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CANCERWORLD

Lorelei Mucci

What If the world's leading prostate cancer epidemiologist opened a restaurant?

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The People Behind the Progress in Oncology is science. But it is also stories. It is policy. It is power. It is knowledge. It is culture. It is trust. And above all it's personal. This is the lens through which we bring you to look at this April 2025 issue—an edition that spans leadership-defining careers, cutting-edge research, policy reforms, ethical dilemmas, and the emotional flow of cancer care.

We open with two extraordinary lives in conversation with science.

Dr. Philip Kantoff shares lessons from 28 years at Dana-Farber, his leap into building Convergent Therapeutics, and his belief that mentorship is the most powerful legacy a physician-scientist can leave behind. His journey—from a top- academic institution to entrepreneurial innovation—is both inspiring and instructive for the next generation of oncology leaders.

Dr. Lorelei Mucci offers something equally powerful. One of the world's leading prostate cancer epidemiologists, Dr. Mucci opens up about the intersections of ambition, motherhood, mentorship, and identity. How do you balance professional excellence and private life, and how do you keep personal integrity? She answers with clarity—and courage.

We then turn to Dr. Miriam Merad, recipient of the 2025 Sjöberg Prize, whose work on immune cells has transformed the landscape of tumor immunology. In this profile, we draw an arc between basic science and clinical application. Alongside her story, Prof. Urban Lendahl, Secretary of the Sjöberg Prize, explains the prize's global relevance—and what made Dr. Merad's contribution stand out.

From there, the issue dives into a series of timely and challenging topics.

One of our most poignant features explores the decision to pursue pregnancy in the setting of advanced breast cancer. It raises hard questions: Can treatment be safely paused? Who decides what's ethical? How do we support women navigating deeply personal, medically complex decisions? The answers are not easy—but they matter.

We spotlight emerging data showing that low-dose aspirin may reduce recurrence in PI3K-altered colorectal cancers. It's a reminder that progress comes not only from the newest drug, but from revisiting old ones with a new lens.

We also ask a long-taboo question in metastatic breast cancer: Is it possible that some patients might actually be curable? Slowly but steadily, the evidence for this achievement is building up. In this piece, we examine how clinicians are beginning to separate signal from noise and change the paradigm with respect to long-term survival.

As a powerful novelty report, we descrive a Phase 1 trial of a personalized neoantigen vaccine—early, yes, but promising. It's a further step in how individualized cancer immunotherapy comes from shadow to light.

Policy also takes center stage. In an exclusive interview, MEP Nikos Papandreou discusses the role of the SANT committee, the EU Cancer Plan, and the push for liquid biopsy policy.

Finally, we explore the state of psycho-oncology through the eyes of someone who spent a year listening—to patients, clinicians, caregivers. What emerges is not just an article, but a reckoning with the mental and emotional toll of cancer in a world still recovering from collective trauma.

This issue is more than updates. It's about perspective. It's about nuance. And it's about people. Oncology doesn't develop in the vacuum. It happens in real time, in real lives, across borders, across disciplines, across all we know, and what we still do not know.

We express a thank you to all those who read us. Oncologists, researchers, patients advocates, policy leaders, entrepreneurs. You are the community that keeps oncology progress and person's hope going. Your attention encourages better science, better system, and better care.

The next appointment will be the next issue, we'll be waiting for you.

Adriana Albini

What If the World's Leading Prostate Cancer Epidemiologist Opened a Restaurant?

A conversation with Lorelei Mucci - a Harvard scientist, a mother, a leader

Gevorg Tamamyan

I always close my interviews with a signature question: "Who should I speak with next?"

It's a small but revealing moment - a window into whom the giants of oncology admire, learn from, and find truly compelling.

When I posed the question to Dr. Philip Kantoff, his answer came without hesitation: "My wife, Lorelei Mucci."

It wasn't just a nod to her professional accomplishments — it was a heartfelt sign of the deep respect she's earned, especially among those who've spent their lives in this field.

From Wyoming to Harvard: Being open to chance and taking different paths

Dr. Lorelei Mucci's career has been marked by unexpected turns, moments of serendipity, and an openness to opportunity. It all began with a genuine interest towards science but something was missing.

"I loved science, but lab work felt kind of lonely," she admits. Wyoming changed everything. "I moved out to Wyoming for a year and a half and worked for a pathologist who covered all of Western Wyoming. And that was fascinating to learn about rural health care and the challenges. He diagnosed everything from cancer to malaria. But I think it got me interested in thinking about science from more the public health perspective," she recalls.

This unexpected detour led her to pursue a career in epidemiology, a field she had never heard of before. After applying to the Harvard School of Public Health, she quickly immersed herself in her doctoral training, which became the launchpad for everything that followed.

"I had a chance to meet somebody who completely changed my life. His name was Dimitrios Trichopoulos and he was a really world-famous cancer epidemiologist. It was his excitement and passion for cancer that truly sparked my own interest in the field. In many ways, I believe my career and life have been shaped by serendipity—by being open to chance and willing to take different paths."

Sweden: The paradise for epidemiologists

Her career then led her to a postdoctoral fellowship at the Karolinska Institute in Sweden, which Dr. Mucci describes as a "paradise for epidemiologists."

"Sweden has national health registers that track every aspect of people's health, which is incredibly valuable for epidemiological research," she explains.

Dr. Mucci worked with the country's famous twin registries. "It was a completely unique resource. To be able to identify a cohort of 200,000 twins followed for 40 or 50 or more years for cancer mortality and be able to really dive deeply into the heritability of cancer was really exciting,"—an experience that would shape her future research.

"What do I want to do that's really different?"

When asked what's next in her distinguished career, Dr. Lorelei Mucci reflects thoughtfully.

"I think asking that question is really something I've also been thinking about for myself: what do I want to do that's really different?" she muses.

Two years ago, she took on a part-time role at the American Cancer Society as a senior scientific advisor. "I've been doing some things that are really different, really exciting," she says.

One such initiative was her involvement with a collaboration between American Cancer Society, the Prostate Cancer Clinical Trials Consortium, and an organization called Trial Library. Together, they developed a program aimed at addressing the lack of diversity in clinical trials for prostate cancer.

"Black men are at much higher risk of prostate cancer, much more likely to die from it, but they represent less than 5% of clinical trial participants," Dr. Mucci explains.

This disparity led her to work on solutions to engage communities and provide them with the resources needed to participate in clinical trials. "It's very different from the traditional epidemiology research."

Exploring Environmental Impacts on Cancer Survival

Beyond prostate cancer, Dr. Mucci is also exploring new areas of research focused on the environment's impact on cancer survival.

"I've become very interested in how things like wildfires, smoke, or floods may impact cancer care, screening, and survival. These environmental factors could also expose individuals to heavy metals or carcinogens, which have long-term consequences on health. What are the long-term consequences of exposure to these factors? How can we study that? How do we assess biomarkers and measure environmental influences in the communities people live in?"

Another exciting avenue Dr. Mucci is exploring involves the link between diet, health, and cancer outcomes. "I'm starting to delve into the idea of how diet can impact health, but also how it can positively influence the environment. A colleague of mine, Walter Willett, developed the Planetary Health Diet Index, a plant forward dietary pattern that also is beneficial for the planet's health. I am working on a funded study examine this dietary pattern to prostate cancer incidence and outcomes in cancer patients," she says.

Why Prostate Cancer? Addressing a Big Unmet Need

When asked why she chose to focus on prostate cancer, Dr. Lorelei Mucci traces the origins of her decision to a bit of serendipity.

"It was an opportunity that came up when I returned from Karolinska," she explains. "I joined colleagues at Brigham and Women's Hospital, and I got involved in some funded research. I didn't know much about prostate cancer back then," she admits. "But what struck me was how little epidemiology had been done on it compared to other cancers like breast or colorectal cancer."

She quickly realized that prostate cancer was a significant health issue.

"Prostate cancer is the leading cause of cancer

among men in over 100 countries. It's a huge burden, and there was so much work to be done in terms of screening, prevention, and treatment," she says.

Prostate cancer research has come a long way, but many of the treatments were introduced before we fully understood how to use them in the best combinations or sequences — not just to improve survival but also quality of life. "In the last ten years, there's been an explosion of new therapies for metastatic prostate cancer," she notes. At the same time, we were learning more about the biology of metastatic prostate cancer," she continues. "There was a big unmet need for research that could guide treatment options."

While clinical studies on prostate cancer were being conducted at single institutions, they did not cover all aspects of survivorship. That's why the IRONMAN registry, a global initiative collecting real-world data from men with advanced prostate cancer, was created.

"We needed to develop a global cohort to understand the real unmet needs in advanced prostate cancer. This is why the IRONMAN cohort was designed to span 15 countries worldwide, addressing gaps in global prostate cancer research, particularly in underserved regions like Africa and the Caribbean, where prostate cancer mortality rates are alarmingly high," she explains.

According to Dr. Mucci, the research in these populations has been minimal. "We're enrolling patients from countries where prostate cancer mortality rates are enormous, and little research has been done to address these disparities."

Rising Prostate Cancer Rates in the U.S.

Dr. Mucci also highlights an alarming trend in the U.S. regarding prostate cancer.

"With the decline in prostate cancer screening in recent years, we're seeing an increase in newly diagnosed metastatic prostate cancer," she explains. "As a result, the number of deaths from prostate cancer is also rising."

The IRONMAN cohort is crucial not only for studying metastatic prostate cancer. "We need to study both populations—those who progress to metastatic cancer and those diagnosed with de novo metastatic disease," she says.

"IRONMAN is a collaborative project of epidemiologists, clinicians, molecular biologists, and patient advocates. I am co-leading this with my husband Phil, as well Daniel George, a medical oncologist at Duke. Dan is a fantastic person and physician-scientist."

Being the best mother or the best researcher?

Dr. Mucci's journey was marked by both personal and professional challenges.

"I've been very fortunate to have fantastic mentors who have helped me navigate through some of the toughest moments," she begins.

However, a particular hurdle weighed on her more than any other. "As an early investigator, there was always the challenge of funding and getting established in the field," she says. "But on a personal level, I think the biggest challenge was how to balance being a mom with being a successful scientist and academic leader. How do you manage those two things?"She continues, "I think I did a good job. Hopefully, my son will say that."

Yet, she acknowledges that no matter how hard she tried, she never felt like she was excelling at both roles. "You're always giving and taking along the way," she reflects. "You never feel like you're being the best mother or the best researcher."

We're being told that we shouldn't study women's health or LGBTQ+ health

Despite being a globally recognized professional, Dr. Mucci still faces challenges, and she openly shares some of the recent ones she has encountered. "The last two months have been some of the most difficult in my career," she admits. "It's so frightening to see what's happening to science, particularly with the growing attacks on public health."

She points out the mounting pressure on various aspects of science and research. "We're being told

that we shouldn't study women's health or LGBTQ+ health," she says. "It's deeply troubling for the future of research."

Her concern extends beyond her own career. "For young investigators, students, postdocs, and junior faculty members, I worry about the future of their careers and funding," she shares. "It's a scary time for them, and it's terrible times for the field overall."

A Legacy of Guidance: The Mentors Who Shaped My Career

Dr. Mucci's career has been shaped by numerous influential mentors, each of whom has left a lasting impact on her personal and professional development. "Phil was one of the colleagues who had a big influence on me," she notes, recalling her connection to her husband Philip Kantoff, who played a pivotal role in her transition to prostate cancer research.

Dr. Mucci explains how she first worked with epidemiologist Meir Stampfer, who connected her with Phil. "As a PhD scientist, if you want to work in prostate cancer, you really need to understand the clinical issues," Stampfer advised. This connection helped Dr. Mucci build a bridge between her research and clinical applications.

Alongside Phil, Dr. Mucci worked closely with pathologist Massimo Loda at Dana Farber and then Weill Cornell, a key mentor who influenced her research in tumor-based biomarkers. "He's a fantastic individual, and I gained a lot of mentorship from him," she shares.

She also highlights Edward Giovannucci, a forward-thinking nutritional cancer epidemiologist. "He would be a fascinating person to work with," Dr. Mucci says, admiring Giovannucci's innovative approach to the field.

Another influential figure in her journey was earlier mentioned Dimitrios Trichopoulos, Dr. Mucci's doctoral mentor. "He always challenged us to not be afraid in our hypotheses," she recalls. "He encouraged us to be bold, take risks, and it's okay to fail."
Despite her accomplished career, Dr. Mucci acknowledges the ongoing importance of mentorship. "As you get older, it's harder," she admits. "Mentorship is different now. It's more about finding colleagues you trust, people with whom you can share your concerns and get constructive feedback."

Leadership is about providing others with the resources and vision to thrive

Dr. Mucci speaks with pride about her mentees, a team of epidemiologists who have been integral to her work. "I have this wonderful group of people. They're all women, and I've seen a significant change over the years in how many women have become interested in prostate cancer epidemiology," she says.

When Dr. Mucci began her career, the field was predominantly male, but the landscape has shifted, reflecting the increasing inclusivity in scientific fields.

In addition to her work with epidemiologists, Dr. Mucci mentors clinical colleagues at Dana-Farber, Brigham and Women's, and Mass General Brigham. "I've also been fortunate to mentor a number of clinical colleagues who are interested in clinical cancer research," she shares, emphasizing her broad reach and influence in both epidemiological and clinical spaces. "I think leadership is providing others with the resources, vision, and opportunities to thrive in an environment. It's about offering guidance when needed and being an advocate for your team."

Dr. Mucci describes her leadership style as collaborative and supportive. "I prefer to lead through consensus building rather than a top-down approach," she explains. She values inclusivity and teamwork, believing that leadership should be about fostering a cooperative environment where everyone can contribute and excel.

Dr. Mucci also serves as the faculty director of the Cancer Epidemiology and Cancer Prevention Program within the Department of Epidemiology at the Harvard T.H. Chan School of Public Health. She explains that each student's journey is unique. "Mentorship is about understanding what each person's goals are. Some students come to gain research experience, some want to learn how to

teach, and others are looking to pursue a PhD."

