A Conversation Between Elisabeth de Vries and Johannes Czernin

Elisabeth de Vries[1] and Johannes Czernin[2]

[1]University Medical Center Groningen, University of Groningen, Groningen, The Netherlands; and [2]David Geffen School of Medicine at UCLA, Los Angeles, California

Johannes Czernin, editor in chief of *The Journal of Nuclear Medicine,* initiated in 2019 a series of recorded discussions with leaders in nuclear medicine and molecular imaging. For this issue, he talked with Elisabeth de Vries, MD, PhD, a professor of Medical Oncology at University Medical Center Groningen (The Netherlands). She is involved in patient care, teaching, and research, including clinical trials. A primary focus of her multifaceted work is on international collaboration to improve cancer treatment and on interdisciplinary translational research for applications in personalized medicine. These interests include improving cancer care by defining tumor response criteria and defining the scope of clinical benefit from cancer drugs, clinical and translational research in breast cancer and neuroendocrine tumors, and translational oncology and early drug development using molecular imaging to visualize tumor-specific targets and the effects of immunotherapy.

Dr. de Vries is known internationally for her organizational work to improve quality and effectiveness in cancer treatment. She is currently cochair of the Response Evaluation Criteria in Solid Tumors (RECIST) Committee on behalf of the European Organization for Research and Treatment of Cancer (EORTC) and chairs the European Society of Medical Oncology (ESMO) Magnitude of Clinical Benefit Scale working group (2016–current) and the ESMO Cancer Medicines Committee (2018–current). In 2002, she was appointed a member of the Royal Netherlands Academy of Arts and Sciences. She received the ESMO Award in 2009 and is a fellow of the European Academy of Cancer Sciences.

Dr. Czernin: *Dr. de Vries, you are a medical oncologist, and you served as the head of the Department of Medical Oncology at the University of Groningen. But you are also a key figure in molecular imaging and imaging biomarker development and validation. What ignited your interest in molecular imaging?*

Dr. de Vries: I have always combined lab research with clinical research, and I have always tried to bridge the gap between preclinical research and clinical applications. We have a good PET Center here in my hospital, and I was very eager to see whether we could make tracers that would be of interest to get answers for our patients in the clinic. I am involved in tracer development and in deciding which tracers we would like to use, how to conduct informative animal experiments, and how we translate these to the clinic.

Dr. Czernin: *So would you call yourself something like a "translational relevantist"? Someone who bridges the gap between preclinical science and clinical need?*

Dr. de Vries: Beautiful words. I'm also aware that I can't do anything on my own. I have tremendous input from a multidisciplinary team including pharmacologists and radiopharmacists. And nuclear medicine physicians are critically important partners for clinical translation.

Elisabeth de Vries, MD, PhD

Dr. Czernin: *Before we get back to imaging I would like to mention your international leadership in clinical trials design. Many of the trials were unrelated to imaging, but for others imaging parameters were used as predictive or intermediate endpoint biomarkers.*

Dr. de Vries: I like to be involved in smart clinical trial design to get meaningful answers, preferably without the need to enroll too many patients. I also believe strongly that not only pharma but also academia should design clinical studies. I do not really know how I became cochair of RECIST (https://recist.eortc.org/). I guess I was asked because of my training as an oncologist and my interest in imaging. The RECIST Working Group comprises representatives of the EORTC, the National Cancer Institute (NCI) in the United States, and the Canadian Cancer Trials Group, as well as several pharmaceutical companies. Its mission is to ensure that RECIST undergoes continued testing, validation, and updating.

I am also involved in the ESMO Magnitude of Clinical Benefit Scale committee. In The Netherlands we already had criteria to determine drug effectiveness. In 2013 ESMO decided to try to develop a scale (https://www.esmo.org/Guidelines/ESMO-MCBS) to determine the impact of newly registered cancer drugs on patients. Initially the scale was considered to be especially relevant for patients in Eastern Europe, where access to important drugs may be difficult. However, we are now seeing worldwide interest in the scale, because all countries have difficulties in prioritizing cancer drugs, which are often quite expensive.

