PROMISE & PROGRESS

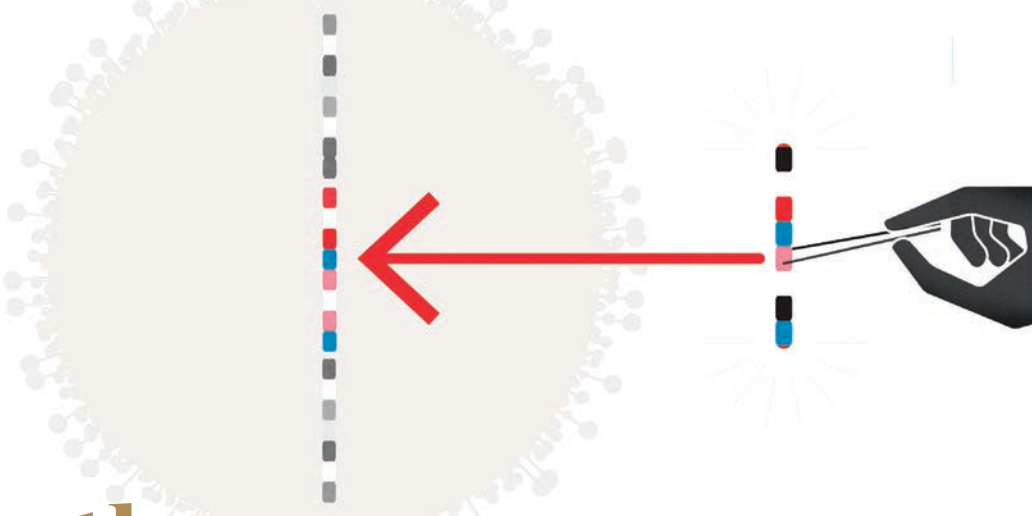
THE SIDNEY KIMMEL COMPREHENSIVE CANCER CENTER AT JOHNS HOPKINS

TURNING RESEARCH INTO RESULTS

1973 – 2023

2010s

Cancer care moves primarily to the outpatient setting, and the Kimmel Cancer Center expands, occupying the largest footprint at Johns Hopkins. Breakthroughs in immunotherapy, using drugs and vaccines to unleash the natural killing power of the immune system against cancer, are a key clinical advance. Multidisciplinary Clinics, with specialists from all fields related to cancer care working together, become the standard, leading to improved therapies and survival.



Immunotherapy

A Game Changer

Therapies that empower the body's own natural defenses became a reality in the mid 2010s, providing unparalleled, long-lasting responses across many cancer types, and even in the most advanced and treatment-resistant cancers.

These discoveries led to the launching of the Bloomberg-Kimmel Institute for Cancer Immunotherapy (BKI) in 2016, started with lead gifts of $50 million each from **Michael Bloomberg** and **Sidney Kimmel**.

As long as cancer has been a recognized disease, doctors have believed the power to eliminate it existed within the immune system.

A VACCINE

Drew Pardoll, BKI director, **Elizabeth Jaffee**, BKI associate director, and former faculty member **Hyam Levitsky**, began in the 1980s deciphering the mechanisms of the immune system, how it works and why it all too often does not work against cancer. As students of the immune system, Pardoll, Jaffee, Levitsky, and collaborators understood that it should be the perfect anticancer weapon, but if the cancer cell was complex in its molecular construction, the intricacies of the immune system were equally complicated.

PARDOLL

JAFFEE

LEVITSKY

"IMMUNE THERAPY IS A GAME CHANGER... WE DON'T THINK THERE IS A SINGLE CANCER THAT THE PATIENT'S OWN IMMUNE SYSTEM ULTIMATELY CAN'T BEAT."

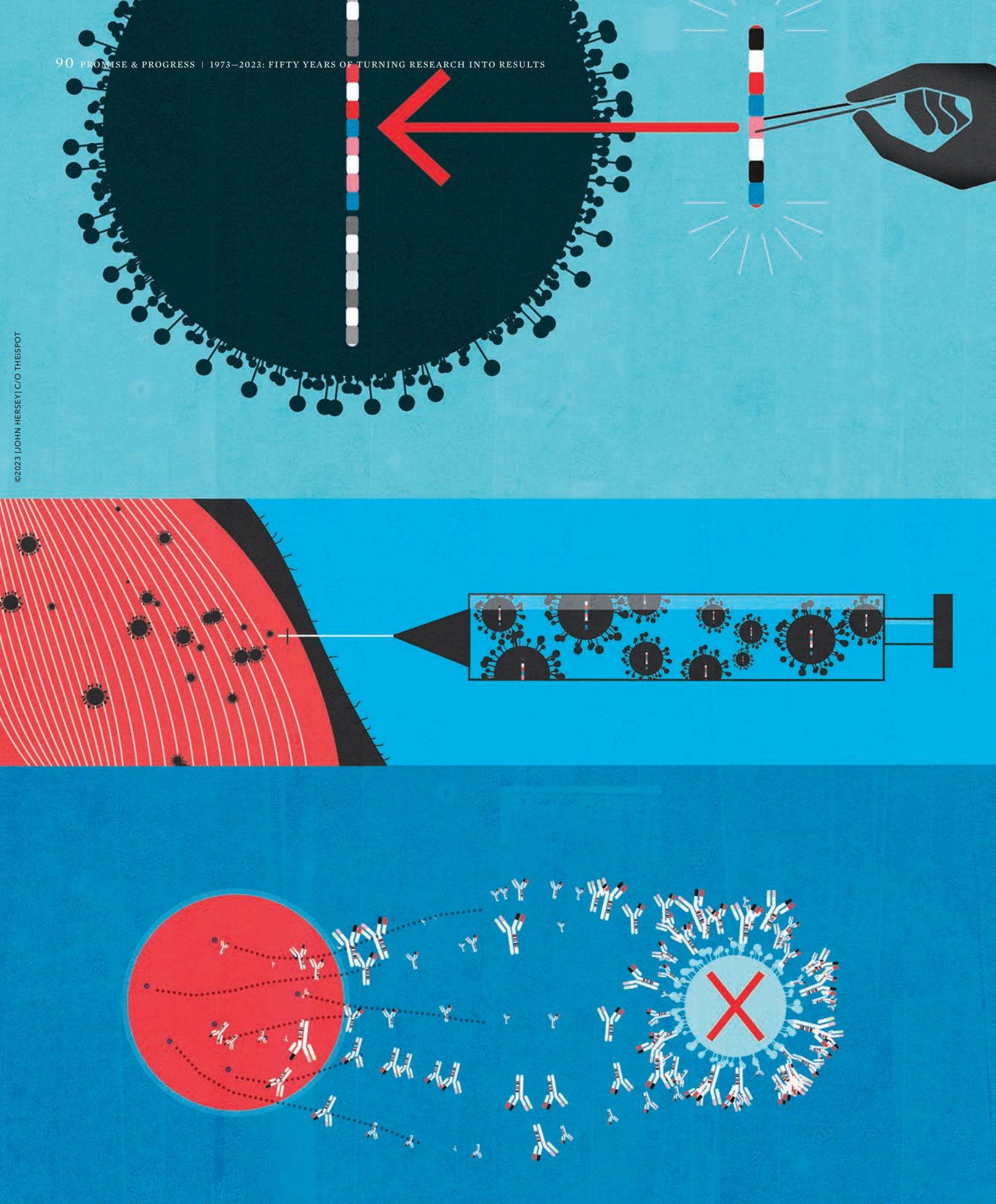
Immune-based therapies reflect a different approach to treatment. Instead of targeting cancer cells, the new therapies target immune cells in and around cancers. Some treatments increase the number of immune cells summoned to the tumor, and others unleash the commands that send the immune cells to work against the cancer. These types of immune therapies have had success alone, but perhaps their greatest power is coming in combining them and, through precision medicine, using the biological clues within each patient's cancer to guide treatment.

