“Welcome to the Golden State”

The 11th Annual Meeting of the International Thyroid Oncology Group convened April 27-29 in Los Angeles, hosted by Dr. Wendy Sacks of Cedars Sinai Medical Center and Dr. Andrew Gianoukakis of the University of California, Los Angeles (UCLA). This stimulating scientific meeting drew upon experts in cancer research to collaborate, network, and share their exciting research findings and ideas.

Meeting presentations were divided into eight sessions covering important topics in thyroid cancer research and treatment, ranging from Thyroid Cancer Genomics & Signaling to Onco-Metabolism & Tumor Environment. Presentations on neural regulation of the cancer genome and the role of the microbiome in cancer progression gave attendees a fresh perspective on current cancer treatment strategies. ITOG members presented their data on active clinical trials and basic science research. Additionally, invited faculty from around the world provided their insights and experiences to stimulate further discussion and potential future directions for thyroid cancer research. ITOG was delighted to host Dr. Akira Miyauchi, President and COO of Kuma Hospital in Kobe, Japan and Dr. Young Kee Shong from the Asan Medical Center in Seoul Korea. These esteemed professors discussed their work on the management and active surveillance of thyroid micro-carcinoma, respectively.

This was ITOG’s first meeting on the west coast. Attendees who arrived early enjoyed a visit to the Getty Center, where they could catch up while absorbing art, innovative architecture and the impressive grounds, all with incredible views of Los Angeles. Midway through the scientific sessions, Professor David Meyer, President and Chief Executive Officer of Los Angeles BioMedical Research Institute, took attendees on an inspiring and personalized tour of the innovative UCLA campus.

In the third annual Rick Abrams Memorial Lectures, ITOG welcomed Professor Dennis Slamon. He is chief of the Division of Hematology/Oncology and executive vice chair for research for UCLA’s Department of Medicine. Dr. Slamon presented his well-known and highly regarded research that led to the development of the breast cancer drug Herceptin, which targets the HER2 mutation, found in about 25 percent of breast cancer patients. ITOG also welcomed Professor Clive Svendsen of Cedars Sinai Medical Center, who discussed using stem cells to model thyroid hormone cell transporter deficiency in children.

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 colleagues. It is a time to reflect, to be inspired, and to forge novel collaborations across disciplines and even countries. We look forward to our 2019 Annual Meeting, which will be hosted by Protocol Chair David Pfister, his colleagues at Memorial Sloan Kettering as well as ITOG colleagues at other institutions located in New York City.
New ITOG Leadership Positions Announced

Professor of Internal Medicine in the Division of Medical Oncology and Section Chief of Endocrine Medical Oncology at the Ohio State University Comprehensive Cancer Center, Dr. Manisha Shah initiated a 3-year term as the role of Chairperson at the 2018 Annual Meeting. The Board of Directors elected Dr. Sareh Parangi to succeed Dr. Shah as ITOG Secretary. Dr. Parangi is a surgical oncologist at the Harvard Medical School, a member of the ITOG Board, serves on the ITOG Finance Committee and recently won the Robert F. Gagel Discovery Award (see announcement in this newsletter).

Dr. Eric Sherman, an oncologist at Memorial Sloan-Kettering (MSK), was elected as the Co-Chair of the Protocol Committee serving alongside current chair and colleague at MSK, Dr. David Pfister, whose term expires next May. Dr. Sherman joins the ITOG Executive Committee with this appointment. Dr. Sherman has been an active participant in the ITOG Protocol Committee, he has presented at numerous ITOG Annual Meetings and is currently leading the ITOG/Alliance trail for Hürthle Cell Carcinoma (refer to Clinical Trials section of newsletter for more details).

ITOG Members also elected Dr. Naifa Busaidy as the newest member of the Board of Directors. Dr. Busaidy is an endocrinologist at the University of Texas, MD Anderson Cancer, has been involved in ITOG for six years, and serves on the Website and Communications Committee. The ITOG community is fortunate to include these effective members and looks forward to benefiting from their continued efforts.
**ITOG and REACT Forge a New Partnership**

The REACT (Research Education Action Cancer Thyroid) Foundation is a 501(c)(3) public charity, dedicated to creating awareness for thyroid cancer and raising funds to support research for new treatment options. ITOG and REACT recently joined forces to specifically focus on finding treatments for medullary thyroid cancer (MTC).

Michelle LeBeau founded REACT in 2011 after battling MTC for two years. There is no known cure for this rare and aggressive cancer and few treatment options exist for patients. Considerable progress has been made recently and promising treatments are on the horizon, thus it is critical for doctors and scientists to have adequate funding for performing rigorous research and conducting clinical trials. Michelle was inspired to make a difference and started a non-profit with those goals in mind. After Michelle passed away from MTC, her mother, Donna LeBeau, and her sister, Kimberly Caplea, have run the organization in her honor.

