FOR PATIENTS, SURVIVORS & THEIR CAREGIVERS

GENITOURINARY CANCERS

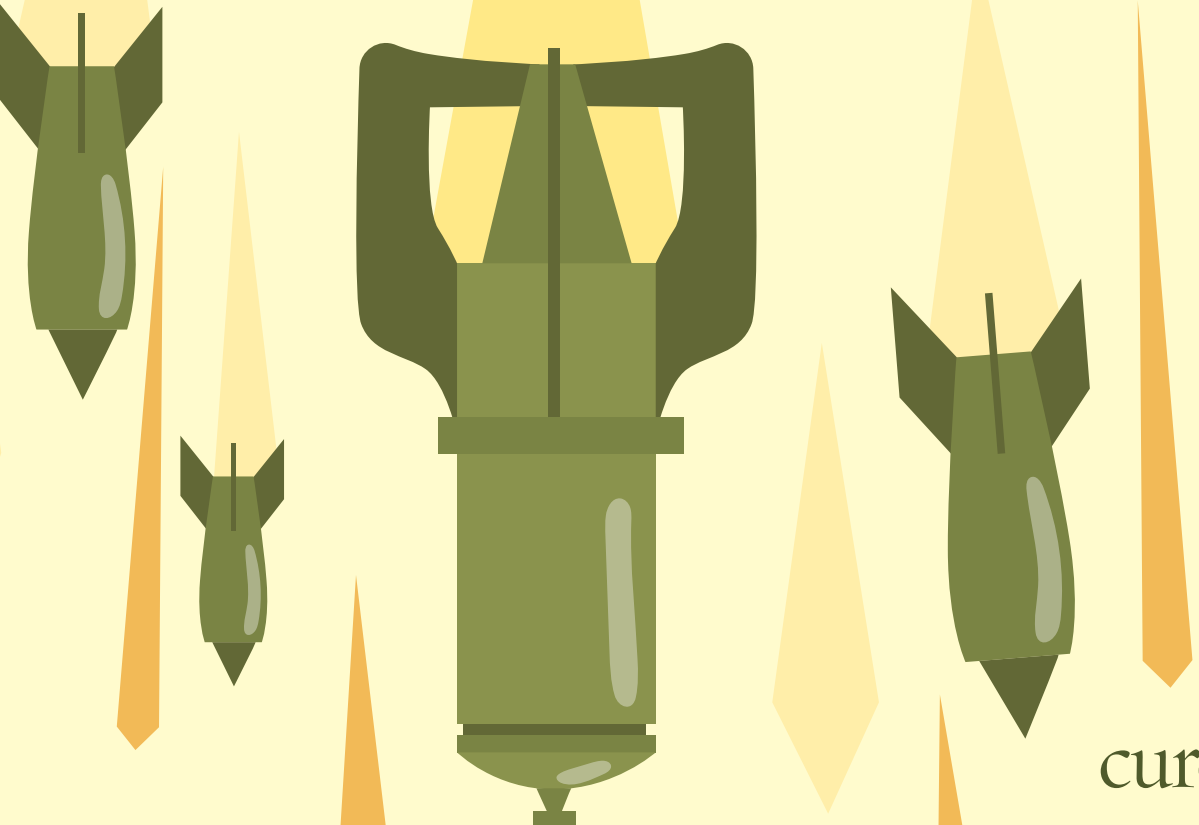
cure®

Cancer Updates, Research & Education®

GENITOURINARY CANCERS
SPECIAL ISSUE · 09.21

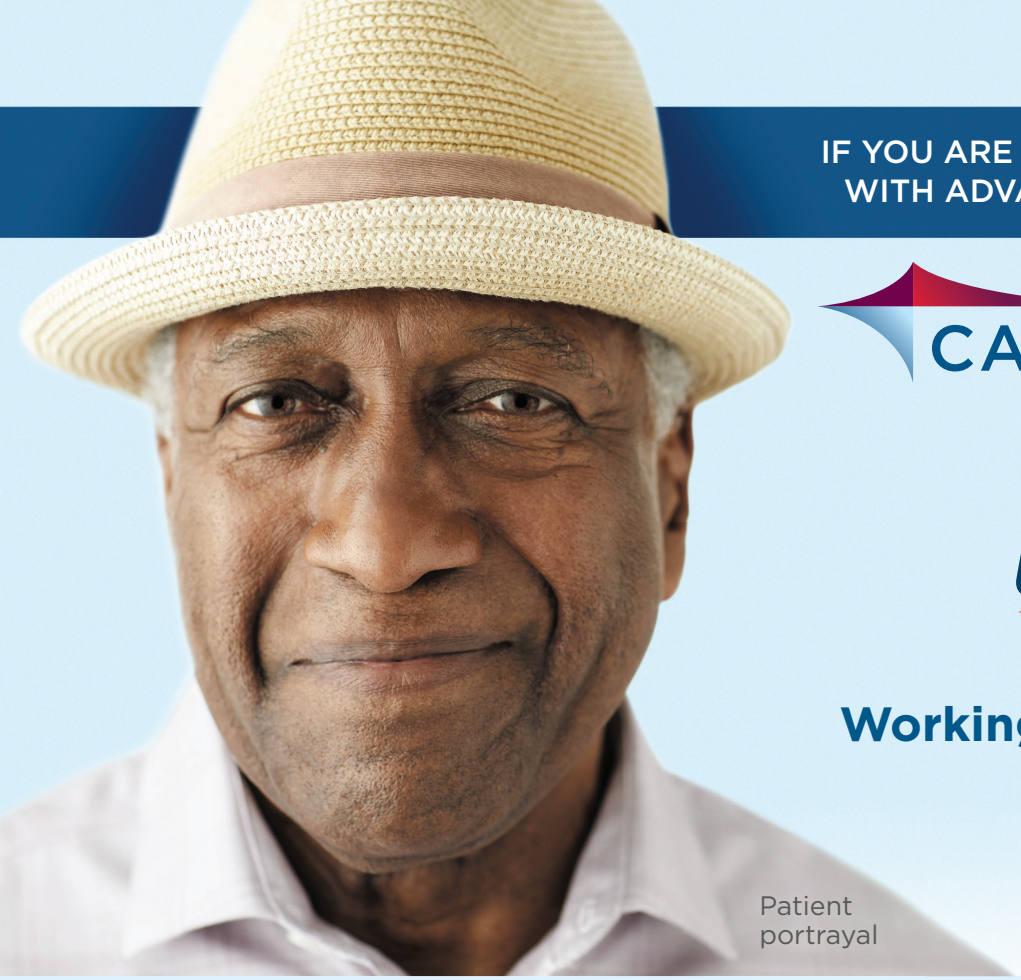
A SMART BOMB FOR PROSTATE CANCER

After decades of research, scientists inch closer to FDA approval for PSMA-targeted treatments that show promise for patients with an advanced form of this disease.



ALSO IN THIS ISSUE

curetoday.com



IF YOU ARE PREVIOUSLY UNTREATED WITH ADVANCED KIDNEY CANCER

CABOMETYX®
(cabozantinib) tablets

+

OPDIVO®
(nivolumab)

Working together for you

Patient portrayal

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
- People with liver cancer (hepatocellular carcinoma) who have been previously treated with the medicine sorafenib.

It is not known if CABOMETYX is safe and effective in children.

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.

CONFIDENT
COLLABORATIVE
BE YOURSELF
DETERMINED
PURPOSEFUL

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 some 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.

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
- Vomiting
- Weight loss
- Constipation
- Difficulty speaking

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 infections

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.
- 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?

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.
- People with liver cancer (hepatocellular carcinoma) who have been previously treated with the medicine sorafenib.

It is not known if CABOMETYX is safe and effective in children.

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.
- 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.

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.
  - 12 hours or more, take the missed dose as soon as you remember. Take your next dose at the normal time.

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?

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.
- **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.
- **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 some 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.

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
- vomiting
- weight loss
- constipation
- difficulty speaking

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.

How should I store CABOMETYX?

- Store CABOMETYX at room temperature 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: 01/2021

EXELIXIS®

02/2021 CA-1895

cure® Contents

GENITOURINARY CANCERS SPECIAL ISSUE · 09.21

EXPERT CONNECTIONS

18

DR. MARK DEANTONIO received PSMA-targeted therapies for prostate cancer after his disease did not respond to other treatments.

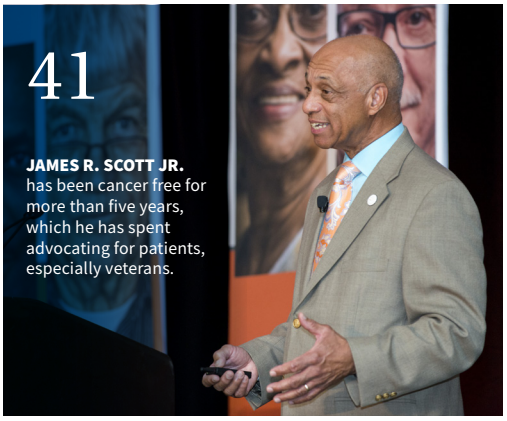
28

JAROD ROY was introduced to immunotherapy and tyrosine kinase inhibitors when obtaining a second opinion.

COVER IMAGE: PCH.VECTOR / STOCKADOBE.COM ADAPTED BY GWEN SKLAS
DEANTONIO BY MATTHEW WATSON; ROY BY SUSAN GARLAND; ERIKSON BY LAURIE SPENDS

JAY ERICKSON was able to start his family shortly after he completed treatment with the help of fertility preservation measures.

34



41

JAMES R. SCOTT JR. has been cancer free for more than five years, which he has spent advocating for patients, especially veterans.

FEATURES

chairman's letter

Treatment for Advanced Cancers

SURGERY TO REMOVE CANCER and even vital organs such as kidneys has been a mainstay of cancer treatment, but today, researchers are striving to find other options for patients. For example, nonsurgical treatments for patients with advanced renal cell carcinoma include the use of immunotherapy (which uses one's immune system to attack cancer cells) and tyrosine kinase inhibitors (which block enzymes that aid in cancer growth).

> "(Treatment options allow) patients and their oncologists to choose which treatment may work best for them."

Fifteen years ago, there weren't many first-line treatment options for patients with this type of cancer, but now we have several — allowing patients and their oncologists to choose which treatment may work best for them.

In this special issue of *CURE*®, we spoke with a patient with metastatic renal cell carcinoma who obtained a second opinion after experiencing tumor growth while on a combination of two immunotherapy drugs. His new doctors suggested he enroll in a clinical trial that was testing an immunotherapy drug with a tyrosine kinase inhibitor. He enrolled and participated, which resulted in the cancer shrinking. "Every scan I had showed a decrease, and the overall reduction of my cancer was 54%," he told *CURE*®. Two other patients interviewed for the story had similar experiences with the combination treatment, highlighting its effectiveness in treating this disease even in earlier stages.

In this issue, we also focus on preserving fertility in men diagnosed with testicular cancer. We spoke with one man who chose to bank sperm after receiving his diagnosis in 2013 because he and his wife were actively trying to have children. After undergoing treatment — and facing some issues with his specimens — he and his wife eventually had two beautiful daughters. Another man wasn't concerned about having children when he received his testicular cancer diagnosis in his mid-20s, but he ended up adopting five children later in life. Despite this diagnosis, men have options when it comes to starting or growing their family.

In addition, you'll meet an Army veteran with bladder cancer that may have been caused by Agent Orange exposure during his overseas tour of duty that included Vietnam, Thailand, Cambodia and Laos. Veterans Affairs recently expanded its presumptive disease list for Agent Orange to include bladder cancer, which has been a long-awaited decision among the veteran community. "This is way overdue but so appreciated," said the Army veteran.

This issue also includes articles on the potential benefit of active surveillance in patients with low-risk prostate cancer, the impact of the recent Food and Drug Administration approval of Trodelvy (sacituzumab govitecan-hziy) for the treatment of metastatic urothelial cancer and much more.

As always, thank you for reading.

MIKE HENNESSY SR.
Chairman and Founder

CURE®

EDITORIAL & PRODUCTION

Editor-in-Chief Debu Tripathy, M.D.
Vice President, Content Kristie L. Kahl
Associate Editorial Director Ryan McDonald
Managing Editor Darlene Dobkowski; editor@curetoday.com
Senior Editor Brielle Benyon
Editor Antonia DePace
Assistant Editor Colleen Moretti
Assistant Web Editor Jamie Cesanek
Copy Chief Jennifer Potash
Copy Supervisors Rachelle Laliberte, Paul Silverman
Medical & Scientific Quality Review Editor Stacey Abels, Ph.D.
Senior Copy Editor Kelly King
Copy Editors Cheney Baltz, Georgina Carson, Kirsty Mackay, Ron Panarotti
Creative Director, Publishing Melissa Feinen
Senior Art Director Gwendolyn Salas
Photo Editor & Department Coordinator Emily Hakkinen

SALES & MARKETING

Vice President, CURE Media Group Erik Lohrmann / elohrmann@mjhassoc.com
Vice President & Executive Producer, MJH Productions David Lepping / dlepping@mjhassoc.com
Executive Vice President, Oncology Professional Relations Donna Short, M.A.
Vice President, Strategic Alliances and Patient Engagement Strategy Sandra Shaw
Director, Patient Education Marty Murphy
Associate Director Brittany Hansen
Strategic Alliance Partnership Manager Brooke Weinstein
Senior Marketing Manager Melissa Hindle
Sales & Marketing Coordinator Samantha Gullace

OPERATIONS & FINANCE

Circulation Director Jon Severn; subscribe@curetoday.com, circulation@mjhassoc.com
Vice President, Finance Leah Babitz, CPA
Controller Katherine Wyckoff

CORPORATE

President & CEO Mike Hennessy Jr.
Vice Chairman Jack Lepping
Chief Financial Officer Neil Glasser, CPA/CFE
Executive Vice President, Global Medical Affairs & Corporate Development Joe Petroziello
Senior Vice President, Content Silas Inman
Senior Vice President Operations Michael Ball
Vice President, Human Resources & Administration Shari Lundenberg
Vice President, Mergers & Acquisitions Chris Hennessy
Executive Creative Director, Creative Services Jeff Brown

CHAIRMAN & FOUNDER
Mike Hennessy Sr.

AN MJH life sciences™ BRAND

MJH Life Sciences, LLC.
2 Clarke Drive, Suite 100
Cranbury, N.J. 08512
609-716-7777

All the stories you read in *CURE*® are reported and edited without the influence of advertisers or sponsors.

