

IMMUNOTHERAPY cure[®]

Cancer Updates, Research & Education[®]

INTRALESIONAL
THERAPIES HELP

BRIDGE

THE GAP BETWEEN
IMPROVED RESULTS AND
LESS TOXICITY

First immunotherapy, intralesional therapy, is making a comeback and producing durable remissions for a subgroup of patients with cancer.

BiTE THERAPY

With Rybrevant recently approved by the FDA, CURE[®] looks further into bispecific antibodies as an emerging therapy.

SIDE EFFECT MANAGEMENT

Learn how to recognize the signs of potential side effects.

CANCER VACCINES

Dive into the most up-to-date research behind the therapy.

INSURANCE COSTS

About 20 million more patients could get their cancer treatments covered thanks to these tips from an expert.

EMERGING THERAPIES

An expansion of T-cell immunotherapy options is on the horizon, says an expert.

LUNG CANCER ADVANCES

A new combo regimen reduces the number of toxic treatments in non-small cell lung cancer.



The potential to celebrate more of life's everyday moments.

Living longer could start with LIBTAYO.

LIBTAYO will not work for everyone.

What is LIBTAYO?

LIBTAYO (Lib-TIE-oh) 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.

Patient portrayal.

Important Safety Information

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

LIBTAYO is a medicine that may treat certain 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 worsening signs or symptoms, including:

- **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:** headache 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, or 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, or loss of appetite
- **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, 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.

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- severe stomach-area (abdomen) pain or tenderness

Liver problems.

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- 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
- genital area
- fever or flu-like symptoms
- swollen lymph nodes

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- chest pain, irregular heartbeat, shortness of breath or swelling of ankles
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- 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

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

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Continued on following page

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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

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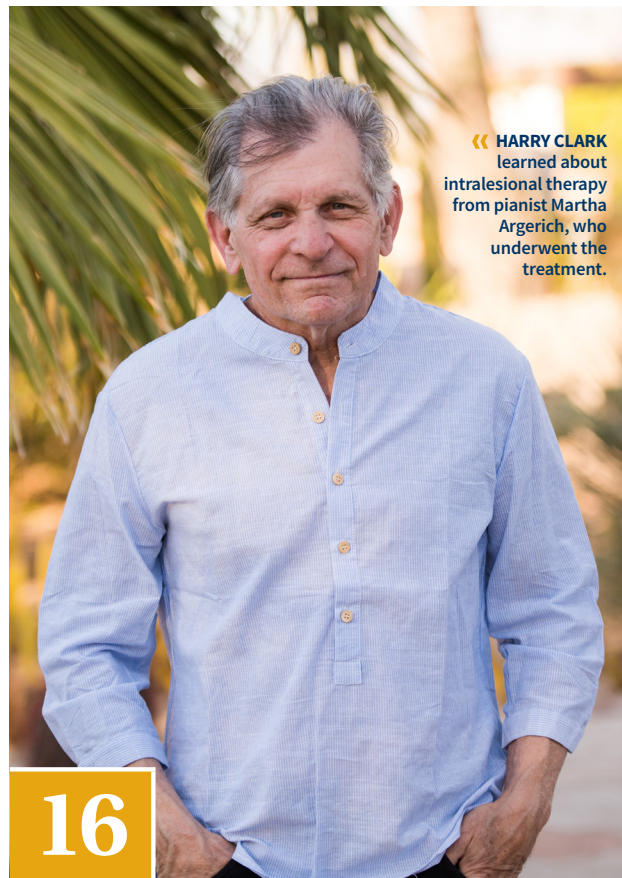
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BiTE therapy could lead to better ways to target the immune system, while minimizing the chance of resistance.



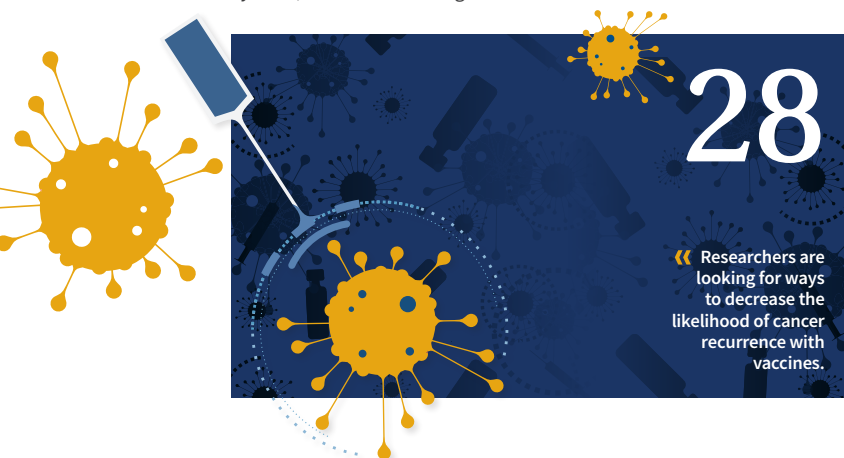
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The Impact of Immunotherapy

FROM IMMUNE CHECKPOINT inhibitors and T-cell therapies to cancer vaccines, immunotherapy is a strong pillar in the treatment of cancer. And thanks to ongoing research and clinical trials, it seems that there are always new immunotherapies emerging — all with the goal of eliminating or reducing cancer from the body. In this special issue of *CURE*®, we dive into many of the latest updates on some of these treatments as well as new and upcoming regimens that are making differences in the lives of patients with cancer.

BiTE therapy, for example, is an emerging treatment in this space that wages a two-pronged attack on tumors via bispecific antibodies. For our feature on BiTE therapy, we spoke with a patient who received a diagnosis of high-risk multiple myeloma. After he underwent years of chemotherapy and Venclexta (venetoclax), his cancer returned. It was then that he

“Thanks to ongoing research and clinical trials, it seems that there are always new immunotherapies emerging.”

qualified for a clinical trial of teclistamab, an investigational bispecific antibody drug in the field. His cancer load dropped 99% after one dose.

As new therapies emerge, old ones are also making a comeback, one of which is intralesional therapy. Considered the first immunotherapy, intralesional therapy teaches the immune system to kill cancerous tumors

throughout the body. We spoke with one patient with melanoma who found this treatment option through music. His wife, who was a fan of pianist Martha Argerich, knew that the musician had received a diagnosis of stage 4 melanoma that spread to her lungs, and had undergone intralesional therapy at John Wayne Cancer Institute in Santa Monica, California. After reaching out to the same cancer center, the patient was treated with the therapy and now credits it with saving his life. He was even inspired to create a musical composition. Both patient experiences show how big a role immunotherapy can play in treating cancer.

Although immunotherapy can greatly affect patients' lives, one of the most common worries involves finances. In this issue, we also speak with an expert about tips for how to approach costs of treatments — even if you've been denied coverage by your insurance. You'll also see an article on the side effects of immunotherapy, symptoms to look out for and the steps to take if you start to develop them. Regarding the future of immunotherapy, we've also spoken with experts on the newest updates in T cells, cancer vaccines and combination therapies. 

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

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Side Effects of Immunotherapy Now Include Interstitial Lung Disease

A PATIENT MAY WALK into the emergency room with a complaint of shortness of breath and dry cough. It could be one of many problems, but these are two main signs of interstitial lung disease. Also referred to as ILD or pneumonitis, the disease is a lung condition that affects as many as 100,000 people in the United States, according to Cedars-Sinai in Los



Angeles. The general mechanism of ILD is inflammation, yet in the majority of these cases, it is not clear what causes the inflammation in the first place, whereas in others, it can be due to specific types of infections. In a time of new cancer therapeutics, however, one particular reason is immunotherapy. Patients with cancer

who are treated with checkpoint inhibitors or immunotherapy, along with other treatments, run the risk of developing ILD as a side effect. Because of this, it is of the utmost importance that they be aware of the symptoms and side effects.

In this issue of *CURE*®, we speak with three experts on the development of ILD as a side effect of immunotherapy. Regarding this relatively new concept (reported cases of lung distress associated with immunotherapy started coming in around 2017), one expert noted that 2.5% or 3% of patients on immunotherapy develop ILD, and that there is still a lot to learn about the topic. She also spoke on the importance of catching the disease early in order to stop its progression. Another expert said it's not a huge surprise that ILD is a side effect since it tends to be a risk to those with autoimmune disease, the common denominator being an overactive immune system that can cause inflammation in normal tissue.

On the topic of the awareness of side effects, you'll find an article detailing what to keep an eye out for when going through cancer treatment, as well as the best steps to take. Some of the therapies used for this situation are also discussed. 



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is proud to be partners with a number of leading advocacy groups across the country, giving them national reach and visibility for their cutting-edge initiatives, programs, content, research and thought leadership.





Who is your **Lung Cancer Hero?** Tell us their story today!

CURE® is now accepting nominations for the 2021 Lung Cancer Heroes® awards! 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 June 30, 2021
curetoday.com/LCH21

Save the date!

The selected heroes along with their nominators, will be interviewed by CURE® and honored at a special reception to be held on Thursday, October 28, 2021. Stay tuned for more information about the celebration, which will kick off Lung Cancer Awareness Month in November.

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ONCOLOGY



Standing FIRM

To avoid the financial burden of costly therapies, patients with cancer receiving immunotherapy treatments should talk with their health care team and not settle for no as an answer from their health insurance provider, according to an expert. By ANTONIA DEPACE

EVEN WITH HEALTH INSURANCE, immunotherapy — along with many other treatments — can be expensive for patients with cancer. In fact, many immunotherapies cost more than \$100,000 a year per patient. Moreover, researchers recently estimated that the cost of oral prescription treatments for cancer will reach \$25 billion by 2030.



JOANNA FAWZY
MORALES, ESQ.

However, there are steps patients can take to avoid a financial crisis as much as possible, according to Joanna Fawzy Morales, Esq., cancer rights attorney and CEO of Triage Cancer. CURE® recently spoke with Morales about these steps, as well as what other programs may help to alleviate costs.

Q: What are some options that patients can look into when it comes to paying for immunotherapy?

A: Whenever a patient is considering (a) particular treatment, it's incredibly important for them to talk with their health care team if they have concerns about what it's going to cost them. What someone might pay for immunotherapy greatly depends on what type of insurance they have, and how adequate that insurance is. Many people choose their health insurance policy by the monthly premium without understanding the out-of-pocket maximum on a policy, and that's actually one of the most important things to look at

when buying a health insurance. We actually think that one of the primary ways that people can reduce financial toxicity is by having adequate health insurance where they've made a conscious choice to pick a plan with the lower out-of-pocket maximum. If you have an out-of-pocket maximum that's \$6,000 a year — some employer plans go up to \$20,000 a year — that's a huge burden for patients to pay out of pocket — especially for a higherpriced treatment, which can include some of the newer medicines like immunotherapies.

We want to try to help people address the immediate need for out-of-pocket costs, but we also want to try to help them moving forward. If they're in a position where they can



change plans and actually lower their out-of-pocket, at least we can help address the ongoing financial burden and then just help people address the current cost that they have. Talking with the health care team is going to be very important to address those costs because they might have suggestions on how they can help lower (them). One of those could be talking with the pharmaceutical company that makes that particular drug. There are copay assistance programs that those companies offer to patients to help reduce the copays and other out-of-pocket costs that someone might be experiencing. There are also private foundations and organizations that have financial assistance programs to address those costs.

Q: Are there any private foundations you can highlight here?

A: Patients can look specifically at cancer-related organizations that are specific to a type of cancer. For example, if you have leukemia or lymphoma, you can look at the Leukemia & Lymphoma Society for their assistance programs. Then, there are organizations that are not disease specific. They include the PAN Foundation or the HealthWell Foundation, which provide different

“What someone might pay for immunotherapy greatly depends on what type of insurance they have and how adequate that insurance is. – JOANNA FAWZY MORALES, ESQ.”

types of financial assistance to help offset those out-of-pocket costs.

