FROM THE CO-CHAIRS

PETER J. O’DWYER, MD (LEFT), AND MITCHELL D. SCHNALL, MD, PhD
MAY 2019

Our semi-annual meetings are such a hive of urgent interactions, it can be difficult to catch all the activities that one might wish to. This can be especially true of some that are new or unfamiliar. For the past couple of years, we have sought to re-engage physicians, nurses, and scientists involved in the research and care of cancer patients across the trajectory of their disease. Through the resources of the ECOG Research and Education Foundation, we have supported the participation of disciplines that we have felt were under-represented. The initial example was the re-energizing of the Surgery Committee under the leadership of Drs. Charles Staley and Bruce Averbook – more about their substantial progress in a later issue.

At the recent meeting in Boston, we invited Dr. Michael Soulen to form a sub-committee of the surgery committee with a focus on Interventional Oncology, therapies focused on local diseases. Interest in this opportunity was high, and 25 interventionists assembled for the inaugural meeting. This was also attended by a wide variety of researchers with disease-specific interests. Ten concepts were discussed, and it seems likely that at least three of these will be proposed as clinical trials – an energetic and productive start. The opportunity for practice-changing studies in this arena is substantial, both in establishing the value of widely used interventions, and in defining new approaches and novel clinical settings. Correlative studies have the potential to define populations that may benefit or not, and to investigate how local therapies influence tumor biology. Such projects likely have high potential for independent funding. Please invite the participation of your interventionist colleagues who may not be aware of this activity; Dr. Soulen can be reached via email at michael.soulen@pennmedicine.upenn.edu.

In this issue, we also recognize the ground-breaking achievements of Elisabeth Paitetta, PhD, whose official role has been as Director of the Leukemia Translational Research Laboratory and the Leukemia Tissue Bank for the past 34 years, and whose retirement was recognized by a symposium in her honor at the recent EA meeting in Boston. How much more than that title has Elisabeth been to ECOG-ACRIN! It must be remembered that biological advances in cancer care often originated in leukemia research, from which they spread to influence the treatment of solid tumors. Elisabeth was the driver of sample acquisition, sample handling, application of state-of-the-art diagnostic techniques, and storage of these valuable cells for later analyses. She provided real-time diagnostic analyses to sub-type leukemia in a CLIA-approved setting, in a time-frame that could benefit the patient. She stimulated collaborative studies beyond ECOG-ACRIN, across the leukemia community, to make discoveries that empower rising generations of researchers. And beyond the leukemia samples, her influence on all aspects of tissue banking has contributed to high quality research in all of our correlative activities. We have asked Elisabeth to provide insights to us in the area of minimal residual disease (MRD), the major barrier to cure in AML and other cancers. We look forward to her continuing involvement in EA, even as she makes plans for a pied-a-terre in her native Austria, and will continue to seek her advice and wise counsel. We have been privileged in ECOG-ACRIN to have the participation of such an impactful, collegial, and dedicated colleague in our collective efforts to cure cancer.

Dr. Paitetta (center) with colleagues and friends at her retirement celebration
The clinical significance of measurable residual disease (MRD) in acute myeloid leukemia (AML): The ECOG-ACRIN experience

Elisabeth M. Paietta, PhD

The standard definition of complete remission, which is based on the finding of 5% morphologically recognizable leukemic blasts in the bone marrow by light microscopy, was the first attempt to use the level of persistent disease after treatment as a predictor of overall response. When it became apparent that morphologic evaluations were not sensitive and specific enough to detect residual disease eventually leading to relapse, various methodologies were introduced to better assess the quality of response. Initially, the term Minimal Residual Disease (MRD) was used to represent these submorphologic disease levels. More recently, we have come to understand the many aspects which determine MRD levels, including: (1) the methodology of MRD assessment; (2) the selection of peripheral blood versus bone marrow, sample quality, and uneven distribution of MRD in the marrow; (3) the timing of MRD assessments during treatment; (4) the clinically relevant level of MRD with various therapies, and 5) the association of MRD with pre-therapeutic prognostic factors, in particular, genetic aberrations. As a result, MRD now stands for Measurable Residual Disease, appreciating the dynamic quality of MRD levels.

