

LUNG CANCER

cure[®]20TH anniversary

Cancer Updates, Research & Education[®]

SPECIAL ISSUE • 04.2022

SCRATCHING
the SUREFACE

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PATIENTS WITH LUNG CANCER WHO HAVE THE KRAS G12C MUTATION MAY STRIKE LUCKY AS NEWER INVESTIGATIONAL THERAPIES HAVE DEMONSTRATED TO BE EFFECTIVE

ALSO IN THIS ISSUE

20 YEARS OF CURE

How two decades full of progress have changed the treatment landscape.

NAVIGATING THE END

Patients and caregivers should ask questions and find support during an end-stage cancer diagnosis.

A COMPLICATED APPROVAL

Why a recent FDA approval may create more questions than answers.

A NEW PATH

Anti-TIGIT therapy is making its way into the treatment space, providing hope for some patients.

KEYTRUDA IS A BREAKTHROUGH IMMUNOTHERAPY.



FOR TODAY

KEYTRUDA is a potential first treatment for **3 out of 4 patients** with advanced non-small cell lung cancer (NSCLC).

KEYTRUDA is also used to treat **more patients** with advanced lung cancer than any other immunotherapy.

FOR THE FUTURE



Ongoing clinical trials are exploring if KEYTRUDA can help treat more patients.

KEYTRUDA may be your first treatment for advanced NSCLC, either in combination with chemotherapy or used alone as a chemotherapy-free option.

Ask your doctor if KEYTRUDA is right for you.

KEYTRUDA is a prescription medicine used to treat a kind of lung cancer called non-small cell lung cancer (NSCLC).

➤ KEYTRUDA + CHEMOTHERAPY, NONSQUAMOUS

It may be used with the chemotherapy medicines pemetrexed and a platinum as your first treatment when your lung cancer has spread (advanced NSCLC) **and** is a type called “nonsquamous” **and** your tumor does not have an abnormal “EGFR” or “ALK” gene.

➤ KEYTRUDA + CHEMOTHERAPY, SQUAMOUS

It may be used with the chemotherapy medicines carboplatin and either paclitaxel or paclitaxel protein-bound as your first treatment when your lung cancer has spread (advanced NSCLC), **and** is a type called “squamous.”

➤ KEYTRUDA USED ALONE, PD-L1 POSITIVE

It may be used alone as your first treatment when your lung cancer has not spread outside your chest (stage III) and you cannot have surgery or chemotherapy with radiation, **or** your NSCLC has spread to other areas of your body (advanced NSCLC), **and** your tumor tests positive for “PD-L1” **and** does not have an abnormal “EGFR” or “ALK” gene.

➤ KEYTRUDA AFTER CHEMOTHERAPY, PD-L1 POSITIVE

It may also be used alone for advanced NSCLC if you have tried chemotherapy that contains platinum and it did not work or is no longer working **and**, your tumor tests positive for “PD-L1” **and** if your tumor has an abnormal “EGFR” or “ALK” gene, you have also received an “EGFR” or “ALK” inhibitor medicine that did not work or is no longer working.

PD-L1 = programmed death ligand 1;
EGFR = epidermal growth factor receptor;
ALK = anaplastic lymphoma kinase.

IMPORTANT SAFETY INFORMATION

KEYTRUDA is a medicine that may treat certain cancers by working with your immune system. KEYTRUDA can cause your immune system to attack normal organs and tissues in any area of your body and can affect the way they work. These problems can sometimes become severe or life-threatening and can lead to death. You can have more than one of these problems at the same time. These problems may happen any time during treatment or even after your treatment has ended.

Call or see your health care provider right away if you develop any signs or symptoms of the following problems or if they get worse. These are not all of the signs and symptoms of immune system problems that can happen with KEYTRUDA:

- **Lung problems:** cough, shortness of breath, or chest pain.
- **Intestinal problems:** diarrhea (loose stools) or more frequent bowel movements than usual; stools that are black, tarry, sticky, or have blood or mucus; or severe stomach-area (abdomen) pain or tenderness.
- **Liver problems:** 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 (tea colored); or bleeding or bruising more easily than normal.
- **Hormone gland problems:** headaches that will not go away or unusual headaches; eye sensitivity to light; eye problems; rapid heartbeat; increased sweating; extreme tiredness; weight gain or weight loss; feeling more hungry or thirsty than usual; urinating more often than usual; hair loss; feeling cold; constipation; your voice gets deeper; dizziness or fainting; changes in mood or behavior, such as decreased sex drive, irritability, or forgetfulness.
- **Kidney problems:** decrease in the amount of your urine; blood in your urine; swelling of your ankles; loss of appetite.
- **Skin problems:** rash; itching; skin blistering or peeling; painful sores or ulcers in your mouth or in your nose, throat, or genital area; fever or flu-like symptoms; swollen lymph nodes.
- **Problems can also happen in other organs and tissues.** Signs and symptoms of these problems may include: chest pain; irregular heartbeat; shortness of breath; swelling of ankles; confusion;

Important Safety Information is continued on the next page.

**Teresa is a
real patient**



keytruda.com/lung

IMPORTANT SAFETY INFORMATION (continued)

sleepiness; memory problems; changes in mood or behavior; stiff neck; balance problems; tingling or numbness of the arms or legs; double vision; blurry vision; sensitivity to light; eye pain; changes in eyesight; persistent or severe muscle pain or weakness; muscle cramps; low red blood cells; bruising.

- **Infusion reactions that can sometimes be severe or life-threatening.** Signs and symptoms of infusion reactions may include chills or shaking, itching or rash, flushing, shortness of breath or wheezing, dizziness, feeling like passing out, fever, and back pain.
- **Rejection of a transplanted organ.** Your health care provider should tell you what signs and symptoms you should report and they will monitor you, depending on the type of organ transplant that you have had.
- **Complications, including graft-versus-host disease (GVHD), in people who have received a bone marrow (stem cell) transplant that uses donor stem cells (allogeneic).** These complications can be serious and can lead to death. These complications may happen if you underwent transplantation either before or after being treated with KEYTRUDA. Your health care provider will monitor you for these complications.

Getting medical treatment right away may help keep these problems from becoming more serious. Your health care provider will check you for these problems during treatment with KEYTRUDA. They may treat you with corticosteroid or hormone replacement medicines. They may also need to delay or completely stop treatment with KEYTRUDA if you have severe side effects.

Before you receive KEYTRUDA, tell your health care provider if you have immune system problems such as Crohn's disease, ulcerative colitis, or lupus; have had an organ transplant or have had or plan to have a bone marrow (stem cell) transplant that uses donor stem cells (allogeneic); have had radiation treatment in your chest area; have a condition that affects your nervous system, such as myasthenia gravis or Guillain-Barré syndrome. If you are pregnant or plan to become pregnant, tell your health care provider. KEYTRUDA can harm your unborn baby. If you are able to become pregnant, you will be given a pregnancy test before you start treatment.

Use effective birth control during treatment and for at least 4 months after your final dose of KEYTRUDA. Tell them right away if you think you may be pregnant or you become pregnant during treatment with KEYTRUDA.

Tell your health care provider if you are breastfeeding or plan to breastfeed. It is not known if KEYTRUDA passes into your breast milk. Do not breastfeed during treatment with KEYTRUDA and for 4 months after your final dose of KEYTRUDA.

Tell your health care provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements.

Common side effects of KEYTRUDA when used alone include feeling tired; pain, including pain in muscles; rash; diarrhea; fever; cough; decreased appetite; itching; shortness of breath; constipation; bones or joints and stomach-area (abdominal) pain; nausea; and low levels of thyroid hormone.

Common side effects of KEYTRUDA when given with certain chemotherapy medicines include feeling tired or weak; nausea; constipation; diarrhea; decreased appetite; rash; vomiting; cough; trouble breathing; fever; hair loss; inflammation of the nerves that may cause pain, weakness, and paralysis in the arms and legs; swelling of the lining of the mouth, nose, eyes, throat, intestines, or vagina; mouth sores; headache; weight loss; stomach-area (abdominal) pain; joint and muscle pain; and trouble sleeping.

These are not all the possible side effects of KEYTRUDA. Talk to your health care provider for medical advice about side effects.

Please read the adjacent Important Information About KEYTRUDA and discuss it with your oncologist.

You are encouraged to report negative side effects of prescription drugs to the FDA. Visit www.fda.gov/medwatch or call 1-800-FDA-1088.

Having trouble paying for your Merck medicine?

Merck may be able to help. www.merckhelps.com

IT'S TRU. KEYTRUDA®
(pembrolizumab) Injection 100 mg

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Important Information About KEYTRUDA® (pembrolizumab) injection 100 mg. Please speak with your healthcare professional regarding KEYTRUDA (pronounced key-true-duh). Only your healthcare professional knows the specifics of your condition and how KEYTRUDA may work with your overall treatment plan. If you have any questions about KEYTRUDA, speak with your healthcare professional. **Rx ONLY**

What is the most important information I should know about KEYTRUDA?

KEYTRUDA is a medicine that may treat certain cancers by working with your immune system. KEYTRUDA can cause your immune system to attack normal organs and tissues in any area of your body and can affect the way they work. These problems can sometimes become severe or life-threatening and can lead to death. You can have more than one of these problems at the same time. These problems may happen anytime during treatment or even after your treatment has ended.

Call or see your healthcare provider right away if you develop any new or worsening signs or symptoms, including:

Lung problems

- cough
- shortness of breath
- chest pain

Intestinal problems

- diarrhea (loose stools) or more frequent bowel movements than usual
- stools that are black, tarry, sticky, or have blood or mucus
- severe stomach-area (abdomen) pain or tenderness

Liver problems

- 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 (tea colored)
- bleeding or bruising more easily than normal

Hormone gland problems

- headaches that will not go away or unusual headaches
- eye sensitivity to light
- eye problems
- rapid heartbeat
- increased sweating
- extreme tiredness
- weight gain or weight loss
- feeling more hungry or thirsty than usual
- urinating more often than usual
- hair loss
- feeling cold
- constipation
- your voice gets deeper
- dizziness or fainting
- changes in mood or behavior, such as decreased sex drive, irritability, or forgetfulness

Kidney problems

- decrease in your amount of urine
- blood in your urine
- swelling of your ankles
- loss of appetite

Skin problems

- rash
- itching
- skin blistering or peeling
- painful sores or ulcers in your mouth or in your nose, throat, or genital area
- fever or flu-like symptoms
- swollen lymph nodes

Problems can also happen in other organs and tissues.

These are not all of the signs and symptoms of immune system problems that can happen with KEYTRUDA. Call or see your healthcare provider right away for any new or worsening signs or symptoms, which may include:

- chest pain, irregular heartbeat, shortness of breath, swelling of ankles
- confusion, sleepiness, memory problems, changes in mood or behavior, stiff neck, balance problems, tingling or numbness of the arms or legs
- double vision, blurry vision, sensitivity to light, eye pain, changes in eyesight
- persistent or severe muscle pain or weakness, muscle cramps
- low red blood cells, bruising

Infusion reactions that can sometimes be severe or life-threatening. Signs and symptoms of infusion reactions may include:

- chills or shaking
- dizziness
- itching or rash
- feeling like passing out
- flushing
- fever
- shortness of breath or wheezing
- back pain

Rejection of a transplanted organ. Your healthcare provider should tell you what signs and symptoms you should report and monitor you, depending on the type of organ transplant that you have had.

Complications, including graft-versus-host-disease (GVHD), in people who have received a bone marrow (stem cell) transplant that uses donor stem cells (allogeneic). These complications can be serious and can lead to death. These

Continued on next page.

complications may happen if you underwent transplantation either before or after being treated with KEYTRUDA. Your healthcare provider will monitor you for these complications.

Getting medical treatment right away may help keep these problems from becoming more serious. Your healthcare provider will check you for these problems during treatment with KEYTRUDA. Your healthcare provider may treat you with corticosteroid or hormone replacement medicines. Your healthcare provider may also need to delay or completely stop treatment with KEYTRUDA if you have severe side effects.

