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## USING A ROBOT TO PERFORM MASTECTOMIES, A NEW JERSEY SURGEON SETS OFF A FIRESTORM OVER SURGICAL OUTCOMES

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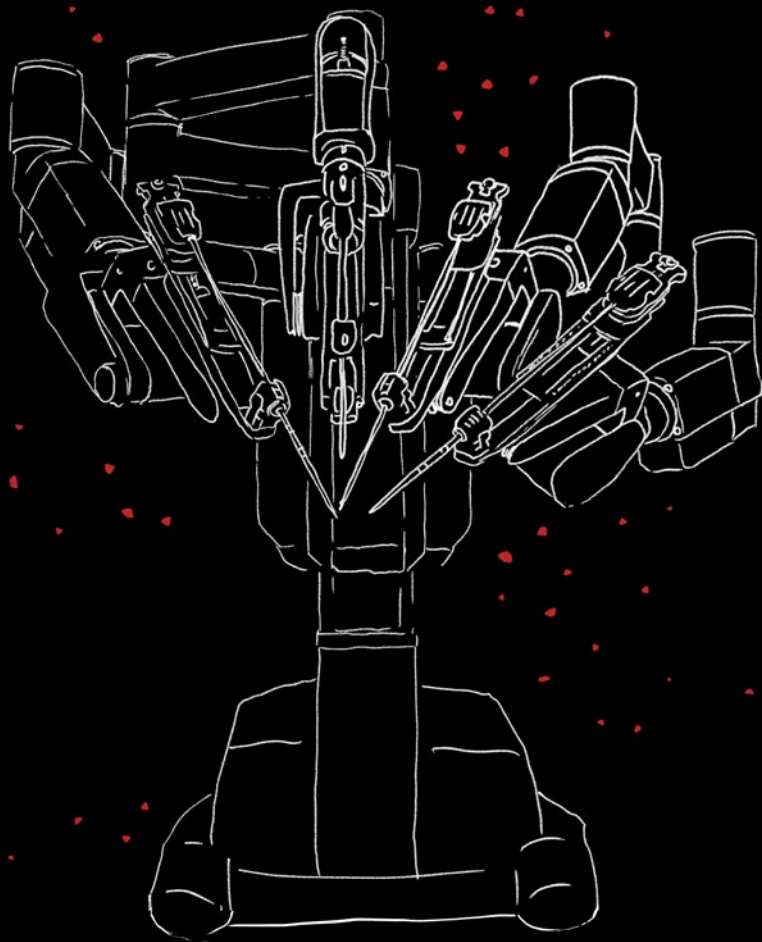
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# USING A ROBOT TO PERFORM MASTECTOMIES, A NEW JERSEY SURGEON SETS OFF A FIRESTORM OVER SURGICAL OUTCOMES

**HOW MUCH RIGOR SHOULD BE REQUIRED WHEN SURGEONS INNOVATE? FDA'S ADVISORY ASKS FOR LONG-TERM CANCER-RELATED DATA.**

*By Matthew Bin Han Ong*

Last August, Stephen A. Chagares, a breast surgeon, made an announcement that startled some of his colleagues at New Jersey's Monmouth Medical Center.



At internal meetings and in a press release, Chagares declared that he would perform a robotic mastectomy—a new and relatively untested minimally invasive surgical procedure. According to the press release, his first patient, Yvonne Zucco, 56, was being treated for stage IIa breast cancer.

“Dr. Chagares is proud and honored to lead the first program of its kind in the United States,” declared the press release dated Aug. 23, 2018. “Robotic Mastectomy with immediate reconstruction opens the door to a new era of mastectomy and a new outlook for patients, offering a modern approach to an operation which has been so physically, emotionally, and psychologically scarring until now.”

Following this announcement and additional marketing by Chagares, his colleagues at Monmouth, a teaching affiliate of the Rutgers Robert Wood Johnson Medical School, started to raise questions:

Is it safe to use a robotic surgical system in breast cancer? How would you do it? Is it necessary? Where are the oncologic data supporting the procedure? Might Chagares be proposing a solution in search of a problem?

When new surgical techniques are used in patients with cancer or in tissues that might harbor cancer, surgeons must ensure that malignancies—diagnosed or undiagnosed—will not be sent flying through the patients’ bodies. This is a basic principle of cancer surgery.

The only way to know that harm is avoided is to ask the right questions and design studies to answer those questions. Monitoring patients in the short term and relying on patient satisfaction metrics is not a guarantee of long-term safety, experts say. When you don’t look for long-term consequences, you don’t find them.

At Monmouth Medical Center, Chagares didn’t propose to perform robotic mastectomies under a surgical trial protocol, insiders say.

Zucco, the patient, seemed happy with the procedure and the outcome. “I am a cancer survivor. I sought many opinions and consultations in order to decide how I wanted my mastectomy performed,” she wrote in a comment thread on Chagares’s Facebook page. “I educated myself and know the research and data. I am also fully aware of my operation, the outcome and all discussions at Breast Center Conferences. There are other people out there that have done their research and decided this is the best option for them. They should be given this opportunity just like me!”

Chagares declined to speak with this reporter, stating that protection of patient confidentiality is involved. Zucco didn’t respond to a Facebook message.



**FDA regulations require that significant risk studies intended to evaluate the safety and effectiveness of a device must first receive an Investigational Device Exemption.**

– FDA



In December, Monmouth halted the use of minimally invasive robotic mastectomy in all surgical indications, issuing a statement that cited safety concerns. The hospital declined to discuss its rationale for signing off on the surgeries and ultimately halting them.

Breast cancer experts say that two principal indications for the procedure include patients with breast cancer and patients with BRCA mutations who would be eligible for prophylactic mastectomy.

High-risk patients must be operated on according to oncologic surgical principles, cancer surgeons say. This requires en bloc removal of malignant breast tissue, making sure that the entire gland is taken out in one piece and with good margins. This also applies to breast tissue with the potential to develop into cancer, experts say.

These surgical principles ensure that any mass containing cancer or undetected malignancies isn’t broken up, thereby reducing the risk of disseminating cancer cells.

Chagares isn’t the only surgeon to perform robotic mastectomies. The Cancer Letter has found that the procedure has been performed in at least one other U.S. institution, Northwell Health’s Long Island Jewish Medical Center.

There is no consensus on the procedure. Memorial Sloan Kettering Cancer Center and MD Anderson Cancer Center, for

example, fundamentally disagree on robotic mastectomy. Multiple academic institutions, including MD Anderson and the University of Pennsylvania, have plans to study robotic mastectomies in surgical trials. MSK has no such plans.

In March 2018, surgeons at Northwell Health performed a robotic bilateral prophylactic mastectomy on a 45 year-old woman in an “off-label” setting, with approval from the institution’s Institu-

tional Review Board for a “practice of medicine” protocol.

Now, Northwell Health, MD Anderson, and two institutions in Chicago are in the process of drafting a trial protocol to evaluate the safety and effectiveness of robotic mastectomy. The study is funded by Intuitive Surgical, the dominant manufacturer of robotic surgical devices.

The multicenter trial is designed to study the procedure in patients with breast cancer and patients who would be eligible for prophylactic mastectomy. Penn’s protocol aims to enroll only patients with BRCA mutations.

Usually, minimally invasive robotic procedures are employed for surgery in hard-to-reach-and-see parts of the human anatomy. Robotic arms can enhance vision and precision, enabling surgeons to manipulate and excise tissue deep within the body. In many situations, the robot eliminates the need for large incisions required for open surgery, speeding recovery, and reducing the risk for postoperative surgical morbidity and other complications.

The premier device for robotic surgery, the da Vinci Surgical System, made by Intuitive Surgical, requires a sizable investment. The price tag ranges between \$500,000 and \$2.5 million, and surgeons who specialize in minimally invasive procedures and hospitals that own these machines are understandably focused on expanding the uses for this equipment.

## FDA sounds a note of caution

In the absence of long-term safety data, off-protocol use of robotic mastectomy is inappropriate, said Laurie Kirstein, a breast surgical oncologist at Memorial Sloan Kettering Cancer Center.



Chagares, with his first robotic mastectomy patient, Yvonne Zucco, 36 hours after the procedure. — Source: [Stephen A. Chagares; Facebook](#)

“We don’t do [robotic mastectomies] currently,” Kirstein said to The Cancer Letter. “We do not believe the safety of this procedure for cancer treatment has been demonstrated and do not think it should be performed outside of an IRB approved protocol with appropriate informed consent.

“We discussed it as a group under the leadership of our chief of breast surgery,

Dr. Monica Morrow, fairly recently in the last few months, to assess the procedure from an oncologic perspective. It’s very hard to adopt a new procedure that hasn’t been really tested, when the one we have is so good, and we know is safe.”

A conversation with Kirstein appears on [page 14](#).



FDA's stance on this controversy has just changed in recent weeks.

In December 2018, in the course of reporting this story, The Cancer Letter queried FDA about whether robotic surgical devices should be used for mastectomy.

"Does FDA plan on issuing an advisory or guidance to curtail the routine use of robotic mastectomy outside the confines of a prospective clinical trial and absence of Level I data?" this reporter asked the agency.

On Feb. 28, FDA issued a safety advisory, indicating that device manufacturers looking to market surgical tools for use in the prevention or treatment of cancer may now be required to study long-term oncologic endpoints in surgical trials "for time periods much longer than 30 days" (The Cancer Letter, [March 1](#)).

"At this point, given the recent FDA statement on robotic surgery and since the safety of the procedure has not been demonstrated, it's not something we are pursuing at Memorial Sloan Kettering," Kirstein said.

FDA's communication could be interpreted as signaling changes in the way medical devices are regulated—specifically, surgical tools that are used in settings where cancer could be present.

The advisory reads: "The FDA encourages academic and research institutions, professional societies, robotically-assisted surgical device experts, and manufacturers to establish patient registries to gather data on the use of robotically-assisted surgical devices for all uses, including the prevention and treatment of cancer. Patient registries may help characterize surgeons' learning curves, assess long-term clinical outcomes, and identify problems early to help enhance patient safety."

Chagares appears to have read this communication as encouragement

from the agency to expand the use of the technology. On his Facebook page, the surgeon wrote: "I was even more pleased to see Actions bullet point #3 wherein the FDA clearly 'encourages... use of robotically-assisted surgical devices for all uses, including the prevention and treatment of cancer.'"

Though Chagares's plans ran into opposition from the outset, he did initially receive approval from the hospital's Institutional Review Board to perform bilateral robotic nipple-sparing mastectomies on at least two patients—[Zucco](#), and [Brian Thomson](#), a 34 year-old man who, according to a press release, experienced rapid growth of painful breast tissue.

"On Sept. 28, Brian and Dr. Chagares made history with the first male bilateral robotic nipple-sparing mastectomy ever performed in the world," Chagares wrote in the Oct. 5, 2018 press release. "Dr. Chagares is proud and honored to offer this surgery to his patients of any gender identity. Dr. Chagares and his patient, Brian Thomson, are available to interview should media outlets see fit to include this historical event in their publications."

A version of this press release appears [here](#).

Multiple sources with direct knowledge of the situation who spoke on condition that their names would not be used said that Chagares, who reportedly did not propose a clinical trial protocol, didn't receive an okay from FDA to use the da Vinci robot on Zucco and Thomson in an investigational setting.

Generally, it's legal to use a drug or device in an indication that has not been cleared or approved by FDA, because the agency doesn't regulate the practice of medicine.

"Health care professionals generally may legally prescribe or use approved/cleared medical products for unap-

proved uses when they judge that the unapproved use is medically appropriate for their individual patients," FDA said to The Cancer Letter. "In some cases, such use may expose health care professionals to legal liability."

In this instance, FDA considers robotic mastectomies to be of "significant risk," which means surgeons and institutions are required to seek an exemption from the agency to study the procedure on-protocol, officials said.

"FDA regulations require that significant risk studies intended to evaluate the safety and effectiveness of a device must first receive an Investigational Device Exemption," FDA officials said. "Therefore, while individual health care providers may make individual treatment decisions in the best interests of their patients, any health care provider or health care facility formally studying the safety and effectiveness of the da Vinci for mastectomy would be expected to have an IDE."

Ari Brooks, director of endocrine and oncologic surgery, director of the Integrated Breast Center at the University of Pennsylvania Health System and professor of clinical surgery at Penn Medicine, said he will not perform robotic mastectomies outside an investigational setting.

"Absolutely not! No. I'm not doing anything until I have an FDA IDE. I'm not doing it until there's consent and it's IRB-approved," Brooks said to The Cancer Letter. "I'm not doing it. I'm not screwing around."

A conversation with Brooks appears on [page 28](#).

Brooks, who has written a trial protocol for prophylactic robotic mastectomies, but after the FDA advisory he has revised that protocol to include assessment of cancer-related outcomes. His study isn't funded by industry.

“That was my [original] intention, to do only prophylactic, that the first trial would probably be 20 patients, maybe 30, because that’s the learning curve,” Brooks said. “And it would be all just looking at cosmetic and satisfaction and that’s it. And that was the study.”

“As soon as the FDA announcement came out, I got some emails asking me to start having some meetings with the leadership of the hospital to find out how to move forward. We asked how we’re going to do this after the FDA advisory, and, well, we’re just going to have to tell the patients we have to follow them after surgery for 10 to 20 years. And that’s what we’ll do.”

“I conceded that with these patients, we have to follow them long-term. So, we will. I don’t have a problem with that,” Brooks said. “And, you know, it’s right. It’s a good thing, really. They shouldn’t just study patients for 30 days.”

“I get it. At a hospital up north, they’re like, ‘Oh yeah, we’ll take anything out with a robot.’ We don’t learn anything from that.”

“So, no, it has to be done as a study.”

## “Best day ever in surgery”

An Aug. 23 press release issued on Chagares’s behalf by a practice with which he is affiliated describes robotic mastectomies as “groundbreaking.”

“Dr. Stephen Chagares, a board certified General and Breast Surgeon also certified in robotic surgery, is proud to offer this option to breast cancer patient Yvonne Zucco,” the [press release](#) states. “After learning about the benefits of the RNSM, Ms. Zucco eagerly made an appointment with Dr. Stephen Chagares and his colleague Dr. Andrew Elkwood of The Plastic Surgery Center, in their Monmouth County offices.”

Last October, local media characterized robotic mastectomy as a “breakthrough.”

One local news outlet declared that Chagares was leading “the way into the future with a procedure that will change the lives of many breast cancer and BRCA-positive patients ... Chagares is clearly moved by what this will mean for so many women, saying that his first RNSM procedure was his best day ever in surgery.”

Zucco, the patient, was diagnosed with stage IIa cancer in her left breast, and underwent four months of chemotherapy. According to a press release, Chagares removed “breast tissue via a single incision under the armpit.”

In December, Monmouth Medical Center halted the use of the procedure.

“At Monmouth Medical Center, patient safety is our utmost priority,” hospital administrators said to The Cancer Letter. “As such, we are constantly assessing the safety of our procedures and the services we perform. After evaluating robotic mastectomy, Monmouth Medical Center has decided to suspend the procedure until further review.”

The institution is a member of the RWJBarnabas Health system and a teaching affiliate of the Rutgers Robert Wood Johnson Medical School. According to its website, the health system treats over three million patients a year, employs 32,000 people in the region, and provides comprehensive cancer services.

The hospital’s suspension of robotic mastectomies had national implications in the ongoing debate over whether the procedure is safe, necessary, and cost-effective.

The American Cancer Society estimated that about 266,120 new cases of invasive breast cancer would be diagnosed in 2018. According to a [2017 report](#), 106,295

breast reconstruction procedures were performed that year by members of the American Society of Plastic Surgeons—a 39% increase in procedural volume since 2000.

The number of women undergoing mastectomies every year in the U.S. may exceed 200,000, since less than half of all women who require mastectomy are currently offered breast reconstruction surgery, and fewer than 20% elect to undergo immediate reconstruction.

