

# Molecular Imaging in Breast Cancer

## Martine Piccart and Géraldine Gebhart Talk with David Mankoff About 2 Generations of Research

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**D**avid Mankoff, MD, PhD, the Matthew J. Wilson Professor of Research Radiology at the University of Pennsylvania Perelman School of Medicine (Philadelphia) and an associate editor for *The Journal of Nuclear Medicine (JNM)*, talked with breast cancer oncology and molecular imaging (MI) leaders Martine Piccart, MD, PhD, and Géraldine Gebhart, MD, PhD. Dr. Piccart, an honorary professor of oncology at the Université Libre de Bruxelles (ULB; Belgium) and scientific director at Institut Jules Bordet (Brussels), and Dr. Gebhart, Oncologic Clinical Director of the Nuclear Medicine Department of the Hôpital Universitaire de Bruxelles, are mother and daughter.

Dr. Piccart is an international leader in medical oncology with a focus on breast cancer research. In 1999, she cofounded the Breast International Group (BIG), the largest network of groups conducting clinical breast cancer research in the world. She is a member of the Belgian Royal Academy of Medicine and served as president of the European Cancer Organization, the European Organization for the Research and Treatment of Cancer, and the European Society for Medical Oncology (ESMO). Dr. Piccart also served on the American Society of Clinical Oncology (ASCO) board, as well as on the board of the American Association for Cancer Research. She has published over 600 peer-reviewed articles and received multiple awards.

Dr. Gebhart is a rising star in oncologic MI and focuses on breast cancer research. She studied medicine at ULB. In 2009, with a solid background in internal medicine, she began her work in nuclear medicine under the supervision of Patrick Flamen, MD, PhD, at the Institut Bordet. She focused on MI as an emerging field in oncology. Her PhD project was on the contribution of MI to early evaluation of response to anti-human epidermal growth factor receptor 2 (anti-HER2) agents in breast cancer. She played lead roles in seminal studies testing PET as a predictive and response biomarker for HER2-targeted breast cancer, including the NEOALTTO and ZEPHIR trials, and was a key contributor to the recently published PHERGAIN study. Gebhart has been recognized with *JNM* Editor's Choice Award for 2013, the Alavi-Mandell Award for a *JNM* article published in 2013, and the 2023 Marie Curie Award from the European Association of Nuclear Medicine (EANM).

**Dr. Mankoff:** Martine and Géraldine, it is a pleasure to speak to you as leaders in breast cancer oncology and MI, as well as medical oncology and nuclear medicine collaborators in breast



Martine Piccart, MD, PhD (left), and Géraldine Gebhart, MD, PhD (right)

cancer research at Jules Bordet and in leading international trials. As an oncologist and as an imager who both work in breast cancer, what do you see as the greatest areas of need in which MI can impact breast cancer treatment and outcomes?

**Dr. Piccart:** The last decade has witnessed the successful development of several new anticancer drugs for the 3 main breast cancer subtypes: cyclin-dependent kinase 4 and 6 inhibitors and selective estrogen receptor downregulators (SERDs) for luminal disease (2/3 of patients); anti-HER2 monoclonal antibodies, tyrosine kinase receptor inhibitors, and antibody-drug conjugates (ADCs) for HER2-positive disease (~15% of patients); and immune checkpoint inhibitors and ADCs for triple-negative breast cancer (TNBC; ~12% of patients). These agents are quite expensive, and there is a huge unmet need for clinically useful biomarkers allowing a better selection of patients likely to benefit from

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these drugs. As a result, many patients are over- or undertreated. In advanced breast cancer, disease heterogeneity is increasingly recognized as a limiting factor for the efficacy of targeted drugs. This is, in our view, an area where MI could play a critical role.

**Dr. Gebhart:** The ZEPHIR imaging study in advanced HER2 breast cancer nicely showed how HER2 PET can predict the anti-tumor efficacy of the ADC trastuzumab emtansine: only patients showing a strong and generalized uptake of <sup>89</sup>Z-trastuzumab across their metastatic sites enjoyed a prolonged time to treatment failure.

**Dr. Mankoff:** *What do you see as the biggest hurdles for moving breast cancer MI from early-stage studies into clinical practice?*

**Dr. Piccart:** As noted, MI should be viewed as a powerful biomarker with the potential to reduce overtreatment as well as undertreatment. This great potential is largely ignored by the community of medical oncologists. Indirect proof of this is the very limited space given to MI in famous cancer congresses such as those of ASCO or ESMO.

