

Tracking Trends From Web-based Sources, Translational Research, the FDA, and Patient Registries

First Patient Treated in TRACE Renal Registry

NASHVILLE—Vanderbilt University Medical Center has treated the first patient to be included in a new registry—Tracking Renal Tumors After Cryoablation Evaluation (TRACE).

The registry will allow physicians and Galil Medical to follow and evaluate the use and effectiveness of cryotherapy treatment for patients with renal tumors. “TRACE is an opportunity to prospectively assess the effectiveness and safety of cryoablation in the management of renal cell carcinoma in a rigorous, scientific way across multiple institutions and surgeons using a standardized treatment platform and data collection instrument,” said Peter Clark, MD, associate professor in the Department of Urologic Surgery at Vanderbilt Medical Center.

Galil Medical launched the TRACE Registry in May of 2010 and expects to enroll about 250 patients at 10 sites in the US.

WILEX Successfully Completes Phase 1 Study With the MEK Inhibitor WX-554

MUNICH—WILEX AG has successfully completed a phase 1 dose escalation study with the mitogen-activated protein kinase (MAPK) inhibitor, WX-554, demonstrating for the first time, activity in humans. Mitogen-activated protein kinase has been shown to play a central role in signal transduction and has been linked to a multitude of biological processes such as cell division, cell differentiation, and cell death. The MAPK signalling pathway is overexpressed in more than 30% of cancers, resulting in uncontrolled cell growth and proliferation.

The trial aimed to determine safety, tolerability, and the optimal dose for the inhibition of the MAPK system by WX-554. The study, which was conducted in Germany, tested 5 increasing WX-554 dose levels, each administered once by a 15-minute infusion to 25 healthy male volunteers. In addition to safety and tolerability, the pharmacokinetic and pharmacodynamic properties of the MAPK inhibitor were also investigated. The substance was safe and well tolerated by the 25 volunteers. The MAPK signal transduction pathway was inhibited in a dose-dependent manner reaching complete inhibition at 1 mg/kg body weight.

Paul Bevan, PhD, head of research and development and a member of the Executive Management Board of WILEX AG, said: “We are delighted with the positive results of WX-554 in this study. With it, we have a further product in our clinical pipeline which, due to its mecha-

nism of action, could be used in many oncological indications. We will now initiate the further development of this promising agent with the clinical testing of an oral formulation.”

Hopkins Team Manages RCC in Vena Cava

BALTIMORE—Renal cell carcinoma may metastasize to the inferior vena cava, posing a major risk of thrombosis from its location in this largest of veins.

“If it’s just blocking the vena cava and not invading into the wall,” says Mohamad Allaf, MD, “for many people, this occlusion is the biggest threat to their life.” But now, adds Dr Allaf, with the help of a specialized team and a meticulously choreographed, multidisciplinary approach, this clot is often very treatable. “If we take that threat away, and there’s no metastasis, many are actually cured of their disease.” Some people also need medical therapy to manage any remaining tumor.

Dr Allaf, Director, Minimally Invasive and Robotic Surgery, Johns Hopkins Hospital, works with a group of surgeons whose combined expertise covers the entire vein; his territory includes the urologic areas. If the tumor lies below the diaphragm, he usually turns to vascular surgeon James Black, MD. “Often, we need to open up or even resect the vena cava and then reconstruct it,” Dr Allaf explains. When the tumor sits closer to the heart, a cardiothoracic surgeon steps in. “Sometimes we put patients on bypass,” added Dr Allaf, “so that we can get good access to the vena cava near the heart. At times we’ll even open up the heart to remove the tumor.”

The team mobilizes as soon as a patient comes in and is identified as a good surgical candidate. Dr Allaf, along with urologists Edward Schaeffer, MD and Ronald Rodriguez, MD, oversees the initial evaluation. “Often,” he says, “we’ll admit patients to the hospital the same day we see them, because a tumor thrombus is a ticking time bomb.”

Overcoming TKI Resistance With IL-8

GRAND RAPIDS, MI—Van Andel Research Institute (VARI) researchers say they have reversed resistance to sunitinib. Most patients who respond to sunitinib develop a resistance to the drug after 1 year of treatment. Kidney cancer is among the 10 most common cancers in both men and women, affecting nearly 50,000 Americans in 2009 and killing more than 11,000. Renal cell carcinoma (RCC) accounts for 9 out of 10 kidney cancers, and clear cell (ccRCC) is the most common subtype, accounting for 8 out

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of 10 RCC cases.

The research is a critical step forward in understanding the mechanisms of response and resistance to the new standard of care therapies in renal cell carcinoma such as sunitinib," said Brian Rini, MD, Solid Tumor Oncology, Cleveland Clinic Taussig Cancer Institute. Sunitinib received FDA approval in 2006 and is a standard of care for both ccRCC and gastrointestinal stromal tumors. The drug is being investigated as a possible therapy for breast cancer colorectal cancer, and non-small cell lung cancer.

Researchers found that ccRCC tumor cells that had developed a resistance to sunitinib had increased secretion of interleukin-8 (IL-8). Administering sunitinib and IL-8 neutralizing antibodies sensitized tumors to sunitinib treatment. Researchers also found that IL-8 may serve as a useful biomarker to predict patients' response to sunitinib treatment.

"The development of ccRCC resistance to sunitinib treatment is of major clinical concern," said VARI Distinguished Scientific Investigator Bin Tean Teh, MD, PhD, whose laboratory published its findings in *Cancer Research*. "It is now of critical importance to validate these findings in the clinical setting." Another study from Dr Teh's laboratory also published in *Cancer Research* this month looked into exactly how sunitinib works. The study found that the treatment does not target tumor cells but rather the tumor's blood supply.

Proteins May Hold Genetic Clues to ccRCC Mechanisms

JACKSONVILLE, FL—Researchers at the Mayo Clinic in Jacksonville say they have found several genetic clues to understanding how the most common type of kidney cancer grows and turns deadly.

Comparing healthy kidney cells to those overtaken by cancer, scientists identified 4 proteins that they say account for some of ccRCC quirks. Those quirks include the fat cells that make it appear clear and the stem cell-like behavior that makes it resistant to chemotherapy and radiation.

Their findings could lead to the development of targeted medicines or combinations of existing drugs to attack kidney cancer at its molecular level. However, some of the clues are based on speculation and may require years of further analysis to confirm.

"Before this study, we didn't know what to test," said Han W. Tun, MD, a Mayo Clinic hematologist and oncologist. "Now we have a target." Dr Tun's study is the first to examine kidney cancer's entire genome — a molecular "forest" of 25,000 individual genes — to sift out a few promising genetic "trees." Dr Tun and fellow researcher John Copeland, PhD, also of Mayo Clinic Florida, said they targeted parts of the genome known to be responsible for the cell's growth and survival — the better to kill it off later. Four proteins stood out. In each case, they barely existed in the cancer cells. In a related study published earlier, other Mayo researchers found that kidney cancer easily develops when one of Dr Tun's genes, GATA3, is turned off. Further lab tests — manually turning genes "on" and "off" and watching the results — are necessary to confirm whether the other 3 proteins play important roles as well. **KCJ**