FOR PATIENTS, SURVIVORS & THEIR CAREGIVERS

KIDNEY CANCER

CURE® 20TH anniversary

Cancer Updates, Research & Education®

SPECIAL ISSUE · 12.2022

A SEA CHANGE IN TREATMENT

HIF-2 ALPHA INHIBITORS ARE TRANSFORMING THERAPY FOR PATIENTS WITH RENAL CELL CARCINOMA AND VON HIPPEL-LINDAU DISEASE.

ALSO IN THIS ISSUE

SIDE EFFECTS
Balancing risk and benefit of treatments

***CURE*® TURNS 20**
Refining treatment for Wilms tumor to reduce toxicities.

RENAL CELL CARCINOMA
Immunotherapy offers patients with sarcomatoid RCC more options and improved outcomes.

curetoday.com

Patient portrayal

IF YOU ARE PREVIOUSLY UNTREATED WITH ADVANCED KIDNEY CANCER

CABOMETYX®
(cabozantinib) tablets

+

OPDIVO®
(nivolumab)

Working together for you

Scan to learn more at **CABOMETYX.com**

INDICATIONS AND IMPORTANT SAFETY INFORMATION

What is CABOMETYX?

CABOMETYX is a prescription medicine used to treat:

- People with kidney cancer (renal cell carcinoma). CABOMETYX may be used:
  - Alone to treat people with renal cell carcinoma (RCC) that has spread (advanced RCC)
  - In combination with nivolumab when your cancer has spread (advanced RCC), and you have not already had treatment for your advanced RCC

It is not known if CABOMETYX is safe and effective in children younger than 12 years of age.

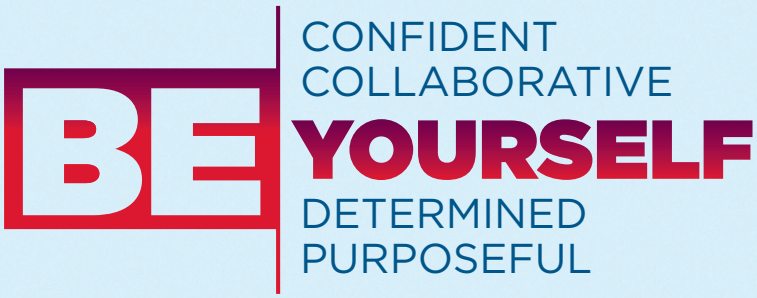
What are the possible side effects of CABOMETYX?

CABOMETYX may cause serious side effects, including:

Bleeding (hemorrhage). CABOMETYX can cause severe bleeding that may lead to death. Tell your healthcare provider right away if you get any signs of bleeding during treatment with CABOMETYX, including:

- Coughing up blood or blood clots
- Vomiting blood or if your vomit looks like coffee grounds
- Red or black (looks like tar) stools
- Menstrual bleeding that is heavier than normal
- Any unusual or heavy bleeding

A tear in your stomach or intestinal wall (perforation) or an abnormal connection between 2 parts of your body (fistula). Tell your healthcare provider right away if you get tenderness or pain in your stomach area (abdomen) that is severe or that does not go away.



Talk to your doctor about how CABOMETYX® + OPDIVO® may help you

The following support services are available for people who take CABOMETYX:

- Ongoing educational support through **BE CONNECTED**
- Cost and financial support with Exelixis Access Services (**EASE**)
  Terms and Conditions Apply

Blood clots, stroke, heart attack, and chest pain. Get emergency help right away if you get:

- Swelling or pain in your arms or legs
- Shortness of breath
- Feel lightheaded or faint
- Sweating more than usual
- Numbness or weakness of your face, arm, or leg, especially on one side of your body
- Sudden confusion, trouble speaking or understanding
- Sudden trouble seeing in one or both eyes
- Sudden trouble walking
- Dizziness, loss of balance or coordination
- A sudden severe headache

High blood pressure (hypertension). Hypertension is common with CABOMETYX and sometimes can be severe. Your healthcare provider will check your blood pressure before starting CABOMETYX and regularly during treatment with CABOMETYX. If needed, your healthcare provider may prescribe medicine to treat your high blood pressure. Tell your healthcare provider if you develop severe headaches, nose bleeds, tiredness or confusion, vision changes, chest pain, trouble breathing, irregular heartbeat, or blood in your urine.

Diarrhea. Diarrhea is common with CABOMETYX and can be severe. If needed, your healthcare provider may prescribe medicine to treat your diarrhea. Tell your healthcare provider right away if you have frequent loose, watery bowel movements.

A skin problem called hand-foot skin reaction. Hand-foot skin reactions are common and can be severe. Tell your healthcare provider right away if you have rashes, redness, pain, swelling, or blisters on the palms of your hands or soles of your feet.

Please see additional Important Safety Information and brief summary of full Prescribing Information on the following pages.

CABOMETYX® (cabozantinib) tablets + OPDIVO® (nivolumab)

Liver problems. Liver problems may happen during treatment with CABOMETYX. When CABOMETYX is taken in combination with nivolumab, severe changes in liver function tests may happen more often than if you take CABOMETYX alone. Your healthcare provider will do blood tests to check your liver function before and during treatment with CABOMETYX. Tell your healthcare provider right away if you develop symptoms of liver problems including: yellowing of your skin or the whites of your eyes, severe nausea or vomiting, pain on the right side of your stomach area (abdomen), dark urine, bleeding or bruising more easily than normal.

Adrenal gland problems. Your healthcare provider will monitor you for this problem. Your healthcare provider may prescribe hormone replacement therapy or corticosteroid medicines if needed. Tell your healthcare provider right away if you develop any of the following signs or symptoms: extreme tiredness, dizziness or fainting, weakness, nausea, or vomiting.

Protein in your urine and possible kidney problems. Symptoms may include swelling in your hands, arms, legs, or feet. Your healthcare provider will check you for this problem during treatment with CABOMETYX.

Severe jaw bone problems (osteonecrosis). Your healthcare provider should examine your mouth before you start and during treatment with CABOMETYX. Tell your dentist that you are taking CABOMETYX. It is important for you to practice good mouth care during treatment with CABOMETYX. Tell your healthcare provider right away if you develop any symptoms of jaw problems, including: jaw pain, toothache, or sores on your gums.

Wound healing problems. Wound healing problems have happened in people who take CABOMETYX. Tell your healthcare provider if you plan to have any surgery before or during treatment with CABOMETYX.

- You should stop taking CABOMETYX at least 3 weeks before planned surgery.
- Your healthcare provider should tell you when you may start taking CABOMETYX again after surgery.

Reversible posterior leukoencephalopathy syndrome (RPLS). A condition called reversible posterior leukoencephalopathy syndrome can happen during treatment with CABOMETYX. Tell your healthcare provider right away if you have headaches, seizures, confusion, changes in vision, or problems thinking.

Change in thyroid function. CABOMETYX can cause changes in your thyroid function, including changes to thyroid hormone levels in your blood. Your healthcare provider will do blood tests to check your thyroid function before and during treatment with CABOMETYX.

Decreased calcium level in your blood (hypocalcemia). CABOMETYX can cause you to have a decreased amount of calcium in your blood. Your healthcare provider will do blood tests to check you for this problem and give you calcium if needed. **Tell your healthcare provider right away if you get any of the following signs or symptoms:**

- Muscle stiffness or muscle spasms
- Numbness or tingling in your fingers, toes, or around your mouth
- Seizures
- Sudden weight gain
- Swelling of your arms, hands, legs, and ankles

Your healthcare provider may change your dose, temporarily stop, or permanently stop treatment with CABOMETYX if you have certain side effects.

The most common side effects of CABOMETYX include:

- Tiredness
- Decreased appetite
- Nausea and vomiting
- Weight loss
- Constipation

The most common side effects of CABOMETYX when used with nivolumab include:

- Tiredness
- Mouth sores
- Rash
- Low thyroid hormone levels (hypothyroidism)
- Pain in muscles, bones, and joints
- Decreased appetite
- Nausea
- Changes in the way things taste
- Stomach-area (abdominal) pain
- Cough
- Upper respiratory tract infection

CABOMETYX may cause fertility problems in females and males, which may affect your ability to have children. Talk to your healthcare provider if you have concerns about fertility.

These are not all of the possible side effects of CABOMETYX. Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

If your healthcare provider prescribes CABOMETYX in combination with nivolumab, also read the Medication Guide that comes with nivolumab.

