

## New Drugs for Myeloproliferative Neoplasms Ease Suffering and Extend Life

By Sarah Bronson

**A new class of drugs has redefined treatment for patients with myeloproliferative neoplasms by easing their symptom burden while extending their lives.**

Clinicians who treat patients with these difficult-to-cure diseases—including myelofibrosis, polycythemia vera, and essential thrombocythemia—have shifted their focus toward easing symptoms, reducing disease-associated biological abnormalities, improving quality of life, and prolonging survival.

“This significant symptom reduction is more than palliation—it is life altering,” said Srđan Verstovsek, M.D., Ph.D., a professor in the Department of Leukemia at The University of Texas MD Anderson Cancer Center who has led and is leading numerous trials of new treatments for myeloproliferative neoplasms.

### Myelofibrosis treatment

Of the myeloproliferative neoplasms, myelofibrosis—marked by an uncontrolled growth of bone marrow cells, reactive bone marrow fibrosis, and a subsequent lack of red



*A patient with advanced myelofibrosis is shown in April 2008 (left), when he began treatment with ruxolitinib, and in January 2014. His symptoms and quality of life improved dramatically with treatment. Reprinted with permission from Verstovsek S. Blood 2014;123(12):1776–1777.*

blood cells—is the most aggressive. Myelofibrosis can cause enlargement of the spleen or liver, systemic symptoms related to inflammation, and anemia. These issues together can lead to cachexia, difficulty walking, and poor performance status; patients with myelofibrosis typically die within 5–7 years of their diagnosis.

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# New Drugs for Myeloproliferative Neoplasms

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## *JAK2 inhibitors*

Until recently, no treatments were approved for myelofibrosis, and the disease was treated with the off-label use of drugs such as hydroxyurea, thalidomide, lenalidomide, and steroids. But in late 2011, the JAK2 inhibitor ruxolitinib was approved by the U.S. Food and Drug Administration (FDA) for the treatment of myelofibrosis. And phase III trials of newer JAK2 inhibitors, pacritinib and momelotinib, for the treatment of myelofibrosis are under way at MD Anderson.

JAK2 inhibitors can effectively treat organomegaly and systemic symptoms caused by myelofibrosis. Nearly all patients with myeloproliferative neoplasms have mutations that activate the intracellular JAK/STAT pathway; indeed, JAK2 inhibition has led to responses in patients with or without a JAK2 gene mutation.

“The antiproliferative and anti-inflammatory effects of JAK2 inhibitors are evident, and people treated with these drugs get better. They don’t have any more bone aches, itching, and sweating; they gain weight; and they walk more. And now we know that with good control of these symptoms, we actually can make people live a few years longer,” Dr. Verstovsek said.

Ruxolitinib was approved for the treatment of myelofibrosis not because it can cure the disease but because it can make the disease much more bearable. Dr. Verstovsek said, “Drugs are usually approved on the basis of how many patients have their disease eliminated and how long that lasts. But with myelofibrosis, the FDA has recognized the need to address the suffering that this disease brings to patients and the benefits of improving the symptoms—helping people enjoy life again, travel, do what they want, and live longer—without eliminating the disease. We are realizing that this type of strategy makes a difference in patients with myeloproliferative neoplasms.”

Researchers intend to continue improving this type of treatment and combining JAK2 inhibitors with other

## “This significant symptom reduction is more than palliation—it is life altering.”

– Dr. Srdan Verstovsek

new drugs to increase the inhibitors’ efficacy and decrease their side effects.

### *Path to definitive treatment*

JAK2 inhibitors and other drugs currently used to treat myelofibrosis and other myeloproliferative neoplasms do not cure the disease. Chemotherapy followed by stem cell transplantation is the only treatment with the potential to cure myelofibrosis. But most patients with myelofibrosis are too sick to withstand the process, and the few who do undergo transplantation are at a significant risk of dying from complications of the transplant, such as graft-versus-host disease.

However, treatment with JAK2 inhibitors has been shown to help some patients with myelofibrosis become healthy enough to undergo transplantation successfully. The targeted therapy thus not only treats symptoms and improves functional status in these patients but also improves the chances of a cure for some. Dr. Verstovsek said, “With further progress in symptom-controlling treatment, we hope that the number of patients eligible for the transplant will increase and that we will eventually be able to cure more people. So that’s another path forward.”

