INTERNATIONAL THYROID ONCOLOGY GROUP

Fall 2017

'Welcome to Dur'm, y'all!'

The 11th Annual ITOG meeting was held at the Washington Duke Inn in Durham, North Carolina, hosted by ITOG member Dr. Julie Ann Sosa from Duke University. The agenda included transdisciplinary groundbreaking research from endocrinologists, oncologists, surgeons, pathologists, epidemiologists, basic and translational scientists, and environmental scientists from ITOG, Duke, and the National Institutes of Health (NIH). The 82 attendees from as far away as Australia and Italy heard about the latest clinical trial updates, and the first 'town hall' provided an opportunity for brainstorming about the future directions of ITOG. Meeting presentations were broken into five sessions covering important topics in thyroid cancer research and treatment, including Signaling, Advanced & Anaplastic Cancer, and Clinical Trials. Dr. Keith Bible from the Mayo Clinic and Dr. Maria Cabanillas from MD Anderson Cancer Center led a panel discussion and first ITOG debate about "Genomic tumor interrogation of thyroid cancers: Research tool, clinical tool, or both?" Several speakers also highlighted the patient perspective in advanced thyroid cancer clinical trials.

Dr. Julie Ann Sosa

To the delight of sports fans (and a few hobbyists) amongst the ITOG membership, the intensive science was punctuated by a springtime baseball game (the Durham Bulls beat the Buffalo Bisons 3-0!) and a tour of the Cameron Indoor Stadium and the Duke Basketball Museum led by Dr. Georgia Beasley, a member of the Duke Basketball Hall of Fame and now a member of Duke's surgery faculty. Members not only made it to the floor of Cameron and the locker rooms, but several took to the courts to shoot some hoops; check out Dr. Sherman in action! Dr. Matthias Gromeier from Duke University delivered the second annual Rick Abrams Memorial Lecture; his research around "Immunotherapy Strategy with Recombinant Poliovirus" uses a re-engineered poliovirus to attack cancer cells, initiating a secondary antitumor immune response. Dr. Sam Wells, an endocrine surgeon who started his career at Duke and who became a leader in the effort to develop vandetanib for the treatment of advanced medullary thyroid cancer, received the Jean Vicks Inspiration Award for his lifetime of service to ITOG and the thyroid cancer community.

The Annual Meeting offers an opportunity for ITOG members to get to know each other and to share cutting-edge science, facilitating opportunities for innovation and discovery with new colleagues. It is a time to reflect, to be inspired, and to forge novel collaborations across disciplines and even countries. We are already looking forward to our next Annual Meeting, which will be hosted by Dr. Wendy Sacks and Dr. Andrew Gianoukakis at UCLA in Los Angeles, CA in the spring of 2018.

ITOG Leadership Updates


Dr. Manisha Shah

The Board of Directors has elected Dr. Manisha Shah to a three-year term as the new Chair of ITOG. Dr. Shah currently serves as ITOG Secretary, Co-Chair of the Protocol Committee and has been on the Executive Committee for three years. She previously served as Chair of the Membership Committee and, along with her colleague Dr. Matthew Ringel, hosted the 2012 ITOG Annual Meeting at Ohio State University where she is a professor of Internal Medicine in the Division of Medical Oncology. Dr. Shah was the lead investigator for ITOG's first clinical trial, the results of which were recently published in the prestigious Journal of Clinical Oncology. Not only does Dr. Shah have outstanding clinical, research and publishing experience, she has been involved with ITOG since the beginning and has served in several leadership roles. One of Dr. Shah's greatest attributes is her infectious enthusiasm for the mission of ITOG. Dr. Shah will assume the role as Chair at the 2018 Annual Meeting at UCLA. At that time, current Chair Dr. Lori Wirth will continue to serve on the Executive Committee for one year. Dwight Vicks was reelected as ITOG Treasurer.

ITOG recognized the outstanding service of four Board members who completed their terms at the Duke Annual Meeting: Dr. Michael Demeure, a surgical oncologist at the Hoag Family Cancer Institute; Dr. Rossella Elisei, an endocrinologist at University of Pisa, Italy; Dr. Yuri Nikiforov, a pathologist at the University of Pittsburgh Medical Center; and Dr. Mike Tuttle, and endocrinologist at Memorial Sloan-Kettering.

Four members of ITOG were elected to serve a three-year term on the Board: Dr. Elizabeth Grubbs, a surgical oncologist at MD Anderson Cancer Center; Dr. Alan Ho, an oncologist Memorial Sloan-Kettering; Sareh Parangi, a surgical oncologist at Harvard Medical School; and Dr. Gregory Randolph, a surgical oncologist at Massachusetts Eye and Ear Infirmary.

