No benefit from pazopanib in advanced kidney cancer after surgery to remove metastases

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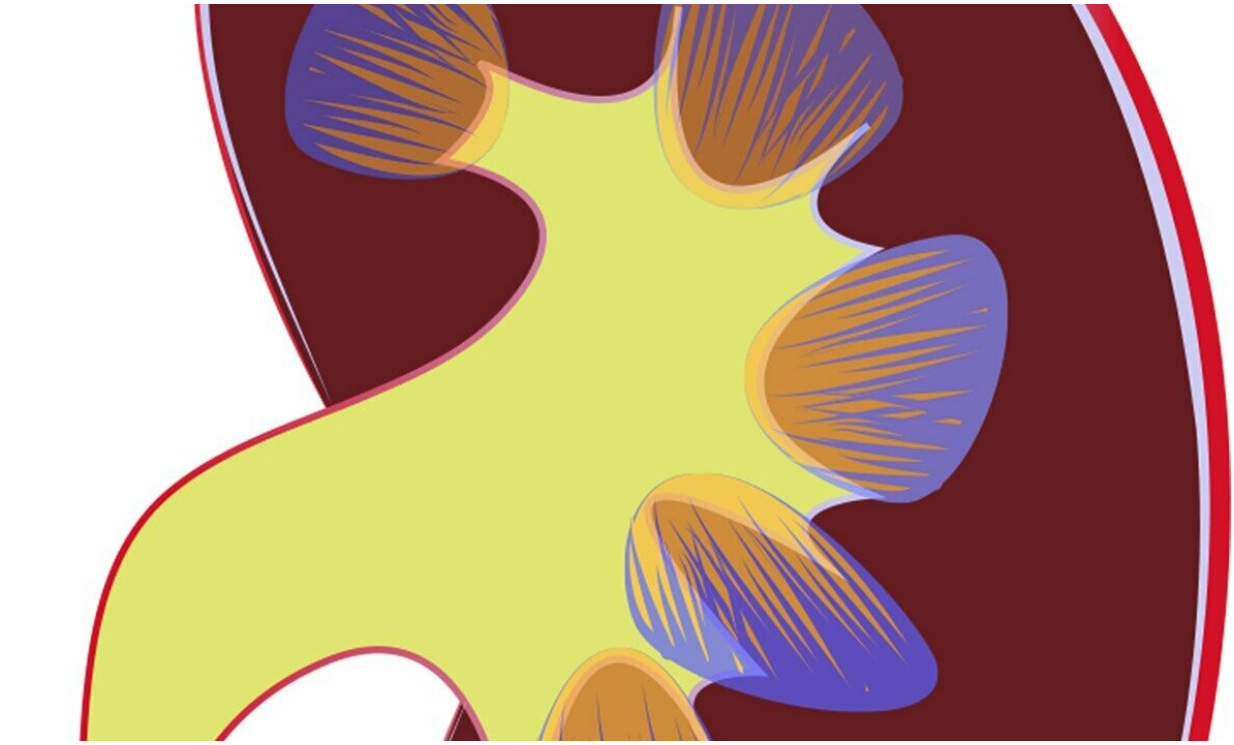

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The E2810 research study was conducted to determine whether taking the oral drug pazopanib (Votrient) following surgery to remove further metastases in patients with advanced renal cell carcinoma would improve

their disease-free survival. The trial was designed and conducted by researchers in the ECOG-ACRIN Cancer Research Group with funding from the National Cancer Institute, part of the National Institutes of Health. Results from the study were presented today at the 2019 meeting of the American Society of Clinical Oncology in Chicago, showing that the study did not meet its primary endpoint of disease-free survival (Meeting Abstract 4502).

"E2810 found that pazopanib treatment for one year did not improve the chance of survival without disease recurrence," said lead investigator Leonard J. Appleman, MD, Ph.D., a medical oncologist at the University of Pittsburgh and UPMC Hillman Cancer Center. "This finding is important because these patients are at particularly high risk of recurrence, and treatments shown to benefit patients with metastatic disease in place have been attractive to study after surgery to completely remove all visible sites of cancer." These findings are consistent with earlier studies with other VEGF tyrosine kinase inhibitors.

There are about 58,000 new diagnoses of renal cell carcinoma, or kidney cancer, annually in the US. Of these, about 20-30 percent are advanced, or Stage IV, cancer at diagnosis. Surgical removal of the entire kidney (nephrectomy) or partial nephrectomy is standard for patients with localized kidney cancer and select patients with metastatic disease.