### *Targeting anemia*

Although JAK2 inhibitors can benefit many patients with myelofibrosis, myelofibrosis with anemia as the chief symptom is less likely to respond to JAK2 inhibitors. For patients with anemia and other symptoms, JAK2 inhibitors may improve other symptoms, but the anemia will likely persist. Several drugs for treating myelofibrosis-related anemia are being tested in clinical

trials at MD Anderson, including the activin receptor antagonist sotatercept.

## *Antifibrotic agents*

Another new direction in myelofibrosis research is the direct treatment of the fibrosis. Dr. Verstovsek said, “We are testing antifibrotic medications that target the underlying biological problem in the bone marrow with the hope that the fibrosis itself will resolve and thus improve the red blood cell count, decrease symptoms, and shrink the spleen.” Two phase II trials at multiple institutions, including MD Anderson, are testing the antifibrotic drugs PRM-151 and GS-6624, alone or in combination with the JAK2 inhibitor ruxolitinib. The PRM-151 trial recently completed enrollment for its first phase and will soon begin enrolling patients for its second phase, but the GS-6624 trial has completed enrollment.

## *Polycythemia vera and essential thrombocythemia treatment*

Patients with polycythemia vera, an uncontrolled growth of bone marrow cells that increases the total blood volume, and those with essential thrombocythemia, an overproduction of platelets, have a near-normal life expectancy but also have an increased risk of thrombosis. In these patients, treatment usually focuses on decreasing the risk of thrombosis.

Patients with polycythemia vera usually are treated with regular phlebotomies. Patients with polycythemia vera often also receive aspirin to reduce the risk of thrombosis, as do patients with essential thrombocythemia. Patients with either disease who have an extremely high risk of thrombosis often are given the chemotherapy agent hydroxyurea to try to permanently normalize blood counts.

However, in about 20% of patients with polycythemia vera, hydroxyurea does not lead to a durable response or causes intolerable side effects. Until recently, these patients had few other options, as other cytotoxic chemotherapy agents carry a significant risk of transforming the disease into acute

myelogenous leukemia.

In a recently completed phase III trial led by Dr. Verstovsek at MD Anderson, patients whose polycythemia vera could not be managed with hydroxyurea received either the JAK2 inhibitor ruxolitinib or the best available treatment option as judged by the treating physician. A significantly greater percentage of patients who received ruxolitinib had decreased red blood cell counts, decreased spleen volume, improved symptoms, and normalized white blood cell and platelet counts compared with the patients who received alternative treatments; and the patients who received ruxolitinib appeared to have a lower rate of clotting. Ninety-four percent of patients whose disease responded to ruxolitinib continued to show a response for at least 1 year, and most adverse events from the drug were low grade.

Ruxolitinib and other JAK2 inhibitors are being tested both in patients with polycythemia vera and in patients with essential thrombocythemia; two such trials for momelotinib are under way at MD Anderson.

### Sequencing myeloproliferative neoplasms

Researchers at MD Anderson and elsewhere have been sequencing blood and bone marrow samples from patients with myeloproliferative neoplasms to analyze the incidences of specific mutations in myelofibrosis, polycythemia vera, and essential thrombocythemia. Several mutations have been associated with particular diagnoses: for example, the JAK2 V617F mutation occurs in almost all patients with polycythemia vera and in about half of patients with myelofibrosis or essential thrombocythemia. In contrast, CALR gene mutations are seen in a small proportion of patients with myelofibrosis and essential thrombocythemia but never in patients with polycythemia vera.

Characterizing the genetic profiles of myelofibrosis at different stages also may reveal genetic changes that coincide with the transformation of this disease into acute myelogenous leukemia,

## CLINICAL TRIALS: Myeloproliferative Neoplasms

**A phase II, open-label, prospective study of PRM-151 in subjects with primary myelofibrosis, post-polycythemia vera myelofibrosis, or post-essential thrombocythemia myelofibrosis (2013-0051).** Principal investigator (PI): Dr. Srdan Verstovsek. The goal of this study is to learn if PRM-151 can help to control myelofibrosis. Two dosing schedules will be compared. Some participants will also receive ruxolitinib.


