



WINTER 2023 NEWSLETTER

2023 ANNUAL MEETING

THE "GO TO" MEETING FOR THYROID CANCER RETURNS TO IN-PERSON

This year, ITOG's Annual Meeting returned to an in-person format at the Università Delgi Studi Di Napoli in the beautiful seaside of Naples, Italy. Hosted by Drs. Domenico Salvatore and Martin Schlumberger, 86 ITOG members united to collaborate and share the science and discoveries centered on finding a cure for advanced thyroid cancers. Drs. Mabel Ryder and Christine Spitzweg collaborated with meeting hosts and task force leaders to develop a robust agenda. The theme of the 2023 meeting was 'actionable' items that focused on new opportunities for clinical trial development within ITOG. Keynote speakers included Dr. Paolo Ascierto, who summarized the major clinical trial advances in melanoma, Dr. Ester Olandi, who introduced the use

This year's meeting was also focused on identifying and addressing clinical gaps in care. Topics of debate included comparing chemoradiation to targeted therapy for unresected BRAF-mutant anaplastic thyroid cancers (ATC), lenvatinib to dabrafenib with or without trametinib for BRAF-mutant differentiated thyroid cancers (DTC), and optimal timing of selective RET-inhibitor therapy for patients with metastatic medullary thyroid cancers (MTC). These debates highlighted gaps in current practice that the ITOG community can influence through clinical trials and multicenter registries.



Hosted by Drs.
Domenico Salvatore &
Martin Schlumberger

of radiotherapy in thyroid cancer, Dr. Isabell Borget, who provided a lecture on biostatistical strategies in the development of clinical trials, and Dr. Romana Neeta-Maier, who presented her work on reprogramming myeloid progenitors in advanced thyroid cancers.

Lastly, a myriad of clinical trial concepts was presented for management of treatment-refractory cancers. One was XL-092, a multi-kinase inhibitor monotherapy, versus its combination with nivolumab. Other trials included comparing an SGK1 inhibitor with a BRAF/MEKi in BRAF-mutant ATC, HER2-BRAF inhibitor combination in RAI R DTC, and pemetrexed -carboplatin salvage therapy. Immune focused novel options included eganelisib (PI3Ky-targeting TAMs) in combination with nivolumab.

Members from MD Anderson Cancer Center also presented a GRASSROOT study, an observation trial for ATC patients with multicenter potential. The goal is to help move one or more of these concepts into clinical trial development in the next two years. Several novel immune driven therapies, using donor killer T cells that have been engineered to target thyroid cancer specific proteins (TSH-R, ICAM-1) are in development using CAR-T technology. Novel approaches for peptide receptor radionuclide therapy (PRRT) in advanced thyroid cancers were also discussed.

The 2023 ITOG in-person and hybrid meeting addressed important care gaps, strengthened current clinical trials, and inspired new ideas with doctors and scientists across the world in ITOG's mission to find a cure for advanced thyroid cancers.

OUR MISSION

To catalyze a cure for the most challenging thyroid cancers through the collaborative efforts of our unique multidisciplinary team of leading physicians, scientists, and advocates to design, coordinate, and prioritize state-of-the-art clinical trials and correlative science.

INTERNATIONAL THYROID ONCOLOGY GROUP STATE-OF-THE-ART CLINICAL TRIALS

ITOG grew out of the need for novel treatments in advanced thyroid cancer, and was ultimately inspired by thyroid cancer patients such as Jean Vicks - a mother, a coach and an avid outdoor enthusiast. After the initial meeting in 2003, the organization was formally incepted at the inaugural



meeting in Atlanta, GA in 2006. Founding members included Drs. Robert Gagel, Samuel Wells Jr, Steven Sherman, and Mr. Dwight Vicks. Since then, ITOG's membership has grown to include prominent scientists and leading clinicians in the field of thyroid cancer.

In 2023, ITOG's membership includes 122 leading physicians, scientists, and advocates from 16 countries: Australia, Brazil, Canada, China, France, Germany, Israel, Italy, Netherlands, Saudi Arabia, Singapore, South Korea, Spain, Switzerland, United Kingdom, and United States. ITOG is organized in 12 committees and 7 task forces that work toward the common goal of finding new therapies for thyroid cancer, training the next generation of clinicians and scientists, and raising public awareness of the importance of thyroid cancer research.

Through the tireless effort and commitment of its members and advocates, ITOG has successfully completed seven clinical trials (Table 1). Three ITOG clinical trials are currently enrolling patients (Table 2).