She advises tailoring the experience to meet each student's personal goals. "It's about finding what's right for each person and helping them along the way."

Be Bold in Your Ideas and Collaborate Generously

Dr. Mucci has key advice for those pursuing a career in cancer epidemiology. "Be bold in your ideas," she suggests. "The successful cancer epidemiology research I see now involves collaborations with people from diverse fields—clinicians, basic scientists, and more. It's not just about your own research; it's about working together with others to make a real impact."

Then she adds a message that ties it all together:

"Learning how to be a generous and thoughtful collaborator is one of the best things you can do," she says.

Two Leaders, One Direction

Dr. Mucci shares a humorous yet insightful story about the dynamics of having two leaders in a family. "Before we were a couple, we were friends and colleagues for such a long time," she begins. "I think we have a really strong foundation of trust and mutual support."

Throughout their careers, Dr. Mucci and Dr. Phil Kantoff have collaborated extensively. "We published around 80 papers together. We've collaborated really successfully. And I think our style of leadership and approach to science is not dissimilar. I think we have similar thoughts about that. But there was a time when we took a kayak out together, a double-person kayak, and I was in the front and he was in the back. But we were both trying to steer the boat."

These moments are an analogy for the occasional difficulty of having two strong leaders. "It can sometimes be hard to have two people who are both used to leading things," she admits."But I've learned so much from Phil about leadership. He's been a successful leader in so many different environments. The way he navigates people with such diverse personalities is truly fantastic," she smiles.

If not this, then Pasta

When asked what she would pursue if not cancer epidemiology, Dr. Mucci's answer is as heartfelt as it is unexpected. "I would open a restaurant," she says with a smile. "It would be an Italian restaurant. It would be small and quaint, with a beautiful patio for when the weather is nice to sit outside. It would be a place where people could come together, share a meal, and maybe learn to cook as well."

Dr. Mucci didn't take long to decide on the location for her restaurant. "It will probably be on Martha's Vineyard, which is a place that is really special to us," she says.

She also shares a personal connection to cooking with her partner, Dr. Philip Kantoff.

"Phil and I both love to cook," she notes. "Who cooks better? We both have very different styles. He's the master of the grill, a perfectionist with it. We work really well together. We actually love cooking together."

Success is Feeling Proud of the Impact We're Making

What Success Means to Dr. Mucci?

"I think success is waking up every morning and feeling really excited about the work that I'm doing," she shares.

For Dr. Mucci, success is not just about individual accomplishment, but about making a meaningful difference in the world through her work and mentorship.

"It's about feeling proud that my mentees and my team are succeeding as well. And ultimately, knowing that we might be having an impact on public health."

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CANCERWORLD

PHILIP KANTOFF

I REALLY CARE ABOUT PEOPLE

I wanted to be a scientist when I grew up

Boston. The city where old bricks and new ideas stand side by side. Where science, education, and innovation breathe together. The wind cuts through the streets of New England, sharp and relentless. If I were fifty pounds lighter, it might carry me away.

Dr. Philip Kantoff waits for me in a café next to his office. He wears a vest with the Convergent Therapeutics logo. The elevator took us to his office. The glass windows behind him open to the landscape of downtown Boston. The skyline watches over a man who has spent his life changing the course of cancer treatment.

The fight against cancer has been long. He has been in it from the start—twenty-eight years at Dana-Farber, leading genitourinary oncology and solid tumor oncology; then Chair of Medicine at Memorial Sloan Kettering. He has built teams, mentored leaders, driven research, and changed the way prostate cancer is treated.

Now, he sits here, in Boston-the city where breakthroughs happen

The city where he still shapes the future of cancer care. But long before he became one of the defining figures in modern genitourinary oncology, he was just a young man who loved science. “I was in high school when I first got intrigued by genetics,” he begins. “I spent summers doing research. I wanted to be a scientist when I grew up.”

That passion for science led him down an unexpected path. “My college interviewer at Brown University asked me why I wasn’t applying for the seven-year medical program,” he recalls. “I hadn’t really considered it, but I thought-why not?” So, he applied. He got in. And without realizing it at the time, he took a path that would shape his future in medicine and greatly contribute to the progress of oncology.

From Brown to the NIH

Brown University became his academic home. He spent seven years in Providence, Rhode Island-four in undergraduate studies, three in medical school-immersing himself in science and medicine. Then came residency. “I did my residency in internal medicine at NYU Bellevue in New York,” he says.

But medicine alone wasn’t enough. His love for research pulled him back to the lab. “I wanted to go back and do research,” he explains. “So, I went to the National Institutes of Health and worked on gene transfer, gene therapy, using retroviral vectors.” It was a transformative experience.“I was involved in cutting-edge research. It was an incredible time in my life.”

Then came the next step—fellowship. “I applied for fellowships and decided to go Dana-Farber,” he says. “My intention was to be there for a short time and then move on to a career as a basic/translational scientist.” But life had other plans.

28 Years at Dana-Farber: A Legacy in Oncology

The short stay at Dana-Farber turned into nearly three decades. “I never imagined working in genitourinary oncology,” he admits. “But the person running the

Gevorg Tamamyan

I really care about people: Philip Kantoff

Life in science and medicine

program had left, and they needed someone to take over. It was an opportunity." So, he took it.

At first, he was just learning. Then, he opened a laboratory. Then, he started running clinical trials.

"I was very fortunate because medical oncology fellows wanted to work with me after their first year of fellowship," he says. "When that happens, your program expands, and you can do more."

More meant publishing groundbreaking research. More meant leading large clinical trials. More meant securing major grants—millions of dollars to push prostate cancer research forward.

One of the defining moments of his career came when he secured a SPORE grant. "It was a very large grant," he recalls. "It brought all the institutions at Harvard together around prostate cancer. It was a productive time for me."

Soon, his responsibilities grew beyond research. "I took on a more administrative role," he says. "I became the head of solid tumor oncology. Then, the Chief Clinical Research Officer at Dana-Farber."

But the biggest challenge was yet to come.

New York, New York

In 2014, Memorial Sloan Kettering Cancer Center made an offer: they wanted him to become Chair of Medicine.

"It was a heavy administrative role," he says. "But I took it on in 2015." For six years, he oversaw a department of 500 faculty members. It was a massive undertaking.

"I maintained a small clinical practice," he says. "But I was mostly focused on leadership and research." Then, in 2021, life shifted again. "I got married and decided to move back to Boston," he says.

And with that decision, he made another one: he would start something new.

A New Challenge: Building Convergent Therapeutics

Starting a biotech company was a different kind of challenge. "In 2021, it was just me and a couple of other people," he recalls. "It was called Convergent Therapeutics. My old friend Neil Bander was still at Cornell, but he joined as Chief Scientific Officer."

The mission? To create radioantibodies—targeted treatments for prostate cancer. They focused on a specific protein: prostate-specific membrane antigen (PSMA).

"Our approach was to take an antibody and link it to actinium-225, an alpha-emitting radionuclide," he explains. "Alphas are much more powerful than other types of radiation because they're large helium nuclei," he continues. "They have a short path length, so you can deliver very precise radiation without a lot of collateral damage."

Before Convergent even existed, studies were already underway at Cornell, where Bander and Scott Tagawa, a leading medical oncologist, were testing the J591 antibody linked to actinium-225—what would later become CONV01-a. The results were remarkable.

"In the first experiment, a single dose of CONV01-a was given, and 45% of patients responded," Dr. Kantoff says. "Their PSA levels dropped below 50%, and some had durable responses. Then, in a multi-dose experiment, the responses were even more impressive." But running a biotech company came with steep learning curves.

"I knew medicine and science. I knew leadership," he says. "But I had to learn finance, fundraising, manufacturing, and regulatory affairs. It was a completely different world."

Yet, as always, he adapted.

Convergent's flagship study, CONVERGE-01, is now treating patients at two critical points in their cancer journey: First, after treatment with Pluvicto, a small-molecule beta emitter targeting PSMA, when no clear next step exists.

Second, before Pluvicto or chemotherapy, to see if earlier intervention can drive better outcomes.

"So far, things are going extremely well," Philip Kantoff says. "We're accruing patients, we're not encountering any problems, and we're seeing good activity."

For a physician who has spent decades advancing prostate cancer research, the move into biotech represents a new chapter—one with potentially game-changing implications.

Mentors Who Shaped Me

Throughout his career, Dr. Kantoff had many mentors.

"My first inspiration was my 10th-grade biology teacher," he recalls. "He had so much energy and inspired a lot of us to go into science."

At Dana-Farber, some of the biggest names in oncology helped guide him. "George Canellos, Robert Mayer, and Thomas Frie were mentors of mine at Dana Farber," he says.

"These were giants in the field of oncology. They gave me opportunities, encouraged me to do research, and taught me how to care for patients."

"I worked in the Molecular Hematology laboratory at the NIH," he explains. He was involved in gene transfer and gene therapy. "I spent four years as a postdoc learning how to approach science at the highest level."

"I've learned a lot from a lot of people along the way, and I think I'm a good listener and observer of other people. I like to surround myself with people who are very talented, who are smarter than I am, that I can learn from."

I don't tell people what to do

In 2024, Dr. Kantoff received ASCO's Teaching Award.

"It was a great honor to be recognized for my mentorship of very talented people I have worked with" he says.

Mentorship has been one of the most rewarding aspects of his career. "I've had so many talented mentees," he says. "Levi Garraway, now Chief

Medical Officer at Roche Genentech. Bill Sellers, who was head of oncology at Novartis. Matthew Smith, William Oh, Daniel George, Mary-Ellen Taplin to name a few—so many brilliant and talented people."

"I've gained as much from the people that I've mentored as they've gained from me. So, it's got to be a two-way street with mentorship," he reflects.

But for him, mentorship is about guidance, not control.

"I don't tell people what to do. I tell them what not to do," he says. "I create opportunities and let them grow."

Advice for Young Oncologists

For those starting a career in oncology, Dr. Kantoff offers clear advice.

"Find what you're most passionate about," he says. "The field of medicine has so many opportunities. But the fundamental core of being an oncologist is compassion—taking care of patients. The medicine part while remaining challenging is something you can master. But every patient is unique. Every patient is going through one of the hardest moments of their life."

He also warns against losing the human side of medicine.

"With all the advances in AI, some say doctors may no longer be necessary," he says. "But nothing can replace the human touch, empathy, and compassion in oncology. Understanding what people are going through. Walking into a room and making a connection. Being a source of guidance and comfort."

Advice for People Starting a Biotech

For those launching biotech startups, his advice is simple. "Hire the right people," he says. "In academic medicine, we understand science and medicine, but biotech is a different world. You need experts in finance, regulatory affairs, and manufacturing."

And patience is key. "Building a biotech is a long game," he adds. "It's about managing complexity-raising money, running trials, scaling up. It's not for the faint of heart."

The Future of Cancer Treatment

What excites him about the future of oncology?

"Radiopharmaceuticals," he says without hesitation. "We've only scratched the surface of what can be done with targeted radiation." Immunotherapy is another major frontier. "Checkpoint inhibitors have been a game-changer," he says. "But there's so much more to uncover in harnessing the immune system against cancer."

Outside of work, Dr. Kantoff enjoys the simple things

"I love my family," he says. "I have four children. Aaron manages a biotech venture fund. Emily is a psychiatric nurse practitioner. She works at UCSF's cancer center, helping patients deal with the psychological impact of their disease. Sydney oversees a team that manages the culture, events and space for a large public advertising tech company. My stepson, Ethan, is finishing college at Bowdoin and is studying in Australia."

His wife, a prominent epidemiologist at Harvard, Prof. Lorelei A. Mucci, has been a research partner for years. "We've worked on many projects together," he says.

And then, there's cooking and tennis. "I love to play doubles," he says. "I used to play basketball, but my body can't take it anymore. Tennis is my game now." Music has always been a part of his life, too.

What's Next?

Dr. Philip Kantoff has spent a lifetime learning, leading, and innovating. And he has no plans to stop. Because for him, the work is never done. The discoveries are never over. And the next breakthrough is always just around the corner.

Miriam Merad and the 2025 Sjöberg Prize: A Celebration of Innovation in Cancer Immunotherapy

Yeva Margaryan

Every year, the Sjöberg Prize, established by the **Royal Swedish Academy of Sciences**, honors researchers whose scientific discoveries in oncology are reshaping the understanding and treatment of cancer.

The award stands alongside the most prestigious accolades in science, not only highlighting landmark breakthroughs but fueling ongoing innovation.

In 2025, the prize was awarded to **Dr. Miriam Merad**, whose pioneering work on **tissue-resident macrophages** has redefined the understanding of cancer immunity.

Her research, once met with skepticism, is now at the forefront of cancer treatment strategies.

The award comes not only as recognition of past achievements but as a catalyst for her future work, particularly in the emerging field of **immunoprevention**—a concept that seeks to intercept cancer before it takes hold.

In our in-depth conversation with Dr. Miriam Merad and Urban Lendahl, Secretary of the Sjöberg Prize Committee, we explore the significance of the award, the groundbreaking discoveries that earned Merad this prestigious recognition, their transformative impact on cancer treatment, and the inspiring journey of the scientist behind it all.

A Journey Shaped by Purpose

Dr. Merad's journey began in Paris, where she was born to Algerian parents pursuing medical fellowships.

Soon after, her family moved to Algeria, a nation rebuilding its healthcare system in the wake of independence.

Growing up in this transformative period, she was immersed in an environment where medicine was more than a profession—it was a mission. "My parents were deeply committed to their work," Dr. Merad recalls. "They weren't just doctors; they were rebuilding a country, shaping a future. There was a sense of solidarity, a belief that medicine could truly change lives."

Spending long hours in the hospitals where her parents worked, she developed an early appreciation for medicine. But it was her exposure to Algeria's underdeveloped oncology care that left a lasting impression. "Cancer treatment wasn't a priority in a country focused on managing acute diseases first," she explains. "I remember visiting an emerging cancer center and feeling heartbroken for the patients."