**A phase I/II, open-label, dose-escalation, multi-center study to assess the safety, tolerability, pharmacokinetics, and pharmacodynamics of orally administered NS-018 in patients with primary myelofibrosis, post-polycythemia vera myelofibrosis, or post-essential thrombocythemia myelofibrosis (2011-0090).** PI: Dr. Verstovsek. The goal of this study is to find the highest tolerable dose of NS-018 that can be given to patients with myelofibrosis. The safety of this drug will also be studied.

**A phase II, prospective, open-label study to determine the safety and efficacy of sotatercept (ACE-011) in subjects with myeloproliferative neoplasm-associated myelofibrosis and anemia (2012-0534).** PI: Dr. Verstovsek. The goal of this study is to learn if sotatercept can help to control myeloproliferative neoplasm-associated myelofibrosis and anemia. The safety of this drug will also be studied.

**A phase II, open-label, randomized study to evaluate the safety and efficacy of momelotinib in subjects with polycythemia vera or essential thrombocythemia (2013-0977).** PI: Dr. Verstovsek. The goal of this study is to learn if momelotinib can help to control polycythemia vera and/or essential thrombocythemia. The safety of this drug will also be studied.

**Open-label study to assess the long-term safety and efficacy of momelotinib in subjects with primary myelofibrosis, post-polycythemia vera myelofibrosis, post-essential thrombocythemia myelofibrosis, polycythemia vera, or essential thrombocythemia (2014-0145).** PI: Dr. Verstovsek. The goal of this study is to learn about the long-term safety of momelotinib in patients with primary myelofibrosis, post-polycythemia vera myelofibrosis, post-essential thrombocythemia myelofibrosis, polycythemia vera, or essential thrombocythemia. Researchers also want to learn if momelotinib can help to control the disease. ■

### FOR MORE INFORMATION

Visit [www.clinicaltrials.org](http://www.clinicaltrials.org) or [www.mdanderson.org/mpncenter](http://www.mdanderson.org/mpncenter). 

mia, which typically kills the patient in about 5 months. At MD Anderson, the world's largest tissue bank and clinical database specific to myeloproliferative neoplasms are being used to look for the genetic events that lead to this transformation.

"Many people have concluded that the accumulation of multiple mutations makes myelofibrosis more aggressive and more likely to transform to acute leukemia," Dr. Verstovsek said. "So we

are analyzing the relationships between multiple genetic abnormalities. We have created a 28-gene panel to better understand the influence of these mutations on overall outcomes, and every patient undergoes this testing. But we aren't using this type of analysis in clinical practice yet." ■

### FOR MORE INFORMATION

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# Neoadjuvant Targeted Therapy May Offer Multiple Benefits for Patients with Locally Advanced Renal Cancer

By Kathryn L. Hale

**Despite definitive treatment with nephrectomy, locally advanced renal cancer recurs in 20%–30% of patients, substantially reducing their chance for long-term survival. To prevent such recurrences and prolong survival, urologic oncologists are studying the integration of targeted molecular therapies with surgical treatments.**

## **Patients with metastatic disease surviving longer**

The new approaches for locally advanced renal cancers have emerged from what has been learned by treating metastatic disease.

Because conventional cytotoxic therapies are not effective against renal cancers, the recommended treatment for locally advanced renal cancers is usually nephrectomy. For metastatic renal cancers, however, surgery is indicated in only a few well-selected patients; and most patients with metastatic disease had few options until the introduction of targeted therapies less than a decade ago.

Targeted therapies fight cancer by inhibiting proteins such as vascular endothelial growth factor receptors and tyrosine kinases that stimulate tumor angiogenesis or promote tumor growth in other ways.

Since the introduction of these agents for the treatment of renal cancer, said Christopher Wood, M.D., a professor in the Department of Urology at The University of Texas MD Anderson Cancer Center, “Many patients with metastatic disease are living significantly longer than expected; the overall survival time has more than doubled. Some of these patients are now living for years, whereas before the median survival was less than 1 year.”

## **Targeted therapy for locally advanced disease**

The promising results of targeted therapy in patients with metastatic renal cancer prompted urologic oncologists to ask whether targeted agents could be effective in prolonging survival in patients with nonmetastatic disease. For these patients, surgery in the form of partial or radical nephrectomy offers a chance at a cure; however, the disease may recur after surgery, significantly shortening survival.