Subscriptions: *CURE*® is FREE to cancer patients, survivors or caregivers who live in the U.S. FREE bulk subscriptions are available for physicians, cancer centers and other organizations. Subscriptions may be obtained at www.curetoday.com/subscription, or by calling 800-210-2873 or requested via email to subscribe@curetoday.com.

CURE® (ISSN 1534-7664, USPS 022-616) is published quarterly for cancer patients, survivors and caregivers by CURE Media Group, LLC, Inc., 2 Clarke Drive, Suite 100, Cranbury, NJ 08512. Periodicals postage paid at Princeton, NJ and additional mailing offices. POSTMASTER: Send address changes to *CURE*®, P.O. Box 606, Cranbury, NJ 08512.

Progress Through Collaboration

PROSTATE CANCER AFFECTS nearly 250,000 patients in the United States annually, making it the second most common cancer among men. In addition, between 10% and 20% of men with prostate cancer are resistant to treatment, meaning that their disease did not respond to other therapies including chemotherapy and anti-androgen therapy.

Prostate-specific membrane antigen (PSMA)-targeting agents are gaining lots of traction in the prostate space, with radioligand lutetium-Lu-117-PSMA-617 (^{177}Lu-PSMA-617) possibly being the closest to potentially obtaining approval from the Food and Drug Administration (FDA). This technology allows PSMA-targeting agents to attach to cancerous cells, rather than normal tissues, giving the treatment greater selectivity for tumor cells and sparing normal tissue.

Recent data from the VISION clinical trial presented at this year's American Society of Clinical Oncology Annual Meeting demonstrated that adding ^{117}Lu-PSMA-617 to standard-of-care treatment in patients with advanced-stage PSMA-positive metastatic castration-resistant prostate cancer improved survival compared with standard of care alone. Those findings led to the therapy receiving FDA breakthrough therapy designation, which may expedite its approval.

In this special issue of *CURE*®, we speak with three experts to learn more about what makes PSMA-targeted therapies unique, how they work to target cancer cells and how they may change the treatment landscape for prostate cancer. We also spoke with two patients treated with ^{117}Lu-PSMA-617, one of whom credits the therapy for allowing him to meet his first grandchild. The second patient, after being diagnosed, learned as much as he could about ^{117}Lu-PSMA-617 and even traveled to Germany to access it outside a formal clinical trial.

Thanks to the efforts of researchers and to the participation of patients who enrolled in the VISION trial, we are now on the cusp of an important approval by the FDA in treating patients with treatment-resistant prostate cancer. Advancements like these would not be possible without patients and their supporting friends and families. This highlights the importance of being aware of and participating in available clinical trials (if acceptable after careful consideration). It is important that the whole community understand that basic research and clinical trials can continue to improve outcomes for patients with cancer.

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

DEBU TRIPATHY BY MIKE KITADA; LUNG ART: SPECTRAL DESIGN / STOCKADOBE.COM

Strength in Numbers

CURE® is proud to partner with several leading advocacy groups across the country. Our shared goal is to connect patients and their caregivers to valuable resources and support to assist with navigating the cancer journey.

Scan the QR code with your mobile device to visit curetoday.com and check out our advocacy group partnerships.

STRATEGIC cure® ALLIANCE

A Promising Option

A recently approved antibody-drug conjugate provides another much-needed treatment choice for patients with locally advanced and metastatic urothelial cancer.

By DARLENE DOBKOWSKI, M.A.

THE FOOD AND DRUG ADMINISTRATION (FDA) granted accelerated approval to Trodelvy (sacituzumab govitecan-hziy) for the treatment of locally advanced and metastatic urothelial cancer, giving patients another option if they did not respond to platinum- based chemotherapy or immunotherapy.

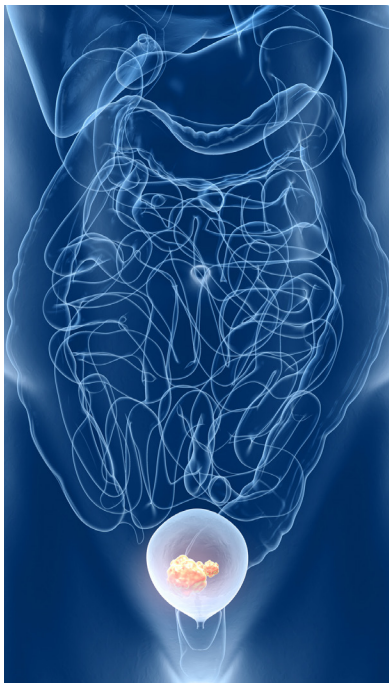
In particular, antibody-drug conjugates, which are a form of targeted therapy, utilize monoclonal antibodies linked to a drug that bind to specific proteins to kill cancer cells without harming other cells. Before the FDA approval, this patient population had few options if the cancer did not respond to chemotherapy or PD-1 or PD-L1 antibodies, (a) form of immunotherapy.

"We had an antibody-drug conjugate called enfortumab vedotin (Padcev), which was approved in 2019, (but) there are now patients who cannot receive that due to preexisting severe neuropathy," said Dr. Shilpa Gupta, director of genitourinary medical oncology at Cleveland Clinic, in an interview with *CURE*®. "(For) those who progressed on (Padcev), there are very limited options still. … (Trodelvy) is certainly an option that is promising for these patients who historically did not have any."

Trodelvy was previously approved by the FDA for another indication: triple-negative breast cancer.

"A lot of doctors have been using (Trodelvy) in the community, but there's not a whole lot of awareness about it for urothelial cancer," Gupta said.

This recent FDA approval for locally advanced and metastatic urothelial cancer is based on findings from the TROPHY clinical trial, which assessed the effect of Trodelvy in 112 patients with locally advanced or metastatic urothelial cancer who had received prior treatment with platinum chemotherapy and either anti-PD-1- or PD-L1-based immunotherapy. Treatment with Trodelvy contributed to an overall response rate of 27.7% and a median duration of response of 7.2 months.



Treating metastatic urothelial cancer with Trodelvy confers similar response rates as other therapies.

"If you look at it in the perspective of immunotherapy, which has been (a) really very powerful class of drugs since 2016, those response rates have also only been in the 20% or so range," Gupta said. "Still, (immunotherapy) is so widely used, but unfortunately, the majority of patients don't respond to that. … Chemotherapies can achieve (an overall response rate of) 10% to 20% max, and immunotherapy has not done any better in that regard. For these (previously) treated patients, this is in line with what we would see with other therapies."

Some side effects associated with Trodelvy include neutropenia and diarrhea, both of which can be either prevented or managed, Gupta said. She added that an ongoing phase 3 study is assessing whether the survival improvement from Trodelvy can continue over a longer period of time versus salvage chemotherapy, an approach used if cancer has not responded to other treatments.

More research is also needed to determine the best treatment sequence for patients with locally advanced or metastatic urothelial cancer.

"At some point, we have to be able to use these different therapies available in a patient's journey," Gupta said. "Nobody really knows if it is better to give Trodelvy before (Padcev) or vice versa. We also have (an) FGFR3 inhibitor approved (called Balversa, or erdafitinib)."

"The sequence question has not really been defined to date. At some point, a patient should be able to receive these different therapies that are approved. And that is what (the Trodelvy approval) represents: an (additional option) for these patients."

'Don't Rush — Get Educated'

Monitoring, rather than immediately treating, patients with low-risk prostate cancer may be a better approach. *By* DARLENE DOBKOWSKI, M.A.

STUDY FINDINGS HAVE SHOWN for years that active surveillance may be preferable for patients with low-risk prostate cancer compared with treatment, and recent study results presented during Europe's largest urological conference highlighted the potential for greater benefit in patients older than 60 with lower-risk prostate cancer.

To better understand the meaning of these findings, *CURE*® spoke with Dr. Peter R. Carroll, a member of the UCSF Helen Diller Family Comprehensive Cancer Center and professor in the department of urology at the University of California, San Francisco. Carroll conducts a research program in this area and sees the advantages of active surveillance. Still, he worries that this age cutoff may be preventing other patients from benefiting from this approach.

"I see a fair number of patients less than age 60 years who may be candidates for surveillance," he said. "Active surveillance is about timing of treatment for many. 'Does this cancer need to be treated right now?' is the perspective of many. Younger patients have a lower rate of (cancer) upgrading (to an increased risk) compared to older patients who tend to have worse cancers. … Although (younger patients) have a longer life expectancy and they are more likely to require treatment compared to older patients, many if not most of those with low-grade cancers can avoid the immediate side effects of treatment and still be treated for cure later as needed. It's kind of counterintuitive to many, but it's true."

Specifically, active surveillance includes monitoring patients over time with periodic imaging, PSA measurements and, less commonly, biopsies to identify preclinical progression of the cancer when they are still eligible for curative treatment. Carroll mentioned that in men with low-risk disease on surveillance, approximately 1 in 3 requires treatment in three to five years, which may increase to 50% over a 10-year period. Currently, an active surveillance regimen is tailored around a patient's individual risk.

"Now we're understanding much more clearly who's at risk for (cancer) upgrading and when," Carroll explained. "The risk (for cancer progression) is characterized by things like PSA density, genomics (and) imaging, so we're identifying a patient population who needs less-intensive surveillance. Someone may require more intensive surveillance, but that's being refined. I think we're making it less burdensome."

Carroll added that 20 years ago, almost everyone diagnosed with prostate cancer received treatment, but in the past decade, oncologists employed a refined treatment strategy so that patients were treated selectively. Recently, urologists have been aiming to limit the number of patients who undergo biopsy, especially for those who are unlikely to have cancer and those with very low-volume, low-grade cancers, which are generally indolent. Newer screening practices combining biomarkers and imaging have decreased biopsy rates by approximately 30% to 40%, Carroll said.

He advises doctors to have a conversation with their patients about low-risk prostate cancer before a biopsy is performed.

"I tell a patient before biopsy, 'Recognize we may identify a cancer in you that I'm going to tell you not to treat,'" Carroll said. "When you have that conversation before the biopsy, it's much easier to have the conversation (about active surveillance) afterward."

Although many study findings

have established that active surveillance can help patients with low-risk prostate cancer and the approach has been recommended in major cancer guidelines in the U.S. and Europe, active surveillance is "not put into practice as consistently as we'd like," Carroll noted.

Carroll also mentioned that other factors could play a role in the low usage of active surveillance in these patients. For example, oncologists, urologists and radiation oncologists are trained to deliver treatment, and there are strong economic drivers of delivering care. In addition, patients often hear the word "cancer" and think it's a lethal disease "even though we know that in many instances, it's not," Carroll said.

While undergoing active surveillance, patients may benefit from participating in lifestyle management, which combines diet and exercise to hopefully reduce the risk of disease progression. (Of note, a specific diet and/or exercise regimen best suited to reduce this risk is a matter of much debate.) Carroll mentioned another important advantage of lifestyle management during active surveillance.

> "When you decide on a path (of) treatment (including active surveillance), you want it to be a well-informed decision."
>
> – DR. PETER R. CARROLL

"When patients are doing something (like diet and exercise), they tend to be more compliant with surveillance," he noted. "I think people like to be doing something. It's been our impression that those people who do lifestyle management tend to be more compliant and less anxious about the disease state." Also, he noted, that lifestyle management lowers the risk of many common diseases such as cardiovascular disease and diabetes.

After patients receive a diagnosis, it's important for them to take their time processing the information, researching and becoming better educated to make the best decision for them.

"If you get a diagnosis of prostate cancer, don't rush. Get educated," Carroll advised. "That's the No. 1 thing I would tell people. ... Understand your disease. When you decide on a path (of) treatment (including active surveillance), you want it to be a well-informed decision. That takes a little time and effort."

It's 'Never Too Late to Change'

Although study results link obesity to better outcomes in prostate cancer, an expert stresses the importance of working toward a healthy lifestyle after receiving a diagnosis. *By* DARLENE DOBKOWSKI, M.A.

PATIENTS WITH METASTATIC castration-resistant prostate cancer may have better outcomes if they are obese, according to findings from a recent study. Despite these conclusions, however, patients should not gain excessive weight to obtain this protective effect, according to an expert.

"While the results of this study mirror other studies, I worry about the messaging that obesity is good because I don't think that's the right message from these (findings). Rather, this is an interesting research study that suggests something about obesity is associated with better outcomes in very late-stage disease. It is now our jobs to figure out what that is," said Dr. Stephen J. Freedland, professor of urology, Warschaw Robertson Law Families Chair in Prostate Cancer and director of the Center for Integrated Research in Cancer and Lifestyle at Cedars-Sinai Medical Center in Los Angeles, in an interview with *CURE*®.

One possibility is that obese men have higher estrogen levels, and this may contribute to better outcomes. He added that estrogen therapy was previously assessed as a treatment option for high-risk prostate cancer, but it has fallen out of favor because of side effects such as heart attacks and strokes.

Freedland, who has previously conducted research on the effects of obesity on prostate cancer, interprets the conclusion of the study in another way.

"The more likely conclusion is if you are obese, it means you're not cachectic (having significant weight and muscle loss)," he explained. "You're not in that late end-stage, weight-loss, wasting-away form of cancer. Of course, those patients (with obesity) are going to do better than the patients (with significant weight loss from cancer). It's less likely that obesity itself is a good thing."

One of the study researchers noted that this obesity benefit may be from the higher doses of chemotherapy in patients who are obese, but Freedland disagrees.

"They are getting a little bit higher doses of chemotherapy, but it's proportional to their body weight," he said. "I don't think that's going to make a huge difference, as many men don't get any chemotherapy. Obese people tend to have high inflammation levels. There's this thought that inflammation early on is probably bad for cancer and can drive changes that make cancers grow, but in the very late stages, that same inflammation may actually help fight the cancer."

Freedland is concerned that after seeing the study results, patients with obesity who receive a diagnosis of prostate cancer may not be as motivated to correct their obesity.

"If you're obese and you get prostate cancer, you are more likely to die than someone who has normal weight and got the cancer," Freedland explained. "Some data suggest weight loss can reduce the risk of getting high-grade prostate cancer. There's a good argument to be made (for) avoiding obesity in the first place and, if you are obese, trying to lose weight. In the very late stage of life when there's two years to live, might obesity be functioning differently? It's possible."

This analysis, among others, leaves researchers with more questions than answers, Freedland said. These include whether the effects of obesity are reversible (particularly in early-stage prostate cancer), whether it's different in Black men versus White men and how obesity interplays with physical activity.

