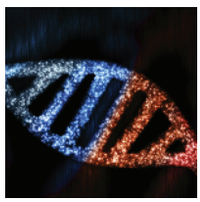
Clinical Trials

Major finding: The next-generation ALK inhibitor alectinib overcomes acquired crizotinib resistance in NSCLC.

Concept: Alectinib crosses the blood–brain barrier and leads to objective responses in patients with CNS metastases.

Impact: Alectinib may be effective in refractory *ALK*-rearranged NSCLC and benefit patients with CNS involvement.

ALECTINIB IS ACTIVE IN CRIZOTINIB-RESISTANT *ALK*-REARRANGED NSCLC



Treatment with the FDA-approved ALK inhibitor crizotinib leads to objective responses in approximately 60% of patients with *ALK*-rearranged non–small cell lung cancer (NSCLC), but acquired resistance develops in the vast majority of patients. The central nervous system (CNS) is a particularly common site of progressive disease in crizotinib-treated patients, suggesting that ALK inhibitors that not only can overcome acquired crizotinib resistance but also penetrate the blood–brain barrier are needed. Gadgeel, Gandhi, and colleagues evaluated the next-generation ALK inhibitor alectinib in 47 patients with crizotinib-resistant *ALK*-rearranged NSCLC, including patients with asymptomatic CNS metastases, in a single-arm, open-label, multicenter phase 1/2 study. The primary objective was to determine the recommended phase 2 dose, and secondary objectives included evaluation of safety, activity, and pharmacokinetics. In a report on the dose-finding part of the study, the authors showed that alectinib was well tolerated at all dose levels, with the most common adverse events being low-grade fatigue, myalgia, and peripheral edema, and noted that alectinib had favorable pharmacokinetics. Of 44 evaluable patients, 24 (55%) had an objective response, including one complete response, and 16 (36%) had stable disease. Encouragingly, among the 21 patients with CNS metastases at baseline, 6 (29%) had a complete CNS response, 5 (24%) had a partial CNS response (including one patient with leptomeningeal carcinomatosis), and 8 (38%) had CNS disease stabilization. Consistent with these findings suggesting that alectinib effectively penetrates the blood–brain barrier, measureable levels of alectinib were found in the cerebrospinal fluid (CSF) of 5 of 5 patients with CNS metastases analyzed, with a linear relationship between CSF and plasma alectinib levels. These initial findings suggest that alectinib has promising antitumor activity and can penetrate the CNS in patients with crizotinib-resistant *ALK*-rearranged NSCLC. ■

Gadgeel SM, Gandhi L, Riely GJ, Chiappori AA, West HL, Azada MC, et al. Safety and activity of alectinib against systemic disease and brain metastases in patients with crizotinib-resistant ALK-rearranged non-small-cell lung cancer (AF-002JG): results from the dose-finding portion of a phase 1/2 study. Lancet Oncol 2014;15:1119–28.

Hepatocellular Carcinoma

Major finding: CDK9 is necessary for the proliferation and maintenance of MYC-driven hepatocellular carcinoma.

Mechanism: MYC-driven proliferation requires CDK9-mediated transcription elongation of MYC target genes.

Impact: CDK9 may serve as a therapeutic target in a subset of MYC-overexpressing tumors.

MYC-DRIVEN TUMORS ARE DEPENDENT ON CDK9-MEDIATED TRANSCRIPTION ELONGATION

Hepatocellular carcinoma (HCC) is an aggressive and deadly disease with a one-year survival rate of less than 50%, underscoring the need to identify effective targeted therapies. The *MYC* oncogene drives tumor proliferation in multiple cancer types, including HCC, by regulating gene transcription, protein translation, and DNA replication; however, therapeutic strategies to target MYC have thus far been unsuccessful. Huang, Lujambio, and colleagues applied a custom shRNA library to a MYC-driven murine HCC model in order to identify candidate drug targets that are necessary to sustain the addiction of HCC cells to MYC. Among the top candidates, depletion of cyclin-dependent kinase 9 (CDK9), which stimulates transcription elongation by RNA polymerase II, significantly decreased HCC cell proliferation. This effect was reproducible across several murine and human HCC cell lines and was specific to MYC-overexpressing cells, suggesting that CDK9 is critical for the growth of MYC-driven HCC. This idea was further supported pharmacologically, as disruption of CDK9 activity with the kinase inhibitor PHA-767491 reduced the proliferative capacity of several HCC cell lines, similar to CDK9 knockdown. MYC expression levels positively correlated with sensitivity to CDK9 inhibition, and gene expression in inhibitor-sensitive cells was enriched for MYC-dependent transcriptional signatures. CDK9 mediated the transcription elongation of multiple MYC target genes in MYC-overexpressing HCC cells, demonstrating the dependence of MYC-driven tumors on CDK9 activity. Consistent with this notion, forced overexpression of MYC in low MYC–expressing cells increased the transcription elongation of MYC-dependent genes and conferred sensitivity to CDK9 inhibition. Furthermore, silencing of CDK9 impaired MYC-driven tumor formation and inhibited the growth of established murine liver tumors and human HCC xenografts, establishing an essential role for CDK9 and transcription elongation in MYC-mediated oncogenesis. These results suggest CDK9 as a potential therapeutic target for the treatment of MYC-addicted cancers. ■

Huang CH, Lujambio A, Zuber J, Tschaharganeh DF, Doran MG, Evans MJ, et al. CDK9-mediated transcription elongation is required for MYC addiction in hepatocellular carcinoma. Genes Dev 2014;28:1800–14.