Dr. Czernin: *Did you assess drug cost effectiveness?*

Dr. de Vries: No, here we currently don't take cost into account. We look only at aspects such as disease-free survival, overall survival, toxicity, and quality of life.

Dr. Czernin: *You emphasized your focus on smart clinical trials to limit the number of patients needed for enrollment. This can be done through patient stratification and also response assessments, 2 key requirements for true precision oncology, which is currently almost exclusively understood in the context of genomics. The NCI Molecular Analysis for Therapy Choice (MATCH) trial and other trials in which specific cancer mutations were identified and matched to targeted drugs provided disappointing results, with only a small number of patients ending up with matching therapies. Outcomes may not have been improved. Was part of the mistake to believe that many cancers have a single oncogene addiction?*

Dr. de Vries: When I saw initial data from such studies, I was somewhat disappointed. At the moment I'm going through a fairly positive phase. I do agree that it has been simplistic to think that a single mutation will tell you across tumor types whether a drug will work. But with current trials we get more information on certain subgroups of patients. So, we become much better informed. International data sharing will help. We will get more information about small subgroups and, thus, have better understanding about what is really meaningful for specific patient groups.

Dr. Czernin: *You also used whole-body predictive PET imaging biomarkers in the context of patient stratification. Do you believe that imaging can play a significant role as a predictive biomarker?*

Dr. de Vries: I really hope so. We have finalized the accrual of a multicenter breast cancer study that is now in the phase of follow-up and data analysis. In this study, patients with newly diagnosed metastatic breast cancer underwent treatment after standard staging with CT and ^{18}F-FDG PET, and they also received ^{89}Zr-trastuzumab PET imaging for HER2 detection and ^{18}F-fluoroestradiol PET imaging for estradiol receptor detection. Response assessments were performed with CT, but we also acquired an early FDG PET scan. Moreover, tumor biopsy was performed. In several patients more than 1 biopsy was performed to address heterogeneity in receptor expression. It is standard of care today to rebiopsy patients with breast cancer during the course of their disease because of known changes over time in relevant tumor characteristics. This is a very complex and challenging disease. In addition, we have collected, as a noninvasive approach, circulating tumor DNA. In this study we want to evaluate the clinical utility of the experimental PET scans in the setting of metastatic breast cancer at first presentation. The information will also tell us about tumor heterogeneity to design smarter trials in the future. You can imagine that if most lesions are receptor positive and 2 lesions are not that you may want to treat those 2 lesions separately or differently. We hope to have firm data early next year. This kind of study provides a great amount of treatment stratification information. If molecular imaging could help, patients and clinicians would benefit tremendously.

Dr. Czernin: *You mentioned that you use RECIST as response marker. Why not FDG? Are the data in your view not sufficiently robust?*

Dr. de Vries: Yes. That's basically the reason. RECIST was developed to create robust and standardized response criteria. RECIST was drafted and criteria were validated and verified by a data warehouse approach populated from clinical studies. This approach was originally developed for drug studies and drug registration studies to secure an early read-out of drug effects (i.e., measurement of response rate and determination of progression-free survival). Here, progression-free survival is seen as a potential read-out of overall survival. RECIST was initially established for chemotherapy. However, we also tested the criteria for a warehouse filled with data from studies with targeted agents, and RECIST works well for these treatments, too.

FDG PET is included in RECIST v1.1, but only to confirm progressive disease when indicated. The problem with FDG PET has been that we have not been able to build a warehouse where we can validate the data. We always had problems with standardization of image acquisition and analysis. Now a subgroup within the RECIST committee will soon publish an article describing aspects to take into account to establish a warehouse approach to generate sufficient data.

Dr. Czernin: *Early reductions in tumor FDG uptake are associated with improved outcomes across most, if not all, cancers. If FDG uptake is not reduced, the treatment will not work. Don't you deprive patients of the opportunity to get these early assessments despite the absence of the warehouse approach? Do you use FDG for treatment monitoring in your clinical practice?*

Dr. de Vries: Not routinely. But there may be special situations, for example, to confirm progressive disease next to standard RECIST v1.1. Moreover, patients treated according to standard of care may not be evaluable according to RECIST because of bone lesions only, and then a different situation occurs.