The moratorium on robotic mastectomies at Monmouth was enacted in response to concerns from the medical staff, sources said.

“The concern for the robotic mastectomy is that the first part of the dissection is actually done blindly,” said MSK’s Kirstein. “There is no visualization, and the robot is only really used for the far-medial, or the piece that is closest to the chest bone. So, there’s a concern about being able to see what you’re doing and making sure you’re actually getting out enough tissue.”

“There were concerns for other surgeons, where they took out the tissue in pieces, rather than in one en bloc section—so it’s very hard or impossible to evaluate margins, for example, for a cancer, if you haven’t taken it out in one piece. You’ve sort of chopped it up into pieces. And so, oncologically, we know that’s not the right way to treat patients.”

On his [website](#), Chagares states that he has “obtained specialty training in breast surgery at Memorial Sloan Kettering Cancer Center in New York City and is a board certified breast surgeon.”

It’s unclear what Chagares means by “specialty training in breast surgery” at MSK, officials at the cancer center say.

“We have a record from 1990 for Stephen Chagares as a non-employee rotating Surgery Resident from Mon-



mouth Medical Center,” an MSK spokesperson said to The Cancer Letter. “It looks like he did a two-month rotation here during his intern/PGY 1 year from 9/1/1990 through 10/31/1990.



**I’m not doing anything until I have an FDA IDE. I’m not doing it until there’s consent and it’s IRB-approved. I’m not doing it. I’m not screwing around.**

– Ari D. Brooks



“We were not able to determine whether that two-month rotation involved the breast surgical service, but I believe the duration of his experience at MSK speaks for itself. We are reviewing the matter and his claims.”

A spokesperson for Chagares disputed MSK’s statement.

“Dr. Chagares is still in the OR. I may be able to help as I used to work for my father who was a general/breast surgeon many moons ago,” the spokesperson, Marianne Maggs, said in an email to The Cancer Letter. “Dr. Chagares did receive specialty training in breast surgery at Memorial Sloan Kettering Cancer Center. I do not know, off the top of my head, specifically the ‘amount of time’ designated by the Monmouth Medical Center Residency Program for their specialty breast training.

“I know it was completed as part of the MMC Residency Program guidelines. In 1990, breast surgery was a standard pillar of general surgery and breast fellowships did not exist. Twenty-nine years ago, most breast surgeons weren’t afforded the opportunity for this specialty training. MMC had an excellent working relationship with MSKCC.”

The [press release](#) announcing the procedure on Zucco states that Chagares had also received specialty training in Italy: “Dr. Chagares, a board-certified breast surgeon, has been performing

mastectomies for 23 years and robotic operations for years. Upon invitation to The European Institute of Oncology in Milan, Italy, Dr. Chagares trained under Dr. Antonio Toesca, the pioneer of robotic mastectomy.”

Toesca didn’t respond to questions from The Cancer Letter.

Toesca is listed as principal investigator on a prospective randomized trial sponsored by the European Institute of Oncology, according to ClinicalTrials.gov. The [protocol](#) was posted on Feb. 21, 2018, last updated on Jan. 15, and has an actual enrollment of 82 participants.

“This project is a superiority trial comparing robotic nipple sparing mastectomy and immediate breast robotic reconstruction with conventional open technique,” the protocol states. “The primary endpoint is to evaluate patient satisfaction.”

The estimated completion date for the trial is Dec. 31, 2019.

“When they’re done with enrollment, he’ll give us the one-month follow-up on those endpoints—the cosmetic satisfaction and all that,” said Penn’s Brooks, who is not involved in the Toesca study.

The secondary endpoints in Toesca’s study include “post-operative outcome considering complications, post-operative pain, reduction of the average length of stay of patients, long term oncological outcome of the two different surgical techniques.”

“Then, you’re going to have to hold your breath for another five to 10 years to get the data for the recurrences and other oncologic endpoints,” Brooks said. “There’s nothing. The study needs to be done.”

MSK’s breast surgery team, too, has concluded that there are no prospective clinical trial data proving that robotic mastectomy doesn’t worsen cancer outcomes.

“Zero. There are no studies doing that,” Kirstein said. “The only study that has been published so far was an Italian study, in which they reported patient-reported outcomes such as patient satisfaction, length of stay and cosmetic outcome. That’s it. There were no volumetric studies, there were no cancer-related studies. Nothing.

“The technique has also become a little bit more popular in the United States, without, so far, any data showing that it’s oncologically safe.”

## **Intuitive Surgical cautioned a surgeon**

Asked by this reporter about the controversy at Monmouth, a spokesperson for Intuitive Surgical said the company had cautioned “a surgeon” about off-label use of its device.

The company didn’t identify the surgeon who had been thus cautioned.

“In accordance with federal and international regulations, Intuitive’s policy is not to support, promote, or train on off-label procedures performed using our surgical systems,” company officials

said to The Cancer Letter. “When Intuitive learned that a surgeon intended to perform a mastectomy using the da Vinci Surgical System, Intuitive reminded the surgeon that the procedure was off label and encouraged the surgeon to follow appropriate procedures at his institution for performing off-label procedures.

“No Intuitive representative participated in or observed the procedure.”

Monmouth’s decision came shortly after an internal review conducted at MSK came to a similar conclusion.

“When you are going to change what you do drastically, you really should have Level I data showing that it’s at least not inferior to what you’re doing,” Kirstein said. “This is a major change, a major deviation. A major change in the standard of care and in the technique.”

MSK breast surgeons decided that they would not perform the procedure, whether at the mother ship in New York City or at a satellite campus, MSK Monmouth, located a 20-minute drive from Monmouth Medical Center.

“The issue for us is that you have a procedure that is going to be much longer than your standard mastectomy,” said Kirstein, who also treats patients at MSK Monmouth. “It’s a lot more expensive than your standard mastectomy, and we’re not really sure that it’s cosmetically better in the long run than what we already do for, let’s say, a nipple-sparing mastectomy or other ways to do it.”

Before the Feb. 28 FDA safety communication, surgical trials on robotic mastectomy had to account only for the safety and effectiveness of the procedure in the short term—without an experimental design that controls for cancer-related endpoints. This means that, to date, robotic mastectomy has not been demonstrated to be either superior or non-inferior in the oncologic

setting, when compared to standard-of-care procedures.

“The only studies that have been done for the robotic mastectomy have been on cosmesis and patient satisfaction and length of stay and things like that,” Kirstein said. “There have been no studies whatsoever to show if it’s oncologically equivalent, or not inferior, to what we already do in terms of recurrence and whether that recurrence risk impacts overall survival.”

## MD Anderson: “Immediate and long-term outcomes”

With the FDA safety communication, it’s no longer possible to dismiss the worst-case scenario, whereby novel minimally invasive procedures lower survival of patients who are otherwise healthy—especially when there is a significant risk of exposure or dissemination of existing or undetected disease.

When new procedures go into routine use without anyone asking life-and-death questions, patients may die of metastatic disease without anyone ever knowing that their lives had been shortened—or how and why.

Patients who give the procedure a five-star rating four weeks after surgery may be dead three years from now, because their disease had been inadvertently spread during surgery.

“We are not currently doing [robotic mastectomies],” said Kelly Hunt, chair of the Department of Breast Surgical Oncology, and a professor in the Division of Surgery at MD Anderson Cancer Center. “However, we have a couple of surgeons who have been credentialed in robotic surgery, and one principal investigator with over 12 years of robotic experience.”

A conversation with Hunt and colleague Jesse C. Selber, director of clinical research, MD Anderson Cancer Center, appears on [page 20](#).

“We wrote a protocol and will be investigating this procedure in a prospective study,” Hunt said to The Cancer Letter.

Proponents of robotic mastectomy say that, since the technical aspects of the robotic surgery are similar to the open procedure, there is no reason to believe that the oncologic outcomes would be different.

“The challenge of nipple-sparing mastectomies is trying to achieve a precise dissection through a small incision with minimal illumination and a limited ability to see and reach tissue planes,” said Jesse Selber, professor and director of clinical research at the Department of Plastic Surgery at MD Anderson. “The robot provides the surgeon with a crystal clear, magnified, front-row seat to the most-technically difficult part of a nipple-sparing mastectomy. We think this could result in better outcomes.

“It’s important to make clear that the oncologic principles of the robotic mastectomy are identical to the open procedure,” Selber said to The Cancer Letter. “The plane of dissection is identical; the way the specimen is removed, oriented and labeled is identical; the margin evaluation and permanent pathologic evaluation is identical.”

In the trial, the robotic procedure will only be used in patients with C-cup breasts and smaller, Selber said.

“This is often the upper limit of size for patients considered for open nipple-sparing mastectomy. After the robotic dissection is complete, the entire breast specimen is removed en bloc, or in one piece, through the same incision in which the ports were placed,” Selber said. “Before we extend the procedure to more technically challenging, larger-breasted patients, we want to make sure it’s feasible and effective in patients who meet standard, open nipple-sparing mastectomy criteria.”

The initial version of the trial protocol does not include cancer-related outcomes as primary endpoints, because it is designed to assess 30-day safety and feasibility for evaluation by FDA.

“The safety and feasibility study we are proposing is not adequately powered to draw conclusions about oncologic outcomes,” Selber said. “Recurrence is a longer-term outcome, so the time horizon needed to establish recurrence rates must be measured in years, like the cervical cancer study from MD Anderson you just referenced.

“This is very different than establishing the safety and feasibility of a technique, which evaluates 30-day morbidity of the operation itself. A study of oncologic outcomes would require hundreds of patients and years of data collection. That work absolutely needs to be done, but would be scientifically inconclusive in the context of a study designed to evaluate the feasibility of a surgical technique.

“That said, oncologic outcomes will be secondary endpoints in the study, which means they will be officially tracked and reported on for the study period. And we will certainly follow all of the study patients with routine surveillance for the rest of their lives, as with all our cancer patients.”

After FDA issued the Feb. 28 advisory, an MD Anderson spokesperson said:

“At MD Anderson, patient safety is paramount. Our experts are working with the FDA for appropriate clearances prior to initiating any studies on minimally invasive surgical approaches to mastectomy in select patients,” the spokesperson said to *The Cancer Letter*. “Any study also will be subject to MD Anderson’s Institutional Review Board approval and monitoring for quality and safety. This research will explore immediate and long-term outcomes of the procedure.”

## Six years of unpleasant surprises

If surgeons do not account for confounding variables that may have an impact on oncologic outcomes—i.e. unintentional fragmentation or exposure of malignant tissue, and incomplete removal of breast tissue—MSK’s Kirstein and other experts say that robotic mastectomy could:

- Lower overall survival for patients who have breast cancer by increasing the risk of dissemination of disease via exposure of malignant tissue fragments,
- Spread incidental or preoperatively undetected cancers, which are found in about one in 10 women undergoing prophylactic mastectomies,
- Exponentially increase the risk of disease recurrence,
- Increase the risk of disease onset in patients with BRCA mutations, and
- Worsen survival outcomes in patients who undergo mastectomy, who would no longer receive screening for malignancies that may develop because of leftover tissue.

“Just recently, the study out of MD Anderson on robotic hysterectomies for cancer was published, suggesting poorer outcome with the robotic surgery,” Kirstein said. “None of those studies have been undertaken in breast cancer and robotic surgery, and that is concerning.”

Minimally invasive procedures can be useful, and in many surgical specialties they offer an improvement over the standard of care. However, in settings where robust prospective clinical and epidemiological data have not been generated, surgeons cannot make assumptions, experts say.

“Memorial’s decision is very reasonable, especially in light of [The New England Journal of Medicine](#) studies that showed that minimally invasive surgery worsened outcomes in patients who underwent laparoscopic and robotic radical hysterectomies,” said Otis Brawley, the Bloomberg Distinguished Professor of Oncology and Epidemiology at the Johns Hopkins School of Medicine. “That’s a very recent finding.”

Are minimally invasive surgical specialties especially prone to adopting new procedures and technologies as the standard of care—before prospective Level I safety data is generated?

After six years of unpleasant surprises, many experts agree that this trend has been painfully well documented in gynecology and gynecologic oncology:

- By 2013, power morcellation had become a standard of care over 20 years, without prospective studies that controlled for cancer-related outcomes. The procedure, which breaks up uterine tissue, contributed to harm and early deaths in a subset of women—who number in the hundreds, if not thousands—by disseminating occult or missed malignancies ([How Medical Devices Do Harm](#), *The Cancer Letter*).
- In April 2018, Yale University researchers found that when all uterine cancers are taken into account, prevalence of cancers undetected at the initiation of hysterectomies was almost as high as one in 70, in contrast to FDA’s one-in-350 estimate that focused on missed sarcomas and the 1 in 10,000 frequency of leiomyosarcoma cited by gynecologists for decades (*The Cancer Letter*, [May 18, 2018](#)).
- In October 2018, two groundbreaking papers published in *The New England Journal of Medicine* by gynecologic oncologists demonstrated that women who were subjected to minimally invasive



surgery for early-stage cervical cancer were four times more likely to die from that disease within three years, three times more likely to have a recurrence within three years, and had shorter survival, compared to women who underwent open surgery (The Cancer Letter, [Nov. 2, 2018](#)).

“These results highlight the hazards of assuming the oncologic equivalence of a new method of performing a cancer operation and adopting it widely in the absence of Level I evidence,” Stephen Rubin, chief of the Division of Gynecologic Oncology, professor in Department of Surgical Oncology, and Paul Grotzinger and Wilbur Raab Chair in Surgical Oncology at Fox Chase Cancer Center, said to The Cancer Letter.

The debate over power morcellation and minimally invasive approaches to cervical cancer show that surgeons shouldn’t make assumptions, said Brian Slomovitz, director of the Division of Gynecologic Oncology, Department of Obstetrics and Gynecology at the University of Miami, Miller School of Medicine, and co-leader of the Gynecologic Cancers Site Disease Group at Sylvester Comprehensive Cancer Center.

“It shows that, in a clear way, we can’t make assumptions in anything we do. The assumption that robotic surgery would be just as good as open surgery is clearly demonstrated here that it’s not a fair assumption,” Slomovitz said to The Cancer Letter. “We need to carefully evaluate the way we’re doing things and not just assume that one way is good because it’s associated with a shorter hospital stay, or it’s associated with small incisions.

“As surgeons who care for patients that could have deadly diseases, ‘getting the tumor out’ is not simply the answer, but how we get the tumor out and in what fashion, and whether that affects the biology and aggressiveness of the disease—we learn that here, and we learned that in morcellation for sarco-

ma and other uterine cancers, that it does matter.”

If these experts are right, without epidemiological data, and in the absence of studies with oncologic outcomes as primary endpoints:

- Surgeons cannot assume that the tissue, especially tumors or masses that are at risk for developing cancer, is benign.
- Surgeons cannot assume that new techniques are oncologically safe—i.e. minimally invasive procedures would not spread existing disease or undetected disease.
- Surgeons cannot assume that innovative changes to the standard of care would yield outcomes that are superior to established techniques, particularly in settings where cancer-related outcomes are a concern.

When surgeons innovate, how much rigor should be required? And how much risk is acceptable?

If surgeons realize, retrospectively, that patients who might have otherwise done well have been sacrificed for a decade or two at the altar of innovation—they will find that saying “Oops, sorry...” isn’t good enough.

Who is responsible for preventing avoidable harm?

“I strongly, strongly believe that our academic institutions need to lead these studies,” Penn’s Brooks said. “Otherwise, we would still be doing radical hysterectomies for early-stage cervical cancer patients with the robot.

“I think we should not avoid these studies because of the fear that something bad could happen. Until you study, you don’t know.

“If it’s a long study, it’s a long study. I’m not that old. I’ll be around when it’s done.”

“

This is very different than establishing the safety and feasibility of a technique, which evaluates 30-day morbidity of the operation itself. A study of oncologic outcomes would require hundreds of patients and years of data collection.