Q: What are the top three pieces of advice you can give to patients?

A: I would say the first thing is to talk with your health care team; express your concern about what it's going to cost and see if they have suggestions on how to address those financial expenses. The second is to reach out if you need help paying for the bills, because there is help available, but you have to seek it out. You have to actually ask for the help. The third is if you get denied because your health insurance plan refuses to cover your immunotherapy, you should appeal that decision. I often talk about the appeals process as the best-kept secret of our health care system, because most people take no for an answer, and unfortunately, that places a huge burden on patients.

We know that about 42 million claims were denied in 2019, and only 0.02% of those claims were actually appealed. So that's about 200,000 claims out of 42 million, but we know that when people go through the appeals process and get external appeals, about 50% of the time, across the country, patients are winning those appeals and getting their care covered by their insurance company. Fifty percent of these 42 million claims is about 20 million people who could have gotten their care covered by their insurance company, which means that about 20 million people either paid for care out of pocket that their insurance company should have paid for, which obviously contributes to the financial burden, or they just didn't get the care because they couldn't afford to. That's really tragic — that people aren't getting access to the care that their health care team prescribed, and they don't know their rights to appeal. 

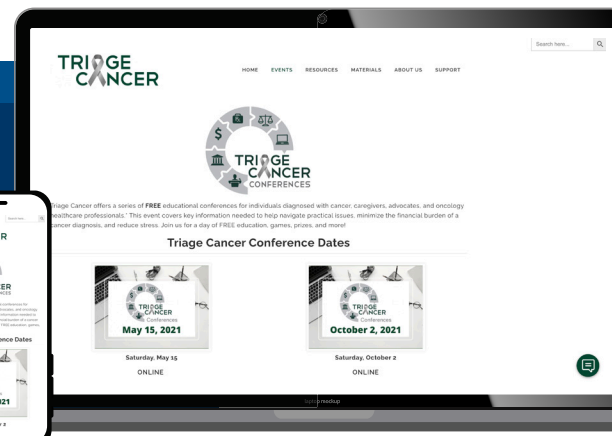


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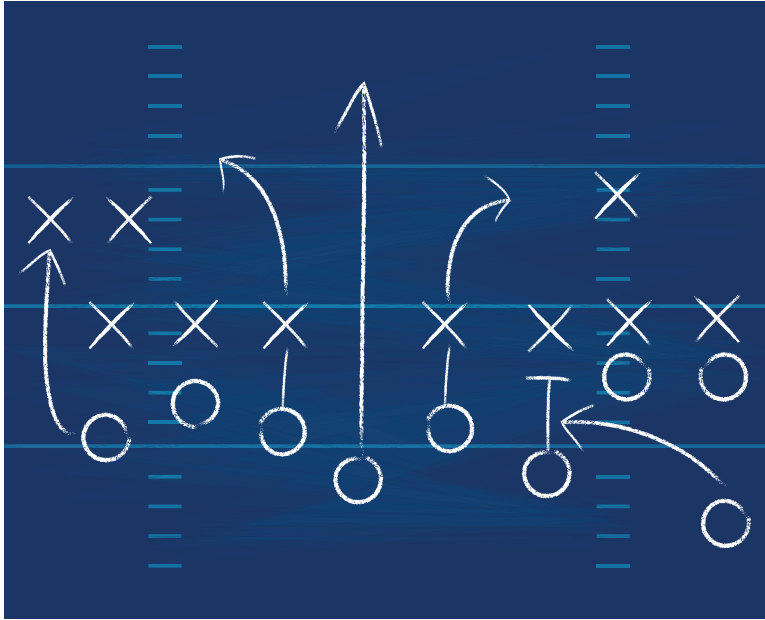


Learn more about managing finances after a cancer diagnosis during Triage Cancer's free, educational conference October 2.

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side EFFECTS



ACT FAST

Experts urge patients to stop playing the wait-and-see game: There's no 'playbook' for immunotherapy-related toxicities, and side effects can be managed if caught early.

By ANTONIA DEPACE

ADVANCEMENTS IN THE IMMUNE checkpoint inhibitor space have given some patients a new treatment option for cancer outside traditional chemotherapy or surgery options. Currently, there are seven inhibitors approved by the Food and Drug Administration: Yervoy (ipilimumab), Tecentriq (atezolizumab), Bavencio (avelumab), Libtayo (cemiplimab-rwlc), Imfinzi (durvalumab), Opdivo (nivolumab) and Keytruda (pembrolizumab). With these immunotherapies, however, come the possibility of side effects, and according to experts, it's of the utmost importance that patients are aware of them.

SIDE EFFECTS & SYMPTOMS TO LOOK OUT FOR

● BRAIN INFLAMMATION

Confusion, fever, mood/behavior changes, extreme light sensitivity, seizures, neck stiffness

● EYE PROBLEMS

Blurry or double vision, other vision problems, eye pain or redness

● HEART PROBLEMS

Inflammation of heart muscle, irregular heartbeat

● HORMONE GLAND PROBLEMS

Extreme tiredness, weight loss/gain, constant headaches, hair loss, sweating, rapid heartbeat, dizziness/fainting, constipation

● LIVER PROBLEMS

Yellowing of skin or whites of eyes, severe nausea or vomiting, pain on right side of stomach, dark urine, bleeding or bruising more than usual

● LUNG PROBLEMS

Shortness of breath, new/worsening cough

● SKIN PROBLEMS

Rash, redness, immunotherapy-related dermatitis

● INTESTINAL PROBLEMS

Diarrhea, more bowel movements than usual, stools with blood, darker stools, tarry stools, sticky stools, severe pain in stomach area

● KIDNEY PROBLEMS

Blood in urine, decreased amount of urine

● JOINT OR MUSCLE PROBLEMS

Severe or persistent muscle or joint pain, severe muscle weakness

● NERVE PROBLEMS

Numbness or tingling in hands or feet; unusual weakness in legs, arms or face

*This information was gathered from the National Comprehensive Cancer Network "Understanding Immunotherapy Side Effects" infographic.

Mild side effects can occur in 30% to 50% of patients, whereas serious side effects occur in less than 5%, according to the National Comprehensive Cancer Network. “Typically, I frame it such as that unlike chemotherapy, which is a poison to both good and bad cells, the immunotherapy is working to boost the patient’s own immune system to detect and get rid of the cancer cells,” said Bobbie Khan, a clinical nurse coordinator at Georgetown Lombardi Comprehensive Cancer Center and MedStar Georgetown University Hospital in Washington, D.C., on educating patients. Sometimes, Khan explained, the immune system is pushed into hyperdrive and begins to attack healthy organs and tissues. This often leads to inflammation in normal tissue including organs that can lead to the side effects and toxicities of immunotherapy.

Side effects can include encephalitis (brain inflammation), hormone gland problems (such as thyroid abnormalities), pneumonitis (lung inflammation), kidney inflammation, skin irritations or rashes, colitis (large bowel inflammation), hepatitis (liver inflammation), nerve problems, eye problems, and myocarditis or arrhythmia (heart problems). Symptoms of these side effects can show up as fever, yellowing of the skin, diarrhea, shortness of breath, worsening cough and muscle weakness, among others. Most of the side effects can be reversed by specific treatments.

“Very rarely, (immunotherapy) can cause very devastating side effects that are refractory to treatment, such as inflammation in the brain,” noted Dr. Aiwu Ruth He, an associate professor of medicine at Georgetown Lombardi Comprehensive Cancer Center and Georgetown University Medical Center. Although most side effects are sudden and resolved in a matter of days to weeks with or without treatment, toxicities can last for months or years.

According to Khan, who works on He’s team, the most important step for

WHAT TO IN CASE SIDE EFFECTS OCCUR

- 1** Create a list of medications and make sure caregivers know where to find it.
- 2** Have the oncologist’s emergency contact and daytime number programmed or accessible, and ensure physicians’ offices have correct patient information on file.
- 3** Report any changes, even those not on a list of common side effects, quickly. Don’t wait to see if symptoms go away.

patients — besides recognizing their symptoms — is to call their oncologist on first notice. If patients don’t call right away, it can “create a cascade of effects in the body that are difficult to control once the dominoes start falling,” she emphasized. Another important point to recognize is that side effects can show up during or after immunotherapy and most often occur further into treatment.

Dr. Patrick Ott, clinical director of the Melanoma Center at Dana-Farber Cancer Institute and associate professor of medicine at Harvard Medical School in Boston, said he’s seen patients develop toxicities after being on immunotherapy for over a year. “It would be unusual if a patient starts immunotherapy and then after a couple of days or even after a week or two, they’re already having the toxicities,” he explained. “More commonly, they are on the treatment for four or

five, six weeks, and then that’s when the onset of these toxicities occurs. Sometimes it could be many months into the treatment.”

Ott says side effects often affect only one system, but not always. “There’s no playbook,” he said.

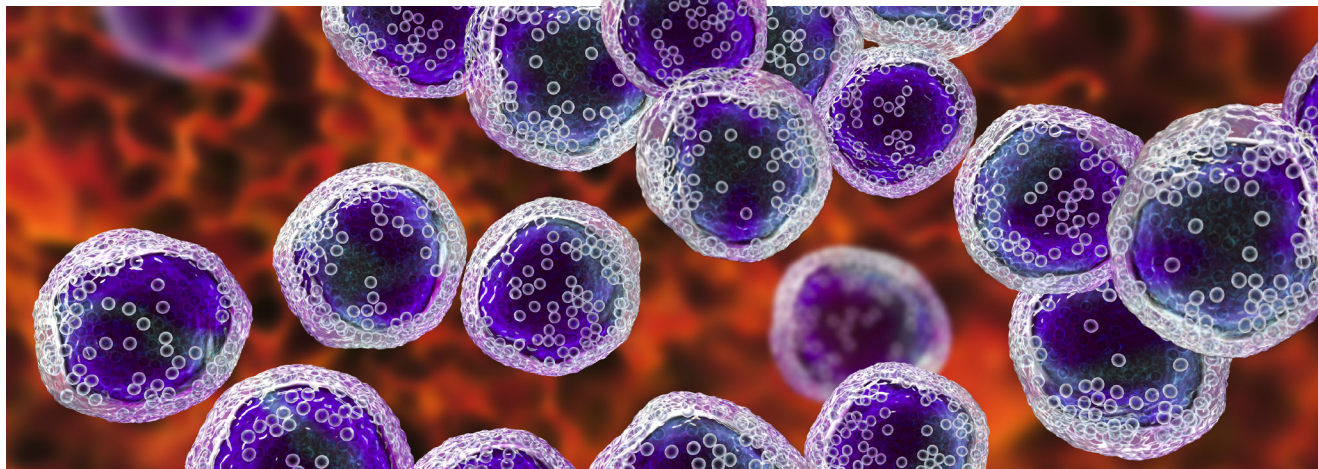
Treating Side Effects and Toxicities of Immunotherapy

Treatment of side effects and toxicities often requires immunosuppressive drugs such as corticosteroids. Sometimes additional steroids or combination therapies are needed, depending on the severity of the side effect. In order to treat the side effects, patients have to take a pause from their immunotherapy treatment, which may cause worry about how that will affect outcomes. “When we give corticosteroids, it actually does not seem to impact the efficacy of the treatments,” Ott explained. “We have many patients who have their treatment stopped or held because of the toxicity, but the cancer actually still continues to respond, even off treatment.”

Ott noted that tinkering with doses has been shown to make a difference, particularly when checkpoint inhibitors are used in combination, such as Yervoy and Opdivo. For example, lowering the dose of Yervoy made the combination less toxic, particularly in lung cancer, where the doses commonly used in melanoma could not be tolerated. “Yervoy and its dosing made a pretty fundamental impact on the toxicity,” he said.

