

# Precision Medicine Clinical Trials

## A Conversation Between Peter O'Dwyer and Lale Kostakoglu

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**L**ale Kostakoglu, MD, MPH, a professor of Radiology and Chief of Nuclear Medicine and Molecular Imaging in the University of Virginia Health System (Charlottesville, VA), talked with Peter J. O'Dwyer, MD, a professor of Medicine at the University of Pennsylvania (Philadelphia) and a medical oncologist with expertise in gastrointestinal (GI) and pancreatic cancers. Dr. O'Dwyer has been the Group Co-Chair of the ECOG-ACRIN Cancer Research Group since May 2017. ECOG-ACRIN is a membership-based scientific organization that designs and conducts cancer research involving adults who have or are at risk of developing cancer. The network includes more than 1,300 academic and community-based cancer centers and hospitals in the United States and around the world, with approximately 15,000 oncology professionals involved in sponsored research.

Within ECOG-ACRIN, Dr. O'Dwyer co-chairs the landmark National Cancer Institute (NCI) Molecular Analysis for Therapy Choice (MATCH) precision medicine cancer trial. He is the CEO and chair of the Board of Managers of PrECOG, LLC, and president of the ECOG Research and Education Foundation.

Dr. O'Dwyer received his medical degree from the University of Dublin, Trinity College (Ireland), and completed his residency at the Hammersmith Hospital (London, U.K.). After a fellowship at the Baltimore Cancer Research Center (MD), he became a senior investigator in the Division of Cancer Treatment at NCI (Bethesda, MD). He previously led the Developmental Therapeutics Programs at Fox Chase Cancer Center (Philadelphia, PA) and the University of Pennsylvania. He has authored more than 350 scientific articles and participates in numerous national and international organizations.

**Dr. Kostakoglu:** *Let's start with your inspiring trans-Atlantic experience. Would you like to tell us about your background and the pivotal decisions that shaped your career path?*

**Dr. O'Dwyer:** That's an interesting question. Actually, my career path has been formed in the United States. I have links with Europe just because many of my colleagues through the years have gone from junior to more mature positions there, and a lot of research is based on personal links. We're fortunate within ECOG-ACRIN to have a strong presence in Europe, South America, Asia, and Canada to establish new member relationships. Particularly in Asia, where South Korea is the most important country for us to focus on right now because we have shared studies there. It's been difficult to go beyond that because of various regulatory issues, particularly in South America. To generate scientific ideas and design new trials,

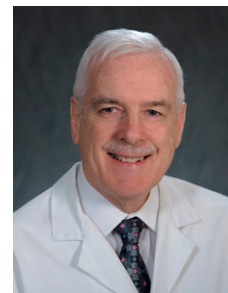
we often collaborate with global research consortia, such as the International Rare Cancers Initiative and others.

I think these international interactions really help us focus on the global impact of our studies and assist us in carrying out ECOG-ACRIN's strong commitment to advancing standards of care in broad populations of cancer patients and those at risk. We seek patient diversity in all clinical trials, including African-American patients, patients with Hispanic ethnicity, and Asian groups. For example, our current Tomosynthesis Mammographic Imaging Screening Trial (TMIST) is highly diverse. I think that precision medicine, where we tailor treatment to the individual, is helping us increase awareness of how important it is to include diverse patient populations in our trials to ensure that the results apply to all.

**Dr. Kostakoglu:** *Thank you so much for that background. Can we talk about your leadership role more specifically now? You're wearing at least 2 hats: 1 as an active researcher in the GI and developmental therapeutics programs at the University of Pennsylvania and the other as the national co-chair of the ECOG-ACRIN group. If we start from developmental therapeutics, could you tell us what this focus fosters and how it integrates translational research with clinical program resources?*

**Dr. O'Dwyer:** Although I continue to see patients at the Abramson Cancer Center at the University of Pennsylvania, I have relinquished any UPenn leadership roles to focus more on ECOG-ACRIN. But, certainly, developmental therapeutics has informed my approach to clinical research in GI cancers and more broadly. Having had responsibility for an R01-funded research lab for about 20 years, this type of research is my background. Developmental therapeutics programs are the main idea generators for clinical research; our role is to link academic medical centers to a broader community to allow translational research efforts to have maximum impact. Unfortunately, resources from the government are decreasing. Now, more than ever, institutions need to develop partnerships to be able to conduct these studies. We're constantly talking with the senior leadership of the NCI about ways to increase the impact of translational research.