Before you take CABOMETYX, tell your healthcare provider about all of your medical conditions, including if you:

- Have had a liver problem other than liver cancer.
- Have a recent history of bleeding, including coughing up or vomiting blood, or black tarry stools.
- Have an open or healing wound.
- Have high blood pressure.
- Have a low calcium level in your blood (hypocalcemia).
- Plan to have any surgery, dental procedure, or have had a recent surgery. You should stop treatment with CABOMETYX at least 3 weeks before planned surgery.
- Are pregnant, or plan to become pregnant. CABOMETYX can harm your unborn baby.
  - — If you are able to become pregnant, your healthcare provider will check your pregnancy status before you start treatment with CABOMETYX.
  - — Females who are able to become pregnant should use effective birth control (contraception) during treatment and for 4 months after your final dose of CABOMETYX.
  - — Talk to your healthcare provider about birth control methods that may be right for you.
  - — If you become pregnant or think you are pregnant, tell your healthcare provider right away.
- Are breastfeeding or plan to breastfeed. It is not known if CABOMETYX passes into your breast milk. Do not breastfeed during treatment and for 4 months after your final dose of CABOMETYX.

Tell your healthcare provider about all the medicines you take, including prescription or over-the-counter medicines, vitamins, and herbal supplements. CABOMETYX and certain other medicines may affect each other, causing side effects.

What should I avoid while taking CABOMETYX?

Avoid drinking grapefruit juice, eating grapefruit, or taking supplements that contain grapefruit or St. John's wort during treatment with CABOMETYX.

Please see additional Important Safety Information on the previous pages and brief summary of full Prescribing Information on the following pages.

EXELIXIS®

CABOMETYX® (cabozantinib) tablets

Consumer Brief Summary for CABOMETYX® (Ka-boe-met-iks) cabozantinib tablets

Please read the Patient Information before you start taking CABOMETYX and each time you get a refill. There may be new information.

If your healthcare provider prescribes CABOMETYX in combination with nivolumab, also read the Medication Guide that comes with nivolumab.

What is CABOMETYX?

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- People with kidney cancer (renal cell carcinoma). CABOMETYX may be used:
  - Alone to treat people with renal cell carcinoma (RCC) that has spread (advanced RCC).
  - In combination with nivolumab when your cancer has spread (advanced RCC), and you have not already had treatment for your advanced RCC.
- People with liver cancer (hepatocellular carcinoma) who have been previously treated with the medicine sorafenib.
- Adults and children 12 years of age and older who have a type of thyroid cancer called differentiated thyroid cancer (DTC) that has spread (locally advanced or metastatic), **and**,
  - has progressed after treatment with a VEGFR-targeted treatment, **and**
  - your DTC can no longer be treated with radioactive iodine, or you are not able to receive radioactive iodine treatment.

It is not known if CABOMETYX is safe and effective in children younger than 12 years of age.

Before you take CABOMETYX, tell your healthcare provider about all of your medical conditions, including if you:

- Have had a liver problem other than liver cancer.
- Have a recent history of bleeding, including coughing up or vomiting blood, or black tarry stools.
- Have an open or healing wound.
- Have high blood pressure.
- Have a low calcium level in your blood (hypocalcemia)
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How should I take CABOMETYX?

- Take CABOMETYX exactly as your healthcare provider tells you to take it.
- **Do not** take CABOMETYX with food. Take CABOMETYX at least 1 hour before or at least 2 hours after eating.
- Swallow CABOMETYX tablets whole.
- **Do not** crush CABOMETYX tablets.
- If you miss a dose and your next scheduled dose is in less than 12 hours, take your next dose at the normal time. Do not make up the missed dose.

What should I avoid while taking CABOMETYX?

Avoid drinking grapefruit juice, eating grapefruit or taking supplements that contain grapefruit or St. John's wort during treatment with CABOMETYX.

What are the possible side effects of CABOMETYX?

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  - red or black (looks like tar) stools
  - menstrual bleeding that is heavier than normal
  - any unusual or heavy bleeding
- **A tear in your stomach or intestinal wall (perforation) or an abnormal connection between 2 parts of your body (fistula).** Tell your healthcare provider right away if you get tenderness or pain in your stomach-area (abdomen) that is severe or that does not go away.
- **Blood clots, stroke, heart attack, and chest pain.** Get emergency help right away if you get:
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  - sweating more than usual
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How should I store CABOMETYX?

- Store CABOMETYX at room temperature between 68°F to 77°F (20°C to 25°C).

Keep CABOMETYX and all medicines out of the reach of children.

General information about the safe and effective use of CABOMETYX.
Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. Do not use CABOMETYX for a condition for which it was not prescribed. Do not give CABOMETYX to other people, even if they have the same symptoms you have. It may harm them.
You can ask your pharmacist or healthcare provider for information about CABOMETYX that is written for health professionals.

Manufactured for Exelixis, Inc. Alameda, CA 94502
For more information, go to www.cabometyx.com or call 1-855-292-3935.
This brief summary is based on CABOMETYX® (cabozantinib) Patient Information. Issued: 09/2021

EXELIXIS®

09/2021 CA-1895-1

cure® 20TH anniversary Contents

KIDNEY CANCER SPECIAL ISSUE · 12.22

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ALEX HEARN

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publisher's note

Running the Race

"IT'S A MARATHON, not a sprint" is a common phrase that applies to many challenges in life, particularly to patients who've been diagnosed with cancer. Their race is a long one, riddled with ups and downs, whether it be at diagnosis, throughout treatment, after treatment or even during survivorship. A patient with kidney cancer who receives treatment with newer agents such as immunotherapy drugs and tyrosine kinase inhibitors, for example, may experience side effects as the therapy effectively reduces tumor size — and may become nervous about the possibility of their treatment dose being lowered or even stopped. However, findings from clinical trials have demonstrated that dose reductions or even stopping treatment until side effects are resolved may still result in effective treatment of the disease.

> "Their race is a long one, riddled with ups and downs."

In this special issue of *CURE*®, we spoke with two patients treated with tyrosine kinase inhibitors and immunotherapies for kidney cancer who experienced side effects during treatment. These side effects included high blood pressure, an underactive thyroid and elevated liver enzymes, all of which were managed with medications. And they continued to respond to their treatments despite these challenges.

We also spoke with two other patients with renal cell carcinoma and von Hippel-Lindau disease who have benefited from treatment with targeted drugs called hypoxia-inducible factor-2 alpha inhibitors, which represent a novel approach for treating these kidney cancers.

Also in this issue, an expert discusses how the treatment of sarcomatoid renal cell carcinoma has vastly changed during the past few years with the Food and Drug Administration's approval of immunotherapies. We also spoke with a pediatric oncologist to learn more about how the treatment of Wilms tumor has evolved the past 20 years, as part of our 20th anniversary content series.

Other topics addressed in this special issue include different surgical options for kidney cancer, what we can learn from "failed" clinical trials and the importance of becoming an active participant in one's care.

As always, we hope you find our stories inspirational and informative. Thank you for reading.

MIKE HENNESSY JR.
President & CEO
MJH LIFE SCIENCES®

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Genetic Targets Open the Door to New Treatment Options

TARGETED THERAPIES ARE DEFINED as drugs that block critical functions specific to cancer cells, selectively disabling them and sparing normal cells. Hypoxia-inducible factor-2 (HIF-2) alpha inhibitors represent a new class of drugs that is transforming the lives of patients with renal cell carcinoma (RCC) and von Hippel-Lindau (VHL) disease. These drugs attack a unique signal that makes certain cancer cells grow aggressively. VHL disease, which typically required multiple surgeries to remove tumors, may now be managed by a therapy that shrinks tumors in sensitive areas of the body, including the kidney, brain and spine, while reducing the risk often associated with undergoing surgery.

> "Discovering different genetic mutations to target ... continues to add to the excitement."

HIF is a protein typically kept in check by the VHL protein that is produced in patients with normal VHL genes, and it serves as an oxygen sensor. But when VHL is mutated, the HIF protein is allowed to accumulate, and the cell inappropriately behaves as though it is in a low-oxygen state, setting off a cascade of processes down the line that promote the growth of abnormal blood vessels and facilitate the development of cancer.

Unfortunately, a therapy was not available to target the effects of this genetic mutation in patients with RCC until 2021, when Welireg (belzutifan), the first HIF-2 alpha inhibitor, was approved by the Food and Drug Administration for the treatment of RCC and VHL disease. This new class of drugs can also be used to treat patients with clear cell RCC without VHL disease because these tumors can still have abnormalities in the VHL protein.