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

- have immune system problems such as Crohn's disease, ulcerative colitis, or lupus
- have received an organ transplant
- have received or plan to receive a stem cell transplant that uses donor stem cells (allogeneic)
- have received radiation treatment to your chest area
- have a condition that affects your nervous system, such as myasthenia gravis or Guillain-Barré syndrome
- are pregnant or plan to become pregnant. KEYTRUDA can harm your unborn baby.

Females who are able to become pregnant:

- Your healthcare provider will give you a pregnancy test before you start treatment with KEYTRUDA.
- You should use an effective method of birth control during and for at least 4 months after the final dose of KEYTRUDA. Talk to your healthcare provider about birth control methods that you can use during this time.
- Tell your healthcare provider right away if you think you may be pregnant or if you become pregnant during treatment with KEYTRUDA.
- are breastfeeding or plan to breastfeed. It is not known if KEYTRUDA passes into your breast milk. Do not breastfeed during treatment with KEYTRUDA and for 4 months after your final dose of KEYTRUDA.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements.

How will I receive KEYTRUDA?

- Your healthcare provider will give you KEYTRUDA into your vein through an intravenous (IV) line over 30 minutes.
- In adults, KEYTRUDA is usually given every 3 weeks or 6 weeks depending on the dose of KEYTRUDA that you are receiving.
- In children, KEYTRUDA is usually given every 3 weeks.
- Your healthcare provider will decide how many treatments you need.
- Your healthcare provider will do blood tests to check you for side effects.

- If you miss any appointments, call your healthcare provider as soon as possible to reschedule your appointment.

What are the possible side effects of KEYTRUDA?

KEYTRUDA can cause serious side effects. See “What is the most important information I should know about KEYTRUDA?”

Common side effects of KEYTRUDA when used alone

include: feeling tired, pain, including pain in muscles, rash, diarrhea, fever, cough, decreased appetite, itching, shortness of breath, constipation, bones or joints and stomach-area (abdominal) pain, nausea, and low levels of thyroid hormone.

Side effects of KEYTRUDA when used alone that are more common in children than in adults include: fever, vomiting, upper respiratory tract infection, headache, and low levels of white blood cells and red blood cells (anemia).

Common side effects of KEYTRUDA when given with

certain chemotherapy medicines include: feeling tired or weak, nausea, constipation, diarrhea, decreased appetite, rash, vomiting, cough, trouble breathing, fever, hair loss, inflammation of the nerves that may cause pain, weakness, and paralysis in the arms and legs, swelling of the lining of the mouth, nose, eyes, throat, intestines, or vagina, mouth sores, headache, weight loss, stomach-area (abdominal) pain, joint and muscle pain, and trouble sleeping.

Common side effects of KEYTRUDA when given with

chemotherapy and bevacizumab include: tingling or numbness of the arms or legs, hair loss, low red blood cell count, feeling tired or weak, nausea, low white blood cell count, diarrhea, high blood pressure, decreased platelet count, constipation, joint aches, vomiting, urinary tract infection, rash, low levels of thyroid hormone, and decreased appetite.

Common side effects of KEYTRUDA when given with axitinib

include: diarrhea, feeling tired or weak, high blood pressure, liver problems, low levels of thyroid hormone, decreased appetite, blisters or rash on the palms of your hands and soles of your feet, nausea, mouth sores or swelling of the lining of the mouth, nose, eyes, throat, intestines, or vagina, hoarseness, rash, cough, and constipation.

These are not all the possible side effects of KEYTRUDA.

Call your healthcare provider for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

General information about the safe and effective use of KEYTRUDA

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. You can ask your pharmacist or healthcare provider for information about KEYTRUDA that is written for health professionals.

Based on Medication Guide usmg-mk3475-iv-2112r048 as revised December 2021.

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cure²⁰TH anniversary Contents

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Treatment Advancements Lead to ‘Tremendous Growth’

RECENT ADVANCEMENTS SURROUNDING THE development of biomarker-targeted therapies have revolutionized the treatment of lung cancer.

According to the American Cancer Society's 2022 report on cancer statistics, the percentage of patients living at least three years after diagnosis rose

from 19% in 2001 to 31% in 2015 through 2017.


In this special issue, and to reflect on CURE®'s 20th anniversary, we highlight the science that ultimately led to these advancements. We speak with several patients whose lives have been altered by the development of targeted therapies.

“There has been a tremendous growth in this area,” says one expert from Vanderbilt-Ingram Cancer Center in Nashville, Tennessee. “Instead of taking an all-comers approach for a given drug, we (can

now) say this drug is going to work for patient A, but not patient B because of some biomarker of response to the therapy. This is the heralding of precision medicine or personalized medicine in lung cancer.”

But we also acknowledge that more work needs to be done to ensure that patients continue to live instead of just being alive, as one patient so eloquently put it.

CURE® also speaks with Sarah Miretti Cassidy, of Cancer Hope Network, about the support that is available to patients and their loved ones during the difficult time of an end-stage cancer diagnosis.

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

MIKE HENNESSY JR.
President & CEO
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Who is your **Lung Cancer Hero?** Tell us their story today!

CURE® is now accepting nominations for the 2022 Lung Cancer Heroes® award! Share the story of a hero who has inspired change, exemplified compassion, or made a significantly positive impact in the lives of those affected by lung cancer.

Submit your nomination by May 15, 2022
curetoday.com/LCH22

The selected heroes along with their nominators, will be interviewed by CURE® and honored at a special reception to be held in Fall 2022. Stay tuned for more information about the celebration.

2022 Lung Cancer Heroes® is proudly sponsored by Takeda Oncology.



ONCOLOGY

A Step Forward


AS WE CONTINUE OUR transition to biologically and genomically directed cancer therapies, RAS gene mutations, that represent one of the first discovered, have remained an elusive target. Activating mutations in this class of oncogenes, specifically KRAS, have made a big step forward scientifically and clinically just in the last couple of years. Previously, KRAS was seen as an “undruggable” mutation, and as such has been one of the major unmet needs in our cancer armamentarium. This mutation not only leads to a more aggressive disease pattern in many cancer types, but also makes patients more resistant to other biological therapies. Through elegant cellular and molecular studies and innovations drug design, key advancements have been made to bring a new generation of drugs to the clinic.

Early results are showing great promise. One inhibitor, Lumakras (sotorasib), is approved by the Food and Drug Administration (FDA) to treat the KRAS G12C mutation in lung cancer. The approval came quickly following the results demonstrated in the CodeBreaK 100 clinical trial, making Lumakras the first targeted therapy for metastatic KRAS G12C-mutated NSCLC.

One patient featured in this special issue of *CURE*® benefited from being on the trial. She saw significant improvements in her symptoms within 10 days of being on the

drug, and within four weeks had a noticeable decrease in the size of the tumors in her lungs. She was only able to take the drug for five weeks because tumors in her brain and spine continued to grow — but she attributes stabilization of the lung cancer to Lumakras.

Another promising drug, adagrasib, received FDA breakthrough therapy designation in June 2021. Additionally, a new drug application was accepted this February for patients with previously-treated KRAS G12C-mutated NSCLC.

All these drugs have made great headway; one patient even discusses that she felt she won the lottery after learning she had the KRAS-G12C mutation and was able to be treated with Lumakras. With more clinical trials underway, even more progress is around the corner for patients with KRAS G12C-mutated NSCLC. Ultimately, we expect to make progress in other cancers — notably in pancreatic cancer that exhibits KRAS mutations in 95% of cases, but predominantly affecting different base pairs in the same gene location: G12D, G12V and G12R. These mutations affect different amino acids on the KRAS protein and are not inhibited by Lumakras or adagrasib. Success on this front will require additional discovery, but important groundwork has been laid. 



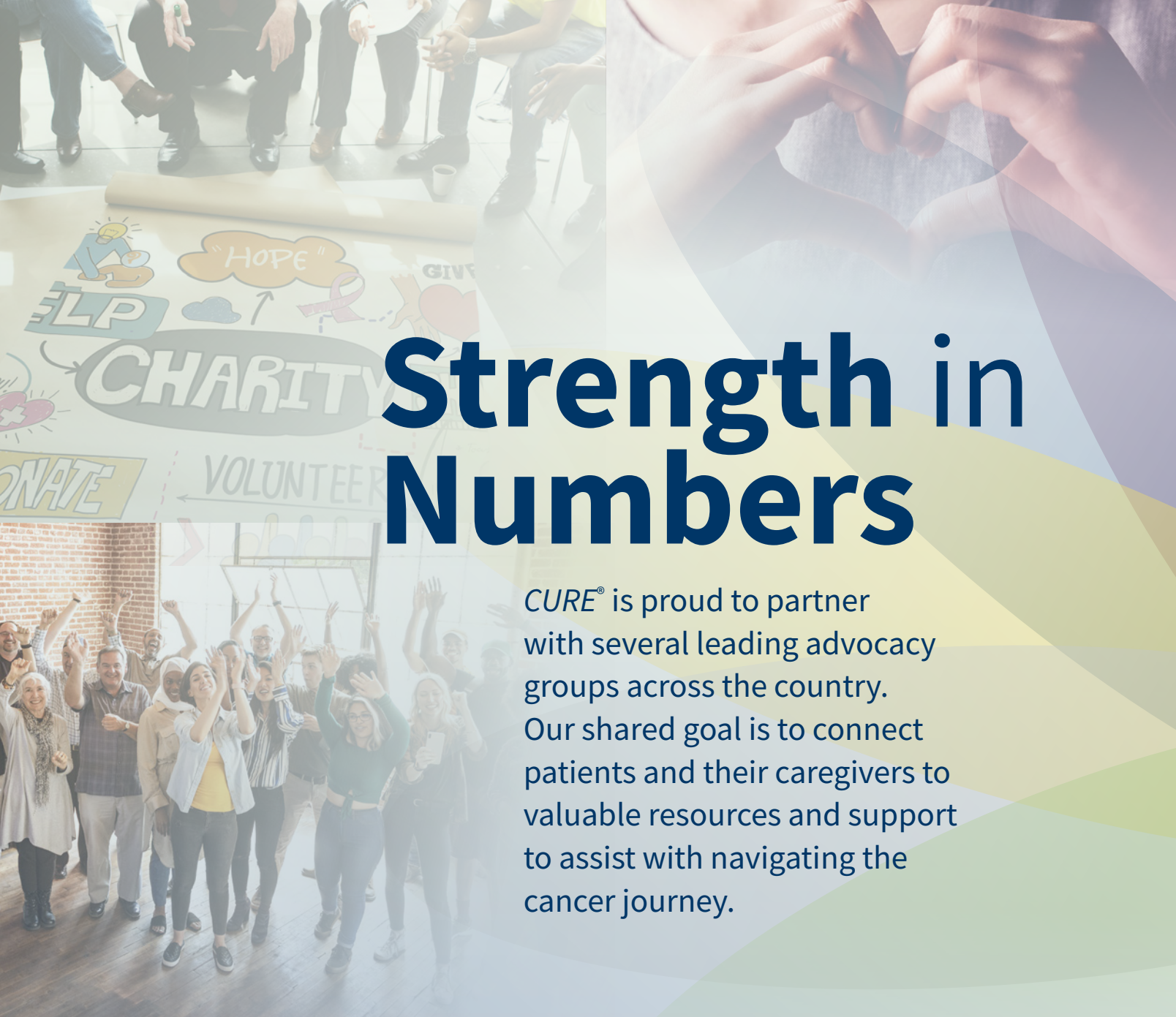
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Strength in Numbers

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.



What You Don't Know May Be **Critically** Important



Patients who are part of an advocacy group may be better equipped to understand biomarker testing during a lung cancer diagnosis and feel more empowered. *By COLLEEN MORETTI*

WHEN IT COMES to understanding biomarker testing and its results, there is a gap between those patients in upper socio economic status (SES) levels who have a relationship with a lung cancer patient advocacy group and those who are from lower SES communities, and may not yet be connected to the resources of advocacy organizations, according to recent survey results.

Biomarker testing (which can look for genes, proteins and other substances in the patient's tumor tissue or blood) can provide information about a patient's cancer and help guide treatment decisions, said Nikki Martin of the LUNGevity Foundation in an interview with *CURE*®. The practice has become common in lung cancer management, with nine biomarkers that have targeted therapy drugs approved by the Food and Drug Administration in this setting.