One of the first immunotherapies developed at the Kimmel Cancer Center was a therapeutic cancer vaccine called GVAX, the first genetically engineered vaccine in history to be tested in patients. The novel vaccine supercharged immune cells, which tend to be tolerant of cancer, to seek out and destroy cancer cells throughout the body.

Pardoll, Jaffee, Kimmel Cancer Center Director **William Nelson**, and former faculty member **Jonathan Simons** first tested GVAX in kidney cancer.

It's greatest success, however, came in pancreatic cancer, leading to several long-term sur-

SIMONS



vivors (see story on page 84) of this often lethal diagnosis. Jaffee, who originally created the pancreatic cancer GVAX in her laboratory and led the pancreatic cancer studies, even opened a GMP (Good Manufacturing Practice) facility at the Kimmel Cancer Center to produce the vaccine for clinical studies.

Jaffee continues to work with young faculty members to develop and study better iterations of the vaccine, adding gene mutation-directed components, combining the vaccine with other immunotherapies, and using modified bacteria to augment the immune response.

MORE POWER

Researchers believed there was still much more power in the immune response that remained untapped and could be used against cancer.

Unlike viruses and bacteria that are easily recognized by the immune system because they are so different, cancer originates from the body's own cells. As a result, it has all of the cellular mechanisms that are used by normal cells at its disposal.

Center team of multispecialty collaborators— seasoned investigators and young clinician-scientists— figured out how to reset the cellular controls hijacked by the cancer cell and restore power to the immune system.

Cancer co-opts them selectively, using them like superpowers to grow, spread, and cloak themselves from the immune system. It took time for the technology to catch up with the scientific ideas. A Kimmel Cancer

Center team of multispecialty collaborators—seasoned investigators and young clinician-scientists— figured out how to reset the cellular controls hijacked by the cancer cell and restore power to the immune system.

As the therapies began to unfold, the results were unparalleled. Some patients who were months, even weeks, from dying survived, some five years and longer after treatment.

IMMUNE CHECKPOINT BLOCKADES

TOPALIAN

In 2012, **Suzanne Topalian,** BKI associate director, saw more than 8,000 practicing oncologists and clinical cancer scientists from all over the world fill the lecture hall at the 2012 annual meeting of the American Society of Clinical Oncology (ASCO) to hear her speak.

BRAHMER

It was not the first time a standing-room only crowd had come to hear a Kimmel Cancer Center researcher discuss this new type of immune therapy. Just a day before, Thoracic Oncology Program director **Julie Brahmer**, presented findings on an immune checkpoint blockade study in lung cancer. It marked a changing tide in clinical cancer research. Immunology studies had never before received this level of attention at ASCO meetings. "The session chair announced Brahmer's presentation saying, 'Nobody in this room ever before believed immunotherapy could make a difference in lung cancer. Today, that is all going to change,'" recalls Pardoll.

With remarkable and lasting results in about 20% to 50% of patients with advanced cancers that resisted all other types of therapy, oncologists wanted to know more. Scholarly journals and the news media alike were reporting on drugs that caused lethal melanoma skin cancers, kidney cancers, and lung cancers to melt away and stay away. The therapies were new, first tested in patients in 2006.

These long-lasting responses that continued even after therapy was stopped and did not cause the side effects of nausea, vomiting, hair loss, and low blood counts, that had become so characteristic of cancer chemotherapy, are the reason the ASCO meeting auditoriums were filled to capacity. Doctors were anxious to learn how and when they could get this new therapy for their patients.

CHECKPOINTS

The source of the excitement was an immune target called PD-1. It is what immunology experts call an immune checkpoint. The results in laboratory research and these early clinical trials showed it to be one of the strongest influencers of an immune response to cancer identified. It—and other similar proteins—are responsible for cancer's ability to avert an immune attack.

One of the primary functions of the immune system is to distinguish organisms that are foreign to our bodies from our own cells. "Our cells are constantly presenting our own proteins to our own immune system," explains pathologist **Bob Anders**, and the immune system must leave them alone.

ANDERS

In the same way it recognizes bacteria and viruses as foreign, the patrolling immune system can recognize abnormal cells that have a mutation

in their DNA. The mutation confers a subtle biochemical mark that the immune system can distinguish from the normal protein.

"When immune cells come upon something that shouldn't be there, they generate an immune reaction," says Anders. "This is the go signal. When the job is done and the invading cells are taken care of, theimmune system issues a "stop" signal."

These stop signals are controlled by immune checkpoints like PD-1. In cancer, malignant cells hijack the "stop" signal to maintain their own survival, even though they have lots of mutations that allow the immune system to easily distinguish them from their normal counterparts. They send a deceptive message to cancer-killing immune cells that there is no problem. Immune cells arrive at the tumor, but they are duped with a false message that everything is OK.


TAUBE

"Essentially, they're told to go home. There is nothing to see here," says pathologist **Janis Taube**.

Drugs that block PD-1 release these restraints, unharnessing the power of the immune system against the cancer.