"We have a situation of obese people being at higher risk of getting aggressive prostate cancer and dying from it," he said. "If we can figure out why and what's driving that, not only is (it) going to help us correct obesity-driven prostate cancer, but (it) will give us insights into prostate cancer in general that we can apply and help everybody."

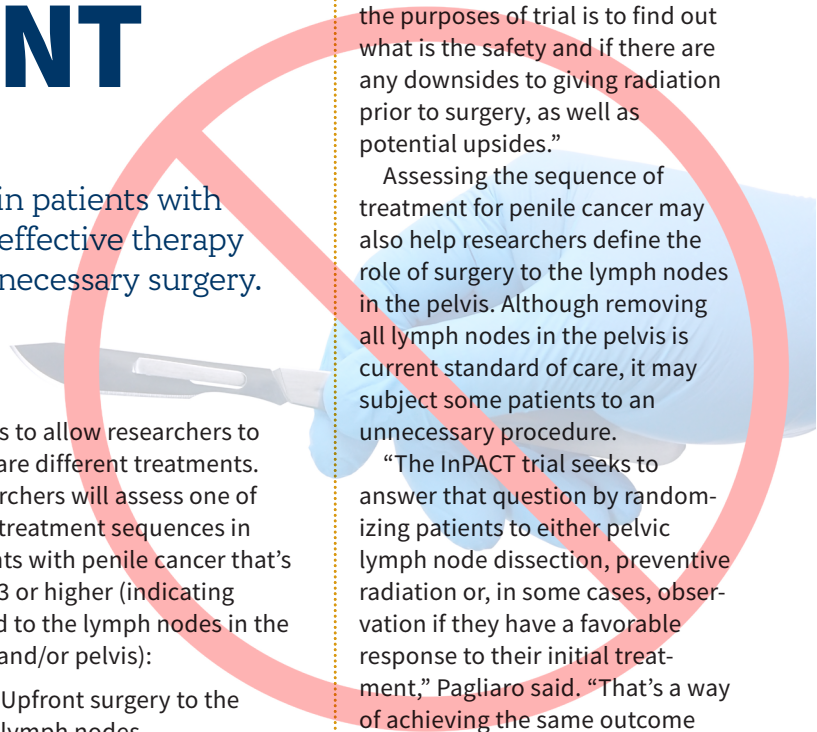
Freedland concluded with important advice: "If you are obese, it's never too late to change."

DENIS / STOCK.ADOBE.COM

REEVALUATING TREATMENT

A first-of-its-kind trial underway in patients with penile cancer may lead to a more effective therapy sequence, potentially avoiding unnecessary surgery.

By DARLENE DOBKOWSKI, M.A.



BECAUSE DEVELOPMENTS ARE lacking in systemic therapy for the treatment of patients with stage 3 or higher penile cancer, a trial in this patient population may provide a glimpse into the most effective treatment sequence.

The InPACT trial, which is currently enrolling patients in the U.S., Canada and U.K., aims to find an improved way to cure this rare cancer; penile cancer affects less than 1% of patients with cancer, according to the American Society of Clinical Oncology. Approximately 2,210 men in the United States will receive a diagnosis of penile cancer in 2021, with an estimated 460 men dying from the disease this year.

"Metastatic penile cancer is a potentially fatal cancer but also potentially curable," Dr. Lance C. Pagliaro, a consultant in the division of medical oncology and professor of oncology at Mayo Clinic in Rochester, Minnesota, told *CURE*®. "We look at strategies to combine different treatment modalities — surgery with chemotherapy or radiation with chemo — to control and ultimately cure the largest percentage of patients that we can."

For the past 10 years, the standard of care in these patients has been cisplatin-based chemotherapy. The InPACT study is historic because it is the first randomized clinical trial for this disease, with patients placed into groups to allow researchers to compare different treatments. Researchers will assess one of three treatment sequences in patients with penile cancer that's stage 3 or higher (indicating spread to the lymph nodes in the groin and/or pelvis):

- Upfront surgery to the lymph nodes.
- Neoadjuvant (or preoperative) chemotherapy, followed by surgery (representing the current standard treatment regimen).
- Neoadjuvant chemoradiotherapy, followed by standard surgery.

"Patients come to us with different extent of disease," said Pagliaro, who is also a principal investigator for the trial at Mayo Clinic. "Whether it's one lymph node involved or multiple lymph nodes in the groin or lymph nodes in the pelvis greatly impacts the chance of cure and the risk of death. The researchers of the InPACT trial aim to help us understand how to calibrate the treatment to what the patient needs."

Although surgery upfront and surgery after chemotherapy are not technically new treatments, chemoradiation followed by surgery is a new approach that is "not normally done," Pagliaro said. "It's a new approach because you're combining all three (chemo, radiation and surgery), and one of the purposes of trial is to find out what is the safety and if there are any downsides to giving radiation prior to surgery, as well as potential upsides."

Assessing the sequence of treatment for penile cancer may also help researchers define the role of surgery to the lymph nodes in the pelvis. Although removing all lymph nodes in the pelvis is current standard of care, it may subject some patients to an unnecessary procedure.

"The InPACT trial seeks to answer that question by randomizing patients to either pelvic lymph node dissection, preventive radiation or, in some cases, observation if they have a favorable response to their initial treatment," Pagliaro said. "That's a way of achieving the same outcome with less-invasive treatment."

Pagliaro explained that even though this trial will provide more insight into the treatment of penile cancer, oncologists can still effectively treat patients while awaiting results, which could take three to five years to analyze.

"If there has been spread to one or more lymph nodes, it's not a hopeless situation," he said. "Penile cancer is a disease where we can cure some of those patients and have done for years with surgery alone, but what we're trying to do by combining surgery with radiation and/or chemotherapy is to cure a larger percentage of those patients with limited spread of disease."

Patients with symptoms potentially indicating penile cancer should see a doctor immediately.

"We do see cases of men who are embarrassed or just don't want to deal with it," Pagliaro said. "Allowing time for cancer to spread and grow is not a good thing. So I encourage men that have any kind of symptom or concern to get checked out right away."

Medical World News®

BLADDER CANCER

Smoking Increases Recurrence Risk

Patients who don't quit the habit after a diagnosis have a fourfold higher chance of the disease returning. By ANTONIA DEPACE

SMOKING MAY SIGNIFICANTLY increase the risk of non-muscle invasive bladder cancer recurrence, according to study findings.

"Having bladder cancer is not good, but having bladder cancer and continuing to smoke is worse," Dr. Nancy Dawson, an expert in urologic cancer who was not an author of this study, told *CURE*®.

The study, performed at the Notre Dame des Secours University Hospital in Lebanon, showed that patients with high levels of urinary cotinine, a specific biomarker of tobacco smoke exposure, may have a four-times increased risk of non-muscle invasive bladder cancer recurrence.

"It's interesting that (the researchers) could sort out who had the highest risk based upon this urine level, but it gets away from what the real message should be, which is: If you're smoking and you continue to smoke, you will have a much higher chance (of the cancer coming) back in your bladder — and when it comes back, it may be more aggressive and it may spread," said Dawson, a professor of medicine and oncology and director of the genitourinary medical oncology program at Georgetown Lombardi Comprehensive Cancer Center at Medstar Georgetown University Hospital in Washington, D.C. "What you need to do is try to quit smoking."

According to the Centers for Disease Control and Prevention, cigarette smoking is responsible for 1 in 5 deaths every year and is the leading cause of preventable disease, disability and death. In addition, the American Cancer Society estimates that 83,000 new cases of bladder cancer will be diagnosed this year. Of these cases, approximately 1 in 3 bladder cancers will be invasive.

"We know that smoking is a major risk factor for getting bladder cancer," Dawson said.

For newly diagnosed non-muscle invasive bladder cancer, the standard of care is a transurethral resection of the bladder tumor, also known as TURBT. This procedure is performed by inserting an instrument through the urethra. A resectoscope (a small camera) with a wire loop at the end is used to remove abnormal tissue and tumors, which are then sent to the lab for testing. The procedure does not require any surgical incisions.

Data from this study demonstrated that recurrence was observed in 51.85% of patients who smoked, 75% of whom were heavy smokers and 18.18% of whom were moderate smokers. On average, patients had been smoking for 30.3 years.

In the case of recurrence, Dawson said that doctors will likely perform the TURBT procedure again, "but each time they go back, there's that chance that this cancer they scooped out may now be invading into the muscle. Each time that (doctors) go back in there, they're thinning out the wall of the bladder, so you can't do that indefinitely."

In addition, cancer recurring more than three times increases the chances of needing bladder removal surgery and an ostomy (a surgically created opening in the abdomen that allows urine or stool to exit the body).

"That's life altering, and although people adjust to having an ostomy (bag), … that's not something people want to have," Dawson said. "It may help in decision-making about smoking or not smoking … if you realize that you're putting yourself in a scenario (that could result in cancer and even an ostomy bag)."

Dawson added that it's never too late to stop smoking: "Ex-smokers are less likely to have a recurrence, so you can actually improve. It's not like 'I've been smoking all my life, so what good (is it) to stop now?'"

For moderate to heavy smokers who want to quit, Dawson recommended finding a smoking cessation program inside or outside the cancer center and communicating the desire to quit with their health care team.

ICONS-STUDIO / STOCK.ADOBE.COM

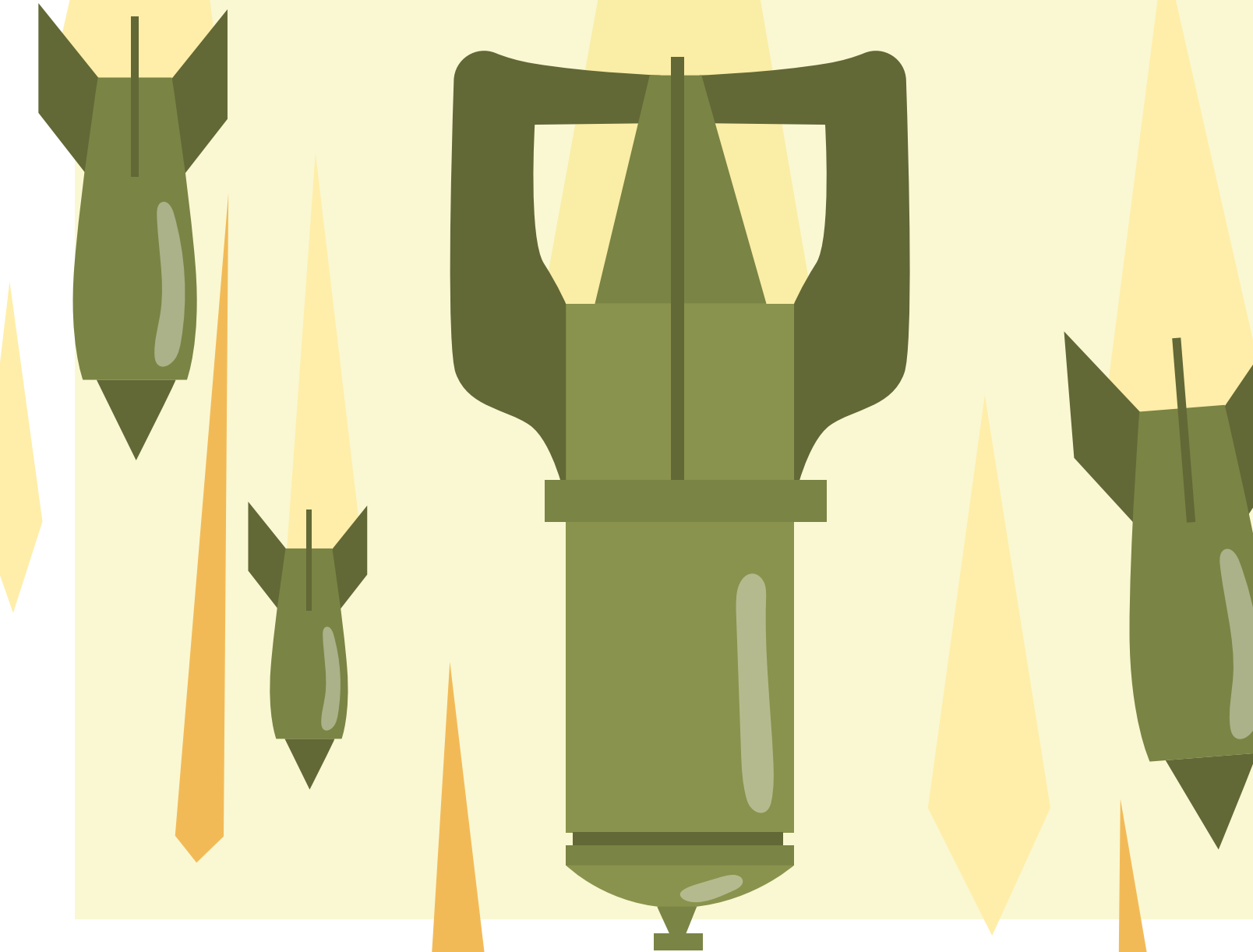
I AM *MORE* THAN A PATIENT.

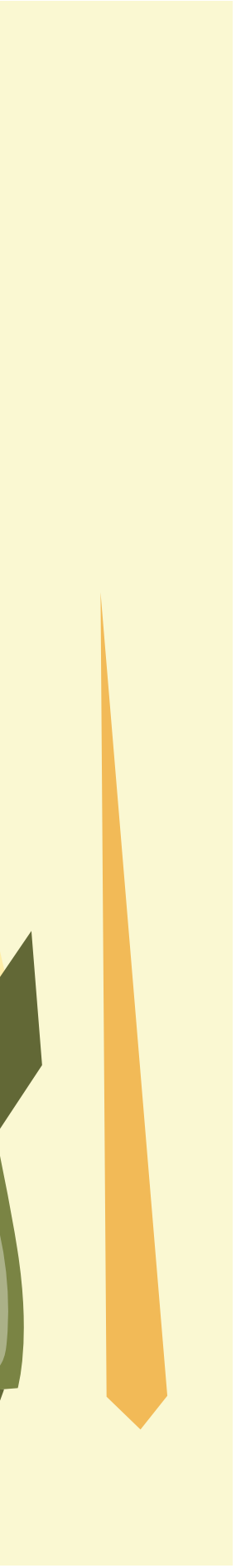
I AM AN *ENTREPRENEUR*, A *FRIEND*, AN *ADVOCATE* AND A *TRAIL BLAZER*.

Those who have gone through cancer are more than their diagnosis. At *CURE*®, we provide insight to everyday people whose lives have been touched by cancer, letting them know that they are not alone. We strive to give readers an identity that extends beyond their diagnosis. *CURE*® makes cancer understandable, and we aim to make life with cancer understandable.