Her path toward oncology crystallized during her early medical training. "I started medical school in Algeria, and during my rotations, I spent time in that very cancer center," she says. "That's when I knew—I was going to dedicate my life to oncology."

Political instability later forced her to leave Algeria, leading her to France, where she completed her medical studies and embarked on a groundbreaking research career that would span continents.

Looking back, she recognizes how those formative years—rooted in resilience, mission, and compassion—became the foundation for the discoveries that would define her career.

The Sjöberg Prize Selection Process

The **Sjöberg Prize** has rapidly established itself as a beacon for transformative cancer research.

Unlike many scientific awards that honor lifetime achievements, the **Sjöberg Prize** is designed to recognize researchers at the height of their experimental prime-scientists whose discoveries are actively reshaping the field.

"We look for research that has made a real difference," Prof. Lendahl says. "We want to see breakthroughs that redefine a field, discoveries that future generations of scientists will look back on as pivotal moments in oncology."

Awarding the Sjöberg Prize is a meticulous process that unfolds over the course of a year. Nominations are solicited from leading cancer researchers worldwide, with a rigorous evaluation system ensuring that the most deserving candidates are recognized. "We cast a wide net to ensure diversity in geography, expertise, and scientific discipline. Every year, we receive nominations from across the globe, and we take great care to maintain fairness and transparency", Prof. Lendahl proudly states.

Once nominations are received, a committee of six experts evaluates the candidates, identifying a shortlist of around 5-10 names. External reviewers are then brought in to provide independent assessments, ensuring that no biases influence the decision-making process.

Dr. Merad's scientific journey and significant discoveries perfectly embody the Prize's philosophy. **Professor Lendahl specifically highlights three pivotal aspects of Merad's research that led to her recognition.**

First is her groundbreaking identification that tissue-resident macrophages arise from embryonic precursors rather than circulating monocytes—a finding that fundamentally challenged prevailing immunological paradigms.

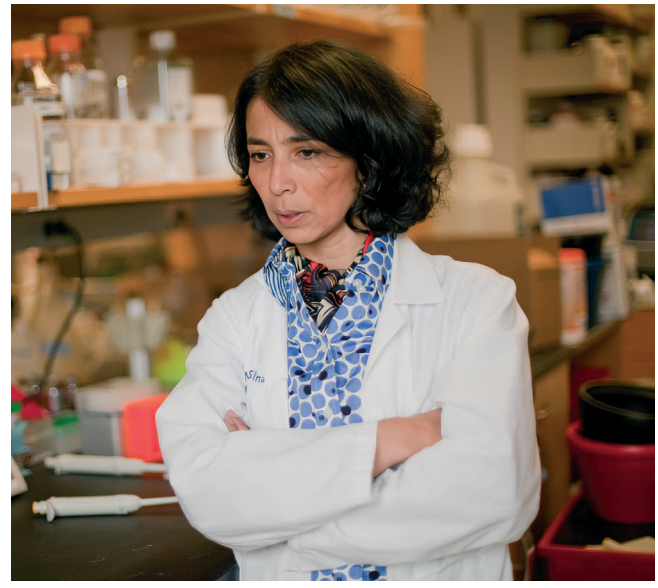
Second, her extensive characterization of macrophages within tumor environments laid crucial groundwork for subsequent research, revealing how these cells can either support or restrict tumor growth.

And finally, Merad's current research is transforming her foundational findings into tangible clinical innovations. Lendahl underscores this point, noting, "Her ongoing research offers compelling proof-of-concept studies indicating how macrophage manipulation could significantly enhance existing immunotherapies."

"This was a fundamental discovery in immunology," concludes Lendahl. "It changed the way we understand the immune microenvironment of tissues, including tumors."

Bridging Immunology and Oncology

Merad's research has laid the foundation for novel immunotherapeutic strategies. While immune checkpoint inhibitors and CAR-T therapies have



revolutionized cancer treatment by harnessing T-cells, her work highlights the underexplored role of the myeloid arm of the immune system. "She has been a strong advocate for the myeloid branch of the immune system," Lendahl emphasizes. "Her recent work shows that macrophages are not passive bystanders but active participants in shaping the tumor microenvironment. By modulating their behavior, we may open new doors for cancer immunotherapy."

In 2024, Merad published two groundbreaking papers in Nature, demonstrating how targeted manipulation of macrophage signaling pathways—such as interleukin-1 and interleukin-4—could reinvigorate anti-tumor immunity. Early clinical trials

have shown promising safety profiles, with some patients exhibiting strong responses.

“We are still in the early days,” Lendahl notes. “But this research has the potential to change how we approach tumors that have traditionally been resistant to T-cell-based therapies.”

A Passion for Oncology: She doesn’t just do science; she lives it.

Dr. Merad’s enthusiasm for oncology is palpable. Her passion is not merely intellectual—it is deeply personal, rooted in years of observation, hands-on research, and an unwavering drive to find better cancer treatments.

When asked about her passion for her work, she simply laughs and responds with an undeniable truth: “I love these cells. That’s true. I love these cells.”

“When you talk to Miriam, you instantly sense her passion,” Lendahl says. “She doesn’t just do science; she lives it. That energy is infectious, and it inspires younger scientists to push the boundaries of what’s possible.”

Her fascination with the immune system’s role in cancer treatment extends beyond scientific curiosity—it is a calling. “For a long time, immunotherapy was dominated by the focus on T-cells. But I was interested in the cells that educate T-cells—the dendritic cells and macrophages,” she explains. Her groundbreaking discovery that tissue-resident macrophages originate from embryonic precursors rather than circulating monocytes was a paradigm shift in immunology.

Dr. Merad’s passion is evident in her meticulous study of dendritic cells. “Dendritic cells are an extraordinary cell type; which role is to take things and present targets to T cells. They are the ones that really educate in a very potent manner. They take, let’s say, tissue antigen, they migrate to the draining lymph node. And there, they interact with naïve T cells and really build these antigen-specific T cell responses in a way that is very unique.”

She explains how her research has led to a greater

Dr. Miriam Meran and Dr. Thomas Marron discussing a new clinical trial based on their laboratory findings

understanding of immune system manipulation. “We identify a subset of dendritic cells that are really very good at priming T cells against tumor antigen or against viral antigen. Because they prime specifically what we call CD8 T cells.”

From Lab to Treatment: Bringing Dr. Merad’s Discovery to Clinical Practice

For Dr. Merad, oncology research is not just about discovery but application. Her work has always balanced basic science with clinical translation.

At her institute, fundamental discoveries and their practical applications go hand in hand. Many researchers in her lab conduct foundational studies, while others work to bring these insights into clinical trials. This seamless integration, she believes, is a key strength of their approach. “It happens that at the same time you are discovering some of these basic mechanisms, colleagues of ours are watching and already thinking about how they can translate them,” she explains.

The lab’s structure fosters this collaboration, bringing together researchers focused on the most fundamental aspects of macrophage biology and those working on real-world applications.

With this award, Miriam and her team are now positioned to advance prevention strategies, using their deep understanding of macrophages to mitigate early cancer progression. For her, science is not just about discovery—it is about ensuring that these discoveries benefit patients.

"Yes, discoveries happen in labs, but then we need translations to help people benefit from these discoveries," she reflects. For her, the process of translation is just as crucial as the breakthroughs themselves. Her hope is that this deepened understanding of dendritic cells will lead to more effective immunotherapies.

"Many of us are trying to target them in vivo so that they become more numerous—that's often reduced in the tumor lesions-and more functional."

As Urban Lendahl states, "Miriam's meticulous work provided the most comprehensive molecular map of macrophages within the tumor microenvironment, deeply enriching our understanding of their dual roles in tumor biology... Recognizing the distinct embryonic origin and functions of these macrophages means we can now more precisely target them therapeutically. This approach complements existing therapies targeting lymphoid cells, providing a more comprehensive strategy against cancer."

Dr. Merad's passion for oncology fuels her relentless pursuit of knowledge. While some researchers may approach their work with a clinical detachment, Dr. Merad embraces every nuance of her discoveries with the excitement of someone who knows their work is changing lives.

The Importance of the Sjöberg Prize to Miriam Merad

Dr. Merad speaks with deep appreciation about receiving the Sjöberg Prize. "I am extremely honored. You know, there is always a big honor to receive a prize, especially a prize by peers, right?"

For her, the award is not just about personal achievement but about the broader implications for cancer research. "So, your peers recognize the importance of your work. What I'm very excited about is that I think this prize also recognizes the role of myeloid cells, macrophages, and dendritic cells in cancer treatment."

She emphasizes how this recognition marks a shift in the field. "This was not the case when I started. This was not the case even 10 years ago. And now I think that recognition is important."

Beyond honoring her individual contributions, the prize validates an entire area of research. "It's important for my field because it's important for macrophage biologists and for cancer immunologists that are interested in macrophages."

Dr. Merad hopes the award will serve as motivation for future research. "This would encourage more people also to work on these questions. So, I think it is influential. It's sending a signal that macrophage biology matters in cancer treatment."

Her gratitude to the Royal Swedish Academy of Sciences is evident. "And for this, I am particularly grateful for the Royal Swedish Academy of Science for their recognition."

With the funding secured, Dr. Merad sees the award as a catalyst for the next phase of her work. "So, I am also extremely grateful for the support that I now have to engage into another new area, new focus of ours." Her excitement is clear—this is not just recognition for past work but an investment in the future.

Challenges and Triumphs: Merad's Journey as a Woman in Science

While her professional accomplishments are extraordinary, Merad's path was not without challenges. Acknowledging barriers faced by women scientists, Merad candidly shares her experiences juggling family life and an ambitious scientific career. She emphasizes resilience, transparent communication, and community support as keys to her success.

"Well, yes, there are challenges. You know, I have the habit of never emphasizing the challenges," Dr. Merad acknowledges.

Birgitta Henriques Nordmark, Chair of the Royal Swedish Academy of Sciences (left), presents the Sjöberg Prize to Dr. Miriam Merad. At her right stands Gregory Aminoff Laureate Prof. Simon Billinge of Columbia University, USA.Photo © Patrik Lundin

Dr. Miriam Merad with her sun - Zach

She reflects on the primary struggle many women scientists face: balancing career and family. "Women, especially when they become mothers or partners, often grapple with work-life balance. The expectation that mothers should be more at home than fathers still persists," she explains. "I think that women have this sensibility for their kids that is sometimes more developed than in fathers. Being able to do both well-I found it difficult."

To address these challenges, Dr. Merad has openly shared her experiences. "I wrote a piece called ***Reflections of a Mother Scientist in Nature Medicine***. There, I talk about all the guilt I felt-guilty for not spending enough time with my kids, guilty for not spending enough time in the lab. But in the end, my kids don't even remember me working so hard. They tell me, ''You were so present in my life."

At work, Dr. Merad has been fortunate to find enablers. "I don't think I encountered many challenges, but my dean once told me, 'It's not possible that you didn't.' And maybe he was right—maybe there were derogatory comments, maybe I was the only woman in the room and didn't have the codes. But I just ignored it. I never engage in battles that are useless. I fight only when it's worth it."

Reflecting on Merad's experiences, Lendahl acknowledges the importance of highlighting such stories."Myriam's journey is inspiring not only scientifically but personally. Her transparency about navigating challenges provides invaluable lessons to emerging researchers, especially women who might face similar barriers."

Dr. Merad hopes that the progress made for women in science will not be undone. "We have achieved so many wins, and I hope we don't lose them," she states. She then proudly adds, "And I will be very happy to fight for women who are striving to find their path in medicine, in science, and in society."

About Prof. Urban Lendahl: A Steward of Scientific Excellence

Urban Lendahl, chair of genetics at the Karolinska Institute, has had a distinguished career dedicated primarily to cancer research. With a PhD from Karolinska and postdoctoral experience at MIT, Lendahl quickly rose through the academic ranks, securing early tenure and remaining loyal to Karolinska Institute.

His research centers on the Notch signaling pathway, investigating its role across various cancers, including breast and lung cancer. "Technically I'm working on a signaling pathway called the Notch pathway," Lendahl explains. "We try to understand what Notch does when it's mutated or sort of erroneously expressed in different cancer forms."

His extensive expertise positioned him effectively for leadership roles in prize committees, notably serving as secretary for the Nobel Prize for Medicine and leading the Nobel Committee. Reflecting on his current role, Lendahl shares: "This is my third round, third year as a secretary for the Sjöberg Prize. It's been fun and a privilege to work together with the Royal Society in Sweden for science."

As Secretary of the Sjöberg Prize Committee, his responsibilities encompass coordinating global nominations, structuring evaluations, ensuring procedural integrity, and overseeing communication with global stakeholders.

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Diana Mwango

Seeking to get pregnant when the cancer is advanced

Faced with the sudden knowledge that the life they had expected will be suddenly cut short, some women find hope and existential meaning in trying for a child that that will be theirs for their remaining time, and carry their legacy when they are gone. Diana Mwango reports from Kenya on what that choice can mean for patients and their cancer management.

On December 12, 2024, Grace Atieno held her newborn baby in her arms – a moment that, in many settings, would have been nothing out of the ordinary. But Grace's pregnancy was anything but routine; it was a defiant act of hope.

Grace became pregnant while on treatment for advanced HER2+ breast cancer, which had been diagnosed when she was only 23. The oncologist advised termination of the pregnancy, citing two critical risks: the progression of her cancer if she paused treatment and the risk that the anti-cancer treatments posed to the developing foetus.

But Grace, still only 26 years old, wanted that pregnancy. Indeed, she had planned for it, despite the doctors advising her not to. For two years, while still taking her cancer treatment pills daily, she says, "I prayed, fasted and cried to God to enable me to get pregnant." She would break her fast in the evenings, she recalls, only to swallow her pills.

Grace decided to stop her cancer treatment to safeguard her pregnancy, and she does not regret the decision. Now seven weeks old, she says her baby is a bundle of joy that outweighs the burden of the progression of the disease.

Before pausing her treatment, the metastases had been confined to her lung. "Now I have resumed, but the doctor says the cancer has spread to the brain, there is also a new tumour in the other breast. I also recently developed tinnitus. My ears ache but the doctors are optimistic that I shall be okay. I pray that God adds me many years to see my child grow," she says.