"For (patients with) non-small cell lung cancer (NSCLC) biomarker testing

is a critical piece of their care because it helps the provider select the most appropriate treatment for that patient's type of lung cancer. ... Without that information, a patient and provider won't know what is the most appropriate treatment," said Martin, senior director of precision medicine initiatives at LUNGevity Foundation.

However, little is known about patients' perception of biomarker testing — particularly those in low SES and medically underserved communities. According to a study of patients with NSCLC presented at the 2021 American Society of Clinical Oncology Annual Meeting, there is a gap of more than 10% in White patients receiving biomarker testing with next generation sequencing compared to Black patients.

LUNGevity (a lung cancer patient advocacy group) in partnership with Patient Advocate Foundation (a patient advocacy group providing financial advocacy and other

resources for low income patients) surveyed patients with lung cancer to analyze their understanding of biomarker testing. Martin explained that the goal was to survey patients inside the LUNGevity network, who tend to represent patients from high SES communities, and patients outside their network with a focus on lower income patients, people with varying types of insurance including Medicaid and uninsured and people from more diverse racial backgrounds. Martin explained that because many people in a disease-specific organization such as LUNGevity tend to represent higher income and White patient perspectives, it is important to understand the experiences, points of view and barriers that medically underserved communities are facing with biomarker testing. In addition to the survey, focus groups were conducted afterward to better understand the survey responses.

UNDERSTANDING TESTING

Regarding learning about biomarker testing, 66% of the patients from the LUNgevity group of respondents and 40% of those in the general population group reported having their doctor bring up the topic of biomarker testing. Additionally, 85% and 52% of patients from those groups, respectively, reported undergoing biomarker testing. Of those patients, 78% and 54%, respectively, had to see only one doctor in order to have biomarker testing ordered for the patient.

Results of the survey also demonstrated that patients from LUNgevity were more likely to have multiple mutations tested at a single time (55%) compared with those in the general population group (31%). Although testing for multiple mutations has a relatively long turn-around time, 46% of patients from LUNgevity received results within 14 days, compared with 34% of patients in the general population group.

The focus groups conducted after the survey revealed that the patients from LUNgevity were more likely to understand the term biomarker testing and what it entails, compared with those in the general population group. Patients in focus groups reported:

- “I heard of it (biomarker testing). Don’t know too much about it, just heard of it as far as the name. (It was) not discussed with me,” said a Black patient.
- “(It is) custom medicine. They take your tissue or blood, trying to look for these mutations to get your specific cancer under wraps. It’s really precision medicine. Customized to your specific cancer and can avoid chemo,” said a younger patient from an urban area.

Patients also reported that they did not know when biomarker testing was being done, because it blends in with other tests. One patient from a small, rural town said: “(I heard about it) during the first biopsy, my report had EKG, etc., and know from reading that they can treat you with targeted therapies. I didn’t know that they were doing it.” Martin said these focus groups

were eye-opening in that many patients did not know what biomarker testing was when asked — specifically those of lower yearly income (less than \$50,000).

UNDERSTANDING RESULTS

Most patients in the LUNgevity (93%) and general population groups (76%) reported being informed of the results of their testing and a similar percentage reported that having access to these results was important. However, roughly half the patients reported not having results shared with them and less than a quarter of patients in both groups received a printed copy.

Additionally, 84% of patients from the LUNgevity group had their doctor explain the results, compared with 55% of patients in the general population group. And another 21% of those in the general population group had another health care professional explain the results to them. Although results were explained, only 65% and 56% of patients reported understanding the results in the LUNgevity and general population groups, respectively.

Focus groups confirmed the survey data that oncologists were the ones to explain biomarker testing and results. However, confidence in oncologists varied by patient ethnicity and age. Both younger and older patients from urban areas had the best connection with their oncologists, whereas patients of color, those from rural areas or who were low income reported not getting as much time with oncologists as desired, according to the focus groups. Patients specifically reported that:

- “The doctors see 10 patients a day. Each of us have different kinds of cancers. ... The person most likely to talk to you about biomarker testing is the person you spend the most time with and that’s in your treatment center. I spend 30 minutes with doctors. I spend six hours with the nurses in the immunotherapy treatment,” said one low-income patient.
- “The pulmonologist never mentioned biomarkers. I have to think if anyone knew, it was my oncologist who changed my chemo cocktail. I also

had a radiation oncologist, but he didn’t do bloodwork, strictly scans. I assume my oncologist knew what my biomarker was. I would be interested to go back and ask him about that,” said another low-income patient.

Martin said this showed a clear gap between those who were involved in a patient advocacy group and those who were not. “This underscored, not only is there an access issue in terms of having (biomarker testing) prescribed. But there’s also a communication gap in terms of how much information is being shared with patients to ensure they comprehend this critical, foundational piece of care,” she explained.

THE IMPORTANCE

Martin said it was clear that patients involved with advocacy groups have access to resources to expand their knowledge about testing and treatment, whereas those who are not yet part of such a group might not have an opportunity to get connected to resources and information that may benefit them. “It’s clear that there were a lot of patients who were just learning about this as a part of participating in the focus groups,” she said. Being educated on treatments and practices such as biomarker testing throughout one’s cancer journey can allow a patient to feel more confident when choosing next steps in treatment, Martin added.

To feel more comfortable in that setting, Martin encourages patients to find an advocacy group that is the right fit and use it to their benefit. Groups often have resources and educational outlets that can help guide patients through their treatment journey. Additionally, some people may benefit from talking to patients who have gone through similar journeys.

For those not involved in a patient advocacy group, Martin said, “It can be a chance to learn more about their care and become more empowered to ask their providers the right kind of questions that could maybe have some impact on making treatment decisions that could be a better fit for them.”

A Step **FORWARD**

Spurs Another Thought-Provoking Option



The recent approval of Opdivo plus chemo may be beneficial for some patients with NSCLC, further highlighting the need for multidisciplinary care. *By COLLEEN MORETTI*

IN MARCH 2022, the Food and Drug Administration approved Opdivo (nivolumab) plus a platinum-doublet chemotherapy for patients with resectable non-small cell lung cancer (NSCLC). It was the first immunotherapy approved to be administered to patients prior to surgery (neoadjuvant therapy), making it “hugely important,” said Upal Basu Roy, executive director of research at the LUNgevity Foundation. “This approval definitely fills a huge unmet need in this population for sure, especially the neoadjuvant space, because this is the first drug approval in the neoadjuvant space after chemotherapy,” he explained in an interview with *CURE*®.

Previously, patients with diagnoses of early-stage NSCLC had different options, including either chemotherapy before (neoadjuvant) or after surgery (adjuvant).

IMPROVEMENT

The approval was based on results of the phase 3 CheckMate-816 trial, which

compared Opdivo plus platinum-doublet chemotherapy (179 patients) with platinum-chemotherapy alone (179 patients). Results demonstrated a significantly improved event-free survival (time after treatment ends when a patient remains free of certain complications or events) with Opdivo plus chemotherapy, at 31.6 months, compared with chemotherapy alone at 20.8 months. “That, in my mind, is not an incremental increase; it’s a huge increase,” Basu Roy added.

Additionally, Opdivo plus chemotherapy resulted in a 37% reduction in the risk of disease progression, recurrence or death. Pathological complete response rate (no viable tumor left at the time of surgery) was 24% in the group that received Opdivo plus chemotherapy compared with 2.2% in the group that received chemotherapy alone. Dr. Melina Elpi Marmarelis, a medical oncologist and assistant professor of medicine at the Hospital

of the University of Pennsylvania, Philadelphia called this striking.

“I would say that the snippet of results that we’ve received is good but we’re still waiting for, first of all, longer-term follow-up,” she said in an interview with *CURE*®. “(And) second of all, for more information about the number of patients (who) made it to surgery (and) whether there was surgical complication with this approach. The main thing we worry about in neoadjuvant clinical trials is that delaying surgery will lead to worse outcomes for patients.”

However, Basu Roy explained, this combination did not delay surgery — which is what was great about adding the immunotherapy to chemotherapy in this setting. Additionally, quality of life was similar in both groups before and after surgery, so adding immunotherapy did not affect that either.

“This particular approval is sort of a landmark approval because it’s hitting the quantity-of-life end point, which

“Early-stage lung cancer is still a deadly disease and any progress toward improving it is a step forward.”

—DR. MELINA ELPI MARMARELIS

is a longer (event-free survival), but also a quality-of-life end point from a survivorship perspective because it did not add more (side effects) to a patient's treatment,” Basu Roy explained.

Only 10% of patients receiving Opdivo plus chemotherapy experienced side effects that ultimately led to discontinuation. The most common side effects included nausea (38%), constipation (34%), fatigue (26%), decreased appetite (20%) and rash (20%) — and Basu Roy attributes most of these to the chemotherapy.

COMPLICATING DECISIONS

Although this represents a significant approval for this population, Basu Roy and Marmarelis agree it may make treatment decisions more complicated. “I think right now, this actually creates more questions than answers at this point. We have approvals for immunotherapy in the neoadjuvant and adjuvant spaces, as well as approvals for targeted therapy in the adjuvant space. We don't yet have a good framework to think about how to combine or prioritize these. So, all of these approvals are changing our multidisciplinary workflow tremendously,” Marmarelis explained.

What that means, she added, is that patients will most likely need to start seeing a multidisciplinary team much earlier in treatment, rather than just a surgeon. Basu Roy agreed and said that with all the approvals there are different treatment options for this patient population, so patients should be treated by a multidisciplinary team including a surgeon, radiation oncologist and medical oncologist.

“I think I would be remiss in not pointing out, as a patient advocate, that in some ways this particular

approval makes the treatment in early-stage lung cancer a little bit more complicated. ... This care decision needs to be taken with a lot of thought and that's why a multidisciplinary team for the treatment of early-stage lung cancer has become even more important,” Basu Roy added.

He advises patients to have open communication with their multidisciplinary care team and ask questions like why they are choosing this therapy, whether they are the right candidate for these treatment options and what the treatment decision-making process is. By asking these questions and advocating for themselves, patients can become empowered and be partners in their own care, he concluded.

Marmarelis also mentioned the importance of patients advocating for themselves, specifically in early-stage disease. She said this approval highlights the growing need for complete molecular testing at the time of biopsy. In the study that led to the approval, patients with EGFR and ALK mutations were excluded because of a known decreased efficacy of immunotherapy in this population, meaning these patients will need more personalized treatment. Patients should be advocating early for that. “I think advocating for complete genotyping of the tumor is really important, and advocating early on because the process does take several weeks often to receive those results,” she said.

Although this approval may create more uncertainty on which treatment a patient should receive, it is significant nonetheless. “Early-stage lung cancer is still a deadly disease and any progress toward improving it is a step forward,” Marmarelis concluded. ■

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NEXT-GENERATION SEQUENCING Is ‘Treatment Changing’ — But What Is It?

A closer look at why it is important for patients with non-small cell lung cancer, specifically for the EGFR exon 20 alteration. By COLLEEN MORETTI

NEXT-GENERATION SEQUENCING

(NGS) is a test that can be done in patients with non-small cell lung cancer (NSCLC) and that identifies mutations in the cancer; this can then drive treatment decisions. One expert said all patients should be advocating for undergoing NGS testing, regardless of disease staging.

“It’s important for patients to be educated on this, because the more we know about a patient’s cancer, the better we can design a personalized treatment plan. Not all lung cancers are alike, and with the help of biomarkers we have been able to help patients with lung cancer live longer,” said Dr. Melinda Hsu.

Hsu, assistant professor of hematology and oncology at the University Hospitals Seidman Cancer Center in Avon, Ohio, discussed NGS testing for the EGFR exon 20 alteration mutation and what it means for patients during an interview with CURE®.

Q: What is NGS testing? What can it tell us, about the EGFR exon 20 alteration?

A: NGS ... is a way to assess for the presence of clinically relevant biomarkers by sequencing DNA of the

cancer. NGS is done in different ways and usually is performed on a sample of the cancer tissue. In patients with lung cancer, NGS testing can identify the presence of a targetable gene alteration driving growth of the cancer. There are targeted drugs, mostly pills, which have been developed specifically for some of these biomarkers for patients with (NSCLC). The EGFR exon 20 insertion mutation is one of those biomarkers. When NGS testing identifies this biomarker, it can help determine treatment options for a patient with lung cancer depending on the stage of their disease. There are ... several alterations of the EGFR gene (that) seem to drive the growth of NSCLC and using NGS testing to confirm which specific mutation is present is treatment changing.

