MedicalXpress

First-in-class ERK1/2 inhibitor safe, shows early efficacy in patients with advanced solid tumors

December 15 2017

The novel ERK1/2 kinase inhibitor ulixertinib displayed an acceptable safety profile and had clinical activity in patients whose tumors had mutations in the MAPK cell-signaling pathway, according to data from a phase I clinical trial published in *Cancer Discovery*, a journal of the American Association for Cancer Research.

"A great number of cancers, including melanoma and lung cancers, have mutations in the MAPK/ERK pathway, and while current therapies target proteins in this cascade, many patients develop resistance to current drugs," said Ryan J. Sullivan, MD, assistant professor of hematology and oncology and member of the Termeer Center for Targeted Therapies at Massachusetts General Hospital. "The common denominator in these failed therapies is that the cancer has found a way to activate ERK. Therefore, the development of ERK inhibitors is a crucial next step to target this aberrant pathway."

The MAPK/ERK pathway is essential for key cellular processes, and mutations along this pathway may result in uncontrolled cellular growth, which can lead to cancer. The RAS gene, an upstream regulator within the MAPK/ERK cascade, is mutated in roughly 30 percent of human cancers. Mutations in BRAF, another gene in this pathway, often occur at codon V600 in malignant melanoma, where combined BRAF/MEK inhibition is the current standard of care. Atypical BRAF mutations (non-V600) are found in a variety of cancers. There is no targeted therapy for

patients with atypical BRAF-mutant cancers, said Sullivan.

The ERK gene is the final regulator in the MAPK/ERK pathway, and when upstream inhibition of this protein cascade fails, ERK signaling is reactivated, resulting in renewed MAPK signaling, Sullivan explained. "Targeting ERK for inhibition may allow the opportunity to thwart resistance from upstream mechanisms," he noted. Preclinical studies had shown ERK inhibition to overcome resistance to BRAF and MEK inhibitors.

Sullivan and colleagues tested the ERK inhibitor ulixertinib in an open-label, first-in-human study. They enrolled 27 patients in the dose-escalation phase and 108 in the dose-expansion phase. All patients had advanced solid tumors, and more than 65 percent had BRAF-mutant cancers. Of the patients, 24 percent had received prior BRAF and/or MEK therapy and 51 percent had received prior immunotherapy.

In the dose-escalation phase, the recommended phase II dose (RP2D) of ulixertinib was determined to be 600mg twice daily. The dose-expansion portion of the trial tested the RP2D of ulixertinib in six groups of patients whose tumors had BRAF, NRAS, or MEK mutations, the majority of whom were not treated with prior MAPK-targeted therapy. Partial responses (PR) were seen in 12 percent and 14 percent of evaluable patients in the dose-escalation and dose-expansion cohorts, respectively. PR and/or disease stabilization was seen in all groups, including solid tumors with atypical BRAF mutations.

"It was exciting to see responses in some patients, especially those with non-V600 BRAF mutations," said Sullivan. "We also saw responses in some patients with BRAF V600 mutant melanoma who had progressed on prior BRAF/MEK inhibitor therapy. ERK inhibition may be a potential way forward for these populations."

Patients treated at the RP2D had near-complete inhibition of ERK as verified in blood samples. Side effects were comparable to other MAPK inhibitors, and the most common treatment-related adverse event (AE) was rash. No AEs above grade 3 were observed.

"This study shows that ulixertinib is tolerable and has activity in a subset of patients with mutations in the MAPK pathway," said Sullivan. "The results of this study can be built upon to develop better treatment regimens for these patients."

Sullivan anticipates that ERK inhibitors will likely be used in combinatorial therapies, and they may supplement pre-existing regimens, such as BRAF/MEK inhibition. "I think we'll see very complex combinations tailored to specific cancer subtypes, and ERK inhibitors deserve to be part of the repertoire," Sullivan said.

Based on data from this trial, ulixertinib has received the U.S. Food and Drug Administration's Fast Track designation.

Limitations of the study include a small pool of expansion cohorts, as is consistent with a phase I trial, and lack of tumor pharmacodynamic analysis.

Provided by American Association for Cancer Research