

## 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.

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## Initial 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+thyr...> For questions related to the trial please contact Manisha H. Shah, MD at 614-293-4680 or [manisha.shah@osumc.edu](mailto:manisha.shah@osumc.edu).

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**Categories:**

[Patient Care](#)

## **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 utmost 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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**Categories:**

[Philanthropy](#)

## Leadership within ITOG Expands



Recognizing Dr. Sherman's leadership

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.

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.

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.

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.

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### **Categories:**

[Education](#)

## ITOG Scientists Outline Important Research Benchmarks

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](mailto:matthew.ringel@osumc.edu).

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**Categories:**

[Research](#)

## **Cabozantinib impact on thyroid tumor shrinkage**

Dr. Manisha Shah, ITOG investigator, discusses the impact of cabozantinib on thyroid tumor shrinkage. Watch the video here:

<http://bit.ly/1H4Xw6O>

Click [here](#) for the video.

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## A Truly International 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](http://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. Filetti 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.

### **Posted:**

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## **Clinical trial of a very well tolerated drug for an uncommon form of thyroid cancer**

The drug Pioglitazone (Actos) is being used in a clinical trial for thyroid cancers that contain a specific mutation called PAX8-PPARgamma. PAX8-PPARgamma is uncommon, but is found in some thyroid cancers of the following types: follicular; follicular variant of papillary; and poorly differentiated.

An exciting aspect of this trial is that pioglitazone has few if any side effects, and in fact it is FDA-approved for the long term therapy of diabetes. The only potentially significant side effects are mild fluid retention and mild weight gain. The drug is specific for PAX8-PPARgamma and is not expected to work in other thyroid cancers.

The clinical trial investigators will test the patients' original tumor specimens for PAX8-PPARgamma. The thyroid cancer must be progressing and not treatable by surgery or radioiodine.

There are 5 participating sites: University of Michigan (Ann Arbor), U Colorado (Denver), Ohio State U (Columbus), MD Anderson (Houston), and U Pennsylvania (Philadelphia). The principal investigator is Ronald Koenig, MD, PhD, University of Michigan.

The trial requires 3 visits to a participating site over 6 months. Patient travel money is available.

Additional information about the trial is available at [clinicaltrials.gov](http://clinicaltrials.gov):

<https://clinicaltrials.gov/ct2/show/NCT01655719?term=NCT01655719&rank=1>

If you are interested in participating please contact: Timothy Muth, 734-615-8914, [tmuth@med.umich.edu](mailto:tmuth@med.umich.edu).

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## Molecular characterization of thyroid cancers reported at ITOG Annual Meeting



Thomas GiordanoThe 2015 ITOG International Meeting was recently held in Rome, Italy, where Dr. Thomas Giordano presented the lead talk on a new comprehensive analysis of thyroid cancer from The Cancer Genome Atlas (TCGA) Research Network, a federally funded project to elucidate the molecular characterization of various cancer types. Dr. Giordano's findings are extremely important to the thyroid cancer community and will potentially change the way thyroid cancers are classified and diagnosed. Further, the identification of new markers of aggressive tumors could allow for better targeting of tailored treatments to individual patients.

Thyroid cancer incidence has increased three-fold over the last 30 years. While the tumors are often slow-growing and easily treated with a combination of surgery, radioactive iodine, and thyroid hormone, a subset of patients will develop more aggressive and deadly thyroid cancers. Until recently, the classification of papillary thyroid carcinoma (PTC) as benign or malignant relied on surgery to remove some or all of a patients' thyroid, even if there was an 80% chance that the cancer would not develop.

Dr. Giordano, Professor of Pathology at the University of Michigan Medical School, was the project co-lead for TCGA thyroid cancer analysis along with Dr. Gad Getz, director of Cancer Genome Computational Analysis at the Broad Institute of MIT/Harvard. In this study, published in *Cell*, October 2014, the authors performed a comprehensive molecular characterization of papillary thyroid carcinomas from 496 patient samples to identify all of the genetic mutations that play a role in cancer progression. They found several new cancer drivers, as well as new variations of existing genes and, in doing so, identified markers of aggressive tumors.

One interesting observation from the study is that the thyroid cancer genome is relatively "quiet", with fewer genetic mutations than in other common cancers, possibly explaining why the disease is generally slow to progress. Fewer mutations enabled researchers to highlight the key signaling pathways involved in driving thyroid tumors. Prior to this study, the percentage of PTC with no known oncogenic drivers was approximately 25%, making diagnosis and treatment relatively broad in scope. This exhaustive approach uncovered the genetic drivers of more of these cancers, whittling the number of unknown genetic drivers down to 3.5 percent.

The oncogenic drivers can be pared down to two primary groups: *BRAF V600E* and *RAS* mutant-PTCs. Interestingly, within these two primary groups, in particular the *BRAF* group, numerous different subtypes of thyroid cancer exist. To date, thyroid cancers associated with *BRAF*, for example, had been grouped in the same category, yet this study revealed additional layers of genetic diversity and found that certain subtypes of *BRAF*-mutated thyroid cancers are associated with higher risk and less differentiated cancers. This impressive study described the genomic landscape of thyroid cancer at a refined molecular level and will serve as a springboard for critical discussions in the thyroid community. One initial recommendation is for researchers and pathologists to consider reclassifying thyroid cancer based on molecular signatures to better reflect their underlying behavior. Reclassifying the disease based on genetic markers, while difficult, could situate thyroid cancer patients to benefit from more precision-based therapies. This new information will also help physicians separate those patients who need aggressive treatment from those whose tumor is never likely to grow or metastasize. This diagnostic refinement could have widespread impact as a large number of patients receive indeterminate diagnoses on their nodules each year.

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### Categories:

[Research](#)

## ITOG Trial #1 Completes Enrollment

The first clinical trial initiated by ITOG in the fall of 2013 has completed its planned enrollment, 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. [L1L1] [SEP1SEP1]

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 to full enrollment. 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).

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Twenty-five patients are currently undergoing treatment and it is anticipated that analysis of the primary outcomes and will be completed in the next 6 months.

More information related to the trial is available

at <http://clinicaltrials.gov/ct2/show/NCT01811212?term=cabozantinib+in+thyroid&rank=2> [L1L1] [SEP1SEP1] For questions related to the trial please contact Manisha H. Shah, MD at 614-293-4680 or [manisha.shah@osumc.edu](mailto:manisha.shah@osumc.edu)

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