Reducing tumor size is one thing, but being able to do that with tolerable side effects increases the appeal of new drug targets. Some patients treated with HIF-2 alpha inhibitors have reported manageable side effects such as borderline anemia, fatigue and other symptoms associated with a dampened response to low oxygen levels.

Discovering different genetic mutations to target for the treatment of patients with RCC, among other cancers, continues to add to the excitement of drug development in this area. As we look to the future, it will be interesting to see what else is in the pipeline that produces such a strong impact on patients both in the short and long term.

DEBU TRIPATHY, M.D.
EDITOR-IN-CHIEF
Professor of Medicine
Chair, Department of Breast Medical Oncology
The University of Texas MD Anderson Cancer Center

MIKE KITADA

sarcomatoid renal cell carcinoma

From Limited Options to a 'Game Changer'

FDA-approved immunotherapies offer patients with metastatic or recurrent sarcomatoid RCC more treatment choices and improved outcomes. *By* DARLENE DOBKOWSKI, M.A.

ADVANCEMENTS IN THE TREATMENT of sarcomatoid renal cell carcinoma (RCC) have given patients more options, particularly those with metastatic or recurrent disease whose options were limited.

Approximately 10% of patients with RCC have a form of the disease with sarcomatoid features, such as cells shaped like ovals or spindles, said Dr. Mohit Gupta, a urologic oncologist and the director of clinical research for the department of urology at MedStar Georgetown University Hospital in Washington, D.C.

"Essentially (sarcomatoid cells look different) under the microscope," Gupta explained. "What that means for the patient is that (it) is actually an aggressive type of cancer. … Patients who have these types of features often present at very advanced stages or with what's called metastatic disease, basically cancer that has spread to other parts of the body outside the kidney itself."

Gupta noted that approximately 15% of patients who first present to a urologist with sarcomatoid RCC are diagnosed with stage 4 cancer. He emphasized the importance of reporting symptoms to oncologists, especially upon diagnosis of RCC, because bone pain and changes in mental status may indicate that the disease has spread to other areas of the body, most commonly the lungs, liver, bone or brain.

IMPROVED OUTCOMES WITH IMMUNOTHERAPY

If RCC has not spread, surgeons should aim to remove the cancer either with a partial nephrectomy (removal of part of a kidney) or a bilateral nephrectomy (removal of both kidneys).

"The most important thing, just like for any kidney cancer, is that 100% of the tumor is removed and that when the pathology doctors look under the microscope, they have something called negative margins, which means 100% of the cancer was removed," Gupta said.

If the pathology report indicates that the RCC has sarcomatoid features, the patient may be treated with immunotherapy. Keytruda (pembrolizumab) was approved by the Food and Drug Administration (FDA) in November 2021 for the treatment of patients with RCC, including patients with sarcomatoid RCC.

DR. MOHIT GUPTA

In the KEYNOTE-564 clinical trial that supported this FDA approval, patients with RCC, including those with RCC with sarcomatoid features, underwent nephrectomy and received once-weekly treatment with Keytruda every three weeks for one year. Treatment reduced the risk for disease recurrence by nearly 30%.

"What was most interesting was that for the patients who had sarcomatoid features on their pathology, this medication did even better," Gupta said. "It actually helped those patients even more compared (with) patients who didn't have sarcomatoid features. So there is luckily a treatment option in case a patient goes through surgery and they have this on their final pathology."

Gupta noted that before this FDA approval, there wasn't much in terms of treatment for patients with sarcomatoid RCC.

"We just prayed and hoped that the cancer didn't come back," he said. "There wasn't much that we could do. And the problem was when (the cancer) did come back, we also had very limited options."

Patients with metastatic sarcomatoid RCC or those with recurrent disease now have more treatment options thanks to immunotherapy. Metastatic or recurrent sarcomatoid RCC was previously treated with chemotherapies and vascular endothelial growth

factor tyrosine kinase inhibitors (VEGF-TKIs), but these treatments had minimal effect on disease with sarcomatoid features. Now, however, patients with sarcomatoid RCC often respond well to the immunotherapy combination of Yervoy (ipilimumab) and Opdivo (nivolumab). Compared with VEGF-TKIs, Opdivo plus Yervoy significantly improves overall survival and progression-free survival in patients with sarcomatoid RCC.

"What we have found is that this immunotherapy works extremely well for these types of patients," Gupta said. "That has really been a game changer for us, both for patients with metastatic cancer upfront and for patients whose cancer has come back."

ADDRESSING UNMET NEEDS

Even with all the progress made in treating patients with sarcomatoid RCC, not everyone responds to the current immunotherapy options, so more research is needed to find treatments to help these patients.

More research is also needed to determine how to best manage patients with metastatic disease. Gupta mentioned that before immunotherapy, patients with metastatic sarcomatoid RCC were treated with cytoreductive nephrectomy, which is a surgery to remove as many cancer cells as possible and may include surrounding organs. Now researchers are wondering whether it might be beneficial to administer immunotherapy before potential surgery.

"For patients who have that sarcomatoid-type kidney cancer, because the immunotherapy works so well, what we're doing now is giving them immunotherapy upfront because what we're seeing is that if we operate on them first, oftentimes the cancer comes right back or it grows even faster while the patient is recovering from surgery," Gupta said. "Instead of doing that, we are basically giving ... immunotherapy upfront for the patients that respond and are still healthy. And basically, all their other sites of disease shrink to just the kidney mass itself, (and then we) operate on them. But if (they don't respond to therapy) or the cancer continues to grow, then we also spared patients from an unnecessary surgery." C

LEARN MORE ONLINE
SCAN the QR code for a collection of content on kidney cancer.

What Patients Should Know About Surgery as a Treatment Option

An expert explains the different types of operations for this disease and what to expect after these procedures. *By* BRIELLE BENYON

FROM TRADITIONAL OPEN SURGERY to minimally invasive surgery, multiple surgery options are available for patients with kidney cancer.

When determining what surgery to choose, patients and clinicians must discuss which option will be the safest and offer the best cancer control, explained Dr. Eric A. Singer, a urologic oncologist at Rutgers Cancer Institute of New Jersey in New Brunswick.

MINIMALLY INVASIVE PROCEDURES

"With minimally invasive surgery, the incisions are smaller. It's the same big operation on the inside, but smaller incisions, which often translates to a faster recovery," Singer said in an interview with *CURE*®.

Minimally invasive surgery, which can be done by hand (laparoscopically) or robotically, can be used for full and partial removal of the kidney, a surgical procedure called a nephrectomy. After creating a small incision, the surgeon uses special tools to take out all or part of the kidney.

Another type of surgery for smaller tumors that does not require a major incision is percutaneous ablation. The surgeon will put in a probe or needle and either use heat or extreme cold to destroy the tumors.

Although minimally invasive procedures can result in less pain and blood loss and be easier to recover from, not all patients with kidney cancer are eligible for these procedures.

OPEN KIDNEY CANCER SURGERY

Singer mentioned that in his practice, about 25% of kidney cancer surgeries are open surgeries.

These can be the safest option for some patients — especially those with larger or complicated tumors that require a team of clinicians (such as a vascular surgeon, surgical oncologist, cardiac surgeon and other team members).

"(An open surgery) is going to give everyone the exposure that they need to make the surgery safe and work best," Singer said.

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POST-SURGICAL RECOVERY

After a patient undergoes kidney cancer surgery, the recovery is similar to that of most other major surgeries, according to Singer, who noted that patients and their providers should be on the lookout for bleeding or infection.

Patients who had a partial nephrectomy may also be at risk for urinoma, a rare complication that occurs when urine leaks out of the kidney.

"Fortunately, the risks of those things are all very, very low in terms of how we do modern kidney surgery," Singer said. "The biggest things that we're looking at after surgery is making sure pain is controlled, getting people up and moving, and making sure that we have people on the right medicine at the right doses."

Singer explained that patients receiving certain drugs that affect kidney function may need to have their doses altered.

Ultimately, Singer emphasized that patient-provider communication is key after kidney cancer surgery so that any potential complications can be quickly addressed.

"I hate surprises," he said. "If there's something going on, we want to know about it so we can make sure that everybody's on the same page and on the right path to recovery."

