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Everolimus improves progression-free survival for patients with advanced, nonfuctional neuroendocrine tumors

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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, nonfunctional neuroendocrine tumors (NET) of the lung and gastrointestinal tract.

James C. Yao, M.D., professor and chair, The University of Texas MD Anderson Cancer Center's Department of Gastrointestinal Medical Oncology, presented the findings today in Vienna, Austria during the presidential session of the European Cancer Congress, co-sponsored by the European Cancer Organisation and European Society for Medical Oncology.

NETs develop from cells in the neuroendocrine system, which is responsible for producing specific hormones that regulate the functions of different organs in the body. NETs can be slow-growing or aggressive, and are found most commonly in the lungs or gastrointestinal system. Nonfuctional NETs are those that do not secrete a hormone. About 80 percent of all NETs are nonfunctional, and therefore, patients often have few side effects and are diagnosed later, explains Yao.

According to Yao, the incidence of NETs is 5.25 per 100,000, with the occurrence on the rise. Data from population-based registries indicate that more than 51 percent of NETs appear in the GI tract, 27 percent in

the lungs and six percent in the pancreas, says Yao.

Everolimus, an immunosuppressant drug 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.

Yao and MD Anderson have a long history of development with the drug for neuroendocrine tumors. In 2011, the once-daily regimen was approved as frontline therapy for pancreatic neuroendocrine tumors (pNET), with Yao and MD Anderson leading all phases of clinical research - from early studies to the pivotal Phase III trial showing everolimus' progression-free survival benefits.

"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,: said Yao. "MD Anderson's single-center study conducted with the agent in neuroendocrine tumors showed promising activity and resulted in the confirmatory large international trials and the drug's subsequent approval. This study also builds on MD Anderson efforts and covers the rest of neuroendocrine tumors, including the lung and the GI tract."

For many of these patients there are few to no treatment options available. For example, there are no therapies approved for lung NETs, which account for more than 25 percent of all NETs and are more aggressive, explains Yao.

The international double-blind trial, RADIANT-4, enrolled 302 patients with advanced, nonfunctional NETs of the lung or GI tract. The media age of participants was 63. All were randomized to receive either 10 milligrams of everolimus or placebo, with a two-to-one ratio, everolimus

to placebo, respectively. Most common tumors included nonfuctional NETs of the lung and the small intestine, 30 and 24 percent, respectively. The primary endpoint was progression-free survival. Both groups were well matched for prior therapy.

Everolimus was associated with a statistically significant 52 percent reduction in the risk of progression or death and an increase in median progression-free survival of more than seven months. The researchers also found a trend toward improved overall survival; however, survival analysis was an interim analysis, and too early to conclusively determine at this time. Both survival and quality of life data will be analyzed in follow-up analyses.

Everolimus was well tolerated. Common side effects associated with the therapy include: an inflammation or ulceration of the mouth known as aphthous ulceration, rash, diarrhea, fatigue and infections.

"We were pretty confident that the drug would be active in this broader range of neuroendocrine tumors but the magnitude of the treatment benefit is wonderful to see - even stronger than we saw in previous studies," says Yao. "The field of treating these diseases has changed so drastically over the last decade and to be able to potentially offer patients for whom there were no options a therapeutic benefit is very exciting."

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

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