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– Jesse C. Selber

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Kirstein spoke with  
Matthew Ong, a reporter with  
The Cancer Letter.

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CONVERSATION WITH  
THE CANCER LETTER

## MSK's Kirstein: Robotic mastectomy not demonstrated to be safe for treatment or prevention of breast cancer

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We do not believe the safety of this procedure for cancer treatment has been demonstrated and do not think it should be performed outside of an IRB approved protocol with appropriate informed consent.

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**Laurie J. Kirstein**  
*Breast surgical oncologist,  
Memorial Sloan Kettering Cancer Center*



The Breast Surgical Service at Memorial Sloan Kettering Cancer Center has decided not to adopt—or study—robotic surgical devices in mastectomies, said Laurie Kirstein, a breast surgical oncologist at MSK.

“We discussed it as a group under the leadership of our chief of breast surgery, Dr. Monica Morrow, fairly recently in the last few months, to assess the procedure from an oncologic perspective,” Kirstein said. “There have been no studies whatsoever to show if it’s oncologically equivalent, or not inferior, to what we already do in terms of recurrence and whether that recurrence risk impacts overall survival.

“And so, it’s very hard to adopt a new procedure that hasn’t been really tested, when the one we have is so good, and we know is safe.”

On Feb. 28, FDA issued a safety advisory, indicating that device manufacturers looking to market surgical tools for use in the prevention or treatment of cancer may now be required to study long-term oncologic endpoints in surgical trials “for time periods much longer than 30 days” (The Cancer Letter, [March 1](#)).

“At this point, given the recent FDA statement on robotic surgery and since the safety of the procedure has not been demonstrated, it’s not something we are pursuing at Memorial Sloan Kettering,” Kirstein said.

*Kirstein spoke with Matthew Ong, a reporter with The Cancer Letter.*

**Matthew Ong:** Thank you for discussing this with me. I became aware of robotic mastectomies after Dr. Stephen Chagares started doing it at Monmouth Medical Center and widely advertised the procedure. When did MSK start thinking about robotic mastectomies?

**Laurie Kirstein:** We don’t do them currently. We do not believe the safety of this procedure for cancer treatment has been demonstrated and do not think it should be performed outside of an IRB approved protocol with appropriate informed consent.

So, we discussed it as a group under the leadership of our chief of breast surgery, Dr. Monica Morrow, fairly recently in the last few months, to assess the procedure from an oncologic perspective. But that was only fairly recently, as the technique has also become a little bit more popular in the United States, without, so far, any data showing that it’s oncologically safe.

**How did your team arrive at the decision to not perform the procedure at MSK?**

**LK:** The only studies that have been done for the robotic mastectomy have been on cosmesis and patient satisfaction and length of stay and things like that.

There have been no studies whatsoever to show if it’s oncologically equivalent, or not inferior, to what we already do in terms of recurrence and whether that recurrence risk impacts overall survival.

And so, it’s very hard to adopt a new procedure that hasn’t been really tested, when the one we have is so good, and we know is safe.

As a group, we discussed it, and the question of whether any of us were interested in learning how to do robotics—potentially come up with an IRB or come up with some sort of clinical trial, in which we could test the technique in a more rigorous, oncologic way—was brought up amongst the group.

At this point, given the recent FDA statement on robotic surgery and since the safety of the procedure has not been demonstrated, it’s not something we are pursuing at Memorial Sloan Kettering.

The issue for us is that you have a procedure that is going to be much longer than your standard mastectomy. It’s a lot more expensive than your standard mastectomy, and we’re not really sure that it’s cosmetically better in the long run than what we already do for, let’s say, a nipple-sparing mastectomy or other ways to do it.

**Can you explain in greater detail why it’s not cosmetically better and why current standard of care is, as you said, so good that there is no immediate reason to move to robotic techniques?**

**LK:** What we have today is, let’s say that a patient wants to have a nipple-sparing mastectomy, which is what the robotic offers—we do them now with incisions that are incredible well-placed, so that they are either in the inframammary fold or somewhere that heals that you don’t see it.

Even though the incisions are a little larger than what they do with the robotic mastectomy, you can see much better, you have much more better visualization so that you can see the tissue planes that you need to dissect in order to make sure that you are really getting out all the breast tissue—with the technique that's current.

You really want to make sure you get out all the breast tissue. You want to make sure you can see all the way around when you are doing a dissection, and you want to take it out in one piece, or en bloc.

And the concern for the robotic mastectomy is that the first part of the dissection is actually done blindly. There is no visualization, and the robot is only really used for the far-medial, or the piece that is closest to the chest bone. So, there's a concern about being able to see what you're doing and making sure you're actually getting out enough tissue.

There were concerns for other surgeons, where they took out the tissue in pieces, rather than in one en bloc section—so it's very hard or impossible to evaluate margins, for example, for a cancer, if you haven't taken it out in one piece. You've sort of chopped it up into pieces. And so, oncologically, we know that's not the right way to treat patients.

So, for now, we have these great techniques to be able to hide our incisions and so, and it's a quick, much faster procedure. It's much less expensive, so patients in the long run look great.

It's easy to do a mastectomy and leave a lot of breast tissue behind and really look good, because then it's nice and soft, and it's supple. But that's not a good cancer procedure.

So, unless you can see what you are doing, and you can make sure that you're

really doing everything that you're supposed to, it's not safe for the patient.

**What's the risk profile of patients coming in for breast surgery, generally? I understand that even patients who choose prophylactic mastectomies because of atypia or BRCA mutations are high-risk.**

**LK:** Correct.

**Are any of these patients low-risk?**

**LK:** So, those are not low-risk patients. The patients who are at average risk for breast cancer are those who are, obviously not high-risk—so, patients who don't carry BRCA mutations, patients who haven't been diagnosed with a TPR lobular carcinoma in-situ.

The concern about robotic mastectomies on that population—those patients are screened regularly, at much more regular intervals than the average population; right?

So, we see these patients a couple of times of year. Sometimes they are screened with MRIs in addition to mammograms. If they were to have an inadequate robotic mastectomy, they would no longer be getting screened, because they would be told that they had a mastectomy, and therefore the tissue that was left behind, which is usually a fair amount in robotic mastectomies, is at much higher risk for developing breast cancer. And then they're not being screened. So, that's of concern.

**What are the chances of finding an incidental or preoperatively undetected cancer at the time of prophylactic mastectomy for women?**

**LK:** In the BRCA population, it's about 10 percent of the time there's some incidental cancer that's found; nine out of 10 times that's ductal carcinoma in-situ.

When you look at the average-risk patients, it's usually even lower than that. Once in a while, you'll see patients who had a reduction mammoplasty, like a breast reduction, and they will have a DCIS.

If they had a negative mammogram beforehand, and they will incidentally, have a DCIS, and that doesn't happen very often, but it does happen.

**So, is robotic mastectomy appropriate for any population in women?**

**LK:** No, we haven't been able to prove that yet. We've not been able to prove that at all. We haven't been able to prove that it's a procedure that can be done that's adequate compared to the ones that we already have.

**And that includes fragmentation or leaving tissue behind?**

**LK:** It follows that, right.

Lumpectomies leave breast tissue behind as well, but that is done with good margins. This might be rhetorical: what's the difference here?

**LK:** The difference is that, after a lumpectomy, patients routinely receive radiation treatments to the remaining breast tissue.

Multiple randomized clinical trials have demonstrated that this controls any undetected cancer that might be left behind. Radiation is not routine after a mastectomy. In addition, women having a lumpectomy are followed with breast imaging including mammograms.

When you have a mastectomy, robotic or otherwise, there's no imaging that's being done to screen. If there's tissue left behind, nobody's screening that tissue for cancer.

I see. So, is there a problem with framing these robotic procedures that we're talking about as "mastectomies"?

**LK:** You could say that. Yes.

Because when you call something a mastectomy—and for good reason—you are promising the patient that you're removing the entire breast to lower or eliminate the risk for recurrence of disease, or tissue with malignant potential being left behind?

**LK:** Correct.

But, with robotic "mastectomies," you're saying that there is no certainty of that, as we know it?

**LK:** Correct.

In your review of existing literature, including European and Italian studies on this matter, do these studies take into consideration cancer-related outcomes or cancer risk as primary endpoints?

**LK:** They haven't. Zero. There are no studies doing that. The only study that has been published so far was an Italian study, in which they reported patient-reported outcomes such as patient satisfaction, length of stay and cosmetic outcome. That's it. There were no volumetric studies; there were no cancer-related studies. Nothing.

But, for at-risk populations—which includes all women, it seems—shouldn't cancer-related outcomes be the primary focus?

**LK:** Yes, if you think about it as akin to the other surgical specialties, which have adopted robotic procedures, such as gynecologic oncology and colorectal surgery, they did side-by-side evaluations of robotics vs. standard open procedures, or laparoscopic procedures,

and they did a rigorous study with thousands of patients, with long-term follow up. Both of those studies have shown that it is not the best procedure in terms of risk-recurrence, for different populations.

Just recently, the study out of MD Anderson on robotic hysterectomies for cancer was published, suggesting poorer outcome with the robotic surgery.

The two practice-changing papers that were published in NEJM in October.

**LK:** Right. And there were similar issues with colorectal surgery. None of those studies have been undertaken in breast cancer and robotic surgery, and that is concerning.

Are we looking at parallel scenarios here in minimally invasive surgery? In gynecology—for instance, power morcellation for presumed benign hysterectomies and myomectomies, and you mentioned minimally invasive radical hysterectomies for cervical cancer—these procedures were adopted as the standard of care before prospective data testing cancer-related outcomes had been generated.

**LK:** Right. That's what we're concerned about.



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When you are going to change what you do drastically, you really should have Level I data showing that it's at least not inferior to what you're doing.

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Was MSK worried that this might happen in breast surgery as well, that if your department did not look at this in a prospective way, this might have evolved into a new standard of care without Level I safety data?

**LK:** That is correct. We all want that Level I data before adopting new procedures or drug therapies especially for cancer patients, right?

When you are going to change what you do drastically, you really should have Level I data showing that it's at least not inferior to what you're doing.

That being said, we have no current plans to study this at MSK, and, given the recent FDA statement, don't consider it a priority.

And when you say “drastically,” you mean this is not just a tweak to the standard of care? What do you call this?

**LK:** This is a major change, a major deviation. A major change in the standard of care and in the technique.

So, the main takeaway is that there is no apparent or real advantage of robotic mastectomies over existing standard of care, as far as MSK is concerned?

**LK:** Correct.

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Hunt and Selber spoke with  
Matthew Ong, a reporter with  
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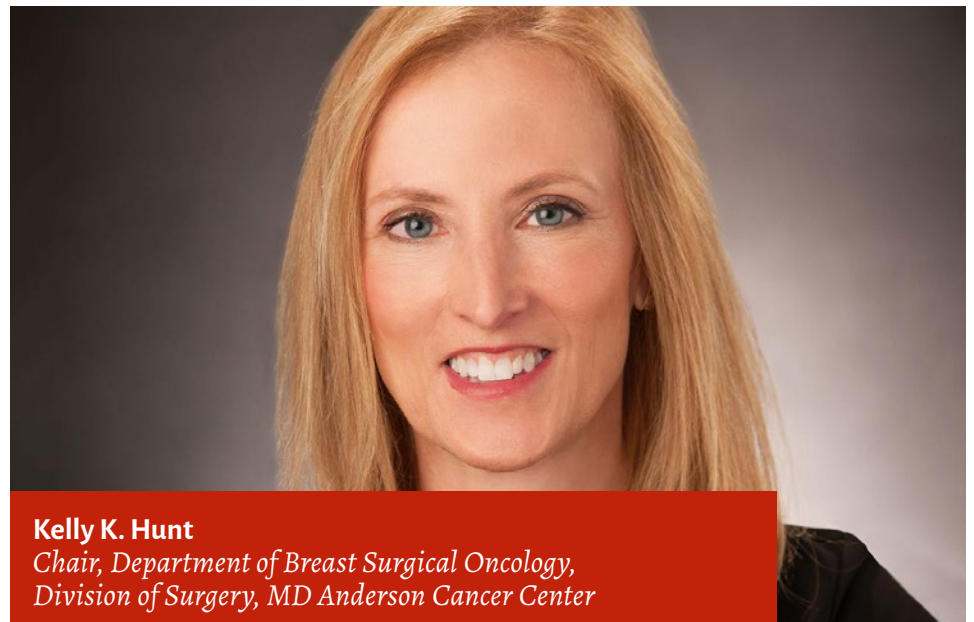
## MD Anderson's Hunt and Selber: We will study immediate and long-term outcomes of robotic mastectomy in a prospective trial

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For the nipple-sparing robotic mastectomy, we're doing this as an IRB protocol, because we want to define the endpoints. We also want to be able to measure those prospectively.

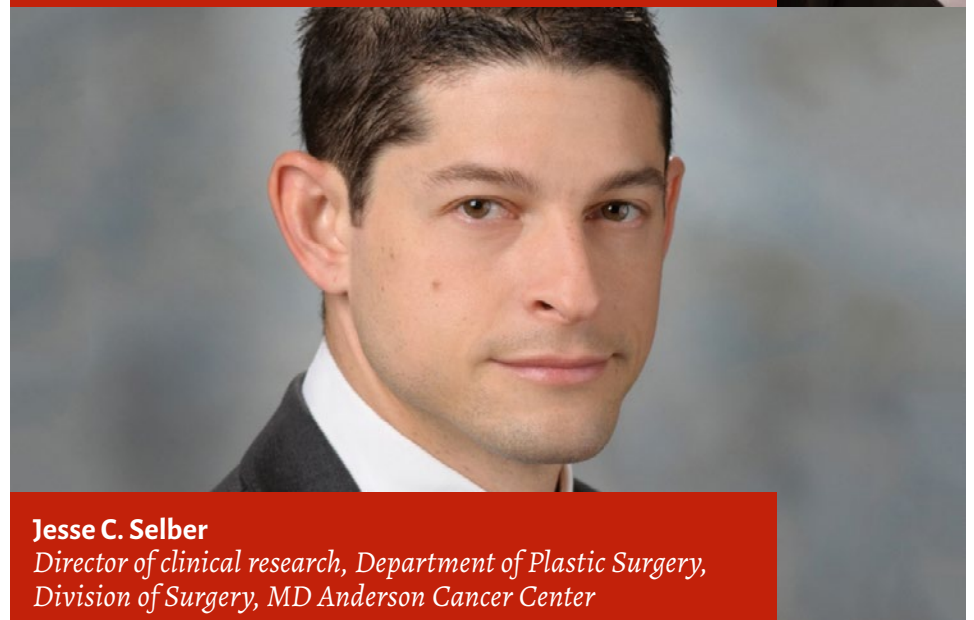
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– Kelly K. Hunt



**Kelly K. Hunt**

*Chair, Department of Breast Surgical Oncology,  
Division of Surgery, MD Anderson Cancer Center*



**Jesse C. Selber**

*Director of clinical research, Department of Plastic Surgery,  
Division of Surgery, MD Anderson Cancer Center*



Robotic mastectomy deserves to be studied, because the procedure may improve cancer-related outcomes, surgeons at MD Anderson Cancer Center say.

Both robotic and open procedures allow the surgeon to follow oncologic principles, said Jesse Selber, professor and director of clinical research at the Department of Plastic Surgery at MD Anderson.

“The plane of dissection is identical; the way the specimen is removed, oriented and labeled is identical; the margin evaluation and permanent pathologic evaluation is identical,” Selber said. “In fact, because of this improved precision and visualization, there is reason to believe that oncologic outcomes might be improved, because the surgeon will have a better view of the breast tissue that needs to be removed.”

The breast gland can be removed en bloc via robotic surgery, said Kelly Hunt, chair of the Department of Breast Surgical Oncology, and a professor in the Division of Surgery at MD Anderson.