Average survival for patients with Stage IV disease is about two to three years and long-term survival is uncommon. These were the patients being studied in trial E2810 (NCT01575548).

Following initial surgery, select Stage IV patients may undergo another surgery to remove one or a very limited number of metastases that develop (oligometastases). This approach (metastasectomy) can remove all evidence of disease and can sometimes lead to durable control of disease, meaning no presence of disease for months or even years.

However, most patients ultimately recur. No systemic therapy has been shown to benefit this population, thus, the current standard of care outside of a clinical trial remains surveillance following the surgery to remove the metastases.

Pazopanib is an inhibitor of VEGFR and other kinases that is approved by the US Food and Drug Administration for patients who have metastatic renal cell carcinoma. However, it has not been tested in patients with no evidence of disease following a surgery to remove the metastases, and is considered experimental in this situation.

E2810 was a randomized, double-blind, placebo-controlled trial to test the hypothesis that pazopanib would improve disease-free survival in Stage IV patients with no evidence of disease following a surgery to remove the metastases. The researchers were testing the multi-modality approach of metastasectomy and post-operative systemic therapy with pazopanib.

"The trial did not show a benefit and in fact, there was a suggestion that the patients who received pazopanib had a shorter lifespan," said Dr. Appleman. "This observation was not statistically conclusive and longer follow up of the patients who participated in this study may clarify this observation."

From August 2012 to July 2017, 129 eligible patients were enrolled into the trial by physicians at 58 clinical sites across the US. The sites are affiliated with one or more of the four Network Groups in the NCI National Clinical Trials Network that address cancer in adults. These groups include the Alliance for Clinical Trials in Oncology, ECOG-ACRIN Cancer Research Group, NRG Oncology, and SWOG.

Patients were randomized 1:1 to receive pazopanib starting at 800 mg daily versus placebo for 52 weeks. Patients were stratified by 1 versus >

1 site of resected disease, and by disease-free interval ? versus > 1 year. Clinical assessments for toxicity and patient reported outcomes were performed every 4 weeks, and restaging scans were performed every 12 weeks.

The median follow-up from randomization was 30 months (range 0.4—66.5 months). More than half the patients have had a recurrence of their cancer either during the treatment period or in later follow up. Most (83 percent) of the patients are still alive and some have begun further treatment.

In 2016, *The Lancet* published the final results of ECOG-ACRIN's definitive phase III trial, E2805, which found no role for sunitinib or sorafenib in preventing recurrence of locally-advanced renal cell carcinoma.

"Given the results of E2810, the role of adjuvant VEGFTKI therapy appears to be limited for both primary resected kidney cancer at high risk for recurrence and for resected metastases," said co-investigator Naomi B. Haas, MD, a medical oncologist at the University of Pennsylvania and co-chair of the ECOG-ACRIN Genitourinary Cancer Research Committee. "This may be due to the absence of tumor blood vessels to target, compounded with an intolerable side effect profile in many patients. The focus has now turned to the role of immune checkpoint inhibition in both settings."

The role of perioperative and/or post metastasectomy immune checkpoint inhibitors is being addressed in four ongoing randomized phase III trials for renal cell carcinoma patients:

- PROSPER RCC/EA8143 (805-patient goal) is an ECOG-ACRIN trial sponsored by the National Cancer Institute evaluating nivolumab with or without nephrectomy

(NCT03055013)

- KEYNOTE 564 (950-patient goal) is studying pembrolizumab in patients who have undergone nephrectomy (NCT03142334)
- IMmotion010 (778-patient goal) is evaluating atezolizumab in patients who have undergone nephrectomy (NCT03024996)
- RAMPART (1,750-patient goal) is a three-arm trial assessing durvalumab alone or in combination with tremelimumab, compared to active monitoring, for patients with localized disease who have undergone nephrectomy (NCT03288532)

Patient reported outcomes and laboratory correlates will be reported separately.

More information: Naomi B Haas et al. Adjuvant sunitinib or sorafenib for high-risk, non-metastatic renal-cell carcinoma (ECOG-ACRIN E2805): a double-blind, placebo-controlled, randomised, phase 3 trial, *The Lancet* (2016). DOI: 10.1016/S0140-6736(16)00559-6

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