Q: Which patients should be tested for this alteration?

A: I believe that all patients with NSCLC should have NGS testing, regardless of the stage of their disease. Patients with lung cancer who never smoked or did not smoke much, are more likely to have a targetable biomarker like the EGFR exon 20 alteration, but that should not preclude

testing. Right now, the two Food and Drug Administration (FDA)-approved drugs specifically (targeting) EGFR exon 20 are only available for patients with metastatic, or stage 4, lung cancer in the second-line setting (after the patient has progressed or not responded to standard-of-care first-line treatment of platinum-based chemotherapy with or without immunotherapy). However, I believe that patients with earlier-stage lung cancer should also have NGS testing done of their tumor, for prognostic information and because the use of targetable drugs is moving into the adjuvant setting (for example, the use of Tagrisso [osimertinib] in patients with EGFR exon 19 or 21 alterations after surgery). And unfortunately, the recurrence of rate of localized or locally advanced NSCLC is still high and having the NGS testing up front can guide treatment decisions if the cancer recurs.

Q: How can NGS testing for this alteration be beneficial to patients? Can it help guide treatment decisions or prognosis?

A: NGS testing for the EGFR exon 20 alteration guides prognosis and treatment decisions for patients with

metastatic NSCLC. Unfortunately, patients with metastatic EGFR exon 20 altered-NSCLC have historically had a poorer prognosis than others when treated with chemotherapy. If their cancer does not respond to first-line standard of care treatment, however, there are two drugs, Exkivity (mobocertinib; a pill) and Rybrevant (amivantamab-vmjw; an infusion), which are now FDA approved. Knowing about an EGFR exon 20 alteration through NGS at the time of diagnosis gives hope to our patients that there is another option for treatment if standard of care doesn't work or stops working and can also expedite treatment at progression rather than waiting for NGS testing to be done then.

Q: Should patients be advocating for themselves to have NGS testing for this alteration? How can they do that?

A: Patients should absolutely advocate to have NGS testing


done, for this biomarker and the other biomarkers found in lung cancer for which we have targeted therapies. Patients should ask their oncologist (whether) NGS has been done on their cancer tissue when they meet them or confirm that it will be done on their biopsy if not yet done. Here at Seidman Cancer Center, we have reflex (automatic) NGS testing done for the most common lung biomarkers on all of our patients' pathology found to be NSCLC, so our patients don't even need to ask for it. Hopefully someday that will be possible for all patients with lung cancer.

Q: Are there any current gaps or limitations in this space?

A: Sometimes there is not enough tissue from a biopsy for NGS testing. When that happens, it may be possible to do a liquid biopsy, or a blood draw, to try and identify any biomarkers. Liquid biopsies rely on the aggregate presence of circulating

tumor DNA in the bloodstream for NGS testing. Unfortunately, if the liquid biopsy is negative on NGS testing, that does not absolutely rule out the presence of a targetable biomarker as liquid biopsy testing is less sensitive than that performed on tumor tissue. If the suspicion is high, a patient will need to have another biopsy to assess for biomarkers on NGS.

Q: Is there anything else that patients should know about NGS testing for EGFR exon 20?

A: The EGFR exon 20 insertion mutation is less common than the other EGFR mutations, for which targeted therapies have been FDA approved for over 15 years. Careful attention to NGS reports to determine which EGFR alteration is present has an impact on treatment decisions. Targeted therapies used to treat EGFR exon 19 and exon 21 mutations are ineffective for the EGFR exon 20 alteration. 

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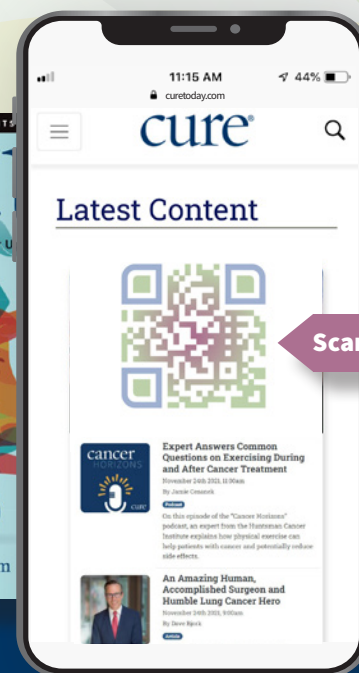
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'Simply Remarkable'

Over the past two decades, advancements in the lung cancer space have led to a drastic paradigm shift in how patients are now treated, ultimately leading to substantial improvements in survival and patient quality of life. *By RYAN MCDONALD*

PEG BERENS OF Newport Beach, California, was 54 when she developed a mild wheeze in January 2020.

At first, she brushed it off as she had a history of asthma. However, within a month, her condition worsened. After undergoing a chest X-ray at a nearby clinic, Berens was diagnosed with pneumonia.

The treatments prescribed for the infection didn't work, and she kept getting sicker. She was hospitalized and was sent to receive a chest scan. Her lungs were inflamed, and her pulmonologist saw a spot on her liver. She was released and told to get her liver biopsied.

On April 1, 2020, Berens received the shocking news that she had stage 4b non-small cell adenocarcinoma of the lung. The cancer had also spread to her entire spine, pelvis, lymph nodes and liver.

"It's shocking to think that a few months before I was fine, and the next thing you know, get a terminal diagnosis," she says.

Berens, a never smoker, was referred by her physician, Dr. Nishan Tchekmedyian, regional medical director for City of Hope Orange County in California, to undergo biomarker testing.

She recalls he said, "This is of extreme importance. Because if you have this ALK gene (mutation), there's targeted therapies for it and that's going to make a huge difference."

Biomarker testing, according to the National Cancer Institute, offers insight into the possible presence of genes, proteins and biomarkers or tumor markers that can provide information about a person's cancer. This type of testing is imperative because certain cancer treatments, such as targeted therapies, work best in patients whose disease is shown to have a mutation.

Because she was declining so rapidly, Berens received chemotherapy while she waited for the results of her genetic test to return. Ten days later, the results showed that she was ALK-positive.

"This was a very positive thing to happen in this really terrible situation, because it meant that there were targeted therapies available, and that meant hope," she says.

During this time, Berens was on oxygen and could barely take a few steps before having to catch her breath. She and her husband began getting their affairs in order as they thought she wouldn't live past three months. That is, she notes, until she was prescribed Alecensa (alectinib).

"(It was) like going from my deathbed, practically, to off of oxygen," Berens says. "And then within a couple of weeks, I'm able to walk around again, and within a month, I'm going on walks in our neighborhood. It was really a miracle."

Along with Berens, countless patients, including Gina Hollenbeck of Collierville, Tennessee, have derived some benefit from biomarker-driven therapies.

At 38 years old, Hollenbeck, a former nurse, was diagnosed with stage 4 lung cancer that had already metastasized to her brain in 2015. Her doctor recommended that she immediately receive genomic testing.

“He’s like, ‘Gina, I want to send away for this test. It might determine that you are actually eligible for a little pill instead of doing IV chemo,’” she recalls.

The test determined that she had ALK-positive disease. She first started on Zykadia (ceritinib), but her insurance would not cover the \$16,000-a-month cost since it was only Food and Drug Administration (FDA)-approved for patients whose disease progressed on or was intolerant to first-line Xalkori (crizotinib). She notes that she was only able to start Zykadia because friends and family raised \$30,000 via a GoFundMe page. For the first two months, she started with second-line treatment and in that time her disease disappeared.

But she had to switch to Xalkori once she could no longer afford the second-line treatment. Within four weeks, Hollenbeck says, she developed five brain metastases. Since she fit the criteria for Zykadia, her insurance now covered it. After she started back on Zykadia, there was no evidence of disease.

A DIFFERENT TIME

Personalized cancer treatments that are tailored to an individual’s disease based on the results of a biomarker test weren’t always the norm.

Twenty years ago, there was tremendous pessimism when a person was diagnosed with lung cancer, recalls Dr. Edward S. Kim, physician-in-chief and senior vice president at City of Hope Orange County.

“They were going to get cytotoxic chemotherapy and it would not work that well,” he says. “From a clinician standpoint, it was managing which drug and treatment schedule a patient would probably most tolerate without harming them.”

Findings from the ECOG 1594 trial, published in *The New England Journal of Medicine* in 2002, further validated this notion when the data showed that, out of four different platinum-based doublet chemotherapies, there was no difference in survival.

“Pretty much the conclusion was for clinicians to define the one (regimen) they perceive has the most tolerable side effect profile and use that,” Kim says.

The standard of care, he says, was to use two chemotherapies as a front-line treatment option, and then one chemotherapy in the second line if a patient’s disease worsened.

“That was pretty much it,” he remembers.

But over the next decade, developments in the lung »

“ (My oncologist was like, ‘Gina, I want to send away for this test. It might determine that you are actually eligible for a little pill instead of doing IV chemo.’ ”

— GINA HOLLENBECK



» A genomic test determined that **HOLLENBECK** had ALK-positive lung cancer.



➤ **PEG BERENS** takes a selfie outside of City of Hope Orange County the day she received a blood draw to participate in a clinical trial.

cancer space would make way for an era that would ultimately change the lives of thousands of patients.

BIOLOGICS BEFORE BIOMARKERS

The earliest lung cancer biologic introduced to the public, according to Kim, was Iressa (gefitinib).

At the time, study results were showing that treatment with Iressa — a once-daily oral therapy — induced response rates and survival rates similar to what had been seen previously with chemotherapies.

But this development was made outside of the biomarker space, meaning researchers were just testing the safety and efficacy of a biologic medication compared with infusion-delivered chemotherapy in patients with lung cancer.

There were also other biologics being testing in this patient population, many of which would receive FDA approval. However, as Kim points out, none of these developments occurred in connection with the presence of biomarkers.

As he recalls, the time from 2000 to 2012 was a transitional period in the lung cancer space.

“(The space went) from second-line chemotherapy finally being validated, and that was against best supportive care, so not a great way to prove something is that much better, to biologic agents, to the story of

(Iressa) which was fast tracked, approved and then pulled off the market because its large phase 4 study didn’t meet its survival end point,” Kim adds encapsulating the developments.

Then, in 2009, results from the BATTLE study published in *Cancer Discovery*, showed that providers could use new biopsies and predefined biomarkers to prospectively match patients to targeted therapy.

“We needed to move in the direction of utilizing genetic markers to direct lung cancer therapy,” he says.

In the same year, researchers published findings in *The New England Journal of Medicine* that showed that overall survival (time from diagnosis or treatment start when patients are alive) was similar in patients who received Iressa versus those treated with carboplatin and paclitaxel, including a subgroup of patients who had EGFR positive disease.

“That is what led to this whole now second decade of biomarker discovery and implementation in lung cancer, and it first started with EGFR mutations,” mentions Kim.

TREMENDOUS GROWTH

In the span of 20 years, the state of the art in lung cancer has transformed from the emergence of histology-based care to nine different genomic alterations with

“Even though I got probably the worst diagnosis in the world, I’m really glad I got it now as opposed to 15 years ago.”

— PEG BERENS

FDA-approved therapies, according to Dr. Christine M. Lovly.

“There has been tremendous growth in this area,” exclaims Lovly, an associate professor of Medicine and Cancer Research at Vanderbilt-Ingram Cancer Center in Nashville, Tennessee. “Instead of taking an all-comers approach for a given drug, we (can now) say this drug is going to work for patient A, but not patient B because of some biomarker of response to the therapy. This is the heralding of precision medicine or personalized medicine in lung cancer.”

Kim echoed Lovly’s sentiment about all the developments in the space. “Over the past 20 years, the lung cancer journey has been nothing but simply remarkable.”

ONE OF THE FIRST 200

John Hallick of Black Earth, Wisconsin, was diagnosed with stage 4 metastatic cancer of the lung and bronchus in February 2018.