The first clinical reports of checkpoint inhibitors in melanoma were exciting and peaked interest, but there was skepticism about how applicable they would be in other cancers. The anecdotal successes in immune therapy over the last three decades had largely been in melanoma and kidney cancer. There have been rare cases of these cancers occasionally going into spontaneous remission, so experts long maintained that, by nature, these types of cancers had a way of engaging the immune system. Yet even in melanoma and kidney cancer, earlier immunotherapies led to remission of the cancer less than 10% of the time. No other type of cancer was considered to be responsive to immune interventions, so the new therapy was greeted with guarded optimism.

That all changed in 2012 when the Kimmel Cancer Center group published the results of anti-PD-1 therapy that induced remissions in 25% of melanomas and, surprisingly, in lung cancer patients too. Lung cancer had never before responded to an immune therapy, and the remarkable activity of anti-PD-1 in a small number of lung cancer patients proved what cancer immunologists long believed—if understood, the immune system could be used to fight any cancer. These early trials tested the anti-PD-1 drug in patients who had already received many previous therapies and had exhausted all standard therapies.

"Anti-PD-1 has become a cancer juggernaut," says Pardoll. "There are now seven FDA-approved antibodies that block this checkpoint pathway. It is the most commonly targeted in all of cancer therapy."

DEVELOPED FROM SCRATCH


CHEN

Pardoll first became interested in the PD-1 in 2000, when he came upon a partner protein, called PD-L2. **Lieping Chen**, a collaborator of Pardoll's at the Kimmel Cancer Center, and now at Yale, had just discovered PD-L1, the other partner protein to PD-1, and showed that it's expression in many types of cancer, including lung cancer, was was highly elevated compared to normal cells. Although lung cancers had not responded to other past immune therapy attempts, this discovery provided new evidence that it had the potential to work and was the reason the Kimmel Cancer Center team included lung cancer patients in the first anti-PD-1 trial.

"We developed this idea from scratch at the Kimmel Cancer Center," says Pardoll.

As soon as the components of the PD-1 pathway were discovered in 2000, Pardoll and Chen saw the potential of blocking it. They began working to develop the first anti-PD-1 antibody. Topalian, Brahmer, immunology and genitourinary cancer expert **Chuck Drake**, now cancer immunology leader at Johnson & Johnson, and research nurse **Alice Pons** took it to patients. They found stronger and more frequent responses in melanoma and kidney cancer than previous immunotherapies, but it was Brahmer's lung cancer patients that were game changers. The most common cancer killer had never previously responded to any immunotherapy.


DRAKE

It was the moment Pardoll staked his career on when he left the laboratory of world renowned cancer genetics researcher and pioneer **Bert Vogelstein** in the 1970s to branch out on his own and start his cancer immunology lab.

For Topalian, it felt like redemption. She worked with **Steven Rosenberg** at the National Cancer Institute for 20 years, exploring interferons and interleukins, cellular messengers critical to immune responses. In the 1980s, they had garnered similar excitement as a potential broad-based immune treatment for cancer.

The cover of *Time* magazine boasted the headline "Interferon: The Cure for Cancer." When the celebrated treatment failed to live up to expectations—most of which had been generated by an eager news media desperately waiting for the grand-slam victory that had been promised when the "war against cancer" was announced in 1971—the field of cancer immunology was nearly crushed.

Topalian saw it differently, however. Interferon wasn't the blockbuster immunotherapy people had hoped for, but it was a start.

"It was the first evidence that a drug that acted only through the immune system could fight very advanced cancer," says Topalian. "That was impor-

tant because it told us we were on the right track with immunotherapy and needed to keep working on this."

Unfortunately, others outside the field of cancer immunology had begun to doubt the promise of immune treatments in cancer. Immunotherapy discussions at the large national cancer meetings were sparsely attended, and research funding was hard to come by. In true Kimmel Cancer Center fashion, the immunology research team remained undeterred.

A MILESTONE

As they began to dig deeper into the responses of lung cancer and other cancer patients in the PD-1 clinical trials, they began to learn more about what drives an immune response.

Immune therapies appear to work more slowly over time, and it's looking now like they work better for longer. Some of this was learned almost serendipitously, as cancers that initially looked like they were not responding to immune treatments, with more time, began to shrink.

"The immune system has been living with cancer for years. To make it not be so happy living with the cancer takes some time," said Drake.

Eventually, it all rested upon what was learned with science and technology—powerful new ways to look inside the DNA of cancer cells and computerized data mining that measures and quantifies the subtlest of changes and differences among seemingly similar cancers. The mechanisms that make therapy work in one patient and not in another are now being teased out with platforms like ASTRO-PATH and MANAFEST, developed by Bloomberg~Kimmel Institute investigators.

Remarkable responses were occurring in a significant number of patients, putting the framework for a potentially broad-based treatment for cancer in place. What started in melanoma, kidney cancer, and lung cancer was expanded across all cancer types and has spurred over 10,000 new clinical trials among collaborators across the country and around the world.

This success revealed that the immune system could be employed against cancers beyond melanoma and kidney cancer. As important, it provided definitive proof that there was a common force at work to shut down an immune response to cancer.

The clinical studies provided clear evidence that for lung cancer patients whose infiltrating T cells express PD-1 or whose tumor cells express PD-L1, immune therapy works better than the best chemotherapy drugs and with far fewer side effects. In addition, patients with late-stage lung cancers frequently become resistant to chemotherapy, but Brahmer says that patients who respond to immune therapy tend to continue responding, and roughly 15% appear to be cured.

"In my 20 years in practice, I have never seen anything like this. We're reporting many year survival rates in lung cancer patients who honestly would not typically be around," says Brahmer. "This is truly a milestone in cancer medicine."

A GAME CHANGER

One of the ways cancer immunology experts improved response was by combining immunotherapy drugs, and the findings have since led to FDA approvals for immunotherapy/chemotherapy combinations in several cancer types, including lung cancer, melanoma, gastric cancer, liver, and breast cancer.

"These drugs and drug combinations are turning clinical therapeutics on its head," says Pardoll. "This is a game changer."


POWELL

One of the recently-approved immunotherapy combinations is anti-LAG-3 and anti-PD-1. LAG-3 was shown by Drake, **Jonathan Powell** and other Bloomberg~Kimmel Institute collaborators to shut down immune responses to cancer cells, similar to PD-1. Unlike PD-1, however, inhibiting LAG-3 by itself did not create the same robust response that occurred with anti-PD-1 therapies. However, the researchers found that combining two drugs—one that targets PD-1 and another targeting LAG-3—works in synergy to boost the immune response against cancers.

