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Benefit of novel drug in breast cancer seen in blood within weeks

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Clinical benefit from use of a novel histone deacetylase inhibitor drug may be determined by examining blood cells days after a patient receives treatment. The drug, entinostat, is the first histone deacetylase inhibitor successfully tested in a randomized, placebo-controlled study in metastatic breast cancer — and is the first to show that clinical outcome can be predicted shortly after administration.

The findings, reported at the AACR-NCI-EORTC International Conference: Molecular Targets and Cancer Therapeutics, held Nov. 12-16, 2011, represent an advance in the goal to offer patients only those therapies that will help treat cancer effectively, the researchers said.

"The ability to have a marker of benefit within the first several weeks of using this drug represents an exciting advance in personalized medicine," said lead researcher Peter Ordentlich, Ph.D., executive director of translational science and a founder of Syndax Pharmaceuticals Inc. in Waltham, Mass. Syndax Pharmaceuticals developed entinostat, an oral small-molecule drug that inhibits enzymes that alter the packaging of DNA inside the nucleus, which controls gene expression.

"The goal of entinostat in breast cancer is to extend the benefit of hormone therapy and delay the time that patients will need to use chemotherapy," said Ordentlich. More than 160,000 women are diagnosed each year with estrogen receptor (ER)-positive invasive breast cancer, and many are treated with agents that block the hormone. But most women become resistant to these therapies, and entinostat,

combined with antihormone agents, is meant to extend their benefit, he said.

To test that strategy in ER-positive metastatic breast cancer, Syndax Pharmaceuticals conducted ENCORE-301, a randomized, placebo-controlled, phase 2 study (n=130) testing the use of exemestane, an aromatase inhibitor, with either entinostat or placebo.

Results of the clinical trial, released in September, showed that the combination therapy delayed cancer progression by 27 percent (4.3 vs. 2.3 months) compared with exemestane treatment alone. At a median follow-up of 18 months, overall survival was also significantly longer with exemestane plus entinostat than with exemestane plus placebo (26.9 vs. 20.3 months).

In this subset analysis, researchers examined blood samples from 49 patients (27 received combination therapy) to evaluate whether changes in circulating blood cells that reflected the activity of the histone deacetylase (HDAC) inhibitor could be detected. Researchers measured protein lysine acetylation, a biological marker of entinostat activity, in B cells, T cells and monocytes in blood samples taken at pretreatment and one, eight and 15 days after therapy with entinostat, which is taken once a week.

While levels of lysine acetylation after one day were not linked to clinical benefit, levels measured eight and 15 days after therapy were related to clinical benefit, Ordentlich said. Researchers found that patients with elevated levels of protein lysine acetylation had a 68 percent reduced risk for disease progression compared with those patients who did not have sustained elevated levels.

Researchers found that hyperacetylation was also associated with longer median progression-free survival across cell lines: B cells, 8.5 vs. 1.9

months; T cells, 6.6 vs. 1.8 months; and monocytes, 6.2 vs. 1.9 months. "Those patients who were able to maintain acetylation did well," Ordentlich said.

He added that entinostat's long half-life and unique pharmacology allow researchers to quickly gauge the agent's activity. In this way, "we gain insight into how to use HDAC inhibitors, as a class of cancer drugs, in a variety of solid tumors," he said.

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