

Lenvatinib shows promise for patients with radioiodine-refractory thyroid cancer

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In a pivotal Phase III study led by researchers at The University of Texas MD Anderson Cancer Center, the oral anti-angiogenic therapy lenvatinib has shown dramatic improvement in progression-free survival in patients with advanced radioiodine-refractory thyroid cancer.

The global study, led by Steven I. Sherman, M.D., associate vice-provost for Clinical Research, and professor and chair, Endocrine Neoplasia and Hormonal Disorders, MD Anderson, is published in the *New England Journal of Medicine*, and could offer a new treatment paradigm for a group of patients for whom, until recently, there has been no new effective treatment since the 1940s. Preliminary findings were first reported at last year's American Society of Clinical Oncology Annual meeting; the published study includes updated data.

According to the American Cancer Society, 62,450 people will be diagnosed with [thyroid cancer](#) in 2015 and 1,950 will die from the disease. It's the fastest growing cancer type, says Sherman, with rates of refractory disease also on the rise. Until recent therapeutic advances, historically, radioactive iodine has been the only treatment available to patients with metastatic thyroid disease, explains Sherman. While it does offer cure to a select group of patients, more than half do not respond to the therapy.

"For decades, in this patient population, the treatment was often to repeat ineffective doses of radio-active iodine, and possibly salvage therapy with chemotherapy," says Sherman the study's senior author and

the international principal investigator. "About 10 years ago, with the growing availability of novel targeted agents and multi-targeted kinase inhibitors, we began to recognize potential for treating this subgroup of patients with anti-angiogenic therapy and sought to enroll those with refractory disease in clinical trials."

MD Anderson has a long history of studying lenvatinib, with investigators leading both Phase I and II studies. The institution was the first to study the therapy in refractory thyroid cancer patients. It also led the global Phase III trial; Mouhammed Habra, M.D., associate professor, Endocrine Neoplasia and Hormonal Disorders, was the institution's principal investigator of the Phase III trial.

The international, randomized, Phase III double-blind study enrolled 392 patients - all of whom had progressive, refractory disease - from 21 countries. Patients were randomized at a two-to-one ratio to receive either the study drug or placebo, respectively. In total, 261 received lenvatinib and 131 received a placebo. At the time of disease-progression, patients in the placebo arm could receive lenvatinib. The primary endpoint was progression-free survival; secondary endpoints tested response rate, overall survival and safety.

For those who received the study drug, the median progression-free survival rate was 18.3 months, compared with 3.6 months in those who received placebo. The overall response rate in the study arm group was 64.8 percent (with four complete and 165 partial responses), and 1.5 percent in the placebo arm. The median overall survival was not reached in either group.

For patients with advanced and metastatic disease, lenvatinib and this class of drugs is the first potential for improved overall survival.

"In our study, we not only saw a dramatic improvement in progression-

free survival, there was also a 65 percent response rate - almost unprecedented results for thyroid cancer patients with such advanced disease. We also found a strongly suggestive trend in how long patients lived, and a small number of patients had a complete response. While we couldn't identify tumor mutations that might predict response, this represents a very exciting area of study going forward in hopes of possibly offering cure to a greater number of patients," says Sherman.

The drug is not without side effects - more than 40 percent of patients that received lenvatinib experienced some reaction, with hypertension being the most common, but could be managed, says Sherman. Other side effects included: diarrhea, fatigue, nausea, decreased appetite and weight; 37 patients discontinued the drug because of adverse effects. Also, six of 20 deaths that occurred during the treatment period were determined to be drug-related by their treating physicians.

"The side effect profile is actually quite typical for this class of drugs. We've learned over the years to be aggressive about dosing modifications and coming up with clever ways of helping patients tolerate the medication where drug effectiveness is maintained but with a minimum of those side effects. It's paramount that patients are selected carefully and physicians giving the drug focus on symptom support," says Sherman.

A number of follow up studies with lenvatinib are in development, including in other types of thyroid cancers, and in combination with other novel therapies for radioiodine refractory [patients](#).

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

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