Events That Bring Hope and Information

CURE® EDUCATED PATIENT® SUMMIT

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Lung Cancer - April
Skin Cancer - May
MPN - May
Breast Cancer - June

Summits are held on Saturdays at 11am ET | 8am PT

**Stay tuned for event details to be announced!*

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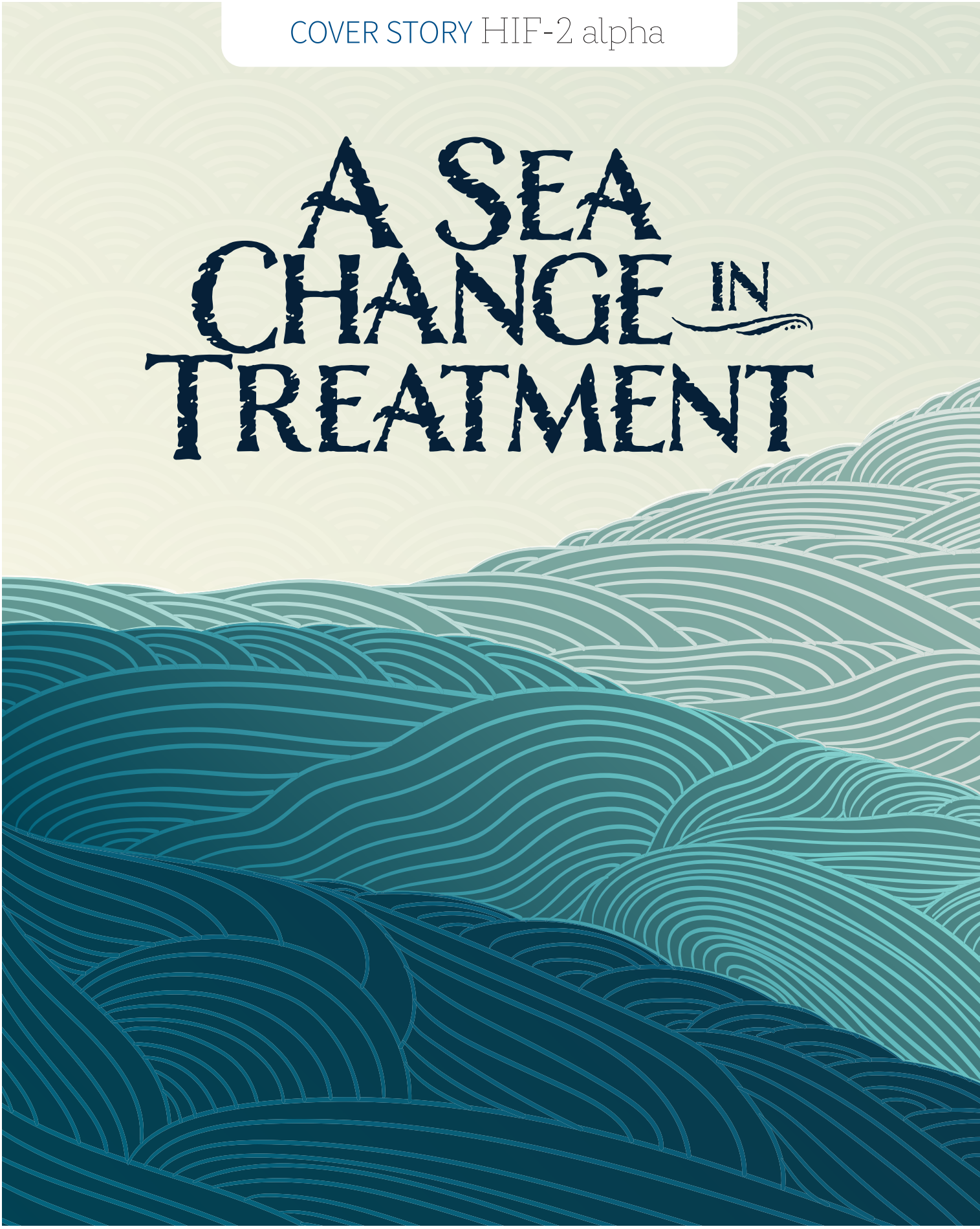
A Sea Change in Treatment



HIF-2 alpha inhibitors are transforming therapy for patients with renal cell carcinoma and von Hippel-Lindau disease.

By SONYA COLLINS

Sean Korbitz had his first bout with cancer — a brain tumor discovered after six months of nausea and vomiting — in 2007. Since then, the 36-year-old has had multiple surgeries and procedures on 40 brain tumors and is under surveillance for 12 tumors in his pancreas, three on his spine and several lesions on his kidneys, which doctors are treating as renal cell carcinoma.

Before that first brain tumor in 2007, the Denver-based media professional had no idea that he carried a gene mutation that would cause him to get tumors again and again throughout his body for his entire life. With von Hippel-Lindau (VHL) disease, he could expect to live to approximately age 60 at best and to spend his now-limited years in and out of the hospital for dozens of, or even a hundred, surgeries to remove tumors.

"In my case, it was going to be guaranteed brain surgeries. It was so traumatic," Korbitz says. "It affects everything in your life: relationships, your physical body, career. Everything is completely affected for months, years and sometimes a decade. I'm still dealing with issues from my 2007 brain surgery." »

When Korbitz eventually developed lesions on his kidneys, which were found in 2016 during the routine scans that people with VHL disease undergo every year, doctors told him there was nothing they could do yet. Surgery would compromise his kidney function, and there weren't any approved drugs for renal cell carcinoma caused by VHL disease. His care team would monitor the growths until one of the tumors measured at least 3 centimeters — a sign that the cancer was likely to spread soon — and then they would surgically remove as many and as much of the tumors as they could.

But that care plan changed last year when Welireg (belzutifan), a first-in-class targeted drug known as a hypoxia-inducible factor-2 (HIF-2) alpha inhibitor, was approved by the Food and Drug Administration (FDA) to stop this exact kind of kidney cancer in its tracks.

HIF-2 alpha inhibitors are bringing new hope to people with cancers caused by VHL disease, and they are also showing promise for clear cell renal cell carcinomas in people who do not have VHL disease.

"I think these drugs are a game changer," says Dr. Eric Jonasch, a professor of medicine at The University of Texas MD Anderson Cancer Center in Houston and lead investigator on the Welireg clinical trial that earned the drug's recent FDA approval. "Like tyrosine kinase inhibitors in 2005 and checkpoint antibodies in the mid-20-teens, I think this is the next sea change in treatment of renal cell carcinoma."

CLEAR CELL RENAL CELL CARCINOMA AND THE VHL GENE

A mutation in the VHL gene is the primary driver of most clear cell renal cell carcinomas, both in people with and without the genetic VHL disease. Clear cell renal cell carcinoma accounts for about 3 out of 4 cases of kidney cancer.

ALEX HEARN

People who have VHL disease carry a mutation in the VHL gene that is part of their own DNA. Those who don't have the disease but who develop clear cell renal cell carcinoma typically have mutations in the VHL gene as well in their tumors, but in their cases, the mutation is acquired in the affected cells in the kidney and not in all the cells of the body.

A normal VHL gene produces VHL protein, which interacts with hypoxia-inducible factor (HIF) protein when oxygen levels are normal, but uncouples from HIF when oxygen levels fall, thereby functioning as an oxygen sensor. A mutated cell, on the other hand, lacks functional HIF, which prevents cells from sensing oxygen. The cell inappropriately senses a low-oxygen state (known as hypoxia) and accumulates HIF-2 alpha. This protein, in turn, sets off a cascade of cancer-promoting processes down the line.

"Accumulation of this protein activates downstream processes that allow for cell growth and angiogenesis — that's the (formation) of new blood vessels," explains Dr. Kristen Millado, a hematologist and medical oncologist at Baptist Health Miami Cancer Institute. "In kidney cancer, inappropriate production of these downstream proteins allows for the overgrowth of cells and carcinogenesis."

People with renal cell carcinoma are treated with drugs such as Sutent (sunitinib malate), Cometriq (cabozantinib) and Inlyta (axitinib) that block angiogenesis, which is one of the downstream cancer-promoting processes that high HIF-2 alpha causes.

"Combination targeted therapy and immunotherapy really changed the paradigm of kidney cancer treatment in the last five years," Millado says. "And now, HIF-2 alpha inhibitors offer another novel approach."

KORBITZ previously undergone numerous surgeries to remove 40 tumors. He hasn't had to undergo surgery since starting treatment.

HIF-2 alpha inhibitors latch onto the HIF-2 alpha protein and prevent it from triggering damaging downstream processes in the first place.

WELIREG RECEIVES FDA APPROVAL IN VHL DISEASE

Last year, the FDA approved Welireg, the first HIF-2 alpha inhibitor for the treatment of renal cell carcinoma, central nervous system hemangioblastomas and pancreatic neuroendocrine tumors in people who have VHL disease. The approval was based on initial results from an ongoing clinical trial in which half of patients with renal cell carcinoma responded to the drug.