In instances where a side effect doesn’t respond to an immunosuppressant, He said she will often perform a biopsy to see if there are specific immune cells that a different immunosuppressant can target. “Normally, we don’t do it unless we are really puzzled about what has caused (the side effect) or it has not responded to the initial intervention,” He noted. ■

compiled by DARLENE DOBKOWSKI, MA



Progression-Free Survival of Five Years Is Possible for Patients With Mantle Cell Lymphoma

A high-intensity, first-line immunochemotherapy with maintenance therapy led to high response rates and long-term remissions.

PATIENTS WITH MANTLE CELL LYMPHOMA (MCL)

who were treated with first-line immunochemotherapy followed by maintenance therapy demonstrated promising responses, with improved survival outcomes, according to a study published in the *American Journal of Hematology*. The treatment consisted of first-line immunochemotherapy followed by maintenance therapy.

“Majority (of patients) achieved (complete response) after initial two cycles, paving the way for shorter immunotherapy induction,” the study authors wrote. “Several patients (16%) have been in remission for more than 10 years, and no new long-term toxicities were observed.”

Researchers assessed this immunochemotherapy regimen in 44 patients with untreated mantle cell lymphoma. After treatment, 22 patients received maintenance therapy with Thalomid (thalidomide), whereas the other 22 patients received maintenance therapy with Rituxan (rituximab). The immunochemotherapy regimen consisted of methotrexate, Lipodox (doxorubicin), cyclophosphamide, vincristine, ifosfamide, cytarabine and etoposide, according to the study.

Several factors were assessed during follow-up, including progression-free survival (time from treatment

initiation to disease progression, disease relapse, or all-cause death), overall survival (duration of time when a patient is still alive after starting treatment) and safety. Follow-up times ranged from less than one month to 16 years, for a median of 7.2 years.

Most patients in the study (93.2%) achieved a complete response, during which all signs of cancer disappear as a response to treatment. In addition, 4.5% of patients achieved a partial response and 2.3% of patients did not have their treatment responses assessed.

Five-year progression-free survival was achieved in 55.6% of patients, with a median progression-free survival of 7.9 years. Overall survival at five years was 83.3%, and median overall survival was not reached, meaning that survival among the study population was greater than 50%.

Researchers also assessed responses of six patients with a blastic variant, or a very aggressive form of the disease. These patients had a five-year progression-free survival rate of 20.8% and a five-year overall survival rate of 60%.

“Importantly, this regimen shows promising efficacy in patients with blastic (MCL), a subgroup associated with very poor survival,” the study authors concluded. ■

Improving Overall Survival in Melanoma Brain Metastasis

FDA approval of immunotherapies and BRAF/MEK inhibitors may have affected overall survival, with a six-month gain between 2010 and 2014 and 2015 and 2019.

PATIENTS WITH MELANOMA BRAIN metastasis (when cancer spreads to the brain) have had improved prognosis over the past five years, which may be due to the Food and Drug Administration (FDA) approval of several immunotherapies and BRAF/MEK inhibitors, according to results in *Cancer*.

Melanoma accounts for 6% to 12% of all metastatic brain tumors, and survival after this diagnosis has historically been poor, as overall survival was between four months and six months, according to the study. Over the past decade, the FDA has approved immunotherapies in the form of checkpoint inhibitors including Opdivo (nivolumab), Yervoy (ipilimumab) and Keytruda (pembrolizumab), in addition to targeted therapies such as BRAF and MEK inhibitors — such as Zelboraf (vemurafenib) and Tafinlar (dabrafenib) — which target these specific mutations that can fuel cancer growth in melanoma.

In the current study, researchers analyzed data from 425 patients (mean age, 59 years; 72% were men) with melanoma brain metastases who were treated at Memorial Sloan Kettering Cancer Center between 2010 and 2019. These patients represented a total of 2,488 brain metastases.

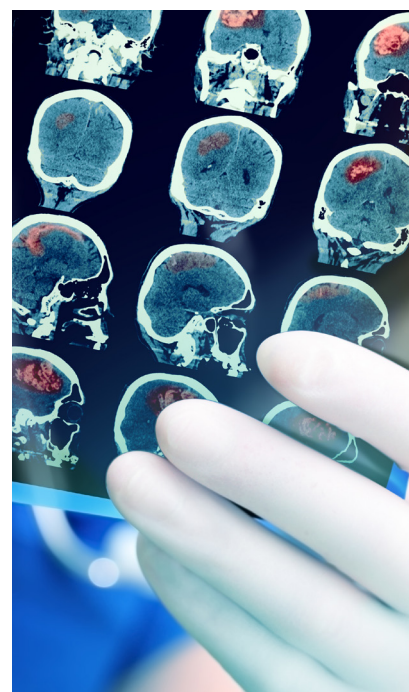
The median overall survival from when patients received a diagnosis of melanoma brain metastasis was

8.9 months. Patients who received a diagnosis of a melanoma brain metastasis between 2015 and 2019 had longer overall survival than those who received a diagnosis between 2010 and 2014 (13 months versus 7 months).

Researchers determined that several factors shortened overall survival, including the increasing number of brain metastases at diagnosis, leptomeningeal dissemination (a particular pattern of metastasis), higher serum levels of lactate dehydrogenase (an enzyme that converts sugar into energy), earlier melanoma brain metastasis diagnosis, presence of extracranial disease (cancer outside of the skull) and receiving immunotherapy before a diagnosis of melanoma brain metastasis.

The use of different central nervous system-directed treatments, which did not include the recently FDA-approved therapies, was linked with diagnosis year, presenting symptoms, the size of brain metastasis, the number of brain metastases and the presence of cancer outside the skull.

Patients who underwent craniotomy, a procedure in which a small part of the skull is removed to allow a surgeon to remove the brain tumor, were found to have improved survival compared with those who did not undergo the surgery.



“The number of (brain metastases) at diagnosis, the systemic disease burden and the presence of (leptomeningeal disease) are important prognostic indicators and can guide patient counseling,” the study authors wrote. “As treatment paradigms continue to evolve, both (central nervous system)-directed and systemic trials should be open to and accruing patients with (melanoma brain metastasis) to understand treatment efficacy in this morbid, difficult-to-treat and increasingly prevalent disease stage and to continue improving their prognosis.”

INTRAVESICAL THERAPIES HELP

BRIDGE

An illustration of two male scientists in white lab coats and dark trousers standing on a dark blue bridge structure. They are holding up large, orange, 3D block letters that spell out 'BRIDGE'. The letters are positioned as if they are part of the bridge's deck. In the background, there is a light blue sky and a stylized suspension bridge with white cables and a teal base.

THE GAP BETWEEN
IMPROVED RESULTS
AND LESS TOXICITY

First immunotherapy, intralesional therapy, is making a comeback and producing durable remissions for a subgroup of patients with cancer.

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

In 2011, when Harry Clark was 60 years old, he noticed a mole on his right shin. Even though he grew up under the hot Tucson, Arizona, sun and jokes that he lost his dark bronze tan every November, Clark didn't think much about the dime-sized, dark red spot — and he'd never seen a dermatologist.

"It wasn't causing any discomfort and it didn't grow or change shape," he says. "When I asked my primary care doctor to take a look, he said it was nothing to worry about." Two years later, his new primary care provider saw the mole and immediately sent him for a biopsy.

A talented musician, Clark soon discovered he had melanoma, a disease that strikes over 100,000 Americans each year. Surgeons cut out the diseased skin on his shin. But his stage of melanoma required additional treatment. Clark endured 32 radiation treatments. Then he went through isolated limb infusion, in which doctors isolate the limb from the rest of the body with a tourniquet and then flood the area with heated blood and high-dose chemotherapy. "The treatment is so toxic, you have to be hospitalized," Clark says. »



» **HARRY CLARK** endured isolated limb infusion before he was a candidate for intralesional therapy.

XXX / STOCKADOB.COM; CLARK BY MELISSA HOLLAND



CLARK

traveled weekly to California from Arizona to receive therapy.

Throughout Clark's treatment for advanced stage 3 melanoma, new lesions continued forming. Clark's wife, fellow musician Sanda Schuldmann, thought there might be a solution. A fan of the pianist Martha Argerich, Schuldmann knew that Argerich had received a diagnosis of stage 4 melanoma that had spread to her lungs decades before. She also knew that doctors at John Wayne Cancer Institute in Santa Monica, California, had treated Argerich with something called intralesional therapy.

With intralesional therapies, doctors administer treatment by needle injection directly to the tumor to jump-start the immune system and possibly obliterate cancerous tumors throughout the body. The late Dr. Donald Morton was among the first to repurpose the anti-tuberculosis drug bacillus Calmette-Guerin (BCG) as a first-line intralesional therapy for late-stage melanoma, publishing astonishing results in *Annals of Surgery* in 1974. In the study of 151 patients, Morton and his colleagues found that directly injecting BCG into metastatic melanoma lesions limited to the skin produced a 90% regression of injected lesions and a 17% regression of

lesions that were left untouched. What's more, one-quarter of these patients remained disease free for one to six years. Since BCG is still not Food and Drug Administration (FDA)-approved for the treatment of melanoma, it can be difficult to find physicians who are familiar with using it in this way.

Schuldmann reached out to John Wayne Cancer Institute, where she connected with Dr. Mark Faries, who is now a professor of surgery and co-director of the melanoma program at Cedars-Sinai The Angeles Clinic and Research Institute. Faries, who trained under Morton at the National Institutes of Health, agreed to review Clark's medical records. Within days, Clark learned he was a candidate for BCG intralesional therapy and began traveling to California weekly to receive the experimental treatments. After 15 to 20 BCG injections, Clark's lesions were gone.

Once considered an incurable disease in its advanced form, melanoma has emerged as one of the cancers most responsive to immunotherapy. Immune checkpoint inhibitors have dramatically improved outcomes for patients with late-stage melanoma, with more than half of patients on combination

Yervoy (ipilimumab)/Opdivo (nivolumab) still alive years after treatment. Unfortunately, the remaining half don't respond to treatment, and some experience debilitating side effects that force them to discontinue immunotherapy.

"Intralesional therapies can help bridge this gap by modifying the tumor microenvironment in such a way that the immune system can recognize it as foreign and attack, but without the toxicities of systemic treatment," says Dr. Lynn Schuchter, chief of the division of hematology/oncology at the Abramson Cancer Center at the University of Pennsylvania in Philadelphia. The hope is that injecting these therapies at the tumor site will train the immune system to identify cancerous cells and launch a systemic and sustainable attack. For patients like Clark with late-stage disease that hasn't metastasized to distant sites, intralesional therapy can produce durable remission.

INTRALESIONAL THERAPY EXPLAINED

Intralesional therapy is the oldest form of immunotherapy and dates back to the 1890s. In its early stages, intralesional therapy was made with neutralized, non-live bacteria and other stimulatory proteins without a clear understanding of the immune system. "More recently, we've learned why the immune system shuts down closer to the level of the tumor, and now we have drugs that can make the tumor visible to the immune system," says Dr. Genevieve Boland, surgical director of the therapeutic intralesional program at Massachusetts General Hospital in Boston.

The goal of intralesional therapies is to attract the body's killer T cells and draw them toward the tumor. In fact, one of the first approved immunotherapies for melanoma was the inflammatory cytokine interleukin-2 (IL-2) because cytokines attract T cells to tumors. Unfortunately, agents like IL-2 and BCG fell from favor because of systemic side effects and inconsistent results. Patients experienced significant toxicities ranging from anaphylaxis to changes in blood pressure and heart rate with IL-2.

"We've now learned that the immune system doesn't work the same way that other drugs work," Faries says. "There's a sweet spot for how much stimulation you need to induce the desired effect." And you can get there by using the tumor as a weapon against itself.

The idea behind intralesional therapy is to activate both innate and adaptive immunity to transform the patient's tumor into a personalized vaccine. The innate immune system is ready to roll when faced with a threat. It automatically kicks in when a person cuts a finger, develops strep throat or needs to fight off the common cold. Adaptive immune cells need to be trained and activated to fight disease.



