

Medulloblastoma

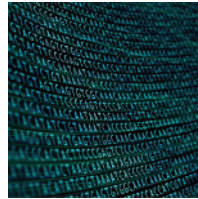
Major Finding: Germline mutations in *GPR161*, encoding a Sonic Hedgehog regulator, predispose to medulloblastoma.

Mechanism: Copy-number loss of heterozygosity of *GPR161* underlies the development of infant medulloblastoma.

Impact: This study identifies a previously unknown Sonic Hedgehog medulloblastoma risk syndrome.

GERMLINE *GPR161* MUTATIONS ARE ASSOCIATED WITH INFANT MEDULLOBLASTOMA

Medulloblastomas most often appear to occur sporadically, but heritable causes have been identified in some cases. Begemann, Waszak, and colleagues describe a previously unknown medulloblastoma predisposition syndrome caused by heterozygous germline mutations in *GPR161*, a gene encoding a G protein-coupled receptor that regulates Sonic Hedgehog (SHH). The index patient had developed *TP53*^{WT} SHH medulloblastoma (SHH-MB) at the age of 12 months and subsequently developed tumors of several other types. Analysis of genomic data from a 1,044-patient medulloblastoma cohort identified five additional patients with mutations in *GPR161*, all of whom had developed SHH-MB at a young age, with a median age of onset of 1.5 years. None of these six patients had mutations previously known to drive medulloblastoma. In five of the six patients, loss of the wild-type copy of *GPR161* had occurred as a result of 1q copy-number neutral loss of heterozygosity (cnLOH), a genetic



alteration that had not previously been associated with medulloblastoma. An analysis of genomic data from patients with pediatric SHH-MB revealed that 1q cnLOH was only present in tumors harboring germline *GPR161* mutations. In total, the authors estimate that 5% of infant SHH-MBs are attributable to *GPR161* mutations. Heterozygosity for these mutations is rare in the general population; the carrier frequency is approximately 1 in 42,000 to 1 in 125,000 individuals. In summary, this study identifies a previously unknown medulloblastoma predisposition syndrome, providing information that not only will enable genetic counseling for carriers but also may yield insights into underlying processes that can drive medulloblastoma in patients without the mutation. ■

Begemann M, Waszak SM, Robinson GW, Jäger N, Sharma T, Knopp C, et al. Germline GPR161 mutations predispose to pediatric medulloblastoma. J Clin Oncol 2019 Oct 14 [Epub ahead of print].

Clinical Trials

Major Finding: Lazertinib is safe and shows preliminary evidence of efficacy in non-small cell lung cancer.

Approach: In a phase I/II trial, the EGFR tyrosine kinase inhibitor lazertinib was tested in 127 patients.

Impact: The phase II part of the study is ongoing; larger trials of lazertinib are warranted.

LAZERTINIB IS SAFE AND EFFECTIVE IN NON-SMALL CELL LUNG CANCER

In patients with non-small cell lung cancer (NSCLC), administration of an EGFR tyrosine kinase inhibitor (TKI) is often initially successful but universally leads to resistance, most commonly via a threonine-to-methionine mutation at position 790 of EGFR. In a first-in-human, open-label, phase I/II clinical trial, Ahn and colleagues investigated the use of the third-generation EGFR TKI lazertinib in 127 patients with locally advanced or metastatic, EGFR-mutant NSCLC who had previously experienced disease progression on or following treatment with a first- or second-generation EGFR TKI. Primary endpoints were objective response rate, response duration, proportion of patients with disease control, tumor shrinkage, and lazertinib pharmacokinetics. Progression-free survival, overall survival, and (for patients with brain metastases) intracranial objective response rate and intracranial progression-free survival were secondary endpoints. In the dose-escalation phase, involving 38 patients, no dose-limiting toxicities were observed. In the dose-expansion phase, 94% (119/127) of patients experienced at least one adverse event, the most common of which were grade 1 to 2 rash (30%; 30/127) and pruritis (27%; 34/127). No treatment-related deaths were deemed to have occurred. Overall, 52% (66/127) of patients had partial

responses and 2% (3/127) had complete responses, for a total of 54% (69/127) with objective responses. Thirty-two percent (41/127) of patients exhibited stable disease. In subgroup analysis, patients harboring *EGFR*^{T790M}-mutant tumors were more likely to have an objective response than those without (64% versus 37%; 69/108 versus 7/19). Of the 18 patients with brain metastases, eight (44%) had objective responses, indicating that lazertinib can cross the blood-brain barrier. The median duration of response was 15.2 months, and the median progression-free survival was 9.5 months; these measures were again somewhat more favorable for patients with *EGFR*^{T790M}-mutant tumors. The results of this trial, the phase II portion of which is ongoing, show that lazertinib is generally safe and well tolerated and provide preliminary evidence of efficacy. Future studies with multiple arms and larger and more diverse patient populations are justified by this work. ■

Ahn M, Han JY, Lee KH, Kim SW, Kim DW, Lee YG, et al. Lazertinib in patients with EGFR mutation-positive advanced non-small-cell lung cancer: results from the dose escalation and dose expansion parts of a first-in-human, open-label, multicentre, phase 1–2 study. Lancet Oncol 2019 Oct 3 [Epub ahead of print].

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