A community of more than just patients. ***Join us.*** curetoday.com

A SMART BOMB FOR PROSTATE CANCER





PCH.VECTOR / STOCK.ADOBE.COM ADAPTED BY GWEN SALAS

After decades of research, scientists inch closer to FDA approval for PSMA-targeted treatments that show promise for patients with an advanced form of this disease.

By AMY PATUREL, M.S., M.P.H.

In the fall of 2016, Dr. Mark DeAntonio learned he had a mass on his bladder. Doctors suspected stage 4 bladder cancer, and they confirmed the diagnosis with a biopsy. Over the next year, DeAntonio participated in two rounds of intensive chemotherapy, but the cancer didn't regress — it spread. That's when doctors referred him to the University of Southern California to participate in a clinical trial.

It turns out, DeAntonio didn't have bladder cancer after all. "The tumor developed at the end of the prostate near the bladder, where it busted through the bladder wall," says DeAntonio, now 67. "It was prostate cancer all along."

Prostate cancer is the second most common cancer among men, affecting nearly 250,000 Americans annually. It happens most often when men have reached the height of their careers and are heading toward retirement — and it's often highly treatable when diagnosed early. But for 10% to 20% of patients like DeAntonio, the disease can spread throughout the body and be remarkably resistant to treatment, especially the most common initial therapy used — androgen deprivation therapy (ADT). Called metastatic castration-resistant prostate cancer (mCRPC), these cancers grow and spread even in the absence of their preferred fuel: testosterone. »

DR. MARK DEANTONIO received compassionate-use approval from the FDA for treatment with a particular PSMA-targeted therapy.

Since DeAntonio had already received chemotherapy for what he thought was bladder cancer, doctors prescribed ADT. These testosterone-blocking drugs controlled the cancer for several months, but within a year, DeAntonio's PSA level began climbing again.

The cancer was growing.

He tried immunotherapy to stimulate his immune system to fight the cancer, followed by radiation to destroy the stubborn cells. Doctors even recommended surgery to remove his prostate and bladder.

DeAntonio resisted. The procedure wouldn't change his prognosis, but it would severely compromise his quality of life. "The pain and stiffness in my pelvis was debilitating, and moving into noncurative treatments was scary," DeAntonio says. "I was running out of options."

A child and adolescent psychiatrist at the University of California in Los Angeles, DeAntonio ultimately received compassionate-use approval from the Food and Drug Administration (FDA) for six treatments with lutetium-Lu-177-PSMA-617 (^{177}Lu-PSMA-617), a targeted treatment for prostate cancer. Used in Germany, Australia, India and parts of South Africa, ^{177}Lu-PSMA-617 is part of a class of radioactive drugs that target a protein on the surface of prostate cancer cells called prostate-specific membrane antigen, or PSMA.

MATTHEW WATSON

"PSMA is highly overexpressed in prostate cancer cells, whether they're confined to the prostate or have metastasized to other sites," says Dr. Jeremie Calais, an assistant professor of nuclear medicine and theranostics at the David Geffen School of Medicine at UCLA. "While some normal tissues express small amounts of PSMA, the PSMA-targeted radioactive agent preferentially attaches to cancerous cells, not the normal tissues."

PSMA-targeted radionuclides are part of a new class of therapies known as theranostics, which offer both therapy and diagnostic capabilities. Scientists have developed ligands — antibodies and small molecules — that recognize and bind to PSMA. To this ligand, they attach a radionuclide that emits radiation when it decays. Depending on the choice of radionuclide, you get either a smart bomb that delivers molecularly targeted radiation directly to the target or a smart imaging tracer with less radiation that highlights PSMA-avid cells using standard positron emission tomography (PET) imaging techniques. Add it all together, and a growing body of research both in the United States and abroad suggests that taking a PSMA-targeted approach could be a game changer for advanced prostate cancer.

> The PSMA-targeted radioactive agent preferentially attaches to cancerous cells, not the normal tissues.
>
> —DR. JEREMIE CALAIS

A HISTORICAL LOOK AT PSMA

Dating back to the late 1980s and early 1990s, scientists were laser-focused on identifying tumor-specific targets that could help them distinguish cancerous cells from normal cells.

At the time, Dr. Neil Bander, now director of urological oncology research at Weill Cornell Medicine in New York, suspected that targeting PSMA could serve as a powerful weapon in the battle against prostate cancer — but researchers didn't yet understand how to harness its potential.

Targeting PSMA diagnostically and therapeutically isn't new. "The first PSMA imaging agent was approved more than 20 years ago," says Dr. Scott Tagawa, medical director of the Genitourinary Oncology Research Program at Weill Cornell Medical College. Since then, researchers have been targeting PSMA in myriad ways from chemotherapy and antibody-drug conjugates to radionuclides, an approach that investigators expect to gain FDA approval in the coming months.

What makes PSMA unique? It's consistently overexpressed in prostate cancer cells. PSMA should not be confused with PSA, a protein produced by cells of the prostate gland that may indicate prostate cancer at elevated levels. Normal prostate cells are also PSMA positive, but cancerous cells boast 100 to 1,000 times more PSMA than healthy tissue. The more stubborn and resistant to treatment the prostate cancer, the more PSMA on the surface of the cells. So if you target PSMA, you're selectively targeting the cancer.

As luck would have it, one of the first-line treatments for prostate cancer — ADT — increases the load of PSMA on the surface of cancer cells. "PSMA levels are tightly linked to the androgen receptor pathway, and they increase as resistance to hormone therapy develops," Tagawa says. So, in a sense, taking ADT is like using a homing beacon to detect an elusive target. Add a radioactive payload to the mix, and you have a veritable molecular grenade delivering cancer-obliterating radiation directly to hormone-resistant prostate cancer cells.

"Because of the radioactivity, we can confirm the therapy is reaching its target on imaging," says Dr. A. Oliver Sartor, medical director of Tulane Cancer Center in New Orleans and a world-renowned prostate cancer researcher. "Radiation does not extend far beyond the cancer cell, so there is little damage to surrounding tissue."

Because the radioactive isotope seeks out PSMA, just as a dog scours the floor for table scraps, the treatment can even find hidden cancerous cells that are too small to see on traditional imaging. The only hiccup: Not every patient with prostate cancer has easy-to-spot PSMA-expressing tumor cells circulating near tumors. Studies suggest that up to 10% of patients with metastatic, treatment-resistant prostate cancer have tumors that don't light up on imaging.

The jury is out on whether patients who are PSMA negative or PSMA weak are less likely to respond to treatment. In addition, most patients with prostate cancer in the United States can't access imaging with a PSMA-targeted agent — at least not yet.

TRAVELING FOR TREATMENT

For the past several years, researchers in the United States have been testing PSMA-targeted treatments, specifically »

DR. MARK DEANTONIO avoided serious complications while undergoing treatment.

MATTHEW WATSON

^{177}Lu-PSMA-617, in patients with mCRPC that didn't respond to prior therapies. They have demonstrated that 95% of prostate cancers are PSMA positive and that PSMA spikes in response to ADT. They even have high-powered imaging that shows the treatment is reaching its target. Yet the FDA has not approved PSMA-targeted agents for the treatment of prostate cancer. And until recently, PSMA imaging was only available at two sites in California (UCLA and UCSF), or as part of a clinical trial.

But that tide is about to change. Earlier this year, the FDA approved another PSMA PET imaging agent that will make PSMA PET imaging available throughout the United States. More importantly, for therapy, the FDA granted breakthrough therapy designation to ^{177}Lu-PSMA-617 after a phase 3 clinical trial showed improvements in survival among patients with mCRPC. For the trial, Sartor and his colleagues enrolled more than 800 patients with mCRPC that had disease progression on other treatments and a positive PSMA PET scan. Trial participants randomized to the ^{177}Lu-PSMA-617 group were 40% less likely to die and 60% less likely to show disease progression on imaging versus those who received standard of care alone.

"Many of these patients were on their fourth-, fifth- and sixth-line treatments," says Sartor. "The more treatments a patient receives, the more resistant they are to the next line of therapy, so if we can show activity in patients who have already been treated with multiple lines of therapy, we anticipate the response will be even better in patients who are treatment naive."

While these targeted treatments await approval, patients like 66-year-old Steve G.* are getting creative. Steve had a prostatectomy in 2015, but because he hadn't received chemotherapy, he wasn't eligible for PSMA-targeted trials in the United States. A computer scientist, Steve made it his mission to learn everything he could about prostate cancer — and he wasn't opposed to hopping around the globe to get the best care. "It's in my DNA," Steve jokes.

In the early '80s, the surgeon who pioneered nerve-sparing prostatectomies, Dr. Patrick Walsh, operated on Steve's father at Johns Hopkins Medicine. "That set the precedent for me," says Steve, who ventured to New York to see the top surgeons and oncologists in the country, then to UCLA to get a PSMA PET scan and finally to Germany — five times — so doctors could inject him with ^{177}Lu-PSMA-617.

"The 'compassionate use' program in Germany allows for the use of untested therapies in patients who have exhausted all approved treatment options," Sartor says. But German investigators only treat patients whose PSMA PET scans light up like a neon sign that reads "targetable cancer cells HERE!" With this carefully curated population, they're able to achieve striking response rates.

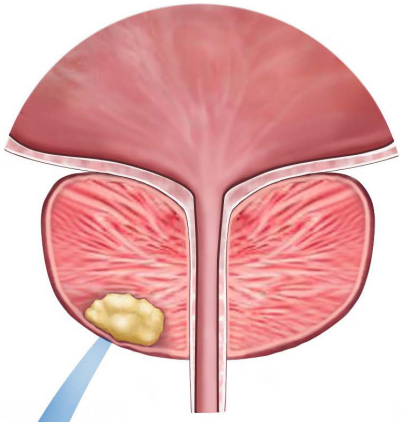
So if patients are willing to take the risk — and can afford multiple trips to Germany — they can access promising, but unproven, treatments outside a formal clinical trial. In fact, the growing number of American patients who make that trek are adding to the repository of data showing that targeted radionuclides could provide hope, and even durable remissions, in patients with mCRPC.

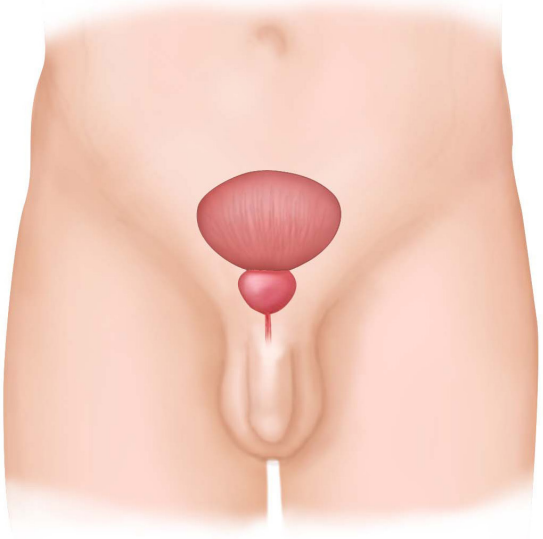
Steve says the experience of receiving ^{177}Lu-PSMA-617 in Germany is both similar and different than in the United States. Staff ensure that they have paid upfront. Then they give patients the traditional hospital wristband before directing them to the nuclear medicine ward. "The facility in Munich is like a labyrinth of old buildings connected by walkways," Steve says. "You travel the hallways walking on solid ground and then shift to walking on wood. It's quite quaint."

*Last name omitted for anonymity.

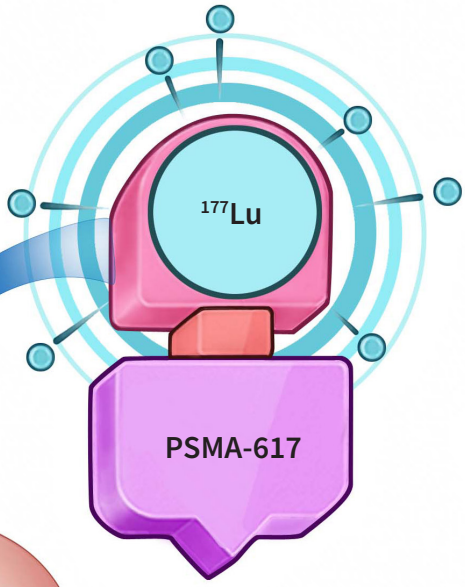
HOW PSMA-TARGETED THERAPIES WORK

PSMA-targeted therapies are a form of monoclonal antibodies that are manmade versions of immune proteins and attach to the PSMA protein on prostate cancer cells, according to the American Cancer Society. This antibody acts like sonar by bringing the radioactive molecule or drug to the cancer cells, which may aid in its effectiveness. PSMA is targeted because cancer cells carry higher amounts of this protein than healthy tissue, which adds to the cancer's stubbornness.

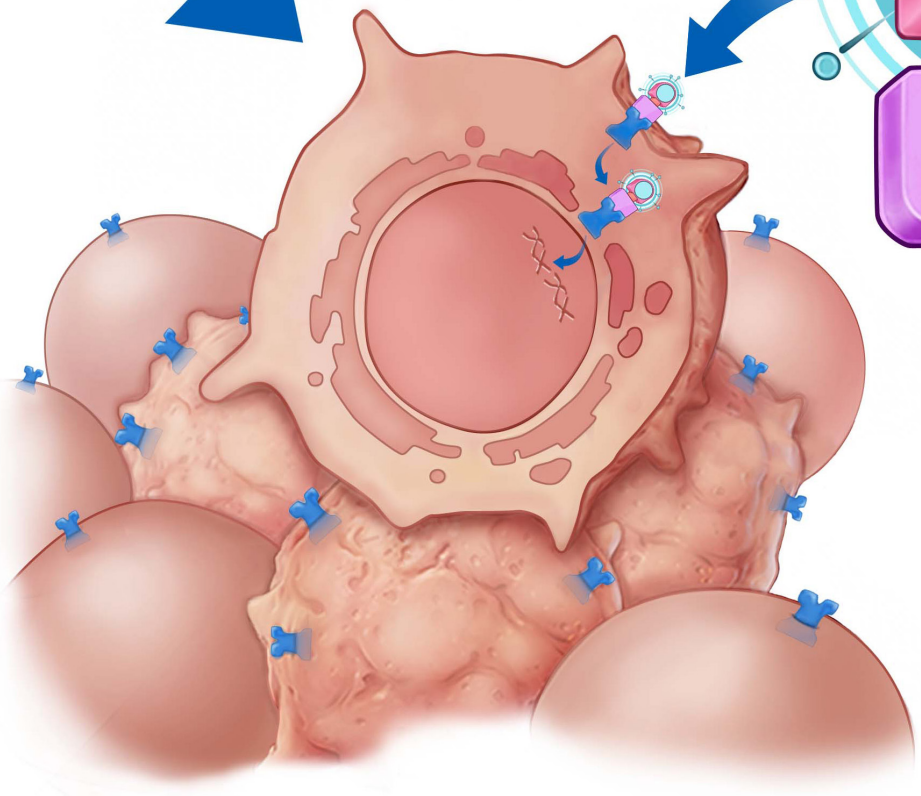




Prostate cancer often begins when cells within the prostate gland grow uncontrollably. Most prostate cancers are adenocarcinomas, which develop from gland cells that produce prostate fluid, which is then added to semen.