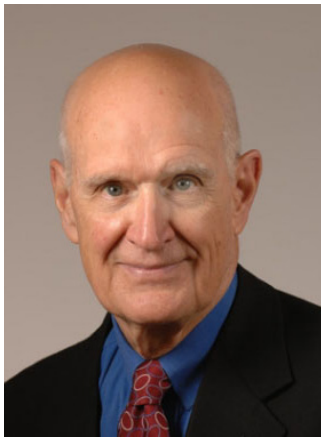

Dr. Elizabeth Grubbs


Dr. Alan Ho


Sareh Parangi


Dr. Gregory Randolph

Dr. Samuel Wells, Jr. honored with Jean Vicks Inspiration Award


Dr. Samuel Wells, Jr.

When Dr. Robert "Bob" Gagel assembled the founding members of ITOG, he said, "We need Sam Wells to run this." The timing was perfect. Dr. Samuel Wells, Jr. had recently stepped down from leading the American College of Surgeons Oncology Group (ACOSOG) when he agreed to serve as ITOG's first Executive Director. Dr. Wells had the experience and foresight to establish the appropriate organizational structure to support ITOG's mission. He met with the National Institutes of Health (NIH), Congress and Contract Research Organizations (CRO) and, with this critical support network in place, established ITOG as a stand-alone clinical trials organization. He brought his passion for medullary thyroid cancer, experience as a clinical investigator and respect as a leader in the field to create the solid foundation that anchors ITOG today. Dr. Wells has been the principal investigator for many pivotal clinical trials, including the development of caprelsa (vandetanib) as the first targeted therapy approved for medullary thyroid cancer patients.

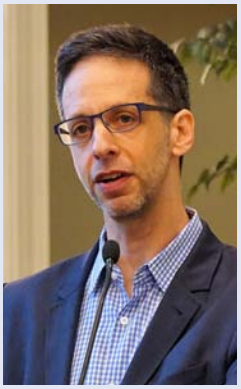
The ITOG Board created the Jean Vicks Inspiration Award to honor those that make extraordinary contributions to its success. The namesake, Jean Vicks, was one of the inspirations for creating ITOG. The award has been given only once before to Elizabeth and Michael Ruane. Dwight Vicks and ITOG Protocol Chair Dr. David Pfister presented this honor to Dr. Samuel Wells, Jr. at the 2017 ITOG Annual Meeting at Duke. Dr. Pfister spoke of how Dr. Wells remains one of the most highly respected investigators and how his work is among the most significant in advancing the field of thyroid oncology.


Jean Vicks

Robert F. Gagel Discovery Award


Dr. Robert Gagel

Dr. Gagel is a founding member of ITOG and tireless advocate for thyroid cancer patients and research. In honor of his contributions to ITOG and advances in thyroid cancer treatment, the ITOG established a grant to further the development of novel treatments for thyroid cancer.


Dr. Yariv Houvras

The inaugural recipient of this two-year award was Dr. Yariv Houvras, a medical oncologist and scientist at Weill Cornell Medical College in New York City. At the ITOG Annual Meeting at Duke University in April 2017, Dr. Houvras presented a progress report on this award, which he is using to examine the effects of kinase inhibitors on thyroid and vascular endothelial cells. Using zebrafish models, scientists from Dr. Houvras' lab are examining the FDA approved kinase inhibitor, lenvatinib, to better understand the precise mechanism of its action. As Dr. Houvras explained, "a major advantage of the zebrafish model is the ability to visualize thyroid cells in a living organism, and to study the effects of the drugs that we use in clinic. By doing this in a whole organism we can see effects on blood vessels and thyroid cells."

The ITOG Committee for Correlative Sciences, chaired by Dr. James Fagin, has now received applications for the second Robert F. Gagel ITOG Discovery Award. This committee will review the numerous research proposals submitted by ITOG members, including preclinical studies, mechanism-based correlative studies of thyroid cancer clinical trials, and proposals for resources to assist in the identification of subjects for ITOG-sponsored clinical trials. An announcement of the second grant recipient will be made at the Annual ITOG Meeting in 2018.

Clinical Trials

Thyroid cancer is the most common endocrine neoplasm and the incidence continues to rise worldwide. For many patients, standard therapy is effective for achieving long-term survival. Unfortunately, patients who develop aggressive or recurrent disease represent a considerable therapeutic challenge, thus the search for novel treatment strategies for these difficult cases remains a key component of ITOG's mission. ITOG has partnered with pharmaceutical companies and other cancer groups in a concerted effort to make headway in finding a path forward for these aggressive tumor types. Below, please find a brief description of ITOG's active clinical trials efforts.