DENIS MCGLYNN

continued to develop cancerous lesions on his scalp after being treated with the checkpoint inhibitor drug Opdivo.



"These adaptive immune cells help create the right microenvironment for the fighter T cells to come in and do their job," Boland says. And since doctors inject therapies directly into the tumor, they can deliver drugs safely and at a much higher dose than systemic drugs like checkpoint inhibitors.

USING VIRUSES TO ACTIVATE THE IMMUNE SYSTEM

Denis McGlynn of Camden-Wyoming, Delaware, received his first melanoma diagnosis in 2011 at 65 years of age. After multiple surgeries to treat the aggressive skin cancer, the married father of two and grandfather of five had his first experience with immunotherapy in June 2019. Within days of completing 13 months on Opdivo, McGlynn experienced debilitating side effects.

"I was lying on my back for five days because every joint in my body ached," recalls McGlynn. The steroid medication prednisone instantly quieted his pain temporarily. Today, he still takes 6 milligrams of prednisone daily for the autoimmune effects. »



After being treated with T-VEC, **McGLYNN's** lesions started to heal. He hasn't seen any lesions since his last treatment in October 2020.



To make matters more complicated, McGlynn continued to develop cancerous lesions on his scalp. That's when his doctor suggested he visit Penn Medicine for intralesional treatments with an agent called T-VEC (talimogene laherparepvec). "I had multiple lesions, and the T-VEC injections took only five or six seconds each," McGlynn says. "When I came back two weeks later, all of the lesions were either healing or gone."

T-VEC is a genetically engineered herpes virus that obtained FDA approval in 2015 to treat patients with stage 3 or stage 4 melanoma who have injectable lesions but who are not eligible for surgery. Intralesional T-VEC works in these cases because it's a modified virus, and research suggests viruses are among the best agents to reactivate a tumor's microenvironment.

"The immune booster is attached to the virus and the virus has the ability to enter cells. When you inject this conjugate of the herpes virus with the immune booster into a melanoma nodule, it's like raising a red flag and saying, 'hey, immune system, here I am — attack me,'" Schuchter says.

Called an "oncolytic virus" because of its ability to selectively target, infect and annihilate tumor cells, T-VEC essentially trains the immune system to identify and attack the cancer not only in the injected tumor but also all tumors susceptible to the immune response — and in some cases, it produces complete responses.

"These oncolytic viruses rupture the tumor and kill cancerous cells while simultaneously stimulating the immune system," Boland says. "We can create this superactive immune response locally, at the site of the tumor,



We can create this superactive immune response locally, at the site of the tumor, while limiting or even eliminating the toxicities associated with traditional immunotherapy.

—DR. GENEVIEVE BOLAND

while limiting or even eliminating the toxicities associated with traditional immunotherapy.”

In McGlynn’s case, the treatment was wildly successful. He hasn’t seen

a lesion reappear since his last treatment in October 2020.

Researchers are investigating other potential targets for melanoma, including other viral vectors, such as coxsackieviruses, HF-10, adenovirus, reovirus, echovirus and Newcastle disease virus. They’re also exploring another class of drugs to boost “innate immunity” — the immune system’s first responder cells that trigger T cells to kill tumors. Like viruses, these therapies activate the warning signs required for the immune system to launch an effective attack against a foreign invader. “Ideally, this sets off a strong reaction within the body that can turn an immunologically ‘cold’ tumor into a ‘hot’ one,” Boland says.

No matter which agents doctors choose, side effects of intralesional therapies tend to be minimal, particularly compared with systemic treatments. The most common

complaints relate to soreness at the injection site and mild fatigue. However, a small subgroup of patients may develop inflammatory syndromes like those doctors see with checkpoint inhibitor therapy.

INTRALESIONAL THERAPY BEYOND THE SKIN

Down the line, combination treatment with intralesional therapy and checkpoint inhibitors may even play a role in the treatment of complicated tumors, such as stomach and pancreatic cancer. “The tumor microenvironment of pancreatic cancer has a lot of fibrous tissue, so the local tumor environment acts like a shield hiding the cancer from the immune system,” Schuchter says. “Using ultrasound guidance and other techniques, doctors can inject therapy directly into the tumor to help the immune system recognize cancerous cells and destroy them.”

Unfortunately, scientists don’t know yet who is most likely to respond to treatment. They don’t know whether it’s best to use intralesional therapies as a first-line approach or a last-ditch effort.

“Even though we inject T-VEC directly into tumors, it’s still a weakened form of the herpesvirus, and that makes it potentially dangerous,” Schuchter says. “Patients also have to cover the lesions for a week, and staff

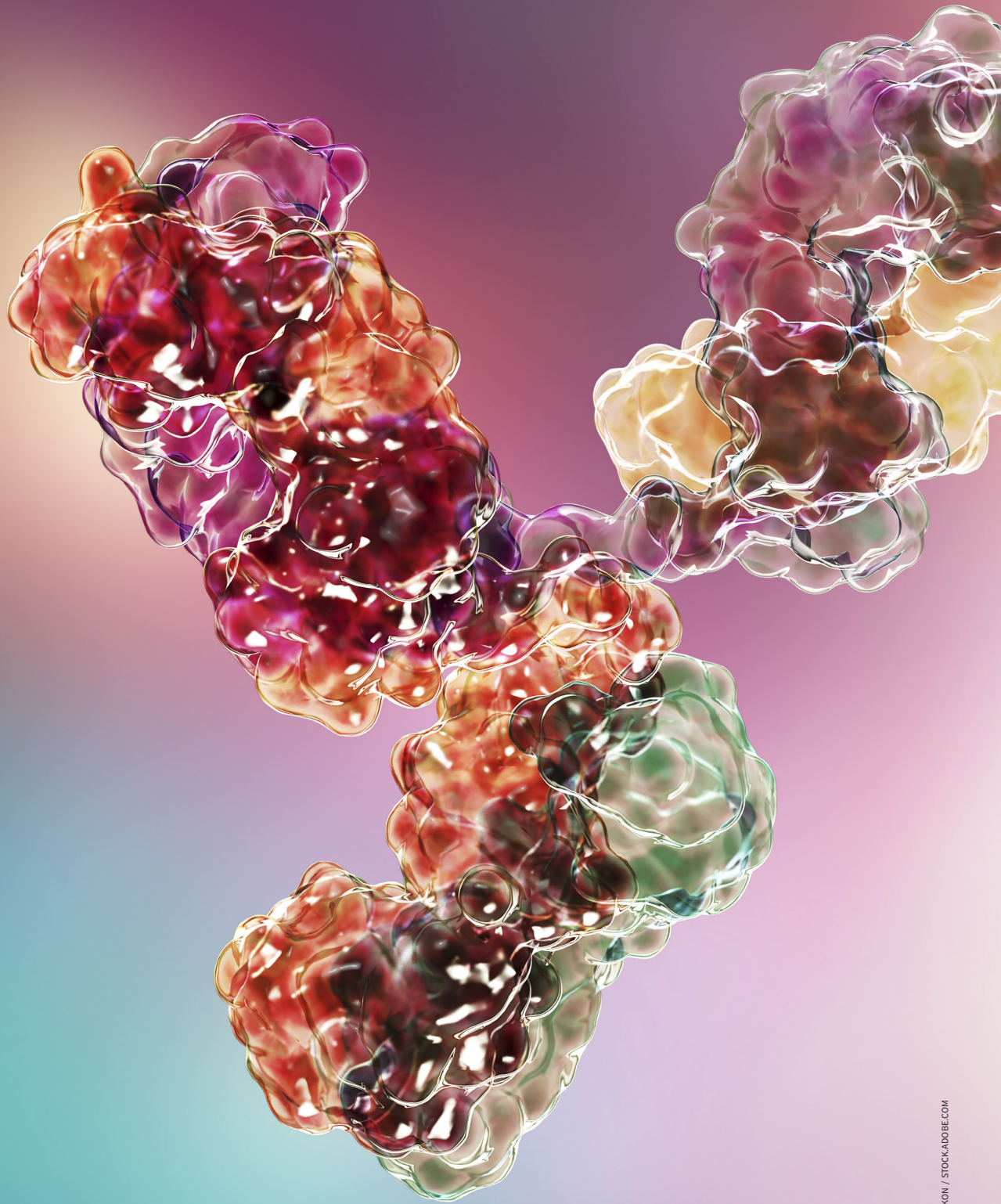
have to implement a variety of safe handling practices.”

Some clinics reserve a specific room for intralesional therapies and perform the procedure only at the end of the day. Others have strict preparation and cleaning requirements. And all intralesional therapies require consistent refrigeration. This level of preparation, time, training and logistics can be challenging or even impossible for community clinics.

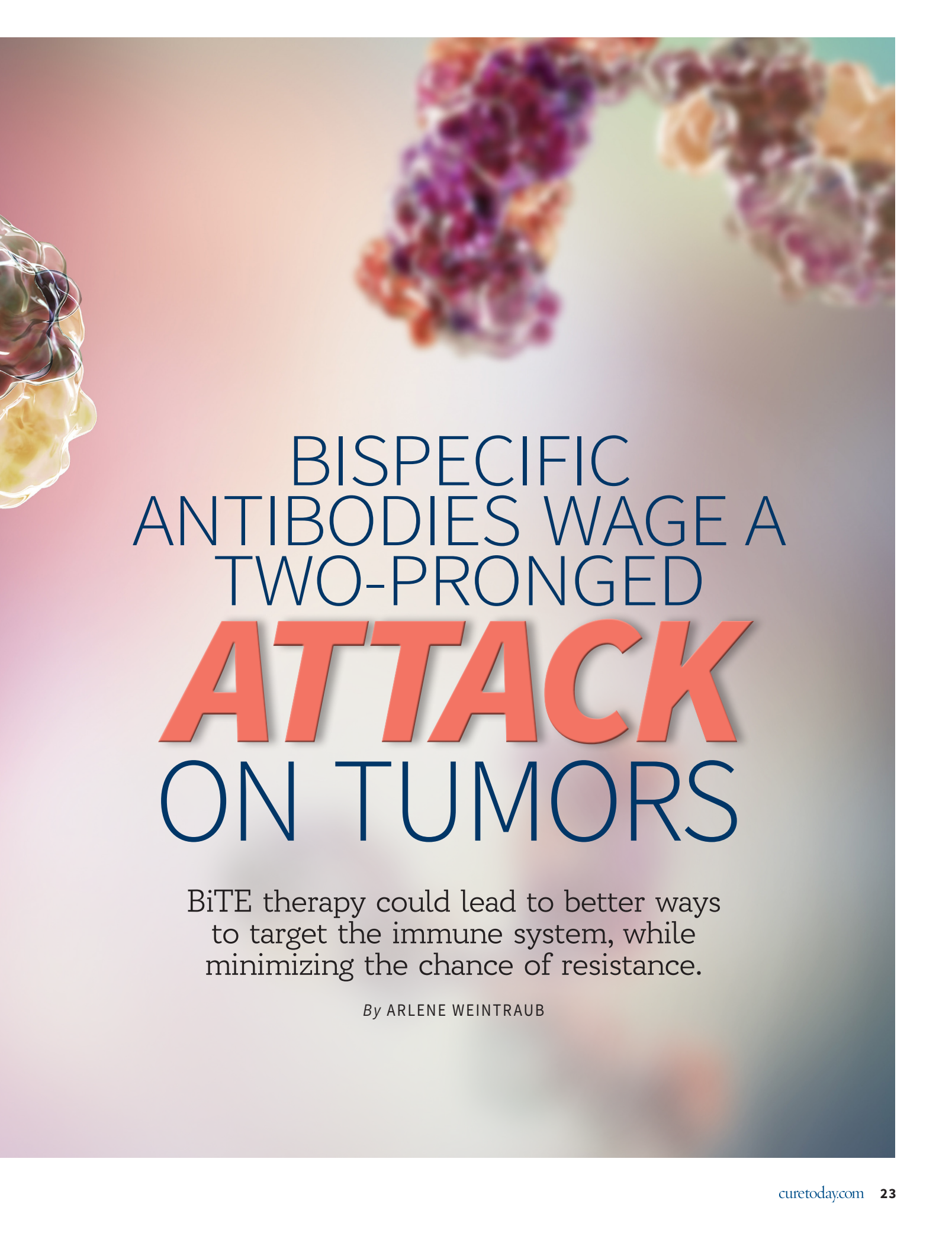
“It’s important not to overhype intralesional therapy since it’s relevant for only a small subset of patients,” Schuchter says. But when it works — and sometimes it does work — patients reclaim their lives and enjoy decades-long survival. Innovations to this type of therapy with newer drugs are entering clinical trials.