The ECOG-ACRIN Leukemia Committee has retrospectively studied MRD for its clinical significance in two trials of AML. E2906 compared standard 7ET3 daunorubicin and cytosine arabinoside induction chemotherapy with clofarabine in patients 60 years or older in the hope that the purine nucleoside antimetabolite would yield comparable outcome with less toxicity. Disappointingly, the study was suspended early because of inferior overall survival (OS) with clofarabine (p=0.003). The ECOG-ACRIN Leukemia Translational Research Laboratory was able to determine MRD by flow cytometry at the time of complete hematologic remission (CR) in a fraction of patients. A level of 0.1% detectable blasts in the marrow defined MRD positivity. Irrespective of therapy, 40% of patients were MRD negative at CR. When analyzed by treatment arm, MRD status affected outcome only in the clofarabine arm. While patients who remained MRD positive after clofarabine did extremely poorly (worse than MRD positive patients after standard induction), MRD-negative remitters did not fare significantly differently whether they were treated with standard therapy or clofarabine. These results suggest that intensive postremission therapy would be necessary in patients who remain MRD positive after clofarabine treatment.

The second trial was E1900 in AML patients 17-60 years old. In this comparison of induction intensification, the higher dose of daunorubicin (90mg) resulted in superior OS when compared to standard-dose daunorubicin (45mg) in combination with standard cytosine arabinoside (p=0.003). While one third of patients were MRD negative at the time of CR, irrespective of daunorubicin dose, MRD negative patients after the higher daunorubicin dose had significantly better OS than MRD negative patients after the standard dose (p=0.05). On the other hand, MRD-positive remitters did equally poorly irrespective of induction intensity. This observation suggests that the response after 90mg daunorubicin was of better quality than that after the 45mg dose. In an extension of this study, we found that patients with intermediate-risk genetics who were MRD negative at CR had OS indistinguishable from MRD-negative favorable risk patients. In both genetic risk groups, MRD positivity at CR significantly reduced OS. On the other hand, MRD status had no effect on outcome in the unfavorable genetic risk group. These data indicate that within each conventional risk category, MRD status provides independent prognostic information.
Linda Arn is the Senior Lead Auditor in ECOG-ACRIN Cancer Research Group's Audit and Quality Control Program. She co-chairs the Southeast Minnesota Chapter of the Society of Clinical Research Associates (SOCRA), and previously served as a member of SOCRA's Board of Directors as well as its Communications Chair.

What are clinical research associates (CRAs) and how do they contribute to successful clinical research programs?

Clinical research associates, or clinical research professionals (CRPs), cover many different roles. There is no “typical” CRA. There are regulatory CRAs, nurse CRAs, and pharmacist CRAs. Some of the research coordinators I meet have master’s degrees in nursing. Some have PhDs, and some have been physicians in other countries but have not taken their US board exams. I also meet people who start straight out of high school and train on the job, so the title encompasses a wide variety of people.

Clinical research associates are the staff who analyze patient charts and confirm their eligibility for trials. CRAs answer questions, ensure test schedules are followed, and record patient data in a timely manner. CRAs are the bread and butter of clinical research programs.

What are the responsibilities of CRAs and what might an average day look like?

There is never an average day. A CRA might not finish whatever he or she planned to do at the beginning of the day because, as the day goes along, a patient matter might arise. There might be someone who has an adverse event, and then the CRA must complete adverse event reporting. There is no such thing as a typical day, but generally, CRAs are doing patient follow-up and ensuring they are being treated appropriately. Regulatory specialists process amendments and verify that consent forms are up-to-date. Some coordinators are also responsible for ordering drugs – there are numerous tasks and responsibilities for CRAs.

How did you become involved in clinical research?

I started out at Mayo Clinic working with dialysis and kidney transplant patients, but eventually needed a break from that. I knew I wanted a job in research because I think clinical trials are so important – how do we know if something is or is not going to work unless we try it? I accepted a position as the Lung Coordinator at North Central Cancer Treatment Group and stayed there for some time. Eventually, I moved toward auditing because I like teaching, and I feel an important aspect of the audit is teaching.

I have been Lead Auditor at ECOG-ACRIN for a number of years now, and really enjoy my work interacting with the sites – seeing how they work and getting a sense of the whole picture. By the way, my plans were to become a home economics teacher following high school. Due to unforeseen circumstances, my plans changed and I have found my niche in oncology clinical trials.

Can you talk a little bit about the Society of Clinical Research Associates (SOCRA) and your work there?