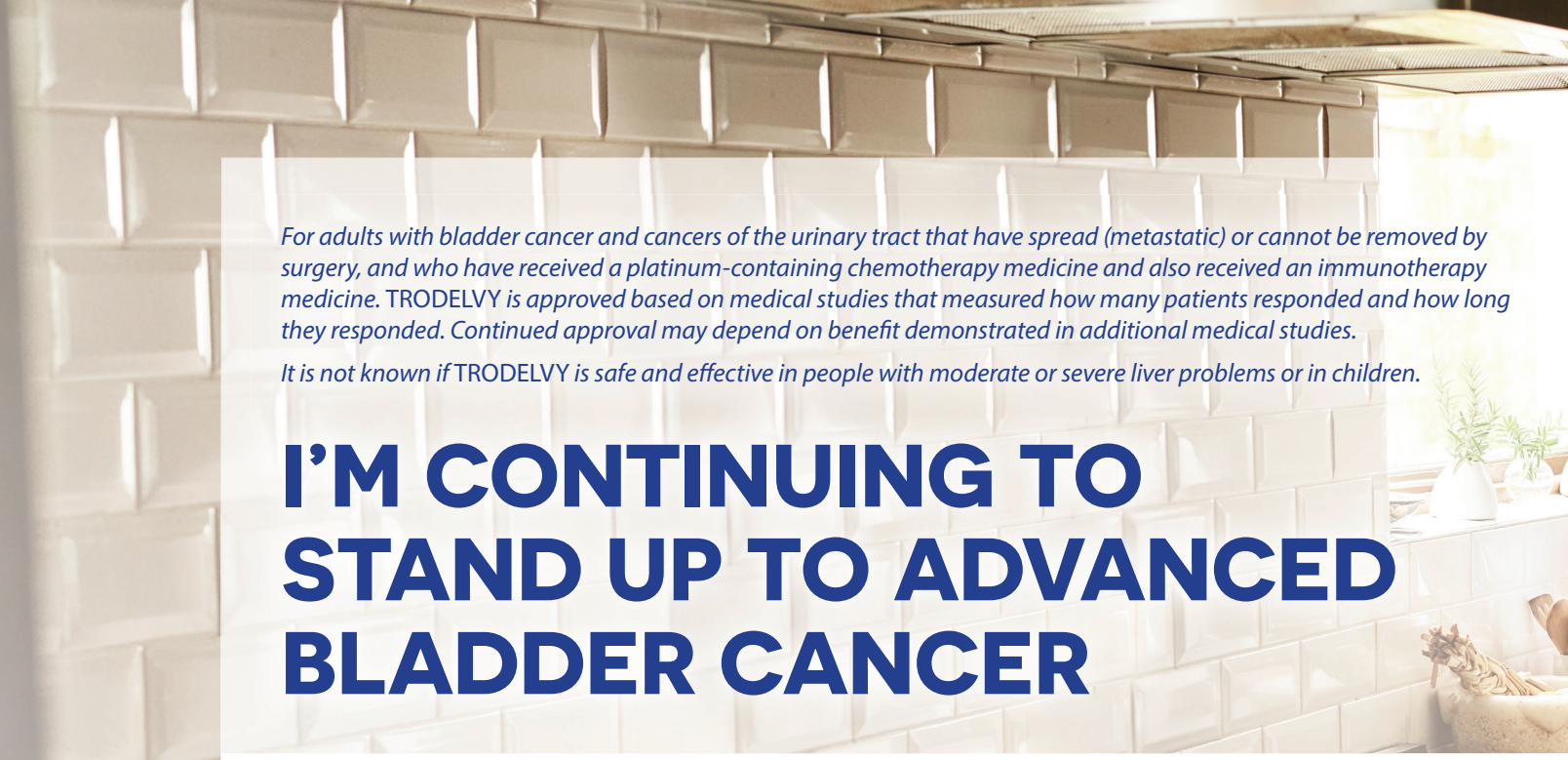


Ligands, which are antibodies and small molecules, recognize and bind to PSMA. They attach a radionuclide that emits radiation when it decays.



Prostate cancer cells and other nearby cells decay during this process. Also, hidden cancer cells are detected with these therapies that are often missed with traditional imaging modalities.

continued on page 27 »



For adults with bladder cancer and cancers of the urinary tract that have spread (metastatic) or cannot be removed by surgery, and who have received a platinum-containing chemotherapy medicine and also received an immunotherapy medicine. TRODELVY *is approved based on medical studies that measured how many patients responded and how long they responded. Continued approval may depend on benefit demonstrated in additional medical studies.*

It is not known if TRODELVY *is safe and effective in people with moderate or severe liver problems or in children.*

I'M CONTINUING TO STAND UP TO ADVANCED BLADDER CANCER

WHAT IS TRODELVY?

TRODELVY® (sacituzumab govitecan-hziy) is a prescription medicine used to treat adults with bladder cancer and cancers of the urinary tract that have spread (metastatic) or cannot be removed by surgery, and who have received a platinum-containing chemotherapy medicine and also received an immunotherapy medicine.

It is not known if TRODELVY is safe and effective in people with moderate or severe liver problems or in children.

IMPORTANT SAFETY INFORMATION

TRODELVY can cause serious side effects, including low white blood cell count and diarrhea:

- **Low white blood cell count (neutropenia)** which is common and can sometimes be severe and lead to infections that can be life-threatening or cause death. Your healthcare provider should check your blood cell counts during treatment. If your white blood cell count is too low, your healthcare provider may need to lower your dose, give you a medicine to help prevent low blood cell count with future doses of TRODELVY, or in some cases may stop TRODELVY. Your healthcare provider may need to give you antibiotic medicines if you develop fever while your white blood cell count is low. **Call your healthcare provider right away if you develop any of the following signs of infection:** fever, chills, cough, shortness of breath, or burning or pain when you urinate.
- **Severe diarrhea.** Diarrhea is common and can be severe. Your healthcare provider should monitor you for diarrhea and give you medicine as needed to help control it. If you lose too much body fluid (dehydration), your healthcare provider may need to give you fluids and electrolytes to replace body salts. If diarrhea happens later in your treatment, your healthcare provider may check you to see if it may be caused by an infection. Your healthcare provider may decrease your dose or stop TRODELVY if your diarrhea is severe and cannot be controlled with anti-diarrheal medicines.
  - **Call your healthcare provider right away** the first time that you get diarrhea during treatment with TRODELVY; if you have black or bloody stools; if you have symptoms of dehydration, such as lightheadedness, dizziness, or faintness; if you are unable to take fluids by mouth due to nausea or vomiting; or if you are not able to get your diarrhea under control within 24 hours.

Do not receive TRODELVY if you have had a severe allergic reaction to TRODELVY. Ask your healthcare provider if you are not sure.

Allergic and infusion-related reactions which can be serious and life-threatening. Tell your healthcare provider or nurse right away if you get any of the following symptoms during your infusion of TRODELVY or within 24 hours after: swelling of your face, lips, tongue, or throat; hives; skin rash, itching, or flushing of your skin; fever; difficulty breathing or wheezing; lightheadedness, dizziness, feeling faint, or pass out; or chills or shaking chills (rigors).

GILEAD

Nausea and vomiting are common with TRODELVY and can sometimes be severe. Before each dose of TRODELVY, you will receive medicines to help prevent nausea and vomiting along with medicines to take home with instructions about how to take them. Call your healthcare provider right away if you have nausea or vomiting that is not controlled with the medicines prescribed for you. Your healthcare provider may decide to decrease your dose or stop TRODELVY if your nausea and vomiting is severe and cannot be controlled with anti-nausea medicines.

Before receiving TRODELVY, tell your healthcare provider about all of your medical conditions, including if you:

- have been told that you carry a gene for UGT1A1*28, which can increase your risk of getting side effects with TRODELVY, especially low white blood cell counts, with or without a fever, and low red blood cell counts.
- have liver problems.
- are pregnant or plan to become pregnant. TRODELVY can harm your unborn baby. Your healthcare provider should check to see if you are pregnant before you start receiving TRODELVY. TRODELVY may cause fertility problems in females, which could affect your ability to have a baby. Talk to your healthcare provider if fertility is a concern for you.
  - Females who can become pregnant should use effective birth control during treatment and for 6 months after your last dose of TRODELVY. Talk to your healthcare provider about birth control choices that may be right for you during this time.
  - Males with a female partner who can become pregnant should use effective birth control during treatment and for 3 months after your last dose of TRODELVY.
  - Tell your healthcare provider right away if you or your partner become pregnant during treatment with TRODELVY.
- are breastfeeding or plan to breastfeed. It is not known if TRODELVY passes into your breastmilk and can harm your baby. Do not breastfeed during treatment and for 1 month after your last dose of TRODELVY.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements. Certain medicines may affect the way TRODELVY works.

The most common side effects of TRODELVY include feeling tired or weak, hair loss, decreased red blood cell count, constipation, decreased appetite, rash, and stomach-area (abdominal) pain or discomfort.

These are not all of the possible side effects of TRODELVY. Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

Please see Important Facts about TRODELVY, including Important Warning, on the next page.

Ask your healthcare provider where **TRODELVY** *may fit in your plan*

TRODELVY™
sacituzumab govitecan-hziy
180 mg for injection

TRODELVY™
sacituzumab govitecan-hziy
180 mg for injection

TRODELVY® (troh-DELL-vee)
(sacituzumab govitecan-hziy) for injection, for intravenous use

MOST IMPORTANT INFORMATION ABOUT TRODELVY

TRODELVY can cause serious side effects, including:

- **Low white blood cell count (neutropenia)** which is common and can sometimes be severe and lead to infections that can be life-threatening or cause death. Your healthcare provider should check your blood cell counts during treatment. If your white blood cell count is too low, your healthcare provider may need to lower your dose, give you a medicine to help prevent low blood cell count with future doses of TRODELVY, or in some cases may stop TRODELVY. Your healthcare provider may need to give you antibiotic medicines if you develop fever while your white blood cell count is low. **Call your healthcare provider right away if you develop any of the following signs of infection:**
  - fever
  - cough
  - burning or pain when you urinate
  - chills
  - shortness of breath
- **Severe diarrhea.** Diarrhea is common and can be severe. Your healthcare provider should monitor you for diarrhea and give you medicine as needed to help control it. If you lose too much body fluid (dehydration) your healthcare provider may need to give you fluids and electrolytes to replace body salts. If diarrhea happens later in your treatment, your healthcare provider may check you to see if it may be caused by an infection. Your healthcare provider may decrease your dose or stop TRODELVY if your diarrhea is severe and cannot be controlled with anti-diarrheal medicines.

Call your healthcare provider right away:

- the first time that you get diarrhea during treatment with TRODELVY
- if you have black or bloody stools
- if you have symptoms of dehydration, such as lightheadedness, dizziness or faintness
- if you are unable to take fluids by mouth due to nausea or vomiting
- if you are not able to get your diarrhea under control within 24 hours

ABOUT TRODELVY

TRODELVY is a prescription medicine used to treat adults with:

- breast cancer that is estrogen and progesterone hormone receptor (HR) negative, and human epidermal growth factor receptor 2 (HER2)-negative (also called triple-negative breast cancer) that has spread to other parts of the body (metastatic) or cannot be removed by surgery, **and** who have previously received two or more prior treatments, including at least one treatment for metastatic disease.
- bladder cancer and cancers of the urinary tract that have spread or cannot be removed by surgery. TRODELVY may be used if you have received a platinum-containing chemotherapy medicine **and** also received an immunotherapy medicine.

It is not known if TRODELVY is safe and effective in people with moderate or severe liver problems or in children.

Do NOT receive TRODELVY if you have had a severe allergic reaction to TRODELVY. Ask your healthcare provider if you are not sure.

POSSIBLE SIDE EFFECTS OF TRODELVY

TRODELVY can also cause serious side effects, including:

- **Allergic and infusion-related reactions** which can be serious and life-threatening. Tell your healthcare provider or nurse right away if you get any of the following symptoms during an infusion or within 24 hours after:
  - swelling of your face, lips, tongue, or throat
  - hives
  - skin rash, itching, or flushing of your skin
  - fever
  - difficulty breathing or wheezing
  - lightheadedness, dizziness, feeling faint or pass out
  - chills or shaking chills (rigors)

IMPORTANT FACTS

This is only a brief summary of important information about TRODELVY and does not replace talking to your healthcare provider about your condition and your treatment.

POSSIBLE SIDE EFFECTS OF TRODELVY *(cont'd)*

- **Nausea and vomiting** are common with TRODELVY and can sometimes be severe. Before each dose of TRODELVY, you will receive medicines to help prevent nausea and vomiting along with medicines to take home with instructions about how to take them. Call your healthcare provider right away if you have nausea or vomiting that is not controlled with the medicines prescribed for you. Your healthcare provider may decide to decrease your dose or stop TRODELVY if your nausea and vomiting is severe and cannot be controlled with anti-nausea medicines.

The most common side effects of TRODELVY include feeling tired or weak, hair loss, decreased red blood cell count, constipation, decreased appetite, rash, and stomach-area (abdominal) pain or discomfort.

TRODELVY may cause fertility problems in females, which could affect your ability to have a baby. Talk to your healthcare provider if fertility is a concern for you.

Before and during treatment with TRODELVY, your healthcare provider will need to do tests to monitor your health. Tell your healthcare provider right away if you have any new symptoms while taking TRODELVY.

