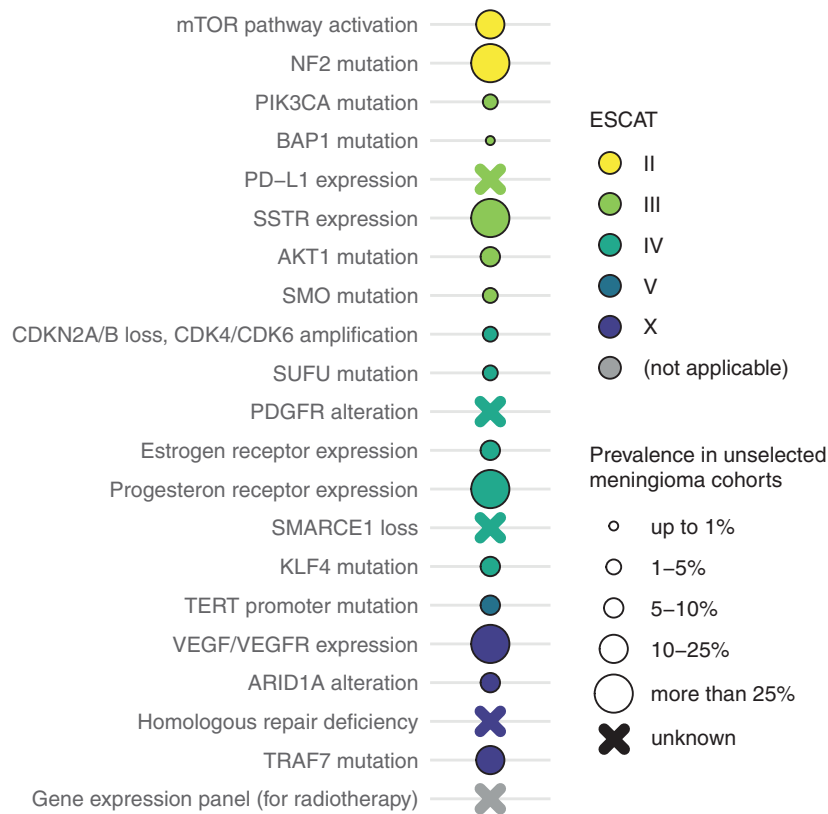
should be guided by morphology (cell density, prominent nuclei, high nucleus/cytoplasm ratio, and mitotic count), supported by immunohistochemistry (Ki-67, pHH3). This selection is suggested on the understanding that the more aggressive areas will determine the outcome. Morphological evaluation, and 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.<sup>13</sup> 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,<sup>14</sup> 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] vs 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 otherwise determined target regions that were interrogated by the test or a reference where to find 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.<sup>15</sup> 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 (eg, retention of the kinase domain in a tyrosine kinase receptor) should be checked before reporting the presence of a gene fusion.<sup>14,16</sup>

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 the quality of bisulfite conversion, classifier version(s) used, highest scoring methylation category/categories with the respective calibrated score(s), and subclassification 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 (eg, sequencing).<sup>14</sup>

Integrated inspection of morphology, NGS, and/or methylation data is essential to assess the molecular data in the context of tumor cell content. Typically, this is not a similar challenge in meningioma tissue as, for example, in diffuse glioma. Yet, low fractions of canonical, presumably early mutations (*NF2*, *AKT1*, *TRAF7*, *SMO*) or low amplitudes of



**Figure 1.** Overview of the frequency and ESCAT score of molecular targets found in meningiomas. Numbers as found in the 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).

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 a description of potential heterogeneity, which controls were used and evaluated, and optimal information on the applied clone.<sup>17</sup>

## Attributing Pathogenic Significance to Findings

Estimating and attributing the pathogenic 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.<sup>15,18</sup> For instance, a variant with a relatively high germline frequency is unlikely to be pathogenic, while an exon-located missense variant resulting

in a different amino acid or nonsense variant is more likely to be pathogenic.

