ITOG INTERNATIONAL THYROID ONCOLOGY GROUP

Fall 2015

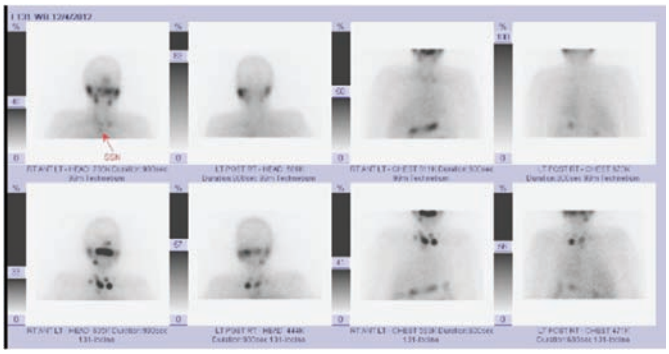
Update on ITOG Selumetinib Trial

Dr. Alan Ho

The selumetinib clinical trial led by Dr. Alan Ho of Memorial Sloan Kettering Cancer Center in New York, NY is now open. The trial evaluates the effectiveness of selumetinib to enhance uptake of radioactive iodine (RAI) for treatment of advanced thyroid cancer. This is a large, multicenter, investigator-initiated, randomized, placebo controlled Phase II trial of selumetinib in patients with RAI-avid, recurrent or metastatic thyroid cancer of follicular cell origin.

Radioiodine is a key therapy for patients with metastatic thyroid cancer of follicular origin, yet many patients have tumors that do not adequately concentrate RAI, leading to diminished clinical effectiveness. Laboratory studies first suggested that aberrant mitogen-activated protein kinase (MAPK) activation suppresses RAI uptake in thyroid cancers, a process that can be reversed with drugs that selectively inhibit this pathway. This observation led ITOG members Dr. Jim Fagin and Dr. Alan Ho to clinically test the idea that blocking MAPK signaling with the MEK1/2 inhibitor selumetinib (AstraZeneca) can restore RAI incorporation in RAI-refractory thyroid cancers. The initial clinical trial of 20 patients established that this approach could enhance RAI uptake and efficacy in a subset of patients. This encouraging work was published in the February 14th, 2013 issue of the New England Journal of Medicine and is the basis for this larger clinical trial of 94 planned patients with RAI-avid disease.

This is ITOG's second clinical trial and is coordinated by the Academic and Community Cancer Research United (ACCRU). It is funded in part by AstraZeneca as well as generous philanthropy donated to ITOG. To participate, patients must have recurrent and/or metastatic thyroid cancer with at least one tumor that still takes up RAI. Patients who meet all eligibility criteria will be randomized to treatment with selumetinib versus placebo, administered twice daily for 4 weeks. RAI therapy will be given concomitantly with placebo or selumetinib during the fourth week of treatment, after which all therapy is discontinued and patients are monitored for response. Additionally, tumor and blood samples will be analyzed for markers that may predict which patients may benefit from this strategy as well as shed further light on how MAPK signaling contributes to RAI resistance.



RAI uptake enhanced with MAPK inhibition on whole body scan. ITOG's selumetinib trial will investigate the potential for selumetinib to improve efficacy of RAI.

If you are interested in participating in the trial, please contact one of the study centers listed below:

Location	Site Name	Date Active	PI	PI Phone	PI Email
US, California	UC San Diego Moores Ca Ctr	Planned 11/2015	Gregory Daniels	858-822-5378	gdaniels@ucsd.edu
US, District of Columbia	MedStar Washington Hospital Ctr	7/8/15	Kenneth Burman	202-877-2749	kdb35@georgetown.edu
US, Massachusetts	Dana-Farber/Mass General	10/26/15	Lori Wirth	617-643-4971	lwirth@partners.org
US, Minnesota	Mayo Clinic	9/22/15	Mabel Ryder	507-284-2511	ryder.mable@mayo.edu
US, New York	Memorial Sloan Kettering Ca Ctr	7/22/15	Alan L. Ho	646-888-5334	hoa@mskcc.org
US, North Carolina	Duke University Med Ctr	7/15/15	Julie Ann Sosa	919-684-8239	julie.sosa@duke.edu
US, Ohio	Ohio State University Med Ctr	7/2/15	Jennifer Sipos	614-293-0003	jennifer.sipos@osumc.edu
US, Texas	M D Anderson Ca Ctr	7/15/15	Ramona Dadu	713-792-2841	rdadu@mdanderson.org