Nearly two decades after the discovery of LAG-3 as an immune checkpoint, **Evan Lipson**, a clinical researcher who trained with Topalian and skin cancer expert **William Sharfman**, completed a five-year clinical trial that showed combined anti-LAG-3 and anti-PD-1 immunotherapy improved melanoma responses, compared to anti-PD-1 alone, resulting in a 2022 FDA approval of the combination.

Combined approaches using another checkpoint inhibitor, known as anti-CTLA-4, and anti-PD-1 drugs also have been studied, and Pardoll believes that as more immune regulatory genes are identified, more combinations will be revealed. In some cancers, they say, it may be necessary to block multiple immune checkpoints to control a cancer.

"Immune therapy is a game changer, but we have only just scratched the surface," says Pardoll. "We continue the research to take us the rest of the distance, but we don't think there is a single cancer that the patient's own immune system ultimately can't beat."

MAJOR MILESTONES OF THE BLOOMBERG~KIMMEL INSTITUTE FOR CANCER IMMUNOTHERAPY

HISTORIC FDA APPROVALS

• Nivolumab (anti-PD-1) was approved for lung cancer, after a BKI-led clinical trial showed the drug quadrupled the survival rates of lung cancer patients when compared to chemotherapy. Pembrolizumab was also approved for lung cancer patients based on BKI research.

• The FDA approved two immunotherapy treatments based on the results of clinical studies led by the Bloomberg~Kimmel Institute for Cancer Immunotherapy. Coming just weeks apart, the approvals marked the culmination of years of research starting with laboratory discoveries by BKI scientists that were later transferred to patients in clinical trials led by its clinical investigators. A nivolumab/chemotherapy combination was approved for early non-small cell lung cancer (NSCLC), the leading cancer killer in the U.S. It marked the first FDA approval for neoadjuvant (before surgery) therapy for early stage lung cancer. An immunotherapy combination of nivolumab and relatlimab — a new immunotherapy drug targeting the LAG-3 immune checkpoint discovered by Bloomberg~ Kimmel Institute scientists — was approved for the treatment of advanced melanoma, an aggressive and deadly type of skin cancer.

• The historic 2017 approval of pembrolizumab (anti-PD-1) for all cancers that have mismatch repair deficiency/microsatellite instability — a genetic alteration and biomarkers for response to immunotherapy discovered at the Kimmel Cancer Center and BKI in a clinical trial led by **Dung Le** and **Luis Diaz**—was the first ever drug approval not tied to a specific cancer type.

• Based on this approval, pembrolizumab was also approved for the first line treatment of patients with inoperable advanced colorectal cancer that has spread to the other places of the body and has mismatch repair deficiency/microsatellite instability. It marked the first major change in colorectal cancer for the first line of treatment in decades and the first that does not also require patients get chemotherapy.

• Pembrolizumab was approved as the initial treatment for people with advanced Merkel-cell carcinomas, a type of skin cancer, based on a multi-center trial led by **Suzanne Topalian**.

• A BKI-led discovery revealed Lag-3 as an immune checkpoint. A new immunotherapy drug developed by BKI researchers, in collaboration with Bristol Myers Squibb, was shown in clinical trials to stop the progression of advanced melanoma skin cancer and improve survival rates in patients. Based on the results of these clinical trials, the FDA approved the immunotherapy as standard of care for melanoma.

• Another groundbreaking FDA decision came when pembrolizumab was approved to treat patients with recurrent or metastatic Merkel cell carcinoma. The approval was the result of a clinical study co-led by **Suzanne Topalian**, and other investigators at the BKI, Fred Hutchinson Cancer Research Center in Seattle and 11 other U.S. medical centers. Topalian also led a study using immunotherapy before surgery against Merkel cell carcinoma, reporting that the therapy eliminated the cancer in nearly half of the 39 patients treated.

IMMUNOTHERAPY BEFORE LUNG CANCER SURGERY

In 2016, a national clinical trial led by BKI lung cancer expert **Patrick Forde** showed that giving anti-PD-1 immunotherapy before surgery for patients with non-small cell lung cancer gets ahead of the cancer, killing more of the cancer and stopping it from spreading and coming back, extending survival. The treatment worked so well, that by the time of surgery, the tumors in many patients had nearly or completely disappeared. Two years after the study, all but one of the lung cancer patients continued to do well. With surgery alone, about half of patients usually relapse within two years.

Forde predicted the findings would be practice changing, and he was right, as FDA approvals soon followed. The work has inspired more than 70 similar clinical trials across the U.S., exploring the benefits of earlier use of immunotherapy in lung and other cancers.

Forde's findings were published in the prestigious *New England Journal of Medicine* in 2016 and at the 2017 annual meeting of the American Association for Cancer Research.

MICROBIOME

The gut microbiome, made up of more than 100 trillion organisms, traditionally aids in digestion and metabolism functions, but as BKI researcher and microbiome researcher **Cindy Sears** discovered, it also has an impact on the body's response to cancer immunotherapy.

Sears uncovered two bugs, that when present together, drive colon cancer development through an unexpected cancer-promoting type of immune response. This finding has underpinned a 2000-patient public health initiative that uses a simple stool test to find out if colon polyps, a precursor to cancer, are more common when these two types of bacteria are detected together.

In other research, Sears and **Fyza Shaikh** reported that microbes in the stool of patients who respond to immune checkpoint blockade reveal a heightened immune response against primary tumors and metastatic tumors. The constant recirculation of immune lymphocytes through the gut and lymph tissue amplifies immunity throughout the body in patients through cytokine production, substances secreted by immune cells.

A big data analysis led by Sears also found ties between antibiotics and a slightly increased risk of colon cancer. Because antibiotics could kill beneficial bacteria and allow dangerous ones to thrive, some of the surviving bacteria could be encouraging benign polyps to grow and transform more quickly into malignant tumors, Sears explains. She and her colleagues concluded that a single course of antibiotics could boost the risk of colon cancer a decade later. Half a month or more of lifetime antibiotic exposure was associated with a nearly 8% increased risk of colon cancer, and the risk increased to 15% at the 30-day mark.

The study emphasizes the need for more judicious use of antibiotics, which Sears says are often improperly prescribed or over-prescribed. Decreasing antibiotic exposure could mean 50,000 – 100,000 fewer people a year die from colon cancer around the world, she said.