“My one wish is that more people knew that intralesional therapy is an option,” Clark says. He is so indebted to BCG — he credits the drug with saving his life — that he partnered with a musicologist friend from his Peabody Institute days to develop a musical composition using notes B, C and G for Faries. “It’s probably the first fugue for a drug,” he says. Now that’s something to sing about. ■

FEATURE BiTE therapy



KATERYNA KON / STOCKADOB.COM



BISPECIFIC ANTIBODIES WAGE A TWO-PRONGED **ATTACK** ON TUMORS

BiTE therapy could lead to better ways to target the immune system, while minimizing the chance of resistance.

By ARLENE WEINTRAUB



MICHAEL HERMAN's cancer returned after a treatment regimen of chemotherapy and the targeted drug Venclexta.



After Michael Herman received a diagnosis of high-risk multiple myeloma in 2013, he started a treatment journey that included several years of chemotherapy and the targeted drug Venclexta (venetoclax tablets), which is investigational for the disease and was designed for patients whose cancers have certain genetic abnormalities. The medicines worked well, but as is often the case with multiple myeloma, Herman's cancer eventually returned.

In July 2019, Herman qualified for a clinical trial of teclistamab, an investigational drug that's part of an emerging class of immunotherapy medicines known as bispecific antibodies. He traveled from his home in Galena, Maryland, to the University of Pennsylvania in Philadelphia to get the treatment: a weekly shot in the abdomen.

After just one dose of teclistamab, Herman's cancer load dropped 99%. His disease is no longer detectable, and the study investigators have told him he can stay on the drug

as long as it continues to be effective. In terms of side effects, Herman experiences some aches and pains, but says that it doesn't affect him from getting around.

"When I was diagnosed, I was told my life expectancy was four years," says Herman, 59, a retired corporate real estate manager. "This drug doubled that. It's a wonderful thing."

Teclistamab is one of several bispecific antibodies being developed to treat a range of cancers. Bispecific antibodies are designed to simultaneously bind two targets — a target on immune cells and another on tumor cells — pulling them together to unleash an immune attack against the cancerous cells. In the case of teclistamab, the two targets are an antigen called CD3 in the immune system's T cells, and BCMA, which is an antigen that's overexpressed in multiple myeloma.

Several other bispecific antibodies are under development to treat blood cancers and a wide range of solid tumor types, including cervical, gastric, brain and liver.



➤ **MICHAEL HERMAN** and his wife, **ANGELA HERMAN**.

“The idea behind combination immune therapies, which include bispecific antibodies, is to find ways to better target the immune system from the get-go, to minimize the chance

of resistance or improve the chance of getting a good response,” says Dr. Deborah Wong, an oncologist at UCLA.

The first, and so far only, bispecific antibody on the market, Blincyto (blinatumomab), is approved by the Food and Drug Administration (FDA) to treat some patients with acute lymphoblastic leukemia (ALL). The drug, referred to as a bispecific T-cell engager (also referred to as BiTE), has one arm that attaches to CD3 and a second that binds to the antigen CD19 on the surface of cancerous B cells.

In a trial of patients with relapsed or resistant B-cell precursor ALL, Blincyto increased the rate of complete remissions from 20% among patients on standard-of-care chemotherapy to 42%. In a pediatric study released in March 2021, 69% of children treated with Blincyto were still alive after nearly two years, and 93% showed no sign of disease. In a phase 2 study released in May 2021, there was a 95% response rate among patients with Philadelphia chromosome-positive ALL who received Blincyto plus the targeted drug Iclusig (ponatinib), showing the potential of treating patients without the need for chemotherapy, the researchers said.

Bispecific antibodies can cause side effects, including cytokine release syndrome, a severe inflammatory response marked by high fever, body aches and other symptoms. Although Herman experienced cytokine release after his first shot of teclistamab, he has had minimal side effects since then.

BROADENING THE REACH OF IMMUNOTHERAPY

Bispecific antibodies could bring immunotherapy options to patients who aren't eligible for treatments like CAR T cells, which are personalized therapies that entail removing immune cells from patients and engineering them to recognize and attack their cancer. Although these T-cell therapies can be lifesaving, they present challenges that could be avoided with bispecific antibodies, says Dr. Joshua Richter, assistant professor of medicine, hematology and medical oncology at the Icahn School of Medicine at Mount Sinai in New York.

“CAR-Ts are not off-the-shelf products, so they take time for manufacturing, whereas bispecifics are off the shelf,” Richter says. And even though there is a risk of side effects with bispecific antibodies, they are titratable, meaning they can be given in small doses to start and then in larger doses after the immune system is given a chance to adapt. “We are concerned about giving CAR-Ts to older people because some can get quite sick (from cytokine release),” Richter says. “It's nice to have a more titratable alternative.” »

It wasn't until 2019,
six years after his
diagnosis, that **HERMAN**
qualified for a clinical
trial of teclistamab.



Several bispecific antibodies aimed at multiple myeloma are in clinical trials now, some of which are showing early promise. In a phase 1 dose-ranging study of an intravenous formulation of teclistamab, for example, 58% of patients on the recommended dose for phase 2 trials showed a partial response and 30% had a complete response. Although 70% of participants experienced cytokine release, none had symptoms severe enough to prompt them to pull out of the trial. Other side effects included anemia, a drop in white blood cells and fatigue. A phase 2 study of the drug in multiple myeloma is ongoing and recruiting patients.

Another trial of a BCMA-CD3-targeted bispecific antibody, elranatamab, was paused in May because of cases of peripheral neuropathy reported by some patients. The drug's developer, Pfizer, was asked to investigate the cases and report what it finds to the FDA. Patients in the trial who were benefiting from the drug were able to stay on it, but no new patients will be accepted until the investigation is complete.

There are other promising approaches to multiple myeloma in early-stage testing, Richter says, including a

bispecific antibody called cevostamab, which targets CD3 and FcRH5, an antigen expressed on the surface of almost all multiple myeloma cells. Interim results from an ongoing phase 1 study that were reported in December showed an overall response rate of 53%. Responses were even seen in patients who had failed five previous treatments.

Another prospect in multiple myeloma is a bispecific antibody called GBR1342, which targets CD3 and CD38, an antigen implicated in the disease and other blood cancers. The drug, now in phase 1 testing, received orphan drug designation from the FDA in 2019, which could expedite its development path.

There are several bispecific antibodies in development to treat other blood cancers, including acute myeloid leukemia (AML). For example, a drug called flotetuzumab targets CD3 and CD123, a molecule called an interleukin-3 receptor that's prevalent on malignant cells in AML. In a trial of the drug in patients who had relapsed after other therapies, 32% of participants achieved a response, and more than half of those were able to go on to receive stem cell transplants, which put them in remission.

The flotetuzumab trial results highlighted another potential advantage of bispecific antibodies, which is that they may offer patients a bridge to other treatments that could result in more durable remissions, such as stem cell transplants. The ALL treatment Blincyto has also been shown to offer some patients a good lead-in to stem cell transplants. In a trial comparing the drug to standard-of-care chemotherapy, the overall response rate to Blincyto was 44%, and 24% of the patients receiving the drug went on to have stem cell transplants.

Oncologists at The University of Texas MD Anderson Cancer Center in Houston are now testing Blincyto in patients with newly diagnosed ALL, and there are encouraging early results. Last year, researchers reported results from a small trial in which patients with ALL started with four cycles of chemotherapy and then were placed on maintenance treatments that included Blincyto. There was a 100% response rate, and 79% of patients stayed in remission for two years.

“Historically, we can cure about 40% to 50% of elderly patients with ALL, so if this response rate holds over time, it will be a tremendous improvement, essentially doubling survival rates,” said Dr. Marina Konopleva, a professor and physician-scientist in the department of leukemia and stem cell transplantation at MD Anderson.

Phil Briggs, who received a diagnosis of ALL in January 2018, was treated with Blincyto in the fall of 2020, after his cancer stopped responding to standard-of-care chemotherapy. He found the drug to be far more tolerable than chemotherapy, which had caused him to lose his appetite and drop more than 50 pounds, in addition to developing peripheral nerve damage. Aside from a slight skin irritation, “I felt fantastic,” says Briggs, 62, who is being treated at MD Anderson.

Briggs’ courses of Blincyto came in a portable pump, allowing him to receive the agent on an outpatient basis without having to go to the hospital. After four months on the drug, he was able to undergo a stem cell transplant and is now in remission. “I felt so much better that I was able to go straight from (Blincyto) to the stem cell transplant without any side effects,” says Briggs, who is now planning to go back to work as an insurance salesman.

BRINGING BISPECIFICS TO SOLID TUMORS

Targeting solid tumors with immunotherapy has been difficult because they lack a single target for immune cells to latch on to, and the environment that surrounds them

may not be conducive for immune cells to readily attack the cancer cells. The two-pronged design of bispecific antibodies could help overcome those hurdles.

Several bispecific antibodies being developed to treat solid tumors include one treatment group that targets an immune checkpoint like PD-L1 or CTLA-4, inhibiting it so the immune system can launch an attack.

For example, a bispecific antibody called FS118, which is now being tested in a phase 1 trial in solid tumors, has one treatment group that inhibits PD-L1 and another that blocks another immune checkpoint called LAG-3. Initial results from a trial released last year showed that patients who had been treated with PD-1 or PD-L1 blockers and became resistant to them had durable stabilization of their disease on FS118.

A bispecific antibody called XmAb20717 blocks PD-1 and CTLA-4 and is being tested in patients with a number of solid tumor types. The response rate in a trial reported last November was 19% and included a complete remission in one patient with melanoma. Partial responses were seen in patients with ovarian cancer, non-small cell lung cancer (NSCLC) and castration-resistant prostate cancer.

Other bispecific antibodies in development to treat solid tumors target disease-promoting genetic mutations. One of these agents was recently approved by the FDA.

