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First-in-class investigational therapeutic shows early promise for lymphoma patients

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Pevonedistat is a first-in-class, investigational small-molecule inhibitor of the NEDD8-activating enzyme, explained Shah. "This enzyme is part of the ubiquitin-proteasome system, which is the target of a number of FDA-approved anticancer therapeutics, including bortezomib (Velcade), which is used to treat multiple myeloma and various types of lymphoma. Pevonedistat also alters the ability of cancer cells to repair damaged DNA," he said.

Shah and colleagues enrolled 44 patients in the phase I clinical trial, 17 with relapsed/refractory multiple myeloma and 27 with relapsed/refractory lymphoma. Twenty-seven patients received escalating doses of pevonedistat on schedule A, which was days one, two, eight, and nine of a 21-day cycle, and 17 received escalating doses of the therapeutic on schedule B, which was days one, four, eight, and 11 of a 21-day cycle.

Three patients achieved a partial response: one with relapsed nodular sclerosis Hodgkin lymphoma, one with relapsed diffuse large B-cell lymphoma, and one with relapsed peripheral T-cell lymphoma. Another 30 patients, 17 with lymphoma and 13 with multiple myeloma, achieved stable disease.

The maximum tolerated doses were 110 and 196 milligrams per meter squared on schedule A and B, respectively. Serious adverse events, including anemia, neutropenia, and pneumonia, were experienced by eight patients on each schedule.

Shah said, "The most important findings from our study are that pevonedistat hits its target in cancer cells in patients, can be given safely, and has modest activity in heavily pretreated patients with relapsed/refractory lymphoma, suggesting that we are on the right path. Although pevonedistat had modest activity as a single agent treatment, we expect greater activity when it is given in combination with standard therapy, and there are a number of combinations currently in clinical testing for acute myeloid leukemia."

"The pharmacodynamics data showed that pevonedistat hit its target in cancer cells in patients at low doses," he added. "This is important because it may mean that we do not need to escalate the dose in future trials to increase anticancer activity; this has the potential to increase the risk:benefit ratio of pevonedistat."

Shah added that the researchers are very grateful to all the patients who enrolled in this and other trials because without patients, progress against cancer cannot be made.

According to Shah, a limitation of this study is that this is a phase I clinical trial that enrolled only small numbers of patients, all of whom were very heavily pretreated, which may limit assessment of how active pevonedistat could be.

The study is published in the *Clinical Cancer Research*, a journal of the American Association for Cancer Research.

Provided by American Association for Cancer Research