ITOG Leadership Expands

The Board of Directors has elected Dr. Lori Wirth as the new chair of ITOG. She will serve a three-year term. Dr. Wirth previously chaired the Protocol Committee, the group responsible for selecting ITOG clinical trials, and also served as ITOG Secretary. Dr. Wirth is the Medical Director of the Center for Head and Neck Cancers at Massachusetts General Hospital. Dr. Manisha Shah, an oncologist at Ohio State University, joins the Executive Committee as the newly elected ITOG Secretary. Dr. Shah was previously chair of the Membership Committee and served on the Protocol Committee, all while opening ITOG's first clinical trial. The ITOG Board expanded the Executive Committee to include the Chair of the Protocol Committee.

Chair Dr. Wirth, Secretary Dr. Manisha Shah, and Drs. Bob Gagel and Andrew Gianoukakis at the Annual Meeting

Protocol Chair Dr. David Pfister

Dr. David Pfister was elected the Protocol Chair. Dr. Pfister previously chaired the Nominating Committee and the Anaplastic Cancer Task Force. He is Chief of the Head and Neck Oncology Service at Memorial Sloan Kettering in New York, NY.

Board member Dr. Julie Ann Sosa

Dr. Julie Ann Sosa, Chief of Endocrine Surgery at Duke University, was elected as the newest member of the ITOG Board of Directors. She succeeded Dr. Robert Smallridge, who completed an outstanding two terms on the Board and still serves as the Chair of the Finance Committee.

Chair Dr. Lori Wirth and Annual Meeting host Dr. Sebastiano Filetti recognize the outstanding leadership of outgoing Chair Dr. Steve Sherman.

ITOG recognized the exceptional leadership of its outgoing chair, Dr. Steve Sherman, at the Annual Meeting. Dr. Sherman's vision of a more formal organizational structure for ITOG was successful in bringing greater involvement from ITOG membership, which nearly tripled during his tenure to the current roster of 70 of the best scientists and physicians focused on thyroid cancer. Moreover, ITOG initiated its partnership with Academic and Community Cancer Research United (ACCRU), fully accrued its first clinical trial, opened its second clinical trial, and improved cooperation with our international colleagues under his leadership. Dr. Sherman was one of the original founders of ITOG and previously contributed his many talents as Treasurer, Secretary and Board member. Beyond all of these significant achievements, Dr. Sherman has been an innovator, leading by example as an endocrinologist who performed clinical trials with novel systemic therapies at MD Anderson Cancer Center. Dr. Sherman will remain on the Executive Committee for one more year.

A Truly International Annual Meeting

Dr. Sabastino Filetti and Dr. Martin Schlumberger, the outstanding hosts of the Annual Meeting

For the first time in ITOG history, the Annual Meeting was held in Europe. ITOG members Dr. Sebastiano Filetti and Dr. Martin Schlumberger hosted an exceptional two-day gathering at Sapienza Università di Roma in Rome, Italy, where Dr. Filetti is a member of the faculty. The inspiring agenda was complete with presentations of groundbreaking research, the latest results from clinical trials, and innovative approaches employed in other cancer diagnoses that could be translated for thyroid cancer research. Dr. Thomas Giordano gave an extremely informative talk on the molecular characterization of thyroid cancer from The Cancer Genome Atlas (TCGA) effort, a description of which can be found on the ITOG website (www.itog.org). The presentations were split between the US and European members and included special guests from Sapienza Università di Roma and Institut Gustave Roussy in Paris, France.