These are not all of the possible side effects of TRODELVY. Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

BEFORE RECEIVING TRODELVY

Tell your healthcare provider about all of your medical conditions, including if you:

- have been told that you carry a gene for UGT1A1*28, which can increase your risk of getting side effects with TRODELVY, especially low white blood cell counts, with or without a fever, and low red blood cell counts.
- have liver problems.
- are pregnant or plan to become pregnant. TRODELVY can harm your unborn baby. Your healthcare provider should check to see if you are pregnant before you start receiving TRODELVY.
  - Females who can become pregnant should use effective birth control during treatment and for 6 months after your last dose of TRODELVY. Talk to your healthcare provider about birth control choices that may be right for you during this time.
  - Males with a female partner who can become pregnant should use effective birth control during treatment and for 3 months after your last dose of TRODELVY.
  - Tell your healthcare provider right away if you or your partner become pregnant during treatment with TRODELVY.
- are breastfeeding or plan to breastfeed. It is not known if TRODELVY passes into your breastmilk and can harm your baby. Do not breastfeed during treatment and for 1 month after your last dose of TRODELVY.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements. Certain medicines may affect the way TRODELVY works**.**

HOW TO RECEIVE TRODELVY

- Your healthcare provider will give you TRODELVY into your vein through an intravenous (IV) line.
- TRODELVY is given 1 time each week, on Day 1 and on Day 8 of a 21-day treatment cycle.
- You will receive the first dose over 3 hours; if well-tolerated, future doses may be given over 1 to 2 hours.
- Before each dose, you will receive medicines to help prevent infusion reactions, and nausea and vomiting.
- You will be monitored for side effects during and for at least 30 minutes after you receive each infusion of TRODELVY.
- Your healthcare provider may slow down or temporarily stop your infusion if you have an infusion-related reaction, or permanently stop TRODELVY if you have a life-threatening infusion-related reaction.
- Your healthcare provider will decide how long you stay on treatment.

GET MORE INFORMATION

This is only a brief summary of important information about TRODELVY. Talk to your healthcare provider or pharmacist to learn more.

To learn more, go to TRODELVY.com or call 1-844-TRODELVY (1-844-876-3358)

GILEAD

« *continued from page 23*

Against a backdrop of gray walls and dim lighting, staff insert an IV to draw blood for testing and then flood the patient's system with fluids. The additional fluid coaxes their body to excrete any radiation that isn't attached to the cancer. Steve had an IV dripping for more than an hour before the five-minute infusion.

"When it's time for (^{177}Lu-PSMA-617), the technician turns on the pump and practically runs out the door," Steve says. "You have to quarantine for a minimum of three days before they release you back into the world in order to comply with strict emission standards in Germany."

^{177}Lu-PSMA-617 has a half-life of around a week, so patients emit measurable amounts of radiation for weeks after the treatment.

After Steve received five treatments, two of which took place at the height of the COVID-19 pandemic, his PSA level had become undetectable by various assays — and it has remained undetectable ever since. His last PSMA PET scan at UCLA revealed that his cancer has almost disappeared, although a few slightly PSMA-positive lymph nodes remain.

THE ALPHAS, BETAS AND GAMMAS OF PSMA

Radioisotopes are unstable chemical elements that release radioactive particles. They destroy cancer by damaging its DNA. Different elements release different types of particles, such as alpha or beta, and each behaves in distinct ways.

Isotopes such as actinium 225 and radium 223 emit alpha particles when they decay. These high-energy particles have a very short range and obliterate everything in their path. Beta particles, such as those emitted by ^{177}Lu-PSMA-617, have 2,000 to 4,000 times less energy, depending on the alpha, but travel farther, setting up crossfire in a PSMA-avid tumor. The isotope lutetium 177 has the bonus of emitting a small percentage of gamma rays when it decays, which makes it detectable for imaging. So if alpha-emitting particles are like precisely delivered atomic bombs, lutetium 177 is a radioactive hand grenade with GPS tracking.

In a case study published in *Acta Radiologica Open*, one patient who had significant disease progression on multiple lines of treatment had experienced dramatic results with a PSMA molecule carrying actinium 225. The "before and after" images revealed that the widespread metastatic cancer had completely disappeared. And the patient's PSA levels plummeted from the hundreds and thousands to undetectable.

Unfortunately, it's tough to produce spectacular results like that without some collateral damage. "An alpha particle in the right spot is so powerful it will destroy the target on contact," Tagawa says. "The problem is an alpha in the wrong spot can produce permanent damage."

Historically, scientists have shied away from small molecules because they can readily target normal tissues that express low levels of PSMA, such as the salivary and lacrimal glands. That can lead to dry mouth and dry eye. "Beta particles emitted by (^{177}Lu-PSMA-617) trigger only mild toxicities that are usually reversible. But alpha particles can permanently destroy the salivary glands, and that's not a small problem," says Calais, explaining that without salivary glands, patients cannot taste or eat, and, over time, teeth fall out.

And because the radioisotope is excreted through the kidneys and bladder, there's a risk of kidney toxicity, particularly with the alpha-emitting isotopes. Decreased blood counts may also occur because of effects on the bone marrow. Such serious and often irreversible toxicities with alpha-emitting particles are one reason why beta particles are leading the charge in the United States. Tagawa knows of only four prospective studies using PSMA-targeted alpha particles, and three of the four use antibodies, not small molecules (antibodies are too large to reach those unintended targets).

Fortunately, DeAntonio and Steve both sidestepped serious complications. But even with only ^{177}Lu-PSMA-617, Steve developed dry mouth after his fourth treatment and DeAntonio had a horrible inflammatory reaction after his first injection. "It felt like I had a bad flu along with tremendous pelvic pain. The reaction went away after five days, but two weeks before my second treatment, the pain came back," DeAntonio says.

There isn't enough experience with this treatment to know whether the inflammatory response is a good sign.

DeAntonio's PSA level was also higher after treatment. "If you base my response on lab studies, there has been no improvement in my disease state, but clinically, I'm better," says DeAntonio, who is just about to meet his first grandchild.

For DeAntonio and many other patients with mCRPC, the focus is on the horizon. A whole new class of drugs is emerging for prostate cancer. The idea is to keep the cancer at bay and extend patients' lives long enough to take advantage of new treatment options.

"I'm not expecting a cure," says DeAntonio, "but I have no interest in dying."

LOOKING FORWARD

Emerging data suggest that combining both alpha- and beta-emitting particles may improve outcomes for patients with advanced castrate-resistant prostate cancer (CRPC) and minimize toxicity. Investigators expect radionuclides that target prostate-specific membrane antigen to become standard of care for CRPC in the not-so-distant future. Over time, and perhaps with more refinements, it may even become an earlier-line therapy for patients who recently received a diagnosis.

NOVEL COMBINATIONS Offer New Hope

Immunotherapy and tyrosine kinase inhibitors may potentially change the treatment paradigm for patients with renal cell carcinoma, the most common type of kidney cancer in adults.

By ARLENE WEINTRAUB

After Jarod Roy was diagnosed with metastatic renal cell carcinoma in July 2018, he was put on a combination of two immunotherapy drugs — Opdivo (nivolumab) and Yervoy (ipilimumab) — which had recently been approved by the Food and Drug Administration (FDA) to be used together in previously untreated patients. But his tumors kept growing, so Roy decided to drive two hours from his home in Westlake, Louisiana, to The University of Texas MD Anderson Cancer Center in Houston for a second opinion.

MD Anderson enrolled Roy in a clinical trial of a different combination — the immunotherapy drug Keytruda (pembrolizumab) plus Lenvima (lenvatinib), a drug that works by inhibiting cancer-driving enzymes known as tyrosine kinases. Roy received infusions of Keytruda every three weeks and took Lenvima orally every day. »

SUZY G PHOTOGRAPHY

JAROD ROY was treated with Keytruda and Lenvima, which significantly reduced his metastatic renal cell carcinoma.

JENNIFER POPE

JAROD ROY continues to manage his company and ski with his family because of the effectiveness of the combination treatment.

SUZY G PHOTOGRAPHY

Six weeks after Roy started the regimen, imaging tests showed that the cancer had shrunk more than 20%. "Every scan I had showed a decrease, and the overall reduction of my cancer was 54%," says Roy, 39, who completed 35 doses of Keytruda and is still taking the Lenvima as part of the trial. He continues to manage his company, which maintains exhaust systems for restaurants, and he enjoys skiing every year with his wife and two children.

"I'm a believer in this combination treatment," Roy says. "It definitely did the job for me."

Several combinations of immunotherapy drugs and tyrosine kinase inhibitors (TKIs) have been approved by the FDA for patients with newly diagnosed kidney cancer. In fact, four combinations were recently approved for the first-line treatment of kidney cancer: Bavencio (avelumab) plus Inlyta (axitinib), Opdivo plus Cabometyx (cabozantinib) and Keytruda plus Inlyta. In August, the FDA approved Keytruda plus Lenvima in the first-line setting.

With many more combinations in development, the outlook is bright for patients at the beginning of their treatment journey, says Dr. Amishi Y. Shah, an assistant professor of genitourinary medical oncology at MD Anderson.

"We have a very nice armamentarium of drugs to reach for, and now there are newer agents coming down the pike that are showing some promise," Shah says.

In the trial that led to the approval of Opdivo plus Cabometyx, for example, the overall response rate for the combination was 56% versus 27% among patients taking the TKI Sutent (sunitinib) alone. And median progression-free survival (time when a patient lives with the disease without worsening) was 16.6 months among patients taking the combination, double that of the Sutent group.

Several experimental combinations look promising too, including the treatment Roy is receiving — Keytruda plus Lenvima. In May, the FDA granted priority review for the use of the combination in previously untreated patients, setting up a potential approval this fall.

The FDA sped up its review based on a clinical trial in which 71% of patients taking the combination responded to it versus 36% of patients taking Sutent. Progression-free survival was two years in patients taking Keytruda and Lenvima versus nine months with Sutent. And 16% of patients on the combination treatment had complete responses, meaning the cancer had disappeared or was not detectable radiographically or by physical examination.

"The responses were the highest and longest of any

> Now there are newer agents coming down the pike that are showing some promise.
>
> —DR. AMISHI Y. SHAH

MERYL URANGA controls blood pressure fluctuations with additional medicine while undergoing treatment with the TKI-immunotherapy combination.

immunotherapy-plus-TKI study we have seen," says Dr. Toni Choueiri, director of the Lank Center for Genitourinary Oncology at Dana-Farber Cancer Institute/Brigham and Women's Hospital in Boston and a co-lead investigator for the trial of Keytruda plus Lenvima. "(Once) this gets approved, I would argue it should be used as the first-line treatment."

WEIGHING RISKS AND BENEFITS

There are some caveats with new combination treatments for kidney cancer. Some patients experience onerous side effects, and oncology researchers have yet to determine whether the positive responses to immunotherapy-TKI combinations are long lasting enough to outweigh the potential risks.

The most common side effects are increases in blood pressure and diarrhea. Each TKI has potential side effects because of the blockade of specific kinases. Antiangiogenic drugs target pathways involved in tumor blood vessel formation, so side effects on normal vessels like constriction or impaired healing can cause hypertension, bleeding or clotting events. Immunotherapy causes inflammation in normal tissues like skin, gastrointestinal (GI) tract and endocrine glands, resulting in rash, diarrhea and hypothyroidism. In the trial that Choueiri co-led, more than 90% of the patients taking either the TKI-immunotherapy combination or Sutent alone reported side effects, but the need for investigators to drop the doses of the medicines to get those symptoms under control was greater among patients on the combination. And nearly 10% of patients taking the combination dropped out of the trial.

Meryl Uranga had some trouble controlling her blood pressure after she started taking the Keytruda-Inlyta combination in 2018 for kidney cancer. She had initially been treated with radiation and surgery to remove one kidney and part of her lung — a regimen that put her in an 18-month remission. When the cancer returned, she was put on two immunotherapy drugs but had only a partial response, and some of »

LAUREN LIZ PHOTO

BRUCE SHREFFLER is currently treated with Cabometyx and Opdivo, which shrank his cancer and allows him to be active despite some fatigue.

her tumors grew a little, so her oncologist switched her to the TKI-immunotherapy combination.

The fluctuations in blood pressure were unsettling at first, Uranga says, but her doctor adjusted the dose of a blood pressure medicine until the problem came under control. As for the cancer, "everything was shrunken down or gone," says Uranga, 60, a retired telecommunications project manager who lives in the Atlanta area. "I take a microdose of blood pressure medication if I need to, and I have GI issues, but the impact to my quality of life is very minimal and manageable."

Choueiri expects that ongoing clinical trials will show just how durable the positive effects of these new combinations are and that physicians will grow more and more comfortable with strategies for lessening side effects. "With the TKIs especially, there are a lot of adjustments we can make to figure out the ideal dose that the patient can tolerate while getting the benefit at the same time," he said.

While surgery is generally still the first step in patients with localized kidney cancer, that is no longer the case for many patients with metastatic disease. Before the advent of TKIs and immunotherapy, surgery was often the first line of treatment, says Shah, but now "the pendulum has swung" and drug treatments are tried first in many cases, she says.

When patients respond well to the drugs, subsequent surgery might offer a good way to eradicate the disease altogether, she adds. "One of the best conversations I have is telling a patient they had an absolutely phenomenal response to therapy and there's no evidence of disease except for the primary renal tumor," Shah says. "I've sent a number of these patients to surgery to basically render them clear of disease."

TACKLING RENAL CANCER SUBTYPES

About 25% of patients with kidney cancer are diagnosed with non-clear cell renal carcinoma, which encompasses several subtypes of the disease, including papillary renal cell carcinoma. Traditionally these patients were treated similarly to those with clear cell carcinoma, although recently, some researchers have launched studies aimed at determining whether some combination treatments should be targeted specifically to patients with non-clear cell disease.

Bruce Shreffler enrolled in one of those trials in 2018, about five months after starting treatment for metastatic non-clear cell kidney cancer. He initially took a combination

MITCH WOJNAROWICZ

MITCH WOJNAROWICZ

of two TKIs, Lenvima and Afinitor (everolimus), but only some of the tumors shrank and the GI upset and fatigue were difficult to manage.

So Shreffler traveled from his home in Albany, New York, to Memorial Sloan Kettering Cancer Center in New York City for a second opinion. He was admitted into a trial of Cabometyx plus Opdivo in non-clear cell kidney cancer. After six months, the cancer had shrunk and stopped spreading. "A lot of the tumors were entirely resolved," says Shreffler, 64, a computer contractor and avid outdoorsman whose pre-cancer adventures included climbing all 46 Adirondack High Peaks.