Dr. Czernin: *That is interesting, because in the United States we use it all the time. In fact, it is in many, if not most, places the standard of care.*

Dr. de Vries: If I talk about daily practice, we hardly use it when response measurement according to RECIST is possible. In clinical trials we try to build it into studies so that we hopefully can contribute to a warehouse in the near future.

Dr. Czernin: *Your argument is the "evidence-based medicine" argument. But my counterargument would be that if one had applied this to coronary artery bypass surgery or cardiac transplantation, then these therapies would have been accepted many decades too late.*

Dr. de Vries: I know that reasoning. This is the huge difference between imaging and oncology. We come from a world where we had and have to prove everything we are doing, because by doing trials we show what is meaningful for patients. The other reason is that we are considered to be big spenders within the health care system. So, we must have proof and justify what we are doing. I haven't said that I'm not extremely interested in getting FDG tested to see whether it can be part of RECIST. I really hope we can collect the proper evidence.

> "I hope we will have imaging specialists who are not only interested in pictures or in biopsies. I hope that there will be imagers who have a huge interest in biology, because they can drive the direction in which the imaging field might change—including identifying new ways to team up with physicians regarding novel tracers."

Dr. Czernin: *That's a very interesting problem. How do you validate something that has become the standard of care across many cancers in many countries? Something that is valued by so many oncologists, even absent the warehouse approach.*

Dr. De Vries: As a medical oncologist, I hope that the molecular imaging world buys into standardization and warehouse approaches to get robust answers for several tracers. International collaboration will help to get these answers. I really hope that we will all be eager to go down that path.

Dr. Czernin: *For the future that's clearly something for which we should aim. It's very difficult to come up with a warehouse for FDG, because this would be limited to prospective studies. Nobody will fund prospective clinical trials for response assessments using FDG PET, because it is already the standard of care. Some oncologists send patients for FDG PET/CT scans for each new line of treatment in individual patients and will switch to another line once lesions stop responding metabolically.*

Several new response criteria are available for immunotherapy. What is your view of these various approaches?

Dr. de Vries: The RECIST committee realized that there were different initiatives. Again, we decided to have a joined effort and recognized again the need for the warehouse approach to come up

with robust criteria for the future. Thus far, the RECIST committee has teamed up with investigators and pharmaceutical companies involved in immunotherapy, as well as with the U.S. Food and Drug Administration and the European Medicines Agency. We have designed criteria to help to properly collect data. This was published in *Lancet Oncology* (2017;18[3]:e143–e152). Again, the way you measure response is according to RECIST. However, when patients have progressive disease, we call that unconfirmed progressive disease. If the patient is clinically well and stable, then we can continue treatment and acquire repeat imaging and thereafter decide whether it is really progressive disease or whether it was pseudoprogression. These criteria have been termed iRECIST.

Dr. Czernin: *Do you use all kinds of imaging modalities?*

Dr. de Vries: No. Basically iRECIST is done according to RECIST, so especially CT and MRI, with FDG PET only to confirm progressive disease when indicated.

Dr. Czernin: *Why don't you include FDG when you have the opportunity to create a warehouse?*

Dr. de Vries: If sufficient and good data are available from studies, we definitely could include it in the warehouse and test its performance.

Dr. Czernin: *Who pays for PET studies that are in essence done for these research studies?*

Dr. de Vries: That's a good question. For the research we perform we get money from numerous sources. If PET imaging is part of a drug trial, pharma will pay for it. But we also have numerous other grants, including funding from the Dutch Cancer Society and the European Union.