**Dr. Gebhart:** On the other hand, the MI community should invest more time and energy in the full validation of MI as a biomarker, meaning going beyond analytic/clinical validity and demonstrating clinical utility. This can be best achieved through a much-reinforced crosstalk and collaboration between these 2 worlds. This type of research, however, is not inexpensive and will not always be viewed as attractive by the pharmaceutical industry, given that it could restrict their drug market. Hopefully,

enthusiastic teams able to perform these trials with the needed quality and statistical power.

**Dr. Mankoff:** *You both provide excellent examples of team players at the intersection of breast cancer and imaging. On a related topic, radiopharmaceutical therapy has had a large impact on some endocrine-related cancers, such as thyroid, neuroendocrine, and prostate cancers. However, radiopharmaceutical therapy has had only a limited role in breast cancer thus far. Is this due to the number of other effective systemic therapies for breast cancer, or are there other considerations limiting the use of radiopharmaceutical therapy for breast cancer? What do you see as the areas in which radiopharmaceutical therapy might be helpful?*

**Dr. Piccart:** It is true that radiopharmaceutical therapy for breast cancer is in its infancy. We can see 4 potential explanations: the “wave” of new effective drugs developed for this disease in the last 10 years; the recognition that breast cancer is not a single disease but a collection of “subtypes,” which complicates the design and conduct of trials exploring innovative therapies; the marked heterogeneity in target expression, which has been particularly well documented in HER2-positive breast cancer; and the extra burden that may be imposed by health authorities on trials with radiopharmaceuticals for safety reasons, sometimes associated with limited access to PET devices.

**Dr. Gebhart:** We are hopeful that this situation will improve in the near future, particularly for 2 clinical scenarios: advanced TNBC, a very aggressive subtype with poor clinical outcomes despite the introduction of immunotherapy, and brain metastases.

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“We really need the kind of evidence that oncologists look for in drug trials: well-powered and randomized trials to demonstrate that patients treated with the help of MI guidance do better than patients who do not receive MI ... This is an area in which the model of European–U.S. collaborative trials that has changed treatment practice could support changes in diagnostic practice.”

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governments and charities will understand the value of MI, because it is likely that the cost of sophisticated imaging will be offset by the ability to prescribe the right expensive anticancer drugs for the right patient at the right time.

**Dr. Mankoff:** *Breast cancer was one of the earliest areas in which individualized targeted systemic therapy was used. Targeted therapy remains a key part of breast cancer treatment, with an increasing array of drugs matched to specific targets and with new diagnostic agents that can image these targets. Despite advances in imaging breast cancer targets, such as the estrogen receptor (ER) and HER2, there seems to be relatively slow acceptance of these tools in the breast cancer community. What are the barriers for imagers and oncologists to more widespread acceptance and use of imaging biomarkers to help guide targeted therapy in breast cancer?*

**Dr. Gebhart:** Again, prospective trials designed to robustly demonstrate the clinical utility of an imaging modality are quite expensive and not necessarily welcomed by pharma. In addition, these trials must be conducted with rigor: standardization of the imaging test must be performed in all participating centers. They should ideally be supported by data on cost effectiveness to be able to refute the frequently heard argument that PET scans are “too expensive.”

**Dr. Piccart:** From the viewpoint of an experienced clinical trialist, the high level of multidisciplinary expertise required might discourage many research groups. What is needed is a few

Our colleagues from the Vrije Universiteit Brussel are exploring HER2-targeted nanobodies for refractory brain metastases, and we are currently investigating targets such as prostate-specific membrane antigen or, in the near future, fibroblast-activation protein inhibitor in advanced TNBC.

**Dr. Mankoff:** *Géraldine, you have led groundbreaking trials of novel MI approaches for breast cancer in European studies that have often been well ahead of those in the United States. What's the secret to your ability to implement and perform these trials?*

**Dr. Gebhart:** First, I have greatly benefited from a fantastic research team in the nuclear medicine department at my institute, including Dr. Flamen, an enthusiastic head of unit who trusted me from the beginning. I started my research in collaboration with Zéna Wimana, PhD, MBA, without whose great expertise in the radiopharmacy field I don't think I could have managed an ambitious imaging trial such as ZEPHIR. And I work with 2 brilliant bioengineers, Julie Gaye and Thomas Guiot. Second, with the help of my mother I was introduced to a network of cancer centers in Belgium and The Netherlands with prime interests in novel MI approaches as powerful tools for development of “precision oncology.” In particular, I found great partners in Groningen: for example, Elisabeth de Vries, MD, PhD, and Carolien Schröder, MD, PhD, both medical oncologists with long-standing interest in MI. I also enjoyed working closely with the team of C. Willemien Menke-van der Houven van Oordt, MD, in Amsterdam. Finally, I had the chance to finalize the primary endpoint of the ZEPHIR

study with Magdalena Mileva. Results were presented in the recent EANM congress and recognized with the Marie Curie Award.

