Everolimus improves progression-free survival for patients with rare pancreatic cancer

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In an international Phase III randomized study, everolimus, an inhibitor of the mammalian target of rapamycin (mTOR), has shown to dramatically improve progression-free survival for patients with advanced pancreatic neuroendocrine tumors (pNET), according to researchers from The University of Texas MD Anderson Cancer Center.

The findings were published in the latest New England Journal of Medicine. James C. Yao, M.D., associate professor in MD Anderson's Department of Gastrointestinal Medical Oncology, first presented the at the 2010 European Society for Medical Oncology Congress.

pNET is a more rare and less aggressive form of pancreatic cancer than the more common adenocarcinoma. Also called islet cell carcinoma, pNET involves cells that secrete a variety of hormones. Tumors can be functional and produce high amounts of hormones, or non-functional and not produce any hormones. While pNET tumors account for approximately one percent of pancreatic cancers by diagnosed incidence, they also represent 10 percent by prevalence, because of the longer survival of patients, explained Yao.

"Up until now, there have been no large-scale, well-conducted randomized studies to guide treatment decisions for patients with pancreatic neuroendocrine tumors. In fact, currently, there's only one approved therapy for the treatment of this rare disease," said Yao.

"However, there's disagreement among experts treating patients with neuroendocrine tumors about how effective that therapy is, as it's highly toxic for a disease that is considered relatively indolent."

Everolimus, an immunosupressant agent used to prevent rejection of organ transplants, also has anti-angiogenic properties. It inhibits the mTOR protein, a central regulator of tumor cell division and blood vessel growth in cancer cells. The once-daily oral therapy was approved in March 2009 for advanced renal cell carcinoma, and is currently being tested in a host of other disease sites, including lymphomas, breast, skin, gastric, liver, colon and prostate cancers.

"We became interested in everolimus because we noticed a number of genetic cancer syndromes in the mTOR pathway were associated with neuroendocrine tumors, and others also found that the dysregulation of this pathway in sporadic tumors is also linked to poor prognosis. A single-center study conducted with the agent in neuroendocrine tumors at MD Anderson showed promising activity and resulted in the development of this large international trial."

In a recent manuscript published in Science, multiple mutations in the mTOR pathway were also indentified from pancreatic neuroendocrine tumors, said Yao.

The international double-blind trial, RADIANT-3, enrolled 410 patients with advanced, low or intermediate grade pNET. Patients were randomized to receive either 10 milligrams of everolimus or placebo. The primary endpoint was progression-free survival. Median exposure to everolimus was 38 weeks, compared to 16 weeks on placebo. At progression, patients were unblinded, and those randomized to placebo were offered open-label everolimus.

The researchers found that everolimus was associated with a 65 percent

reduction in the risk of progression and an increase in median progression-free survival of more than six months, from 4.6 to 11 months. Eighteen-month progression-free survival was 34 percent for those in the everolimus arm, compared to 9 percent for the placebo.

"Because treatment options available to patients with pancreatic neuroendocrine tumors are so limited, and the data in terms of the size of the treatment effect is so clear, I do believe this research will have immediate clinical applications," said Yao. "Hopefully, these findings will ultimately lead to a definitive change in the standard of care for those patients with pancreatic neuroendocrine tumors."

Common side effects associated with everolimus include: an inflammation or ulceration of the mouth known as stomatis, rash, diarrhea, fatigue and infections.

At MD Anderson, a follow-up study for the treatment of pNET with everolimus and an IGFR inhibitor is soon to open, and another studying the therapy in combination with bevacizimab was just completed.

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