**Dr. Kostakoglu:** *Shifting the topic to novel therapeutics, we know that owing to the highly adaptive nature of cancers, there is definitely a need for new therapeutic strategies. But what are the principal mechanisms for these novel targeted therapeutics in circumventing the barriers of conventional treatments?*



Peter J. O'Dwyer, MD

**Dr. O'Dwyer:** Hormonal interventions for breast cancer were the earliest targeted therapeutics. In the last few years, the major class of targeted therapeutics has been the kinase inhibitors, beginning with imatinib in chronic myeloid leukemia and GI stromal tumors. Now these are standard drugs in most leukemias and lymphomas, as well as the major solid tumors. This class of drug has had an important impact—in reality, the first to get us beyond chemotherapy. As we've learned more about targeted treatments, their clinical use has become more established and more focused on specific genomic characteristics of patients' tumors.

Understanding mechanisms of resistance and then targeting those novel mutations with more specific drugs have induced longer durations of survival than conventional therapies. A good example is the epidermal growth factor receptor inhibitors that have made such a survival difference for patients with lung cancer. An iterative research process to define exactly how lung tumors were escaping control by the earliest kinase inhibitors has allowed the development of even more specific therapeutics with superior outcomes in both activity and toxicity. Another story is about the targeting of BRAF mutations. In some tumors, like melanoma, the effects are astounding, with high rates of durable response and favorable survival and quality of life. But in colon cancer the effects are much less. In fact, as a result of the NCI MATCH trial, an application is under U.S. Food and Drug Administration review for a tumor-agnostic registration for BRAF-mutated tumors, excluding colon cancer.

**Dr. Kostakoglu:** *That is a nice segue to NCI MATCH, the landmark precision medicine cancer trial. As the co-chair of this trial, could you tell us in what ways MATCH has been successful?*

**Dr. O'Dwyer:** It certainly is a uniquely effective trial—one that is influencing how we will design and conduct precision medicine

As a reminder, this trial continues to offer 2 treatment opportunities (Arm H and Arm Z1M). The other 37 arms are now closed to enrollment, and multiple journals are expected to publish the results of the individual treatment arms. In MATCH, we are looking at single-agent treatments, with the exception of 2 arms that use combinations. We are finding that most of the patients have cooccurring mutations that are known to confer resistance, but we don't currently have a targeted drug for most of the concurrent mutations. This is perhaps the greatest opportunity for the future. We need to think about combinations of targeted therapies with immunotherapy and vaccines to stop the development of drug resistance.

**Dr. Kostakoglu:** *In that vein, what would be the main drivers of these novel combination treatments? Would you foresee paired resistance?*

**Dr. O'Dwyer:** We can talk about this at 2 levels. One is that combination precision medicine trials are in development with sponsorship from the NCI. Within ECOG-ACRIN and together with the Alliance for Cancer Clinical Trials, the SWOG Cancer Research Network, and NRG Oncology, we are developing the ComboMATCH trial. This trial's approach is tumor agnostic, much like the original NCI MATCH trial. However, the principle here is to overcome drug resistance to single-agent therapy by developing genomically directed targeted agent combinations. Another suggestion from the MATCH trial is that while hitting certain drug targets may be useful across tumor sites of origin, several are limited to specific tumor types. ComboMATCH will recognize the importance of cancer tissue type specificity in response to targeted therapy by incorporating randomized arms in specific diseases.

ECOG-ACRIN recently expanded our Developmental Therapeutics Committee with a Genomics Subcommittee to develop

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studies in the future. Just to put it in context, after about 2 years of planning, in the first 3 months after study initiation, our accrual rate was 8-fold higher than expected. Several aspects worked in the trial's favor. First, at a time when DNA sequencing was expensive and it was unclear how it would be funded, the cost of sequencing was covered by the study. By meeting this need for cancer patients, the trial accrued faster than any other large cooperative group trial ever—6,000 patients enrolled for central screening in 15 months. Another positive was that, despite our concerns about being able to reach patients with rare tumors, 60% of accruals represented uncommon tumors (those other than breast, colorectal, non-small cell lung, or prostate cancer). This is very gratifying to observe, because it allows us to think about precision medicine broadly across tumors. It also shows the value of platform trials for patients with uncommon or rare genomically driven cancers. MATCH results will allow us to identify groups in which a specific treatment will be effective, versus others where different treatment strategies should be developed.

Also important, of course, is that we proved that this type of trial is feasible and that there is broad interest among physicians. At the time of development, the size and scope of MATCH had never been attempted. For the NCI and ECOG-ACRIN, it was an enormous undertaking to develop the infrastructure for a national precision medicine trial across all cancers. As a result of this tremendous effort, NCI MATCH is building a knowledge base and laying the groundwork for future precision medicine initiatives.

molecularly informed concepts, particularly combination concepts, to move forward not just through ComboMATCH but also through ECOG-ACRIN and PrECOG. Combination concepts can include immunotherapy, targeted therapies, chemotherapy, or radiation therapy. We hope to do this by actively engaging our industry partners and helping them develop these types of concepts with novel compounds—particularly in areas like rare tumor subtypes.