I got involved with SOCRA years ago, when it was just coming into being. SOCRA was started by oncology CRAs, but its membership has diversified greatly since those days. It is a more universal group now, encompassing all therapeutic areas. Today, SOCRA has 15,600 members and 12,000 of those are certified, which is an impressive number. There are more than 50 chapters and over 40 educational programs, including one specifically for oncology.

SOCRA’s International Certification Program is particularly valuable because it creates a standard of knowledge, education, and experience by which CRAs become recognized as Certified Clinical Research Professionals (CCRP®). Since CRAs come from such varying backgrounds, this certification helps ensure we all have the same fundamental understanding of ethical conduct in clinical trials.

I believe in SOCRA because before it existed, CRAs didn’t have a voice. Many people were doing the same job but didn’t know it. SOCRA gave us a platform.

What is something you would like others to know about clinical research associates and your work?

We are very passionate about our work. We care – about the patients and about the data we are submitting. CRAs are a caring group of people.
ROISIN CONNOLLY NAMED YOUNG INVESTIGATOR OF THE YEAR

Roisin M. Connolly, MBCh, MD, recently of Johns Hopkins University, is the recipient of the 2019 Young Investigator Award, the highest mentorship honor from the ECOG-ACRIN Cancer Research Group (EA). The award recognizes Dr. Connolly's contributions as an active member of the EA Breast Cancer Committee and study chair for E2112, the randomized phase III trial of endocrine therapy plus entinostat or placebo in patients with hormone receptor-positive breast cancer. She also leads the NCI-MATCH (EAY131) trial's Arm J, evaluating the pertuzumab-trastuzumab combination therapy in patients with HER2-aberrant cancers.

"Dr. Connolly is a highly accomplished young investigator and her achievements over the past 11 years, since she joined EA as a first-year fellow at Johns Hopkins, exemplify the spirit of the Young Investigator Award," says Antonio C. Wolff, MD (Johns Hopkins University), chair of the EA Breast Cancer Committee.

To learn more about Dr. Connolly, watch the tribute video.

"It was such an honor and great surprise to receive the Young Investigator Award," says Dr. Connolly. "The many years spent developing and conducting the E2112 trial have been an invaluable learning experience for me, with more still to come. I am so grateful to have worked with the E2112 team who continue to work tirelessly and with great professionalism behind the scenes to help me in this effort, and for the mentorship provided by Drs. Joe Sparano, Kathy Miller, and many others."

Dr. Wolff: "The 600-patient E2112 trial faced a crowded drug development setting, especially after the FDA approval of palbociclib, and was difficult to accrue at first. Roisin diligently worked with the EA Communications team to develop a comprehensive media outreach strategy, including social media, and applied 'elbow grease' by interacting directly with investigators around the country. In view of her efforts, E2112 successfully completed accrual and is ongoing."

Kathy D. Miller, MD (Indiana University), agrees: "Dr. Connolly is the epitome of physician investigators. She took the lead on E2112 from the early concept stage, persisting through three reviews by the NCI Breast Cancer Steering Committee to gain its approval. She guided negotiations with the NCI Cancer Therapy Evaluation Program (CTEP), the FDA, and Syndax, the drug manufacturer, to a compromise trial design. She preserved the ability to determine the impact of entinostat on overall survival (critical to CTEP) while maintaining the potential for accelerated approval based on progression-free survival (important to Syndax). Roisin's calm demeanor and respectful comments frequently brought the group together and she ultimately prevailed."

The award recognizes Dr. Connolly's research contributions beyond E2112. She is a productive investigator in the Translational Breast Cancer Research Consortium. She has co-led or led preoperative clinical trials, like TBCRC 008, testing chemotherapy with the HDAC inhibitor vorinostat in high-risk early breast cancer. In January, she reported in the Journal of Clinical Oncology the primary results of TBCRC 026 (PMID 30721110), which demonstrated the strong negative predictive value of PET imaging to predict response to pertuzumab-trastuzumab therapy. Dr. Connolly co-directed the Developmental Therapeutics Program at Hopkins. She is PI of the NCI's Experimental Therapeutics Clinical Trials Network (ETCTN) phase I trial 9844, (NCT02453620), developed based on preclinical data from her Hopkins collaborators.

