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CENTRAL NERVOUS SYSTEM TUMORS

Targetable signaling pathway mutations and progression of *IDH*-mutant glioma.

[Hiroaki Wakimoto](#) , [Shota Tanaka](#) , [William T. Curry](#) ,
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Abstract

2061

Background: Isocitrate dehydrogenase (*IDH*) gene mutations occur in low-grade and high-grade gliomas. We sought to identify the genetic basis of malignant phenotype heterogeneity in *IDH*-mutant gliomas.

Methods: We prospectively implanted tumor specimens from 20 consecutive *IDH1*-mutant glioma resections into mouse brains and genotyped all resection specimens using a

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CLIA-certified molecular panel. Gliomas with cancer driver mutations were tested for sensitivity to targeted inhibitors *in vitro*. Associations between genomic alterations and outcomes were analyzed in patients. **Results:** By 10 months, 8 of 20 *IDH1*-mutant gliomas developed intracerebral xenografts. All xenografts maintained mutant *IDH1* and high levels of 2-hydroxyglutarate on serial transplantation. All xenograft-producing gliomas harbored “lineage-defining” mutations in *CIC* (oligodendroglioma) or *TP53* (astrocytoma), and 6 of 8 additionally had activating mutations in *PIK3CA* or amplification of *PDGFRA*, *MET*, or *N-MYC*. Only *IDH1* and *CIC/TP53* mutations were detected in non-xenograft-forming gliomas ($P = 0.0007$). Targeted inhibition of the additional alterations decreased proliferation *in vitro*. Moreover, we detected alterations in known cancer driver genes in 13.4% of *IDH*-mutant glioma patients, including *PIK3CA*, *KRAS*, *AKT* or *PTEN* mutation or *PDGFRA*, *MET* or *N-MYC* amplification. *IDH/CIC* mutant tumors were associated with *PIK3CA/KRAS* mutations while *IDH/TP53* tumors correlated with *PDGFRA/MET* amplification. Presence of driver alterations at progression was associated with shorter subsequent progression-free survival (median 9.0 vs. 36.1 months, $P=0.0011$). **Conclusions:** A subset of *IDH*-mutant gliomas with mutations in driver oncogenes has a more malignant phenotype in patients. Identification of these alterations may provide an opportunity for use of targeted therapies in these patients.

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