The first trials of the targeted agents in nonmetastatic renal cancer looked at their effectiveness in the adjuvant therapy setting (i.e., after resection) with the goal of decreasing risk of recurrence. The final results of these trials have not yet been reported, but the investigators agree on one point: the targeted agents were not well tolerated after surgery, especially for a prolonged duration.

Dr. Wood said, “Many patients were not able to tolerate the toxic effects while recovering from surgery and had to take a lower dose or drop out altogether. Others were not willing to tolerate the agents’ toxic effects in the face of a recurrence risk of only 20%–30%.”

These findings led the researchers to test the agents in the neoadjuvant therapy setting (i.e., before surgery) in patients whose tumors were considered resectable.

The neoadjuvant therapy approach in these patients has several potential benefits: elimination of micrometastatic disease, which may decrease the chance of recurrence and prolong survival; shrinking of the primary tumor, which might allow a change in the surgical approach to nephron-sparing partial nephrectomy rather than radical nephrectomy or from open surgery to a minimally invasive approach; and conversion of an unresectable tumor to a resectable one.

One risk of the neoadjuvant therapy approach is that the toxicity of the targeted agent might debilitate patients to the extent that surgery would be more difficult for them. Also, because many targeted agents are antiangiogenic, they may interfere with postoperative wound healing. This is a formidable problem if surgery is “sandwiched” between two periods of targeted therapy.

In the early neoadjuvant therapy trials, patients with locally advanced or metastatic renal cancer were treated with a targeted agent, underwent surgery, and then resumed targeted therapy as soon as possible afterward. The goal of these early trials was to determine whether this approach was safe and effective in preventing recurrence.

Dr. Wood said, “These trials showed that the agents generally were better tolerated as neoadjuvant therapy than as adjuvant therapy. They also showed that the tumor’s response to the therapy was a good litmus test for whether the patient was likely to benefit from surgery.”

Tumors that progressed while the patient was receiving targeted therapy were considered unlikely to be curable by surgery, while tumors that remained stable or, better yet, shrunk were considered very likely to be curable by surgery.

## **Neoadjuvant axitinib shrinks locally advanced tumors**

While the results of the early trials of neoadjuvant targeted therapy for

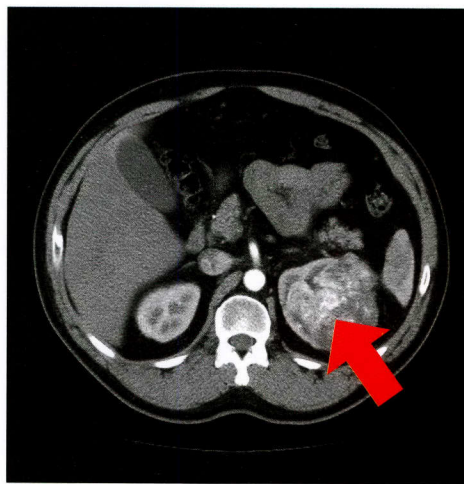
# Multiple Benefits for Renal Cancer

advanced renal cancer were promising, they were not as persuasive as they could have been because the trials' broad selection criteria did not allow researchers to assess treatment efficacy according to tumor resectability or specific tumor subtypes or stages. Also, patients in these studies received varying doses, which allowed researchers to assess safety but limited the efficacy data for each dose. In 2010, Dr. Wood and his colleagues at MD Anderson initiated a trial designed to address these limitations by standardizing patient selection criteria and treatment.

"While there was nothing new about neoadjuvant targeted therapy, this trial was different than the trials that had been reported up until that point," said Jose Karam, M.D., an assistant professor in the Department of Urology and the lead author on the initial report of the trial, which was published in *European Urology* earlier this year. "It was a prospective trial focused on a very specific group of patients: those with stage II or III, biopsy-proven clear cell renal cell carcinoma—the most common type of renal cell carcinoma."

The therapy, the tyrosine kinase inhibitor axitinib, was initiated in all patients at the same dose and schedule. Not only was the duration of therapy standardized, at 12 weeks, but the time between stopping therapy and undergoing surgery also was standardized, at 36 hours. The standardized approach increased the likelihood that any effects observed were actually due to the study drug.