"We saw that tumors decreased in size, and in a small percentage of individuals, we saw complete disappearance of tumors. So it's clearly decreasing the number of tumor cells," explains Jonasch.

More than half of the patients who had a response to the drug continued to respond for more than a year. Many are still doing well on the therapy today, Jonasch says.

Korbitz started taking Welireg in October 2021, just a couple months after its FDA approval. He has now been on the drug for a year. Each scan that he has had during that time has shown a 20% to 50% reduction in the size of the tumors on his kidneys, pancreas and spinal »

CHRIS DE SA has been treated for clear-cell RCC — with his wife, **DEBORA,** by his side — since 2015.

PROVIDED BY CHRIS DE SA

cord. The only tumor that has not changed is the one that doctors continue to watch in his brain. Brain and spinal cord tumors associated with VHL are very vascular (blood vessel rich) because they are driven by abnormalities in VHL.

Before starting Welireg, Korbitz had already had numerous surgeries and procedures to remove 40 tumors. Since starting the drug, he hasn't needed any surgery.

"The idea that I may not have to have any more of those is completely life-changing," Korbitz says. "Every time I see somebody that's had anything to do with the development of that drug, I let them know how thankful I am."

Korbitz's results align with those of patients in the clinical trial. Prior to starting Welireg, each of the 61 patients in the trial underwent, on average, about 20 tumor-reduction surgeries per year. In the two years since starting the drug, there have only been three procedures total among the 61 patients, according to clinical trial findings published in *The New England Journal of Medicine*.

"It's important to note that VHL disease-associated cancers aren't limited to the kidneys," explains Dr. Elaine Lam, an associate professor in the department of medicine in the division of medical oncology at University of Colorado School of Medicine in Aurora. "People with this syndrome may have pancreatic tumors and tumors in their brain, spinal cord, eyes and other areas. This drug seems to be effective at shrinking down those tumors as well." Lam is also the medical oncologist in charge of Korbitz's care.

As time goes on, trial investigators have begun to see a slight uptick in surgeries, but the numbers are still dramatically lower than they were before the patients started Welireg.

That benefit is transformative for people living with VHL disease.

"By the time many of these patients are 30 to 40 years old, they have already had numerous surgeries," Lam says. "This drug has made a tremendous difference in the lives of these young people who are trying to pursue careers, raise families and live their lives."

HIF-2 ALPHA INHIBITORS MAY HELP PATIENTS WITHOUT VHL DISEASE

Since VHL genes play a role in most clear cell renal cell carcinomas — and not just in people who have VHL disease — clinical trials are now underway to find out whether Welireg can get similar results in people who have metastatic renal cell carcinoma but don't have the rare genetic disease.

That's how 44-year-old Chris de Sa got access to the treatment.

Diagnosed with clear cell renal cell carcinoma in 2015, the Orange County, California-based attorney had a kidney removed to get rid of the cancer. But in 2016, a routine scan found a lesion on his liver, and de Sa was diagnosed with metastatic disease.

From there, he bounced from treatment to treatment. He did well on Sutent at first and stayed on it until the drug became less effective and the side effects became too much to tolerate. Next, he enrolled in an immunotherapy clinical trial that quickly proved not to be beneficial for him.

By this point, the cancer had spread to multiple sites throughout his body. It was growing fast on his liver, and doctors suspected it was in his lungs, too. Tumors on his spine had begun to cause back pain.

"A tumor on my spine was actually hitting a nerve, and I could feel that," de Sa recalls.

Then, in 2018, de Sa got the chance to enroll in the LITESPARK-001 trial under Jonasch's care. In this trial, people with advanced clear cell renal cell carcinoma who do not have VHL disease and have progressed on other treatments receive Welireg alone.

Within about three months, when de Sa had his first scan to see whether the drug was working, all the tumors had begun to shrink. He is among the 1 in 4 patients in the trial who responded to the drug.

Today, after about two years on Welireg, de Sa has no more back pain from the tumor on his spine. The remaining tumors are stable, and the lesions on his lungs have all but disappeared.

"I have zero pain. I've been stable for the past couple of years and continue on that course. My prognosis is very, very good," he says.

> I've been stable for the past couple of years. My prognosis is very, very good.
>
> —*CHRIS DE SA*

About 1 in 6 people in the trial have continued to respond to the treatment after more than three years.

TOLERABLE SIDE EFFECTS

When de Sa says "zero pain," he means none related to Welireg, either. The only significant side effect he continues to have, after two years on the drug, is borderline anemia, which is common with Welireg.

Besides anemia, the other common side effects of Welireg are fatigue and hypoxia (low oxygen levels). Korbitz deals with all of them.

"Living in Denver, at a higher altitude, I get winded, and I get exhausted pretty quick," he says.

A CHANGING LANDSCAPE

Welireg may soon be joined on the market by other HIF-2 alpha inhibitors. Clinical trials are already underway to test other drugs in this class.

NiKang Therapeutics Inc. is currently recruiting adult patients with locally advanced or metastatic clear cell renal cell carcinoma, with and without VHL disease, for a phase 1/2 clinical trial of its as-yet-unnamed NKT2152. The trial will test the dose and efficacy of the drug as a single agent.

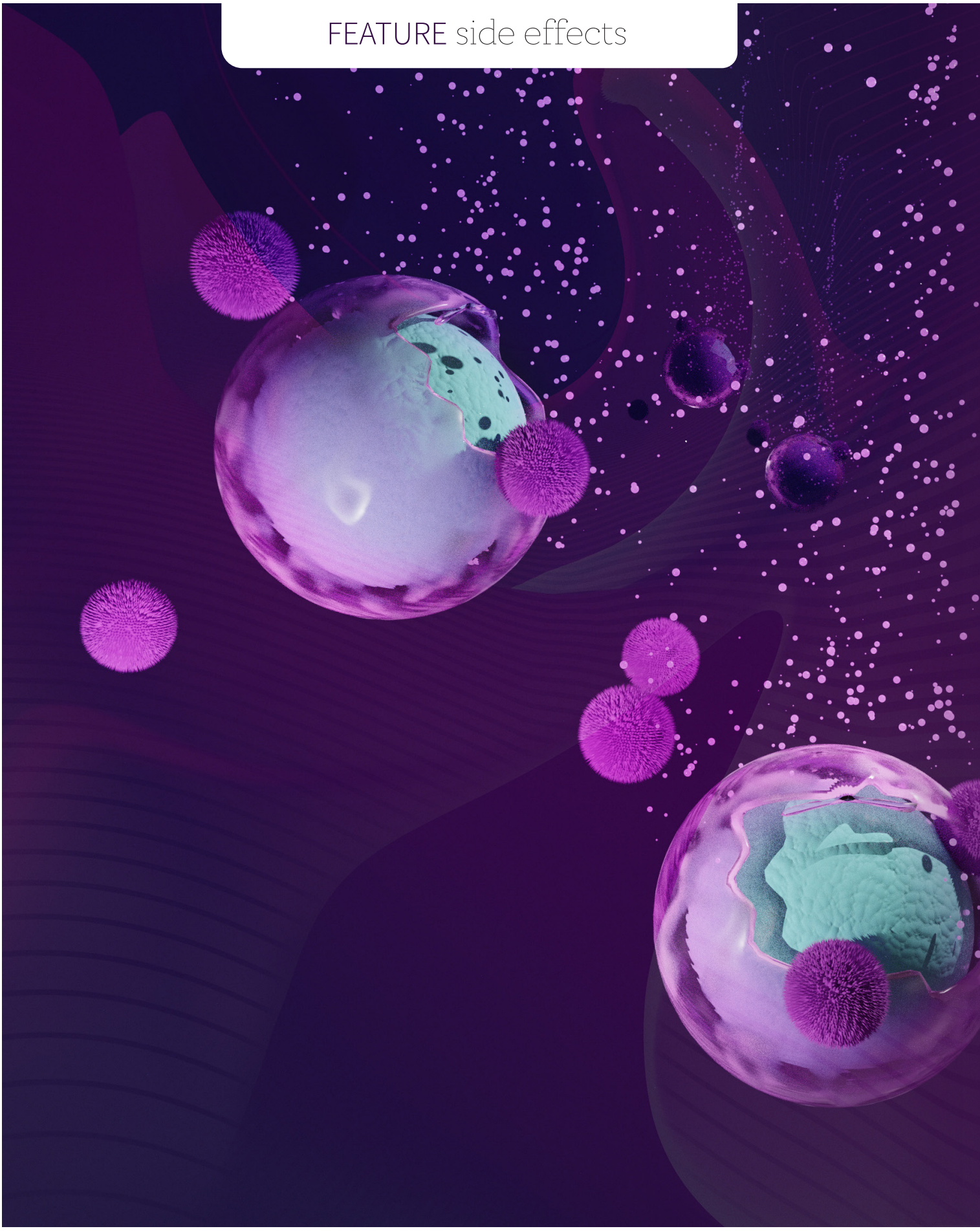
Novartis is also recruiting patients for a study of its own as-yet-unnamed HIF-2 alpha inhibitor, DFF332. This trial is open to adult patients with clear cell renal cell carcinoma and patients aged 12 and older with various types of malignancies that arise from VHL disease and certain other gene mutations. Investigators will study the efficacy of the drug by itself and in combination with other drugs.