BIG DATA

AstroPath: A cancer-imaging platform, called Astropath, developed by BKI researcher **Janis Taube** and astrophysicist **Alexander Szalay**, a Bloomberg Distinguished Professor of Physics and Astronomy, is at the center of ongoing research that applies the technology to the spatial relations in the tumor microenvironment. AstroPath's groundbreaking celestial mapping algorithms can analyze hundreds of millions of cells, so researchers receive a detailed picture of the tumor's location in the body and how it reacts with surrounding tissues.

MANAFEST: BKI researcher **Kellie Smith** was the developer of MANAFEST (Mutation Associated NeoAntigen Functional Expansion of Specific T cells) technology, which helps identify immune cells that recognize proteins produced by cancer-

ous mutations. Smith used MANAFEST to learn about the difference between cancer-fighting immune cells in patients with lung cancer whose tumors do respond to immunotherapies vs. those whose tumors do not respond. In patients whose lung cancers responded to immunotherapy, immune T cells had been completely reprogrammed to be effective cancer killers. In non-responders, though, she found the same T cells were sluggish and sent signals to block the immune response.

Immunotherapy Before Surgery Could Advance Care of Merkel Cell Skin Cancer
In what is believed to be a first-of-its-kind study, BKI researchers evaluated the safety of a type of immunotherapy before surgery in patients with Merkel cell carcinoma. **Suzanne Topalian**, Bloomberg~Kimmel Professor of Cancer Immunology, **William Sharfman**, the Mary Jo Rogers Professor of Cancer Immunology and Melanoma Research, and **Janis Taube** reported that the treatment eliminated pathologic evidence of cancer in nearly half of the study participants undergoing surgery. In patients whose tumors responded, this treatment approach offers the potential to reduce the extent of surgery and may also slow or eliminate tumor relapses that often occur after surgery.

A DRUG NAMED DON

Jonathan Powell, former BKI researcher, and Johns Hopkins Drug Discovery director **Barbara Slusher**, developed a drug called DON that interferes with metabolism of cancer cells. Tumors kill by growing, and they require nutrients—lots of them—to sustain this growth. Blocking cell pathways that enable this growth by providing amino acids, glucose, and lipids that nourish tumor cells can have an antitumor effect.

Tumor cell metabolism can be considered a kind of immune checkpoint because it creates an environment that turns off the immune response, the researchers said. Blocking these nutrients is cancer specific. All cells need nutrients, but normal cells don't require the extraordinarily high levels demanded by rapidly dividing cancer cells. Cutting off the biological supply line of these nutrients slows the growth of cancer cells without harming normal cells. Adding a checkpoint blocker like anti-PD-1 allows the immune system to sweep in and finish the job on the weakened cancer cells.

The drug was licensed to Dracen Pharmaceuticals and is currently being studied in clinical trials.

DRUG COMBINATION FOR ADVANCED LIVER CANCER

For years, a vast majority of liver cancer patients were not considered candidates for surgery to remove tumors. That may be changing, due to a study by BKI researchers that led to a new immunotherapy/targeted drug combination that makes potentially curative surgery possible for many liver cancer patients.

The treatment combines the immune response-boosting anti-PD-1 immune checkpoint blocker nivolumab and cabozantinib, a drug that blocks specific proteins that help cancer cells grow. The two drugs have been used separately and in combination to treat advanced liver cancer before, but the BKI research was the first time they were studied for their ability to get patients to potentially curative surgery.

In a small study, 75% of the patients treated were able to have their cancer successfully removed after receiving the new therapy, and 1/3 of the patients had 10% or less of their tumor remaining after receiving the drug treatment.

ADDING IMMUNOTHERAPY IMPROVES MESOTHELIOMA SURVIVAL

An international, multicenter study led by BKI researchers found that combining the immunotherapy drug durvalumab with two chemotherapy drugs, pemetrexed and either cisplatin or carboplatin, extended survival. This provides a new treatment option for patients who have inoperable pleural mesothelioma, a cancer of the tissues lining the lungs.

MARK FOUNDATION CENTER FOR ADVANCED GENOMICS LAUNCHED

The Mark Foundation for Cancer Research and BKI announced a $10 million commitment to fund novel work to advance immunotherapy research and provide lifesaving breakthroughs for cancer patients. The Mark Foundation Center for Advanced Genomics and Imaging is co-led by **Janis Taube**, professor of dermatology and pathology and co-director of the Tumor Microenvironment Technology Center and BKI director **Drew Pardoll**.

BLOOMBERG~KIMMEL PROFESSORS OF CANCER IMMUNOTHERAPY ANNOUNCED

The BKI named three inaugural Bloomberg Professors of Cancer Immunotherapy:

- **Jonathan Powell** developed a drug that simultaneously strengthens immune cells within tumors and weakens cancer cells. He has since gone on to continue his research in the biotech industry.
- **Cynthia Sears** linked the collusion of two types of gut bacteria to a cancer causing immune response in colon cancer.
- **Suzanne Topalian** was at the center of the groundbreaking studies that led to anti-PD-1 and anti-PD-L1 immunotherapies.
- **Dung Le** is the newest Professor. She is a gastrointestinal cancer expert who led the clinical trials that established a genetic defect called mismatch repair deficiency/microsatellite instability as predictor of response to immunotherapy with drugs that block the PD-1 immune checkpoint.

INTERNATIONAL IMMUNOLOGY LEADERS JOIN BKI

World-renowned immunology researchers **Erika Pearce**, a molecular biologist, and immunologist **Edward Pearce**, joined the Bloomberg~Kimmel Institute for Cancer Immunotherapy as Bloomberg Distinguished Scholars. They will continue their promising path of research, providing important information about how the human immune system is activated, evaded and reprogrammed.

As Bloomberg Distinguished Professors, Edward and Erika Pearce join an interdisciplinary cohort of scholars working to address major world problems and teach the next generation.

CHI VAN DANG RETURNS TO JOHNS HOPKINS

Chi Dang returned to Johns Hopkins, with primary appointments in the Kimmel Cancer Center's Bloomberg~Kimmel Institute for Cancer Immunotherapy and the Department of Biochemistry and Molecular Biology.

Dang is best known for defining the function of MYC, the first cancer gene known to act as a switch, turning on metabolic pathways and mechanisms that are advantageous for cancer cells. He showed that MYC alters the metabolic pathways in cancer cells, and tumor cells become addicted to certain nutrients. This landmark research from 1997 opened up the field of cancer metabolism, a major area of study in the BKI.