The fifth annual REACT “Wine and Dine on the Rooftop” event was held on July 28th in Chicago, IL and it was a huge success. ITOG researcher Dr. Lori Wirth, who shared recent advancements in treating MTC, inspired participants. The total funds coming to ITOG amount to $250,000 and will be designated for MTC research. The turnout and support for Michelle’s cause that was demonstrated so warmly at this fundraiser was a true testament to the wonderful young woman that she was.

ITOG is elated to have partnered with REACT. REACT continues to have a strong base of supporters and the REACT name and mission will remain, but will be managed by ITOG going forward. Our concerted efforts can help realize Michelle’s goal of catalyzing better treatment options - and eventually a cure - for MTC.

**Robert F. Gagel Discovery Award**

Dr. Gagel is a founding member of ITOG and a tireless advocate for thyroid cancer patients and research. In honor of his invaluable contributions to ITOG and advances in thyroid cancer treatment, a grant was established in his name to further the development of novel treatments for thyroid cancer. After a selective peer-review process, the 2017 Robert F. Gagel ITOG Discovery Award was granted to Dr. Sareh Parangi, MD, a highly accomplished endocrine surgeon at Massachusetts General Hospital and Harvard Medical School in Boston. She focuses her clinical efforts on endocrine surgery and applies her basic science knowledge and expertise to tumor progression in thyroid cancer.

At the ITOG Annual Meeting at UCLA, Dr. Parangi presented a progress report on this award. In her talk, titled “The role of myeloid-derived suppressor cells in the response to targeted therapies in advanced thyroid cancer,” she described progress to date on ways in which immune therapies can be combined with molecularly targeted therapies to help patients with advanced thyroid cancer. In the last few years, attention has focused on how cancers evade the human immune system and the development of immunotherapies to help a patient’s immune system detect and destroy cancer cells. These strategies typically employ a combination therapy designed to target both the tumor and the immune response. This approach has led to remarkable patient survival stories in various cancer types.

However, resistance to immunotherapy has also been observed, and identifying indicators of response and mechanisms of resistance is urgently needed to design rational combination therapies that might circumvent resistance. The overall goal of Dr. Parangi’s work is to harness the power of the immune system to treat advanced and aggressive thyroid cancers. Dr. Parangi is optimistic about her progress and states “Our ITOG supported work sheds light on another layer of treatment strategy for drug resistant thyroid cancers”. She will use the Gagel funds to develop blood markers that may indicate if a particular patient is having a strong antitumor immune response. Developing new blood tests and laboratory models will enable researchers to assess specifically how patients’ immune cells are responding to a specific therapy.

The ITOG Board of Directors is very excited about these advancements and the ITOG community looks forward to following the progress of this groundbreaking work.

Photo: left to right, Kimberly Caplea (Michelle LeBeau’s sister, REACT leader), Donna LeBeau (Michelle LeBeau’s mother, treasurer of REACT), and Lori Wirth (former ITOG chair) attend the annual “Wine and Dine on the Rooftop” event.
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. Patients who develop aggressive or recurrent diseases 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.

Collaborative ITOG and Alliance trial to optimize treatments for Hürthle cell thyroid cancer patients

Hürthle cell thyroid cancer represents about 5% of all differentiated thyroid cancers. While most thyroid cancer studies group Hürthle cell, papillary, and follicular thyroid cancers together, research indicates that Hürthle cell thyroid cancers are genetically distinct from papillary and follicular thyroid cancers. To date, prospective clinical trials have not evaluated therapies specifically for Hürthle cell thyroid cancer.

In a concerted effort to find optimal treatment strategies for Hürthle cell thyroid cancer, ITOG is elated to join forces with the Alliance for Clinical Trials in Oncology foundation. Alliance develops and conducts clinical trials with promising new cancer therapies and utilizes rigorous science to develop robust treatment and prevention strategies for cancer. This collaborative trial, Alliance A091302, is a randomized phase 2 study of sorafenib with or without everolimus in patients with radioactive iodine refractory Hürthle cell thyroid cancer. Alliance and ITOG researchers will assess the efficacy of using everolimus along with sorafenib tosylate versus sorafenib tosylate alone in treating patients with advanced radioactive iodine Hürthle cell refractory thyroid cell cancer. Researchers will determine whether the combined therapy will increase shrinkage of thyroid cancer and prevent tumors from growing, or whether it causes more side effects than sorafenib tosylate alone.

This is a randomized study for patients with metastatic Hürthle cell thyroid cancer for whom radioactive iodine is ineffective. Participants will be randomized to either receive sorafenib alone or sorafenib in combination with the study drug, everolimus. If a patient receives sorafenib alone and the tumor starts to progress while on the drug, they can “cross-over” and receive everolimus alone.

This trial is based on a phase 2 study of sorafenib and everolimus in patients with metastatic thyroid cancer. In the previous investigation, nine patients had Hürthle cell thyroid cancer and seven of them had major responses to the combination. Preclinical data with Hürthle cell thyroid cancer suggest that the pathway targeted by everolimus is important for this type of tumor to grow.

