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distant metastatic disease, and the ten-year survival rate for patients with metastatic tumors that fail to respond to RAI is approximately 10 percent.

According to [James A. Fagin, MD](#), Memorial Sloan Kettering's Endocrinology Service Chief and senior author on the study, many trials have tested strategies for overcoming RAI resistance in metastatic thyroid cancers, but none have been successful. Previous studies have shown that a cell's ability to absorb RAI is controlled by the MAPK pathway, so Dr. Fagin and his colleagues examined whether selumetinib, an MAPK inhibitor, could reverse RAI resistance by inhibiting the signaling of genetic mutations in this pathway. The approach proved effective, especially in patients with thyroid cancers that contain a mutation in the *RAS* gene – a component of the MAPK pathway.

"Blocking this key pathway increased the uptake of iodine, making radioiodine treatment potentially effective once again," said Fagin, who led this research in cells and in mice.

Following a five-day low-iodine diet, researchers administered selumetinib to 20 patients with tumors resistant to radioiodine. After four weeks, patients underwent a diagnostic scan that measured how much RAI their tumors would absorb. In eight patients, including all five with an *NRAS* gene mutation, selumetinib increased iodine uptake enough to allow patients to undergo RAI therapy.

Following RAI, five patients had confirmed partial responses and three had stable disease. In seven of the eight patients, outcomes remained unchanged during six months of follow-up. All eight patients had a decreased level of serum thyroglobulin – a protein in the blood used to screen for advanced thyroid cancer – and none experienced serious side effects from selumetinib.

"An advantage of this therapeutic strategy is that only a short course of drug therapy is required to elicit a significant clinical effect," Fagin said, adding that "the initial results show promise for *RAS*-mutant disease, but the hope is that a larger trial will shed light on whether selumetinib can be effective for a broader range of advanced thyroid cancer subtypes."

Memorial Sloan Kettering will lead the international, multicenter phase III clinical trial of selumetinib later this year. The trial, which will be sponsored by AstraZeneca, will enroll patients who have recently had their thyroid gland removed – a procedure known as total thyroidectomy – due to thyroid cancer that has spread to nearby tissue or lymph nodes.

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