While the focus of ITOG is centralized in the development of clinical trials targeted to find cures for progressive thyroid cancer, the creation of patient registries will critically inform the biology and clinical behavior of the disease. Among these

registries, the medullary thyroid cancer registry is led by Drs. Julie Ann Sosa and Elizabeth Grubbs; the acquired resistance to kinase inhibitors registry is led by Drs. Lori Wirth, Rory Clifton-Bligh, and Matti Gild; and the redifferentiation registry is led by Drs. Sophie Leboulleux, Lori Wirth, and Alan Ho. We are excited to report that a neoadjuvant clinical registry is in the development stages. We invite the medical community to get involved in ITOG and enjoy the expertise of this selected group of physicians, scientists and advocates who devote their efforts to finding cures for thyroid cancer. ITOG is committed to ensuring an inclusive recruitment of patients to clinical trials and strives to address inequalities inherent to geographic distribution of resources. ITOG welcomes new ideas, different outlooks, and a broad participation. Get involved!

Dr. Laura Boucai
Dr. Ashish Chintakuntlawar
Dr. David Shonka

Table 1. ITOG Completed Studies.

Name	Number	Drug	Status
The Combination Targeted Therapy With Pembrolizumab and Lenvatinib in Progressive, Radioiodine-Refractory (RAIR) Differentiated Thyroid Cancers (DTC): A Phase II Study	NCT02973997	Pembrolizumab and Lenvatinib	Completed accrual. Estimated completion 10-08-2023.
An Open-Label, Single-Arm, Multicenter, Phase 2 Trial of Lenvatinib for the Treatment of Anaplastic Thyroid Cancer (ATC)	NCT02657369	Lenvatinib	Completed. Results published ¹ .
Phase II Study of XL184 (Cabozantinib) in Combination With Nivolumab and Ipilimumab (CaboNivoIpi) in Patients With Radioiodine-Refractory Differentiated Thyroid Cancer Whose Cancer Progressed After One Prior VEGFR-Targeted Therapy	NCT03914300	Cabozantinib, Ipilimumab, Nivolumab	Completed accrual. Estimated completion 1-15-2024.
Randomized Double-Blind Phase II Study of Radioactive Iodine (RAI) in Combination With Placebo or Selumetinib for the Treatment of RAI-Avid Recurrent/Metastatic Thyroid Cancers	NCT02393690	Selumetinib	Completed accrual. Estimated completion 12-31-2023.
Phase II Study of Cabozantinib in Patients With Radioiodine-Refractory Differentiated Thyroid Cancer Who Progressed on Prior VEGFR-Targeted Therapy	NCT01811212	Cabozantinib	Completed. Results published ² .
A Phase 1/2 Study of Oral Selpercatinib (LOXO-292) in Patients With Advanced Solid Tumors, Including RET Fusion-Positive Solid Tumors, Medullary Thyroid Cancer, and Other Tumors With RET Activation (LIBRETTO-001)	NCT03157128	Selpercatinib	Recruiting. Estimated completion 9-1-2024. Some results published ³ .
Randomized Phase II Study of Sorafenib With or Without Everolimus in Patients With Radioactive Iodine Refractory Hurthle Cell Thyroid Cancer	NCT02143726	Sorafenib and Everolimus	Completed accrual. Estimated completion 8-6-2024.

Table 2. Current ITOG Clinical Trials.

Name	Number	Drug	Status
Neoadjuvant Treatment With Selpercatinib in RET-Altered Thyroid Cancers	NCT04759911	Selpercatinib	Recruiting at MD Anderson Cancer Center and University of Michigan Health System.
Restoration of Radioiodine Uptake With Selpercatinib in RET Fusion-Positive Radioiodine-Refractory Thyroid Cancer: A Phase 2 Study Performed in Collaboration With the International Thyroid Oncology Group (ITOG)	NCT05668962	Selpercatinib	Recruiting at Massachusetts General Hospital.
A Phase 1 Trial of concurrent Intensity Modulated Radiation Therapy (IMRT) and Dabrafenib/Trametinib in BRAF Mutated Anaplastic or Poorly Differentiated Thyroid Cancer	COH 21308	Dabrafenib, Trametinib, and Intensity Modulated Radiation Therapy	Recruiting at City of Hope. Soon to open at Ohio State University and MD Anderson Cancer Center.

NEW MECHANISMS OF A TYROSINE KINASE INHIBITOR:

PERICYTES ENHANCE THE INHIBITORY EFFECTS OF LENVATINIB ON ANAPLASTIC THYROID CARCINOMA CELLS

Carmelo Nucera Research Team · Harvard Medical School · Boston, Massachusetts

Anaplastic thyroid carcinoma (ATC) is a rapidly fatal cancer with a median survival of a few months. Effective, durable management of ATC will rely on an understanding of the role not only of genetics, but also of the tumor microenvironment. For example, pericytes have been shown to play a key evasive role for thyroid carcinoma cells. Although their role in ATC has not yet been clearly defined, pericytes may enhance tumor viability. Research has

shown that co-implantation of ATC cells with pericytes increases the ability of ATC to grow. Research has also shown that when ATC cells are co-cultured with pericytes, there is increased sensitivity to the drug lenvatinib, which has been shown to improve outcomes in radioiodine-refractory, well-differentiated thyroid carcinoma. This research found that lenvatinib had greater inhibitory effects on BRAF^{WT/V600E}-ATC tumor cells with greater pericytes prevalence. Therefore, the presence of pericytes and quantification of their abundance could be a crucial prognostic indicator of effective lenvatinib treatment in patients with ATC.