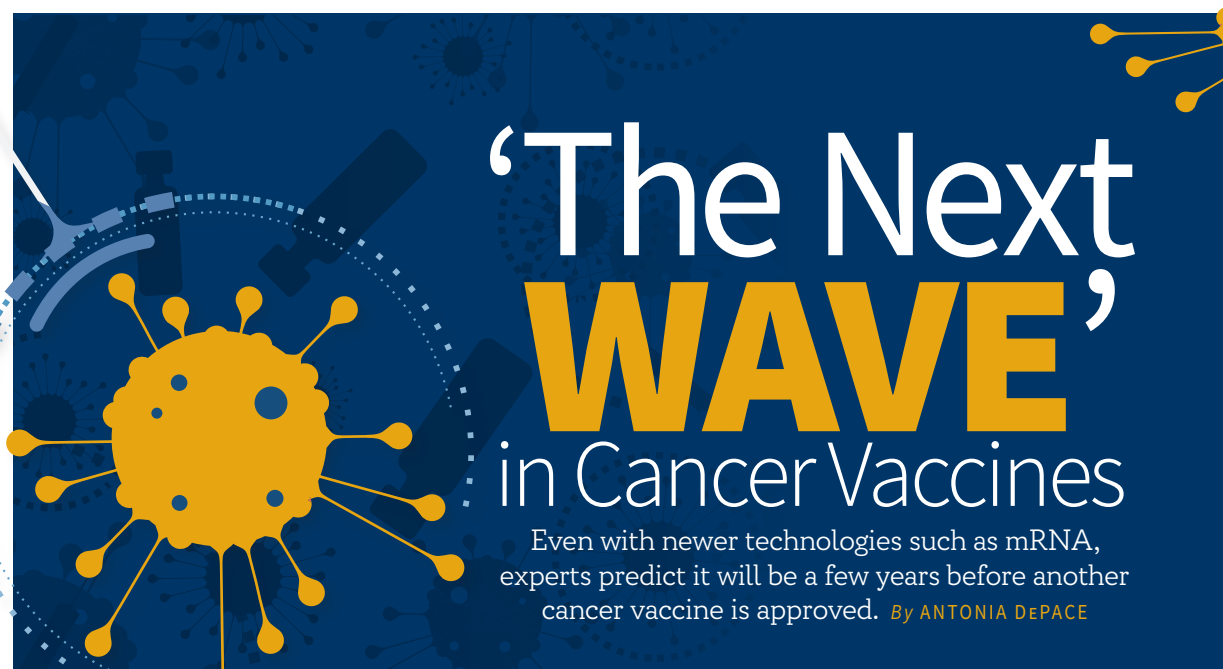
Called Rybrevant (amivantamab-vmjw), it targets EGFR and MET in NSCLC with abnormalities in those genes. It is the first fully human, bispecific antibody approved in lung cancer. The approval was based on results from the phase 1 study, where the response rate to the drug was 40% in patients who had previously been treated with platinum chemotherapy, and 74% of patients saw their disease stabilize.

With so many bispecific antibodies in development across a range of cancer types, many patients could benefit from enrolling in clinical trials of these new therapies, says Wong. “Clinical trials are a good option to consider, especially if you’ve already been on standard therapies,” she says. “It may be that patients who responded well to their initial therapy and then developed resistance could be good candidates for bispecific antibodies.”

And because bispecifics target the immune system, they could improve the prognosis for many patients, Wong says: “The beauty of immunotherapy is that the immune system has a long memory, so there’s a potential for patients to have long-lasting responses to these drugs.”

When I was diagnosed, I was told my life expectancy was four years. This drug has doubled that. It’s a wonderful thing.

—MICHAEL HERMAN



EARLIER THIS YEAR, BioNTech co-founder and chief medical officer Özlem Türeci stated that the messenger RNA (mRNA) technology used to develop two of the COVID-19 vaccines currently available in the United States could be used to treat another disease that affects millions of people around the world: cancer. The technology, which has been around since the 1990s but wasn't widely used until now, carries instructions into the body to make proteins that prime it to attack a specific virus. "The same principle can be applied to help a patient's immune system to attack a tumor," Dr. Julie Rosenberg, head of global clinical development at OncoPep, said in an interview with *CURE*®. The biotechnology company focuses on developing targeted immunotherapies and is currently focusing on PVX-410, an investigational cancer vaccine being studied in patients with multiple myeloma and triple-negative breast cancer.

The discussion of mRNA's potential to be used in the cancer field comes more than a decade after the Food and Drug Administration approved the first cancer vaccine: Provenge (sipuleucel-T). In 2010, it was approved for the treatment of advanced prostate cancer. Provenge is composed of a patient's own stimulated dendritic cells — a type of immune cell responsible for "educating" the immune system on what to target. During the process, the dendritic cells are exposed to prostate antigens. Provenge is known for its toxicity, and Rosenberg noted that newer, less toxic vaccines that are in development are being studied in clinical trials. Side effects of Provenge can vary, depending on the patient, but include chills, fatigue, fever, headache, muscle pain and loss of appetite. "It's basically a cellular therapy where you take people's cells out of their arm, you

send them to a factory, teach the cells how to recognize prostate cancer and give them back to patients," said Dr. Thomas Marron, director of the early phase trials unit at The Tisch Cancer Institute and assistant professor of medicine at Icahn School of Medicine at Mount Sinai in New York. Overall, the goal of a cancer vaccine is to teach the body how to recognize something foreign.

Marron added that cancer vaccines can also help a patient's immune system learn what to be on the lookout for when it comes to their specific cancer. "One of the reasons why patients might not respond to the new immunotherapies used to treat many cancers is their immune system might not have been taught how to recognize the cancer from the get-go," he said. "A patient's T cells, which are really the soldier cells of your immune system, may not have been trained to recognize mutated protein acts."

Since Provenge, there has been only one other approved cancer vaccine. Talimogene laherparepvec is used to treat melanoma that has recurred after surgery. "(An) effective cancer vaccine must target tumor antigens that may have low immunogenicity in the tumor environment or that may mutate to evade the immune response," Rosenberg added.

Many Cancer Vaccines Under Investigation

There have been plenty of clinical trials that have assessed cancer vaccines. "It's really not that the vaccines haven't worked. They just haven't worked well enough," said Dr. George Peoples, the founder and CEO of Cancer Insight and professor of surgery at the Uniformed Services University in Bethesda,

Maryland. Peoples leads research and testing in immunotherapy developed under the military's Cancer Vaccine Development Program. Of note, there are no other vaccines on the brink of approval, but there are many under investigation.

Marron is one of the researchers behind some of these cancer vaccines, one of which he described as "super personalized." In an interview with *CURE*, Marron used the example of a patient with lung cancer to explain his trial that was presented at the American Association for Cancer Research (AACR) annual meeting. Even when a tumor is surgically removed, these specific patients have a 50% or higher chance of the cancer eventually coming back, according to Marron.

"Our goal with the personalized vaccine was to create what we call an adjuvant therapy, which is a therapy that you get after surgery to further decrease the likelihood of cancer coming back," he said.

In Marron's recently completed phase 1 study that was presented at the AACR annual meeting, 15 patients were enrolled to test the safety and efficacy of an adjuvant personalized neoantigen peptide vaccine.

It was this study that computer scientist Marc Baum found while researching prophylactic immunotherapy, otherwise known as preventive cancer treatment. He previously received a diagnosis of bladder cancer at 54, and had just been declared cancer-free. "I did it for myself," Baum said. "I'm (also) a scientist, so I wanted to help out and give back to the future (patients with cancer)."

Marron's trial successfully administered the vaccine to 87% of patients over the course of 27 weeks, and results showed that the vaccine was well tolerated, with only half of the patient population

experiencing mild side effects. Data also found that there was T-cell growth, as well as reactivity to synthetic neoantigens (proteins that form on cancer cells and help the immune system respond to and attack cancer cells).

"Personalized (cancer) vaccines were new news out there, and I just got lucky that there was one that fit," Baum explained. Of note, Baum is still cancer free.

There are several variables behind the rigorous process of getting a new cancer vaccine approved, but the largest lies within the disease, according to Peoples. For diseases such as COVID-19, the vaccine is designed to generate a response against a bacteria or virus, but for cancer, the disease starts within the body's normal cells, which makes it harder for the immune system to recognize it. In turn, Peoples says, a cancer vaccine has to train the immune system to recognize and destroy unhealthy cells. "That's a really big ask for the immune system," he said. "(Because of this,) cancer vaccines have trailed far behind infectious disease vaccines."

Over the past two or three decades, most of the research behind cancer vaccines was driven by the goal to figure out a way to identify potential targets on cancer cells so the immune system could be trained to recognize the difference. More recently, checkpoint inhibitors proved successful at this. Because they allow T cells to regain their ability to recognize and kill cancer cells, their use in combination with T-cell therapies has been a huge step in the right direction. "Their underlying benefit has really closed the loop, if you will, on some of our understanding on cancer vaccines," Peoples said. He describes the combination as a "natural marriage," since bringing the two together

keeps the T cells from being turned off, so to say, by the tumor, leading to an immune response. "We now prove the immune system has the capacity to recognize and destroy cancer," he explained, noting that there's an outpouring of clinical trials to explore these different combinations.

Next Wave for Cancer Vaccines

In response to this research, Peoples mentioned that the focus will switch to how to best use those vaccines in terms of testing in the right patient population. "That's really the next wave for cancer vaccines," he said.

Peoples broke it down using the example of a patient with breast cancer who has a 30% to 40% risk of recurrence. He says the recurrence could occur over the next two to three years. "(For) a clinical trial to test a vaccine, where we're trying to see if we can reduce a recurrence rate from 30% or 40% down to 10% or 20%, and we have to wait three years to find out if we've done anything ... that's a very long, very expensive, very laborious trial," he noted.

This serves as a huge obstacle in getting cancer vaccines approved — especially considering the already rigorous clinical trial process. "A comprehensive vaccine development process can take eight or more years to complete," Rosenberg explained.

However, Peoples emphasized, the most important thing to remember is that there is information out there to create an effective cancer vaccine. "Additionally, there are some new vaccine technologies coming down that are extremely exciting, some of which will come from this pandemic," he said. "(And) we'll continue to look for those rationale combinations that will be required to be able to overcome disease burdens in patients with metastatic disease." ■

Identifying Interstitial Lung Disease

Patients taking checkpoint inhibitors or immunotherapy in combination with other treatments need to be aware of this potential side effect and the associated symptoms.

By MARILYN FENICHEL

A DRY COUGH, FATIGUE AND CHEST PAIN are all signs of COVID-19, but for those on cancer treatments, another culprit may be at fault. Interstitial lung disease, also referred to as ILD, is a potential side effect of immunotherapy, which works by activating the immune system to better attack rapidly growing cancer cells. CDK 4/6 inhibitors, another potent cancer therapy, works by a different mechanism — interrupting the activity of CDK 4/6 proteins that activate the cell cycle and cell division. Both of these treatments can cause ILD.

Although “ILD” is an umbrella term for more than 200 diverse lung disorders, they all have the common characteristic of causing inflammation that can lead to scarring of the lungs if left untreated. The inflammation makes it difficult for patients to breathe and get oxygen into the bloodstream. The term “pneumonitis,” which refers to lung inflammation, includes infectious causes, yet is often used interchangeably with ILD when it occurs in patients who are receiving drugs such as immunotherapy or CDK inhibitors.

The development of ILD as a side effect to immunotherapy has only recently been better characterized. “We were aware from clinical trials back in 2015 that (programmed cell death, or PD-1/PD-1 ligand inhibitors), a kind of immunotherapy used

to treat non-small cell lung cancer and other solid tumors, can cause lung toxicity,” says Dr. Karthik Suresh, a pulmonologist at Johns Hopkins Medicine in Baltimore. “But according to the literature, it is a rare event. About 2.5% to 3% of patients on immunotherapy develop ILD. But there is still much to learn about this relatively new phenomenon.”

Although ILD can occur in patients with any kind of solid tumor, it appears to be most prevalent in patients with non-small cell lung cancer, where underlying lung disease is more common. ILD can also develop from CDK 4/6 inhibitors prescribed for breast cancer, but this side effect occurs infrequently. According to Dr. Hope Rugo, director of breast oncology and clinical trials education at the University of California San Francisco Helen Diller Family Comprehensive Cancer Center, a safety analysis of the adjuvant monarchE trial showed that about 2.9% of patients receiving the CDK 4/6 inhibitor Verzenio (abemaciclib) developed ILD/pneumonitis. Most of these events were asymptomatic, and about 50% received treatment with antibiotics or steroids.

The way to ensure that the ILD doesn’t progress is for both patients and physicians to be vigilant and to catch it early. “Patients should know that if they have a cough, and are experiencing shortness

of breath or excessive fatigue, they should let their doctors know immediately,” says Suresh. “The faster the condition is diagnosed, the better the outcome.”

