

Targeted therapy combination effective for patients with advanced cholangiocarcinoma and BRAF mutations

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In a Phase II trial led by researchers at The University of Texas MD Anderson Cancer Center, the combination of dabrafenib, a BRAF inhibitor, and trametinib, a MEK inhibitor, achieved a 51% overall response rate (ORR) in patients with cholangiocarcinoma marked by the BRAF V600E mutation.

This trial represents the first prospective study for [patients](#) with BRAF-mutated cholangiocarcinoma, or [bile duct cancer](#), and suggests this targeted therapy combination could serve as a much-needed [treatment option](#) for patients with treatment-resistant advanced disease. The trial results were published today in *Lancet Oncology*.

"In this study, we saw that the dabrafenib and trametinib combination demonstrates clinical benefit and should be considered as a therapeutic option for these patients," said lead author Vivek Subbiah, M.D., associate professor of Investigational Cancer Therapeutics. "These findings also reinforce the need for routine testing of BRAF mutations in patients with biliary tract cancers. As we move forward with precision oncology, we're seeing that alterations present in these rare cancers are actionable and the patients do benefit from targeted therapies."

This study is part of an ongoing Phase II, open-label, multicenter trial testing the efficacy and safety of the combination therapy in patients with a variety of BRAF V600E-mutated rare cancers. The bile duct

cohort enrolled 43 patients, all of whom had received at least one prior line of therapy.

Trial participants were 91% Caucasian, 5% Asian (Japanese heritage), 2% Asian (East Asian heritage) and 2% white (Arabic/North African). The [median age](#) was 57, with women accounting for 56% and men 44% of participants.

Bile duct cancer is a rare disease diagnosed in about 8,000 people each year in the U.S. Most cases are diagnosed at advanced stages, and thus clinical outcomes are generally poor, with a five-year survival rate below 20%. Standard of care includes surgery, when possible, and chemotherapy.

In patients with advanced disease, [median overall survival](#) with chemotherapy treatment is less than one year, so there is a significant unmet need for effective new treatment approaches, explained Subbiah.

Mutations in the BRAF gene are found in 5-7% of those diagnosed with bile duct cancer, and patients with the BRAF V600E mutation are more likely to have poor outcomes. Trials with single-agent therapies targeting BRAF have been effective for treating these patients, but have shown significant toxicities, including secondary malignancies.

However, combining these agents with MEK inhibitors, which act downstream in the same signaling pathway, have proven effective and are FDA-approved for use in other cancer types, including melanoma, lung cancer and anaplastic thyroid cancer. These agents are not currently approved by the FDA to treat cholangiocarcinoma.

In the current trial, the combination therapy achieved an ORR of 51% (22 patients) according to investigator assessments. The median duration of response was 8.7 months, with seven patients seeing an ongoing

response beyond 12 months.

Median progression-free survival was 9.1 months and median overall survival was 13.5 months, with 56.4% and 35.8% of patients still alive at 12 months and 24 months, respectively.

All patients experienced at least one adverse event, with the most common being fever, nausea, vomiting, diarrhea and fatigue. Twenty-four patients (56%) experienced a Grade 3 or 4 adverse event, the most common of which was an increase in gamma-glutamyltransferase, an enzyme found in the liver and bile ducts. According to the authors, these side effects were consistent with those seen previously from this combination in other [cancer](#) types.

"The trajectory of cholangiocarcinoma is changing rapidly," said co-author Milind Javle, M.D., professor of Gastrointestinal Medical Oncology. "Targeted therapy has made meaningful inroads, and this study is an excellent example of that. This is an important development for patients with cholangiocarcinoma and BRAF V600E mutations, who often have limited treatment options."

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Provided by University of Texas M. D. Anderson Cancer Center

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