Shreffler's treatment includes daily doses of Cabometyx and one infusion per month of Opdivo. His oncologists told him he will stay on the regimen as long as the cancer is stable, and he's fine with that, especially since the side effects have been much easier to tolerate than they were for the combination of two TKIs. A high-fiber diet is enough to keep his digestion under control, and although he has a touch of fatigue, he's able to ride his bicycle 15 miles in less than an hour, he says.

"I can't climb the mountains that I used to, but I'm as active as I can be," Shreffler says.

In June of this year, positive data from the trial of Cabometyx and Opdivo in non-clear cell renal carcinoma were released at the American Society of Clinical Oncology annual meeting. Among 32 patients with papillary carcinoma, the response rate was 47.5%, and some of the responses correlated with specific genetic mutations found in patients' tumors.

In fact, there's a major push underway in kidney cancer research to find biomarkers, including genetic mutations, that can help oncologists personalize treatments, says Dr. Chung-Han Lee, a medical oncologist at Memorial Sloan Kettering Cancer Center. "We're trying to understand how we can use genetic sequencing to predict patient outcomes," Lee says. "Those kinds of predictive biomarkers will improve patients' outcomes just by getting them on the best treatment earlier."

Even though TKI-immunotherapy combinations are moving into the frontline treatment setting, for some people, starting on two immunotherapy drugs instead might still be a good idea, Lee says. For example, immunotherapy combinations can be beneficial for patients who have no other underlying illnesses and are not experiencing severe symptoms from the cancer. "In the majority of people who do get significant shrinkage of their disease from combination immunotherapies, the effects seem to be durable, meaning they last beyond three years," he says.

It's not yet clear how long positive responses to TKI-immunotherapy combinations will last — the clinical trials needed to determine that durability have not yet been completed. Still, starting with one of those combinations can be a good idea for patients who are very sick from the cancer "because we can see a very rapid response," Lee says.

Now that two-drug combinations are well entrenched in the care of patients with kidney cancer, researchers are considering a new question: Could three drugs be even better than two? One ongoing phase 3 trial is combining the TKI Cabometyx with two immunotherapy drugs that stimulate the immune response in different ways, Yervoy and Opdivo. "With two different mechanisms of action, you're able to kill more cancer cells because cancer can be sensitive to one pathway but not the other," Choueiri explains. "The same may be true of three drugs."

Several new TKIs are under development, and that could lead to new combination strategies for kidney cancer in the future. In March, the FDA approved Fotivda (tivozanib) for patients with advanced renal cell carcinoma who have relapsed after two or more prior therapies. The approval was based on a response rate of 18% versus 8% for another TKI, Nexavar (sorafenib).

Now a new clinical trial has started comparing Fotivda plus Opdivo to Fotivda alone. Lee says he's looking forward to seeing the results of that trial, particularly because Fotivda seems to produce fewer side effects than other TKIs. "It's very well tolerated," he says, "and that can certainly be a benefit for our patients."

MD Anderson's Shah adds that even though there's still a lot to learn about how combination therapies can best be matched to patients, the rapidly growing selection of treatments for kidney cancer is exciting.

"It has changed the outlook in the field," she says, "and led to great improvements in survival."

Sperm banking is one of the few options men have to preserve their fertility amid a testicular cancer diagnosis.

TESTICULAR CANCER AND FUTURE *Fertility*

Despite this diagnosis, men have options when it comes to starting or growing their family.

By LEAH LAWRENCE

When Jason Midkiff, 46, was diagnosed with testicular cancer 20 years ago, he was not concerned about whether he could have children in the future.

"I was pretty focused on my career and didn't have a significant other at the time," Midkiff recalls. "I think of myself as having been young, dumb and foolish."

To be fair, Midkiff was facing an aggressive form of testicular cancer called pure embryonal carcinoma. Testicular cancer is subdivided into seminoma and non-seminomas, with embryonal carcinoma falling in the non-seminoma category. Embryonal carcinoma, which occurs in about 3% to 4% of testicular cancers, according to the American Cancer Society, tends to grow rapidly and spread outside the testicle.

Midkiff first noticed some swelling in one of his testicles at age 26. Swelling is a common symptom of testicular cancer but can be due to multiple causes. Midkiff's primary care physician initially treated him for inflammation before ultimately recommending he undergo an ultrasound. »

JASON MIDKIFF was not focused on having children when he received a diagnosis of testicular cancer.

PROVIDED BY MIDKIFF

TILIALUCIDA / STOCK.ADOBE.COMA

The ultrasound revealed a mass, and Midkiff was referred to a urologist for a biopsy.

"I had a surgery to remove the mass and was scheduled to undergo a second surgery to remove some of the lymph nodes in my groin," Midkiff says.

His urologist initiated a conversation about possible infertility prior to his second surgery. Unfortunately, Midkiff says, he figured it would not be a big deal for him.

Today, a father to five adopted children, Midkiff says he is not sure he would do anything differently.

"Hindsight can be tough," he says. "But I can't imagine my life without the kids I adopted."

EFFECTS OF CANCER

A testicular tumor is a space-occupying lesion in the testicle that will destroy some of the sperm-producing tissue in that space and consequently decrease sperm production, explains Dr. Larry I. Lipshultz, a professor of urology and chief of the Scott Department of Urology's Division of Male Reproductive Medicine and Surgery at Baylor College of Medicine in Houston.

In fact, studies have shown that 30% to 50% of men diagnosed with testicular cancer have low sperm counts or dysfunction of available sperm at diagnosis.

"Testicular cancers can also produce certain hormones, such as human chorionic gonadotropin (HCG), alpha-fetoprotein or lactate dehydrogenase, that can upset the endocrine system and disrupt normal sperm production," Lipshultz says.

The standard of care for treating testicular cancer is radical orchiectomy — removal of the entire affected testicle.

"Almost right away, men with testicular cancer are down one sperm-producing unit," says Dr. Sarah Vij, a male infertility and andrology specialist at Cleveland Clinic. "Additionally, many men who have testicular cancer will require additional therapy like chemotherapy or radiation to the remaining testicle."

Men treated with orchiectomy alone have the lowest risk of long-term fertility concerns, Vij says.

Some men, like Midkiff, may require retroperitoneal lymph node dissection to remove the retroperitoneal lymph nodes, where testicular cancer often spreads first. In some cases, this surgery can affect the nerve bundles that control the way semen exits the body, causing retrograde ejaculation, explains Dr. Matthew T. Campbell, an assistant professor of genitourinary medical oncology at The University of Texas MD Anderson Cancer Center in Houston. During retrograde ejaculation, semen flows back into the man's bladder instead of out through the penis, resulting in infertility.

> The discussion about infertility is hard to have, but it (needs) to be (talked about) upfront.
>
> —DR. SARAH VIJ

In addition, chemotherapy and radiation can be toxic to spermatogenesis — the sperm-producing process. The chemotherapy drugs used to treat testicular cancer including cisplatin and ifosfamide tend to be the most toxic to the testicles, Campbell says.

"Chemotherapy agents are a standard of care for men with metastatic testicular cancer or used to prevent the recurrence of testicular cancer, and while they can contribute to infertility, not all men who receive (this treatment) will have lifelong infertility," Campbell says.

"Another important piece of the puzzle is that treatment with orchiectomy, and later with chemotherapy, can cause low testosterone levels," Campbell adds. "Low testosterone can impact fertility by affecting a man's sex drive, causing erectile dysfunction, and reduce production of sperm."

In addition to the cancer and its treatments, other traditional risk factors such as age, smoking, alcohol use and obesity are associated with infertility in men.

FERTILITY PRESERVATION

At the time of diagnosis, the main priority should be the cancer diagnosis and survival, Vij emphasizes.

"The discussion about infertility is hard to have, but it (needs) to be (talked about) upfront," she says. "We recommend that all men with testicular cancer do sperm banking. Ideally, this is done prior to removal of the testicle."

Sperm banking is the process of collecting semen and examining it under a microscope to count sperm cells to determine how healthy they are. The sperm cells are then frozen and stored. This process is sometimes called sperm cryopreservation.

JAY ERICKSON chose sperm banking after his testicular cancer diagnosis in 2013.

LAURIE SPENS

A small population of men may not be able to provide ejaculate or do not have sperm present in the ejaculate. In these men, surgeons can try to remove sperm from the testicle during the orchiotomy (a surgical procedure to remove one or both testicles), Vij says. This process is called testicular sperm extraction.

Jay Erickson, 46, chose to bank sperm after receiving a testicular cancer diagnosis in 2013. He says the disease was pretty advanced at diagnosis, with the initial ultrasound showing a large mass in his abdomen with tumors throughout his lymph node system and lungs. The physicians initially thought Erickson had sarcoma, but bloodwork eventually showed elevated levels of the hormone HCG.

Erickson's physicians told him he had pure testicular choriocarcinoma, another rare form of testicular cancer occurring in about 0.19% of all testicular tumors. »

Through fertility preservation before cancer treatment, **JAY ERICKSON'S** daughter **JUNIPER** was born a few months after his last surgery, which he says was a big part of his healing.

LAURIE SPENS

Choriocarcinomas tend to be aggressive, and Erickson was told that this type of cancer was not always responsive to chemotherapy.

Prior to his diagnosis, he and his wife had been trying to get pregnant.

"During that initial conversation, we discussed prognosis, medical details and a treatment plan, but when infertility came up, it was really not on my radar," Erickson says. Recalling the details of that day still elicits emotions for him. "I was going to start chemotherapy in two or three days, and the people at (Memorial) Sloan Kettering (Cancer Center) had a fertility specialist right there at the appointment with a messenger standing by — ready to bring a (sperm) specimen to a Manhattan cryopreservation bank that day."

The details are hazy, Erickson says, but the specialists told him that there would be a good chance to have children using banked sperm and in vitro fertilization (IVF). To improve the couple's chances of success, the specialists said, he should bank as many specimens as he could in the days leading up to start of his treatment.

Over the next year or so, Erickson endured the orchiotomy, several rounds of chemotherapy, a retroperitoneal lymph node dissection and several surgeries to remove masses from his lungs and a small bowel obstruction. During his treatment, he and his wife made the decision to initiate IVF.

"I had been able to bank three specimens. We were told one was not good quality, and we had one failed round of IVF," Erickson says. "It was the last vial, our last hope."

Their daughter Juniper, 6, was born only a few months after Erickson completed his last surgery. His daughter's birth, he says, was a big part of his healing.

JAY ERICKSON, and his wife, **KATIE ROSE,** have another child, **IRIS**, who was conceived naturally at a time when the couple thought they should consult adoption lawyers.

LAURIE SPENS

TRYING TO CONCEIVE

Men treated for testicular cancer may still be able to have children naturally after their diagnosis. Vij says men who are treated with only surgery may not need to wait at all to attempt to have children. Treatment with chemotherapy and radiation, however, warrants waiting.

In general, Lipshultz recommends that men wait at least two years to try to have children naturally.

"Sperm production takes three to four months, so if you want to have sperm that have not experienced the impact of the chemotherapy or the testicular cancer itself, men need to wait at least a year or four cycles of sperm production," Lipshultz says.

If men want to try to have a childly naturally, Campbell recommends trying for at least a year before consulting a fertility specialist. »

"There is always a major component of psychosocial change that occurs post-treatment for testicular cancer that can contribute to stress, body image concerns or other things that could potentially impact fertility as well," Campbell says.

Midkiff says that after he completed his treatment, he and his first wife tried to get pregnant for a period of time.

"I knew, though, that something was different (afterward) based on the volume of semen," Midkiff says.

Tests confirmed azoospermia, which means there is no sperm in a man's semen. Midkiff admits that he briefly thought about not being able to pass along biological traits to his child and about his wife not having the opportunity to be pregnant and carry a baby.

"I worked in education, though, and kids are a pretty big part of my life," Midkiff says. "The idea of fostering or adopting kids was something I had already wanted to do anyway, so we ended up going that route."

Today, he has two kids, ages 18 and 16, with his first wife and three more children, ages 11, 10 and 6, with his second wife.

After using their last specimen to conceive their daughter Juniper, Erickson and his wife also considered adoption. Erickson had undergone sperm analysis after his treatment and received a diagnosis of teratospermia, a condition characterized by abnormally shaped sperm.

"We were researching and meeting with adoption attorneys when my wife got pregnant," Erickson says. That pregnancy was their daughter Iris, now 4 years old.

> "The idea of fostering or adopting kids was something I had already wanted to do."
>
> — JASON MIDKIFF

PRIORITIZING FERTILITY

Campbell says that every man diagnosed with testicular cancer should be counseled on sperm banking at the initial diagnosis and that these conversations should be part of standard of care.

"I see patients who are coming in with a diagnosis of testicular cancer, and I refer them for sperm banking," Campbell says. "I go through the reasons why sperm banking should be considered, even if patients are not interested in conceiving in the near future."

Campbell says that conversations about fertility should also occur with men who say they're done having children.

"We discuss the fact that with testicular cancer treatment, there is no guarantee that they will be infertile," Campbell says. "They have to still be careful of having children unintentionally."

For those men who choose to bank sperm, Lipshultz says there are issues related to cost and access. A lot of the cryopreservation banks are in major urban areas, but some banks do offer mail-in sample kits.

The average cost of initial sperm banking and analysis is about $1,000, with a yearly fee of approximately $300 for storage, according to the Alliance for Fertility Preservation. These fees can vary based on location. The cost of testicular sperm extraction can be much higher, between $6,000 and $16,000. One must also consider the cost of using the sperm for artificial insemination, which costs about $1,000 per cycle, or IVF, which can be $15,000 or more.

IN RETROSPECT

Midkiff was diagnosed with testicular cancer in October 2001 and finished his treatment in March 2002. He has had no cancer scares since then. Although he did not undergo any type of fertility preservation, he says he has no regrets.

"The No. 1 thing I would tell someone is don't wait," Midkiff says. "My cancer was so aggressive that if I had waited, I wouldn't have made it."

Erickson is more than six years out from his last treatment and still undergoes annual follow-up screening. He is very grateful he was able to bank sperm and encourages others to do the same.

"Bank as much as possible so that you have options," Erickson says. "You don't have to make a decision that day. Bank it and then forget about it, and focus on yourself, healing and getting better. That is No. 1."

Erickson likened sperm banking or other methods of fertility preservation to the proverb "Trust in God, but tie your camel." Have faith but take action.