His oncologists at Mayo Clinic in Rochester, Minnesota, recommended he undergo biopsies to identify any potential biomarkers. Three weeks later, his tests showed that he had a MET exon 14 skipping mutation. The problem was there were no FDA-approved treatments that targeted his mutation.

“They threw everything they had at me,” notes Hallick.

He received the chemotherapy Alimta (pemetrexed) and the immunotherapy Keytruda (pembrolizumab) for the first five months, but there were mixed results.

“I lost half my hearing, half my hair, 65 pounds and feeling on the bottom of my feet,” he says. “And (treatment) killed most of my red blood cells and I had to receive red blood cells a few times.”

But then, a clinical trial assessing the safety and efficacy of Tabrecta (capmatinib) began recruiting patients, and Hallick qualified to be enrolled.

“I was No. 2 at Mayo and part of the first 200 (patients in the phase 2 trial) and I’ve been on the drug since then,” he says. “It just changed the world.”

The results of this trial led to the FDA approval of Tabrecta in May 2020.

A BIG AREA OF NEED

While huge strides have been made in this space, Lovly explains that there’s still a tremendous amount of work that needs to be done.

“While (targeted therapies) often have quite dramatic responses, their response is not sustained; we’re not curing patients in the metastatic setting,” she says.

“Patients can have a dramatic response, feel dramatically better, but at a certain point in time, their disease is going to start to progress because the tumor learns a way to circumvent the therapy. And so, we really need better first-line treatments.”

Hollenbeck is one of those patients for whom targeted therapies have stopped working. This past October, she was running three miles a day and taking part in CrossFit. But now, her quality of life has been decreasing because her cancer is growing. She’s receiving IV chemotherapy, but currently finds herself confined to a recliner not able to do those tasks that she loves to do.

“My hope is that we can find a way to prevent resistance with targeted therapies, and that people can truly live instead of just being alive,” she says. “There’s a huge difference between progression-free survival (time during and after treatment when the patient lives without disease progression) and actually having a high quality of life. But I also knew that if I hadn’t had these targeted therapies, I sure wouldn’t be alive six years after my diagnosis.”

‘WORST DIAGNOSIS IN THE WORLD’

Berens, whose disease stopped responding to Alecensa after seven months, went on Lorbrena (lorlatinib) in fall 2020 along with chemotherapy a few weeks later to attack the cancer even more. Although she is no longer receiving the chemotherapy because of the toxicity, she remains on Lorbrena and has enrolled in a trial at City of Hope assessing if there are any additional genomic mutations driving her new progression.

“Even though I got probably the worst diagnosis in the world, I’m really glad I got it now as opposed to 15 years ago,” she says. “If I had gotten this diagnosis then, I would have just been given standard chemotherapy, and the life expectancy at that point was anywhere from three to 18 months. Now, with the advent of these targeted gene therapy drugs, our average life expectancy for an ALK patient is now six years. (And) six years is a lot better than three to 18 months and I strongly believe that if it wasn’t for these medications ... I wouldn’t be here.” ■



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- **Skin problems:** rash, itching, skin blistering or peeling, painful sores or ulcers in mouth or nose, throat, or genital area, fever or flu-like symptoms, or swollen lymph nodes
- **Problems can also happen in other organs and tissues. These are not all of the signs and symptoms of immune system problems that can happen with LIBTAYO. Call or see your healthcare provider right away for any new or worsening signs or symptoms, which may include:** chest pain, irregular heartbeat, shortness of breath or swelling of ankles, confusion, sleepiness, memory problems, changes in mood or behavior, stiff neck, balance problems, tingling or numbness of the arms or legs, double vision, blurry vision, sensitivity to light, eye pain, changes in eyesight, persistent or severe muscle pain or weakness, muscle cramps, low red blood cells, or bruising
- **Infusion reactions that can sometimes be severe.** Signs and symptoms of infusion reactions may include: nausea, chills or shaking, itching or rash, flushing, shortness of breath or wheezing, dizziness, feel like passing out, fever, back or neck pain, or facial swelling
- **Rejection of a transplanted organ.** Your healthcare provider should tell you what signs and symptoms you should report and monitor you, depending on the type of organ transplant that you have had
- **Complications, including graft-versus-host disease (GVHD), in people who have received a bone marrow (stem cell) transplant that uses donor stem cells (allogeneic).** These complications can be serious and can lead to death. These complications may happen if you underwent transplantation either before or after being treated with LIBTAYO. Your healthcare provider will monitor you for these complications

In a study,
**LIBTAYO was proven to help patients with
advanced NSCLC live longer versus chemotherapy**



Median overall survival (OS)*

- At 22.1 months, **half of the patients taking LIBTAYO (178 out of 356 patients) were alive** versus 14.3 months for patients taking chemotherapy (177 out of 354 patients)

*Median overall survival (OS) is the time in a trial—expressed in months or years—when half of the patients are still living.

More patients were alive with LIBTAYO compared with chemotherapy

- As of March 2020, results from the trial showed that **248 out of 356 patients (70%) taking LIBTAYO were alive**, compared with 213 out of 354 patients (60%) taking chemotherapy[†]

Individual results may vary.

[†]Patients were enrolled between June 27, 2017, and February 27, 2020. Patients were treated with LIBTAYO for an average of 27 weeks. The study is still ongoing, and patients will be followed up for up to 4 years.

Important Safety Information (continued)

Getting medical treatment right away may help keep these problems from becoming more serious. Your healthcare provider will check you for these problems during your treatment with LIBTAYO. Your healthcare provider may treat you with corticosteroid or hormone replacement medicines. Your healthcare provider may also need to delay or completely stop treatment with LIBTAYO if you have severe side effects.

Before you receive LIBTAYO, tell your healthcare provider about all your medical conditions, including if you:

- have immune system problems such as Crohn's disease, ulcerative colitis, or lupus
- have received an organ transplant
- have received or plan to receive a stem cell transplant that uses donor stem cells (allogeneic)
- have a condition that affects your nervous system, such as myasthenia gravis or Guillain-Barré syndrome
- are pregnant or plan to become pregnant. LIBTAYO can harm your unborn baby

Females who are able to become pregnant:

- Your healthcare provider will give you a pregnancy test before you start treatment
- You should use an effective method of birth control during your treatment and for at least 4 months after your last dose of LIBTAYO. Talk with your healthcare provider about birth control methods that you can use during this time

- Tell your healthcare provider right away if you become pregnant or think you may be pregnant during treatment with LIBTAYO

- are breastfeeding or plan to breastfeed. It is not known if LIBTAYO passes into your breast milk. Do not breastfeed during treatment and for at least 4 months after the last dose of LIBTAYO

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements.

The most common side effects of LIBTAYO include muscle or bone pain, tiredness, rash, and diarrhea. These are not all the possible side effects of LIBTAYO. Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088. You may also report side effects to Regeneron Pharmaceuticals and Sanofi at 1-877-542-8296.

Please see additional Important Safety Information on the previous page and Brief Summary of full Prescribing Information on the following pages.

You are encouraged to report negative side effects of prescription drugs to the FDA. Visit [fda.gov/medwatch](https://www.fda.gov/medwatch), or call 1-800-FDA-1088.

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Explore what could be possible with LIBTAYO
Scan this QR code with your phone to learn more, or visit LIBTAYO.com/NSCLC



IMPORTANT PATIENT INFORMATION ABOUT LIBTAYO® (cemiplimab-rwlc) INJECTION

Please speak with your healthcare provider regarding LIBTAYO. Only your healthcare provider knows the specifics of your condition and how LIBTAYO may work with your overall treatment plan. If you have any questions about LIBTAYO (pronounced Lib-TIE-oh), speak with your healthcare professional. Prescription Only.

What is the most important information I should know about LIBTAYO? LIBTAYO is a medicine that may treat certain types of cancers by working with your immune system. LIBTAYO can cause your immune system to attack normal organs and tissues in any area of your body and can affect the way they work. These problems can sometimes become severe or life-threatening and can lead to death. You can have more than one of these problems at the same time. These problems may happen anytime during treatment or even after your treatment has ended.

Call or see your healthcare provider right away if you develop any new or worse signs or symptoms, including:

Lung problems.

- cough
- chest pain
- shortness of breath

Intestinal problems.

- diarrhea (loose stools) or more frequent bowel movements than usual
- stools that are black, tarry, sticky, or have blood or mucus
- severe stomach-area (abdomen) pain or tenderness

Liver problems.

- yellowing of your skin or the whites of your eyes
- dark urine (tea colored)
- severe nausea or vomiting
- bleeding or bruising more easily than normal
- pain on the right side of your stomach area (abdomen)

Hormone gland problems.

- headache that will not go away or unusual headaches
- urinating more often than usual
- eye sensitivity to light
- hair loss
- eye problems
- feeling cold
- rapid heartbeat
- constipation
- increased sweating
- your voice gets deeper
- extreme tiredness
- dizziness or fainting
- weight gain or weight loss
- changes in mood or behavior, such as decreased sex drive, irritability, or forgetfulness
- feeling more hungry or thirsty than usual

Kidney problems.

- decrease in your amount of urine
- swelling of your ankles
- blood in your urine
- loss of appetite

Skin problems.

- rash
- painful sores or ulcers in mouth or nose, throat, or genital area
- itching
- skin blistering or peeling
- fever or flu-like symptoms
- swollen lymph nodes

Problems can also happen in other organs and tissues. These are not all of the signs and symptoms of immune system problems that can happen with LIBTAYO. Call or see your healthcare provider right away for any new or worsening signs or symptoms which may include:

- chest pain, irregular heartbeat, shortness of breath or swelling of ankles
- confusion, sleepiness, memory problems, changes in mood or behavior, stiff neck, balance problems, tingling or numbness of the arms or legs
- double vision, blurry vision, sensitivity to light, eye pain, changes in eyesight
- persistent or severe muscle pain or weakness, muscle cramps
- low red blood cells, bruising

Infusion reactions that can sometimes be severe. Signs and symptoms of infusion reactions may include:

- nausea
- dizziness
- chills or shaking
- feel like passing out
- itching or rash
- fever
- flushing
- back or neck pain
- shortness of breath or wheezing
- facial swelling

Rejection of a transplanted organ. Your healthcare provider should tell you what signs and symptoms you should report and monitor you, depending on the type of organ transplant that you have had.

Complications, including graft-versus-host disease (GVHD), in people who have received a bone marrow (stem cell) transplant that uses donor stem cells (allogeneic). These complications can be serious and can lead to death. These complications may happen if you underwent transplantation either before or after being treated with LIBTAYO. Your healthcare provider will monitor you for these complications.

Getting medical treatment right away may help keep these problems from becoming more serious. Your healthcare provider will check you for these problems during your treatment with LIBTAYO. Your healthcare provider may treat you with corticosteroid or hormone replacement medicines. Your healthcare provider may also need to delay or completely stop treatment with LIBTAYO if you have severe side effects.

What is LIBTAYO? LIBTAYO is a prescription medicine used to treat people with a type of lung cancer called non-small cell lung cancer (NSCLC). LIBTAYO may be used as your first treatment when your lung cancer has not spread outside your chest (locally advanced lung cancer) **and** you cannot have surgery **or** chemotherapy with radiation, or your lung cancer has spread to other areas of your body (metastatic lung cancer), **and** your tumor tests positive for high “PD-L1,” and your tumor does not have an abnormal “EGFR,” “ALK,” or “ROS1” gene. It is not known if LIBTAYO is safe and effective in children.

Before you receive LIBTAYO, tell your healthcare provider about all your medical conditions, including if you:

- have immune system problems such as Crohn’s disease, ulcerative colitis, or lupus
- have received an organ transplant
- have received or plan to receive a stem cell transplant that uses donor stem cells (allogeneic)
- have a condition that affects your nervous system, such as myasthenia gravis or Guillain-Barre syndrome
- are pregnant or plan to become pregnant. LIBTAYO can harm your unborn baby.

Continued on following page

IMPORTANT PATIENT INFORMATION ABOUT LIBTAYO® (cemiplimab-rwlc) INJECTION

Females who are able to become pregnant:

- Your healthcare provider will give you a pregnancy test before you start treatment with LIBTAYO.
- You should use an effective method of birth control during your treatment and for at least 4 months after the last dose of LIBTAYO. Talk to your healthcare provider about birth control methods that you can use during this time.
- Tell your healthcare provider right away if you become pregnant or think you may be pregnant during treatment with LIBTAYO.
- are breastfeeding or plan to breastfeed. It is not known if LIBTAYO passes into your breast milk. Do not breastfeed during treatment and for at least 4 months after the last dose of LIBTAYO.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements.