An Immunotherapy Pioneer

Research nurse Alice Pons recalls the first clinical trials of immunotherapy drugs


PONS

Alice Pons is a pioneer in cancer immunotherapy. In 2007, she administered some of the first treatments in clinical trials of anti-PD-1 and anti-PD-L1 immunotherapies.

These new cancer therapies were developed based on research at the Johns Hopkins Kimmel Cancer Center that showed cancer cells co-opted natural on/off switches of the immune system, called immune checkpoints, to shut down the immune response to cancer. The new drugs, researchers believed, had the power to re-ignite the immune response.

Ultimately, they transformed the cancer treatment paradigm, mainstreaming immunotherapy as a cancer medicine. However, in 2007, they were trailblazers, as phase I clinical trials began to evaluate the safety and determine the dosing for these promising new drugs that were about to be given for the first time to patients.

New therapies showed that cancer cells co-opted natural on/off switches of the immune system, called immune checkpoints, to shut down the immune response to cancer. The new drugs, researchers believed, had the power to re-ignite the immune response.

Pons recalls administering the first doses of the drugs in patients with advanced cancers who were out of options. Many of them were near death, she recalls.

"Desperation," is the word that best describes the mood, she says. "These patients had tried a lot of therapies that did not work against their cancers. This was their last chance."

They wanted the drug to be the thing that finally worked for them, but if it didn't, maybe what the nurses, doctors and researchers learned from them would help others in the future. Patients wanted to find a greater meaning in their battle against cancer, for them and for their families, says Pons.

The anti-PD-1 and anti-PD-L1 immunotherapies were different than the chemotherapies that had led to the dreadfully common characteristics that grew to define cancer, and the fear associated with the disease. The treatments, while lifesaving for many, often came with debilitating side effects. Essentially, they worked by poisoning rapidly reproducing cells, which meant they killed cancer cells, hair cells, gut cells and more, causing patients to lose their hair and suffer from nausea and vomiting. It is not an overstatement to say many patients feared treatment as much as the disease.

The patients Pons was treating in these immunotherapy clinical trials had already received many rounds of chemotherapy. "They were worn out," she says. "When we told them these drugs did not usually cause hair loss or nausea and vomiting, they were ready to give it a try."

From the very first infusion, it was clear this treatment was different, Pons says. It truly was a new frontier. They didn't know what to expect, so they were hyper-vigilant.

"We took vital signs every 15 minutes," says Pons. "Almost immediately, we could see this was not like chemo. When you give chemo, patients get sick. With this, they did not.

It took a year before they began to see responders. The immunotherapy drugs worked best against melanoma, a type of lung cancer called non-small cell lung cancer, and kidney cancer.

Pons says they were elated when some patients began to respond to the immunotherapy. "I would be sitting with the different doctors when they got the results that it was working. They couldn't wait to tell the patient. Of course, the patients were very happy," she says.

Then, she says, trepidation set in, and they began to worry about how long it would last. Would they get to the next scan and find the cancer had come back?

Pons worked so closely with patients and families, it was impossible not to become emotionally invested. She was beyond excited about the responses but admits she remained skeptical.

For Pons, it wasn't about the science, the proof was in the patient standing in front of her.

"We didn't know why it worked in melanoma and a few kidney cancer and lung cancer patients but not in other cancers. I was stoked for the mela-

noma patients because they had been striking out for so long," says Pons. "I was so deep in the trenches with the patients that sometimes the broader picture eluded me. The doctors were confident. They would tell me it was going to work, but I found it hard to believe until it a happened a couple of times over a couple of scans."

As more responses to the treatment became long-lasting, extending years, her relationships with the patients and families did as well. This was unusual because most patients with advanced cancers died within months. She was invested.

"Every time a patient came back for a scan, I would get a pit in my stomach. 'What if it comes back?' I'd think to myself, and I knew the patient had the same worry."

Her thoughts immediately turn to a patient whose cancer came back after two years. "It was heartbreaking. I had let my guard down and believed the immunotherapy would make it a lasting remission," she says.

Fortunately, for many patients, there have been long remissions. In fact, some have lasted 15 years and are considered cured, says **Drew Pardoll**, director of the Bloomberg~Kimmel Institute for Cancer Immunotherapy.

Still, one of the key areas of research remains focused on figuring out who will respond and then among responders what makes the treatment stop working.

"There is much left to learn," says Dr. Pardoll. "We're getting better at predicting who will respond in the first place, but we still don't know why some people who respond relapse years later."

Another area of major focus, and again one where the Bloomberg~Kimmel Institute for Cancer Immunotherapy led the way, was in detecting and managing side effects. The immunotherapy drugs worked by unleashing the immense power of the immune system, and sometimes the immune system attacked healthy tissue and organs in addition to cancer cells.

Just as this type of immunotherapy was new, so were its side effects. They were not as obvious as chemotherapy side effects.

"They crept up and were harder to detect," says Pons. "They were outside of my realm of experience having done chemo for so long."

"We can't minimize the autoimmune side effects because there were people who sacrificed their lives on the way because they were already suffering from toxicities caused by chemotherapy, and now on top of that, they had autoimmune side effects," she adds. "We got hit pretty quickly with what worked and didn't work and with warning signs about something coming and heading it off at the path. It was hard in the beginning, but we figured out fast how to recognize warning signs and how to manage them."

When the Bloomberg~Kimmel Institute-developed therapies were proven in clinical trials, received FDA approval, and now were being administered by community practices, the importance of recognizing and managing side effects became even more evident.

"We had patients coming to us because their immunotherapy was poorly managed in the community."

Managing side effects was a science of its own that many beyond the walls of the Bloomberg~Kimmel Institute did not appreciate. Our experts engaged a broad range of specialists—endocrinologists, rheumatologists, dermatologists, and more—to develop the standard of care and ensure doctors and patients recognized the warning signs, which to an untrained eye could be easy to miss.

In general, serious side effects occur in about 20% of patients, but at the Bloomberg~Kimmel Institute, it's much lower at 5% to 10%. Pons says it is the expertise here that makes the difference.

Pons credits the doctors and scientists who developed the treatment protocols for making Johns Hopkins a standout.

"Had I not been on this team, with **Suzanne Topalian** at the helm, it would have been a lot different. She kept our noses to the grindstone and instilled in all of us the importance of focus and attention to detail. I am very thankful for that. This strong leadership and commitment to patient care is what makes the Kimmel Cancer Center and the Bloomberg~Kimmel Institute special."