“There’s no reason why you would not be able to remove it en bloc,” Hunt said. “Of all the robotic mastectomies that I’ve seen, and a couple of our surgeons have participated in training courses, and it’s very feasible to remove.

“So, it’s not a matter of suctioning it out through a small hole or something like that. That’s not what we would be doing.”

The MD Anderson protocol, which is designed to also enroll patients at Northwell Health Long Island Jewish Medical Center and two institutions in Chicago, will be studying long-term oncologic outcomes. The trial is funded by Intuitive Surgical, manufacturer of the da Vinci Surgical System.

“At MD Anderson, patient safety is paramount. Our experts are working with the FDA for appropriate clearances prior to initiating any studies on minimally invasive surgical approaches to mastectomy in select patients,” an MD Anderson spokesperson said to The Cancer Letter. “Any study also will be subject to MD Anderson’s Institutional Review Board approval and monitoring for quality and safety. This research will explore immediate and long-term outcomes of the procedure.”

*Selber and Hunt spoke with Matthew Ong, a reporter with The Cancer Letter.*

**Matthew Ong: Are robotic mastectomy procedures being performed at MD Anderson Cancer Center?**

**Kelly Hunt:** We are not currently doing them. However, we have a couple of surgeons who have been credentialed in robotic surgery, and one principal investigator with over 12 years of robotic experience.

We wrote a protocol and will be investigating this procedure in a prospective study.

**In crafting the protocol, what’s your thinking in terms of endpoints and considerations for the prospective trial? What’s the goal here?**

**KH:** Our goal is to investigate the use of robotic procedures for nipple-sparing mastectomies. We would like to use them specifically for those procedures, because, when working with plastic

surgery, we tend to make our incisions either in the axilla or in the inframammary fold below the breast, which makes it more difficult to access all of the breast tissue in order to perform a complete mastectomy.

When you’re trying to access the tissue and skin through these incisions above the nipple and laterally, getting to those areas can be challenging, and currently available retractors are not very useful.

Also, the surgeon tends to have to get into uncomfortable positions in order to have good visualization of the entire operative field. The advantage of the robot is that it allows you to get into remote areas more easily with better visualization. We can use the robot to get into positions that your hand and wrist cannot really achieve without significant difficulty for the surgeon.

**In general, what’s involved in the robotic process?**

**Jesse Selber:** The challenge of nipple-sparing mastectomies is trying to achieve a precise dissection through a small incision with minimal illumination and a limited ability to see and reach tissue planes. The robot provides the surgeon with a crystal clear, magnified, front row seat to the most-technically difficult part of a nipple-sparing mastectomy. We think this could result in better outcomes.

Initially, the surgeon makes a four-to-five-centimeter incision, lateral to the breast, at about the level of the nipple. Some initial dissection is performed to create an optical cavity and a confluent space within which to place the instruments. The slender robotic arms are then passed through a port manager, which is fitted into the incision. The port manager separates the arms in space and maintains an airtight seal for insufflation.

**The device being the da Vinci Surgical Systems?**

**JS:** Yes, the da Vinci, by Intuitive Surgical, is the only currently commercially available robotic surgical system. After the robotic dissection is complete, the entire breast specimen is removed en bloc, or in one piece, through the same incision in which the ports were placed. The specimen is oriented, imaged in pathology, and sent for frozen section or permanent histologic analysis, depending on the indication for the mastectomy (risk reduction vs. cancer treatment).

This process is routine for any type of mastectomy. Any subsequent reconstruction would also be performed through the same incision.

**Will the prospective trial be looking at whether this is a reliable way of removing breast tissue en bloc without, as much as possible, leaving any malignant tissue or tissue with malignant potential behind?**

**KH:** Exactly. Right.

**But for now, we don't know if that is consistently achievable?**

**KH:** Correct. So, there are a lot of reasons why we would or would not do a nipple-sparing procedure—not only if the tumor's approaching the nipple. Going back almost 30 years when people

first started doing skin-sparing surgeries, the idea was to remove the nipple and the areola complex. So, you made an incision around the areola.

To do a skin-sparing procedure, we're trying to save the entire skin envelope, except for the nipple and areola, and remove all of the underlying breast tissue. There is a normal anatomic plane between the superficial fat under the skin and the actual mammary gland tissue.

When a surgeon does a skin-sparing mastectomy, they make an incision around the nipple areola complex. They sometimes make a little extension out toward the axilla or lower down toward the inframammary fold, depending on what's needed based on the size of the breast. And so then the surgeon uses specific devices to literally lift the skin off of the mammary gland, which is sent to pathology for examination.

Instead of "nipple-sparing," some people call it a total skin-sparing mastectomy, meaning we've left the skin, the nipple skin and the areola. In order to do that, we don't like to make the incision around the nipple areola, because that can interfere with the blood supply to the nipple. Therefore, you're more likely to end up with nipple loss. So it's better if you can make your incision somewhere else.

I call these "remote" incisions because they're off the breast. We're trying to keep scars off of the breast as much as possible. A lot of people think of it as cosmetic, because you're not putting the scar in the breast, but that's not the only issue. The medical issue is blood supply to the nipple. Some of that blood supply comes through the skin, but some of it comes through the breast, underneath the nipple.

**Just to clarify, when you say remote, are these incisions specific to certain techniques?**

**KH:** No. The access incision can be remote, whether you're doing it the standard way with electrocautery, with robotics, or when done laparoscopically. The techniques may be similar across diseases, but there are many differences between diseases such as breast cancer and cervical cancer.

**Right, the anatomy is completely different. For instance, in one case, you are dealing with tissues deep inside the abdominal and pelvic cavity, whereas the other is on or much closer to the surface?**

**KH:** It's that, but it's also that some of these breast cancers are usually deep in the parenchyma, surgeons aren't touching them, manipulating them with the instruments.

**So, just to make sure I really understand this, only one incision is made, or are there a number of small port incisions? An ideal situation is one in which you would only make one incision?**

**JS:** Yes. There is one single incision. The specimen is removed in its entirety through the initial incision, remote from the breast, as Dr. Hunt described, and

specifically designed to accommodate the instruments, the specimen, and any post-mastectomy reconstruction.

The procedure is very similar to an open nipple-sparing mastectomy, only with better precision and visualization. The robotic technique we will be using is very close to the way that it's been described and published by Ben Sarfati in Paris and Antonio Toesca in Milan. It's become a relatively standardized approach that many surgeons are beginning to consider because of the potential benefits over the traditional approach.

What's the cutoff point in terms of breast size for this procedure?

**JS:** In our protocol, we are targeting C-cup breasts and smaller. This is often the upper limit of size for patients considered for open nipple-sparing mastectomy. So, the indications for the robotic cohort in the proposed study are comparable to those for an open nipple-sparing mastectomy.

Before we extend the procedure to more technically challenging, larger-breasted patients, we want to make sure it's feasible and effective in patients who meet standard, open nipple-sparing mastectomy criteria.

I did notice that the prospective protocol you mentioned does not include oncologic endpoints.

**JS:** That's correct.

We touched briefly on this—recent studies in cervical cancer show that overall survival was worsened for women who were subjected to minimally invasive procedures. As you know, that was an incidental finding in a trial studying non-inferiority of laparoscopic and robotic radical hysterectomies vs. open radical hysterectomies. Gyn-oncs believed that it was equivalent or better—and that indeed appeared to be the case for short-term outcomes—but not three to five-year outcomes.

The concern here as well is, if you're not looking directly at cancer-related outcomes—especially in a new surgical procedure involving patients with cancer or at-risk patients—is there a risk that you're subjecting women to some unforeseen harm that you may be missing, because you're not controlling for it? I understand that the anatomy here is different, of course.

**JS:** That's not the way that I would characterize it. The safety and feasibility study we are proposing is not adequately powered to draw conclusions about oncologic outcomes.

Let me explain that statement: Cure rates for early-stage disease in patients who would be candidates for nipple-sparing mastectomy are high, meaning recurrence and residual cancer rates are very low. In a clinical study, this event rate is called the effect size.

Because the effect size is very small, the number of patients, or sample size, needed to establish an oncologic outcome is very large. This combination of sample size and effect size determines the study's statistical power.

In addition, recurrence is a longer-term outcome, so the time horizon needed to establish recurrence rates must be measured in years, like the cervical cancer study from MD Anderson you just referenced.



The robot provides the surgeon with a crystal clear, magnified, front row seat to the most technically difficult part of a nipple-sparing mastectomy. We think this could result in better outcomes.

— Jesse C. Selber



This is very different than establishing the safety and feasibility of a technique, which evaluates 30-day morbidity of the operation itself. A study of oncologic outcomes would require hundreds of patients and years of data collection. That work absolutely needs to be done, but would be scientifically inconclusive in the context of a study designed to evaluate the feasibility of a surgical technique.

That said, oncologic outcomes will be secondary endpoints in the study, which

means they will be officially tracked and reported on for the study period. And we will certainly follow all of the study patients with routine surveillance for the rest of their lives, as with all our cancer patients.

It's important to make clear that the oncologic principles of the robotic mastectomy are identical to the open procedure. The plane of dissection is identical; the way the specimen is removed, oriented and labeled is identical; the margin evaluation and permanent pathologic evaluation is identical.

In addition, the technical aspects of the robotic surgery are similar, but potentially better than the open surgery, which is already performed through a small incision with limited access. The robot here simply functions as a more precise extension of the human hands and eyes, seeing into difficult to reach areas of the dissection.

In fact, because of this improved precision and visualization, there is reason to believe that oncologic outcomes might be improved, because the surgeon will have a better view of the breast tissue that needs to be removed.

**Based on what you know from existing evidence, can tissue fragmentation be avoided? Will tissue with malignant potential be left behind?**

**KH:** I need to go back and say that people have been doing the skin-sparing, nipple-sparing surgery for a long, long time.

And in doing that, people have done studies to compare the oncologic outcomes and amount of breast tissue left behind. When we used to do radical or

modified-radical mastectomies, surgeons removed most of the skin of the chest wall with the breast and axillary lymph nodes.

When skin-sparing mastectomies were introduced, clinicians did studies looking at punch biopsies, small biopsies along the skin to include subcutaneous tissue, especially underneath the breast along the inframammary fold and other areas in the standard mastectomy procedure and skin-sparing procedures.

The studies found that the amount of breast tissue left behind was the same with both procedures. This is not malignant tissue, but residual breast tissue. There were no differences in oncologic outcomes between the different procedures. So, when we are doing a skin-sparing or nipple-sparing mastectomy, we try to pay attention to the anatomy of the mammary gland in order to remove as much of the breast tissue as possible.

The challenge is that the breast tissue does extend, sometimes, beyond those traditionally described anatomic landmarks. Also, the Cooper's ligaments extend from the breast itself up to the skin. We know that breast cells do go along those ligaments.

We tell our patients that we know when we do a mastectomy, no matter which technique is used, we're not removing 100 percent of the breast tissue.

It's not really feasible, partly because the breast tissue is not a different color than the subcutaneous fat or tissue.

We try to follow what we know are the normal anatomic landmarks, and we do the procedure as basically an anatomic resection of the gland.

**I see. Is the goal, however, still the same, i.e. to basically remove as much as you can, because that's what a mastectomy is designed to do?**

**KH:** Exactly. I have participated in robotic surgery for other indications, and in my experience, you can visualize things much better with the robot than you can with a standard skin-sparing or nipple-sparing procedure.

Again, because you're working through these small incisions where it is sometimes difficult to fully illuminate all areas and the surgeon is having to sort of torque their head and neck around to be able to see in these small spaces. To get to the areas under the clavicle and out toward the armpit we are always striving to assure that we have removed all of the breast tissue.

So, in my experience, I would think that the robotic access may provide better visualization than what we have with the standard approaches.

Of course, having no scars on the breast is something we would like to offer patients, but better visualization would make us feel like we've done a more complete resection. The robot allows for that type of access.

Also, in order for us to try to remove all the breast tissue, we have to pull up on the skin of the breast, sometimes vigorously to get up over the nipple, up to the tissue under the clavicle. It can be a long distance, depending on the size of the breast.

And so, sometimes we're putting a lot of tension on those skin flaps, which can cause problems with blood supply and viability as well. With the robotic proce-



dures, the instruments and insufflation lift the skin up, allowing better visualization without so much pressure and tension on the skin.

Since one of the goals here is to remove breast tissue en bloc—is that possible, as we know it?

**KH:** Correct. There's no reason why you would not be able to remove it en bloc. Of all the robotic mastectomies that I've seen, and a couple of our surgeons have participated in training courses, and it's very feasible to remove.

So, it's not a matter of suctioning it out through a small hole or something like that. That's not what we would be doing.

That would be against oncologic surgical principles.

**KH:** Yes. Morcellating surgeries are absolutely not something we would do. And usually, for the nipple-sparing, skin-sparing mastectomies, the tumors are smaller, and the location in the breast is known.

They can be larger, but usually for patients that have more advanced disease, we're doing standard mastectomies, because of the nature of the tumor.

With these-nipple sparing and skin-sparing procedures, we're generally doing these for patients with smaller, earlier-stage disease. We know where the tumor is, and it's always our plan to remove the breast and the tissue around that without any fragmentation.

But breast cancer is a little bit different from other cancers in that core needle

biopsies are done all the time for diagnosis. These core biopsies are done through the skin, through the breast parenchyma into the breast, into the tumor. The tumor tissue is then extracted through that small core biopsy incision and assessed.

After decades of this in practice, we have not seen that that causes the tumor cells to seed at the incision site of the core biopsy.

So, basically, whoever is doing it with only cosmesis and patient satisfaction as the primary endpoint—meaning, doing robotic mastectomy via only one incision for cosmetic purposes and then forcing the entire gland through one incision, or breaking it up—whoever is doing it that way, is doing it wrong?

**KH:** It's ideal not to break up the tissue into little pieces and remove it, then the pathologist will not be able to assess the margins. We always look at the margins of resection to be sure we haven't left any tumor behind on the skin or on the muscle or in the surrounding anatomic region.

Margin assessment is standard procedure for breast surgery, so we certainly don't want to miss the opportunity to assess the margin.

However, sometimes when you're removing the breast tissue—the nature of the breast tissue, it has both breast lobules and parenchyma. It also has some fatty tissue just like other organs in our body. Sometimes, part of that tissue may, as you're pulling to remove it, come apart.

That's not a major issue, but certainly taking the breast or removing the skin

and then pulling the breast and cutting it up into small pieces to get it out through a small incision is not ideal.

And it's also not ideal to take a large mass of breast tissue and try to pull it en bloc through a small incision, because you have to make an appropriate-size incision anyway?

**KH:** Right.

You mentioned MD Anderson is doing this as a prospective trial, and you're not offering this as a routine procedure. As a matter of principle, would it be wrong for individual physicians or provider institutions to advertise and offer robotic mastectomy to patients outside a surgical clinical trial? Which would be the opposite of MD Anderson's approach?

**KH:** At MD Anderson, we have a committee that specifically evaluates new technology and how it should be introduced into the operating theater.

And we always want to assess a new indication for an existing technology. And so, that would be where the robotic mastectomy comes in. MD Anderson surgeons have done thousands of robotic procedures for other diseases or other indications.

The question is, should it be done for mastectomies? We have a process at MD Anderson whereby we applied through our institution for the privilege of doing

these same robotic procedures with existing technology for mastectomies.

We had to demonstrate that: the surgeon has been credentialed; pathologists understand how the tissues are going to be assessed, or what implications there are with respect to this type of procedure; and the whole team has been credentialed for utilizing the robotic platform.

There were multiple other criteria that our institution had to evaluate before we're able to move forward.

Then we have a committee that assessed, "Okay, is this something that can move forward? As long as the patient signs a consent, then it does not need an IRB protocol? Or, is this something that should be done as an IRB protocol?"