Phase 1 study of LOXO-292 in patients with RET mutations and rearrangements

Rearranged during transfection (RET) is activated by mutation or rearrangement in diverse cancer types. Point mutations in RET account for approximately 60% of medullary thyroid cancer (MTC). RET fusions have been identified in approximately 2% of non-small cell lung cancer, approximately 10-20% of papillary thyroid cancer, and a subset of other cancers. Several multikinase inhibitors (MKIs) exist in the clinic with anti-RET activity, such as cabozantinib and vandetanib, yet the potency of the RET inhibition is limited by off-target toxicities, suggesting potential for a RET-specific kinase inhibitor to offer clinical benefit. Loxo Oncology has developed a potent and selective investigational new oral drug (LOXO-292) now in clinical development for the treatment of patients with cancers that harbor abnormalities in RET. LOXO-292 was demonstrated to show selective inhibition of RET activity with minimal action on highly related kinases, good oral bioavailability and favorable pharmacokinetic properties in animal models, making it a highly promising new therapeutic candidate.

Dr. Lori Wirth, ITOG Chair

Loxo Oncology has partnered with ITOG to evaluate LOXO-292 in a global, multi-center, open label, phase 1 trial in adult patients with advanced solid tumors. This is a first-in-human trial designed to evaluate the safety, tolerability, pharmacokinetics and preliminary anti-tumor activity of LOXO-292. Eligible patients will have MTC, RET-fusion non-small cell lung cancer, advanced solid tumor harboring a RET gene alteration, and other cancers expressing elevated RET activity. This trial is currently recruiting at multiple institutions with a plan to enroll more than 100 patients overall.

Additional information related to the trial can be found at https://clinicaltrials.gov/ct2/show/NCT03157128. For questions related to the trial, please contact Dr. Lori Wirth, Massachusetts General Hospital, at lwirth@mgh.harvard.edu.

Phase 2 trial of lenvatinib for the treatment of anaplastic thyroid cancer

Anaplastic thyroid cancer (ATC) is a rare form of thyroid cancer, accounting for 1-2% of all diagnoses. While ATC is rare, it is one of the most aggressive solid tumors. Treatment of ATC is difficult due to its aggressiveness and because ATC cancer cells develop resistance to conventional chemotherapy agents. This is a single-arm, open label phase 2 trial investigating a potential treatment for ATC with lenvatinib; an oral targeted therapy that

inhibits multiple tyrosine kinases involved in cancer cell growth and spread. Lenvatinib is FDA-approved for the treatment of RAI-refractory differentiated thyroid cancer, and it is hoped that lenvatinib may also offer an effective therapy for the treatment of ATC.

This trial, sponsored by Eisai Inc., is being performed in collaboration with ITOG. There are currently 22 active sites internationally. Eligible patients will have confirmed histological diagnosis of ATC and no prior treatment with lenvatinib or other tyrosine kinase inhibitors.

Additional information related to the trial can be found at https://clinicaltrials.gov/ct2/show/NCT02657369. For questions related to the trial, please contact Dr. Lori Wirth, Massachusetts General Hospital, at lwirth@mgh.harvard.edu.

Radioactive iodine (RAI) in combination with placebo or selumetinib for the treatment of recurrent or metastatic thyroid cancers

This is a randomized, double-blind Phase 2 trial evaluating the effectiveness of selumetinib, compared to placebo, to enhance uptake of radioactive iodine (RAI) in patients with recurrent or metastatic thyroid cancer of follicular cell origin. Many thyroid cancers absorb iodine. Because of this, RAI is a key therapy for patients with metastatic thyroid cancer, yet many patients have tumors that do not adequately concentrate RAI, leading to diminished clinical efficacy of RAI treatment. Studies indicate that abnormal mitogen-activated protein kinase (MAPK) activation suppresses RAI uptake in thyroid cancers, a process that can be reversed with drugs, such as selumetinib, which selectively inhibit this pathway. In this study, we will test whether administration of selumetinib in conjunction with RAI treatment can increase absorption of RAI, thus providing a more effective way to treat these cancers.

Eligible patients must have confirmed RAI-avid, progressive thyroid carcinoma of follicular origin, including papillary, follicular, or poorly differentiated subtypes. Patients who meet all eligibility criteria will be randomized to treatment with selumetinib versus placebo prior to RAI. Tumor and blood samples will also be analyzed for markers that may predict which patients could benefit from this strategy as well as provide information on how MAPK signaling contributes to RAI resistance. This clinical trial is sponsored by the Academic and Community Cancer Research United (ACCRU) and plans to enroll 100 patients. There are currently 9 actively recruiting sites in the United States.