Thyroid. 2023;33(7):835-848.



DR. HERBERT CHEN WINNER OF THE FOURTH ROBERT F. GAGEL ITOG DISCOVERY AWARD

The Robert F. Gagel ITOG Discovery Award is named after Dr. Bob Gagel, a founding member and first President of ITOG. It grants \$100,000 to an ITOG member whose scientific proposal has direct and tangible translational implications toward developing novel and improved treatments for thyroid cancer. Dr. Herbert Chen was chosen among several outstanding applications for his work on pharmacological upregulation of SSTR2 for imaging and therapy of medullary thyroid cancer (MTC). Dr. Chen provided the following summary on his work.

On January 26, 2018, the US Food and Drug Administration approved a new method of treatment for a specific type of tumors in the stomach, intestines, and pancreas called gastroenteropancreatic neuroendocrine tumors (NETs). This method uses

radiolabeled peptides to target somatostatin receptor subtype 2 (SSTR2), a common marker in NETs. Multiple studies have shown because a thyroid NET called medullary thyroid cancer (MTC) possesses this marker, patients whose cancer cannot be removed through surgery can benefit from this new radiotherapy. However, MTC patients with low SSTR2 levels are not eligible for SSTR2-specific imaging and treatment. To overcome these difficulties, we proposed using a pharmacological compound to increase concentrations of SSTR2 receptors on thyroid NET cells. Our method uses valproic acid (VPA), a drug approved by the FDA for the treatment of seizures and bipolar disorder. By looking at tissue from MTC patients, we found that 70% of MTC cases did not have enough SSTR2 for the approved imaging method (Fig. 1A). We also



found that VPA increased the amount of SSTR2 on the surface of cancer cells (Fig. 1B). When we treated mice with VPA before imaging with a special advanced imaging technique, we greatly improved the detection of tumors and found that almost invisible tumors became detectable nodules (Fig. 1C). Based on these findings, we proposed utilizing VPA to increase the eligibility of MTC patients to receive new imaging and therapy who may not qualify for the current approved treatments.

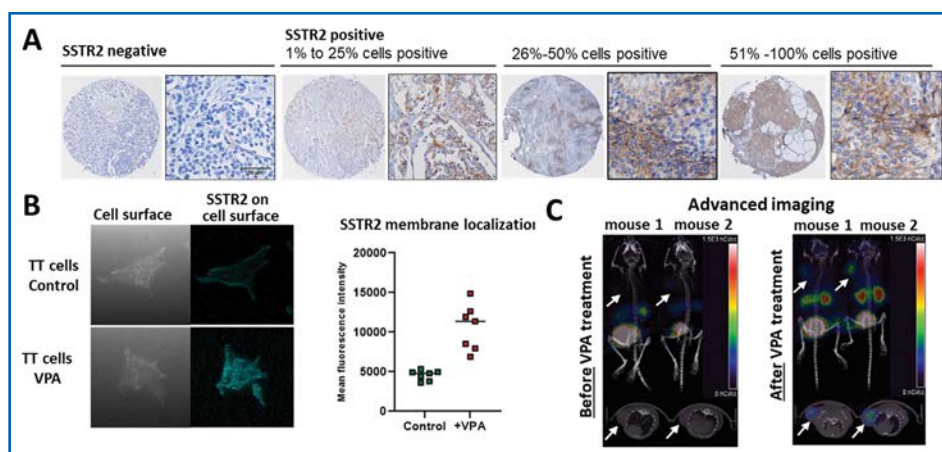


Fig. 1: SSTR2 level in MTC specimens, basal and pharmacologically induced. (A) The analysis of MTC tissues revealed differential expression of SSTR2. 70% patients were assessed as negative and 30% positive but with different level of SSTR2 concentration. **(B)** Special microscopy technique confirmed MTC – TT cell surface image and increased level of SSTR2 pharmacologically stimulated by valproic acid (VPA). **(C)** Mice implanted with NET cells under the skin developed tumors. The treatment with VPA improved tumor detection as confirmed by advanced imaging technique.