Another NCI-funded precision medicine trial in development is MyeloMATCH, which targets genomically defined subgroups of acute myeloid leukemia and myelodysplastic syndromes. A further example is iMATCH, which stands for Immunologic MATCH. Both trials are in development with SWOG.

At another level, I think these precision medicine initiatives of the NCI will pave the way for further advancements in the management of particular tumors. Importantly the payors want to see these data. If convincing, the results from these trials are likely to be addressed in National Comprehensive Cancer Network (NCCN) guidelines in the future. These guidelines are essential to the payors as objective evidence for effective treatments.

**Dr. Kostakoglu:** *These are fascinating trials. In your opinion, will MATCH results lead to paradigm shifts for cancer management in the near future?*

**Dr. O'Dwyer:** Sure, and these will even have implications for cancer biology. Think about this: We've identified mutations that are associated with cancer development—namely driver mutations, which are critical to tumor survival—but, given that not all

cancers with the mutation respond, the question arises as to whether we have the right definition of driver mutations? To answer that question, we've interrogated the Cancer Genome Atlas (TCGA) and other molecular characterizations of cancer at a broad level. We now can understand how to characterize a driver mutation at the very earliest stage of carcinogenesis. We can ask: What are the other acquired biologic characteristics that could promote therapy resistance? And can we be better at selecting patients who have the best chance of responding to therapy so that we can have a starting point in the clinic based on biologic studies? And, of course, can we detect and intervene to target these mutations as early as possible to prevent cancer ever arising?

**Dr. Kostakoglu:** *MATCH also has a radiogenomics substudy. How is that study going? It's always challenging to get the tissues and the imaging data to match with them.*

**Dr. O'Dwyer:** Those studies have been approved, and we are in the process of collecting material and associated data both for histopathologic and for radiomic analysis of CTs, PETs, and MRIs. This project will be a major component of ECOG-ACRIN's data science effort going forward. We are forming a data science committee to analyze how big data can contribute to interpretation of the MATCH results, how they relate to patient outcomes, and also how they relate to the genomics to define patient eligibility for treatments. We see this effort needing to coordinate widely with other platforms (including whole-exome or whole-genome sequencing), as well as radiomic and pathomic characterization of tumors for large data science analyses.

**Dr. Kostakoglu:** *When do you think these exciting results will be available in the public domain?*

**Dr. O'Dwyer:** I'm not sure, but I think it will be within a 1- to 2-year time frame, probably not longer than that, because it is really important to get these data out there soon.

**Dr. Kostakoglu:** *Exactly; can't wait. Changing gears a bit: As one of the national leaders within the National Clinical Trials Network (NCTN), could you just briefly tell us what NCTN is and how it is structured?*

**Dr. O'Dwyer:** NCTN is a funding instrument from the NCI and a structure under which grants are awarded to individual cooperative groups to conduct clinical trials to prove the efficacy of experimental cancer therapeutics. It's a vital structure for cancer research. What's the difference between the cooperative groups and the NCTN as a whole? The 6 groups themselves are each legally distinct entities with their own separate identities. They include the Alliance for Clinical Trials in Oncology, Canadian Cancer Trials Group, Children's Oncology Group, ECOG-ACRIN Cancer Research Group, NRG Oncology, and SWOG Cancer Research Network.

There are regular meetings among the group chairs. In addition, the group chairs meet regularly with the director and senior leadership of the NCI—collectively known as the "Cabinet." The Cabinet is an important forum in which to establish ways to work together to advance the goals of the NCI director, to accelerate the development of cancer research, and to remove potential barriers going forward. But, of course, NCTN and the group trials that it funds don't exist in a vacuum. They exist in a community-wide competition with clinical trials funded by other entities—with the pharmaceutical and biotech industries being the largest. The NCTN groups have a vision that our trials need to be cutting edge, so we need the most advanced and effective drugs to be in the mix. NCTN provides an important avenue for the groups to access these drugs and include them in our trials, particularly in less common

diseases where industry trials could be lacking. Bringing effective treatments faster to cancer patients is really our main mission.