Learning More About ILD

Data began to emerge in 2015 suggesting that PD-L1 inhibitors could result in ILD. One study conducted in Europe looked at 1,826 patients with cancer admitted to the hospital between December 2015 and April 2016. Of that group, 64 patients, or 3.5%, developed ILD. Most of the cases were of moderate severity, but 9.4% had serious disease. The majority of the patients were men and former smokers.

Although this study identified characteristics of patients who developed ILD, most studies have not found smoking or gender to be risk factors for this disease. At this point in time, studies have not identified any clear-cut risk factors. “Immunotherapy-related ILD is a relatively new phenomenon, so we’re asking basic questions, trying to pinpoint who is likely to get it,” says Suresh. “We’re looking at the nature of the inflammation and how damage occurs. Because PD-L1 inhibitors release the brakes on immune activity, and we’re seeing activated immune cells along with ILD in patients with non-small cell lung cancer, it is logical to conclude that those with vulnerable lungs are more susceptible to ILD.”

Dr. Tanzira Zaman, medical director of Interstitial Lung Diseases at Cedars-Sinai in Los Angeles, concurs, adding that the presence of an autoimmune disease also appears to be a risk factor. “If patients already have an overactive immune system, it’s not surprising that kicking it up even more would result in ILD,” she says.

The first reported cases of lung distress associated with

THE MOST COMMON SIGNS OF ILD

If any of the symptoms below arise, experts recommend contacting a health care team.



Dry, hacking cough that does not produce phlegm



Shortness of breath



Extreme fatigue and weakness



Labored breathing, which can be either fast or shallow



Unexplained weight loss



No appetite



Mild chest pain



Bleeding in the lungs

**This information is courtesy of Cedars-Sinai*

CDK 4/6 inhibitors began trickling in about 2017, with isolated cases reported in a study of women with breast cancer receiving Kisqali (ribociclib). In another study, one woman died after receiving Ibrance (palbociclib). Interestingly, this research also shows that some women tolerate Kisqali but not Ibrance, and vice versa.

“Fortunately, most identified cases were grade 1, which is asymptomatic and found only on imaging,” says Rugo. “Although most symptoms occur early, ILD also may emerge several months or even a year after treatment is started. For this reason, respiratory

symptoms that emerge at any point during treatment should be taken very seriously, and patients should be told to contact their doctors right away if such symptoms develop.”

Challenging Diagnosis, More Straightforward Treatment

The symptoms of ILD resemble many other respiratory infections, congestive heart failure or even COVID-19, making diagnosis challenging. “If a patient has shortness of breath, fatigue, a cough or less energy than usual and is taking a checkpoint inhibitor, then ILD must be considered,” Suresh points out. “The patient’s oncologist may »

decide to consult with a pulmonologist at this point in the process. Patients should be told what to look for as well.”

One of the first steps in the diagnosis process is having a CT scan done. These images may show an abnormality called ground glass opacity, which appears as gray areas on the scan. Bronchoscopy, a procedure where a thin tube is placed into the nose or mouth and extends to the lungs, may be performed to obtain a sample from the lungs and to rule out other causes of inflammation. Pulmonary function tests quantify lung function and also shed light on the degree of inflammation, including infections. “Sometimes patients are totally asymptomatic, and ILD is picked up through CT screening,” notes Zaman. “On the other hand, these tests can also alert us to a more serious case, which will guide subsequent treatment.”

If a patient has no or mild symptoms, the oncologist, often in consultation with a pulmonologist, may decide to keep the patient on the checkpoint inhibitor; if that decision is made, monitoring the individual for signs of worsening lung disease is essential. If the ILD is more serious, treatment is stopped and the patient is put on steroids for six to eight weeks.

The decision about whether to resume treatment with a checkpoint inhibitor after a bout of ILD can be a difficult one to make, especially since these drugs work well and are successful at keeping the cancer at bay. “If the case wasn’t too bad and the checkpoint inhibitor was working for that patient, then it may be possible to go back on the treatment,” explains Dr. Carlos Henrique Dos Anjos, a medical oncologist at Memorial Sloan Kettering Cancer Center in New York. “But if the patient had a severe case of ILD, then an alternative therapy will have to be found.”



Next Steps in Tracking ILD

With growing awareness of the possibility of ILD from immunotherapy and other treatments, clinicians are now considering ways to monitor for it in real time. Dr.

Kelly Westbrook, an oncologist from the Duke Cancer Institute in Durham, North Carolina, and her team developed such a protocol for women with HR-negative, HER2-positive breast cancer receiving Enhertu (fam-trastuzumab deruxtecan-nxki), a type of therapy known as an antibody drug conjugate. This therapy combines chemotherapy with a HER2-targeting antibody to treat metastatic breast cancer. Although not immunotherapy, Enhertu is given to women who have tried many other types of treatment.

“One of the reasons that we wanted to set up this monitoring protocol is that the overall response rates in the trials, which led to approval of Enhertu, were so impressive that we wanted to be able to use it without dose interruptions or dose delays, but we were concerned about the high risk of significant ILD noted in the trials,” says Westbrook. “During clinical trials, almost 9% of patients did develop ILD, and fatal outcomes due to ILD and/or pneumonitis occurred in 2.6% of patients — a number that was somewhat surprising. For that reason, we wanted to be particularly attentive to this potential problem.”

The protocol involved chest imaging and pulmonary function

“Although ILD doesn’t happen often, it can be serious.”

— DR. TANZIRA ZAMAN

tests before treatment began and then every six weeks during therapy. If pulmonary functioning declined more than 10%, a pulmonologist was called in for a consultation. Fifteen patients were part of the data presented from this study in December 2020; currently, data from over 30 patients are being analyzed.

“Fortunately, we have only had one patient develop ILD thus far; another two patients developed respiratory symptoms that turned out not to be ILD, but because of our protocol, we were able to minimize treatment delays despite those symptoms,” says Westbrook.

Although the protocol has potential for widespread use for patients receiving any drug that could cause ILD, it may be difficult to manage in small community hospitals. The tests can be time-consuming and an extra burden for patients. For this reason, Westbrook and her team are not planning additional studies right now, but that could change.

At this point, the best defense against ILD is patient education and awareness. “Empowering patients to think about this possibility while on any form of immunotherapy is the way to get a diagnosis quickly,” says Zaman. “Although ILD doesn’t happen often, it can be serious. When patients alert their doctors to this problem as soon as they start experiencing any symptoms, the medical team can make a decision about treatment promptly, increasing the chances of a successful outcome.” ■

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LESS IS MORE

Novel combo regimen reduces number of toxic treatments in patients with NSCLC.

By ANTONIA DEPACE

LESS MAY BE MORE in the treatment of metastatic or recurrent non-small cell lung cancer (NSCLC), according to the results of a recent clinical trial.

“The results are significant because they show that we may not need four cycles of chemotherapy with immunotherapy to have good efficacy,” said Dr. David Carbone, a professor of medicine and director of the James Thoracic Center at The Ohio State University Wexner Medical Center in Columbus and an author on the study, in an interview with *CURE*®.

Carbone and colleagues recently published data that evaluated two cycles of chemotherapy — instead of the standard four cycles alone — combined with the immunotherapies Opdivo (nivolumab) and Yervoy (ipilimumab) in patients with metastatic or recurrent NSCLC.

Data from that trial — known as CheckMate-9LA — demonstrated that treatment with Opdivo and Yervoy plus two cycles of chemotherapy reduced the risk of death among patients by 31% compared with the chemotherapy-only regimen.

Moreover, the results indicated that patients assigned to the Opdivo-Yervoy regimen had an overall median survival (defined as the time from randomization to date of death due to any cause) of 14.1 months versus the 10.7 months in the group that was given four cycles of chemotherapy alone. Overall survival

was also longer in the combination group regardless of programmed death-ligand 1 levels or tumor histology (the description of the tumor’s characteristics).

Overall, Carbone and colleagues noted that the longer the follow-up, the more the combination therapy seemed to improve survival rates.

Of note, these results led the Food and Drug Administration to approve the combination regimen earlier this year for the treatment of these patients.

Advantage of Less Chemo

What’s significant about the results of this trial is that not only does the combination regimen appear to improve overall survival in patients,

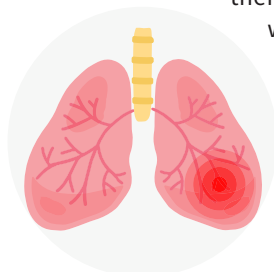
but it also gives them a less toxic treatment option.

Recent estimates from the Centers for Disease Control and Prevention indicate that about 650,000 patients with cancer in the United States receive chemotherapy. And although chemotherapy drugs kill fast-growing cancer cells, they also come with potential debilitating side effects and toxicities such as fatigue, hair loss, nausea and anemia.

“It’s not a chemo-free regimen, but it’s only two cycles of chemo instead of four,” Carbone said regarding the Opdivo-Yervoy regimen. “People really do not like chemotherapy, and as someone who’s had chemotherapy, I know what that’s like. There is an advantage to not having (as much).”

He noted that the combination also helps patients with squamous cell cancers avoid two cycles of full-dose paclitaxel, which can be toxic. For those with non-squamous cell cancers, he mentioned that the standard treatment is the KN189 regimen, which includes the chemotherapies carboplatin and pemetrexed, as well as the immunotherapy Keytruda (pembrolizumab). During this regimen, pemetrexed is given every three weeks for two years, with steroids at every cycle. “With the standard chemotherapy-plus-Keytruda regimen, you have maintenance chemotherapy that goes on for two years, and that confers a chronic toxicity from the chemotherapy,” Carbone explained. “The (Opdivo-Yervoy regimen) eliminates all of these chemotherapy doses except for two and all of the two years of steroid doses, which might help the durability of response.”

“I think patients should be aware that it’s an available and reasonable option,” Carbone concluded, adding that there is potential to use this concept in cancer settings other than NSCLC, though that hasn’t been investigated. “It is a great time in lung cancer, but there’s still a long way to go, that’s for sure.” ■



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Meredith McKean, MD, MPH

Associate Director, Melanoma &
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*Sarah Cannon Research
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- Potential treatment options with topical medications, surgery and radiation
- Psychosocial effects of living with cancer
- Being aware and proactive about signs and symptoms of skin cancers



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What are OPDIVO and YERVOY?

OPDIVO and YERVOY are prescription medicines used to treat people with a type of advanced stage lung cancer called non-small cell lung cancer (NSCLC). OPDIVO may be used in combination with YERVOY as your first treatment for NSCLC when your lung cancer has spread to other parts of your body (metastatic) **and** your tumors are positive for PD-L1, but do not have an abnormal EGFR or ALK gene.

It is not known if OPDIVO and YERVOY are safe and effective when used in children younger than 18 years of age.

What is the most important information I should know about OPDIVO and YERVOY?

OPDIVO and YERVOY are medicines that may treat certain cancers by working with your immune system. OPDIVO and YERVOY 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 serious or life-threatening and can lead to death and may happen anytime during treatment or even after your treatment has ended. You may have more than one of these problems at the same time. Some of these problems may happen more often when OPDIVO is used in combination with YERVOY.

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

- **Lung problems:** new or worsening 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 (abdominal) 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 the amount of urine; blood in your urine; swelling in your ankles; loss of appetite
- **Skin problems:** rash; itching; skin blistering or peeling; painful sores or ulcers in mouth or nose, throat, or genital area
- **Eye problems:** blurry vision, double vision, or other vision problems; eye pain or redness

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 OPDIVO and YERVOY. 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 eye sight
- Persistent or severe muscle pain or weakness; muscle cramps
- Low red blood cells; bruising

Getting medical help right away may help keep these problems from becoming more serious.

Your healthcare team will check you for these problems during treatment and may treat you with corticosteroid or hormone replacement medicines. Your healthcare team may also need to delay or completely stop your treatment if you have severe side effects.