For the nipple-sparing robotic mastectomy, we're doing this as an IRB protocol, because we want to define the endpoints. We also want to be able to measure those prospectively.

Sometimes, when you go back retrospectively, the data is not clear, and so, it's hard to report accurately on the success, or lack thereof.

So, after evaluating all the different parameters, we elected to do this as a prospective IRB protocol.

Right. And the protocol, as you describe it, is it accurate to say that it's essentially a formal investigational study and surgical clinical trial?

**KH:** Exactly.

I see. Are there plans to specifically look at cancer-related outcomes in a separate study, and is that relevant?

**JS:** These patients will be followed as we follow all mastectomy patients, with regularly scheduled surveillance guided by a multi-disciplinary team. This is critical to ensuring disease free survival and detecting recurrence, if it happens. These are basic principles of surgical oncology and we take them very seriously in every disease site we treat.

How long do you expect it will take to complete enrollment?

**JS:** Approximately a year, but that's subject to enrollment. This is a multi-institutional study, so enrollment at each site will only play a part in the time required for total enrollment.

This is also an early-days question, but once the trial is completed and you find that robotic mastectomy isn't inferior to standard of care—where 30-day safety and efficacy outcomes are concerned—would that be sufficient evidence to support offering robotic mastectomies as a routine procedure at MD Anderson?

**JS:** That is a decision that will be made collectively with the Food and Drug Administration. This is an IDE, or Investi-

gational Device Exemption study. That means that the FDA has reviewed the protocol and given investigators permission to use the device "off-label" for the purpose of gathering data. Based on that data, the FDA can then make an evidence-based decision whether or not to grant a 510k indication for "on-label" use.

Based on the data provided from the study, the FDA will ultimately decide whether this is an appropriate use of the device. We believe it is; many others also believe that it is, which is why it is being introduced in multiple centers around the world.

The difference between evaluating the technique in coordination with the FDA and under IRB guidance is that everything is done in a controlled and regulated fashion. It's critical to be absolutely sure that we're not only doing the right thing, but doing the thing right.

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It's critical to be absolutely sure that we're not only doing the right thing, but doing the thing right.

—Jesse C. Selber

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Brooks spoke with  
Matthew Ong, a reporter with  
The Cancer Letter.

A



CONVERSATION WITH  
THE CANCER LETTER

## Penn's Brooks: Surgeons should study oncologic endpoints for years, not just 30-day outcomes

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We asked how we're going to do this after the FDA advisory, and, well, we're just going to have to tell the patients we have to follow them after surgery for 10 to 20 years. And that's what we'll do.

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**Ari D. Brooks**

*Director, Integrated Breast Center,  
University of Pennsylvania Hospital System,  
Director, Endocrine and Oncologic Surgery  
Professor of Clinical Surgery, Penn Medicine*



The University of Pennsylvania was planning a short-term trial for robotic mastectomies, but after an FDA advisory, investigators decided to revise that protocol to include assessment of cancer-related outcomes, said Ari Brooks, director of endocrine and oncologic surgery, director of the Integrated Breast Center at the University of Pennsylvania Health System, and professor of clinical surgery at Penn Medicine.

"I'm not doing anything until I have an FDA Investigational Device Exemption. I'm not doing it until there's consent and it's IRB-approved," Brooks said. "I'm not doing it. I'm not screwing around."

Brooks had originally written a trial protocol that would assess 30-day outcomes of prophylactic robotic mastectomies for patients with BRCA mutations. His study isn't funded by industry.

On Feb. 28, FDA issued a safety advisory, indicating that device manufacturers looking to market surgical tools for use in the prevention or treatment of cancer may now be required to study long-term oncologic endpoints in surgical trials "for time periods much longer than 30 days" (The Cancer Letter, [March 1](#)).

"We asked how we're going to do this after the FDA advisory, and well, we're just going to have to tell the patients we have to follow them after surgery for 10 to 20 years," Brooks said. "And that's what we'll do."

"In the Bassett Center for BRCA at Penn, they're followed anyway, because they have the BRCA gene, so we'll follow them. We'll follow them for 10, 20 years, it's okay."

"I don't have a problem with that. And, you know, it's right. It's a good thing, really. They shouldn't just study patients for 30 days."

*Brooks spoke with Matthew Ong, a reporter with The Cancer Letter.*

**Matthew Ong: How did you learn about robotic mastectomy, and what led you to design your protocol?**

**Ari Brooks:** Back in 2017, there was a presentation at the London breast meeting. I didn't actually go; my plastic surgery buddy went. And Benjamin Sarfati, from France, was presenting his video about the robotic mastectomies he was doing. There are two centers—one in Paris, and one in Milan, with Antonio Toesca.

So, I actually just emailed Sarfati and asked if I could go, and I just went. The hospital didn't pay. Intuitive [Surgical] didn't pay. I just wanted to see for myself, because I was having a hard time understanding why.

Yes, we could do it, but why? Actually, I didn't even know how you could do it. I had gone to Intuitive with Dr. Suhail Kanchwala, my plastic surgeon, just to help out with the development of the robotic flap, and they told me, "Oh yeah, there's this robotic thing going on," and I just couldn't figure it out.

Anyway, I went to Paris and watched them do one, and I was blown away. It's a difficult case for us—a nipple-sparing mastectomy can be a very hard case, because you're trying to do it cosmetically, you're trying to keep it to a tiny hole, and your visibility's terrible. You're working with a lighted retractor and a really long bovie (cautery), and you're trying to see. It's not great.

When he put in the robot after mobilizing the skin off the breast using tumescence (saline injection and scissor dissection from a distance) he put the robot in, and it was amazing. He has 3x magnification, he can use other instru-

ments and pick up the bleeders and stop the bleeding, he can see if something is hanging down that should be included with the mastectomy specimen; he can you know, see the tissue planes far away from the incision much better than we ever can when we do a regular, open nipple-sparing procedure.

So, that was amazing. And then, when he got the breast out and the breast comes out in one piece from the incision that he makes—and the incision is further from the nipple than I would make—but it comes out, and looks just like my specimens, nothing different, and he's not morcellating or anything like that.

Then, the plastic surgeon will take over. He literally inserts an implant and it's already, the breast is already breast-shaped, because he hasn't divided the muscle, the nipple's still there, the attachments of the skin to the cleavage and to the curve under the breast, all that's still there, and the incision is far away, and so he just throws the implant in there, and he sews up the incision that's a mile away from the implant.

He doesn't have to worry about infection. He doesn't have to worry about sticking it behind the muscle, and then the patient wakes up and she's got no pain and cosmetically, it's beautiful. So, I saw that when I was there, and then I became kind of a believer. So, now I understand why.

Anyway, soon after, the papers came out in the New England Journal of Medicine about early-stage cervical cancer, and there's a survival difference and that's crazy. I was blown away by that. So then, I've been writing a protocol, and I talked to Intuitive Surgical about funding, and they said they didn't want to. I actually was happy, because their contracts take so long and they would want to own the data. This way I can be an independent investigator.

As you may know, Intuitive is funding a multicenter trial with MD Anderson Cancer Center, Northwell Health Long Island Jewish Medical Center, and two other sites in Chicago.

**AB:** Yes. I talked to them before, and they said they would consider me, but they hadn't decided, so they told me they didn't want me—I was like, "No problem." So, last year, I wrote the protocol myself. I asked to borrow their protocol to see if I could match the same dates and data points that they're collecting in the same surveys.

I'm sure they won't enroll enough patients, and eventually, in order to get the paper out, you probably want to get a larger N. So, I'm structuring the study so my patients can be included.

How did the Feb. 28 FDA safety communication affect your protocol?

**AB:** It hasn't been submitted yet. As soon as the FDA announcement came out, I got some emails asking me to start having some meetings with the leadership of the hospital to find out how to move forward.

Basically, I get it. My study is written; it excludes cancers, so it's all prophylactic. We do a large volume of prophylactic mastectomies here because we have the Bassett Center.

For BRCA patients?

**AB:** Yes. But I don't have buy-in from anybody yet. That was my intention, to do only prophylactic, that the first trial would probably be 20 patients, maybe 30, because that's the learning curve. And it would be all just looking at cosmetic and satisfaction and that's it. And that was the study.

We asked how we're going to do this after the FDA advisory, and, well, we're just going to have to tell the patients we have to follow them after surgery for 10 to 20 years. And that's what we'll do.

Right, because we're talking about prophylactic surgery, not cancer surgery.

**AB:** Yes. In the Bassett Center for BRCA at Penn, they're followed anyway, because they have the BRCA gene, so we'll follow them. We'll follow them for 10, 20 years, it's okay. But that's number one.

Number two, the Italian study is enrolling patients with cancer, and looking at ClinicalTrials.gov, it's looking at mostly cosmetic stuff, but they are randomizing minimally invasive vs. open nipple-sparing. I think that's a very worthwhile thing and it's something I'd like to get to, but obviously, I have to get good enough at this in order to be able to randomize.

Otherwise, it's going to be crappy new surgery vs. good old surgery, so.

Is this the study led by Dr. Toesca, with long-term cancer-related outcomes as secondary endpoints?

**AB:** Yes. A couple of years ago, he published his first paper on feasibility and

all that. In this study, he includes cancers. The actual enrollment is 82 participants right now. Number one endpoint is patient satisfaction, one year. Average length of stay, one month. Post operative complications, one month.

Okay, here it is. Cumulative incidence of local recurrence, five years. That makes sense, with a cancer study. Cumulative incidence of axillary occurrences, five years, and cumulative incidence of distant occurrences, five years. The survival rate—disease-free survival and overall survival—all that is done in five years.

Anyway, that's what I want to do, too. I'll try to match up, so that our data can be combined. But, I'm not doing that first. My first priority is going to be getting good at it.

Have you performed any robotic mastectomies outside of an investigational setting?

**AB:** I have not. Absolutely not! No. I'm not doing anything until I have an FDA IDE. I'm not doing it until there's consent and it's IRB-approved. I'm not doing it. I'm not screwing around.

I get it. At a hospital up north, they're like, "Oh yeah, we'll take anything out with a robot." We don't learn anything from that. So, no, it has to be done as a study.

So, your protocol initially was designed to evaluate 30-day safety and effectiveness, and when FDA issued the safety communication, you decided to include long-term oncologic endpoints?

**AB:** Yes. I conceded that with these patients, we have to follow them long term. So, we will. I don't have a problem with that. And, you know, it's right. It's a good thing, really. They shouldn't just study patients for 30 days.

Are you planning on submitting the data to FDA? Meaning, are you looking for the agency to approve the use of robotic surgical devices in mastectomy?

**AB:** I don't care if the FDA approves it or not. I want to do the study and I'm not sponsored by Intuitive. They would love to get labeling, but I don't care.

I wrote and prepared an IDE for the FDA so they will be able to get my data, we're going to collect it under current FDA guidelines. They can look at the data and decide if they support it or not.

We have the whole center for FDA trials here at Penn. We'll participate, and if FDA uses our data and they approve it, great. But if they don't, okay, then maybe we've done a good thing.

I don't know the Italian study design as far as how they're going to do their follow up, but in general with mastectomies, you just examine the patient every year. It's not hard, because, if there's a recurrence, you check under the skin, and you could do imaging in people—when we do any other mastectomy, we're not doing imaging to follow up. We're not doing ultrasound. We don't need to.

Plus, patients that are enrolled in this study, at least in the first one, the breasts would be pretty small, so it will be very easy to examine them. Toesca's study says it will include A, B, C, D

cup sizes, and that's really big. I cannot imagine doing that.

So, robotically, I'm not planning to do larger and larger breasts.

How many patients are you aiming to enroll?

**AB:** The Italian study says there's 82 enrolled. That's a pretty high-volume center. And we actually have a high-volume center, too, for mastectomy—not at their rate—because of our Bassett Center. I think we can enroll. I doubt we'll get to 82 in a year, but I think we can enroll in this trial without a problem.

Has Dr. Toesca published preliminary results from his trial?

**AB:** Not from the randomized trial yet. You can see he's published a couple other things recently, and when they're done with enrollment, he'll give us the one-month follow-up on those endpoints—the cosmetic satisfaction and all that.

Then, you're going to have to hold your breath for another five to 10 years to get the data for the recurrences and other oncologic endpoints.

Which means, to date, there are no data on long-term cancer-related outcomes.

**AB:** No, there isn't. There's nothing. The study needs to be done. A cancer center or a high-volume center needs to do

this study. We have to show it's good or it's not good.

Otherwise, we would still be doing radical hysterectomies for early-stage cervical cancer patients with the robot. Now we know that's probably not a good idea, and we're not doing it.

Did we miss anything?

**AB:** No. I strongly, strongly believe that our academic institutions need to lead these studies. I think we should not avoid these studies because of the fear that something bad could happen. Until you study, you don't know.

Right, even if these studies are expensive, difficult and take a long time to conduct?

**AB:** Yes. If it's a long study, it's a long study. I'm not that old. I'll be around when it's done.

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If it's a long study, it's a long study. I'm not that old. I'll be around when it's done.

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# Chief Administrative Officer/ Associate Director for Administration and Finance

## THE OPPORTUNITY

As a member of the senior leadership team, the Chief Administrative Officer/Associate Director for Administration and Finance (CAO) of the UC Irvine Chao Family Comprehensive Cancer Center (CFCCC) provides extensive operational and administrative oversight within a complex matrixed cancer center. The CAO will provide leadership for all matters pertaining to the administration of the research, programmatic, clinical, training and education, and strategic planning activities of the organization. This includes finances, human resources, space and facilities management, institutional relations, program planning and development, research coordination, education and training, and patient care program support. The role, in conjunction with the Center Director, is also responsible for strategic plan development, monitoring and assessment.

The successful candidate will join a diverse and dynamic team of administrators and researchers dedicated to eliminating, preventing and curing cancer through research, education, and clinical practice. The CFCCC is one of only 70 cancer centers in the country recognized by the National Cancer Institute for its scientific leadership, resources, and the depth and breadth of its research in basic, clinical, and population science. Further, CFCCC is one of only 49 cancer centers to achieve Comprehensive designation from the NCI, through demonstration of added depth and breadth of research, substantial transdisciplinary research that bridges these scientific areas, and research-based programs to identify and alleviate the burden of cancer in its catchment area.

The Chief Administrative Officer/Associate Director for Administration and Finance (CAO) reports to, and is directly responsible to, the Cancer Center Director (Dr. Richard Van Etten) for all matters pertaining to the administration of the research, programs, finance, human resources, clinical, training and education, and strategic planning programs of the Chao Family Comprehensive Cancer Center (CFCCC). The principal role of the CAO is to support the Director in fulfilling the mission of the Chao Family Comprehensive Cancer Center within the University of California Irvine (UCI), including, but not limited to, the UCI College of Health Sciences and the School of Medicine, and to oversee the full range of activities and responsibilities of the CFCCC research administration.

The successful candidate will have at least 10 years of leadership experience in a healthcare research environment. The CAO will have outstanding administration abilities and a demonstrated track record of successfully managing multiple disciplined functions and possess strong leadership, operational, financial, communications, decision-making, and communication skills. Experience administering large and complex center grants required. Specifically, experience preparing, submitting, and managing a P30 Cancer Center Support Grant from the National Cancer Institute is desirable.

## ABOUT THE UC IRVINE CHAO FAMILY COMPREHENSIVE CANCER CENTER (CFCCC)

CFCCC is the only National Cancer Institute (NCI)-designated comprehensive cancer center in Orange County, California, the sixth most populous county in the U.S. with approximately 3.2 million residents and significant racial/ethnic and socioeconomic diversity. The catchment area of the CFCCC also includes the southernmost portion of Los Angeles County and the western portions of San Bernardino and Riverside Counties, a total of ~ 4 million people.