Her story is not isolated; it highlights a profound dilemma faced increasingly by oncologists and obstetricians, particularly in Africa, where cultural, religious, and societal expectations around motherhood often clash with medical advice, and where – due in large part to a younger demographic profile – the average age of breast cancer diagnosis is markedly lower than in Western settings.

Managing pregnancy in women with advanced breast cancer

Evidence regarding the risks involved in pregnancy in cancer patients is largely limited to women undergoing treatment for early-stage disease, where treatments are administered for a set period of time.

Matteo Lambertini, an oncology consultant at IRCCS Policlinico San Martino Hospital, in Genova, Italy, who specialises in managing fertility and pregnancy-related issues in women with breast cancer, advises that only patients who have gone through optimal treatment should try for a baby, with the pregnancy being planned in consultation with the doctor.

"I don't advise getting pregnant before completion of treatment, but if one does, oncologists must discuss the risk of stopping the treatment based on risk of recurrence and age of the patient. In some cases, the patient can continue with the pregnancy and stop the treatment. In other cases, the risk of recurrence is very high, so I will definitely advise stopping the pregnancy. It is a very delicate decision to make," Lambertini says.

> **"Most of the treatments we use in metastatic patients cannot be given during pregnancy"**

Advanced breast cancer (also known as stage 4 or metastatic breast cancer) is different, however, says Lambertini, because the disease has become incurable, and optimal management requires being on treatment permanently. Currently there is little evidence about risk of progression from pausing treatment, and what is known about the risk to the unborn from continuing treatment is not encouraging, he says. "So far there is no safety data for pregnant patients with Stage 4 disease. So, we don't know if it's safe to stop the treatment in a metastatic patient, and most of the treatments we use in metastatic patients cannot be given during pregnancy."

Risk to the patient of pausing treatment in breast cancer

Studies on pregnancy in cancer tend to exclude women whose breast cancers are already advanced at the time of diagnosis, so evidence regarding the risks involved in pausing treatments for this group of patients is very sparse, says Matteo Lambertini, a medical oncologist who specialises in the management of breast cancer in young women, with a special focus on the fertility and pregnancy.

However, in women treated for early-stage disease, studies have shown, for instance, that some patients who have low-risk disease and are on endocrine breast cancer therapy can safely stop the treatment to get pregnant.

"The results of a temporary break of endocrine therapy study – the POSTIVE trial – are reassuring. It allowed a two-year break to allow patients to have a pregnancy and then go back to complete treatment," says Lambertini.

"However, my advice is for a patient to discuss the study with her oncologist, because the break is not safe for everyone.If the patient has a very high risk of recurrence, it is not safe to stop the treatment to get pregnant. But pregnancy itself is not a trigger for the recurrence. So, if a patient has a high risk of recurrence and she gets pregnant, she still has a high risk of recurrence, but it is not because of the pregnancy," Lambertini adds.

The study excluded women with advanced cancer; only 6% of the study population had stage 3 disease; and follow up was less than three and a half years. It is unclear what the findings mean for treatment breaks in women with advanced hormone-positive cancers.

Some studies have suggested that maternal immunity is stimulated against cancer cells during pregnancy – the so-called 'foetal antigen hypothesis'. However, the evidence for this is far from conclusive.

Different types of cancer treatment pose different

The image shows Grace Atieno with her seven-week old baby. Photo credit ©Mwamba 2025

risks to different stages of foetal development. Most chemotherapies, for example, are contraindicated only in the first 12–14 weeks of the pregnancy due to the high risk of foetal malformations. However, they can be administered safely after that time.

"Anthracyclines and taxanes, which are the two most used chemotherapy agents, are safe in the second and third trimester," says Lambertini. Trastuzumab, by contrast – a monoclonal antibody used to treat HER2+ breast cancer, which is what Grace has – cannot be given in the second and third trimester, but it can be given in the first trimester, "It is the opposite of how chemotherapy works. Trastuzumab has big molecules; it cannot cross and reach the foetus until week 12 or 14 of gestation," says Lambertini. While trastuzumab is considered non-toxic to the ovaries, it must be discontinued during pregnancy to avoid complications like reduced amniotic fluid levels, which can jeopardise foetal development.

"Hormonal treatments such as tamoxifen, used to treat hormone-positive breast cancers, cannot be used at any point in the pregnancy, he adds. While the impact of most targeted agents, including PARP inhibitors, used to treat breast cancers in women with a harmful BRCA gene, as well as immunotherapies (including PD-1, PDL-1 and CTLA-4 blockade) remains largely unknown. We have no accurate data on the effects of immunotherapy and PARP inhibitors on fertility and pregnancy. We have data in mouse models that show immunotherapy and PARP inhibitors can be toxic for the ovaries, but we don't have data on pregnant women." says Lambertini.

CDK4/6 inhibitors, used to treat hormone-positive, HER2-negative disease, cannot be used either, because they are prescribed in combination with hormonal therapy. Animal studies have also shown foetal harm following exposure.

Managing advanced breast cancer during pregnancy

A 2023 expert consensus statement on the management of cancer during pregnancy, published by the European Society for Medical Oncology, does not touch on the case of women who get pregnant while being treated for metastatic cancer – possibly because it is such a rare occurrence. It does, however, include a statement on managing women who are diagnosed with metastatic disease during their pregnancy.

As a general rule for managing breast cancer at any stage of disease, it states that chemotherapies – cytotoxics – should not be used in the first trimester, as early exposure has been associated with up to 20% risk of major malformations.

In terms of specific guidance on managing metastatic breast cancer in patients who are pregnant, it says that:

- ***Treatment decision making in metastatic disease should be based on the biology and extent of the disease (i.e. imminent organ failure).***

- ***For patients not candidates for treatment with anthracyclines, single-agent paclitaxel, carboplatin and to a lesser extent vinorelbine could be considered starting in the second trimester.***

- ***Tamoxifen, poly ADP-ribose polymerase (PARP) inhibitors or CDK4/6 inhibitors, HER2-targeted therapy (including antibody-drug conjugates) and ICIs such as anti-PD-1/PD-L1 and anticytotoxic T lymphocyte-associated antigen-4 should be avoided during pregnancy.***

Considering the major safety concern associated with the administration of several agents that have been shown to improve survival in the metastatic setting, the consensus statement says that:

- ***Each patient should be properly counselled regarding the risk associated with not administering these agents on her prognosis, versus the risk of foetal complications if they were administered during gestation.***

It adds that multiple factors could influence a patient decision (social, cultural, religious belief, etc), and that "It is of utmost importance that she understands every consequence of the different options to make a fully informed decision."

Why have a child when your cancer is incurable?

In many African societies, a woman's worth can be closely tied to her ability to bear children, and women may face strong social and cultural pressures to fulfil their maternal role before they die. But there are

often profound personal emotional drivers at work as well, says Philip Odiyo, the founding Chairman of the Psycho-oncology Society of Kenya and the founding Vice President of the Association for Psycho-Oncology Society in Africa.

For some women, especially those with metastatic cancer, having a child becomes a way to leave behind a legacy or find new meaning in life, he says. ***"It's about hope, a psychological anchor. A child represents continuity and the will to live," Odiyo explains. "Through the nine months of pregnancy, it is nine months of expectations, of looking forward to something. The child gives them a new drive to wake up every day."***

While that feeling is by no means confined to African women, Odiyo believes it may be particularly deeply rooted in this part of the world.

> **"Africans believe in procreation. If you leave the earth, you must leave your seed behind. When they [relatives and friends] see your child, they will remember, oh, this is so and so's son or daughter," he says.**

His point is well illustrated by the story of Alice Mwang'angi who, two years ago, was diagnosed with cancer with metastases to the liver. Though she is now 45 years old, and on chemotherapy, she does not want to give up on her dream of having a child, and therefore rejected the advice of her oncologist to have a hysterectomy.

"I have fibroids and I bleed heavily. He fears the chemotherapy-induced anaemia may compete with anaemia from the fibroids. But I refused to remove my uterus."

Alice had delayed childbearing, she said, because she had not found "*a suitable partner to start a family with*," but she longs for a child so she can leave a bit of her behind.

"I am a child magnet. Children constantly knock at my door, yet I don't even know their mothers. I remember when I was hospitalised for a month and came back home on crutches. They ran to help carry my luggage inside the house," she says, "I want a mini-me to run to me when I reach home. I'm very beautiful, I want a baby to inherit my beauty gene."

Ethical issues

At the time of her diagnosis, Alice's oncologist did not raise with her questions about her future plans for children and what options she might have. Alice feels he should have. A different doctor did subsequently suggest she might freeze her eggs. That suggestion, however, is seen as ethically questionable by some in the field, due to the very low likelihood of success, given Alice's age and the extent of her disease.

Fertility treatment works better in younger women. And while it is true that more than 10% of women with advanced breast cancer now live with metastatic disease for 10 years or more, the average life expectancy is between two and three years, even without interruptions to their treatments.

When the cancer has spread to the liver, that shortens to an average of less than six months (though Alice has been living with liver mets for two years now).

The authors of a 2023 paper published in **Reproduction and Fertility** argue that suggesting fertility preservation in settings where patients have a very poor prognosis is – as a general rule – unethical, because it offers unrealistic hope of survival, "***and may be interpreted as saying that there is good chance of living to become a parent – because why offer it otherwise?"***

Yet should the question of hopes for a baby be entirely off the agenda when discussing options with patients with advanced breast cancer, given that women like Grace may choose to prioritise having a baby, despite knowing that her cancer is not curable, and that pausing treatment risks worsening her prognosis?

> **"If the patient says, 'I want to take the risk', you tell them 'fine, just don't disappear'"**

Manel Haj Mansour, a medical oncologist at Aga Khan University Hospital in Nairobi, argues that the relationship between the doctor and the patient has changed in recent years, and that while she would advise women being treated for breast cancer

against pregnancy, the decision is theirs.

"We've moved past the era where the doctor makes all the decisions, and the patient simply follows... If the patient says, 'I want to take the risk', you tell them, 'fine, just don't disappear. Come to hospital so we monitor the cancer as the gynaecologist and the neonatologist monitor the mother and baby progress," she says, adding, "Most times, the ones who refuse to terminate pregnancies are more than those who accept."

She comments on the increase in the number of younger patients turning up at her clinic. A few years ago, it used to be anecdotal to have a breast cancer patient who is perhaps 26 years old, she says, ***"Now I can recall I've had about 10 cancer patients who are between 26 and 29 years old."***

Many will be diagnosed at an early stage where the treatment plan aims for a cure, and a long cancer-free life, in which case conversations around family aspirations, and options for fertility preservation are essential. Haj Mansour asks questions such as,

"How strong are your feelings of having a baby? Do you have an immediate plan? Do you have a partner? Have you discussed it with him?"

When the diagnosis is of advanced disease, however, questions of future life plans are not so immediate or prominent in consultations. Yet, arguably, women with advanced disease may feel they have less to lose by pausing their treatment, as they have already lost their chance for a cure.

And the pressures to get pregnant may be all the greater because they cannot put it off, and because becoming a mother and leaving something of themselves behind after they die can give meaning and hope to the last years of their life.

If oncologists can help their patients achieve this, it can be very satisfying, says Haj Mansour, who tells the story of one of her patients who was diagnosed with stage 4 triple-positive breast cancer.

The woman stopped attending for treatment for about two years, and then one day she showed up at her clinic and announced she was pregnant. Haj Mansour was delighted the patient had felt able to come back to her.

"Can you imagine if she had disappeared out of shame that she got pregnant against the doctors' advice? Some patients disappear and come back with complications such as liver failure or paralysis. What we learn as oncologists from such scenarios is that you support the patient, irrespective."

> **"I feel like this is not just her baby, it's our baby. The baby is healthy, and she is physically okay"**

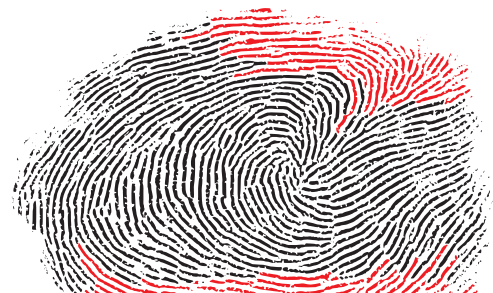
As luck (or biology) would have it, her patient did not experience disease progression over those two years, despite being off treatment. Haj Mansour was then able to monitor her patient throughout the pregnancy, and referred her to a gynaecologist skilled in managing high-risk pregnancies, who reported back on her patient's progress.

Just recently, the patient came to the oncology clinic carrying a six-week-old baby. "I *feel like this is not just her baby, it's our baby, " says Haj Mansour. The baby is healthy, and she is physically okay*."

Even now, there is little sign of progression – the tumour in the mother's lymph node is the same size as it was before coming off treatment and before the pregnancy. "*I told her 'you're defeating science'*," says Haj Mansour.

It would certainly seem that her patient is beating the odds. The experience of Grace, whose cancer, which had already spread to her lungs, progressed further to her brain, affecting her hearing, may be a more common outcome after a treatment break in advanced cancer. And what the impact will be on either of their life expectancies remains unclear.

For now, we lack the evidence to throw a light on that side of things. What is clear, however, is that two women facing a terminal breast cancer diagnosis in their mid-twenties are immensely happy with the decisions they made to put their treatment on hold to pursue their dreams of becoming a mother, and grateful to the oncologists who supported them.



Janet Fricker

Low-dose aspirin reduces colorectal cancer recurrence in patients with PI3K alterations

Taking adjuvant low-dose aspirin daily for three years reduced recurrence of colorectal cancer by 55% in patients with somatic alterations in PI3K signalling compared to those taking placebo.

