AML study reports high response rates with combination targeted therapy

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Initial findings from a multi-national open-label phase Ib study of inhibitory drug therapy for relapsed or refractory acute myeloid leukemia (AML) have demonstrated a complete response in up to 50 percent patients say researchers at The University of Texas MD Anderson Cancer Center .

The patients, age 60 years or older, received therapy with venetoclax in combination with cobimetinib or idasanutlin. The clinical trial followed patients who received therapy for a prior blood disease and who were not eligible for cytotoxic therapy.

Preliminary results from the ongoing dose-escalation study, which demonstrated that the combination therapies can be safely administered with minimal side effects, were presented Dec. 11 at the American Society of Hematology's (ASH) Annual Meeting & Exposition Dec. 8-12 in Atlanta. The trial is headed by Marina Konopleva, M.D., Ph.D. and Michael Andreeff, M.D, Ph.D. , both professors of Leukemia, as well as Naval Daver, M.D., associate professor of Leukemia.

"This is the first clinical study evaluating new oral combinations with venetoclax in AML patients," said Konopleva. "This is significant as effective treatment options for patients with relapsed and/or refractory AML are limited."

Venetoclax, which inhibits the B-cell lymphoma protein (BCL-2) that makes cancer cells resistant to therapy, was previously FDA-approved

for treatment of chronic lymphocytic leukemia (CLL). Idasanutlin is an investigational drug targeting a protein called MDM2 which impacts the tumor suppressor gene p53, while cobimetinib targets a protein known as MEK within the cancer cell and is FDA-approved for treatment of advanced melanoma with BRAF mutation.

Andreeff and Konopleva also led the pre-clinical investigation resulting in the clinical trial. Findings from that research were published in the Dec. 11 online issue of Cancer Cell. The pre-clinical research demonstrated unprecedented in vivo activity, as well as a new molecular mechanism explaining how the inhibitor drugs impact MDM2 which is tied to regulation of p53, and BCL2 - both linked to cell death.

Pre-clinical data also showed that venetoclax plus cobimetinib or idasanutlin may be synergistic. MEK and MDM2 inhibition have been shown to down-regulate a protein in the BCL-2 family, MCL-1, overcoming the major resistance mechanism to BCL-2 inhibition in AML.

"We demonstrated that p53 activation overcomes the resistance to BCL-2 inhibition by promoting MCl-1 degradation and overcoming cell death response by altering cellular response," said Andreeff. "These findings laid the foundation for the development of the current combination clinical trial for AML, bringing together different investigations in my group that extended over 15 years."

Dose escalation is being used in the clinical trial to establish the maximum tolerated dose for each drug combination in elderly patient with relapsed AML, an area of unmet need, according to Daver.

"The best response rates, up to 50 percent in relapsed AML, were seen for the combination of venetoclax and idasanutlin, in line with the preclinical data," he said. "However, these results will require

confirmation in larger patient groups."

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