Evaluation of these features should result in the classification of potential pathogenic significance. Concerning somatic variants in cancer, a 5-tier system has been proposed,<sup>15</sup> similar to what has been established for a longer time for germline variants.<sup>19</sup> 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, 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 this has been a well-characterized diagnostic entity for a 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 resources, and consistency.<sup>20</sup>

## 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),<sup>21</sup> which was also used in the prior EANO guideline on molecular testing.<sup>10</sup> The ESCAT defines 6 levels of clinical evidence for molecular targets according to the implications for patient management (Table 1). While ESCAT was primarily developed for the assessment of genomic alterations, we apply it here in a broader sense and use it also for grading potential biomarkers defined by protein expression or assessed with other methods such as immunohistochemistry or molecular imaging (Figure 1).

## Molecular Testing: When to Test

In meningioma, surgical resection and radiotherapy are established treatment options recommended at initial diagnosis and recurrence.<sup>3</sup> 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.<sup>5</sup> Therefore, outside of clinical trials in the first-line setting, molecular testing intended for the 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 on the risk of recurrence based on molecular markers and subgroups (*TERT*, *CDKN2A/B*, DNA methylation) may already be advisable at initial diagnosis and, depending on the 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.<sup>22</sup> 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.<sup>10</sup> 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 the 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.<sup>5,23–25</sup> 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.<sup>26</sup> 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 2-step inactivation of *NF2*.<sup>27</sup> *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**),<sup>21</sup> opening interesting perspectives, but lacking the basis for a 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.<sup>28</sup> The ErbB2/EGFR inhibitor lapatinib likewise led to slowed tumor growth in another small phase 2 clinical trial.<sup>29,30</sup> The FAK inhibitor GSK2256098 yielded stable disease in 8 of 24 higher-grade *NF2*-altered meningiomas in an uncontrolled phase 2 clinical trial.<sup>31</sup> A prospective phase 2 platform trial has documented a radiographic response rate in 28% (5 of the 18 patients) in evaluable meningiomas

**Table 1.** European Society for Medical Oncology (ESMO) Scale for Clinical Actionability of Molecular Targets (ESCAT)<sup>21</sup>

	ESCAT evidence tier	Required level of evidence	Clinical value class	Clinical implication
Ready for routine use	I: Alteration-drug match is associated with improved outcomes 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.	Drugs administered to patients with specific molecular alterations have led to improved clinical outcomes in the prospective clinical trial(s).	Access to the treatment should be considered a standard of care.
Investigational	II: alteration-drug match is associated with antitumor activity, but the magnitude of the benefit is unknown.	IIA: retrospective studies show patients with the specific alteration in a specific tumor type experience clinically meaningful benefits with the 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	Drug administered to a molecularly defined patient population is likely to result in clinical benefit in a given tumor type, but additional data are needed.	Treatment is to be considered “preferable” in the context of evidence collection either as a 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 types(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.	The drug was 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 but not proved.	Clinical trials are 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. IVB: actionability predicted in silico.	Actionability is predicted based on preclinical studies, no conclusive clinical data are available.	Treatment should “only be considered” in the context of early clinical trials. Lack of clinical data 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 outcomes.	The 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

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associated with NF2-related schwannomatosis.<sup>32</sup> 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.<sup>33</sup> *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.<sup>34</sup> Depending on the series, *PIK3CA* variants have been identified in approximately 1%–5% of meningiomas<sup>11,35,36</sup> 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

*Krüppel-like factor 4 (KLF4)*) but may frequently co-occur with *TRAF7* mutations.<sup>36</sup> *PIK3CA*-mutated tumors are typically encountered in the skull base.<sup>36</sup> *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.<sup>37</sup> 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