Designated as "comprehensive" in 1997, and competitively renewed since that date, CFCCC continues to serve as a vital resource for Orange County and surrounding areas in the fight to alleviate the burden of cancer, integrating world-class research, prevention and the most advanced diagnostics, treatment and rehabilitation programs to provide the best possible care for patients and their families. To do this, CFCCC brings together scientists and clinicians from more than 32 departments across six schools at UC Irvine, including the schools of Medicine, Biological Sciences, Physical Sciences, Information & Computer Science, Engineering, and Business. The Center also has important interactions with the UCI College of Health Sciences and the emerging Schools of Population Health and Pharmacy, the Samueli Institute for Integrative Health, and UCI's NCATS-funded Institute for Clinical & Translational Science.

Members are organized into four thematic research programs that provide an interactive and collaborative infrastructure for scientific cancer discovery, clinical investigation including early phase and investigator-initiated trials, and population-based cancer research. The programs are further linked by the CFCCC Disease-Oriented Teams (DOTs) that bring together basic, translational, patient-centered, and clinical investigators to facilitate the movement of CFCCC discoveries through the pipeline into the clinical arena, and research is supported by seven shared resources that provide our members access to state-of-the-art technology, equipment and expert consultation.



## ABOUT UCI HEALTH:

As the only academic health system in Orange County, UCI Health is a multifaceted organization dedicated to the discovery of new medical frontiers, to the teaching of future healers and to the delivery of the finest evidence-based care. UCI Health is unique in its ability to provide the most compassionate healthcare because we're driven by our passion for innovation, grounded in the best medical and scientific knowledge. [UCI School of Medicine](#), one of the top U.S. medical schools for research, is where groundbreaking research and treatment advances are imparted to the rising practitioners of tomorrow, and [UC Irvine Medical Center is ranked among the nation's best hospitals by U.S. News & World Report — for 18 years and counting.](#)

For further information, please visit:

<https://s3-us-west-2.amazonaws.com/kfpublic/Chief-Administrative-Officer-CFCCC.pdf>

Please direct all inquiries/applications to:

[Caroline.Ellison@kornferry.com](mailto:Caroline.Ellison@kornferry.com)



## IN BRIEF



## Amy Abernethy appointed FDA acting chief information officer



Amy Abernethy, FDA principal deputy commissioner, was appointed the agency's acting chief information officer and lead the Office of Information Management and Technology in addition to her other duties.

Craig Taylor has been acting as FDA's CIO in addition to serving as the Chief Information Security Officer. He will continue to serve as the Chief Information Security Officer.

Abernethy came to FDA earlier this year, leaving her position as chief medical officer, chief scientific officer and senior vice president of oncology at Flatiron Health (The Cancer Letter, [Dec. 17, 2018](#)).

As acting CIO, Abernethy will "bring a new perspective to the FDA's information technology programs and priorities," agency officials said in an announcement of Abernethy's appointment. "She was one of the pioneers in bioinformatics, and her career has focused on how to use software and data to simultaneously accelerate clinical research while informing personalized healthcare and scientific discovery.

"As science and medicine continue to evolve, the FDA's priorities and regulatory science programs will continue to require the efficient and effective application of new technology; including the latest advancements in artificial intelligence, machine learning, data analytics, scientific and high-performance computing, and other technologies to support the specific mission areas of each Center and Office."

## Zihai Li named director of Ohio State Institute for Immuno-Oncology



Zihai Li was named director of the Institute for Immuno-Oncology at Ohio State University Comprehensive Cancer Center-James Cancer Hospital.

He comes to Ohio State from the Medical University of South Carolina, where he was a professor and chair of the Department of Microbiology and Immunology, and co-leader of the Center Immunology Program at Hollings Cancer Center.

Li is an elected member of the American Society for Clinical Investigation and the Association of American Physicians. His primary interests are in the mechanisms of immune regulation in cancer. Some of his research focuses on immunological properties of heat shock proteins in cancer immunotherapeutics against cancer by reprogramming the tumor microenvironment, including regulatory T cells, thrombocytes, and unfolded protein response. His work is supported by NIH, including a program project grant from NCI and four RO1s.

## Eberlein, Tempero, Hoppe, Kolodziej, Burns win NCCN awards

The National Comprehensive Cancer Network announced the recipients of a series of awards honoring individuals whose contributions fueled progress in improving and facilitating quality, effective, efficient, and accessible cancer care over the past year:

- **Timothy Eberlein**,  
*Siteman Cancer Center at Barnes-Jewish Hospital and Washington University School of Medicine*
- ▶ Outgoing board of directors chair Eberlein was presented with a Board of Producers Award.

- **Margaret Tempero,**  
*UCSF Helen Diller Family Comprehensive Cancer Center*
  - ▶ A Board of Producers Award went to Tempero in honor of her long history of contributions to NCCN, which include chairing the NCCN Clinical Practice Guidelines in Oncology Panel for Pancreatic Cancer
- **Richard Hoppe,**  
*Stanford Cancer Institute*
  - ▶ Hoppe received the Rodger Winn Award for expert judgment and commitment to excellence in service of the NCCN Guidelines. As the founding chair of the NCCN Guidelines Panel for Hodgkin Lymphoma, the award is in memory of the first leader of the NCCN Guidelines program.
- **Michael Kolodziej,**  
*ADVI*
  - ▶ Kolodziej was awarded as a Partner in Cancer Care in appreciation for his efforts to engage policymakers, employers, payers, and others to improve the accessibility of high-quality cancer care.
- **Jennifer Burns,**  
*NCCN*
  - ▶ Burns is a Guidelines Coordinator with NCCN's Clinical Information Operations team. She was named the Pat Daulerio Employee of the Year Award recipient by her peers at NCCN. The award honors the memory of a longtime employee in NCCN's meetings department.

## Jonas Bergh wins first ESMO Breast Cancer Award



The European Society for Medical Oncology announced Jonas Bergh from the Karolinska Institutet in Stockholm will receive the newly established 2019 ESMO Breast Cancer Award in connection with the inaugural ESMO Breast Cancer Congress.

The ESMO Breast Cancer Award acknowledges experts who have devoted a major part of their career and made a special contribution to the discovery and development of education, research and clinical practice in the field of breast cancer.

Bergh is Cancer Theme Prefect and Director of Strategic Research Programme in Cancer at the Karolinska Institutet in Stockholm, where he is also member of the Nobel Assembly and holds the Mimi Althainz' Professorship in Oncology.

Bergh is also Senior Consultant in Oncology at the Karolinska University Hospital, acting chair of the Scientific Council in Oncology/Haematology for the European Medicines Agency, Visiting Professor of Breast Cancer Research at Oxford University, and a fellow of the Royal College of Physicians in London, UK.

Bergh's research is mainly focused on breast cancer biology, including alteration of characteristics during progression and tailored breast cancer treatments. He is co-chair of the Early Breast Cancer Trialists' Collaborative Group, whose publications have had a global impact on primary breast cancer treatment, and was Chair of the Swedish Breast Cancer Group between 1995 and 2016.

## Cornelis Melief wins 2019 AACR-CRI Lloyd J. Old Award in Cancer Immunology



The American Association for Cancer Research recognized Cornelis Melief with the seventh AACR-CRI Lloyd J. Old Award in Cancer Immunology during the AACR Annual Meeting 2019.

Melief is an emeritus professor at the Leiden University Medical Center in the Netherlands, as well as chief scientific officer at ISA Pharmaceuticals.

He is being recognized for his discovery of mechanisms of immune recognition of cancer antigens and activation of antitumor responses, and for his role in the development of innovative immunotherapies, including a vaccine against the human papillomavirus, a leading cause of cervical cancer. He currently fo-

cuses on developing new immunotherapies and improving their effectiveness through combination therapies.

As a member of the AACR, he served as a member of the Immunology Advisory Committee from 2005 to 2011, and as a member of the editorial board of the AACR journal *Cancer Research*.

Melief has been recognized with many scientific honors, including the SOFI Prize Leiden in 1986, the AkzoNobel Prize in 1995, the European Federation of Immunological Societies Lecture Award in 2007, the Ceppellini Lecture from the European Society of Immunogenetics in 2009, the William B. Coley Award from the Cancer Research Institute in 2009, and the Queen Wilhelmina Research Prize from the Dutch Cancer Society in 2010.

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## Rosen, Querfeld awarded \$7.5M to develop better treatment for CTCL

City of Hope has received \$7.5 million in grant awards to study cutaneous T cell lymphoma.

NCI awarded two grants valued at \$6.3 million over five years to City of Hope's Steven Rosen and Christiane Querfeld to work on developing improved therapies for CTCL, a disfiguring, incurable cancer that affects about 3,000 new individuals each year.

The Leukemia & Lymphoma Society also gave the researchers two individual grants totaling \$1.2 million over three years. Rosen and Querfeld will approach the problem from different angles in their respective laboratories.

"City of Hope is creating a national model for how to treat CTCL," Rosen, its provost, chief scientific officer and the Morgan & Helen Chu Director's Chair of the Beckman Research Institute, said

in a statement. "Symptoms can include large, disfiguring plaques and tumors on the skin or a red rash that may cover the entire body. You can't imagine the joy in patients' eyes when our experimental treatments mollify CTCL symptoms. We are grateful for the trust the federal government and The Leukemia & Lymphoma Society have in us and our results."

Querfeld, chief of dermatology and director of City of Hope's Cutaneous Lymphoma Program and a Schwartz Ward Family Foundation LLS Scholar, has been studying and treating patients with CTCL for 17 years.

She will use her grants to advance her clinical phase I/II trial that looked at immune checkpoint PD1/PD-L1 inhibition. Her team will map the communication network among the disease's cellular, molecular and immunological microenvironment. Blocking or silencing certain communication networks could eliminate tumors or cancers, she said.

"The result of this newly funded study will allow physicians to use personalized medicine for certain patients with CTCL," Querfeld said in a statement. "We will identify potential therapeutic targets and correlative markers that help guide immunotherapy treatments."

Querfeld was mentored by Rosen, City of Hope's Irell & Manella Cancer Center Director's Distinguished Chair, when she first entered the research world. CTCL has been one of Rosen's research foci since the 1980s. He has identified novel groups of targets to advance the development of therapeutic compounds for this disease.

His NCI and LLS grant awards will build the foundational knowledge scientists need to develop targeted drug therapies for people with CTCL. Specifically, he will look at molecular regulators like p38γ, a protein kinase that is overexpressed in CTCL cells, but not in healthy immune T cells.

Conventional treatments for CTCL work for a few months, and only about

30% of patients respond to treatment, Querfeld said.

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## Olivera Finn receives Richard V. Smalley Memorial Award and Lectureship

Olivera Finn, University of Pittsburgh Distinguished Professor and founding chair of the Department of Immunology, was named the 2019 recipient of the Richard V. Smalley Memorial Award and Lectureship from the Society for Immunotherapy of Cancer, the society's highest honor.

Finn is credited with identifying the first tumor-associated T cell target on human adenocarcinomas in 1989. Her research group also identified certain antibodies in cancers of the breast, pancreas and colon, which led to the development of a potential cancer vaccine currently being tested in clinical trials.

The Smalley Memorial Award, established by SITC in 2005, is presented annually to a clinician or scientist who has significantly contributed to the advancement of research in the field of cancer immunotherapy. The award is named in honor of the past SITC president and charter member of the society.

Finn is the former director of the Pitt Cancer Institute Cancer Immunology Program.

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## Feng Yue named director for cancer genomics at Lurie Cancer Center

Feng Yue was appointed director of the Center for Cancer Genomics of the Robert H. Lurie Comprehensive Cancer Center of Northwestern University.



Yue joins Northwestern from the Penn State College of Medicine, where he was director of bioinformatics in the Penn State Institute for Personalized Medicine. His research focuses on how genetic variants contribute to gene regulation and three-dimensional organization of DNA molecules that influence human diseases.

He was recruited in a joint effort with the department of biochemistry and molecular genetics, the Simpson Querrey Center for Epigenetics, and the Center for Genetic Medicine, and will join Northwestern this summer. His hiring will advance basic, translational and clinical research in cancer genomics, and promote data sharing across disciplines.

“The recruitment of Feng Yue will dramatically impact our research efforts,” Leonidas Plataniotis, director of the Lurie Cancer Center and the Jesse, Sara, Andrew, Abigail, Benjamin and Elizabeth Lurie Professor of Oncology, said in a statement. “We are poised to maximize the potential of cancer genomics and accelerate its translation to precision oncology and individually tailored therapies.”

Yue received his postdoctoral training at the Ludwig Institute for Cancer Research, UCSD School of Medicine.

## ACS awards research and training grants

The American Cancer Society has approved funding for 93 research and training grants totaling \$40,277,750 in the first of two grant cycles for 2019. The grants will fund investigators at 65 institutions across the U.S.; 86 are new grants while seven are renewals of previous grants. All the grants go into effect July 1, 2019.

Highlights of the current cycle:

- **Dirk Hockemeyer**, University of California, will investigate the mechanism by which mutations in the telomerase gene result in cancer cell immortality and to what extent these mutations are driving melanoma progression. Telomerase mutations are found in 10-15% of all cancers and in 70% of melanomas.
- **Taru Muranen**, Beth Israel Deaconess Medical Center, will utilize patient-derived pancreatic cancer organoids together with stromal cells to identify effective drug combinations that could enhance the effectiveness of current therapies in pancreatic cancer, one of the most lethal types of cancer.
- **Daniel Wahl**, University of Michigan, is studying the factors that make glioblastoma multiforme brain tumors resistant to radiation. The aim is to inhibit certain metabolic pathways that appear altered in cancer cells to make radiation treatments more effective.
- **Tyler Risom**, Stanford University, will lead a project that seeks to identify which ductal carcinoma in situ tumors will progress to invasive breast cancer using a new microscope technology: Multiplexed Ion Beam Imaging, which allows 40+ distinct protein markers to be seen simultaneously within a single tumor image. The work has the potential to greatly reduce patient over-treatment and expand the availability of effective drugs for the patients that need it.
- **Avonne Connor**, Johns Hopkins Bloomberg School of Public Health, will investigate the roles of tumor type, overall health status, and socioeconomic status on outcomes for African American and Hispanic breast cancer survivors.
- Two new sites were awarded Training Grants in Clinical Oncology Social Work, University of Rochester and Thomas Jefferson University. Four other sites successfully renewed their existing support. The grants train second-year master’s students to provide psychosocial services to cancer patients and their families.
- Twelve new grants to support doctoral study were awarded to ten oncology nurses and two oncology social workers. **Matthew LeBlanc** of Duke University will work to identify needs among a newly growing group of cancer survivors: those with multiple myeloma. New treatments have led to impressive survival gains. This extended survival comes at a cost; patients are on perpetual treatment as they consistently transition to new medications when previous therapies stop working. He expects that findings from the study will help direct future research, intervention development, and clinical practice.

The American Cancer Society Extramural Research program supports research and training in a wide range of cancer-related disciplines at more than 200 institutions. The program primarily funds early career investigators. In addition, the Extramural Research program focuses on needs that are unmet by other funding organizations.

The Council for Extramural Research also approved 101 grant applications for funding, totaling \$47,290,250 that could not be funded due to budgetary constraints. These “pay-if” applications represent work that passed the Society’s multi-disciplinary review process but are beyond the Society’s current funding resources. They can be and often are subsidized by donors who wish to support research that would not otherwise be funded. In 2018, more than \$7 million in additional funding helped finance 32 “pay-if” applications.

Health Professional Training grants include:



# THE CLINICAL CANCER LETTER

## CLINICAL ROUNDUP



## SU2C-supported trials seek to extend CAR T-cell therapy to solid tumors

Stand Up To Cancer is helping scientists make progress in one of the most important areas of cancer research today: expanding the use of autologous CAR T-cell immunotherapy beyond leukemia and other blood cancers to solid tumors, such as osteosarcoma and mesothelioma.