Gathering in Rome demonstrated the commitment of ITOG to working closely with international members. The venue also provided the opportunity for the leadership of ITOG, ACCRU and EORTC to meet, share their capabilities with ITOG membership and to strengthen collaboration with EORTC. One unifying goal is to open ITOG trials on both sides of the Atlantic.

Drs. Filletti and Schlumberger not only organized an exciting scientific program, they extended a most warm welcome to ITOG members able to make the trip to Italy. The overwhelming participation and attendance at the Annual Meeting is a testament to its value, and fosters the collaborative culture that ITOG has developed. ITOG members Dr. Bryan Haugen and Dr. Rebecca Schweppe at the University of Colorado in Denver will host the 2016 Annual Meeting. The ITOG Annual Meeting has become the "Go To" meeting in the field of thyroid cancer.

Philanthropy Exceeds $2.5 Million

Support for the ITOG mission continues to grow with generous contributions from even more supportive donors. Most donations have come from patients, and families of patients, with thyroid cancer who believe that the multi-disciplinary team of ITOG physicians are making a significant difference in improving the treatment of the most challenging thyroid cancers. ITOG received its single largest donation of $500,000 in 2014 from an anonymous donor. Many of ITOG's member physicians and scientists have also donated to support the organization. Future plans for use of these philanthropic funds not only include an expanded clinical trials portfolio, but support for innovative pilot projects to be initiated by ITOG member researchers, focusing on laboratory research efforts that could lead to future practice-changing clinical trials.

Additional funds have come from charitable events. TA Realty held its annual golf tournament and designated ITOG as the charitable beneficiary for the third consecutive year. This event has contributed over $230,000 to ITOG from hundreds of participants and the continued generosity of Elizabeth and Michael Ruane, recipients of the highest ITOG honor, The Jean Vicks Inspiration Award. Attendees of the TA Realty event were particularly moved by heart-felt remarks from Hürthle cell cancer survivor Elizabeth Ruane. She shared how ITOG member physicians Daniels, Randolph, Tuttle and Wirth have provided her with excellent and compassionate care throughout her cancer journey. "We decided that supporting ITOG was of upmost importance because of the collaborative nature of the organization and the caliber of the physicians that were involved. Great minds working together to help those with thyroid cancer." ITOG Chair Lori Wirth and Treasurer Dwight Vicks were on hand to share the many exciting activities of ITOG and to extend sincere thanks to the Ruane family and the over 350 participants of this inspiring event.

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Would you like to help?
Please visit our website www.itog.org
or contact Dwight Vicks at dwight@itog.org

ACCRU
Academic and Community Cancer Research United

Preliminary Findings of ITOG's First Clinical Trial

Dr. Manisha H. Shah

Preliminary results of the first clinical trial initiated by ITOG have been evaluated, marking a major accomplishment for ITOG. The goal of this multi-institution clinical trial, led by Dr. Manisha H. Shah from Ohio State University, is to examine whether patients who had progression of their thyroid cancer on a VEGFR inhibitor benefit from treatment with cabozantinib. Dr. Shah reported the initial findings this October at the 15th International Thyroid Congress in Lake Buena Vista, Florida. The abstract of her talk was titled: Cabozantinib in Patients with Radioiodine-Refractory Differentiated Thyroid Cancer Who Progressed on Prior VEGFR-Targeted Therapy: Results of NCI- and ITOG-sponsored multicenter phase II clinical trial.

This investigator-initiated clinical trial is truly a collaborative endeavor and every site has participated actively in the process. These efforts have facilitated an impressive timeline in which it took less than two years from the initiation of the clinical trial, October 2013, to full enrollment in January of 2015. The 25 patients enrolled in the trial are divided fairly evenly among the participating cancer centers. A total of five patients are enrolled at Ohio State University Comprehensive Cancer Center and the remaining 20 patients are at Massachusetts General Hospital (4 patients), Mayo Clinic Florida (4 patients), MD Anderson Cancer Center (5 patients), University of Chicago (6 patients), and Medstar Washington Hospital Center (1 patient).