Arrowhead Pharmaceuticals has completed a phase 1 safety trial of its HIF-2 alpha-targeted drug, designed to stop overproduction of HIF-2 alpha. The study was recently published with mixed results.

Trials are also underway to test Welireg in combination with other agents. The LITESPARK-003 trial tested the efficacy of the medication in combination with the targeted drug Cabometyx (cabozantinib) in people who previously received immunotherapy for clear cell renal cell carcinoma. Cabometyx is a kinase inhibitor that blocks several kinases involved growth signaling pathways, including vascular growth factors. Just over 30% of the patients in the trial responded to the combo. About 20% of trial participants were still responding to the treatment nearly two years later.

Ongoing LITESPARK arms will examine Welireg in combination with Keytruda (pembrolizumab) and also Lenvima (lenvatinib), another kinase inhibitor.

"It's very exciting to have a novel approach to the treatment of these kidney cancers," Millado says. "And it will be exciting to follow the long-term results."



RISK VERSUS REWARD:

MANAGING SIDE EFFECTS OF KIDNEY CANCER TREATMENTS

Newer drugs have proven extremely effective but can cause unwanted symptoms that affect safety and quality of life.

By LINDA CHILDERS

When Marissa Willis began feeling pain on her left side in May 2013, she initially thought she might have pulled a muscle during one of her workouts. At 38, the mother of two was in good health and exercised regularly. Yet when the pain persisted, Willis headed to her local urgent care center and was shocked when X-rays revealed a mass on her left kidney.

"I saw my primary care provider the next day for a sonogram, and the next two weeks were a whirlwind of appointments, scans and tests at the University of Kansas Medical Center," says Willis, who lives in Blue Springs, Missouri. "Ten days later, I had a radical left nephrectomy to remove both the tumor and my left kidney."

After her surgery, Willis was doing well until a follow-up imaging test 10 months later found a small spot on her lung.

"Since the spot was less than a centimeter, my oncologist decided it was reasonable to watch the mass and see if would grow," Willis says. »

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MARISSA WILLIS experienced high blood pressure and an underactive thyroid during treatment, both of which were manageable.

Three years later, in 2017, an imaging test determined another spot on her lung was large enough to biopsy. Test results found the cancer had metastasized to her lung, and Willis began four cycles of high-dose interleukin-2, a form of immune-stimulation therapy.

It wasn't until Willis was prescribed her current drug regimen of Votrient (pazopanib), a tyrosine kinase inhibitor that targets cancer-supporting blood vessels, that she began to experience side effects from her cancer treatment.

"I had never had high blood pressure before, but after being on Votrient for a short time, I was diagnosed with both hypertension and an underactive thyroid," Willis says.

Although tyrosine kinase inhibitors and checkpoint inhibitors have proven to be extremely effective in treating patients with renal cell carcinoma, they also carry the possibility of side effects, which can be worrisome for patients.

In Willis' case, her care team had discussed potential side effects with her in advance and monitored her bloodwork and blood pressure levels so that any changes with her health could be immediately addressed.

"My doctor put me on medication to lower my blood pressure and treat my underactive thyroid. I monitor my blood pressure daily and have my thyroid-stimulating hormones levels checked on a regular basis," Willis says. "While I will be on both medications indefinitely, I'm happy to be living a pretty normal life."

RISKS VERSUS BENEFITS

Because treatments for kidney cancer, including immunotherapies and tyrosine kinase inhibitors, carry the risk of side effects, it's important for patients and their oncology care team to weigh the risks versus the benefits of each treatment, according to Dr. Thomas Hutson, director of the urologic oncology program and co-chair of the Urologic Cancer Research and Treatment Center at Baylor University Medical Center in Dallas and a professor of medicine

PHOTO PROVIDED BY MARISSA WILLIS

at Texas A&M University School of Medicine in Bryan.

"Immunotherapies and (tyrosine kinase inhibitors) have shown success in treating metastatic cases by shrinking tumors and offering many patients remission and long-term survival," Hutson explains. "Many of the common side effects tend to be fatigue, skin rashes and chronic muscle-related issues such as cramping or joint pain."

Findings from a study published in the medical journal *JAMA Oncology* in 2021 showed that approximately 40% of patients taking checkpoint drugs as immunotherapy develop acute and chronic complications such gastrointestinal side effects, rash, arthritis or endocrine dysfunction.

If a patient encounters more severe side effects, Hutson says doctors will look at adjusting or lowering the dose of the medication, making the side effects manageable.

"Some patients are reluctant to lower their medication dose, mistakenly believing it will also lower the effectiveness of the medication," Hutson says. "This isn't the case, and when prescribing treatments, doctors take (into) consideration a patient's quality of life. If the medications are taking too much of a toll on a patient and adversely affecting their health, a decision will be made about stopping the medication, since we don't want to continue a high-dose drug regimen that will cause patients to suffer unnecessarily."

Hutson tells patients their cancer journey is "a marathon, not a sprint," and if they need to stop an immunotherapy or tyrosine kinase inhibitor drug — at least temporarily — they can later resume treatment on a lower dose or sometimes even a different drug. He emphasizes that patients should always report side effects to their oncology team.

"Reducing dosages isn't bad," Hutson says. "In clinical trials, dose reductions are quite common, so we always tell patients the medication dose they start at may not be the same dose they stay on. In fact, two-thirds of all (patients with cancer) need to be switched to a lower dose. We strive to balance the side effects with safety and quality of life." Information from clinical trials shows that the rates of response and length of time to when there may be progression of a tumor do not seem to differ among patients who need a dose reduction due to side effects compared to those who may not.

In rare cases, Hutson notes that immunotherapy drugs, especially when combined, can trigger a more severe autoimmune response causing inflammation of the lungs, liver or colon. This was the case for Chase Griffith, 45, of Dallas, who was diagnosed with kidney cancer in December 2018. After Griffith underwent a complete nephrectomy, his follow-up scans showed no sign of cancer — until April 2021, when an MRI and CT scan found that the cancer had metastasized to Griffith's liver.

After meeting with doctors at The University of Texas MD Anderson Cancer Center in Houston and UT »

» **CHASE GRIFFITH'S** cancer spread to his liver, which led to treatment with immunotherapy and tyrosine kinase inhibitors.

SUZI NEELY

> Today, I feel good, and my doctor says I have no new tumors and that my existing tumors have stabilized.
>
> —CHASE GRIFFITH

Southwestern Medical Center in Dallas, Griffith decided his best course of action was to begin a triple-medicine clinical trial using two immunotherapy drugs, Opdivo (nivolumab) and Yervoy (ipilimumab), combined with the tyrosine kinase inhibitor Cabometyx (cabozantinib). The phase 3 clinical trial is comparing treatment with Yervoy and Opdivo followed by Opdivo alone to treatment with Yervoy and Opdivo followed by Opdivo with Cabometyx in patients with untreated renal cell carcinoma that has spread to other parts of the body. Researchers hope to determine if the addition of Cabometyx to the usual treatment will make the therapy more effective at stopping the growth of tumor cells.

"When I went in to get my third dose of the treatment regimen, I had bloodwork done and my oncologist found that (my) liver enzymes were off the charts," Griffith recalls. "Basically, the immunotherapy caused my immune system to attack my healthy liver tissue."

Doctors told Griffith they would immediately stop the therapy and begin a course of steroids to suppress the immune response. Because Griffith had been cautioned ahead of time about potential side effects, he wasn't surprised and believed he was in good hands with his oncology team.

"I was put on 200 milligrams a day of prednisone that I took for several months before doctors began tapering me off the medication," Griffith says. "I got down to 10 milligrams in February of this year and started having the same side effects, including insomnia and an elevated heart rate. After going to an urgent care center, I learned that my liver enzymes were even higher than before."

