Clinical Trial

Major Finding: Sotorasib produced objective responses in 37.1% of patients for a median duration of 11.1 months.

Concept: Activating *KRAS* mutations are common drivers of this cancer and are often associated with smoking.

Impact: A phase III trial evaluating sotorasib in *KRAS*^{G12C}-mutant non–small cell lung cancer is under way.

SOTORASIB IS ACTIVE IN *KRAS*^{G12C}-MUTANT NON–SMALL CELL LUNG CANCER

Activating mutations in *KRAS*, particularly G12C, are the most common genetic driver events in non–small cell lung cancer (NSCLC). Although mutant KRAS has long been thought to be inherently undruggable, the recent development of drugs targeting KRAS^{G12C} have challenged that notion. Following the phase I portion of the CodeBreaK100 trial, which revealed a favorable safety profile and established early evidence of anticancer activity for the irreversible KRAS^{G12C} inhibitor sotorasib in patients with *KRAS*^{G12C}-mutant advanced solid tumors, Skoulidis, Li, and colleagues embarked upon the phase II portion of the trial, which enrolled patients with previously treated *KRAS*^{G12C}-mutant NSCLC. Among the 124 patients whose disease was evaluable for response, 37.1% exhibited objective responses according to an independent central review, with 3.2% of patients having complete responses and 33.9% of patients having partial responses. The median duration of response was 11.1 months, and the median progression-free survival was 6.8 months. Additionally, stable disease was the best response in 43.5% of patients. Among all 126 sotorasib-treated patients, including two who were not included in the response analysis due to lack of measurable disease at baseline, the median overall survival was 12.5 months. The response rate observed in this trial is lower than that seen with tyrosine kinase inhibitors in patients with targetable mutations in receptor tyrosine kinases. This may be attributable to the molecular heterogeneity of *KRAS*-mutant tumors, which are often found in patients exposed to tobacco smoke (92.9% of patients in this trial currently or formerly smoked); further, cross-trial comparisons should be interpreted with caution. The safety profile for sotorasib was as expected based on the phase I results, with the most common treatment-related adverse events being gastrointestinal disturbances (particularly diarrhea, nausea, and vomiting), liver enzyme increases, and fatigue. The results of this trial supported the recent FDA approval of sotorasib for refractory *KRAS*^{G12C}-mutant locally advanced or metastatic NSCLC, and a phase III trial (CodeBreaK200) comparing sotorasib with docetaxel in this context is now under way. ■

Skoulidis F, Li BT, Dy GK, Price TJ, Falchook GS, Wolf J, et al. Sotorasib for lung cancers with KRAS p.G12C mutation. N Engl J Med 2021;384:2371–81.

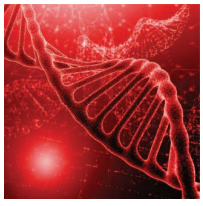
Clinical Trial

Major Finding: Posttreatment circulating tumor DNA (ctDNA) heralded relapse in patients with large B-cell lymphoma.

Concept: ctDNA was detectable at or before radiographic relapse in 94% of patients with disease progression.

Impact: ctDNA measurement may have utility as a disease-monitoring tool following CAR T-cell treatment.

CIRCULATING TUMOR DNA PREDICTS RELAPSE FOLLOWING CAR T-CELL TREATMENT



Treatment with the CD19-directed chimeric antigen receptor (CAR) T-cell therapy axicabtagene ciloleucel has been demonstrated to produce complete responses in patients with large B-cell lymphoma (LBCL) that resists or recurs following chemotherapy. These responses are sometimes lasting, but relapse is common, and its prediction has been a challenge. After a pilot study involving six patients hinted that levels of LBCL-specific circulating tumor DNA (ctDNA) characterized by lymphoma-specific VDJ clonotypes may have prognostic value in this context, Frank, Hossain, and colleagues conducted a prospective clinical trial to evaluate the utility of ctDNA measurement in 72 patients with LBCL treated with axicabtagene ciloleucel. Among all patients, the overall response rate (84.7%), complete response rate (63.9%), and median progression-free survival (10.3 months) were as expected for this population, as was the safety and toxicity profile. ctDNA levels before lymphodepletion were predictive of response to axicabtagene ciloleucel: Specifically, patients with pre-lymphodepletion lymphoma genomes per mL of plasma (LG/mL) values of between 100 and 1,000 had a median overall survival of 19 months, whereas median overall survival was 7.4 months for patients with 1,000 LG/mL or higher. Importantly, among the 60 patients whose disease responded and for whom samples were available for analysis, 83% (25 of 30) of those who had durable responses after a median follow-up period of one year had no detectable ctDNA on day 28 following CAR T-cell infusion, whereas 73% (22 of 30) of those who had disease progression had detectable ctDNA at the same time point. Additionally, all patients whose disease progressed had at least one ctDNA-positive blood sample prior to relapse. In 94% of patients who experienced disease relapse, ctDNA was detected at or before the time of radiographic relapse detection. Although a longer follow-up period would be required to investigate the use of ctDNA measurement for long-term disease monitoring, these findings indicate that this technique may have use as a noninvasive posttreatment surveillance method in the year following LBCL response to axicabtagene ciloleucel. ■

Frank MJ, Hossain NM, Bukhari A, Dean E, Spiegel JY, Claire GK, et al. Monitoring of circulating tumor DNA improves early relapse detection after axicabtagene ciloleucel infusion in large B-cell lymphoma: results of a prospective multi-institutional trial. J Clin Oncol 2021 Jun 16 [Epub ahead of print].