NCI9312/OSU12154/RU241210I is an open label, phase II trial to determine whether patients with radioiodine-refractory, differentiated thyroid cancer (DTC), who progressed on first-line therapy with a VEGFR antagonist, benefit from treatment with cabozantinib. ITOG's mission is to catalyze a cure for thyroid cancer and this clinical trial is coordinated by the Academic and Community Cancer Research United (ACCRU) and is funded by Cancer Therapy Evaluation Program (CTEP) of National Cancer Institute (NCI), a peer-reviewed federally sponsored group. Additional funding for the clinical trial and correlative science is provided by ITOG, which is a 501(c)(3) tax-exempt public charity.

Cabozantinib is an oral multikinase inhibitor targeting several angiogenic proteins such as VEGFR, PDGFR, c-met, as well as RET kinase. The Food and Drug Administration of United States recently approved cabozantinib for patients with progressive medullary thyroid cancer. ITOG is testing this drug for its use in a 2nd line setting for patients with differentiated thyroid cancer who progress on first line VEGFR targeted therapy. Given that c-met may be critical in causing failure of VEGFR targeted therapy, cabozantinib is chosen for testing in 2nd line setting due to its unique activity against c-met. During the trial, the study drug will be administered orally once daily until cancer progression or intolerance. The study will also examine if this drug is effective against bony metastasis.

More information related to the trial is available at http://clinicaltrials.gov/ct2/show/NCT01811212?term=cabozantinib+in+thyroid&rank=2 For questions related to the trial please contact Manisha H. Shah, MD at 614-293-4680 or manisha.shah@osumc.edu.

ITOG Scientists Outline Benchmarks for Correlative Studies in Next Generation Thyroid Cancer Clinical Trials

ITOG is dedicated to improving the survival and quality of life among patients with thyroid cancer. As part of that mission, the Correlative Sciences Committee of the ITOG has thoughtfully developed a position statement regarding the need for robust correlative studies in thyroid cancer clinical trials to further improve the care of patients with this disease. Correlative science is used to reveal relationships between molecular biomarkers, such as changes in genes and proteins, and clinical outcomes. While meaningful advances have been made in treating metastatic and progressive thyroid cancers, it is evident that there is a need for less toxic and more effective treatments. The Correlative Sciences Committee outlines several key points in establishing strategies to coordinate efforts in achieving this goal.

One central issue raised in the position statement is that it is currently difficult to predict which patients are most likely to benefit, or suffer severe side effects, from a given therapy. The development of improved treatments will be enhanced if investigators are able to obtain correlative data at the time of drug initiation, tumor response, and escape/tumor progression. These data will facilitate studies to elucidate mechanisms of drug action and resistance and inform the development of thoughtfully designed clinical trials and individualized therapies. There is also a need for the development and validation of less invasive markers of tumor responses to enable collection of these correlative data. Acquiring tumor tissues from serial biopsies, along with the determination of plasma drug levels and surrogate markers in non-tumor tissues, may be shown to correlate with clinical outcomes providing insight into the drug interaction with the target.

Finally, the Correlative Sciences Committee stresses that clinical trials should be designed to not only assess outcomes and toxicities of a particular treatment, but should also clarify why a particular treatment is or is not effective in different subsets of patients. This additional insight ultimately increases therapeutic progress. The position statement encourages cooperation among funding agencies, researchers, physicians and patients in achieving this common goal of improved outcomes, reduced therapeutic toxicities and increased years of productive life.

The position statement was recently published in the Journal of Clinical Endocrinology & Metabolism and the full text is available at http://press.endocrine.org/doi/pdf/10.1210/jc.2015-2818. Please contact Matthew D. Ringel, MD for more information: matthew.ringel@osumc.edu.