How will I receive LIBTAYO?

- Your healthcare provider will give you LIBTAYO into your vein through an intravenous (IV) line over 30 minutes.
- LIBTAYO is usually given every 3 weeks.
- Your healthcare provider will decide how many treatments you will need.
- Your healthcare provider will do blood tests to check you for side effects.
- If you miss any appointments, call your healthcare provider as soon as possible to reschedule your appointment.

What are the possible side effects of LIBTAYO?

LIBTAYO can cause serious side effects, including:

- See “What is the most important information I should know about LIBTAYO?”

The most common side effects of LIBTAYO include muscle or bone pain, tiredness, rash, and diarrhea.

These are not all the possible side effects of LIBTAYO.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

General information about the safe and effective use of

LIBTAYO. Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. If you would like more information about LIBTAYO, talk with your healthcare provider. You can ask your healthcare provider for information about LIBTAYO that is written for health professionals.

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This is a brief summary of the most important information about LIBTAYO. For more information, talk with your healthcare provider, call 1-877-542-8296, or go to www.LIBTAYO.com





The KRAS G12C gene mutation in non-small cell lung cancer has been deemed “undruggable,” but recent effective therapies have successfully targeted this mutation, leading to shrinking of tumors and longer survival.

By JEANNETTE MONINGER

Atlanta resident Gwen Cesta-Persichetti was visiting family in New York City in July 2020 when she started coughing up blood. “I attended my nephew’s graduation party and then headed to the nearest urgent care,” says Cesta-Persichetti, who was 64 at the time. “I thought I might have pneumonia or perhaps a blood clot from traveling.” But imaging scans showed she had stage 4b lung cancer that had spread to her brain, spine and lymph nodes.

Cesta-Persichetti was no stranger to cancer. Fifteen years earlier, she had a double mastectomy to treat

stage 1b breast cancer. The surgery was followed by five years of Arimidex (anastrozole), an endocrine therapy for hormone receptor-positive breast cancers. “I knew I could handle the cancer treatments,” says Cesta-Persichetti. “It was the stage 4 diagnosis that scared me.” Both her parents had died within six months of receiving stage 4 cancer diagnoses; her mother had breast and lung cancer and her father had prostate cancer. “I didn’t see how anyone could survive cancer in the lungs, brain and spine for very long,” she recalls. “I cried when I realized I might not see my daughter get married the following year.” »

FEATURE

non-small cell lung cancer



GWEN CESTA-PERSICHETTI feels

fortunate that her doctor knew to test for KRAS G12C, which is not always the case for other patients with NSCLC.



The oncologist Cesta-Persichetti met with in New York had a different perspective. A biopsy of the lung tumor showed that Cesta-Persichetti had non-small cell lung cancer (NSCLC), the most common type of lung cancer. Genomic testing on the tumor also showed the cancer was caused by a gene mutation called KRAS G12C (short for Kirsten rat sarcoma viral oncogene homolog). For decades, this mutation was considered untreatable. But a new drug designed to target the aberrantly active RAS protein encoded by the mutant KRAS gene being tested in clinical trials — Lumakras (sotorasib) — was showing tremendous promise in treating KRAS G12C-mutated NSCLC. Cesta-Persichetti's doctor thought she was a perfect candidate.

After radiation therapy to shrink the tumors in her brain, Cesta-Persichetti began taking Lumakras in August 2020. She noticed improvements almost immediately. "Within 10 days, I could take a deep breath without coughing," she recalls. "In fact, I stopped coughing altogether." Imaging scans four weeks later showed a noticeable decrease in the size of the tumors in her lungs and lymph nodes.

More than 120 other participants in the national CodeBreaK 100 clinical trial, which began in 2018, experienced similar results. The Food and Drug Administration (FDA) took notice, giving the drug breakthrough therapy designation in December 2020 and moving it quickly through

the approval process. On May 28, 2021, the FDA approved the drug as the first targeted therapy for metastatic KRAS G12C-mutated NSCLC.

WHAT IS KRAS?

KRAS (pronounced KAY-ras) is a group of genes that help control how cells grow and divide. It is the most frequently mutated gene leading to the development of cancer (what cancer specialists call an oncogene). A mutated KRAS oncogene makes abnormal proteins that fuel the growth and spread of cancer cells. There are different KRAS subtypes, with the G12C subtype linked to not just lung cancer but as many as 3% to 5% of colorectal cancers as well as cancers of the pancreas, endometrium and appendix.

"The KRAS G12C mutation drives lung cancer growth and is associated with poor outcomes with higher rates of relapse, shorter progression-free survival (time during and after treatment when the patient lives without disease progression) and diminished overall survival (time from diagnosis or treatment start when patients are alive) compared (with) other types of lung cancers," says Dr. Bob Li, a medical oncologist and physician-scientist at Memorial Sloan Kettering Cancer Center in New York City.

For reasons that are not clear, White women, Asian males and people who are Black are more likely to have this mutation. The altered gene is not something you are born

with, so you cannot pass it to future generations. “There are some inherited mutations in RAS pathway genes that can lead to rare developmental syndromes known as RASopathies. However, KRAS G12C isn’t one of them,” explains Dr. Ferdinando Skoulidis, associate professor in the Department of Thoracic/Head and Neck Medical Oncology at The University of Texas MD Anderson Cancer Center in Houston. “KRAS G12C is a somatic mutation,

which means something happens after you’re born that changes the DNA in the tissue that becomes cancerous,” he says. “We typically see this mutation in people who have a history of smoking.”

Skoulidis calls tumors with KRAS mutations “one of the worst ones to have because up until now there have been no effective targeted therapies.” KRAS G12C-mutated tumors are resistant to other treatments like EGFR inhibitors. Some people with KRAS G12C-mutated NSCLC may respond to immunotherapies like Keytruda (pembrolizumab) or a combination of immunotherapy and chemo-

HOPE FOR PEOPLE WITH KRAS G12C-MUTATED NSCLC

The development of Lumakras and another promising drug, adagrasib (which received FDA breakthrough therapy designation in June 2021), was made possible after researchers located a hidden pocket or groove in the KRAS G12C protein that only exists when the protein is inactive or dormant. The drugs target these inactive proteins, working their way into the pocket and binding to the protein. “The drugs essentially lock the protein in an inactive state,” says Dr. Hatim Husain, a medical oncologist who treats lung cancer at



CESTA-PERSICHETTI eventually had to stop treatment with Lumakras, but credits it to stabilizing her lung cancer and getting her to her daughters wedding.

“Within 10 days I could take a deep breath without coughing. In fact, I stopped coughing all together.

—GWEN CESTA-PERSICHETTI

therapy. But for those whose tumors do not respond or relapse, the outlook was often bleak.

Researchers first identified the KRAS G12C mutation as a driver of NSCLC in 1982. They would spend nearly 40 years searching for a way to stop it. “The

KRAS protein encoded by the gene is round and smooth, which makes it very difficult for a drug to bind to it,” says Li.

For three decades, the KRAS G12C mutation was deemed undruggable and therefore, untreatable. And then, in 2012, researchers made a remarkable discovery.

Moore’s Cancer Center at UC San Diego Health. “Once that happens, the protein can’t send the signals that cause cancer cells to multiply. Cancer cells start to die, causing tumors to shrink.”

In the CodeBreak 100 clinical trial, Lumakras stopped tumor growth for 8 in 10 people. For 1 in 3 participants, the tumors got substantially smaller. The drug kept tumors stable for at least six months, with a median overall survival time of 12 and a half months. Results from phases 1 and 2 of the KRYSTAL clinical trial of adagrasib are also encouraging. More than 40% of »

FEATURE

non-small cell lung cancer



participants saw tumor shrinkage, whereas close to half had disease stabilization.

The Lumakras treatment involves taking eight 120-milligram tablets each day (for a total of nearly 1 gram). Clinical trials are underway to see whether a lower dose might be equally effective. About 2 in 3 people experience manageable medication side effects like diarrhea, nausea, fatigue and muscle or bone pain. Because elevated liver enzymes are a potential complication, people who take Lumakras need regular tests to assess liver function.

Although Cesta-Persichetti saw tremendous improvements while taking Lumakras, she was only able to take the drug for about five weeks. “My lungs looked great, but the tumors in my brain and spine kept growing,” says Cesta-Persichetti, who now receives Keytruda infusions every three weeks. Still, she credits Lumakras with stabilizing the lung cancer and helping her be around to dance at her daughter’s wedding this past December.

Cesta-Persichetti considers herself fortunate. At the

time of her diagnosis, she had access to top cancer specialists in New York who knew to test for the KRAS G12C mutation. They also knew how to connect her with a clinical trial near her home in Atlanta. “Unfortunately, many people with NSCLC still don’t get molecular testing to check for targetable gene mutations,” says Husain. “There’s a need for better education about genomic tumor testing among patients and their doctors.”

ADVOCATING FOR GENOMIC TESTING OF LUNG TUMORS

Laurie Seligman, a 61-year-old resident of Palmetto, Florida, took it upon herself to learn all she could about NSCLC after receiving a stage 3a diagnosis in January 2018. Her initial treatment included multiple rounds of chemotherapy and radiation therapy followed by Imfinzi (durvalumab).

It was at a LUNgevity Foundation Hope Summit in 2019 that Seligman first heard the words KRAS and genomic

LAURIE SELIGMAN
advocated for testing
and felt like she won the
lottery when they found
she had the KRAS G12C
mutation.

test the tissue for gene mutations. When the tissue sample turned out to be too small for genomic testing, Seligman asked for a blood test. “My doctor tried to dissuade me because insurance companies don’t always cover the costs of tumor testing,” she says. Depending on the test, costs for genomic testing can range from \$300 upwards to \$10,000. Test results showed Seligman had the KRAS G12C mutation. “I was excited

says. The process of moving took all of Seligman’s strength. “I couldn’t pack one box without stopping to rest,” she says. Soon after she relocated to Florida, a trip to an urgent care showed her right lung had collapsed. After undergoing treatment, Seligman started the combination immunotherapies Opdivo (nivolumab) plus Yervoy (ipilimumab). But after receiving just two infusions at the start of 2021, she was hospitalized for almost a month with pneumonitis, a lung inflammation.

After her hospitalization, Seligman learned that since the cancer was now stage 4, she was eligible for the CodeBreak 100 trial. “I started the paperwork in May to enroll in a trial that was getting underway at the Moffitt Cancer Center in Tampa,” says Seligman. Two days before she was scheduled to get a tumor biopsy (the last step before starting the clinical trial) the FDA granted full approval to Lumakras. “Again, it felt like winning the lottery,” she says.

Seligman started taking Lumakras towards the end of June in 2021. “My cough seemed better in just two days, but I thought I was imagining it. It seemed too soon to notice any health changes,” she recalls. But in two weeks, her cough was gone. “It had been a long time since I could have a conversation without getting winded or having a coughing fit.”

Her first imaging scan at five weeks showed a significant reduction in the size of the lung tumors. By the third scan on Jan. 6 of this year her doctor said, “For all intents and purposes, you’ve had a complete response to the drug.” Seligman didn’t know exactly how to interpret those words, but an internet search suggested she was in remission. “I still can’t believe it,” Seligman says. “A year ago, my prognosis was terrible, and now I’m in remission. I know the drug could stop working at any time. I have to hope that if that time comes, there’s another drug — one that’s probably in clinical trials right now — that will help.”