VA Expands Presumptive Disease List for Agent Orange

Bladder Cancer Advocacy Network
BCAN
Leading the way to awareness and a cure

U.S. veterans who served during the Vietnam War and have an illness caused by exposure to the toxic herbicide during military service may now be eligible for disability benefits for three additional conditions. *By* DARLENE DOBKOWSKI, M.A.

THE DEPARTMENT OF VETERANS Affairs (VA) recently added three more presumptive conditions related to Agent Orange exposure — bladder cancer, hypothyroidism and Parkinsonism — which could potentially impact tens of thousands of Vietnam veterans exposed to the tactical herbicide.

"If (patients with bladder cancer) were in the Vietnam War (or potentially certain other places where Agent Orange was used or tested), it would be presumed that their bladder cancer was due to their service — and they could apply for benefits that could include compensation and increased health care eligibility in the Veterans Health Administration," Gina Jackson, a VA spokesperson, told *CURE*®.

"Bladder cancer is predominantly found in males and increases with age," Jackson continued. "It is one of the top five cancers found in men. It is associated with several risk factors including smoking as well as genetic and familial causes but has also been linked in some cases to occupational exposures."

According to a consensus study report published in 1994, approximately 11 million gallons of Agent Orange were sprayed over 20 million acres by the U.S. Air Force from 1962 to 1971 in Vietnam. This was primarily done to defoliate trees and plants to improve observation on the ground and destroy enemy crops.

The VA estimates that of the **9 MILLION** U.S. military personnel on active duty during the Vietnam era, approximately **2.6 MILLION** were potentially exposed to Agent Orange.

"(Epidemiological data in 2014 suggested) an association between bladder cancer and Agent Orange exposure, with higher levels of exposure being associated with an approximately twofold increase in death from bladder cancer," Dr. Vikram M. Narayan, an assistant professor of urology at Emory University School of Medicine and director of urologic oncology at Grady Memorial Hospital in Atlanta, said in an interview with *CURE*®. "But the actual causation of this increased risk has not formally been established. I think that as we see more individuals who may have been exposed to Agent Orange — veterans and others — we're beginning to see persistently higher rates of bladder cancer."

Narayan added that proving causation between Agent Orange exposure and bladder cancer is difficult to do on a population level but that being aware of the possibility may help patients and their families, particularly around screening for bladder cancer.

"There are so many other factors that an individual is exposed to in their lives, whether that be environmental exposures, things they consume, places where they live or grow up and genetic factors as well," he said. »

HARNPON / STOCK.ADOBE.COM

PROVIDED BY BCAN AND SCOTT

"To take something like a singular exposure from a while back and link it conclusively will likely be very difficult. That being said, if you see trends in populations, you can draw inferences, and this is how many of our hypotheses are generated. And at least being aware ... that a link is possible (is) important for patients and families ... so that they can (know) to be screened for bladder cancer and then seek care early, particularly if they have signs or symptoms of the condition."

AN UPHILL BATTLE

James R. Scott Jr. enrolled in the Army in 1967, and his overseas tour of duty included Vietnam, Thailand, Cambodia and Laos, during which he suspects he was exposed to Agent Orange. And he believes that exposure to the herbicide is related to his bladder cancer diagnosis later in his life. Scott said that during his tour of duty, there were no warnings about the potential harm that Agent Orange could cause.

"Agent Orange was housed mainly in the surrounding countries like Thailand, Cambodia and Laos and not stored so much in volume, and it was (flown into Vietnam)," Scott said. "(There were) a lot of ways to get exposed."

Scott originally did not receive disability benefits from the VA when he received a diagnosis of bladder cancer in 2015 at age 69 because the agency did not recognize it as a disease related to Agent Orange exposure — until this recent decision.

"I talked with my urologist, and he said, 'It just doesn't make sense because whatever goes through your system … goes through your bladder to get to the prostate," Scott said. "That was one of the fights that (has) been going on for years and trying to get the government to acknowledge the fact that if it affects the prostate, it had to affect the bladder as well."

Scott first suspected something was wrong when he saw blood in his urine, which a primary care doctor diagnosed as a urinary tract infection. For about a year, the infection would be treated, but then blood would return to Scott's urine. His primary care doctor finally sent him to a urologist for testing, which resulted in the discovery of a tumor the size of an orange as well as two dozen other tumors in his bladder.

"(The doctors) told me at that point that my chances of the cancer (recurring in) my bladder was 100%, so they said I could have the operation to remove my bladder now or later," Scott said. "I figured at the age of 69, it probably would be better for me to do it than when I was 89, so I opted for the surgery."

Scott was also told that if the cancer returned, it would most likely go through the walls of his bladder and metastasize somewhere else in the body, which would make the disease more difficult to control. Scott underwent laparoscopic surgery to remove his bladder after undergoing chemotherapy.

"Losing your bladder is quite a challenge because regardless of which diversionary system you opt with, it's not a turnkey operation," Scott said. "You end up taking a lot of time adjusting to your new normal."

Scott has been cancer free for more than five years, during which he spent his time advocating for patients with

bladder cancer, especially veterans. In conjunction with the Bladder Cancer Advocacy Network, he also traveled to Capitol Hill in Washington, D.C., to speak about his journey with bladder cancer.

"After my surgery, my motivation to get involved, help someone else and show thanks was immediate," Scott said. "I knew that God had given me a test so that I'd have a testimony to help someone else."

Scott said he did not go to the VA before his bladder and prostate were removed in 2015, and his insurance paid for the surgery. Approximately one year after his surgery, however, he went to the VA and started receiving compensation for his disability, which was not associated with his bladder cancer.

"Had I not had good insurance, Lord only knows where I would be today," Scott added. "That's the thing that hurts because there are so many former military people out there who do not have good insurance. They possibly did not get any treatment. They may have just died."

OVERDUE BUT APPRECIATED

Scott said that although he's happy that the VA expanded its presumptive disease list for Agent Orange exposure to include bladder cancer, it's not fair that it took so long.

"This is way overdue but so appreciated," he said, adding that "it really hurts to think about all the (soldiers) and their families who suffered. … People who go home with any type of ailment or deformity because of war, they live with that for the rest of their lives, but not just them, their family, their friends. It changes their whole world."

The additional conditions being added will change not only the lives of patients and their families but also the care paradigm as a whole.

"The fact that this is now an established part of the care paradigm allows patients and physicians (to) hopefully improve the documentation that occurs, allow for better research into who exactly may be exposed and how this comes about," Narayan said. "When I was a trainee, I was involved in the project where we looked at (a group) of patients who had bladder cancer, and we looked back to see which of these patients had Agent Orange exposure. One of the challenges is, it's very hard to track down who clearly may or may not have exposure, and any effort to try and make that better will go a long way to improving the treatments that are offered and the diagnoses that are (made)."

Scott noted that he received a letter from the VA dated June 21, 2021, which detailed how they are reaching out to surviving spouses, children and parents, among others, to help people get their benefits related to bladder cancer. The letter also included instructions on what patients and their families should do, regardless of whether they're already receiving VA benefits.

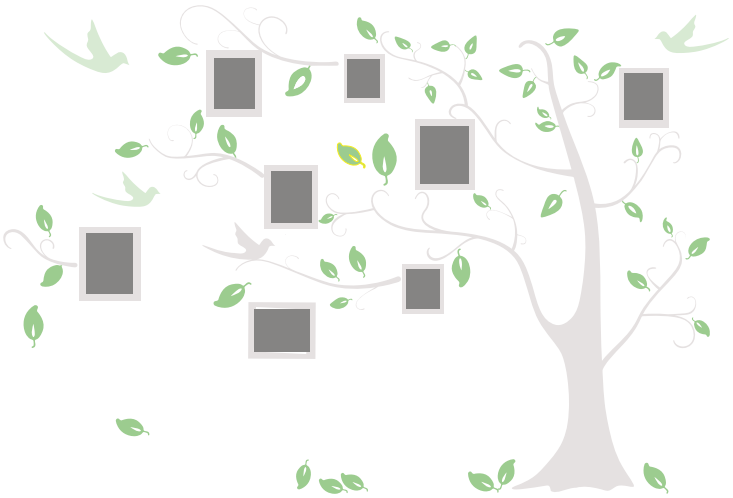
Jackson explained how Vietnam veterans can file a claim.

"We are grateful for the service and sacrifice of the men and women who fought in the Vietnam War," Jackson said. "We encourage Vietnam veterans (and other veterans who may be eligible) to enroll in the Agent Orange Registry if they haven't done so already. The registry is not connected to the compensation or health care system; however, those eligible may opt into a registry examination at no cost to the veteran."

cure TALKS CANCER

SCAN THE QR CODE
Listen to *CURE*®'s podcast with James R. Scott Jr.

A Family Matter



The impact of von Hippel-Lindau disease goes beyond the patient. Receiving a diagnosis of this hereditary cancer should prompt a discussion with relatives also at risk. *By* KRISTIE L. KAHL

AFFECTING AN ESTIMATED 1 in 30,000 people, von Hippel-Lindau disease, or VHL, is a hereditary cancer that many aren't aware of. Such was the case for Stacy Lloyd and her family.

VHL can cause manifestations characterized by blood vessel tumors — that can be benign or malignant — in up to 10 areas of the body due to a mutation in one gene. And people with a mutation in that gene may be at an increased risk for clear cell renal cell carcinoma, a type of kidney cancer.

Lloyd, a board member of the VHL Alliance, experienced her first manifestation at age 10, when a pheochromocytoma (a rare tumor) on the adrenal gland led her to the emergency department. "They couldn't figure out what was wrong with me," she said. "And my grandfather was like, '(Your grandmother) had this weird tumor on her adrenal gland when she was 16.' It was like a lightbulb moment."

CURE® spoke with Lloyd about how a VHL diagnosis can lead to earlier surveillance for the disease and the importance of discussing this hereditary cancer with family members.

Q: Can you explain the genetic risk of VHL?

A: There is a 50-50 chance of the VHL being passed down from parent to child. Only about 20% of VHL cases are actually that de novo kind of first-in-family.

Q: Why is it important to talk about hereditary conditions, especially when someone receives a cancer diagnosis?

A: So VHL isn't something that goes away. I do feel very strongly that it's truly better — and maybe this is a personal feeling — to know what you're dealing with and be empowered as a patient to take care of yourself so that it doesn't get to a point where you are in an emergency situation. For example, not getting those regular eye exams could result in partial or full loss of vision. So family members (who) are at risk (of) this disease should know and be able to seek confirmation through that genetic testing so that they can take care of themselves and detect any tumors early on.

Q: If someone has a family history of cancer, why is it important for them to also consider genetic counseling?

A: I feel like it's a little bit of a personal decision. Some people are open to it and welcome it, and other people don't find as much value. But I think it can be a really powerful tool for patients to educate themselves on the disease and the genetics behind it — what their risk is. And this is important for VHL, but it's also important for other cancer syndromes. (They can learn) what they can expect throughout their life dealing with this (condition), and it is a way to really empower you, as a patient, (and) empower your family (to) be able to have informed conversations about the disease and the management of the disease that will ultimately be with you for a lifetime as it stands today.

Q: How can one family member's genetic testing results impact an earlier diagnosis for another family member?

A: Once VHL is detected in the family, it does prompt others

VECTOR STYLE / STOCK.ADOBE.COM

to get tested. And once (VHL is) confirmed, that surveillance can start. Before you have that diagnosis, you might not be able to get all the actual surveillance that's needed to cover all of the manifestations, whether that be (because of) an insurance issue (or because of) a physician (who) feels more comfortable doing all those different tests once you have a confirmed diagnosis. So (that confirmation) really needs to happen before you can even get the surveillance that might be needed to track some of this.

An early diagnosis can result in that higher quality of life — being able to know (about) and watch some of the tumors that might be small as they grow instead of (ending up in) an emergency situation. … Additionally, any children can be tested at an early age. And that really is super important.

I feel very strongly about regular surveillance for children. I was 10 when my first manifestation happened. It doesn't always wait until a certain age, or it's not something you might just have to deal with when you're older. It's really important to start that surveillance early. And kids also don't know what's going on with their bodies, so they may not even realize that something's wrong. That's something I think is so important about (getting) the genetic testing … early and often and having those conversations as part of a family so that you can get that diagnosis early.

If it's there, start watching out for things as early as possible.

And something else: I think that that sets a tone for the rest of that child's life. Like, I take care of myself. I've been doing this for so many years. It's a part of my routine, right? And I think setting those early habits of taking care of yourself and getting that surveillance and routine testing early on is really important for people over the course of their lifetime to continue to make sure that they're watching out for these (manifestations).

Q: Based on your experience, do you have any advice to start that family discussion?

A: It's not an easy one. At some point, you're not always going to get the response that you want. But I think as much as you can, set an example and be that person (who) is doing the right thing for your health and being supportive. You can only do so much. But I think it's just worth having some transparent, honest communication because it's in the best interest of your family to have those conversations. Just being empathetic and caring about the conversation and being respectful of people's choices are really all you can do.

We are helping to move mountains for myeloma patients

Moving Mountains for Multiple Myeloma (MM4MM) is an award-winning collaboration between CURE Media Group and the Multiple Myeloma Research Foundation (MMRF), which raises funds and awareness for myeloma research.

Since its inception in 2016, Moving Mountains for Multiple Myeloma teams have climbed Mount Kilimanjaro, hiked the Grand Canyon, summited Mount Fuji, trekked the Inca Trail to Machu Picchu, reached Everest Base Camp and conquered Iceland's many landscapes. Our team members have raised over $3 million, 100% of which goes directly to the MMRF, which spearheads and funds critical myeloma research. These amazing journeys are captured via blogs, social media posts and video.

After pausing for the global pandemic, we are back with a new schedule of exciting climbs. Patients, caregivers, loved ones with myeloma, and others impacted directly by multiple myeloma will trek through the wilderness of Alaska's Kenai Peninsula, summit Mount Washington and discover the dynamic terrain of Colorado's Backcountry Continental Divide. They will raise funds for multiple myeloma research and demonstrate that the advancements being made in recent years, led by the MMRF, are helping patients live longer with a higher quality of life than ever before.

To learn more and join a MM4MM team visit:
MovingMountainsForMultipleMyeloma.com

To learn more about the MMRF, visit **TheMMRF.org**

LEARN MORE ABOUT OUR CLIMBS!

2021-2022 TREK SCHEDULE

Alaska Trek
August 16-21, 2021

Mount Kilimanjaro
February 19 - March 1, 2022

Greenland Trek
Summer 2022

Sweden Trek
Summer 2022

Mount Washington
Date to be announced

Colorado Trek
Date to be announced

endurance.themmrf.org/MM4MM