The 12-week treatment duration was chosen on the basis of previous study findings. "We looked at previous trials, most of which had much longer treatment intervals, and noticed that, in most patients who had a response to the targeted agent, that response occurred within the first 60–90 days of treatment," Dr. Wood said. "The data indicated overwhelmingly that if there



Computed tomography scans show a renal tumor (arrows) before (left) and after 12 weeks of neoadjuvant treatment with the targeted drug axitinib.

was no response in the first 90 days, there wasn't going to be a response."

The results of the axitinib trial were exciting: while the objective response rate by internationally accepted statistical criteria was 46%, 100% of the tumors showed some degree of shrinkage, and the median extent of this shrinkage was 28%. The mean tumor diameter decreased from 10.0 cm to 6.9 cm. None of the patients had evidence of progressive disease during the treatment period. In addition, no complications that could be attributed to the study drug were encountered during or after surgery.

The trial also showed that, owing to its tumor-shrinking effects, neoadjuvant axitinib reduced the extent of surgery for some patients. Five of the 24 patients in the trial were able to undergo partial nephrectomy rather than radical nephrectomy; and of the 19 radical nephrectomies, 5 were accomplished by a minimally invasive approach.

"We chose tumor shrinkage as the study endpoint in the axitinib trial because it is an objective measure," Dr. Wood said. He pointed out, however, that some questions remain unanswered. "While the substantial tumor shrinkage we observed seems beneficial, is it clinically meaningful? Does shrink-

ing tumors by 28% allow us to do significantly more partial nephrectomies or more laparoscopic nephrectomies? Does it translate to fewer recurrences or longer survival? We will learn that only through more clinical trials."

"The conversion from radical nephrectomy to partial nephrectomy was meaningful for patients, but they all started the trial with a resectable tumor," Dr. Karam said. "We envision that, ultimately, tumors that are initially considered unresectable might become resectable with neoadjuvant targeted therapy. This could change the outlook for a lot of patients with 'unresectable' disease."

## Resectability and surgical approach

The choice of surgical approach is a subjective judgment by the urologists evaluating the case. Criteria for partial nephrectomy can vary among institutions and from urologist to urologist within an institution. This variability complicates attempts to draw conclusions from clinical trial results. Dr. Karam said, "The axitinib trial had an independent radiologist reviewer who documented tumor size on each scan, but determination of surgical approach

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# New Combination Therapy Offers Potential to Cure *FLT3*-ITD Acute Myelogenous Leukemia

By Roberto Molar-Candanosa

**A new combination therapy using plerixafor, granulocyte colony-stimulating factor (G-CSF), and sorafenib may lead to lasting remissions—and possibly even a cure—for patients with acute myelogenous leukemia (AML) carrying the internal tandem duplication (ITD) mutation in the *Fms*-like tyrosine kinase 3 (*FLT3*) gene.**

The leukemic cells of about 30% of AML patients harbor the *FLT3*-ITD mutation, making it one of the most frequent mutations of AML. With standard AML therapy, these patients have a median survival of only 9 months, and less than 5% are cured.

Several inhibitors of the *FLT3* kinase, including the multiple kinase inhibitor sorafenib, have shown activity against *FLT3*-ITD AML, but none has produced lasting responses in single-agent clinical trials. The new combination therapy is designed to overcome the mechanisms responsible for drug resistance.

## Resistance to *FLT3* inhibition

One reason for the lack of durable response to *FLT3*-ITD AML treatment with single-agent *FLT3* inhibitors is the protective effect of stromal cells in the bone marrow. *FLT3*-ITD mutations activate signaling of the chemokine receptor CXCR4 and its ligand, stromal-derived factor 1 (SDF-1), in the bone marrow. Once activated, the SDF-1/CXCR4 signaling pathway regulates leukemic cell proliferation and mobilization, resulting in resistance to therapy.