"The results of the ALASCCA study are clear and provide the final piece of the puzzle regarding the value of aspirin for patients with colorectal cancer, demonstrating that the effect is seen in patients with **PI3K** mutations. Together with the pre-existing evidence from large observational studies, retrospective genome analyses, and randomised studies involving high-risk patients with hereditary syndromes, as well as the negative **ASCOLT study**, published in **The Lancet** in January 2025 (which did not use a biomarker), I believe that the evidence is sufficient to change clinical guidelines," Anna Martling, the lead author, tells **Cancerworld**. "Notably, this is the first trial to show that somatic alterations in the PI3K signalling pathway, also beyond the **PIK3CA** mutation, predict aspirin response, expanding the targetable patient population substantially." The study, Martling adds, represents the first biomarker-driven randomised trial of adjuvant aspirin in colorectal cancer that has been completed.

Among patients with stage II–III colorectal cancer, 20 to 40% develop metastatic disease. Numerous observational and randomised controlled studies have suggested a protective effect of regular aspirin use on CRC development. Furthermore, favourable outcomes have been associated with aspirin use following CRC diagnosis, suggesting that aspirin might offer a promising agent for adjuvant therapy.

One theory has been that aspirin suppresses cancer-cell growth and induces apoptosis through blockade of the PI3K signalling pathway. A study of patients with CRC taking aspirin, published in the ***New England Journal*** of Medicine in 2012, found that patients with mutated **PIK3CA** genes experienced superior survival to those with wild-type PIK3CA genes. "These findings, though promising, required validation through a prospective trial," says Martling, from the Karolinska Institute, Stockholm.

For the **A**djuvant **L**ow-**D**ose **A**Sa in **C**olorectal **C**Ancer (ALASCCA) trial (**NCT02647099**), patients with stage I–III rectal cancer or stage II–III colon cancer who exhibited somatic alterations in the PI3K signalling pathway were randomised to receive either 160mg aspirin daily or placebo, with

treatment initiated within three months of surgery and continued for three years. For the investigator-initiated study, a total of 3,508 patients from 33 hospitals in the Nordic region were screened for somatic alterations in the PI3K pathway. Of 2,980 patients with a conclusive genomic analysis, 1,130 patients (37%) had an alteration in the PI3K pathway that made them eligible for the trial. Overall, 626 patients (419 with colon cancer and 207 with rectal cancer) were randomised.

These patients were then divided into two groups – group A (patients with a PIK3CA mutation in exon 9 and/or 20) and group B (patients with other **PI3K** mutations, including **PIK3CA** mutations outside exon 9/20 or mutations in **PIK3R1** or **PTEN** genes). Patients in groups A and B were randomly assigned to receive 160mg of daily aspirin or placebo for three years.

Addressing the rationale behind exploring groups A and B separately, Martling explained in an **interview with the Video Journal of Oncology**, "*It might be that, not only the* **PIK3CA** *mutation is of interest, but also the mutations outside that specific region but in the same signal kinase pathway. And that has never been explored before*."

Results at three years showed that patients in group A (those with a **PIK3CA** mutation in exon 9 and/or 20) who took aspirin had a rate of recurrence of 7.7% (95%CI 4.2%–12.5%) versus 14.1% (95%CI 9.2%–20.0%) for those taking placebo (HR=0.49, 95%CI 0.24–0.98; **P**=0.044).

Patients in group B (those with other PI3K mutations, including PIK3CA mutations outside exon 9/20 or mutations in **PIK3R1** or **PTEN** genes) who took aspirin had a rate of recurrence of 7.7% (95%CI 4.2%–12.6%) versus 16.8% (95% CI 11.4%–23.1%) for those taking placebo (HR=0.42, 95%CI 0.21-0.83; **P**=0.013).

For groups A and B combined, patients taking aspirin were 55% less likely to experience recurrence than those taking placebo.

Regarding disease free survival, in comparison to placebo, patients taking aspirin in group A had a 39% improvement (HR=0.61, 95%CI 0.34–1.08; **P**=0.091); while those taking aspirin in group B had a 49% improvement (HR=0.51, 95%CI 0.29–0.88; **P**=0.017).

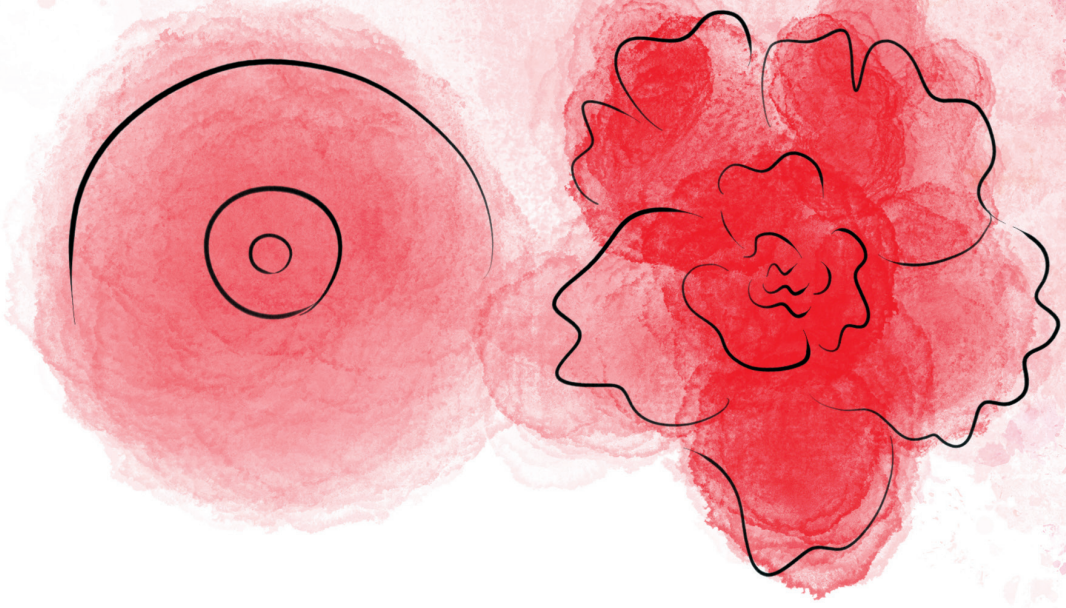
Three patients experienced aspirin-related severe adverse events (one gastrointestinal bleeding, one haematoma, and one allergic reaction).

"*What is interesting is that, in the exploratory arm with mutations in the same signal pathway but outside the* **PIK3CA** *mutation, we saw a stronger effect. A 58% reduction in recurrence, meaning that we can expand the population for this treatment*," says Martling.

Although the trial was not powered for subgroup analyses, the advantage of aspirin compared to placebo could be observed in all subgroups. "*So, no matter which mutation you had, whether you had a colon or rectal cancer, or if it was stage II or III disease, or if you had neoadjuvant or adjuvant treatment, they all had an effect*," said Martling. Notably, she added, there was a stronger effect in females than males which will require further scientific evaluation.

"*A potential explanation, also observed in trials from the cardiovascular field, is that men might require a higher dose than women. We will investigate this intriguing finding in future studies*," says Martling.

Janet Fricker



It's no longer taboo to suggest that some metastatic breast cancers may be curable

It's long been clear that, in most patients with metastatic HER-positive breast cancer, adding effective HER2 blockade to cytotoxics can result in very prolonged responses. Janet Fricker reports on the prospective trials building evidence on whether – and in whom – these responses could amount to a cure.

When Yvonne Fantaci was diagnosed with metastatic HER 2-positive breast cancer in April 2017 she felt blindsided. "To be told I had metastatic breast cancer without ever being diagnosed with a primary breast tumour was shocking," remembers Fantaci, a 67-year-old director of a data company and mother of three adult children, from Danvers, Massachusetts. Images from her first CT scan revealed metastases at 11 different sites throughout her body, including lungs, liver, kidneys and lymph nodes.

To prolong her life, Fantaci received standard first-line treatment for metastatic HER2-positive breast cancer, consisting of a weekly infusion of paclitaxel chemotherapy combined with targeted anti-HER2 therapy in the form of two monoclonal antibodies – trastuzumab and pertuzumab – given by infusion every three weeks. "The infusions became part of my life. After a while the paclitaxel stopped, but I was told that I'd need trastuzumab and pertuzumab for the rest of my life," she says.

But every time Fantaci attended for a CT scan, her medical team would comment on her remarkable progress. "The tumours just kept shrinking.

Eventually, the CT report indicated that they'd shrunk to 3% of their original volume and they stayed at that level for many months.

However, I was told that CT scans just aren't that definitive. Scans may also show dead cancer cells."

This exceptional response has led Fantaci into uncharted territories – a new frontier in HER2-positive metastatic breast cancer that has been made possible by extraordinary recent developments in HER2-targeted agents. As a consequence, she was given the option to join the STOP-HER2 trial, where she volunteered to cease all anti-cancer treatment, under close monitoring.

A milestone in efforts to cure advanced cancers

Twenty-five years ago, receiving a diagnosis of HER2-positive metastatic breast cancer was tantamount to a death sentence. Accounting for around 20% of all cases of breast cancer, the HER2-positive subtype was considered a particularly aggressive form of the disease. "Studies showed patients with HER2-positive breast cancer tended to suffer recurrence more often and earlier than other forms of breast cancer. Metastases also happened in areas of the body that were higher risk, such as the brain," says Paolo Tarantino, a breast oncologist and clinical fellow at Dana-Farber Cancer Institute, Harvard Medical School, in Boston.

The advent of therapies such as trastuzumab and pertuzumab that specifically target the HER2 protein started to transform the outlook of the disease. Around 2005, John Crown, a medical oncologist at St Vincent's Hospital, Dublin, started noticing that a small proportion of patients with metastatic HER2-positive breast cancer were achieving extraordinary results.

"We had a few patients with large burdens of liver and lung metastases whose tumours were just shrivelling up," recalls Crown.

Such anecdotal observations prompted Crown, together with Giuseppe Gullo (then a colleague at St Vincent's), to undertake a retrospective study of all patients treated for histologically proven HER2-positive metastatic breast cancer between May 2000 and March 2007, at either the St Vincent's Hospital or the Humanitas Cancer Centre in Rozzano, Italy. Results, published in **Annals of Oncology** in 2012, revealed that 13 of 84 patients (15%) achieved complete response, and eight (9%) achieved durable complete response (≥5 years' continuous remission).

Such figures were in stark contrast to historical data showing that, with chemotherapy alone, only around 1% of patients with HER2-positive metastatic breast achieved complete response. **"We stuck our necks out and said we believed that HER2-positive MBC [metastatic breast cancer] should no longer be considered an incurable disease, but an occasionally curable disease,"** says Crown.

Arguably, the seismic shift in perceptions of HER2-positive metastatic breast cancer came with publication of the final results of the CLEOPATRA study, which brought the advances in treating this subtype to the attention of the wider oncology community. Published in **Lancet Oncology** in 2020, the data revealed that, after eight years of treatment, 16% of women receiving pertuzumab, trastuzumab, and docetaxel had undergone no progression of disease.

In 2023, even greater numbers of long-term responses in HER2-positive metastatic breast cancer were reported, with publication in **The Lancet** of the results of the DESTINY-Breast03 trial, which delivered the trastuzumab via the antibody drug conjugate (ADC) trastuzumab deruxtecan (T-DXd). "My perception is we've increased long-term responders with HER2-positive MBC from 16% in CLEOPATRA to around a quarter of patients taking T-DXd," says Tarantino. Numbers of patients achieving exceptional results, he adds, are likely to improve further, with more than 200 ADCs currently in development. "ADCs are modular, a bit like Lego, where changing the antibody, linker, or chemotherapy can improve results," he says. The development of ADCs with innovative payloads, or bispecific and trispecific ADCs that simultaneously bind multiple targets, he adds, are likely to lead to even greater improvements.

"All the books about metastatic HER2-positive breast cancer start by stating it's an incurable disease. But that's changing. We're beginning to realise that some patients experience long-disease

control that doesn't affect their life expectancy, and in a few cases, they may even be cured," says Joseph Gligorov, Professor of Medical Oncology at Sorbonne University, Paris.

The ability to block HER2 expression, agrees Crown, "has completely subverted the biology of HER2 positive metastatic breast cancer and transformed the worst type of metastatic breast cancer to have into the best type."

One question is why this **volte-face** should have occurred in metastatic HER2-positive breast cancer, rather than other subtypes? Another is why exceptional responses do not occur nearly so often in metastatic cancers that have originated from other organs? The answer, says Gligorov, can be found in the similarities between HER2-positive breast cancer and chronic myeloid leukaemia (CML) – another cancer where targeted treatments lead to durable complete pathological responses in a subset of patients (see **How today's CML patients can aspire to a drug-free life**). Both are much simpler than other cancers and have one predominant driver – the mutated **HER2** gene in the case of **HER2**-positive breast cancer and the **BCR-ABL** fusion gene in the case of CML.

"The tricky thing about other types of breast cancer and solid tumours is that they often have more than one clone, with each containing different drivers," explains Gligorov, "which means that once you stop treatment other clones can take hold and dominate."

Could this mean I'm cured?

The groundbreaking responses observed in some cases of metastatic HER2-positive breast cancer are now opening the possibility for some patients to consider taking treatment holidays and even stop treatment altogether. Treatment holidays are an important option for patients, says Gligorov, because it allows them to take a break from troublesome side effects, or break free for a while from the regular visits to hospital to do things like going on holiday.

Requests from patients who have achieved a complete response to stop treatment altogether are less frequent, because of the uncertainty involved, as Fatima Cardoso, President of the Advanced Breast Cancer (ABC) Global Alliance, explains. "For patients, stopping treatment is a very personal decision about how averse they are to risk. Even though they may be in complete remission, we've no way of knowing whether stopping treatment will lead to their cancer returning and progression of disease. Some patients get extremely stressed if we talk about stopping, whereas others view it as a good outcome," she says.

> **"Some patients get extremely stressed if we talk about stopping, whereas others view it as a good outcome"**

Fantaci falls firmly into the latter group. She has embraced the idea of stopping treatment and not feeling tethered to the hospital by having to come in every three weeks for infusions. The freedom means that she has been able to start travelling again and spending more time with her children and grandchildren, without being laid low by side effects such as gastrointestinal upsets and fatigue.

"Stopping has allowed me to mentally move on from my cancer," she says.