The research could pave the way for a dramatic expansion of a therapy that has revolutionized treatment of blood malignancies but thus far, has had little impact on the solid tumors that make up most cancer cases.

Difficulties in applying the therapy to solid tumors have included the identification of antigens that will serve as tar-

gets for the CAR T-cells; getting the cells to the tumors, to stay there to attack the cancerous cells, and dealing with the immunosuppressive environment of the tumor.

Two clinical trials supported by SU2C illustrate the promise of CAR T-cell therapy in solid tumors and were featured at a press conference today at the Annual Meeting 2019 of the American Association of Cancer Research, which is also SU2C's Scientific Partner. They are:

- “A phase I clinical trial of malignant pleural disease treated with regionally delivered autologous mesothelin-targeted CAR T-cells: Safety and efficacy.”

Prasad Adusumilli, first author, and Michel Sadelain, senior author, both of Memorial Sloan Kettering Cancer Center. The study was supported in part by the SU2C-Cancer Research Institute Cancer Immunology Dream Team.

“In this phase I clinical trial, intrapleurally administered MSLN-targeted CAR T-cells had no evidence of ‘on-target, off-tumor’ or therapy related toxicity, and there was evidence of CAR T-cell antitumor activity,” the authors reported. “MSLN-targeted CAR T-cell therapy combined with anti-PD1 agents shows encouraging clinical outcomes, thus a combination therapy trial is planned to recruit patients in the second quarter of 2019.

- “Administration of HER2-CAR T-cells after lymphodepletion safely improves T cell expansion and induces clinical responses in patients with advanced sarcomas.”

The trial was supported by the St. Baldrick's Foundation-SU2C Pediatric Cancer Dream Team, among others. Shoba Navai of Baylor College of Medicine is first author. Also, at Baylor are Meenakshi Hegde, senior author; a young investigator on the Dream Team and a 2017 SU2C Innovative Research Grant recipient, and Nabil Ahmed, principal investigator on the trial and a principal investigator on the Dream Team.

The authors concluded: “Administration of lymphodepletion chemotherapy followed by autologous HER2-CAR T-cells is safely tolerated and is associated with objective clinical benefit in some patients with advanced HER2+ sarcoma. Immune correlative studies suggest that the HER2-CAR T-cells given in combination with Flu/Cy lymphodepletion induce endogenous immune reactivity. These findings warrant further evaluation in a phase II study as a single agent or in combination with other approaches.”

## Imvax announce positive results from clinical trial of IGV-001 vaccine in glioblastoma

Imvax Inc. announced positive results from an ongoing phase Ib clinical trial that demonstrate treatment with IGV-001, the company's novel autologous tumor cell vaccine, outperformed standard of care with prolonged overall survival and progression-free survival in patients with newly diagnosed glioblastoma multiforme.

The results, which were presented today in an oral presentation during the Advances in Novel Immunotherapeutics session at the American Association for Cancer Research Annual Meeting 2019, support the continued development of a new immunotherapy paradigm for the treatment of GBM.

The phase Ib trial evaluated the safety and efficacy of IGV-001, an autologous vaccine made from patients' tumor cells and an antisense formulation, in adults with newly diagnosed GBM. Thirty-three patients received one of four vaccine exposures.

SOC treatment (radiotherapy and temozolomide) was initiated four to six weeks after vaccine administration. The primary endpoint was safety and the secondary endpoint was tumor response. Exploratory objectives included assessment of PFS, OS and immune markers. A historical comparator group comprised of 35 newly diagnosed GBM patients treated at the same center evaluated SOC alone.

Treatment with IGV-001 was well tolerated, and 15 of 33 patients (45.5%) experienced no tumor growth as of March 1. Moreover, the cohort treated with the highest vaccine dose demonstrated an improvement of 7.3 months in OS (21.9 months vs. 14.6 months per Stupp) and 3.5 months in PFS (10.4 months vs. 6.9 months when compared against the historical comparator group;  $p=0.031$ ) against SOC treatment alone.

The most prominent survival statistics included those patients with DNA methylation of the MGMT promoter which favors temozolomide treatment. However, PFS for methylated patients was three-fold longer (30.9 months vs. 10.3 months for historic SOC patients per Hegi). This finding is under further investigation for its benefit.

IGV-001 has been developed over the past 20 years at Thomas Jefferson Uni-

versity Hospital in Philadelphia, where three phase I trials directed by Andrews and Hooper have now demonstrated efficacy and safety.

IGV-001 is a first-in-class autologous vaccine in development for the treatment of newly diagnosed glioblastoma multiforme, a lethal and common type of brain tumor. Based on early clinical research, one treatment with IGV-001 has the potential to trigger a multi-pronged immune response, including a short-term innate immune response followed by longer-term powerful adaptive immune activity, that is selectively directed at the patients' tumor cells.

IGV-001 has been granted orphan drug designation for the treatment of malignant glioma by FDA and the European Medicines Agency.

## **ADMIRAL trial data Shows Xospata prolongs OS in adults with leukemia**

Astellas Pharma Inc. announced results from the phase III ADMIRAL clinical trial comparing Xospata (gilteritinib) to salvage chemotherapy in adult patients with relapsed or refractory acute myeloid leukemia with a FLT3 mutation.

The results show that patients treated with Xospata had significantly longer overall survival than those who received standard salvage chemotherapy. The data were shared by Alexander Perl, Abramson Cancer Center, University of Pennsylvania, in a press conference at the American Association for Cancer Research annual meeting.

Results from the ADMIRAL trial show the median OS for patients who received Xospata was 9.3 months compared to 5.6 months for patients who received salvage chemotherapy (Hazard

Ratio = 0.637 (95% CI 0.490, 0.830),  $P=0.007$ ); one-year survival rates were 37% for patients who received Xospata compared to 17% for patients who received salvage chemotherapy.

Xospata was approved by the FDA in November 2018 for the treatment of adult patients who have relapsed or refractory AML with a FLT3 mutation as detected by an FDA-approved test.

Xospata was discovered through a research collaboration with Kotobuki Pharmaceutical Co., and Astellas has exclusive global rights to develop, manufacture and commercialize Xospata.

Xospata was approved by the Japan Ministry of Health, Labor and Welfare for relapsed or refractory AML with FLT3 mutations and launched as Xospata 40 mg Tablets in 2018.

In February 2019, a marketing authorization application for the oral once-daily therapy Xospata for the treatment of adult patients who have relapsed or refractory AML with a FLT3 mutation was accepted by the European Medicines Agency for regulatory review.

Astellas is currently investigating gilteritinib in various FLT3 mutation-positive AML patient populations through several phase III trials.

The phase III ADMIRAL trial (NCT02421939) was an open-label, multicenter, randomized study of gilteritinib versus salvage chemotherapy in adult patients with FLT3 mutations who are refractory to or have relapsed after first-line AML therapy.

The primary endpoint of the trial was overall survival. The study enrolled 371 patients with relapsed or refractory AML and positive for FLT3 mutations present in bone marrow or whole blood. Subjects were randomized in a 2:1 ratio to receive gilteritinib (120 mg) or salvage chemotherapy.

## Single agent umbralisib effective for relapsed slow-growing lymphoma

A study at MD Anderson Cancer Center revealed the investigational drug umbralisib as an effective treatment for patients with relapsed marginal zone lymphoma. Findings from the phase II trial were presented by study co-lead Nathan Fowler, associate professor in the Department of Lymphoma & Myeloma, at the AACR Annual Meeting 2019 in Atlanta.

“Umbralisib is part of a new class of drugs that are quite active in low-grade lymphomas,” said Fowler. “These PI3K inhibitors have shown activity across a spectrum of low-grade lymphomas and are effective in shutting down some of the key signaling that is occurring with MZL.”

The research team reported 55% of patients who had at least six months of follow-up had a partial or complete response after receiving umbralisib, a small-molecule inhibitor that targets a signaling pathway linked to MZL cell growth and expansion. Felipe Samaniego, associate professor in Lymphoma & Myeloma, was co-lead for the study.

The trial enrolled 69 patients, with 38 patients responding favorably and progression-free survival was 71% after one year. The patients received umbralisib orally once a day.

“This study is ongoing and we have yet to reach a median duration of response, although most of the patients who received the drug remain in remission,” said Fowler.

The average MZL patient is diagnosed at about age 60 and is typically treated

with a monoclonal antibody called rituximab either alone or in combination with chemotherapy.

“This disease is initially quite treatable with several good options for patients that result in high response rates,” said Fowler. “Unfortunately, for about 70% of these patients, relapse occurs and there are limited treatment options at that time. That relapse can occur within a year or it can take several years, but most patients will eventually stop responding to standard treatment.”

Fowler’s team was specifically looking at patients who had failed several standard treatment options including chemotherapy or monoclonal antibodies.

“At MD Anderson, we have been fortunate to lead the development of several of these targeted drugs in lymphoma,” he said. “Phase I studies conducted here with PI3K and BTK inhibitors has now resulted in FDA approval of many of these drugs across several types of lymphoma.”

## Study names six risk factors linked to esophageal cancer

The north-eastern region of the Islamic Republic of Iran has some of the highest rates of esophageal cancer anywhere in the world. New results from an international prospective study of 50,000 individuals, recently published online in the journal *Gastroenterology*, provide evidence on how the combined effects of six main risk factors are responsible for the high rates of esophageal cancer in this region.

The results are based on more than 10 years of follow-up of 50,000 individuals as part of the Golestan Cohort Study, which was initiated in 2004 by the Digestive Diseases Research Institute of the Tehran University of Medical

Sciences, the International Agency for Research on Cancer, and NCI.

The six most important risk factors identified were drinking hot tea, smoking opium, low intake of fruits and vegetables, drinking unpiped water, exposure to indoor air pollution, and excessive tooth loss.

The study found that about three quarters of the esophageal cancer cases in the north-eastern region can be attributed to a combination of exposures to the identified risk factors, which are all preventable through education and by improving basic social infrastructure.

The GCS is the largest prospective study of its kind in central and western Asia. It was established to provide a major resource for studying esophageal cancer, through the collection of biological samples and detailed assessments of diet, lifestyle, and different exposures, at enrolment and then every 5 years.

Instead of relying only on self-reported information, the GCS was the first study to also make objective measurements of the suspected risk factors for oesophageal cancer, including the actual temperature at which tea is drunk, and carry out precise oral examinations.

“The GCS was initiated in an area where esophageal cancer constituted about 25% of the reported cancer cases, and the study has made important contributions to the discovery and development of the scientific information on the risk factors for upper gastrointestinal cancers and other noncommunicable diseases,” Reza Malekzadeh, director of the Digestive Diseases Research Institute of the Tehran University of Medical Sciences and is the principal investigator of the GCS, said in a statement.

“The GCS represents a major and long-standing collaboration between scientists in the Islamic Republic of Iran, IARC, and NCI, and it is an import-

ant representation of how medical research can overcome political and economic barriers,” Paul Brennan, head of the Section of Genetics at IARC and is a co-principal investigator of the GCS, said in a statement.

“This study shows how the combination of the risk factors can substantially increase the risk of oesophageal cancer, and strongly suggests that esophageal cancer in high-incidence areas is a multifactorial disease, requiring a combination of exposures for its development. Therefore, this study has important implications for public health and policy, and will aid the translation of knowledge and the implementation of evidence into practice and policy decision-making.”

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## Probiotics linked to poorer response to cancer immunotherapy in skin cancer

In melanoma patients, taking over-the-counter probiotic supplements was associated with a 70% lower chance of response to cancer immunotherapy treatment with anti-PD-1 checkpoint inhibitors, according to a preliminary study from the Parker Institute for Cancer Immunotherapy and MD Anderson Cancer Center. The results were presented at the American Association for Cancer Research 2019 Annual Meeting in Atlanta.

Researchers also found that probiotics were linked to lower diversity in the gut microbiome, previously found to be associated with poorer immunotherapy response.

“These findings about probiotics were a bit surprising to us because the general perception is they make your gut micro-

biome healthier,” first author Christine Spencer, a research scientist at the Parker Institute, said in a statement. “While more research is needed, our data suggests that may not be the case for cancer patients.”

Probiotics are not regulated by FDA.

“Based on our early results, cancer patients and doctors should carefully consider the use of over-the-counter probiotic supplements, especially before beginning immunotherapy treatment,” said senior author Jennifer Wargo, a PICI investigator at MD Anderson.

This is the first clinical study designed to examine the relationships between diet, the gut microbiome and immunotherapy response in cancer patients. In addition to the probiotics findings, the data also show patients who reported eating a high-fiber diet were five times as likely to respond to cancer immunotherapy.

The implications of the research are significant because checkpoint inhibitors—a Nobel Prize-winning type of cancer immunotherapy treatment—only work for 20 to 30% of cancer patients.

The research bolsters the idea that cancer patients might be able to improve how well immunotherapy treatment works by eating, drinking, or avoiding certain foods, beverages and supplements.

“Imagine if you could increase the number of patients who benefit from immunotherapy through something as simple as dietary changes. That would be remarkable,” Spencer said. “It’s probably not going to be that simple, as there are many factors at work. But this study does point to diet playing a role in immunotherapy response via the gut microbiome and we hope these findings will spur more studies on this topic in the cancer research community.”

In recent years, scientists have discovered that the trillions of intestinal microbes that make up the gut microbiome exert significant control over the immune system. Cancer immunotherapy drugs such as checkpoint inhibitors work by engaging the immune system to fight off cancer.

In theory, the makeup of the microbiome could affect the immune system, and in turn, the ability for immunotherapy to work against cancer.

A prior study by Wargo and Spencer was one of the first to explore that idea. In their 2018 Science paper, they and colleagues at MD Anderson found that a more diverse array of microbes in the gut was associated with better response to checkpoint inhibitors for cancer, and that certain types of bacteria in the Ruminococcaceae family were associated with a better response to anti-PD-1 checkpoint inhibition. Other types of bacteria, such as those in the order Bacteroidales, were linked to a poorer outcome.

“There were different types of microbiome profiles, if you will, that were linked to better or poorer response to checkpoint inhibition,” Wargo said in a statement. “For this new study on the diet, microbiome and immunotherapy, we used profiles of responders as the mark of a “good” microbiome when it comes to immunotherapy response.”

The prospective study involved 113 metastatic melanoma patients who were starting treatment at MD Anderson. The researchers prospectively evaluated their microbiomes by sequencing their fecal samples to determine the presence and abundance of various bacteria in the gut. Patients were also asked to take a lifestyle survey to report on their diet and use of supplements and medication.

After following patients through treatment, the researchers found several



correlations between dietary factors and the gut microbiome. They also evaluated those factors in relation to immunotherapy response in a subset that went on anti-PD-1 checkpoint inhibitors.

Overall, Parker Institute and MD Anderson researchers found that diet and supplements appear to have an effect on a patient's ability to respond to cancer immunotherapy, most likely due to changes in the patient's gut microbiome.

Among the findings:

- Over-the-counter probiotic supplement use was linked to a 70% lower chance of response to immunotherapy with anti-PD-1 checkpoint inhibitors in a subset of 46 melanoma patients
- 42% of all patients reported taking over-the-counter probiotics among those who took the lifestyle survey
- Probiotics were linked to lower gut microbiome diversity, previously shown to be associated with poorer response to anti-PD-1 checkpoint inhibitors
- Patients eating high-fiber diets were about 5 times as likely to respond to immunotherapy treatment with anti-PD-1 checkpoint inhibitors
- Patients eating diets rich in whole grains had more bacteria associated with positive response to checkpoint immunotherapy
- Diets high in processed meat and added sugar had fewer bacteria associated with a positive response to checkpoint immunotherapy

While this study focused on correlations rather than root cause, other randomized, controlled clinical trials are underway that are designed to directly answer the question of whether one can manipulate the microbiome—through food,

fecal transplant or other means—to improve cancer immunotherapy response.