BRCA1-associated protein 1 (BAP1) is a member of the Polycomb group family, counteracting polycomb repressive complex 1-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.<sup>38–41</sup> Treatment options have been evaluated in more common BAP1-associated malignancies and involve histone deacetylase (HDAC) inhibitors,<sup>42</sup> enhancers of zeste homolog 2 (EZH2) inhibitors,<sup>43</sup> platinum agents,<sup>44</sup> poly-(ADP-ribose) polymerase (PARP) inhibitors,<sup>45,46</sup> and immunotherapy<sup>47,48</sup> (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 the treatment of several extra-CNS tumor types. For some of these tumor types, treatment indication per approval is dependent on the demonstration of PD-L1 expression using a validated test.<sup>49</sup> There is limited evidence for the clinical efficacy of PD-1/PD-L1 inhibitors in meningioma and a 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 grades 2 and 3 meningiomas met its primary PFS endpoint but did not find a significant correlation between PD-L1 expression and outcome.<sup>50</sup> Another phase II study on nivolumab in meningiomas recurring after surgery and radiation therapy failed to meet its primary endpoint of PFS-6.<sup>51</sup> 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

Somatostatin receptor (SSTR)s 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.<sup>52</sup>

SSTR2 represents an **ESCAT IIIA** target in meningiomas. There is proven efficacy of the radioligand [<sup>177</sup>Lu]Lu-DOTATATE in SSTR2-positive (as determined by PET) neuroendocrine tumors based on randomized clinical trials.<sup>53,54</sup> Furthermore, retrospective series and an interim analysis of a prospective single-arm study suggest potential efficacy for SSTR2-targeted radionuclide therapy in meningioma.<sup>55–58</sup> To date there are no conclusive data on the efficacy of SSTR2-targeted radionuclide therapy from prospective controlled clinical trials in meningioma. The European Organization for Research and Treatment of Cancer is activating the first randomized clinical trial to investigate the efficacy of [<sup>177</sup>Lu]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).<sup>59</sup> Another trial showed efficacy in controlling tumor growth in patients with metastatic neuroendocrine midgut tumors but did not use SSTR status as an inclusion criterion.<sup>60</sup> The efficacy of somatostatin analogs in meningiomas has been investigated in some studies but remains unknown due to methodological limitations.<sup>28,61,62</sup>

At present, SSTR testing by immunohistochemistry or PET as a basis for targeted treatment is 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 downstream 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.<sup>63–65</sup> *AKT1* mutations were not detected in radiation-induced meningiomas.<sup>66,67</sup> 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 *P TEN*).<sup>68</sup> Capivasertib showed activity across several tumor types harboring *AKT1* p.E17K

mutations in a multihistology basket study.<sup>69</sup> Capivasertib has also shown activity in a single patient with *AKT1* p.E17K-mutant metastatic meningioma.<sup>70</sup> Overall, *AKT1* represents an **ESCAT IIIA** target in meningioma.

### Smoothened

Smoothened (*SMO*) is a G protein-coupled receptor encoded by the *SMO* gene and contributes 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 tumor.<sup>63,64</sup> 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 the 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.<sup>71,72</sup> Data regarding the 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.<sup>73</sup> 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 are associated with poor outcomes.<sup>74,75</sup> Testing methods include CGH microarrays, copy number analyses from DNA methylation arrays, NGS, WES, WGS, or fluorescent in-situ hybridization.

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

Suppressor of fused homolog (*SUFU*) is a negative regulator of the hedgehog signaling pathway.<sup>76</sup> 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.<sup>77,78</sup> 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 was investigated and these alterations are a rare cause, compared to *PTCH1* mutations, of nevoid basal cell carcinoma syndrome (also known as Gorlin syndrome).<sup>79,80</sup> Concerning meningiomas, *SUFU* mutations were initially reported in familial cases,<sup>81–83</sup> but further cases demonstrated their occurrence also in sporadic cases with a frequency of up to 5%.<sup>84–86</sup> *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.<sup>63,64</sup> 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.<sup>85</sup> In terms of therapeutic relevance, *SUFU* protein is a downstream effector of *SMO* in the hedgehog pathway, thus *SMO* targeting is not effective.<sup>87,88</sup> Further downstream inhibition of GLI proteins has been evaluated in preclinical models,<sup>89–99</sup> 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