Gligorov stresses that the personal advantages from stopping treatment may be quite limited for patients who are not troubled by safety issues or side effects, because patients do still need to regularly attend hospital for scans to monitor for signs of recurrence.

"It's not only the time involved in coming back to the hospital for scans, but also the anxiety created while they wait for results to see if their disease has returned," says Gligorov. He recognises, however, that there may be financial benefits from coming off treatment, for instance in the US, where even patients with insurance may have co-payments.

Oncologists themselves feel varying levels of confidence when it comes to stopping or pausing treatments in exceptional responders. Cardoso says she has noticed that veteran oncologists can feel more at ease offering this as an option.

"All they have to go on is their clinical sense of what's going to happen. We find the more experienced the oncologist the more at ease they are with stopping treatment or undertaking treatment holidays. They know the disease and have developed a clinical sense of what's going to happen."

Building the evidence

The problem facing oncologists contemplating stopping treatment, says Cardoso, is that the field is currently a 'data-free zone'. "I have to tell patients that I can't be 100% certain their disease won't return, and many aren't comfortable with taking this risk."

Obtaining data has been challenging, she adds, because pharmaceutical companies generally don't follow patients long term to identify those who are exceptional responders. "While this is an interesting question for the academic community, it's not of much interest to companies. It also costs a lot of money to keep trials open," says Cardoso.

Real-world data provided by registries has not proved to be a solution. "We don't even know how many metastatic breast cancer patients exist because national cancer registries don't record relapse, they only record diagnosis and death," says Cardoso.

Currently, a few case series are all there is to go on, such as one compiled by Izzet Dogan from Bakırköy Hospital, Istanbul. In the cohort study published in **Nature Scientific Reports** in 2023, Dogan reviewed outcomes of 15 patients with metastatic HER2-positive breast cancer who had stopped therapy for a variety of reasons – some due to side effects, such as heart failure, and others because they had become weary of treatment. At a median follow-up of 32 months, recurrence was detected in two of them (13.3%).

Addressing the issue, the 6th and 7th International Guidelines for the Management of Advanced Breast Cancer, published in **The Breast** in 2024, recommend that, "Stopping treatment in patients in long term complete remissions has not been adequately studied but should be considered on a case-by-case basis after extensive discussion with the patient."

To gather prospective evidence to guide patients and explore whether the strategy to stop treatment can be applied to exceptional responders more widely, Heather Parsons, an oncologist at Dana-Farber Cancer Institute, initiated the **STOP-HER2 study**, which started in April 2023. Inclusion was based on the US National Cancer Institute definition of 'exceptional responder' as someone who has survived without progression on first-line therapy for at least three years (representing three times the median duration).

The investigators rejected the classic randomisation approach, instead giving patients who met the inclusion criteria a choice about whether they want to stop treatment, and then allocating them accordingly. "We didn't feel it was acceptable to randomise patients. Patients and providers have strong feelings about whether they're willing to stop treatment," says Parsons.

Fantaci had no reservations in opting for the stopping arm. "I wanted something positive to come out of my misfortune that would benefit future generations," she explains.

> **"The real fear is about outcomes if the disease suddenly explodes. We need to know that it can be quickly controlled by restarting treatment"**

One key question addressed in the phase 2 study is about what happens if patients suffer a recurrence? "The real fear is about outcomes if the disease suddenly explodes. We need to know that it can be quickly controlled by restarting treatment and that patients can regain their previous response," says Parsons. This fundamental question, she adds, was asked in the CML stopping trials, where the finding that patients can generally regain their previous deep molecular response has been critical to the widespread acceptance of this approach.

Another aspect of STOP-HER2 is the collection of blood that will be used to measure circulating tumour DNA (ctDNA) and assess whether its presence is associated with the risk of future progression. New generation, ultrasensitive ctDNA assays – which are designed specifically for each patient and track known mutations in an individual's cancer – can now detect very small amounts of ctDNA in blood, and offer the opportunity to identify progression earlier than relying on imaging or symptoms.

While the objective is not to guide trial decisions around restarting treatment (this is being done by CT scans performed every 12 weeks), the investigators hope to collect evidence needed to determine how best to monitor patients in the future. The blood test, they hope, will help put monitoring of breast

cancer patients, who until now relied on RECIST 1.1 criteria (using CT or MRI imaging) on a level with CML, which uses reverse transcriptase-polymerase chain reaction technology to measure blood levels of **BRC-ABL**. "Ultimately, the presence of ctDNA and its dynamics may be able to give us guidance about first whether it's time to stop treatment and then, after stopping treatment, whether the cancer has returned and patients would benefit from restarting," explains Parsons. The phase 2 STOP-HER2 study, which is being run in nine sites across the US, aims to recruit 52 patients in the stopping arm and 30 in the continuation arm.

Predicting which patients may be curable

Crown emphasises that, while some patients with metastatic HER2-positive breast cancer can be cured, they remain the exception. "The overwhelming majority of patients with HER2-positive MBC still die from their disease," says Crown. "So going forward we need to work out how to identify patients who won't achieve long survival with current treatments, and find alternative approaches."

To uncover differences, Naomi Walsh, from Dublin City University, has performed whole genome sequencing on 12 exceptional responders and 11 non-responders, taken from Crown's database at St Vincent's Hospital. Exceptional responders, she discovered, have more repetitive sequences of DNA in their centromeres (the chromosomal structure holding the two chromatids together). "We hope to drill down on the exact regions with centromere amplification. If we can understand the biology of exceptional response and short-term/ conventional response, it might enable us to design new agents," says Walsh. If cancer cell lines with different types of centromeres can be identified, it should be possible to design more personalised treatments for patients.

> **"If we can understand the biology of exceptional response and short-term / conventional response, it might enable us to design new agents"**

Taking a different approach, Stefania Morganti – medical oncologist and research fellow at Dana-Farber – has studied the molecular fingerprint of metastatic HER2-positive tumours by analysing sequencing data generated from OncoPanel testing (a targeted next-generation sequencing assay). Tumours of conventional responders, she discovered, are more likely than exceptional responders to have **PIK3CA** and **MYC** gene alterations. "Such information may allow us to explore whether agents targeting these adverse genes might increase numbers of patients with exceptional responses," says Morganti.

In an effort to help patients in the immediate term, Parsons and her team (including Morganti) have initiated the **SAPPHO** trial, to explore whether currently available medications can be used in a different way in newly diagnosed patients to increase the numbers achieving an exceptional response. The trial, which opened in August 2024, is testing a regimen of medicines taken back-to-back, each of a specific duration, with no delays in between. The approach, explains Parsons, contrasts with conventional regimens, where the second treatment is not initiated until the patient's cancer starts to grow again.

In this single-arm phase II study, treatment begins with standard chemotherapy plus trastuzumab and pertuzumab for 12 weeks. This is immediately followed by the antibody-drug conjugate T-Dxd for 18 weeks; and then tucatinib (a small-molecule inhibitor that crosses the blood–brain barrier), paired with a second antibody-drug conjugate, trastuzumab emtansine (T-DM1), for 12 weeks. Then for one year, patients receive maintenance therapy with trastuzumab and pertuzumab in combination with tucatinib, before stopping treatment altogether. "These medicines hit the same target, but not in the same way, which we think can address heterogeneity and stop the possibility of the cancer escaping control," says Parsons.

The primary endpoint is to see how many patients remain progression-free four years after the start of the study. As a comparator, the investigators plan to use data from the CLEOPATRA trial (16% progression free survival at eight years). "Taking into consideration the additional therapies used in SAPPHO, for the trial to be positive we would need 24% of patients to be progression free," explains Parsons.

The keenly anticipated results from STOP-HER2 and SAPPHO will demonstrate whether there will be a

new treatment paradigm in metastatic HER2-positive breast cancer, where some patients will move from palliative to curative therapy and ultimately stop treatment.

Going forward, the big question is whether this treatment landscape can be replicated in other subtypes of breast cancer and/or in metastatic tumours originating from other organs? If so, this would change the whole rule book, requiring a fundamental revision in our perception of metastatic cancer, from it being a terminal illness with a limited life expectancy to a chronic condition with the potential for a cure. This raises the prospect that one day a much wider group of patients with metastatic cancers may be able to completely stop treatment and have the shadow of cancer lifted from their lives.

Milestones along the road

The road that is leading towards the possibility of a cure or very prolonged treatment-free remission in some patients with metastatic HER2-positive breast cancer began with the development of trastuzumab, the first monoclonal antibody to be approved for treating a solid cancer. Before trastuzumab, patients could expect to live on average two to three years following such a diagnosis.

The human epidermal growth factor receptor 2 (HER2) gene was identified in rat cells by Robert Weinberg from MIT (Cambridge, Massachusetts), who published the finding in Nature in 1984.

Dennis Slamon, from UCLA in Los Angeles, established the link to breast cancer in a paper in Science in 1987. Slamon showed that the HER2 protein was amplified in circa 30% of breast cancers and that amplification correlated with poor prognosis.

Slamon proposed that antibodies might be developed to block HER2 proteins. His heroic struggles to develop the antibody trastuzumab (Herceptin) are depicted in the 2008 film Living Proof.

In a study published in the New England Journal of Medicine in 2001, Slamon showed that adding trastuzumab to chemotherapy led to longer overall survival (OS) – (median OS 25.1 vs 20.3 months; P=0.01). Herceptin, produced in collaboration with Genentech, was approved in combination with paclitaxel in the USA in 1998 and Europe in 2000.

In 2012, approval of pertuzumab, a second monoclonal antibody directed at HER2, with a different but complementary action to trastuzumab, improved outcomes further. Results of the CLEOPATRA study, published in the New England Journal of Medicine in 2012, showed that median progression free survival (PFS) was 18.5 months in patients treated with pertuzumab, trastuzumab, and docetaxel versus 12.4 months in patients treated with placebo, trastuzumab, and docetaxel.

Results at eight years, published in the Journal of Clinical Oncology in 2019, were seen as dramatic. They showed that 37% of patients in the experimental arm were still alive compared with 23% in the control arm (median OS 57.1 v 40.8 months). Even more remarkable was the finding that 16% of patients on the experimental arm had no progression and were classed as 'exceptional responders'. In some cases, the tumours completely disappeared, prompting serious discussion around the possibility of extremely prolonged responses or even cure.

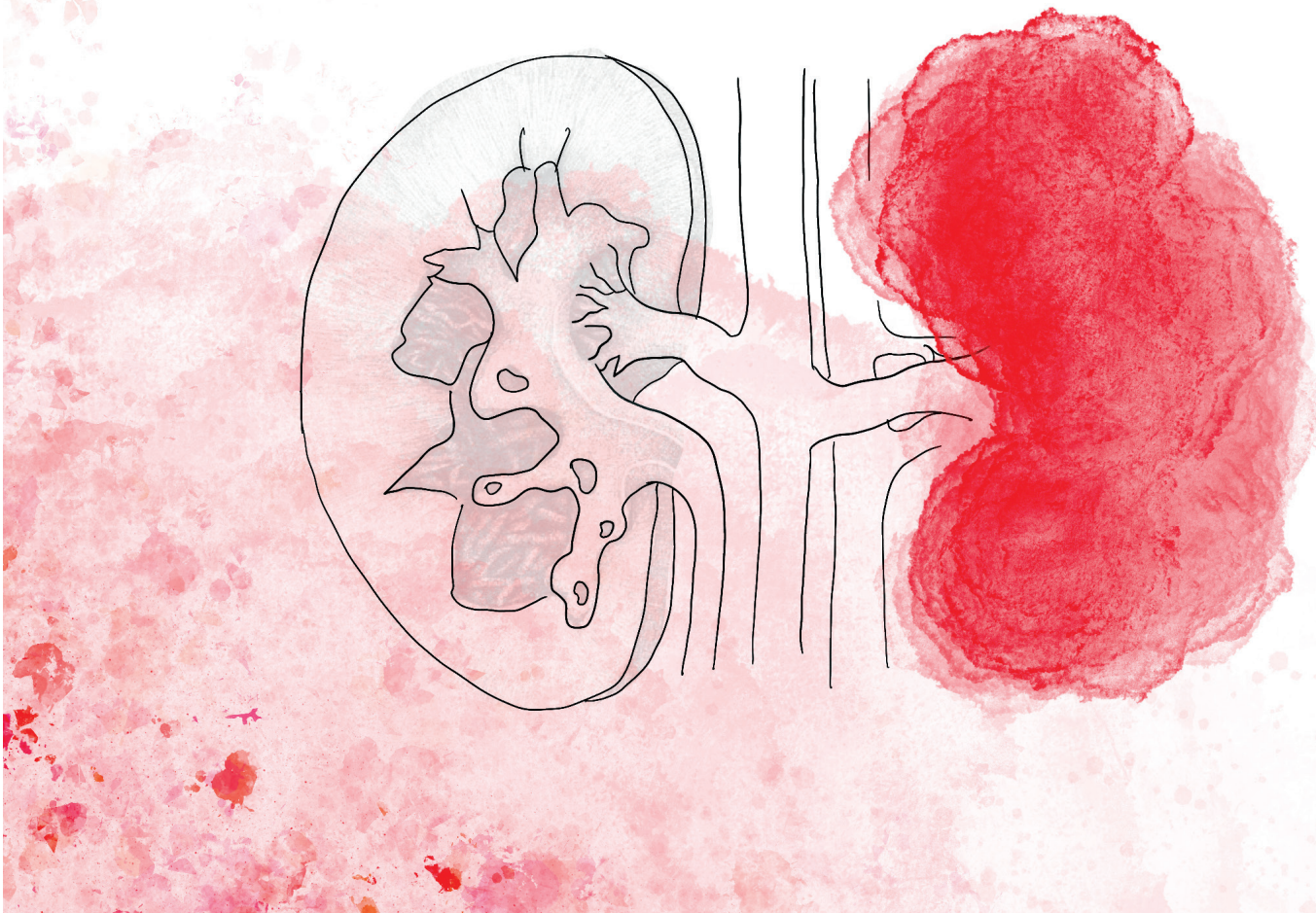
Development of antibody-drug conjugates (ADCs), which combine monoclonal antibodies with cytotoxic payloads, has led to even greater numbers achieving exceptional responses. The initial ADC trastuzumab emtansine (T-DM1) was supplanted by the second-generation ADC trastuzumab deruxtecan (T-DXd), with advances including attachment of more chemotherapy molecules and more easily cleavable linker technology.