Griffith was hospitalized and given both prednisone and the high-level immunosuppressant CellCept (mycophenolic mofetil), which is often prescribed to prevent organ rejection after transplantation. He remained on the drugs for several months.

Because he has chromophobe renal cell carcinoma, a rare form of kidney cancer, Griffith knows his doctors are using novel approaches to create targeted therapies

SUZI NEELY

that stop or slow the growth of his cancer.

"This past February, doctors started me on another (tyrosine kinase inhibitor), lenvatinib (Lenvima), and an mTOR (inhibitor) therapy, everolimus, that have resulted in a 20% shrinkage in my tumor," Griffith says. "Today, I feel good, and my doctor says I have no new tumors and that my existing tumors have stabilized."

FREQUENT COMMUNICATION IS KEY TO MANAGING SIDE EFFECTS

According to Laura Wood, an oncology nurse and former renal cancer center research coordinator at Cleveland Clinic Taussig Cancer Center, high blood pressure, or hypertension, can be a side effect of some of the multikinase inhibitors used to treat kidney cancer since they act by affecting the blood vessels in tumors and can also have effects on normal blood vessels that regulate blood pressure. These drugs include Sutent (sunitinib malate), Lenvima and Inlyta (axitinib). In addition, Wood notes that a class of drugs known as mTOR inhibitors, including everolimus, rapamycin (sirolimus) and temsirolimus (CCI-779), can often cause side effects such as elevated blood sugar, cholesterol and triglycerides.

"We tell patients in advance they shouldn't be surprised if they develop any of these conditions while undergoing cancer treatment," Wood says. "They're very manageable conditions, and (the patient's) bloodwork and symptoms improve after adjustments are made to their cancer treatment and medications are given to treat the side effects. Some side effects may result in long-term symptoms which require ongoing discussions with your oncology team or other specialists to manage."

Wood says it's crucial for health care providers to provide patients with kidney cancer with early and ongoing education regarding potential side effects and for patients to report these as soon as possible to obtain relief and avoid any organ damage or other long-term problems.

Reporting side effects can also help researchers better understand side effects and develop additional strategies on how to best manage them. In 2017, the Severe Immunotherapy Complications Service was launched at Massachusetts General Hospital in Boston to treat and study patients with immune complications from immune checkpoint inhibitors. Many other cancer centers have similar programs and multidisciplinary teams to manage immune-related side effects.

Dr. Naomi B. Haas, an oncologist and director of the prostate and kidney cancer program at Penn Medicine and a professor of medicine at the Hospital of the University of Pennsylvania in Philadelphia, notes that in rare cases, side effects might even be considered something of a positive.

Haas cites an analysis of clinical trials conducted at Dana-Farber Cancer Institute in Boston showing that patients with advanced kidney cancer who were diagnosed with high blood pressure and prescribed medications called angiotensin system inhibitors, including angiotensin-converting enzyme inhibitors and angiotensin system blockers, lived longer and had better outcomes than patients who weren't diagnosed with hypertension and treated with those medications.

Even when patients experience milder side effects, Haas says they should discuss changes with their oncology team. The Kidney Cancer Association offers a printable side effect tracker on its website, www.kidneycancer.org, to make it easier for patients to track their symptoms and inform their oncology team about symptom severity and how often symptoms are occurring.

"In some cases, patients can lose their sense of taste and say their food tastes like cardboard," Haas says. "As a result, they aren't going to eat as much and will ultimately lose weight, which we don't want."

To address this, Haas says oncologists will typically ask a patient to cease taking their medication for a few days to determine whether it's the drug or the disease that's causing the problem. If it's the medication, Haas notes that drugs such as mirtazapine can be prescribed to help stimulate a patient's appetite.

Diarrhea is another common side effect that Haas says can impact both a patient's physical and emotional health. Haas says patients should never be embarrassed to discuss any changes in their health with their oncology team.

"We don't want patients to be miserable or afraid to venture out socially because they're experiencing diarrhea," Haas says. "We can prescribe probiotics and advise changes to their diet to remedy their situation. In severe cases, we might begin steroid therapy."

In cases of renal cell carcinoma, although side effects can initially seem scary, Haas says most are treatable and are outweighed by the benefits patients receive from tyrosine kinase inhibitors and checkpoint inhibitors.

Willis says she has been feeling "pretty good" over the last 2-and-a-half years, especially since her side effects are much more manageable now.

"I know my body well enough on (treatment) now that I'm living a pretty normal life," she says. "Ironically, being active, working out, that helps energy levels and those side effects. ... I'll be on this indefinitely, probably until either I don't need it, or it stops working."

PUSHING THE ENVELOPE

Researchers are refining treatment based on factors to improve the cure rate for children with Wilms tumor and to reduce side effects.

By DARLENE DOBKOWSKI, M.A.

THE CURE RATE for children in the U.S. with Wilms tumor has hovered around 90% for years. Because researchers have continued to learn more about the disease — leading to the development of subgroups of Wilms tumor — their efforts are now focused on refining treatment, reducing toxicity from therapies and increasing the cure rate for patients with higher-risk disease.

In honor of its 20th anniversary, *CURE®* spoke with Dr. Dylan Graetz, assistant professor in the global pediatric medicine department, director of the culture and communication program, and a solid tumor oncologist at St. Jude Children's Research Hospital in Memphis, Tennessee, to learn more about the progress that has been made over the past 20 years in this space and how it has helped children with Wilms tumor.

DR. DYLAN GRAETZ

LEARNING MORE FROM RESEARCH

The year 2002 was unique for the study of Wilms tumor because that is when the Children's Oncology Group, a clinical trials group supported by the National Cancer Institute, took over the National Wilms Tumor Study Group, opening the doors to more research in the space.

Between 2002 and 2005, the National Wilms Tumor Study Group was interpreting findings from its fifth study. Some major takeaways were that children younger than 2 years old with stage 1 favorable histology Wilms tumor had an 84% event-free survival (the time after treatment that a patient is free from complications or events that treatment was meant to prevent or delay) and a 98% overall survival with surgery if the tumor was less than 550 grams.

"For that subgroup of Wilms tumor, even in 2002, there was extremely good survival, but it was also that study that started to teach us about loss of heterozygosity," Graetz said.

Loss of heterozygosity, or loss of one copy of a gene pair, can provide biological clues about the gene's function, generating opportunities to learn more about the disease. This knowledge allowed for the development of different subgroups of Wilms tumor, such as favorable histology (abnormal cancer cells with a good chance for cure) and anaplastic histology (more difficult to treat).

"Right around 2002 to 2005, we were learning that there were certain types of Wilms tumor that we maybe didn't need to do as much for," Graetz said.

REFINING TREATMENT

Oncologists in the U.S. aim to perform surgery upfront for patients with Wilms tumor, followed by chemotherapy, which contributes to the 90% cure rate for some Wilms tumor types since the early 2000s.

"Wilms tumor is one of those tumors that even in the '60s, there was 80% survival for some kids," Graetz said. "But it's really been the last 20 years that we've started to say we need to refine treatment based on some clinical and biological factors."

Some of these factors include age (i.e., those under 2 years old are treated differently), tumor size and tumor volume. This has led to more research focusing on intensifying chemo to improve outcomes in high-risk Wilms tumor and trying to decrease therapy in those who may have lower-risk disease.

"Most tumors occur in kids under the age of 5," Graetz said. "These kids have long lives ahead of them, and we know that our therapy affects those lives for many years to come. So what can we do to reduce the cumulative effects of the treatment we give?"

Graetz added that Wilms tumor is one of the cancers that involves all three treatment modalities: chemo, surgery and radiation. It's also important to determine whether there will be some treatment overlap, which may increase a child's exposure to toxicities.

For example, abdominal radiation can affect a child's intestines and pancreas, among other areas, which may increase the risk for metabolic diseases like obesity and diabetes. The chemo drug doxorubicin, although helpful in treating Wilms tumor, can also lead to a higher risk for heart disease later in life. In addition, children treated with doxorubicin sometimes require lung radiation, which can also affect heart health.

MOVING FORWARD

More effort is being made to reduce the toxic effects of treatments in children with Wilms tumor. Graetz added that a study being conducted at her institution is focused on radiation oncology that may further reduce toxicities in children with Wilms tumor.

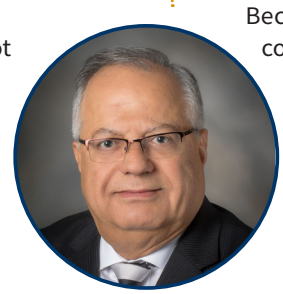
"We're using proton beams for the first time in Wilms tumor to try to reduce the dose and the volume of radiation that these kids are seeing," she said. "Your abdomen has a lot of important organs, so trying to reduce radiation to the organs that don't have tumor is really important."