**Dr. Kostakoglu:** *Talking about that very topic, in a 2021 presentation at the European Society for Medical Oncology, NCTN leadership, including you, reported that NCI-funded randomized trials have generated substantial gains in life years for cancer patients. Could you briefly tell us about that study? I thought the results were fascinating.*

**Dr. O'Dwyer:** This cross-group study (Clinical and scientific impact of National Cancer Institute: Sponsored clinical trial network group treatment trials. *Ann Oncol.* 2021;32[suppl 5]:S1102–S1110) was initiated by SWOG investigators, and we need to give credit to the actual person who did the work, Joseph Unger, PhD, MS, from the Fred Hutchinson Cancer Research Center (Seattle, WA). The analysis systematically reviewed the survival impact of randomized phase 3 trials funded by NCI from 1980 through 2019. Over the past 40 years, adults in the United States diagnosed with cancer gained 14 million years of additional life thanks to the results of cancer clinical trials conducted by the NCTN. Furthermore, more than 80% of the studies influenced care recommendations and formal guidelines. These results strikingly affirm the importance of doing this type of collective research that contributes significantly to the health care system. Dr. Unger's findings are all the more important in this time of increasing costs of clinical research. The return to the American people of government-funded investment in better cancer care has been remarkably solid—a huge impact.

**Dr. Kostakoglu:** *These are amazing results. One last (but not least) issue is unnecessary treatment. Your co-chair at ECOG-ACRIN, Mitchell Schnall, MD, PhD, coined the phrase "one man's cure is another man's overtreatment." How do we bring value to targeted treatments and avoid overtreatment? And, of course, could we use molecular imaging as a complementary prognostic or predictive marker?*

**Dr. O'Dwyer:** Absolutely. The imaging studies in the MATCH trial that we have talked about have real potential to identify populations that are more or less likely to respond. Another recently proposed study would assign risk factors to some cancer patients based on genomic features. There are data to indicate that you can identify high-risk patients using genomic techniques. But imaging features can also be exploited, because they do not always overlap with the genomic features. The idea is to identify patients at the highest risk and initiate appropriately aggressive treatment strategies. With this approach, we could also decrease the number of patients subjected to unnecessary treatments.

This approach to overtreatment dovetails with the need to question the intensity of some therapies being used. ECOG-ACRIN led the definitive Trial Assigning Individualized Options for Treatment (TAILORx), which showed in 2018 that most women with early breast cancer do not benefit from chemotherapy. TAILORx also provided unequivocal evidence supporting the clinical utility of an assay to risk stratify women, leading to changes in NCCN and other treatment guidelines globally.

Within ECOG-ACRIN, multiple active studies are incorporating imaging to be able to stratify risk groups for proper treatment options. I think this type of strategy is going to have important patient outcome implications. You know, ECOG-ACRIN is unique among cooperative groups in that we are charged with developing advanced imaging trials for the NCI's NCTN. This is one of several goals for our expansive Imaging Committee, which is the hub for imaging scientists to engage with the group. The specialty

groups under this committee explore experimental imaging science, immunooncology, quantitative imaging, and radiomics.

Imaging scientists in ECOG-ACRIN develop and conduct trials for early evaluation of new imaging agents and approaches, as well as plans for their broader application, in collaboration with our 12 cancer-type-oriented therapeutic committees. These studies are developed with the help of our Cancer Research Advocates Committee. You know, for a patient who has just been diagnosed with cancer, the idea of decreasing the intensity of care can be frightening—and makes them very hesitant about being part of this type of clinical trial. So there's a complexity here that we're learning about, and our advocates are guiding us in developing ways to help patients understand and partner in this sort of research.

**Dr. Kostakoglu:** *A closing personal question. Being such a busy person, how do you strike a balance between your family life and work schedule? It's probably very difficult.*

**Dr. O'Dwyer:** It really is. But I have tremendous support from the best team of people that I have ever worked with. I'm only half of the leadership of ECOG-ACRIN. The other half is Dr. Schnell, group co-chair of ECOG-ACRIN and chair of the Department of Radiology at the University of Pennsylvania. Mitch is obviously a

real expert, not just in the imaging field but also in health systems and precision medicine. So it isn't as hard to be organized as one would think. It's very important to be grounded in patient care, because, really, that's where the rubber hits the road. Being too far from patients can lead to unrealistic expectations. Again, this is all collaborative, and it's really a joy and a privilege to be able to work in this setting, both from the perspective of ECOG-ACRIN and the University of Pennsylvania, where I work and collaborate. I also have the good fortune to be married to Naomi Haas, MD, a genitourinary (GU) oncologist, also at the University of Pennsylvania, and co-chair of the ECOG-ACRIN GU Committee. Our mutual understanding of the clinical and research requirements and deadlines makes flexibility essential but allows us also to have a life away from these demands.

**Dr. Kostakoglu:** *It has been a truly great pleasure talking to you. We have covered myriad exciting topics. And thanks so much again for your time and willingness to share your valuable perspectives.*

**Dr. O'Dwyer:** Not only do I thank you so much for reaching out but also hope this discussion will be of interest to the readership.

**Dr. Kostakoglu:** *Thank you so much again for your valuable contribution.*