Platelet-derived growth factor receptors (PDGFR)s are established targets in a variety of systemic cancers.<sup>100</sup> 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,<sup>101,102</sup> which raised the possibility of an autocrine loop.<sup>103</sup> Administration of PDGF-BB to meningioma cells in culture stimulated growth while anti-PDGF-BB antibodies inhibited tumor cell growth.<sup>103</sup> 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.<sup>104</sup> Other trials with multikinase inhibitors that targeted PDGFR, such as sunitinib, showed modest activity,<sup>105</sup> 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.<sup>106,107</sup> Therefore, testing for PDGFR alterations is discouraged in routine clinical practice and the use of PDGFR inhibitors should only be considered in the context of clinical trials (**ESCAT IVA**).

## Progesterone Receptor and Estrogen Receptor

The steroid hormone receptors PR and ER are established targets for antihormonal treatment in breast cancer.<sup>108,109</sup> 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 PR inhibitor mifepristone on failure-free or overall survival of unresectable meningioma.<sup>110</sup> 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 is associated with enrichment of PIK3CA mutations.<sup>111,112</sup>

## 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 the development of clear cell meningiomas and is a biomarker for this diagnosis.<sup>113,114</sup> Genes encoding mSWI/SNF complexes are mutated in over 20% of human cancers.<sup>115</sup> They have in common the disruption of members of the functional complex, comprising SMARCA4/2, ARID1A/B, SMARCB1, and SMARCE1 subunits.<sup>116,117</sup> 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.<sup>118</sup> SMARCE1 is an **ESCAT IVA** target.

## Krüppel-like factor 4

KLF4 is a transcription factor involved in a variety of cellular signaling pathways.<sup>119–124</sup> *KLF4* mutations have a high rate of co-occurrence with *TRAF7* mutations. Detection of mutations in *KLF4/TRAF7* is the molecular hallmark of secretory meningiomas.<sup>125</sup> In unselected meningioma groups, *KLF4*-mutated tumors are detected in about 6%–9%.<sup>63,85</sup> Among non-*NF2* meningiomas, *KLF4* mutations can be found in up to 38%.<sup>126</sup> The *KLF* mutation is a typical hotspot mutation, affecting codon 409 which results in a lysine to glutamine exchange (p.K409Q).<sup>122,125</sup> *KLF4* status may be assessed together with other relevant genes, especially *TRAF7* and *NF2*, through NGS panel sequencing.<sup>85</sup> There is only one preclinical study available, showing the potential activity of the mTOR inhibitor temsirolimus in *KLF4* (p.K409Q)-mutated meningioma.<sup>122</sup> *KLF4* represents an **ESCAT IVA** target.

## Telomerase Reverse Transcriptase

Telomerase reverse transcriptase (*TERT*) hotspot mutations have been detected in 5%–6% of all meningiomas and are generally associated with an aggressive clinical course.<sup>127,128</sup> *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 and Vascular Endothelial Growth Factor Receptors

Vascular endothelial growth factor (VEGF) and vascular endothelial growth factor receptors (VEGFR) are well-established targets in cancer.<sup>129</sup> VEGF and its receptors are frequently expressed in meningiomas and are likely to be important for tumor growth and production of peritumoral edema.<sup>130,131</sup> Several retrospective studies have shown the possible benefit of bevacizumab in slowing tumor growth in recurrent meningiomas.<sup>132–137</sup> 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,<sup>138</sup> which appears superior to historical benchmarks of 29% for grade I meningiomas and 26% for WHO grade 2/3 meningiomas.<sup>4</sup> Bevacizumab has also been combined with everolimus in a small uncontrolled prospective study in 18 patients with progressive, refractory meningioma. The best response of stable disease (SD) was observed in 15 patients (88 %) and 6 patients had SD for more than 12 months. Median PFS was 22 months (95 % CI: 4.5–26.8).<sup>139</sup>

