

Clinical Trials

Major finding: Single-agent ibrutinib shows durable activity in relapsed or refractory mantle-cell lymphoma.

Concept: Inhibition of BTK induced a high response rate and was well tolerated in a phase II trial.

Impact: Ibrutinib may improve clinical responses with less toxicity compared with current treatments.

A BTK INHIBITOR IS EFFECTIVE IN MANTLE-CELL LYMPHOMA

Bruton's tyrosine kinase (BTK) is a critical effector of B-cell receptor signaling that has been implicated in the growth and survival of B-cell malignancies, including mantle-cell lymphoma, an aggressive subtype of non-Hodgkin lymphoma. Preclinical and phase I clinical studies have shown that ibrutinib, an oral, covalent BTK inhibitor, has antitumor activity in animal models and was effective in a small group of patients with mantle-cell lymphoma. To further evaluate the efficacy and safety of ibrutinib as a single-agent therapy, Wang and colleagues performed an open-label phase II trial in 111 patients with relapsed or refractory mantle-cell lymphoma. Patients were classified into two groups based on whether they had received more than two prior treatments with the proteasome inhibitor bortezomib, which is approved for patients who experience disease progression after initial therapy. Single-agent ibrutinib treatment induced an overall response rate of 68%, resulting in a complete response in 21% of patients and a partial response in 47% of patients. Similar response rates were observed in both

groups of patients independent of prior bortezomib treatment or risk factors for poor outcome. The median progression-free survival among all patients was estimated to be 13.9 months, and the median overall survival was not reached. Furthermore, the estimated median duration of response was 17.5 months, suggesting that ibrutinib has lasting antitumor activity. Ibrutinib was well tolerated, with the most common treatment-related side effects being grade 1 or 2 adverse events such as diarrhea, fatigue, and nausea; grade 3 or 4 hematologic adverse events were less frequent and included neutropenia and bleeding. These results show that single-agent ibrutinib is highly active in relapsed or refractory mantle-cell lymphoma and suggest that it may be more effective and less toxic compared with currently used treatment regimens for this disease. ■

Wang ML, Rule S, Martin P, Goy A, Auer R, Kahl BS, et al. Targeting BTK with ibrutinib in relapsed or refractory mantle-cell lymphoma. *N Engl J Med* 2013 Jun 19 [Epub ahead of print].

Metabolism

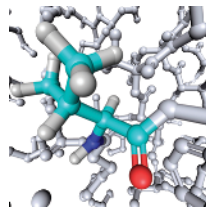
Major finding: Branched-chain amino acid transaminase 1 (BCAT1) drives growth of gliomas with wild-type IDH1.

Mechanism: Mutant IDH1 downregulates BCAT1 in association with altered *BCAT1* promoter methylation.

Impact: Targeting branched-chain amino acid metabolism in gliomas may be an effective therapeutic strategy.

IDH1-WILD-TYPE GLIOMAS ARE DEPENDENT ON BCAT1

Isocitrate dehydrogenase 1 (*IDH1*) and *IDH2* mutations are frequently found in high-grade gliomas and secondary glioblastomas that develop from low-grade gliomas but are rare in primary glioblastomas. Mutant IDH enzymes are believed to metabolically reprogram cancer cells through the neomorphic conversion of α -ketoglutarate (α -KG) to 2-hydroxyglutarate (2-HG), but the metabolic conditions that support the aggressive growth of *IDH*-wild-type gliomas are less clear. Tönjes and colleagues found that expression of branched-chain amino acid transaminase 1 (BCAT1) was significantly higher in gliomas lacking mutations in *IDH1* or *IDH2* than in *IDH*-mutant gliomas, where BCAT1 was essentially absent. In the initial step of branched-chain amino acid catabolism, glutamate and branched-chain α -ketoacids are generated by BCATs through the transfer of an α -amino group to α -KG, suggesting a potential link to the activity of wild-type IDH enzymes, which convert isocitrate to α -KG, as well as to release of glutamate by glioblastoma cells, which facilitates tumor expansion by inducing the excitotoxic cell death of surrounding



neurons. Indeed, BCAT1 expression was strongly downregulated upon *IDH1* knockdown or overexpression of mutant *IDH1* and could be rescued by α -KG, not 2-HG. Furthermore, consistent with the known ability of 2-HG to inhibit the activity of α -KG-dependent enzymes such as 5-methylcytosine hydroxylases, altered *BCAT1* promoter DNA methylation in *IDH*-mutant gliomas was strongly correlated with *BCAT1* downregulation. BCAT1 knockdown or inhibition with a leucine analogue also markedly reduced the proliferation, migration, invasion, and glutamate release of glioblastoma cells *in vitro*, and BCAT1 knockdown significantly blocked tumor growth and glutamate excretion *in vivo*. These findings indicating that *IDH1*-wild-type gliomas are addicted to BCAT1-dependent branched-chain amino acid catabolism thus suggest that selectively targeting this process may have therapeutic benefit. ■

Tönjes M, Barbus S, Park YJ, Wang W, Schlotter M, Lindroth AM, et al. BCAT1 promotes cell proliferation through amino acid catabolism in gliomas carrying wild-type *IDH1*. *Nat Med* 2013;19:901–8.

Note: Research Watch is written by Cancer Discovery Science Writers. Readers are encouraged to consult the original articles for full details. For more Research Watch, visit *Cancer Discovery* online at <http://CDnews.aacrjournals.org>.