**Dr. Mankoff:** *You've had the good fortune to work with other outstanding leaders in the field and have the skill and diplomacy to encourage team science. We in the United States can learn from your success. Martine, you are among the world's leaders in breast cancer oncology and medical oncology in general. What advice can you give us on how best to use PET MI to help oncologists care for their breast cancer patients?*

**Dr. Piccart:** There are 2 families of new drugs that my colleagues are excited about: the ER-targeting agents (SERDs, proteolysis-targeting chimeras, etc.) and the ADCs, which show an exponential growth with more than 100 compounds in development and groundbreaking results already shown for a few of them. It should not be too difficult to convince oncologists that MI will increase our ability to identify the good (or poor) candidates for these agents as well as clarify how best to sequence them with the goal of extending disease control and overall survival. These are very promising new classes of drugs, especially for metastatic breast cancer, where MI assessment of target expression and early response to therapy could be attractive to oncologists.

**Dr. Mankoff:** *Partnerships between imagers and oncologists have been important in advancing MI research and translation of new methods to the oncology clinic. In addition to being leaders in your fields working together, you have unique insights on that partnership as mother and daughter. How has this partnership influenced your research and practice and impacted your careers?*

**Dr. Piccart:** When my daughter decided to specialize in nuclear medicine, I realized how little I knew about the specialty and decided to learn about its multiple facets. It literally opened my eyes.

**Dr. Gebhart:** Living close to a breast medical oncologist is a huge advantage, because I heard my mother complaining about the extremely slow development of predictive biomarkers in her field beyond ER and HER2. This unique context has been instrumental in our desire to bring the 2 communities—the medical oncologists and nuclear medicine specialists—closer to each other.

**Both:** ... and through beneficial complicity!

**Dr. Mankoff:** *Very interesting! This is a wonderful and unique scenario that has benefited breast cancer research and patients. One last question, primarily directed to you, Martine: In my*

*experience in leading studies testing MI biomarkers as adjuncts to tissue biomarkers to help direct individualized breast cancer therapy, there seems to be some hesitancy among oncologists to accept imaging as a way to select a therapy. In the United States, we now have an approved agent to image ER expression, [<sup>18</sup>F]-fluoroestradiol ([<sup>18</sup>F]-FES), with 2 level 1 evidence studies from Korea and Europe showing the equivalence of PET imaging findings and biopsy results. Documentation of ER expression by biopsy is a widely accepted gold standard for selecting ER-targeted therapy; however, many oncologists remain reluctant to use [<sup>18</sup>F]-FES PET results to direct therapy. What will it take to change their minds?*

**Dr. Piccart:** That's an interesting question. We have to be much more ambitious when we collaborate between the 2 specialties (oncology and imaging). We really have to come up with powerful studies that will show that using MI will result in better outcomes for our patients. The benefit of having imaging biomarkers that can avoid therapy when the intended target is absent, stop a treatment early on that's never going to work, or identify a treatment that is going to be quite effective is appealing. But we need to have strong evidence to support these uses of MI—not just the small trials with 30–60 patients that are commonly published. We really need the kind of evidence that oncologists look for in drug trials: well-powered and randomized trials to demonstrate that patients treated with the help of MI guidance do better than patients who do not receive MI. This is a big challenge, because it means conducting prospectively powered multicenter studies in which the use of a diagnostic imaging test is randomized and where imaging and image interpretation are standardized and therapeutic choices are harmonized across centers. You will likely need several hundred patients for this type of study. It will not be easy, but, with collaboration and funding, it can be done. This is an area in which the model of European–U.S. collaborative trials that has changed treatment practice could support changes in diagnostic practice.

**Dr. Mankoff:** *I agree 100%. Let's figure out how to do this! Géraldine and Martine, thank you for the fascinating discussion and chance to talk to 2 leaders in the field with a passion for imaging and breast cancer research. I hope we can follow up on Martine's suggestion to generate international trials to provide level 1 evidence of the ability of MI to improve breast cancer patient outcomes.*