The Parker Institute is now conducting such a trial in collaboration with MD Anderson and Seres Therapeutics. This randomized, placebo-controlled clinical study is evaluating whether a specially designed oral microbiome pill with specific types of bacteria could positively impact a patient's response to checkpoint inhibitors.

The study is open at MD Anderson and the Angeles clinic. For additional information on this trial (NCT03817125) please visit [clinicaltrials.gov](https://clinicaltrials.gov).

In addition, a team of MD Anderson researchers is planning a prospective randomized study in which cancer patients will be provided with different types of diets. Their gut microbiomes will be sequenced to see if and how they change. The study will also evaluate treatment response to immunotherapy.

## Rucaparib maintenance therapy shows clinical responses in pancreatic cancer

Maintenance treatment with the PARP inhibitor rucaparib (Rubraca) was well tolerated and provided clinical responses among patients with advanced BRCA- or PALB2- mutated pancreatic cancer sensitive to platinum-based chemotherapy, according to results from an interim analysis of an ongoing phase II clinical trial presented at the AACR Annual Meeting 2019.

Rubraca is sponsored by Clovis Oncology.

“In this interim analysis, we are finding that patients with platinum-sensitive pancreatic cancer appear to benefit

from treatment with single agent rucaparib,” Kim Reiss Binder, assistant professor of medicine in the Division of Hematology Oncology at The Hospital of The University of Pennsylvania, said in a statement.

“Several patients had complete or partial responses with rucaparib treatment, suggesting that this therapy has the potential not only to maintain the disease, but also to shrink the tumors in some instances,” Reiss Binder said.

Approximately 6 to 8% of patients with pancreatic cancer harbor pathogenic mutations in the genes BRCA or PALB2, Reiss Binder said. Mutations in these genes often coincide with susceptibility to platinum-based chemotherapies, she said.

“While this subgroup of pancreatic cancer patients respond well to platinum-based chemotherapy, prolonged treatment leads to cumulative toxicity, so this approach often becomes unsustainable,” said Reiss Binder. “We wanted to investigate more tolerable maintenance options, as there are no approved treatments in this setting.”

Rucaparib was approved as a maintenance treatment for patients with recurrent ovarian, fallopian tube, or primary peritoneal cancer who respond to platinum-based chemotherapy.

This single-arm, phase II clinical trial is actively enrolling patients with advanced BRCA- or PALB2-mutated pancreatic cancer who have not progressed on prior platinum-based chemotherapy. The patients in the interim analysis had received a median of four months of prior platinum chemotherapy. More than 80% of patients were female.

Patients are treated with 300mg of rucaparib twice daily until disease progression or unacceptable toxicity. The primary endpoint of the study is pro-

gression-free survival. Overall response rate is also being evaluated.

Nineteen of the 24 enrolled patients were evaluable for analysis as of Dec. 31, 2018.

The median PFS at time of analysis was 9.1 months following initiation of rucaparib treatment. The ORR was 37%, which included one complete response and six partial responses. The disease control rate (defined as the sum of PR, CR, and stable disease) was 90% for at least eight weeks. Eight patients remained on rucaparib therapy for at least six months, and two patients have remained on rucaparib therapy for more than one year.

“Although this is very preliminary data, the fact that we’re seeing sustained clinical responses in some of these patients is very exciting,” said Reiss Binder. “Other than the recent tissue-agnostic approval of pembrolizumab for patients with microsatellite instability-high tumors, there really is no other targeted therapy that has shown promise for patients with pancreatic cancer.

“Our results highlight the importance of germline and somatic testing in pancreatic cancer patients,” said Reiss Binder. “The presence of certain mutations can guide treatment strategies, and patients should know to ask their oncologist about getting tested.”

As this was an unplanned interim analysis of an ongoing, small, single-arm study, the results require substantial further validation.

This study is sponsored by the Abramson Cancer Center and is funded by Clovis Oncology. Reiss Binder receives research funding from Clovis Oncology, Tesaro, Bristol-Myers Squibb, and Lilly Oncology.

## DRUGS & TARGETS



## Varian ARIA Oncology Information System awarded CancerLinQ certification

The number of electronic health record systems joining with CancerLinQ to facilitate information sharing continues to grow. CancerLinQ LLC, a wholly owned nonprofit subsidiary of the American Society of Clinical Oncology, announced Varian’s ARIA Oncology Information System is the next Electronic Health Record System to be certified by CancerLinQ after meeting criteria for interoperability and data standardization. This collaboration aims to dismantle barriers to information sharing and streamline access to CancerLinQ for oncology practices using Varian ARIA OIS.

ARIA is a comprehensive electronic medical record and image management system that aggregates patient data into an organized, oncology-specific medical chart with functional components for managing clinical, administrative and financial operations for medical, radiation and surgical oncology.

The ARIA system is designed to provide a seamless flow of information for managing the patient’s entire journey—from diagnosis through follow-up.

CancerLinQ is a health information technology platform working to improve the quality of cancer care for patients by aggregating and analyzing real-world cancer data. The CancerLinQ Certified EHR program recognizes systems that meet specific requirements for interoperability and cancer data standardization.

To become a CancerLinQ Certified EHR and maintain this status, an EHR system must do the following, in addition to fulfilling other requirements:

- Support the creation and maintenance of health records including, but not limited to, individually identifiable oncology and/or hematology patient information;
- Maintain a leading industry standard for the recording of precise, structured, and standardized clinical data;
- Meet certain federal standards for EHR technology, interoperability, privacy, and safety;
- Work to achieve the continuous, secure transfer of data to the CancerLinQ system from patients associated with practices that both participate in CancerLinQ and use the EHR; and
- Participate in efforts among stakeholders in the cancer community to drive improvement of interoperability, establish core data elements, and support efforts to standardize and harmonize data approaches.

## FDA expands use of metastatic breast cancer treatment to include male patients

FDA is extending the indication of Ibrance (palbociclib) capsules in combination with specific endocrine therapies for hormone receptor-positive, human epidermal growth factor recep-

tor 2-negative advanced or metastatic breast cancer in male patients.

The drug is sponsored by Pfizer.

“Today we are expanding the indication for Ibrance to include male patients based upon data from postmarketing reports and electronic health records showing that the safety profile for men treated with Ibrance is consistent with the safety profile in women treated with Ibrance,” Richard Pazdur, director of the FDA’s Oncology Center of Excellence and acting director of the Office of Hematology and Oncology Products in the FDA’s Center for Drug Evaluation and Research, said in a statement.

“Some approved indications for breast cancer treatments do not distinguish by gender, but in certain cases if there is a concern that there may be a difference in efficacy or safety results between men and women, then further data may be necessary to support a labeling indication for male patients.”

Breast cancer is rare in males with only 2,670 cases of male breast cancer estimated in 2019 – less than 1% of all cases of breast cancer. The majority of breast tumors in male patients express hormone receptors.

Men are more likely to be diagnosed at an older age, with a more advanced stage of disease. Metastatic breast cancer is breast cancer that has spread beyond the breast to other organs in the body (most often the bones, lungs, liver, or brain).

When breast cancer is hormone-receptor positive, patients may be treated with hormone therapy (also called endocrine therapy) or chemotherapy. Endocrine therapy slows or stops the growth of hormone-sensitive tumors by blocking the body’s ability to produce hormones or by interfering with effects of hormones on breast cancer cells.

There are several FDA-approved endocrine based therapies available for HR-positive metastatic breast cancer patients. Certain treatments are gender-neutral in their indication, but some therapies have been approved only for women, although they are often prescribed for male patients. According to the current clinical practice standards, male patients with breast cancer are treated similarly to women with breast cancer.

Ibrance was initially approved in 2015. It is a kinase inhibitor, approved in combination with an aromatase inhibitor as the first hormonal-based therapy in women who have gone through menopause and in men, or with fulvestrant in patients whose disease progressed following hormonal therapy.

Pfizer provided the results of an analysis of real-world data from electronic health records as additional supportive data to characterize the use of palbociclib in combination with endocrine therapy (aromatase inhibitor or fulvestrant) in male patients with breast cancer based on observed tumor responses in this rare subset of patients with breast cancer.

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## **FDA issues warning letter to genomics lab for marketing genetic test that claims to predict patients’ responses to specific medications**

FDA issued a warning letter to Inova Genomics Laboratory of Falls Church, Virginia, for illegally marketing certain genetic tests that have not been reviewed by the FDA for safety and effectiveness. The tests claim to predict patients’ responses to specific medications based on genetic variants.

Selecting or changing drug treatment in response to the test results could lead to potentially serious health consequences for patients. The FDA is unaware of any data establishing that Inova’s tests can help patients or health care providers make appropriate treatment decisions for the listed drugs.

The action today reflects the agency’s commitment to monitor the pharmacogenetic test landscape and take action when appropriate to address a significant public health risk.

That letter can be found [here](#).

When the agency has reviewed scientific evidence demonstrating a sufficient relationship between the drug’s effects and genetic variants, information about using genetic test results to manage medication treatment will be described in the labeling.

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## **Nanobiotix receives European approval for Hensify therapy for sarcoma**

Nanobiotix announced Hensify (NBTXR3) has obtained a CE mark for the treatment of locally-advanced soft tissue sarcoma. Hensify is the brand name for NBTXR3 as approved for the treatment of locally-advanced STS.

Hensify was designed by Nanobiotix to physically destroy tumor and activate the immune system for both local control and systemic disease treatment when combined with radiation therapy. In addition to Hensify, NBTXR3 is currently under evaluation in various other indications such as lung cancer, head and neck cancers, liver cancer, and prostate cancer.

Hensify is an aqueous suspension of crystalline hafnium oxide nanoparticles designed for injection directly into a



tumor prior to a patient's first standard radiotherapy treatment. When exposed to ionizing radiation, Hensify amplifies the localized, intratumor killing effect of that radiation.

The dose of X-ray delivered to the tumor is magnified, whilst the dose passing through healthy tissues remains unchanged. Hensify requires a single administration and will fit into current worldwide standards of radiation care.

STSs are rare cancers that develop in different types of soft tissues including fat, muscles, joint structures and blood vessels. Radiotherapy followed by surgery is part of the typical treatment regimen for STS patients in Europe.

The Act.In.Sarc phase II/III trial was a prospective, randomized (1:1), multinational, open label and active controlled two armed trial of 180 adult patients with locally advanced STS of the extremity or trunk wall. The objective of the trial was to evaluate the pre-operative efficacy and the safety of Hensify activated by radiotherapy compared to the standard of care (radiotherapy alone).

The positive Act.In.Sarc study results were presented at the 2018 ASTRO and ESMO Annual Congresses. The trial achieved its primary endpoint with a pathological complete response (<5% viable cancer cells) rate of 16.1% in the Hensify arm compared to 7.9% in the control arm ( $p=0.0448$ ).

In addition, in the subgroup of patients with a more aggressive disease (histologic grade 2 and 3), a pathological complete response was achieved in four times as many patients in the Hensify<sup>®</sup> arm as in the control arm (17.1% compared 3.9%).

Similar safety profiles were observed in the Hensify arm and the radiation therapy alone control arm. Hensify did not

impair the patients' ability to receive the planned dose of radiotherapy and the radiotherapy safety profile was similar in both arms, including the rate of post-surgical wound complications.

Post-approval trials are planned across Europe and discussions on next steps regarding potential further development are ongoing.

## Opdivo shows long-term survival results in NSCLC

Bristol-Myers Squibb Co. announced results from pooled analyses of survival data from four studies (CheckMate -017, -057, -063 and -003;  $n=664$ ) in patients with previously-treated advanced non-small cell lung cancer who were treated with Opdivo (nivolumab).

In the pooled analysis of the four studies, 14% of all Opdivo-treated patients were alive at four years. Notably, in patients with PD-L1  $\geq 1\%$  and  $< 1\%$ , four-year overall survival rates were 19% and 11%, respectively.

In the pooled analysis of the two phase III trials, CheckMate -017 and -057, the four-year OS rate for Opdivo-treated patients was 14% compared to 5% for docetaxel-treated patients. Additionally, exploratory landmark analysis of OS found that of patients who had a complete or partial response at six months, 58% of those treated with Opdivo were alive four years later vs. 12% of patients treated with docetaxel.

Of patients who had stable disease at six months, 19% of those treated with Opdivo were alive four years later vs. 2% of patients treated with docetaxel. The data were presented at the American Association for Cancer Research Annual Meeting 2019 in Atlanta.

Long-term safety data for Opdivo from all four studies were consistent with the known adverse event profile and did not reveal any new safety signals. The discontinuation rate due to treatment-related adverse events was 8.7% in patients treated with Opdivo. The most common treatment-related AE was fatigue (in 21.7% of patients).

"These analyses in a large population of patients with previously-treated advanced non-small cell lung cancer show, for the first time, that response to Opdivo correlates to a survival benefit over many years," Scott Antonia, director of the Duke Cancer Institute Center for Cancer Immunotherapy, said in a statement. "These long-term survival outcomes are particularly interesting given that, historically, the average five-year survival rate for this patient population is approximately 5%."

These pooled analyses were conducted to evaluate the long-term benefit (with a minimum follow-up of four years) of Opdivo and impact of response or disease control on subsequent long-term overall survival.

The pooled analysis of CheckMate -017 and CheckMate -057 represents the longest follow-up from phase 3 randomized trials of previously treated advanced non-small cell lung cancer patients treated with Immuno-Oncology therapy.

OS was estimated for patients with NSCLC across histologies treated with Opdivo in pooled analyses from CheckMate -017, -057, -063, and -003 ( $n=664$ ), and for patients randomized to Opdivo ( $n=427$ ) or docetaxel ( $n=427$ ) in pooled analyses from CheckMate -017 and -057. Other analyses of CheckMate -017 and -057 included estimation of OS in patients alive at six months by response status at six months, and OS in all responders (complete or partial response) from the time of response.



## Findings from ASCO TAPUR trial presented at AACR meeting

Three completed cohorts reporting findings in non-small cell lung cancer, breast, and metastatic colorectal cancer from the American Society of Clinical Oncology Inc.'s Targeted Agent and Profiling Utilization Registry study were presented in poster sessions during the American Association for Cancer Research Annual Meeting 2019.

In addition, all seven pharmaceutical companies currently participating in the TAPUR study have recently renewed their commitment to support it and provide study drugs at no cost for an additional one to three years.

TAPUR study participants are enrolled in cohorts based on their tumor type

(e.g., any advanced solid tumor, multiple myeloma, or B cell non-Hodgkin lymphoma), the genomic alteration of their tumors, and the targeted drug(s) that correspond to those alterations.

Participants are enrolled in two stages and monitored for treatment response. Patient cohorts are either permanently closed after Stage I (less than two responses in 10 participants) or expanded to Stage II for further study and confirmation of a signal of drug activity.

The TAPUR study is designed to evaluate molecularly targeted cancer drugs and collect data on clinical outcomes to learn about potential additional uses of these drugs outside of FDA approved indications. It provides a clinical trial opportunity for patients with advanced cancer who have genomic alterations in their tumors that can be targeted with a TAPUR study drug.

There are currently 113 TAPUR study sites in 20 states and nearly 1,400 participants who have received study therapy. The various drugs and their different targeted therapy options (some drugs are used in combination) are provided to patients at no cost by the seven pharmaceutical companies currently participating: AstraZeneca; Bayer; Bristol-Myers Squibb; Eli Lilly and Company; Genentech, a Member of the Roche Group; Merck; and Pfizer. ASCO is seeking to add relevant targeted therapies.

Based on collaborative work with the FDA and Friends of Cancer Research, ASCO lowered the age of TAPUR study eligibility in 2017 from 18 to 12 years to extend the opportunity for participation to adolescent patients with advanced cancer. Last month, the FDA finalized guidance for industry on expanding clinical trial eligibility criteria based on input from ASCO and Friends. The TAPUR study is registered on ClinicalTrials.gov (NCT 02693535).

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