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 grades 2 and 3 meningioma patients, PFS-6 was 42%,<sup>105</sup> compared to the historic PFS-6 benchmark of 26% for grade 2 and 3 meningiomas.<sup>4</sup> 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 benefits from other multitarget VEGFR inhibitors such as cabozantinib.<sup>140</sup>

While testing for VEGF or VEGFR is not recommended as a molecular predictive biomarker (**ESCAT X**), the 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

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.<sup>141</sup> *ARID1A* gene alterations have been described in 5.4% of meningiomas, with a higher prevalence in recurrent tumors and an association with adverse prognosis.<sup>86,142</sup> Experimental strategies for 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.<sup>141</sup> 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.<sup>141</sup> 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

Homologous recombination deficiency (HRD) is a well-established predictive factor for the magnitude of response to PARP inhibitor therapy in ovarian cancer.<sup>143,144</sup> An association of HRD-like signatures with radiation-associated meningiomas and with the malignant methylation class has been reported.<sup>145</sup> 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

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.<sup>63</sup> 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*.<sup>146</sup> Somatic *TRAF7* mutations have also been identified in normal-appearing leptomeninges.<sup>147</sup> They are not found in radiation-associated meningiomas<sup>64</sup> nor in the pediatric population.<sup>148</sup> Germ-line mutations of *TRAF7* cause congenital heart defects.<sup>149</sup> *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.<sup>150</sup> 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.<sup>151</sup> 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.<sup>152</sup> Heterozygous loss of chromosome 22q that harbors the *NF2* gene, is present in more than half of meningiomas and is an important part of the 2-step inactivation of NF2 activity.<sup>34,153</sup> In meningioma, specific CNVs are associated with increased risk for progression and therefore several models to utilize CNVs for risk prediction have been proposed.<sup>154,155</sup> So far, the most consistent marker is the loss of chromosome 1p.<sup>34,153,156,157</sup> 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)<sup>34</sup> or 1p, 3p, 4p/q, 6p/q, 10p/q, 14q, 18p/q, 19p/q, *CDKN2A/B* and mitotic count (integrated grade).<sup>153</sup>

More recently, meningioma molecular fingerprinting was expanded to the level of whole genome analyses.<sup>11,34,106,158–161</sup> First, epigenetic profiling identified 3 meningioma methylation families termed benign, intermediate, and malignant.<sup>11</sup> 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.<sup>106,159,161</sup> The recent cIMPACT-NOW update 8 provides recommendations on their integration into diagnostics.<sup>22</sup> 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<sup>159,160</sup> or in an integrated prognostic model.<sup>106</sup> Extracting the common divider between molecular groups defined by either epigenetics, transcriptomics, CNV-profiles and *NF2*-status identified 3 prognostic molecular subtypes: low risk *NF2*-altered and *NF2*-wildtype groups and a high(er) risk *NF2*-altered group.<sup>161</sup>

Taken together, CNVs and advanced molecular-based risk prediction models can have 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.<sup>11,34,106,153,158–160,162–168</sup> 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,<sup>160,169</sup> including in patients who were treated with postoperative radiotherapy on prospective clinical trials.<sup>157,166</sup> 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,<sup>160</sup> 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.<sup>166</sup> 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,<sup>166</sup> 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.<sup>170</sup> Collectively, these studies both suggest that molecular high-throughput data may reveal patterns that are able to stratify for cases with differential responses 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 to 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.

## Supplementary material

Supplementary material is available online at *Neuro-Oncology* (<https://academic.oup.com/neuro-oncology>).

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## Author contributions

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

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