THE SILVER LINING IN FAILURE

One expert explains how the road to drug development isn't a smooth one, but progress can be made nonetheless. By DARLENE DOBKOWSKI, M.A.

THE NEWS OFTEN highlights positive clinical trials, in which the outcomes that researchers were hoping for occur, potentially leading to Food and Drug Administration (FDA) approvals. But what happens with trials that miss the mark?

One expert said those "misses" should not be considered a loss altogether, but rather, something that is to be expected and does not mean the end of the road for a particular therapy.



DR. NIZAR M. TANNIR

"We have to accept that reality," Dr. Nizar M. Tannir, professor in the department of genitourinary medical oncology at The University of Texas MD Anderson Cancer Center in Houston, told *CURE*®. "Most trials are going to fail, but a silver lining is … there will be lessons learned from a trial that failed. What went wrong? Was the drug not potent enough? … Maybe we can repurpose a drug or use a drug in a different patient population."

Tannir and colleagues are facing exactly that after the CANTATA clinical trial. Results from the trial were presented at a major oncology conference earlier this year and published in *JAMA Oncology* in September.

In the trial, 444 patients with metastatic clear cell renal cell carcinoma (RCC) were randomly assigned to Cabometyx (cabozantinib) with the glutaminase inhibitor telaglenastat or placebo. No significant difference was seen between the two groups for progression-free survival (the time during and after treatment that a patient lives with the disease without worsening), despite the treatment being well tolerated.

"That was disappointing for me and many of the investigators in the field who participated in the trial and for many people who were hopeful that maybe we will have a new class of agents, a new target for RCC, which is the glutamine pathway and tumor metabolism," Tannir said. "But as we know, many, many trials fail — many trials with promising, encouraging data in earlier-phase trials."

Tannir explained the reasoning behind inhibiting the enzyme glutaminase to treat patients with metastatic RCC.

"Many solid tumors including RCC had increased glutaminase expression when we tested tumor tissues," he said. "The rationale behind that is the tumor cell relies on (certain) pathways for producing energy. A normal cell will produce energy for its survival via glucose (sugar), whereas a cancer cell has a faulty glucose utilization or metabolism, so tumor cells rely more and more on other pathways for survival. One of those pathways is (the amino acid) glutamine."

Because the rationale is there, further research may continue in this area.

"(Results from CANTATA don't) mean that the idea of targeting tumor metabolism or glutamine should be dead," Tannir said. "When you give a treatment, everybody with kidney cancer, even if they all had clear cell (RCC), all of these RCCs are driven differently. You need to see if your drug is going to work. It might work for 10% of the patients, 15% or 20%. We need to identify who are (the) patients who (will benefit most)."

Tannir gave an example of another target with negative trials before it was approved by the FDA — anti-CTLA-4 therapies, which are immune checkpoint inhibitors. The first trial assessing an anti-CTLA-4 therapy was conducted more than 15 years ago in patients with RCC. In this phase 2 trial, patients were treated with a 3-milligram-per-kilogram dose of Yervoy (ipilimumab) and had a 13% objective response rate (a measurable response) to the therapy. However, the dose was deemed too toxic for patients, leading to other studies with other doses. Yervoy was ultimately approved in combination with Opdivo (nivolumab) for RCC, among other indications.

It is important for patients to know how participation in clinical trials is valuable to further the space along.

"Patients need to participate in trials, we need to design and conduct trials, we need to develop new drugs, we need to test new drugs, and I hope patients will see the benefit of this," Tannir said. "We appreciate the trust of patients and families to support (this). It's not easy to participate in clinical trials. There is demand on patients and their caregivers — time, effort, transportation, finances, all this to enroll on a clinical trial."

Tannir added that persistence is also necessary to further the field and develop additional treatment options.

"Do not despair, do not give up and do not be discouraged that the trial was negative," Tannir said. "There will be other (trials) that will be positive. We just have to keep pushing the envelope; I am confident that in the near future we will make cancer history."

Becoming an Active Participant in Care

KidneyCAN
Accelerating Cures

As a part of its "Speaking Out" video series, *CURE*® spoke with Meryl Uranga, on behalf of KidneyCAN, about the importance of working as a team with their clinicians and getting educated before making decisions.

By COLLEEN MORETTI

ALTHOUGH PATIENTS WITH KIDNEY CANCER put their care in the hands of doctors, it truly takes a village for a patient to navigate their cancer journey, including loved ones, caregivers and other members of the cancer team. This collaborative approach may help patients digest the news they receive over time and how they respond to treatment.

As part of its "Speaking Out" video series, on behalf of KidneyCAN, *CURE*® spoke with Meryl Uranga, a kidney cancer survivor and a patient advocate, about working as a team with clinicians, caretakers and loved ones as support throughout your cancer journey and taking a step back to process each part of diagnosis and treatment.

Q: Why is it so important for patients to be their own best advocate, especially when it comes to their care?

A: It's a topic that I'm very passionate (about) and have a very personal connection with. The caretakers and patients that are going to be coming in on your behalf are one of many, many patients that your doctors are going to see, that your clinicians are working with. So you really have to take responsibility for your care, your decisions and, most of all, the empowerment of knowing what's going on with your case. And instead of being someone who's taking direction, you want to be in a mindset of working as a team with your clinicians. And it makes all the world of difference in terms of how your care will go going forward.

Q: How can patients make sure they're effectively communicating with their physicians when it comes to their preference on treatment, quality of life and side effects?

A: I think like in any situation, you have to set expectations at the beginning of the relationship. You need to, first of all, choose a clinician that is going to work with you, do the things that you're looking for and be able to communicate the way that you want to. You want to set the expectation (of), "I want to be an active participant. I want to know what's going on. I want to communicate. I want to be involved in decision-making."

If you have a caretaker that you want to be involved, you need to communicate that because there are, like in any profession, certain areas they're not going to be a good fit. You're going to meet doctors — and I went through a few

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before I found mine because we weren't on the same page. So you have to make sure that those expectations are set and they know what kind of patient you are. There are a lot of people that are very comfortable just taking direction from authority figures like a doctor, (but) if you want to be in that empowerment mindset and you want to be a partner, you have to make sure that they want that as well. I really recommend finding that right fit in terms of experience, specialty areas and the communication style that they're willing to provide and work with you on.

Q: How can a caregiver or a loved one also be a part of this patient-physician communication?

A: Bring them with you, introduce them, let (your care team) know that you want them there, that you want them to have the information that you have, that they will be working with you on decision-making (and that) they may be taking notes. There are a lot of times when, unfortunately, we get not the greatest news — and it can be jarring — so you want to have somebody there with you. Again, as long as you're all on the same page, there'll be a tremendous working experience and relationship. But the thing that I would stress is to make sure that is something that they allow; for whatever reason, they may not do that in their practice. So you have to get that set up — those expectations set and agreed to upfront.

Q: Looking back on your own experience, what is your biggest piece of advice for others when it comes to patient-physician communication?

A: My biggest piece of advice is born from my own experience. When I was diagnosed, I was in a fog. I am normally a very proactive, research-oriented person. But when you get this kind of news, it's very difficult to pick yourself up and get in that mindset right away. And so you kind of go through the motions. My only regret and what advice I give to someone newly diagnosed is: Don't make too many decisions until you can get your feet under you. I personally made some decisions looking back that I would not have done six months later when I got more educated and more involved in learning about what was going on.

So take a breath. Whatever is going on with you, it has been going on for some time, especially with kidney cancer because almost everyone I know — and there's a lot of people that I know that have been diagnosed with this disease — has said that their physicians have said that they've had it for many, many years. It's a very silent, quiet-growing (disease) for a while with no symptoms, no signs. You got a few more weeks, so chill. A lot of people just panic, like, "Get this thing out of me," or "Start my treatment." But become educated. It's hard because you've got that emotional jarring (feeling), your world's upside down, and so you have to take a breath, get some land legs and then start understanding what the next best steps are.

And if I had to do it all over again, which obviously I can't, that's what I would have done. What I was doing was just taking direction and advice from the people that haphazardly diagnosed me. In my case, I think it worked out OK, but within six months and recovering from two major surgeries, I was able to really understand where I needed to be for care and make those changes. Had I done that pre-surgery, I have no way of knowing if it would have been a better outcome, a different outcome. I have no way of knowing, but I highly encourage people to take that time. C

Transcript edited for clarity and conciseness.