Additional information related to the trial can be found at https://clinicaltrials.gov/show/NCT02393690. For questions related to the trial, please contact Dr. Alan Ho, Memorial Sloan-Kettering Cancer Center, at hoa@mskcc.org.

Immunotherapy in combination with VEGFR multikinase inhibition

This 2-arm phase 2 trial is in late stage development and will investigate the potential for immunotherapy checkpoint inhibition to potentiate the benefits of vascular endothelial growth factor receptor (VEGFR) multikinase inhibition in patients with progressive RAI-refractory differentiated thyroid cancer. This study will be sponsored by the Academic and Community Cancer Research United (ACCRU) and the European Organization for Research and Treatment of Cancer (EORTC), and will open at 6 ITOG institutions in the US and 5 in Europe. Stay tuned!

For questions related to the trial, please contact Dr. Bryan Haugen, University of Colorado, at Bryan.Haugen@ucdenver.edu.

Cabozantinib as salvage therapy for patients with differentiated thyroid cancer

The first clinical trial orchestrated by ITOG has been completed, marking a major achievement for the group. This phase II trial, led by Dr. Manisha H. Shah from Ohio State University, found that patients who had progression of their thyroid cancer on a vascular endothelial growth factor receptor (VEGFR) inhibitor could benefit from treatment with cabozantinib. Dr. Shah is elated with the results of the trial: "I am thrilled to share that we have achieved an important milestone in the history of ITOG. Our first ITOG multicenter trial of cabozantinib was a huge success; it showed results that are practice-changing and that we can apply to our patient's treatments right away." This work was recently published in the Journal of Clinical Oncology, one of the premier oncology journals.

Thyroid cancers are classified on the basis of histology, and differentiated thyroid cancer (DTC) accounts for approximately 90% of patients. Traditional treatments for DTC include surgery, radioiodine (RAI), and suppression of thyroid stimulating hormone with levothyroxine, yet there are limited strategies if these approaches fail. RAI-refractory disease represents a major therapeutic challenge, yet some recent success has been achieved with VEGFR inhibitors, including sorafenib and lenvatinib, which are oral multikinase inhibitors approved for RAI-refractory DTC. Unfortunately, for those patients whose cancers are resistant to these VEGFR inhibitor treatments, there are no approved therapies. Correlative studies have found that the tyrosine kinase receptor cMET is implicated in facilitating resistance to VEGFR inhibitors, which is where cabozantinib comes into play. Cabozantinib is an oral multikinase inhibitor that targets cMET in addition to VEGFR, and it has been FDA approved for use in the treatment of medullary thyroid cancer. Due to the promising activity demonstrated in a phase I study, it was hypothesized that cabozantinib would be an effective treatment option for patients with DTC who progressed on first- or second- line VEGFR targeted therapy.

Of the 25 eligible patients enrolled in this phase II, single-arm trial, an impressive 40% showed a partial response, indicating that cabozantinib can be used in 2nd or 3rd line therapy in patients whose cancers progress after first line VEGFR-targeted therapies. The median progression-free survival and overall survival were 12.7 months and 34.7 months, respectively. Cabozantinib was generally well tolerated; the most common treatment-related adverse events were fatigue, weight loss, diarrhea, hand-foot syndrome, and hypertension. To our knowledge, this is the first trial evaluating the use of a multikinase inhibitor specifically after first-or second-line failure of prior VEGF-targeted therapy.

ITOG's first clinical trial (NCT01811212) was conducted at six institutions (Massachusetts General Hospital, Mayo Clinic Jacksonville, Medstar Georgetown University Hospital, Ohio State University, University of Chicago Medical Center, University of Texas MD Anderson Cancer Center) by ITOG investigators. The study was coordinated by the Academic and Community Cancer Research United (ACCRU) and was partially funded by the Cancer Therapy Evaluation Program (CTEP) of the National Cancer Institute (NCI), a peer-reviewed federally sponsored group. Additional funding for the clinical trial and correlative science was provided by ITOG, which is a 501(c)(3) tax-exempt public charity. Besides its direct impact of establishing a new treatment option for our patients, this trial demonstrated that collaboration between these groups is feasible, paving the way for future such trials to be conducted. The completion of this trial is one crucial step towards fulfilling the mission of ITOG's founding members to design, coordinate, and prioritize state-of-the-art clinical trials to catalyze a cure for thyroid cancer.

ITOG

YOU CAN HELP.

ITOG is a 501(c)-3 corporation funded by philanthropy. You can help catalyze a cure for thyroid cancer by donating at www.itog.org/donation or contact Dwight Vicks at dwight@itog.org.