In preclinical studies, the combination of the CXCR4 inhibitor plerixafor and G-CSF was able to mobilize leukemic cells out of the bone marrow's protective microenvironment and into

the bloodstream, where the leukemic cells could be killed by sorafenib. Preclinical studies also showed that plerixafor and G-CSF selectively mobilize leukemic blasts and stem cells and inactivate CXCR4 and other adhesion molecules that bind leukemic cells to the bone marrow. In addition, these studies revealed a mechanism by which CXCR4 inhibition directly sensitizes leukemic cells to chemotherapy via a complex network of transcription factors, microRNAs, and cell death regulators.

## Clinical trial

The new combination therapy was tested at The University of Texas MD Anderson Cancer Center in a phase I clinical trial that opened in 2010 and recently completed enrollment. The clinical trial was the first to use plerixafor,

G-CSF, and sorafenib to mobilize and kill leukemic cells.

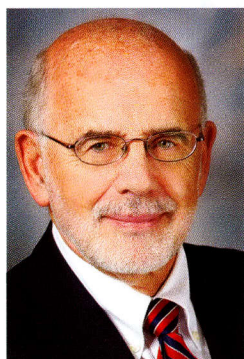
Eligible patients were 18 years or older and had relapsed or refractory *FLT3*-ITD AML. The patients received injections of plerixafor (240 mg/kg) and G-CSF (10 mg/kg) every other day on days 1–13 and oral sorafenib (400–600 mg) twice daily in 28-day cycles.

The overall response rate for patients in the study was 64%: 36% had complete remissions, and another 28% had partial remissions. There were no treatment-related deaths. Also, the combination therapy was shown to be safe for normal stem cells.

Michael Andreeff, M.D., Ph.D., a professor in the Department of Leukemia and the principal investigator of the study, presented the results in June at the 2014 American Society of Clinical Oncology Annual Meeting. "In addition to the high response rates, what was particularly interesting is that we had two patients in the trial who previously had unsuccessful bone marrow transplants but with the new combination therapy had complete remissions lasting 1 year and almost 2 years," Dr. Andreeff said. "With more effective agents that are now becoming available, this therapeutic strategy offers the potential of curing *FLT3*-ITD AML." ■

## FOR MORE INFORMATION

Dr. Michael Andreeff.....713-792-7261



**"With more effective agents that are now becoming available, this therapeutic strategy offers the potential of curing *FLT3*-ITD AML."**

– Dr. Michael Andreeff



# Symptoms of Cancer

## Lasting symptoms can mean cancer or other diseases

**Detecting cancer early can save the patient's life.** Although cancer screening offers the best chance of early detection for many types of cancer, often cancer is found because the patient notices cancer symptoms.

Unfortunately, it isn't always easy to recognize the symptoms of early-stage cancer, and many of these symptoms can also be caused by other, less-threatening illnesses.

Below are some symptoms of a few common cancers. If you experience any of these symptoms for more than 2 weeks, check with your doctor. Most likely, you don't have cancer, but it's important to have your physician address your concern.

### Breast cancer

Breast cancer may cause one or more of the following symptoms:

- a new lump in the breast or armpit;
- swelling of all or part of the breast, even if no lump is felt;
- enlarged lymph nodes in the armpit or neck;
- scaly or red skin on the breast;
- changes in breast size, shape, or skin texture;
- dimpling or puckering of the breast skin;
- nipple discharge (other than breast milk); or
- nipple turned inward or pulled to one side.

It is important to be familiar with your own breasts so you know what "normal" for you feels and looks like.

### Prostate cancer

Often men with prostate cancer do not have any symptoms. If there are symptoms, they vary from man to man, but these are some of the typical signs of prostate cancer:

- frequent urination, especially at night;
- problems passing urine, including difficulty when starting to urinate or trying to hold back;
- not being able to urinate;

- blood in the urine or semen;
- trouble getting an erection; or
- frequent pain or stiffness in hips, lower back, or upper thighs.

Other diseases also can cause these symptoms. Trouble passing urine, for instance, is much more often caused by an enlarged prostate than by cancer. Regardless of the symptoms' underlying cause, your physician may be able to relieve them.

### Oral cancer

Particularly if you smoke, chew, or dip tobacco—or regularly drink alcohol—you should often check your mouth for possible signs of oral cancer.

These are common symptoms of oral cancer:

- white or velvety red patches in the mouth;
- lumps or hardening of tissue in the mouth;
- a sore in the mouth or throat that does not heal;
- difficulty chewing or swallowing or moving the tongue or jaw; or
- persistent bad breath.