What should I tell my healthcare provider before receiving OPDIVO and YERVOY? Before you receive OPDIVO and YERVOY, 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



Talk to your doctor about OPDIVO + YERVOY

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- have received or plan to receive a stem cell transplant that uses donor stem cells (allogeneic)
- have received radiation treatment to your chest area in the past and have received other medicines that are like OPDIVO
- have a condition that affects your nervous system, such as myasthenia gravis or Guillain-Barré syndrome
- are pregnant or plan to become pregnant. OPDIVO and YERVOY can harm your unborn baby
- are breastfeeding or plan to breastfeed. It is not known if OPDIVO or YERVOY passes into your breast milk. Do not breastfeed during treatment with OPDIVO or YERVOY and for 5 months after the last dose of OPDIVO or YERVOY

Females who are able to become pregnant: Your healthcare provider should do a pregnancy test before you start receiving OPDIVO or YERVOY.

- You should use an effective method of birth control during your treatment and for at least 5 months after your last dose of OPDIVO or YERVOY. 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 are pregnant during treatment with OPDIVO or YERVOY. You or your healthcare provider should contact Bristol Myers Squibb at 1-844-593-7869 as soon as you become aware of the pregnancy.

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

Know the medicines you take. Keep a list of them to show your healthcare providers and pharmacist when you get a new medicine.

What are the possible side effects of OPDIVO and YERVOY?

OPDIVO and YERVOY can cause serious side effects, including:

- **See “What is the most important information I should know about OPDIVO + YERVOY?”**
- **Severe infusion reactions.** Tell your healthcare team or nurse right away if you get these symptoms during an infusion of OPDIVO or YERVOY: chills or shaking; itching or rash; flushing; shortness of breath or wheezing; dizziness; feel like passing out; fever; back or neck pain

- **Complications, including graft-versus-host disease (GVHD), of bone marrow (stem cell) transplant that uses donor stem cells (allogeneic).** These complications can be severe and can lead to death. These complications may happen if you underwent transplantation either before or after being treated with OPDIVO or YERVOY. Your healthcare provider will monitor you for these complications.

The most common side effects of OPDIVO when used in combination with YERVOY include: feeling tired; diarrhea; rash; itching; nausea; pain in muscles, bones, and joints; fever; cough; decreased appetite; vomiting; stomach-area (abdominal) pain; shortness of breath; upper respiratory tract infection; headache; low thyroid hormone levels (hypothyroidism); decreased weight; and dizziness.

These are not all the possible side effects of OPDIVO and YERVOY. Call your doctor for medical advice about side effects.

You are encouraged to report side effects of prescription drugs to the FDA. Call 1-800-FDA-1088.

OPDIVO (10 mg/mL) and YERVOY (5 mg/mL) are injections for intravenous (IV) use.

This is a brief summary of the most important information about OPDIVO and YERVOY. For more information, talk with your healthcare providers, call 1-855-673-4861, or go to www.OPDIVO.com.



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Around the Bend

One expert tells patients to 'hang tight' as immunotherapy options are getting better each year. By ANTONIA DePACE

ALTHOUGH IMMUNOTHERAPY

has become a major pillar in cancer, the current generation of T-cell therapies only benefits a minority of patients, one expert says.

"The problem is that we know only a minority of tumor types really benefit in a big way from these drugs," said Dr. Mark Yarchoan, an assistant professor of medical oncology at Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins University in Baltimore. "And even within tumor types where they show a lot of activity, only a subset of patients respond, and fewer patients have really long-term remission."

The use of T-cell therapy began in 1986 when Dr. Steven Rosenberg and colleagues at the surgery branch of the National Cancer Institute started using tumor infiltrating lymphocyte (TIL) therapy, in which doctors test lymphocytes (a type of T cell) to find out which one is best at recognizing tumor cells. From there, the selected lymphocytes are treated with substances that make them grow in numbers. "One of the limitations with (TIL) therapy is that you have to have TIL in your accessible tumor already," said Dr. Lisa Butterfield, vice president of research and development at the Parker Institute for Cancer Immunotherapy, in an interview with CURE®. "CAR-T cell therapy is not specific to one patient's tissue type, so that's certainly a big strength."

"I think the next frontier is, instead of broadly activating T cells, how do we activate T cells against specific cancer antigens?" Yarchoan said, adding that there is already exciting

research underway for this. "Lots of different approaches are being explored, including cancer vaccines, new cellular therapies that utilize T cells that recognize tumor antigens, and bispecific antibodies that bring T cells into the tumor."

When it comes to broadly activating T cells, there are also more checkpoint inhibitors coming — allowing immunotherapy to target alternative checkpoints outside of PD-1, PD-L1 and CTLA-4. There is also positive data circulating on how to keep cancer cells from turning off immune receptor TIGIT, which is present on some T cells and natural killer (NK) cells. Dr. Andrew Ewald is one of the faces behind some of this research.

Ewald, who is a professor and co-leader of the department of cell biology at Johns Hopkins University School of Medicine and professor of oncology and co-director at the Cancer Invasion and Metastasis Program at the Sidney Kimmel Comprehensive Cancer Center, discovered that using antibodies can stop cell receptors like TIGIT and KLRG-1 from manipulating NK cells: lymphocytes in the same family as T cells.

The research, which is in its final stages, found that the NK cells were the most abundant early responders to cancer cells arriving, and were particularly good at killing metastatic cancer cells. Ewald's discovery would keep NK cells in their natural, cancer-killing state.

"It's a way of keeping the good guys on your team and looking for, detecting and killing the cancer cells wherever they are in the body," he said.

Butterfield also noted that new trials using CD19 and CD20 CAR T-cell therapy in hematologic malignancies are showing

success. In CAR-T cell therapy, CD19, a protein expressed on most B cells, the white blood cells that make antibodies, is successfully targeted in cancers such as B-cell lymphomas. In this process, the therapy gets rid of both cancer cells and B cells. "In some

patients, their cancer comes back but doesn't express the CD19 protein on the surface anymore," she said, noting that this could lead to resistance to CD19-directed CAR-T cell therapy. "To deal with that, the tumor can be targeted with CD20, which can often be expressed on the tumors as well as other normal B cells."

Through using both CD19 and CD20 CAR-T cell therapy, the hope is that killer cells won't become ineffective against tumor cells that downregulate one target, and that the therapy will "persist in patients as a one-time treatment that will keep an eye out for tumor cells that express CD19 and/or CD20, and not allow for resistance to one (or the other)," Butterfield said. A study being led by a researcher at UCLA, is currently evaluating this.

"I tell my patients to hang tight because there are better things around the corner," Yarchoan concluded. "I show up to work every day feeling optimistic because our options are so much better than they were a year ago. And I'm really hopeful that they'll be better in a year than they were today." ■



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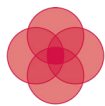


CureToday

SPEAKING OUT HEAD & NECK CANCER



On the Rise



HEAD AND NECK CANCER
ALLIANCE

On behalf of the Head and Neck Cancer Alliance, Dr. Michael Moore spoke with *CURE*® about emerging therapies that potentially offer exciting new options for the future. By KRISTIE L. KAHL

ALTHOUGH RATES OF HEAD and neck cancer have risen, in part because of the human papillomavirus (HPV), emerging therapies such as targeted agents and immunotherapies are paving the way for future treatment of the disease, according to Dr. Michael Moore.

"I would say (immunotherapy) is probably one of the more exciting parts of what we've learned about head and neck cancer in recent years," he told *CURE*® as a part of its "Speaking Out" video series.



DR. MICHAEL MOORE

On behalf of the Head and Neck Cancer Alliance, *CURE*® spoke with Moore, associate professor of otolaryngology-head and neck surgery and chief of head and neck surgery at Indiana University School of Medicine

in Indianapolis, about targeted therapies, immunotherapy and how clinical trials are leading the way for future treatments.

Q: How have genomics and targeted therapies played a role in head and neck cancer treatment?

A: Well, I would say it's an emerging role. And it's not used as commonly in head-neck cancer as it is in some other areas. So molecular testing or targeted therapies essentially are looking at a very specific part of the tumor to see if we can develop a specific drug that will target just that; (the goal is to) weaken the cancer's defense — that is one way to say it — and try to very specifically treat that cancer in a way that will give us the best chance of getting rid of it and potentially try to limit the side effects related to the treatments. This has become a little bit more common now that the ability to analyze these tumors

has become more widely available across the country. But still, the majority of these types of treatment approaches will be in the context of a clinical trial.

Q: Do we have any currently approved targeted therapies for head and neck cancer?

A: That's a great question. I think these are kind of different and are emerging all the time. There are ones that are focused on very specific mutations, such as what's called the BRAF mutation, which is one that can be present in melanoma or certain aggressive cancers, such as thyroid cancer. And other ones will target things like tyrosine kinase inhibitors that have a more focused route to try to combat these tumors. And then there are ones that will be discussed a little later, such as immuno-oncology drugs that focus on the program cell death ligand and the receptor to try to turn the body's immune system



back on. Another example is what's called Erbitux (cetuximab), which is focusing on a specific receptor on cancer cells, really trying to exploit this particular difference in cancer cells compared with normal tissue to try to give the best chance of getting rid of the tumor, but minimizing the side effects of the treatment.

Q: What role has immunotherapy had in head and neck cancer treatment?

A: Cancer has a way of almost turning off the local immune system. It blocks many of the local immune responses to it. Normally, the body would say, "Yeah, that's not part of our normal tissue, we want to get rid of it." And some cancers have a way of blocking that. These immunotherapies have a way of almost inhibiting that blockage, if you will, or turning the immune system back on and allowing your own body's immune system to fight these tumors. These can be incredibly effective. The challenge is if they're only effective in a small minority of cancers. And so, when they do work, they can work extremely well and can give really good and long-lasting results. But

in a high percentage of patients, the responses are much more modest or (patients) may not even respond at all.

Q: Can you discuss the currently available immunotherapies for head and neck cancer?

A: There are two. Opdivo (nivolumab) is one that can be used in patients who have not responded or progressed despite standard therapy, including recent treatment with chemotherapy, including cisplatin. And then Keytruda (pembrolizumab) is another similar amino therapy that can be used and has actually achieved approval for use in the primary setting. When cancer comes back in an area that can't be treated with either definitive surgery or definitive radiation therapy, you can use that as a next avenue for treatment. These are the two (Food and Drug Administration)-approved drugs that are out there. They also have ongoing studies where they're being combined with other standard-of-care, primary treatments for head and neck cancer. I think in the next five to 10 years, they'll likely be integrated much more on the front end of cancer therapy, rather than just offering them to those who don't have other treatment options.

Q: How do clinical trials help to advance these therapies, and why should patients consider joining one?

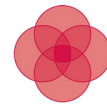
A: These are really what allows us to make our cancer treatment better. We constantly are. It's not just going out and experimenting on people but, rather, we're comparing these treatments to see how we can improve on the current standard approach to therapy. If you were to look back 50 to 60 years ago, all we had were big, morbid surgeries that people were put through and possibly adding radiation therapy. And then we added cisplatin, which is a drug that can be effective in enhancing the

effects of radiation therapy. Now, as we add these other treatments, such as immunotherapy and other targeted therapies, the only way we know if they have any advantage over what we have to offer, currently, is to compare them in a clinical trial.

And with these clinical trials, those who have designed them have been very thoughtful in trying to do so in a way that compares them and then looks to see: Does that give us a benefit in getting rid of the cancer or curing the cancer, or at a minimum, slowing it down or giving a longer life? And/or does it give better quality of life or reduce the level of side effects? That's what many of these clinical trials are. Some are adding new agents to see if those work better than other ones. For example, in the HPV-related cancer, some of the clinical trials are saying these respond fairly well to treatment. Can we actually back off on the severity of treatment, give them just as good of a cancer cure but (with) fewer long-term side effects? I think they're critical as the only way we're going to figure out how best to manage these types of cancers. ■



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We are helping to move mountains for myeloma patients

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

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

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

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

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