"On a clinical trial, we're giving them concierge nursing. I'm responsible for my patients. I want to know; I have to know. I go through the side effects from head to toe with each patient. We're calling, emailing. That accessibility translates into patients being treated for their side effects more quickly. Our goal is to keep everyone safe," she says.

Fast forward to 2023, and now combination therapies of different immunotherapies, and even chemotherapy, given together are improving response rates. Research at the Bloomberg~Kimmel Institute has led to multiple FDA approvals and immunotherapy as a first line treatment for many types of cancer.

Pons becomes emotional when she thinks of the journey from the very first patient she treated to the continuing progress still being made today.

"It was exhilarating. I imagine it is how skydiving feels. In a way, that's what we were doing," she says, referring to all of the unknowns of the first clinical trials. "It achieved one of my objectives in life, to contribute to mankind. This allowed me to do it, and I am forever thankful."

A Historic Decline in Cancer Deaths

Cancer death rates in the U.S. took the "biggest single year drop ever," between 2016 and 2017, according to a January 2020 report by the American Cancer Society.

IMPROVEMENTS IN the screening and treatment of lung cancer, the 2nd most common cancer and leading cancer killer, are a main contributor to this positive trend. **Julie Brahmer**, Director of the Kimmel Cancer Center Thoracic Center of Excellence and Director of the Bloomberg-Kimmel Institute for Cancer Immunotherapy Lung Cancer Program, attributes the improved lung cancer survival to screening programs aimed at people at highest risk of developing lung cancer and new immunotherapies and targeted therapies.

The Kimmel Cancer Center participated in a national lung cancer screening study that showed screening those at high risk leads to early detection of lung cancer and improved survival, Brahmer explains. As a leader of a SU2C-LUNGevity Foundation-American Lung Association Lung Cancer Interception Dream Team, Brahmer is collaborating with scientists and clinicians throughout the country who are working in many fields of lung cancer research, from prevention through early detection and treatment, to develop new ways to stop lung cancer before it progresses to an advanced stage

"There is plenty of opportunity to see these rates decline further," she says. "We may just be seeing the tip of the iceberg."

Brahmer says new treatments that have become available over the last couple of years, particularly new immunotherapies and targeted therapies, also played a key role in the decline in lung cancer deaths. She led the landmark clinical trials that helped earn FDA approval for the immunotherapy drugs nivolumab and pembrolizumab in lung cancer. In some patients, these treatments ignite the body's own natural defenses to attack cancer cells, even advanced cancers that have spread from the lung to other parts of the body.

A clinical trial led by Kimmel Cancer Center lung cancer expert **Patrick Forde** in collaboration with thoracic surgeons **Richard Battafarano**, **Stephen Broderick** and **Stephen Yang** found that, for some patients, giving immunotherapy before surgery can decrease the cancer size in hopes of improving survival.

FORDE

BATTAFARANO

BRODERICK

Brahmer says follow-up data on immunotherapy supports their findings. The immunotherapy drug nivolumab has the longest follow-up to date of these drugs. "Five-year overall survival quadrupled in non-small cell lung cancer, compared with what we would expect from chemotherapy," she says.

Other therapies, known as targeted treatments because they zero in on features of the cancer that drive its growth and spread—such as an EFGR gene mutation or the presence of a cancer-promoting ALK fusion gene in the cancer—are also leading to improved survival, says Brahmer

Although the greatest strides have been made against non-small cell lung cancer, the most common type of lung cancer, Brahmer says there are also promising new treatments for small cell lung cancer, an aggressive and treatment-resistant type of lung cancer. A new treatment combining immunotherapy and chemotherapy for patients with advanced small cell lung cancer received FDA approval last year, she says.

"This is the power of precision medicine," says Brahmer. "There is no longer one-size-fits-all therapy for cancer. We look at each individual patient's cancer and determine the treatment that will best attack the unique characteristics of the cancer."

From Metastic Cancer Survivor to Marathon Runner

A Bloomberg~Kimmel Institute Treatment Saves Another Life

As 37-year-old **Kristina** laced up her running shoes to begin the grueling 26.2-mile New York City Marathon in 2019, she knew where to find the grit, tenacity and determination it would take to make it to the finish line. Baum drew her inspiration from her 7-year battle with metastatic melanoma, a deadly skin cancer.

Her survival—and the ability to take on a marathon—are a testimony to Baum's strength and the power of discoveries at the Kimmel Cancer Center's Bloomberg~Kimmel Institute for Cancer Immunotherapy. Experts there researched and developed the treatment plans that saved Kristina's life—twice.

Baum's cancer story began in 2012 when she noticed a raised bump on her arm. At 30, cancer was the last thing on her mind.

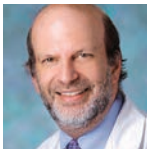
"I thought cancer was an old person's disease," she said.

A biopsy of the bump revealed it was melanoma, and worse yet, it had already spread to nearby lymph nodes. At the time, there were not many effective treatments for patients with melanoma. It was a grim diagnosis.

> **"I thought cancer was an old person's disease."**

She received initial treatment at a hospital near her home in Washington, D.C., with a drug called interferon, a version of the body's own natural protein that works by stimulating the immune system. Melanoma and other cancers sometimes respond to the treatment, but there


LIPSON


KLEINBERG

are many side effects, such as flu-like symptoms and severe fatigue.

Interferon might have been tolerable if it kept her melanoma in check, but in 2016, Kristina learned the cancer had spread to her kidney. She came to the Kimmel Cancer Center to see melanoma expert **Evan Lipson**.

"Learning you have metastatic cancer is not just life-altering, it's life-shattering," says Kristina

She didn't believe she had many options, but Lipson told her about a clinical trial testing a new combination of medicines called immune checkpoint inhibitors. When cancer cells turn off natural immune regulators to avoid recognition by the immune system, these drugs re-ignite the immune response to the cancer.

The combination Lipson had in mind was based on research from the Kimmel Cancer Center's Bloomberg~Kimmel Institute for Cancer Immunotherapy, demonstrating that blocking two of these immune checkpoints, called PD-1 and LAG-3, could work in synergy to boost the immune response.

Research at the Kimmel Cancer Center suggested that radiation therapy might prime the body's immune system to respond better to immunotherapy and more easily recognize and attack cancer.

After two infusions, she was hospitalized with autoimmune meningitis—her own immune system was attacking and inflaming tissues surrounding her brain. Her skin felt like it was on fire. She was weak and had no energy. To add insult to injury, the prednisone given to control the side effects caused her to gain weight. The good news was that the tumor in her kidney was going away.