These symptoms could mean cancer or a less serious medical problem, so it is important to consult your doctor or dentist if you find abnormal areas in your mouth.

### Skin cancer

Skin cancers—including melanoma, basal cell carcinoma, and squamous cell carcinoma—often start as small changes to your skin. While these changes usually are not cancer, they may become cancer over time, which is why it is crucial to have them examined by a doctor.

These are some things to look for:

- a new spot on your skin or a spot that has changed in size, shape, or color;
- a sore that does not heal;
- a spot or sore that becomes itchy, painful, or tender;
- a small, shiny, pale, smooth, or waxy lump;

- a firm, red lump that has a crust or bleeds; or
- a flat red spot that is dry or scaly.

### Lung cancer

Knowing the warning signs of lung cancer is important for both nonsmokers and smokers. While the majority of people who develop lung cancer were once smokers, about 15% never smoked.

These are some lung cancer symptoms you should look for:

- a cough that doesn't go away and keeps getting worse;
- continual chest pain or pain in your arm or shoulder;
- coughing up blood, even a small amount;
- shortness of breath, wheezing, or hoarseness;
- repeated episodes of bronchitis or pneumonia;
- swelling in your neck and face;
- unexplained weight loss or loss of appetite;
- fatigue; or
- changes in fingernails and nail beds.

### Talk to your doctor

Some of the symptoms listed above—such as weight or appetite loss, fatigue, or fingernail changes—could be caused by more than one type of cancer.

If you experience any of the symptoms described above for more than 2 weeks, don't panic; but do see your doctor. Remember that having symptoms does not mean that you have cancer. But in the event you do, detecting cancer early can greatly increase your chances of successful treatment and long survival. ■

— K. Stuyck

### FOR MORE INFORMATION

- Talk to your physician
- Visit [www.mdanderson.org](http://www.mdanderson.org)
- Call askMDAnderson at 877-632-6789

## Neoadjuvant Targeted Therapy for Renal Cancer

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at the end of treatment was up to the urologists.”

Drs. Wood and Karam and some of their colleagues are undertaking a study that will attempt to improve understanding of the criteria urologists use to determine which renal tumors are suitable for partial nephrectomy. Drs. Wood and Karam are asking colleagues at other centers to independently evaluate computed tomography images from the axitinib trial and say whether a partial nephrectomy approach is appropriate for each tumor. The evaluating urologists will be blinded to the patients’ identities and characteristics and to the timing of the imaging studies. Drs. Wood and Karam hope to obtain information that can be applied to establish more objective criteria for determining surgical approach in clinical trials.

### Questions remain

Drs. Wood and Karam emphasized that the neoadjuvant therapy approach to locally advanced renal cancer is not ready for general oncologic practice. Although the axitinib trial showed that neoadjuvant targeted therapy is safe and effective at reducing tumor size, the trial was small and limited to one cancer center. Only larger trials at multiple cancer centers can confirm that neoadjuvant targeted therapy prolongs recurrence-free survival.

While no clinical trials of neoadjuvant targeted therapy in patients with locally advanced renal cancer are currently under way at MD Anderson, Drs. Wood and

Karam and their colleagues are planning more phase II trials that will look at recurrence rate and survival in these patients as well as combinations of targeted agents or of a targeted agent with an immune checkpoint inhibitor. These studies will culminate in a phase III trial that the researchers hope will determine the role of neoadjuvant targeted therapy for locally advanced renal cancer.

One of the most important questions in targeted therapy is how to determine which patients will benefit from which agent or combination of agents. Dr. Karam said, “One of the advantages of a prospective trial like the axitinib trial is that we were able to build into the trial a strategy for systematic collection of patient tissue and fluid specimens through all stages of treatment and follow-up.” Drs. Wood and Karam and their collaborators at MD Anderson’s Institute for Personalized Cancer Therapy are now analyzing these samples to identify molecular biomarkers that might help identify and select patients most likely to benefit from neoadjuvant axitinib.

“This is the great promise of targeted therapy,” Dr. Karam said, “and the data we are generating from this trial should be a big help in designing better targeted therapeutic strategies for patients with renal cancer in the future.” ■

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