Dr. Czernin: *Let's move on to the predictive biomarker issue. If you go by the evidence-based criteria that you just laid out for treatment responses, the predictive biomarker story will be at least as complex and difficult. We have predictive biomarkers and use them in somatostatin receptor– or prostate-specific membrane antigen–targeted imaging. Potential clinical candidates also include AR, HER2, and ER receptor imaging and many more. Again, we would need large-scale international trials to validate the approach. This carries many complications, one being money and the other how to integrate predictive biomarker studies in meaningful clinical trials. So what's your idea here?*

Dr. de Vries: You summarized the issue. We have done an imaging study with ^{89}Zr–PD-L1 antibody imaging. The PD-L1 antibody is an immune checkpoint inhibitor targeting the checkpoint PD-L1. After imaging, patients were treated with the antibody itself. This small study resulted in an article in *Nature Medicine* (2018;24[12]:1852–1858). It appears that PD-L1 uptake in tumor lesions predicts response and survival. We can now, for example, provide the antibody to interested sites in its conjugated form. The sites can perform their own studies and publish their results, and later we can combine the results and hopefully build a robust warehouse to test for the relevance of this approach.

Dr. Czernin: *I completely agree. I think the issue is that the principal investigators need to set quality criteria not only for the procedure, data acquisition, and data analysis but also that these studies need to be read offsite. Reproducibility and reader agreement must be established. As long as the individual investigators comply with all established standards, they can publish their data without any limitation.*

Dr. de Vries: Investigators would also need to agree to submit their data to the central warehouse. People would need to share data. This would be best done as an international multicenter effort, resulting in joint output.

Dr. Czernin: *Funding is a big problem. Recognition is another problem, because especially young investigators need to have their names in prominent positions on papers. There are solutions, of course. Site investigators could assume responsibility for certain diseases and report these under their leadership.*

Dr. De Vries: I agree, it is always important to realize what motivates everyone to be involved. Although all of this is very complicated, there are solutions. A central database from which images are read offsite to take out biases so that the quality of the studies is beyond any doubt would be a nice start.

Dr. Czernin: *Quality depends on training and expertise. Training the next generation of physician scientists has been very important to you. What are your key criteria in trying to attract the best people to become good clinicians or clinician scientists?*

Dr. de Vries: People need to understand how important it is for health care to perform research and therefore to have physician scientists. I'm not saying that if you're a clinician only and do not do research that you're not a good clinician. But I believe that in order to move the profession forward we need physician scientists. A few weeks ago, a perspective article in the *New England Journal of Medicine* (2019;381:399–402) raised concerns about the decreasing number of physician scientists in the United States. I hope to show potential physician scientists that by doing research they create opportunities for patients to access treatments that would not otherwise be available. I hope to show them how gratifying this is. I also hope that I'm able to show them that it's exciting to be part of this process. That also means that I have to be vigorous in getting grants to support young physicians so that they have the opportunity to spend time on research and not just on working hard in the clinic. Physicians tend to be so busy that no time is left to do research. Mentors are, of course, important. It is also important for young physicians to attend meetings that are attended by faculty with diverse backgrounds—meetings where they are taught about clinical trial design and at which they can network.

Dr. Czernin: *This is a very important aspect also for nuclear medicine trainees, who often are somewhat isolated from large-scale clinical trials. If they don't have exposure to other fields, their clinical instincts will remain underdeveloped. Communication and collaboration are very important. As you know, there is an ongoing debate in the United States about nuclear medicine as an independent discipline. Most nuclear medicine clinics around the world are independent, but most United States clinics are divisions of radiology departments. In my view there is tremendous value in independence, as long as nuclear medicine is integrated into the clinical fields with which they work. You have served as a department head. What is your take on academic health centers and how they should be managed? What do you think about the traditional department structure?*

Dr. de Vries: I'm really looking at imaging departments from an internal medicine or oncology point of view. What's exciting in my profession at the moment is the insight into the biology of diseases that we have and that translates into new treatments.

I hope we will have imaging specialists who are not only interested in pictures or in biopsies. I hope that there will be imagers who have a huge interest in biology, because they can drive the direction in which the imaging field might change—including identifying new ways to team up with physicians regarding novel tracers. Much remains to be done. We are now teaming up, for example, with people working on autoimmune diseases because our immune therapy is eliciting these immune responses. This doesn't mean that all imagers have to be interested in biology. Imaging is a huge field, and you have to have departments that allow researchers to have focused interest in certain aspects.

Dr. Czernin: *Thank you, Elisabeth, for taking the time to talk with me and our readers.*