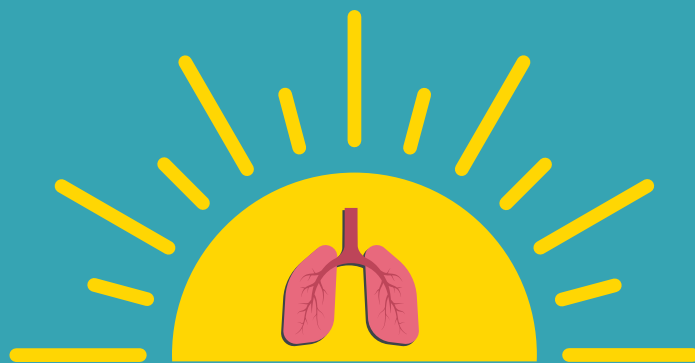
SELIGMAN says after just two days of taking Lumakras her cough improved — she thought she was just imagining it.

testing. “When I asked one of the doctors in attendance whether I should get tested, he said I didn’t need it unless the cancer progressed,” Seligman recalls. But in September 2020, scans found a mass in a lymph node near her clavicle. Before getting the biopsy that would confirm the cancer had spread, Seligman asked her doctor if they could

because I had some knowledge of KRAS. When I heard it was the G12C subtype, I felt like I won the lottery!” she says. “An oncologist I saw for a second opinion had told me there were clinical trials underway to find a treatment for this genetic mutation.”

Seligman, who was living in San Antonio at the time, decided to move to Florida to be closer to family. “I also thought I might have better access to clinical trials in Florida,” Seligman





A New Path Emerges in Treating **LUNG CANCER**

Anti-TIGIT immunotherapy drugs may improve quality of life and survival, while being well tolerated by patients.

By DARA CHADWICK





Byron Warner, 82, remembers when he knew the experimental immunotherapy drug combination he had been taking to combat non-small cell lung cancer (NSCLC) was working. “I go for walks every day and for a long time, breathing was just agony,” he says. “I’d walk to the end of my block and back and it felt like wind sprints in football. But one morning, I went out to walk and I could breathe. It was the most encouraging thing I’ve felt all along.”

The Nashville, Tennessee, resident says he is once again jogging up a hill he struggled to climb before treatment. “I’m really happy,” Warner says.

This is the hope that new immunotherapy drugs targeting an immune checkpoint inhibitor known as TIGIT are bringing to people with lung cancer. TIGIT, short for T cell immunoreceptor with immunoglobulin and ITIM domain, is a new target for immunotherapy drugs that treat cancer that is hoped to build further on the successes seen with standard immunotherapy. »



BYRON WARNER
had his wife, **CINDY**, by his
side while being treated
with a new therapy in
lung cancer.

Therapies that improve quality of life and survival for patients — and that are well tolerated — are the “holy grail,” according to Dr. Jeffrey Clarke, a medical oncologist at Duke Cancer Institute in Durham, North Carolina. “That’s always what we’re looking for and striving for to grow our armamentarium,” he says.

Anti-TIGIT therapies may offer that promise for people with lung cancer in that their mechanisms of action are distinct from that of approved “checkpoint inhibitor” treatments. Although no anti-TIGIT immunotherapy drug has been approved by the Food and Drug Administration (FDA) at this time, clinicians are encouraged by early data from clinical trials.

“It could be even better in some ways than some of the drugs we have,” Clarke says.

IMMUNOTHERAPY TREATMENT IN LUNG CANCER

Immunotherapies are drugs that work to help the immune system destroy cancer. Each day, immune cells (T cells) sweep the body to search for and mitigate bacteria, viruses and cells that should not be there. To protect, the immune system includes built-in stop signs that keep T cells from going too far and destroying healthy cells.

The body creates these stop signs when T cells recognize and bind with certain proteins designed to halt their work. These stop signs are called immune checkpoints. But cancer cells are wily in the way they evolve. They take advantage of these checkpoints to escape notice. When cancer cells can get around immune checkpoints, tumors grow unchecked.

Immunotherapy drugs work by shutting off immune checkpoints to make it easier for T cells to identify cancer. Each of these drugs — known as immune checkpoint inhibitors — works on a specific type of immune checkpoint (sometimes called a pathway).

Immune checkpoints that have FDA-approved therapies for treating

lung cancer include CTLA-4, PD-1 and a protein related to PD-1 (PD-L1). Approved immune checkpoint inhibitors include the PD-1 inhibitors Opdivo (nivolumab), Keytruda (pembrolizumab) and Libtayo (cemiplimab) for some people with NSCLC, as well as the PD-L1 inhibitor Tecentriq (atezolizumab). The CTLA-4 inhibitor Yervoy (ipilimumab) is also used to treat some lung cancers.

Like targeted therapies (drugs targeting cancer cells that have a specific gene mutation), immunotherapies are known as personalized medicine. Dr. Wallace Akerley, a lung cancer oncologist at the Huntsman Cancer Institute at the University of Utah in Salt Lake City, has been studying lung cancer for 30 years and says personalized medicine has changed how clinicians treat lung cancers.

“Now, when we see a patient, we do a panel of biomarkers to define what the cancer’s weaknesses might be,” he says, adding that his clinic looks for gene mutations that can be treated with eight different gene-specific drugs (targeted therapies). The clinic also does an immune panel that looks for PD-L1 expression. The findings, Akerley notes, determine which of three therapies individually or in combination — chemotherapy, targeted therapy or immunotherapy — will be used to treat a patient’s specific lung cancer.

“I’d walk to the end of my block and back and it felt like wind sprints in football. But one morning I went out to walk and could breath. It was the most encouraging thing I’ve felt all along.”

—BYRON WARNER

Those with genetic mutations start on targeted therapy, whereas patients with high PD-1 or PD-L1 expression get immunotherapy. “If you have neither of those, you would be getting a chemoimmunotherapy or even dual immunotherapy,” he says, adding that immune therapies work so well with chemotherapy that most people no longer have chemotherapy alone.

TIGIT: A NEW PATHWAY IN LUNG CANCER IMMUNOTHERAPY

TIGIT is a more recently identified immune checkpoint that is now being targeted with various therapies in clinical trials. Researchers have been studying patient response to anti-TIGIT therapy as a monotherapy (the only treatment given) and in combination with other immunotherapy drugs. »



WARNER was not feeling great after first starting treatment with immunotherapy. But, after a few days felt stronger and remembers when he felt it starting to work.



BYRON WARNER

didn't want to die and leave his wife, so he had no hesitations starting an anti-TIGIT therapy.

“The TIGIT drug has been looked at individually and there's been some activity seen,” Akerley explains. “It's also been used in conjunction with PD-1 inhibition so two checkpoint blockades. There is preliminary data that this is much more effective.”

Warner took part in a clinical trial of an anti-TIGIT drug in combination with another immunotherapy. After being diagnosed with NSCLC — specifically, a 7-centimeter inoperable tumor in his upper left lung — he had six weeks of radiation (five treatments per week) combined with weekly chemotherapy. When he finished this grueling course of treatment, his oncologist, Dr. Melissa Johnson, director of the Lung Cancer Research program at Sarah Cannon Research Institute in Nashville and a medical oncologist with Tennessee Oncology, recommended that Warner enter a study assessing the anti-TIGIT immunotherapy tiragolumab in combination with Tecentriq.

Of note, the drug combination was granted a breakthrough therapy designation by the FDA in early 2021 based on data from the phase 2 CITYSCAPE trial.

Warner was enrolled in the phase 3 SKYSCRAPER-03 which is investigating the safety and efficacy of tiragolumab in combination with the FDA-approved PD-L1 inhibitor Tecentriq against Imfinzi (durvalumab) — an anti-PD-L1 therapy — in people with inoperable stage 3 NSCLC who had been previously treated with a combination of chemotherapy and radiation.

For just over a year, Warner had a monthly infusion of the combined immunotherapies. The results of the trial are not available to the public yet.

There are several anti-TIGIT therapies being studied in clinical trials. Among the drugs being studied in lung cancer treatment are tiragolumab, ociperlimab, vibostolimab and a TIGIT inhibitor known as BMS-986207.

“Treatment of lung cancer has transformed with the introduction of immunotherapy, with significant improvements in survival,” adds Dr. Jessica Bauman, a thoracic oncologist and chief of the Division of Head and Neck Medical Oncology at Fox Chase Cancer Center in Philadelphia. “TIGIT is an intriguing type of novel immunotherapy. When it is blocked, it may enhance the immune system and improve the responses to current immunotherapies. From the early clinical studies, it does look to be most effective in combination with PD-1 or PD-L1 blockade as well.”

Clarke says the data he has seen from anti-TIGIT drug clinical trials in patients with high expression of PD-L1 are the most exciting. “Patients who have the highest expression of PD-L1 seem to have the most benefit,” he explains. “This could help guide us decide who should get this type of treatment versus another type of treatment. I think we need to have more data to tell us for sure who’s going to benefit from this treatment versus who wouldn’t.”

THE SIDE EFFECTS QUESTION

For many people with lung cancer, questions about potential side effects from cancer treatment loom large. Immunotherapy side effects include inflammation, which could involve any organ in the body, according to Clarke. “Rash is very common, as is colitis causing diarrhea,” he says.

In treating cancers with immunotherapy, clinicians want the immune system to be activated to find the cancer and kill it but do not want the immune system to be activated against healthy tissue, Bauman says. That creates a need for a delicate balance when using these drugs.

“We see the immune system causing pneumonitis, hepatitis, colitis, myocarditis, thyroiditis, as well as others,” she says. “Those immune-related toxicities are often treatable with high-dose steroids and patients do well. One of the concerns about using multiple avenues to activate the immune system is that you increase the risk of immune toxicities.”

But early data from studies of immunotherapy combinations that include anti-TIGIT drugs are not showing a significant increase in toxicities, according to Bauman. “Immune toxicities look similar to what is already known from the PD-1 therapies, which have a lower rate of toxicities than some of the other checkpoints that have been studied in trials,” she adds.

Warner notes that treatment is strenuous for people with cancer. “Radiation and chemo together just really sap your strength and your mental energy as well,” he says. “When I went to immunotherapy, I noticed that I was feeling down and a little bit listless for three or four days afterward, but then I came back stronger.”

Warner says he did not experience any rash or gastrointestinal symptoms.

THE POTENTIAL OF ANTI-TIGIT TREATMENTS

Concerns about balancing the benefits of immunotherapy combinations against potential toxicities for people with lung cancer may contribute to the length of the approval process for these drugs. “Over the last decade, there has been so much research into immunotherapies and immunotherapy combinations,” Bauman says. “We’ve had amazing progress on one hand and yet we still have had relatively slow progress.”

But the personalization of lung cancer treatment — including anti-TIGIT therapies now in development — offers significant hope to many people with lung cancer. Clinical trials that include tissue and blood biomarker analysis play a critical role in advancing the state of this science by understanding both the drug impact as well as underlying biology.

“Many patients are certainly open to clinical trials,” Bauman adds. “It depends on the underlying science, where they live, how often they have to come in and the potential risks and benefits.”

Johnson says the mission of every clinical trial is to provide patients, like Warner, with potentially life-changing therapies. “We believe clinical trials should be first, not last, because good outcomes are possible,” she says. “He had the unresectable stage 3 lung cancer the trial was looking for, and he really had a sincere desire to make sure we did everything we could to get rid of the cancer. That’s a perfect patient to talk to about clinical trials.”

Warner says he did not have any reservations about taking part in the anti-TIGIT therapy trial. “I thought, ‘I can take the side effects,’” he says. “What I don’t want to do is pass away from cancer. My wife, Cindy, was always with me. She’s been doing the heavy lifting for about 18 months now.”

Clarke notes that in many ways, the lung cancer community is seeing strides in treatment that it has not seen in decades past. “It’s very exciting, but we still have a long way to go,” he says of anti-TIGIT therapies. “I think we’re all looking forward to the results of these clinical trials.” ■

***EDITOR’S NOTE:** Following the submission of this feature, the drug maker, Genentech, announced that the SKYSCRAPER-02 trial, combining Tecentriq and tiragolumab, failed to reduce the rate of disease progression and death when compared with Tecentriq and chemotherapy only.

***EDITOR’S NOTE:** SKYSCRAPER-03 is an open-label trial that is an ongoing study. Data from the study has not yet readout.



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NOT DONE YET

Take the next step—treat metastatic non-small cell lung cancer (mNSCLC) with epidermal growth factor receptor (EGFR) exon 20 insertion mutations after chemotherapy that contains platinum.

What is RYBREVANT[®] (amivantamab-vmjw)?