Updated results of the DESTINY-Breast03 trial, published in Nature Medicine in 2024, showed median PFS was increased fourfold with T-DXd compared to T-DM1, from 7.2 to 29 months. Median OS increased from 42.7 to 52.6 months.

"The remarkable overall survival benefits seen with many of the anti-HER2 agents developed in the last decades have led to more than doubling of the median survival of patients living with this subtype of metastatic breast cancer and helped change the mentality regarding a possible cure in the near future, at least for some exceptional responders," says Fatima Cardoso, President of the Advanced Breast Cancer (ABC) Global Alliance.

Janet Fricker

Personalised neoantigen vaccine for kidney cancer shows promise in phase 1 study



Personalised neoantigen cancer vaccines (both with and without ipilimumab) elicited anticancer immune responses in nine patients with fully resected clear cell renal cell carcinoma. The investigator-initiated phase 1 trial, published in Nature, February 5 2025, observed no recurrences at a median follow-up of 40.2 months following surgery.

"In this study we were really encouraged to be able to successfully manufacture the vaccine, administer it, and generate immune responses in all nine patients," David Braun, the lead author, tells **Cancerworld**.

For tumours with low mutational burden, such as renal cell carcinoma (RCC), he adds, having an immunologically effective vaccine poses an incredible challenge.

> **"The strong durable activation of T cells indicates that we are able to generate a long-lasting anti-cancer immune response with the vaccine, which can form the foundation for the development of future neoantigen vaccines in RCC."**

Clear cell RCC accounts for 80% of all kidney cancer subtypes. Standard treatment for patients with stage III or 'oligometastatic' stage IV disease is surgery to remove the tumour, followed by adjuvant immunotherapy with the checkpoint inhibitor pembrolizumab.

The KEYNOTE-564 study, published in the **New England Journal of Medicine** last year, showed addition of adjuvant pembrolizumab following surgery was associated with a 38% reduction in risk of death compared with placebo. However, two-thirds of patients will still experience recurrence, leaving limited treatment options.

Neoantigen vaccines, says Braun, offer the potential to transform the efficacy of immune therapy in patients with RCC. *"In immune therapy we often use the analogy of the immune system being like a car, where drugs work by taking the breaks off. But what they can't do is tell the immune system where to go,"* explains Braun, a kidney cancer specialist formerly at Dana-Farber and Harvard Medical School, and now a physician-scientist at Yale Cancer Center.

The consequence of this lack of directionality, he adds, is that immune therapy fails to work for many cancer patients. "*So, the question we asked was whether we could add in a therapeutic vaccine to steer the immune system against the tumour*."

Already in high-risk resected melanoma, a cancer type with a high tumour mutational burden (and consequently large numbers of potential neoantigen vaccine targets), a study in **The Lancet** last year showed the addition of personalised cancer vaccines to pembrolizumab reduced tumour recurrence or death by 44%. However, there have been reservations over whether the approach would work in tumours with low mutational burdens, such as kidney cancer.

"*When you have hundreds of thousands of neoantigens to choose from, as with melanoma, that's a very different story from kidney cancer where there are only about 40 to 100 high-quality coding mutations per tumour*," says Braun.

The current study, led by Braun together with collaborator Toni Choueiri, Director of the Lank Center for Genitourinary Cancer at Dana-Farber and Catherine Wu, Chief of the Division of Stem Cell Transplantation and Cellular Therapies at Dana-Farber, addressed the question of whether a personalised cancer vaccine targeting neoantigens could decrease the likelihood of recurrence in patients with high-risk stage III and IV kidney cancer.

For each individual patient, the first task was to identify the neoantigens that distinguished tumour cells from normal cells in other parts of the body. Neoantigens can be defined as the proteins forming on the surface of cancer cells when certain mutations occur in tumour DNA.

"*Not all mutations result in neoantigens and neoantigens are almost certainly different from person to person, even among patients with similar tumours, leading to the need to identify personalised targets for each patient*," explains Braun.

To develop the vaccine, the team collected tumour material from stage III and IV kidney cancer patients who had undergone surgery. Then, both tumour and blood samples underwent DNA sequencing, and the tumour underwent RNA sequencing, allowing investigators to identify tumour specific mutations

not present on cells in other parts of the body. The next step was to identify the mutations resulting in the formation of neoantigens. Once they had identified the neoantigens they went on to use algorithms to predict whether each neoantigen represented a good immune target.

"*So, there's a sort of funnel to identify the mutations, then the ones likely present at the protein level, and finally a very small number offering good immune targets*," explains Braun.

For each patient, after selecting up to 20 neoantigens, vaccines were synthesised as synthetic long peptides.

The neoantigens were grouped into four separate 'pools' of up to five different neoantigens injected into four different sites of the body – the right arm, left arm, right leg and left leg. Additionally, vaccines were administered both subcutaneously and intradermally.

"*We decided to give the vaccine intradermally to take advantage of the huge reservoir of antigen-presenting cells present in the upper layers of skin, dermis and epidermis*," explains Braun.

Four patients received only the vaccine and five also received small doses of ipilimumab, administered subcutaneously adjacent to vaccination sites.

Results showed the team designed a median of 15 neoantigen-containing peptides per patient. Through a series of analyses, the team found that the vaccines induced an immune response (predominantly CD4+ with some CD8+) during vaccination; that the number of vaccine-induced T cells increased by a mean of 166-fold; and that T cells remained in the body at high levels for up to three years. No major differences were seen between patients who received ipilimumab and those who did not.

Seven out of nine patients were successfully vaccinated with a peptide that contained a neoantigen derived from a cancer driver mutation, including common RCC gene mutations in **VHL, PBRM1, BAP1, KDM5C** and **PIK3CA**.

"*This is important, because driver genes are typically critical for the function of cancer cells, and so it is much more difficult for cancer cells to evade the immune system after 'losing' these targets*," says Braun. In future, he adds, they will 'weight' the algorithm towards these mutations.

In vitro studies also showed vaccine-induced T cells were active against samples of the patients' own tumour cells that had been harvested during surgery.

"Since none of the patients experienced a cancer recurrence, it was important to demonstrate that vaccines were capable of having a direct effect on the tumours," says Braun.

The most common adverse events were low-grade injection site reactions (in 100% of patients) and transient flu-like symptoms in eight out of nine patients. No patient experienced grade 3 or higher dose-limiting toxicity.

This lack of toxicity contrasts to the **New England Journal of Medicine** study last year, which found that 18.6% of kidney patients given adjuvant pembrolizumab encountered grade 3 or higher toxicity, and 21.1% discontinued treatment due to side effects.

"*Our study revealed several notable observations. First, despite RCC being a tumour with low mutational burden, we successfully manufactured a multi-epitope vaccine for every patient enrolled in the trial. Second, most of the patients received a vaccine against neoantigens* derived *from mutations in major RCC driver genes, and these were highly immunogenic*," conclude the authors.

The current study has provided the rationale for a phase 2 study (**NCT06307431**) to compare the combination of V940 (a messenger RNA vaccine) plus pembrolizumab to placebo plus pembrolizumab as an adjuvant treatment in 270 patients with RCC.

The trial, which is run by Merck and Moderna, with both Braun and Choueiri on the scientific advisory committee, and started enrollment last year, will include a bespoke vaccine with up to 34 different neoantigens.

A Vision for Cancer Policy in Europe

An Interview With MEP Nikos Papandreou

CancerWorld had the opportunity to interview **Nikos Papandreou**, Member of the European Parliament and a dedicated advocate for cancer policy reform. With a background in politics, economics, and healthcare policy, Mr. Papandreou has been at the forefront of tackling Europe's cancer challenges. As a member of the **SANT Committee**, he is working to drive meaningful changes in cancer prevention, access, and treatment across the EU.

We are pleased to share his insights on how Europe can better address the cancer burden and ensure equitable care for all as well as the personal and professional motives shaping his decisions in the field.

You have had a diverse career spanning politics, economics, and public policy. For those who may not be familiar with your background, can you tell us a bit about yourself and how your journey led you to focus on cancer-related issues?

My career has been driven by a deep commitment to finding practical solutions to societal challenges, particularly in healthcare and economic policy. With experience spanning international institutions like

the World Bank and advisory roles in Greek socialist governments, I have seen first-hand how policy decisions impact people's lives.

My involvement in healthcare policy, including cancer-related issues, stems from witnessing Greece build a national health system from the ground up. I believe that beyond laws and regulations, systems need the right incentives and flexibility to function effectively—whether for frontline healthcare workers or hospital administrators.

Additionally, my background as a writer has shaped my ability to empathize with different perspectives. Understanding the struggles of individuals—whether due to income disparities or health challenges—has reinforced my dedication to reducing inequities. Cancer policy, in particular, demands this kind of sensitivity and pragmatism, as improving prevention, access, and care requires both systemic reform and human-centred solutions.

As an MEP and a member of the newly formed SANT Committee, what motivated you to take a strong stance on cancer-related issues?

Cancer is one of the most pressing health challenges of our time and is projected to become the leading cause of death in Europe by 2030. It affects us all—not only as patients but also as family members, caregivers, colleagues, and members of our communities. The impact extends beyond health, influencing the way people work, return to work, and participate in society. Addressing cancer is, therefore, not just a healthcare issue but also a social and economic imperative.

As a member of the newly formed SANT Committee, I see a crucial opportunity to ensure that cancer remains a top political priority. The committee plays a vital role in shaping EU policies on public health, food safety, and disease prevention. By focusing on cancer, we can drive forward meaningful policies that improve prevention, early detection, and access to care. My motivation is also personal-I have first-hand experience with the realities of cancer. This drives my commitment to advocating for solutions that make a tangible difference in people's lives.

How do you see the European Parliament's role in shaping policies that directly impact cancer patients, research, and access to care?

Extremely important because the parliament can take a global view and provide all three of the topics with the proper financial and other instruments to

tackle the problem head-on.

The Role of the SANT Committee & Legislative Priorities

What are the key objectives of the SANT Committee in addressing the challenges faced by cancer patients?

The Special Committee on Public Health has a strong mandate to improve public health policies across Europe, with cancer being a central focus. The committee builds on the work of the previous BECA (Special Committee on Beating Cancer) and aims to ensure the effective implementation of Europe's Beating Cancer Plan. Key objectives include continued focus on prevention and early detection, particularly by reducing risk factors such as tobacco and alcohol consumption, air pollution, and unhealthy diets. One of the key actions we are taking early on is to open dialogue with the European Commission on accessing the progress of the EBCP since its launch 4 years ago.

Based on this, the committee will also work on its own initiative report to make sure that gaps are not only identified but that there are concrete steps taken to support Member States in addressing disparities in access to high-quality cancer treatment across Member States, ensuring patients benefit from the latest innovations in medicine, including personalised treatments and advanced therapies. And, of course, we should not forget that improving the quality of life for cancer patients and survivors is key. We need to be addressing challenges such as returning to work, access to psychosocial care, and tackling discrimination.

From your perspective, what are the most urgent gaps in European cancer policies that need immediate attention?

While the EU has made significant progress through Europe's Beating Cancer Plan, several urgent gaps remain, such as inequalities in cancer care, workforce shortages, and limited access to innovative treatments. Access to prevention, early detection, and treatment varies widely across and within Member States. Here, we need to be honest and see the reality - divides between north and south, east and west still affect patients. And not to forget that medical desserts are a real issue across the Member States; let's take, for example, Italy; according to the latest data from 2021, nearly 50% of all **breast cancer care** units are in Northern Italy, 28.8% in the centre and 25.6% in the South.

This example serves to show two concrete issues - data about cancer care remains scarce and often outdated, and this divide is just looking into one area of cancer - breast; many more exist when looking into the care provided for different cancers.

Additionally, the regions with limited access to care facilities also experience higher levels of workforce shortages in oncology. Investment in training and retaining healthcare workers is urgently needed. Finally, while Europe is a leader in cancer research, patients often face delays in accessing the latest therapies due to regulatory barriers, pricing issues, and reimbursement challenges. Up to **526 days** is the time patients in the EU must wait to access an oncology treatment after the European Medicines Agency (EMA) grants an authorisation.

How does the European Parliament, under your guidance, work with research organizations, pharmaceutical companies, and advocacy groups to ensure effective policymaking?

Effective cancer policy requires a multi-stakeholder approach. The Parliament ensures that cancer-related policies are informed by scientific evidence and patient needs by consulting experts from the European Medicines Agency (EMA), research institutions, and patient organisations through organising hearings, mandating studies, and listening, a key responsibility to all members. The European Parliament has a key role in helping secure funding for cancer research through Horizon Europe and other EU programs, ensuring continuous investment in cutting-edge treatments and technologies. By working closely with the European Commission and Member States, Parliament helps track progress on Europe's Beating Cancer Plan, identifying areas where further action is needed.

Launch of the White Paper on ESR1 Mutations & Liquid Biopsy in Metastatic Breast Cancer

A few weeks ago, you hosted the launch of the CPE White Paper on ESR1 Mutations and Liquid

Biopsy in metastatic breast cancer. Why was this a crucial milestone?

The recent launch of the Cancer Patients Europe (CPE) White Paper on ESR1 Mutations and Liquid Biopsy in metastatic breast cancer represents a pivotal advancement in personalised cancer care. Metastatic breast cancer refers to an advanced stage of cancer where the disease spreads to another part of the body. In order to ensure that breast cancer patients receive the right treatment at the right time, we need to shed light on those advancements.

This initiative emphasises the critical role of liquid biopsies in detecting ESR1 mutations, which are key drivers of treatment resistance in metastatic breast cancer. By increasing awareness and accessibility of liquid biopsy testing, the project aims to empower patients and healthcare providers with the knowledge needed to make informed treatment decisions, ultimately improving patient outcomes.

