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SMO mutant olfactory groove meningiomas—the next in line for targeted therapy

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See the article by Boetto et al. on pp. 345–351.

Meningiomas are benign extra-axial lesions comprising nearly 1/3 of primary central nervous system tumors[1] and arise from arachnoidal cap cells of the leptomeninges. Surgical resection has historically been the mainstay of treatment, with radiation as an adjuvant for tumor in surgically inaccessible areas or of higher grade. Meningiomas, however, have been notoriously resistant to systemic therapies. The advent of next-generation sequencing has significantly enhanced our understanding of the genetic foundation of meningioma development and similarly provided potential therapeutic targets. Recent sequencing efforts have identified potential drivers and mutually exclusive subgroups based on recurrent mutations in *NF2*, *AKT1*, *PIK3CA*, *SMO*, *TRAF7*, *KLF4*, *SMARCB1*, and *POLR2A*.[2–7] By clarifying these alterations, there will be increasing opportunities for rational targeted approaches for recurrent or atypical meningiomas that progress despite surgical resection and radiotherapy.

Building upon recent studies emphasizing the spatially distinct mutational profiles for *NF2* wild-type and mutant meningiomas,[2,3] the report by Boetto et al provides compelling insights into the prevalence of *SMO* and *AKT* mutations in olfactory groove meningiomas (OGM). Moreover, their findings point to the functional consequences of these mutations and their potential role as clinically actionable targets. A cohort of 79 OGM was collected from a total of 1439 meningioma samples spanning a 10-year period in a single institution. A total of 43% of patients harbored mutually exclusive mutations in either *SMO* or *AKT* at mutational hotspots, consistent with prior reports.[4] *SMO* mutations were found in 28% of patients and localized either to L412F (26.5%) or W535L (1.2%). The AKT^{E17K} mutation was identified in 15% of patients. Among the 79 patients with OGM, those with *SMO* mutations had a significant increase in anosmia at the time of presentation, likely explained by alterations in defective cilia involved in olfactory processing.[8] Additionally, *SMO* mutations were histologically homogeneous (100% World Health Organization [WHO] grade I and meningothelial) compared with a heterogeneous mixture of *AKT* mutations (67% grade I and 33% grade II; 67% meningothelial, 25% atypical, and 8% chordoid).

Despite the lower grade and slower, albeit nonsignificant, baseline Ki67 index among *SMO* mutations, these mutations resulted in a notably divergent disease course with a 36% recurrence rate compared with either an *AKT* mutation (16%) or nondetectable mutations in *SMO* or *AKT* (11%). Although progression-free survival (PFS) was equivalent at 5 years, the overall difference in recurrence was prominent at 10 years follow-up with a 52% PFS among patients with *SMO* mutations compared with 83% for those with *AKT* mutations and 82% for patients lacking a mutation.

Regarding overall survival, grade I patients with *SMO* mutations had a significant reduction in overall survival compared with *SMO* wild-type patients. On multivariate analysis, WHO grade and incomplete resection were significantly associated with shorter recurrence-free survival. Moreover, there was a notable trend between *SMO* mutations and shortened recurrence-free survival ($P=.06$). While the authors carried out an exhaustive study into the role of *SMO* and *AKT1* mutation in OGM, they were challenged by the relative infrequency of these tumors and their indolent disease progression, which required follow-up of 10 years postoperatively. It is unclear whether the observed trend between *SMO* mutations and overall survival is reflective of a more aggressive natural history for *SMO* mutant OGM or a product of inherent bias in the patient cohort. A larger, multi-institutional cohort with extensive follow-up would help elucidate these possibilities and guide clinical prognostication.

Additionally, conclusions drawn from *AKT* mutations would benefit from an expanded study. The frequency of AKT^{E17K} mutations is consistent with previously published reports[2,7] and is not exclusive to the olfactory groove. The cohort described in this paper includes a heterogeneous collection of WHO grades I and II tumors as well as meningothelial, atypical, and chordoid histologies. Given these factors, a larger analysis of *AKT* mutations across equivalent cohorts of patients spanning various skull-base locations is warranted.

The role of hedgehog and phosphatidylinositol-3 kinase/AKT signaling in non-NF2 meningiomas is increasingly appreciated and has been associated with distinct histologic meningioma subtypes.[2–4,6,7,9] The prevalence of mutations in *SMO* and *AKT* in OGM provides novel insights into the genetic underpinnings mediating meningioma development in the olfactory groove and their association with disease recurrence. Interestingly, none of the 79 patients included in the cohort were treated with systemic therapy. This raises the question for future studies to target these clinically actionable mutations, particularly among patients who are identified as high risk for developing recurrent or atypical meningiomas.

The prevalence of *SMO* and *AKT* mutations in OGM warrants their integration into the findings of recent large-scale meningioma sequencing efforts[2–4] in order to elucidate a series of targetable mutations and associated mutational profiles that will provide even greater prognostic information for clinicians. A recent report by Strickland et al has demonstrated frequent *SMO* and *AKT* mutations in a cohort of 62 anterior skull-base meningiomas.[10] Additionally, *SMO* mutations were associated with a significant increase in tumor volume compared with AKT mutants. Although those findings were in a smaller cohort that included non-OGM,[10] the studies by Strickland et al and Boetto et al emphasize the importance of genotyping resected tissue from OGM.

A recently initiated phase II National Cancer Institute–sponsored cooperative group trial is under way investigating targeted inhibitors for residual or progressive meningiomas demonstrating *SMO* (W535L and L412F) or *NF2* mutations (NCT02523014). Patients enrolled in the *SMO* mutant arm are being treated with vismodegib, an antagonist of the SMO receptor that has been previously approved for basal cell carcinoma, while patients with NF2 mutations are being treated with the focal adhesion kinase inhibitor GSK2256098. The trial will be adding an additional AKT cohort shortly, whereby patients with an AKT mutation will receive an AKT inhibitor. Building upon this trial, the study by Boetto et al suggests the need for further investigation into the role of *SMO* and *AKT* in OGM, with the ultimate goal of implementing targeted therapies for these alterations to complement their surgical resection, limit tumor recurrence, and prevent progressive disease.

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