Dr. Wolff: "Roisin is a caring individual, an excellent physician, a critical thinker, a skilled grant and manuscript writer, and an effective communicator. She brings people together. I have watched her skillfully organize various team members and their individual agendas in multidisciplinary collaborations within Hopkins and across institutions to successfully design, implement, and ultimately report biospecimen-intensive, laboratory-based, clinical translational research projects."

After more than a decade at Hopkins, Dr. Connolly has taken a new academic position at the University College Cork and Cork University Hospital in Ireland. She will continue to lead study E2112, and she has joined Cancer Trials Ireland, an EA Main Member institution since 2009. She will continue her activities with EA and help increase the portfolio of investigator-initiated and cooperative group trials in Ireland.
NEWS IN BRIEF

Is something new or noteworthy happening at your institution? Send your updates to support@ecog-acrin.org and we will do our best to include them in an upcoming issue.

2019 ECOG-ACRIN PAUL CARBONE, MD FELLOWSHIP AWARD RECIPIENT ANNOUNCED

Mehrdad Hefazi Torghabeh, MD of Mayo Clinic received this year’s Paul Carbone, MD Fellowship Award. This award is a one-year research grant that aims to develop and promote excellence in clinical trials leading to improvements in cancer care. His project will focus on developing a novel therapeutic approach for patients with graft-versus-host disease. Watch this video to learn more about Dr. Hefazi and his work.

ECOG-ACRIN LEADERS ON THE MOVE

Jennifer R. Eads, MD of the University of Pennsylvania has replaced Selina M. Luger, MD on the Principal Investigator Committee. At Penn, Dr. Eads is the physician lead for GI clinical research and an associate professor of clinical medicine.

Lecia V. Sequist, MD of Massachusetts General Hospital has replaced Susanna Lee, MD, PhD on the Principal Investigator Committee. At Mass General, Dr. Sequist directs the Center for Innovation in Early Cancer Detection. She is also the Landry Family Associate Professor of Medicine at Harvard Medical School.

Edmund C. Lattime, PhD of Rutgers, The State University of New Jersey has been appointed chair of the Lab Science and Pathology Advisory Committee (LabSAC). He previously served as co-chair of LabSAC and succeeds Stanley R. Hamilton, MD in this new role. Dr. Lattime holds several leadership positions at the Cancer Institute of New Jersey and the Robert Wood Johnson Medical School.

F. Stephen Hodi, MD of Dana-Farber Cancer Institute and S. Vincent Rajkumar, MD of Mayo Clinic have both been named inductees of OncLive’s 2019 Giants of Cancer Care® recognition program. Dr. Hodi is a member of ECOG-ACRIN’s Melanoma Committee and Dr. Rajkumar chairs EA’s Myeloma Committee.

SPRING GROUP MEETING PRESENTATION ON IMPLEMENTATION SCIENCE NOW AVAILABLE

During the Combined Session for Cancer Control and Survivorship, Patient-Reported Outcomes, Health Equity, and Cancer Care Delivery Research, Wynne E. Norton, PhD delivered a presentation on implementation science. View the presentation now.

Dr. Norton serves as program director for the Implementation Science Team in the Office of the Director in the Division of Cancer Control and Population Sciences at the NCI.

GET IN TOUCH WITH THE EA AUDIT TEAM

The ECOG-ACRIN Audit Program is a key component of the Group’s Quality Assurance efforts. Yet, the process can be at times confusing and challenging. The ECOG-ACRIN Audit group has created an email address to provide an easy way for EA sites to ask audit-related questions.

Please use the AskEAudit@ecog-acrin.org email address to ask questions related to the EA audit process, the Clinical Trial Management Branch (CTMB) audit guidelines, or EA Audit work practices.

SAVE THE DATE: ECOG-ACRIN FALL GROUP MEETING IS OCTOBER 24 – 26 IN FORT LAUDERDALE, FLORIDA

Mark your calendar to attend the ECOG-ACRIN Fall 2019 Group Meeting, October 24 – 26 at the Fort Lauderdale Marriott Harbor Beach Hotel in Fort Lauderdale, Florida. Connect with colleagues and learn the latest in basic, clinical, and translational research. The meeting website will open later this summer with additional details, and registration will open in mid-August.

For those planning further ahead, the Spring 2020 Group Meeting will take place April 29 – May 1 (Wednesday – Friday) in Baltimore, Maryland.