Eligibility includes RAI-refractory progressive Hürthle cell thyroid cancer, no prior sorafenib use - the use of other tyrosine kinase inhibitors such as lenvatinib is permitted - good performance status, and healthy liver and kidney function.

The study is currently recruiting patients at Memorial Sloan Kettering Cancer, Mayo Clinic, Ohio State, University of Michigan, and Massachusetts General Hospital. Additional information related to the trial can be found at https://clinicaltrials.gov/ct2/show/NCT02143726. Please contact Eric Sherman (646-888-4234, shermane@mskcc.org) with any questions about the study.

Combination therapy for progressive, radioiodine-resistant differentiated thyroid cancers

This two-arm, phase 2 trial will investigate the potential for immunotherapy check-point inhibition to potentiate the benefits of vascular endothelial growth factor receptor inhibition in patients with progressive RAI-refractory differentiated thyroid cancer. Researchers will assess the effectiveness and safety of this combination therapy for treating patients with differentiated thyroid cancer that has spread to other places in the body or has come back and cannot be removed by surgery. This two-pronged therapy includes the immune checkpoint blocker
pembrolizumab, to stimulate the immune system to attack the cancer, and the multikinase inhibitor lenvatinib, to interfere with the ability of tumor cells to grow and spread.

The phase 2 trial has been open for approximately 6 months. There are two cohorts in the study, with plans to enroll 30 patients each. Currently, there are 11 patients enrolled in cohort 1, in which patients with progressive radioiodine-refractory differentiated thyroid cancer are administered with the combination therapy. These patients have not been previously treated with either drug or any multikinase inhibitor. There are 6 patients enrolled in cohort 2, in which pembrolizumab is administered to patients who have progressive disease on lenvatinib, which is the standard-of-care treatment for these patients.

We have 6 sites currently enrolling patients: University of Colorado Cancer Center, Massachusetts General Hospital, University of Michigan Cancer Center, MD Anderson Cancer Center, Memorial Sloan Kettering Cancer Center, and Los Angeles Biomedical Research Institute at Harbor-UCLA Medical Center. Two additional sites will be open soon, including University of California San Diego Cancer Center and Ohio State University Comprehensive Cancer Center.

This study is sponsored by the Academic and Community Cancer Research United (ACCRU) network in collaboration with the National Cancer Institute (NCI).

Additional information related to the trial can be found at https://clinicaltrials.gov/ct2/show/NCT02973997. For questions related to the trial, please contact Dr. Bryan Haugen, University of Colorado, at Bryan.Haugen@ucdenver.edu.

**ITOG partners with Loxo Oncology to test a potent RET-inhibitor**

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. 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 oral drug (LOXO-292) now in clinical development for the treatment of patients with cancers that harbor RET abnormalities. ITOG has partnered with Loxo Oncology 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.

This study started in May of 2018 and has enrolled 82 patients harboring either RET-fusions or point mutations. Thus far, LOXO-292 has proven to be a potent and selective RET-inhibitor, with effective anti-tumor activity across RET-altered cancers and minimal adverse effects. Patients with varied tumor types have responded quickly and robustly to treatment and most patients have stayed on therapy and remain enrolled in the study. Remarkably, LOXO-292 shows efficacy regardless of starting dose, RET-fusion partner, or prior therapies.

The trial is currently recruiting patients at 38 study locations and plans to enroll more than 100 patients. Eligible patients have medullary thyroid cancer, RET-fusion non-small cell lung cancer, advanced solid tumor harboring a RET gene alteration, and other cancers expressing elevated RET activity.

[Dr. Bryan Haugen and Jena French PhD, principal investigators]
Combination therapy 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 are testing 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 RAI-avid thyroid carcinomas 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 given with standard 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 60 patients. There are currently 9 actively recruiting sites in the United States: MSKCC, DFCI, Mayo, MDACC, OSUCCC, UCSD, UC Colorado, Medstar Georgetown, Hoag Cancer Center and soon opening at Vanderbilt.

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.

A New Influential Advocate for ITOG

Reality TV celebrity, author, entrepreneur, and star of the Real Housewives of New York City Jill Zarin learned about ITOG when her husband Bobby’s thyroid cancer returned two years ago. Unfortunately, Bobby succumbed to the disease this past January, but not without a courageous fight. Jill was by Bobby’s side throughout their 18 years of marriage and was instrumental in coordinating his care with several ITOG physicians and his extensive team.

Jill has advocated for ITOG by asking those to honor Bobby by supporting ITOG, and by including ITOG in her Luxury Luncheon for the second consecutive year. The Luxury Luncheon was held in the Hamptons in July and is a showcase for entrepreneurs, some of Jill’s products, and several of Jill’s numerous admirers. Proceeds from the charity event will help develop better treatments for patients like Bobby. The members of ITOG are extremely grateful for Jill’s support.