Kristina longed to feel well again. She started with long walks, gradually building her strength back. She wanted to try a triathlon, and she made that her goal.

By 2017, she was running five miles a day and was finally beginning to feel like herself again, so in December 2018, when she began experiencing extreme fatigue and vertigo, she chalked it up to over-training.

As part of her follow-up care for her cancer, she had an imaging test called an MRI. Lipson called her with the results.

"I knew it wasn't good. I could hear it in his voice," Kristina recalls.

She learned that the cause of her symptoms was her melanoma, which had appeared again and, this time, it was in her brain. The news was crushing.

"No matter how many times you go through it. It's traumatic. It makes you emotional," says Kristina.

Lipson had another clinical trial in mind for Kristina. This time, in collaboration with radiation oncologist **Lawrence Kleinberg**, he prescribed a treatment that included a course of immunotherapy given in combination with focused beams of radiation aimed at the brain tumor. Research at the Kimmel Cancer Center suggested that radiation therapy might prime the body's immune system to respond better to immunotherapy and more easily recognize and attack cancer.

Less than a year later, after finishing treatment for cancer that had spread to her brain, Kristina was about to realize the goal she set for herself a few years earlier. As she approached the starting line of the New York City Marathon and joined a field of 55,000 other runners, she had a unique driving force, harnessing inspiration from her hard-fought battle against cancer.

"It was one of the hardest things I've ever done. You have to dig deep," says Baum. "That's where you find the reason to keep putting one foot in front of the other."

Kristina, now in her forties, purchased her first home, finished her fifth marathon, and started a new job, leading strategic communications for the American Veterinary Medical Association. She also joined the board of directors of the Melanoma Research Foundation.

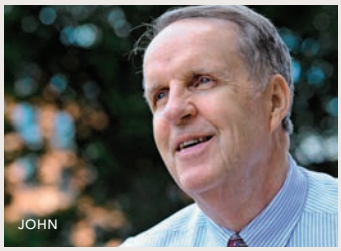
"I wanted to be an advocate for others in the trenches," she says. "As a patient being able to have access to top research is so important. You want to be closer to advancements."

Kristina says she has a special place in her heart for the physicians and nurses doing translational research.

"Being part of a clinical trial and playing an active role in advancing medicine felt very empowering for me," says Kristina. "I want to help make a better journey for others."

"I gained 100 months of quality life..."

One Patient's Journey in this History-Making Clinical Trial


JOHN

John was one of the lung cancer patients who benefitted from the historic clinical trials of anti-PD1 immunotherapy in lung cancer.

In 2015, John, then 68, began coughing up a small amount of blood. The husband and father of eight thought it was strange, but with no pain or other symptoms he was stunned to learn he had the most advanced stage of a common form of lung cancer, known as non-small cell lung cancer. The cancer had already spread to a rib.

There are few diagnoses worse than late-stage lung cancer. The cancer kills more people than any other type of cancer, and few patients survive once it has spread.

"One of my sons was graduating from college, and my daughter was about to leave for a study abroad. I wondered if I would live long enough to see my son graduate or to welcome my daughter back home," John recalls.

The first treatment he received was chemotherapy, and for a time, it worked, but the treatment came at great physical cost, and these side effects were worsening. The simplest tasks became difficult. His body was weakening, and worse, he learned his cancer was no longer responding. He thought he might be out of options.

It was then that his doctor suggested he go meet with **Julie Brahmer**, who was one of the lead investigators on an experimental clinical study of anti-PD-1 immunotherapy in a variety of advanced cancers. John's form of lung cancer was among the cancers that showed unprecedented responses.

The anti-PD-1 drug, called nivolumab, interfered with cancer cell's ability to shut down the immune response to cancer, unharnessing the immune response against cancer.

"I had struggled to sit at my kitchen table. After just four treatments, the tumor shrunk by 65%, and I felt like a human being again," says John. A few more treatments and his rapidly growing lung cancer was nearly gone, and the cancer that spread to his rib was eliminated.

About one-quarter of the lung cancer patients in the study responded to the treatment. The numbers were even higher for melanoma and kidney cancer patients, but it was the lung cancer responses that garnered the most attention.

Anti-PD-1 was the first checkpoint inhibitor to work against lung cancer—and as many as 14 other cancer types —and that's the pivotal difference that excited the cancer world.

Despite the great success, Brahmer and her Kimmel Cancer Center colleagues began to observe that, in some patients, the immune response did not stop at the cancer but rather continued to attack and inflame the lung, skin, gut or other organs. John was among them.

In March 2022, he began having trouble breathing. The immunotherapy, that kept his advanced lung cancer in check for more than eight years was now triggering his immune system to attack his lungs. The persistent inflammation, called pneumonitis, caused scarring in the lungs, leading to significant shortness of breath.

John was not the only patient to experience this side effect. The Kimmel Cancer Center and its Bloomberg-Kimmel Institute for Cancer Immunotherapy (BKI) led the way in research and addressing the challenge, launching a new dedicated initiative for managing side effects of immunotherapy, led by **Jaruska Naidoo**.


NAIDOO

BKI researchers and clinicians are setting the standard of care for how to recognize and treat these types of immunotherapy toxicities.

These side effects can present with a wide range of symptoms, so their management requires the cooperation of many experts. Naidoo and colleagues assembled a group of specialists in every part of the body that has the potential for adverse reactions to immunotherapy and they are on call for the BKI 24/7.

Naidoo attended national cancer meetings with a research nurse to educate other doctors and worked with organizations, like the National Comprehensive Cancer Network, to share what they have learned and to establish standards for managing immunotherapy side effects. They are also assembling a web-based course for doctors.

Despite the limiting toxicities, John continues to battle. He still believes he was in the right place at the right time. He feels fortunate that his diagnosis coincided with advances in immunotherapy. Without it, he points out, he had, at best, nine to 18-months to live.

"Having just passed the 10-year survival milestone in April 2023, I am humbled and grateful to the Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins and Dr. Julie Brahmer, and the team of doctors and nurses who have provided unparalleled expert medical care to me throughout this journey. I am comforted in knowing that I am with the best team of experts in the world," says John. "I gained 100 months of quality life extension. I have been there for college graduations, weddings, and the births of grandbabies. If I had to do it over again, even with the pneumonitis, I would make the same choice. The alternative would be not to be here. Immunotherapy saved my life."