RYBREVANT[®] is a prescription medicine used to treat adults with non-small cell lung cancer (NSCLC) that:

- has spread to other parts of the body (metastatic) or cannot be removed by surgery, **and**
- has a certain abnormal epidermal growth factor receptor "EGFR" gene(s) **and**
- whose disease has worsened while on or after chemotherapy that contains platinum.

Your healthcare provider will perform a test to make sure that RYBREVANT[®] is right for you.

It is not known if RYBREVANT[®] is safe and effective in children.

RYBREVANT[®] is approved based on medical studies that measured how many patients responded to treatment. There are ongoing studies to confirm the continued approval of RYBREVANT[®].

IMPORTANT SAFETY INFORMATION

Before you receive RYBREVANT[®], tell your healthcare provider about all of your medical conditions, including if you:

- have a history of lung or breathing problems
- are pregnant or plan to become pregnant. RYBREVANT[®] can harm your unborn baby.

Females who are able to become pregnant:

- Your healthcare provider should do a pregnancy test before you start treatment with RYBREVANT[®].
- You should use effective birth control (contraception) during treatment and for 3 months after your final dose of RYBREVANT[®].

- Tell your healthcare provider right away if you become pregnant or think you might be pregnant during treatment with RYBREVANT[®].
- are breastfeeding or plan to breastfeed. It is not known if RYBREVANT[®] passes into your breast milk. Do not breastfeed during treatment and for 3 months after your final dose of RYBREVANT[®].

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements.

How will I receive RYBREVANT[®]?

- RYBREVANT[®] will be given to you by your healthcare provider by intravenous infusion into your vein.
- Your healthcare provider will decide the time between doses as well as how many treatments you will receive.
- Your healthcare provider will give you medicines before each dose of RYBREVANT[®] to help reduce the risk of infusion-related reactions.
- If you miss any appointments, call your healthcare provider as soon as possible to reschedule your appointment.

What should I avoid while receiving RYBREVANT[®]?

RYBREVANT[®] can cause skin reactions. You should limit your time in the sun during and for 2 months after your treatment with RYBREVANT[®]. Wear protective clothing and use sunscreen during treatment with RYBREVANT[®].

What are the possible side effects of RYBREVANT[®]?

RYBREVANT[®] may cause serious side effects, including:

- **infusion-related reactions.** Infusion-related reactions are common with RYBREVANT[®] and can be severe or serious.

RYBREVANT® is the only targeted antibody treatment approved specifically for mNSCLC with *EGFR* exon 20 insertion mutations after chemotherapy that contains platinum

In a clinical trial, RYBREVANT® (amivantamab-vmjw) was studied in 81 people* who had mNSCLC with *EGFR* exon 20 insertion mutations whose disease had worsened while on or after chemotherapy that contains platinum



- 40% of people treated with RYBREVANT® after chemotherapy that contains platinum saw their tumors disappear[†] (3.7%) or get smaller (36%)

RYBREVANT® can cause serious side effects, including infusion-related reactions, lung problems, skin problems, and eye problems.

See Important Safety Information below and Patient Information on the following page.

*Most people in the trial were women (59%) and over half never smoked (53%). The main goal of the trial was to measure the number of people who responded to RYBREVANT® overall.

[†]The disappearance of all signs of cancer in response to treatment does not always mean the cancer has been cured.

Talk to your doctor to find out if RYBREVANT® is an option for you

RybreventAndMe.com

EGFR, epidermal growth factor receptor; mNSCLC, metastatic non-small cell lung cancer.

Tell your healthcare provider right away if you get any of the following symptoms during your infusion of RYBREVANT®:

- shortness of breath
- fever
- chills
- nausea
- flushing
- chest discomfort
- lightheadedness
- vomiting
- **lung problems.** RYBREVANT® may cause lung problems that may lead to death. Symptoms may be similar to those symptoms from lung cancer. Tell your healthcare provider right away if you get any new or worsening lung symptoms, including shortness of breath, cough, or fever.
- **skin problems.** RYBREVANT® may cause rash, itching, and dry skin. You may use alcohol-free moisturizing cream for dry skin. Tell your healthcare provider right away if you get any skin reactions. Your healthcare provider may treat you with a medicine(s) or send you to see a skin specialist (dermatologist) if you get skin reactions during treatment with RYBREVANT®. See "What should I avoid while receiving RYBREVANT®?"
- **eye problems.** RYBREVANT® may cause eye problems. Tell your healthcare provider right away if you get symptoms of eye problems which may include:
 - eye pain
 - dry eyes
 - eye redness
 - blurred vision
 - changes in vision
 - itchy eyes
 - excessive tearing
 - sensitivity to light

Your healthcare provider may send you to see an eye specialist (ophthalmologist) if you get eye problems during treatment with RYBREVANT®. You should not use contact lenses until your eye symptoms are checked by a healthcare provider.

The most common side effects of RYBREVANT® include:

- rash
- infusion-related reactions
- infected skin around the nail
- muscle and joint pain
- shortness of breath
- nausea
- feeling very tired
- swelling of hands, ankles, feet, face, or all of your body
- sores in the mouth
- cough
- constipation
- vomiting
- changes in certain blood tests

Your healthcare provider may temporarily stop, decrease your dose or completely stop your treatment with RYBREVANT® if you have serious side effects.

These are not all of the possible side effects of RYBREVANT®.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

General information about safe and effective use of RYBREVANT®

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. You can ask your healthcare provider or pharmacist for information about RYBREVANT® that is written for health professionals.

Please read the Patient Information on the next page and discuss with your doctor.

cp-213277v2

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RYBREVANT®
(amivantamab-vmjw)
Injection for IV Use | 350 mg/7 mL (50 mg/mL)

janssen Oncology
PHARMACEUTICAL COMPANIES OF **Johnson & Johnson**

PATIENT INFORMATION
RYBREVANT (RYE–breh–vant)
(amivantamab-vmjw)
Injection, for intravenous use

What is RYBREVANT?

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What should I avoid while receiving RYBREVANT?

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What are the possible side effects of RYBREVANT?

RYBREVANT may cause serious side effects, including:

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 - shortness of breath
 - fever
 - chills
 - nausea
 - flushing
 - chest discomfort
 - lightheadedness
 - vomiting
- **lung problems.** RYBREVANT may cause lung problems that may lead to death. Symptoms may be similar to those symptoms from lung cancer. Tell your healthcare provider right away if you get any new or worsening lung symptoms, including shortness of breath, cough, or fever.

What are the possible side effects of RYBREVANT? (continued)

RYBREVANT may cause serious side effects, including:

- **skin problems.** RYBREVANT may cause rash, itching, and dry skin. You may use alcohol-free moisturizing cream for dry skin. Tell your healthcare provider right away if you get any skin reactions. Your healthcare provider may treat you with a medicine(s) or send you to see a skin specialist (dermatologist) if you get skin reactions during treatment with RYBREVANT. See “What should I avoid while receiving RYBREVANT?”
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 - eye pain
 - dry eyes
 - eye redness
 - blurred vision
 - changes in vision
 - itchy eyes
 - excessive tearing
 - sensitivity to light

Your healthcare provider may send you to see an eye specialist (ophthalmologist) if you get eye problems during treatment with RYBREVANT. You should not use contact lenses until your eye symptoms are checked by a healthcare provider.

The most common side effects of RYBREVANT include:

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General information about safe and effective use of RYBREVANT

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What are the ingredients of RYBREVANT?

Active ingredient: amivantamab-vmjw

Inactive ingredients: EDTA disodium salt dihydrate, L-histidine, L-histidine hydrochloride monohydrate, L-methionine, polysorbate 80, sucrose, and water for injection.

Product of Ireland

Manufactured by: Janssen Biotech, Inc., Horsham, PA 19044.

U.S. License Number 1864

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For more information, call Janssen Products, LP at 1-800-526-7736 (1-800-JANSSEN) or go to www.RYBREVANT.com.

SPEAKING OUT LUNG CANCER

Navigating the End of Life Does Not Have to Be a Solitary Journey

CURE® spoke with an expert about support for patients and their loved ones during an end-stage cancer diagnosis. BY KRISTIE L. KAHL



 SARAH MIRETTI CASSIDY

PATIENTS WITH END-STAGE CANCER and their loved ones may feel a range of emotions — from relief that the pain and suffering are almost over to shock, denial and often anger. However, there are resources available to aid in this difficult time. As part of its “Speaking Out” video series, *CURE®* spoke with Sarah Miretti Cassidy, director of external affairs at Cancer Hope Network, who discussed the kinds of resources and support available.

Q: What support is available for patients who might have end-stage disease?

A: This is where education really matters. ... Ask, ask, ask or talk, talk, talk. We hope that by the time someone reaches the end of their life that they’ve already been working with a palliative care team. But one of the things that we have found to be helpful is to talk to your hospice team. ... Hospice offers so much more. It offers time. It offers the ability to be with your loved one — and with them, rather than caring for them — because hospice can offer so many resources. And there are other resources through your care team, through your social worker, your navigator ... so that you can enjoy those last few days with the person you love. It’s not easy, right? I was talking with someone the other day and they were saying, “Despite our best efforts, the death rate is still 100%.” And that’s true. None of us are getting out of this alive. But at Cancer Hope Network, and for so many

I think it's an **important** thing to remind our **caregivers** that you don't have to know the right answer. **There isn't a right answer.** It's an awful situation. And it's **OK** not to know and **it's OK to ask for help.**

—SARAH MIRETTI CASSIDY

other professionals, our goal is not only to give you the best quality of life, but also to help people find a good death. We know we'll all leave this world at some point. What's the best way to do that?

So an organization like Cancer Hope Network is here to help provide support for loved ones and caregivers who may be going through anticipatory grief. And then there's a lot of other resources that are available to patients or their loved ones.

Q: What advice do you have for those who may be facing this situation and are unsure how to talk with their providers, or maybe even with their family?

A: This is one of those times when it's OK to outsource the start of the conversation. It's OK to ask your doctor or trusted member of the care team to start that conversation. It's OK to talk with a Cancer Hope Network support volunteer and then start that conversation with, "I was talking to my volunteer, and they mentioned" The important piece is really starting the conversation. Whatever you need to do to start that conversation, whether it means having someone else begin it, talking with someone to work through what you want to say, it's fine. We really encourage people that having the conversation is most important. How it starts is not as important.

Q: On the other side, we have caregivers and loved ones who are also affected by an end-stage cancer diagnosis. What resources are also available for them to deal with a loved one who's near end of life or maybe who has recently passed?


A: We always encourage people to connect with a volunteer, whether through Cancer Hope Network or another organization who is providing that peer support; (to) talk to their hospice team. Many hospice providers or organizations offer support after a loved one has passed. Then, whether you're connecting through your social worker or navigator, your hospice care team, (or) Cancer Hope Network's programs team, ask them for suggestions and resources.

There are a ton of resources out there to help plan for the end of life, whether that be a checklist, whether that be advanced care directives; walking through the practical pieces of the end of life (is) important. It's important to have a DNR (do not resuscitate) or to have discussed that, or to have talked through your advanced care plan. But it's also important to know what's the password to pay the electric bill. ... It's

so important to be looking ahead, and then to listen.

Most of us have not spent a lot of time imagining the end of our life. And giving your loved one the opportunity as a caregiver, to remember to be scared, to be mad, process through those emotions. That can be really important. I think it's an important thing to remind our caregivers that you don't have to know the right answer. There isn't a right answer. It's an awful situation. And it's OK not to know and it's OK to ask for help.

Q: What is your biggest piece of advice for those who might be near their end of life or are mourning the death of a loved one?

A: Find peace where you can. For some folks, that's talking to a therapist (or) that's talking to their spiritual leader, for others it's sitting or walking down memory lane, sometimes it's watching movies — whatever that happens to be, find the peace. Whether it's wonderful, whether it's awful, whether that's both of those extremes in the same five minutes, it's OK (to feel that). And to know that you're not alone. You are not the first person to walk through the process of dying. Oftentimes our caregivers will talk about anticipatory grief: "I'm so sad. But my loved one is still here." And you know, it's OK. I would encourage people to call Cancer Hope Network and get connected to somebody to talk to. There are so many wonderful community groups, so many professionals. Talk to somebody. 



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new



Clinical Trial CORNER



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