What concrete actions should be taken at the European level to accelerate the integration of liquid biopsy into routine cancer care?

Several concrete actions are essential to expedite the integration of liquid biopsies into routine cancer care at the European level. Here are a couple - standardisation of testing protocols will ensure consistency and reliability in diagnostics. We need concrete investment in infrastructure by allocating resources to equip medical facilities with the necessary technology and training for liquid biopsy implementation, which is crucial for widespread adoption. Finally, incorporating liquid biopsy testing into national cancer care guidelines and reimbursement policies will enhance accessibility for all patients.

Many groundbreaking technologies face hurdles in clinical adoption. What legislative or regulatory frameworks can facilitate the rapid implementation of advanced diagnostics like liquid biopsy?

Supportive legislative and regulatory frameworks are necessary to facilitate the rapid implementation of advanced diagnostics like liquid biopsies. What we can champion at the European level is the aligning of regulatory standards across European countries, which can streamline the approval and integration of new diagnostic technologies. But that will only be possible through good collaboration with stakeholders - policymakers, research organisations, pharmaceutical companies, and patient advocacy groups.

Cancer Patients at the Heart of Policy Decisions

You have expressed deep concerns about the well-being of cancer patients. Is there a particular experience or patient story that has shaped your advocacy?

Unfortunately, both my experience and those of many other cancer patients around me show that even in the cases that you get the proper diagnosis, that does not automatically mean you will receive the proper treatment! For some reason, doctors do not always apply the protocols in Greece. Secondly, cancer patients need a special support system because it almost always falls on the family, and that may not be the most appropriate method.

Families can all get depressed together, which does not make for rapid recovery, as one example. Finally, for the young whose illness takes them out of their world and they come back a year later, there needs to

be support for adjustment. To take a few examples.

Europe still faces disparities in access to early detection, innovative treatments, and clinical trials. What steps should be taken to ensure equal access to high-quality cancer care across EU countries?

Addressing disparities in cancer care across Europe requires a multifaceted approach. As already mentioned, we need to implement uniform cancer screening guidelines to ensure early detection is accessible to all citizens, regardless of their location. We need to address the issue of medical desserts by enhancing healthcare facilities and technologies in under-resourced regions to provide timely and effective treatments. And of course, we cannot forget that we still need to target risk factors such as tobacco and alcohol use through educational programs and public health initiatives to reduce cancer incidence.

European Cancer Plan & Beyond

The Europe's Beating Cancer Plan is a major initiative. What tangible progress has been made so far, and where do you see room for improvement?

Europe's Beating Cancer Plan (EBCP) has made significant strides, such as launching the European Cancer Imaging Initiative, which establishes infrastructure for cancer images to enhance diagnostics and treatment through AI integration. Personally, I also congratulate all Member States for launching their national cancer plans and starting to collect data on cancer incidence, treatment and outcomes.

However, despite efforts, as already mentioned, disparities in cancer survival rates can still exceed 30% between certain countries. We need to continue improving public understanding of cancer prevention and treatment options to encourage proactive health management.

How do AI, big data, and digital health tools fit into the future of cancer care in Europe?

AI, big data, and digital health tools are pivotal in transforming cancer care, especially when looking into advancing personalised Treatment Plans. AI can analyse vast datasets to tailor treatments to individual patient profiles, enhancing efficacy and reducing side effects. I recently read about a new pilot project in Sweden, which was launched in April 2024 and focuses on the potential for AI to estimate breast cancer risk. 70,000 women between 40 and 74 years old will undergo breast cancer screening, with 35,000 women checked every two years. Another 35,000 women will receive the same screening with the addition of risk assessments using the developed AI model. This program aims to find structural patterns in images of women's mammography and detect cancer at an early stage. This pilot study could show the capacity of machine learning algorithms to identify subtle patterns in medical images, leading to earlier and more accurate diagnoses.

Final Thoughts

What is your key message to healthcare professionals, decision-makers, and patients in the fight against cancer?

Collaboration is essential. Healthcare professionals should embrace innovative practices and continuous learning. Decision-makers must prioritise equitable access to care and support research initiatives. Patients are encouraged to engage actively in their health journeys, advocating for their needs and participating in preventive measures. Together, we can create a future where high-quality cancer care is accessible to all.

Looking ahead, what specific impact do you hope to make in cancer advocacy and policy by the end of your term?

By the end of my term, I aim to strengthen policies that reduce disparities in cancer care across Europe—and continue to promote innovation and enhanced collaboration by fostering stronger partnerships among EU countries, research organisations, and patient advocacy groups to create a unified front against cancer.

We thank **Nikos Papandreou** for sharing his vision for the future of cancer care in Europe and look forward to seeing how his work on the **SANT Committee** continues to shape the landscape of cancer treatment and policy in Europe.

Adrian Pogacian

(Re) Thinking Psycho-oncology in a world out of balance

What I Learned After A Year Of Interviews

One must imagine Sisyphus happy - Albert Camus

Why me? This is probably the present-day question of every patient with cancer!

One of the consequences of our chaotic reality is cancer, which belongs to that class of diseases that impacts the mental health of the patient and their family; life after the oncological diagnosis will never be the same for any human being.

The first and most important aspect is that cancer influences the **emotions** of every patient, as well as the understanding in the eyes of every human being. Therefore, the common perception is that:

- Cancer is **fear** – the word itself stirs up an imminent danger
- Cancer is **sadness** – the word itself suggests the threat of loss
- Cancer is **anger** – the word itself can bring to mind the thought of a limited life.

In this regard, **Psycho-Oncology** is one of the first domains of health and clinical psychology that have been developed at the borderline of medicine and psychology.

Hence, Psycho-oncology is gaining subspecialty status by currently bringing a set of clinical skills in counselling, behavioural and social interventions in oncology, by providing training programs that teach basic knowledge and skills in the field, by creating a body of academic research concerning relevant clinical aspects in the care of cancer patients.

But, despite the progress in medicine and technology, cancer remains a relentless disease.

The news that a person has cancer is terrible not only for the patient, but also for the family members, and it can bring unexpected changes in the relationships with and between them.

After such a diagnosis, there will be changes in responsibilities and priorities in any family life, and during treatment and recovery, there will be many other challenges.

HOPE to deliver quality results in minimal time

Regarding the field of psycho-oncology, the last IPOS congress theme from Maastricht 2024: **Cancer in Context**, was meant to illustrate an integrative approach regarding the oncological disease. Despite the optimism within panel discussions, there remains the practical and academic gap among psycho-oncological specialists, with a focus on Low and Middle-Income Countries (LMICs) or the lack of trust in psychological counselling in the former Eastern European countries.

While in high-income countries, Artificial Intelligence and E-Health are the current topics of research, some other countries face food insecurity, stigma and inequity in cancer care, themes that should have been on the agenda, too. Moreover, research means huge investments (especially in the oncology field), though there are nations where primary care still can't be achieved.

Unfortunately, we are **living in the paradox of oncology**: the development of medical sciences should have led to further discoveries in the field of cancer psychology, as well as the development of new methods of dealing with fundamental psychological problems and traumas. However, medicine and psychology seem to have gone in different directions.

This paradox was the starting point of my interview series Beyond the Cancer Diagnosis: in order to figure out how deep is this gap and if we can approach oncological disease from a psycho-social dimension. It was not an easy task, but the potential was promising.

I still remember my first interview with **Patricia Moreno**, clinical psychologist and **Gilberto de Lima Lopes Junior**, Associate Director for Global Oncology at the Sylvester Comprehensive Cancer Center, shortly after the Princess of Wales's diagnosis, when the world was both shocked and curious about the subsequent trajectory of the disease. It was for the first time when during an interview with a clinical psychologist and an oncologist we approached

terms like: **coping with cancer, family support and hope over fear**.

Thus, progressively researchers, professionals, CEOs and patients have accepted this challenge to share knowledge and personal opinions on pressing issues in the oncology field, all from a psychosocial perspective.

Consequently, I have learned that we are all committed to the same aim: to improve the Quality of Life of every cancer patient with HOPE as the main trigger in searching for the meaning of life in this new reality or, as **Harriet Cabelly**, grief therapist and cancer survivor, pointed out very nice during our interview: **I don't want to come back empty-handed from hell**!

What I learned during this year

Each person constantly contributes to their own state of health. The word contributes indicates the vital role each person plays in creating their own health. Most of us assume that healing is something that is done from outside and, if we have a medical problem, our responsibility is simply to go to a doctor.

This is true to a certain extent, but it is only a part of the truth. We all contribute to our health through our ideas, our feelings and our attitude towards life in general and illness especially.

The problem arises when the resources regarding the situation (cancer treatment) far exceed those available to the person and it is one of the answers to the question of why the majority of the world population don't take part in screening campaigns. In this regard, **Judy Medeiros Fitzgerald**, an active advocate for breast cancer prevention and founder of the Sisters4Prevention project, explained that this phenomenon is based on the following reasons: the screening indeed is free of charge but, if the result is positive, everything is paid since cancer isn't a low-priced disease. Therefore, the population avoid participating in screening campaigns because they can't afford an eventual diagnosis.

This aspect is particularly important for the reason that we enter the field of self-stigmatization. Stigma became a topic of intense debate due to the lack of psycho-education. Concerning this issue, **Foluke Sarimiye**, Clinical Lecturer in Radiation and Clinical Oncology at the University of Ibadan and University College Hospital, Ibadan, Nigeria argued that children in Nigeria do not touch another one having cancer because they believe that cancer is a contagious disease. Unfortunately, Nigeria is not the only country where this mentality prevailed.

As for the psycho-education in the field of oncology, **Marianne Arab**, Provincial Manager of Psychosocial Oncology, Palliative and Spiritual Care with the Nova Scotia Cancer Care Program, argued that even though executive education is important and school curricula are improving gradually, **"we have a lot of work to do in educating the general public, and in educating ourselves, and then I think we'll have made some inroads in how do we talk to kids about it".**

At this time, Adolescents and Young Adults (AYA) are the most vulnerable category of cancer patients. **Lauren Fryzel**, the Senior Manager of Patient and Community Outreach for the Leukemia and Lymphoma Society (LLS), explain this vulnerability in common terms, because **"patients are getting diagnosed too late, because both the patient themselves are like, oh, it can't be cancer, I'm too young for that. And making assumptions about their health or being afraid to go to the doctor because they don't want to know what's going on. And the other side is the provider side of, it can't be cancer, they're too young for that, right?"**

Moreover, AYA faces multiple barriers to achieving access and equity in cancer care. In this connection, **Betty Roggenkamp**, a recognized specialist in cancer care quality improvement, points out the main barriers, as follows:

1. **Access to care** that recognizes their unique life stage and needs.

2. **Financial burden**, as cancer-related costs can impact their short and long-term financial stability for decades.

3. **Late and long-term effects** – physical, mental, financial, and oncologically that follow them well beyond treatment.

Thus, as professionals, we have to deliver transparent and sincere information about the patient's situation.

The fact that he/she is young is not an excuse and doesn't mean that they will not find out what is really happening to them.

There is a lot of information on social media and Google which can be easy to access but the problem is that there is also a lot of misinformation and, especially, disinformation, that should make us vigilant.

Presently, there are three issues that are most disputed among psycho-oncologists and not only:

1. **Denial of cancer diagnosis** – broadly speaking, denial as a coping strategy varies considerably: ambivalence and ambiguity are often used in the service of denial. Nevertheless, it appears that as long as denial does not affect the patient's adherence to medical instructions, it has great potential to improve their quality of life.

Mila Ogalla Toledo, a young colorectal cancer survivor and AYA (Adolescents and Young Adults) cancer patients advocate, expresses this sharing her own denial experience:

"It is not easy and I think it changes. Like I've been maybe better in the past and I might get the worst anxiety of my life the next year. I do not think that you can control that or manage that. But if you can remind or do your best to remember that it's okay to have those moments and it's okay that every single time that you're going to get an appointment or you're going to do a test, you might feel different about them."

2. **Positive attitude/thinking** - keeping a positive attitude does not guarantee a better chance of survival within cancer patients, since there is no scientific proof with regard to this issue.

Moreover, some researchers talk about the contemporary tyranny of positive thinking which, sometimes, victimizes people. Definitely, defining what constitutes a truly positive attitude is a complex issue. But, being "too positive" all the time can lead to denial, which can prevent you from getting the medical information and treatment you need.

A common approach is shared by **Prof. Cristian Ochoa**, Clinical Psychologist in Psycho-oncology Service and Chief of the Digital Health Program at the Catalan Institute of Oncology; in his view:

"Cancer patients don't need to be positive. Positive is not a mandatory enemy that people have to maintain in such an adverse situation. Positive is sometimes the way that we explain in a popular way how to find our best version, how we can live, fully live in this situation, but it's not mandatory, it's not a kind of tyranny of the patients. It's a kind of natural response."

3. **Too much HOPE is a false hope** – there are a lot of debates about what hope really is: an emotion, a strategy, a mirage, etc. During my interview with Taryn Greene, PhD, Director of Research at Boulder Crest Foundation and the home of Posttraumatic Growth (PTG), she defined the nuances of hope as follows:

"I imagine the cancer area of work is a place where that candle, that flame of hope is especially important ... what I like to say about hope is that sometimes you know that people lose hope that is a piece that happens of in traumatic situations and losing a focus on hope it can feel like you've lost it and that you're never going to find it again... Hope has been defined in the psychological literature as more of a kind of goal-centred concept where folks have identified goals and are able to kind of identify pathways of getting there and able to access motivation to move towards those goals again we're talking about looking forward."

To sum up, when faced with negative daily events, people may choose to suppress negative emotions or express them. While there can be benefits to suppressing or avoiding these, there can also be downsides.

During this year I have learned a lot and faced many challenges walking on this path but the greatest achievement is the words of **Dr. Alberto Costa**, CEO of the European School of Oncology (ESO) which always come into my mind:

> **"You can't be a good (psycho) oncologist if you don't know how to handle the why me question!"**

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