ITOG ELECTS A NEW CLASS TO THE BOARD OF DIRECTORS



CHRISTINE SPITZWEG

Dr. Christine Spitzweg is a professor of medicine and endocrinology at the Department of Internal Medicine IV, University Hospital Munich, Ludwigs-Maximilians-University (LMU) in Munich, Germany. After completing her training, she spent three years at the Mayo Clinic in Rochester, MN, as a postdoctoral research fellow, and currently holds an academic joint appointment with the

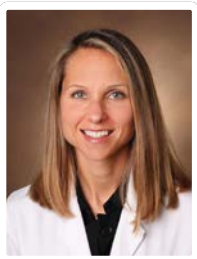
Division of Endocrinology, Diabetes, Metabolism and Nutrition, Dept. of Medicine, Mayo Clinic, Rochester, MN/USA. She is a clinical scientist with a special focus on thyroid cancer, in particular advanced thyroid cancer and endocrine oncology. Prof. Spitzweg is the director of the Interdisciplinary Thyroid Center and the co-chair of the neuroendocrine tumor center at the LMU University Hospital in Munich. Her basic research aims at investigation of the role of the sodium iodide symporter (NIS) as a novel gene as well as thyroid hormone regulation of mesenchymal stem cell biology and angiogenesis. She has chaired the research committee of the American Thyroid Association (ATA) (2011-2013), was a member of the Board of Directors of the ATA (2014-2018) and co-chair of the program committee of the ATA annual meeting in 2021 and the ITOG meeting in Naples in 2023.



LAURA BOUCAI

Laura Boucai is an Associate Member at Memorial Sloan Kettering Cancer Center and an Associate Professor of Clinical Medicine at Weill Cornell Medical College. She graduated from Universidad de Buenos Aires, completed her Internal Medicine Residency at Cornell, and her Endocrinology Fellowship at Albert Einstein College of Medicine. Her research interests include thyroid cancer

biology, specifically the genomic and transcriptomic landscape of thyroid cancer in attempt to find therapeutic strategies for the most advanced forms of the disease. Her current research efforts concentrate on describing the genomic profile of metastatic thyroid cancer and understanding the interaction between the hematopoietic system and the tumor. Dr. Boucai is an active member of the Endocrine Society, the International Thyroid Oncology Group, and the American Thyroid Association. Given her bicultural background and expertise in thyroid cancer, she has been invited to lecture at national and international meetings. She is on the editorial board of the Journal of the Endocrine Society, and she is an Associate Editor of Frontiers in Endocrinology.



LINDSAY BISCHOFF

Dr. Lindsay Bischoff is Associate Professor of Medicine in the Division of Endocrinology at Vanderbilt University Medical Center and the Medical Director of the Vanderbilt Thyroid Center and the Program Director for the Endocrine Fellowship. Her clinical practice focuses on diagnosis and treatment of thyroid cancer. She has served on the American Thyroid Association Finance committee,

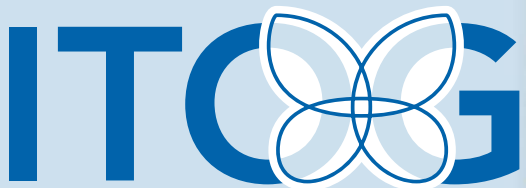
Research Grant Task Force, and has Chaired the Ethics Committee and is currently on the ATA Differentiated Thyroid Carcinoma Guidelines committee. She is Vice-Chair for the Guidelines on Thyroid Carcinoma of the National Comprehensive Cancer Network and Chair of the Publications Committee of International Thyroid Oncology Group. She serves on the editorial boards of Clinical Thyroidology and JCEM Case Reports. Dr. Bischoff completed her residency and fellowship at Thomas Jefferson University Hospital in Philadelphia and was on the teaching faculty at Sidney Kimmel Medical College at Thomas Jefferson University before joining Vanderbilt.



VICTOR BERNET

Dr. Victor Bernet is a Professor of Medicine, Mayo Clinic College of Medicine and served as Chair of the Division of Endocrinology, Mayo Clinic Florida from 2012 to 2022. Dr. Bernet served 21 years in the U.S. Army Medical Corps and retired at the rank of Colonel. He was also the Endocrinology Consultant to the Army Surgeon General and Director of the Army/Navy Endocrinology Fellowship.

Dr. Bernet's academic interests are focused in the field of thyroid nodules and thyroid cancer. Dr. Bernet served as President of the American Thyroid Association 2020-2021 and also as ATA Secretary/ Chief Operating Officer from October 2015 to November 2019. Dr. Bernet is the Mayo Clinic representative on the National Comprehensive Cancer Network guidelines and a member of the ATA Thyroid Nodules Guidelines Task Force. He has been an active ITOG member over the last decade.



We are grateful for your generosity and ask you to continue to help us catalyze a cure for thyroid cancer by donating at itog.org or contacting Dwight Vicks at dwight@itog.org.



Jean Vicks

YOU CAN HELP

DONATE NOW

When Jean Vicks learned of her metastatic thyroid cancer, she turned her fear into action. She inspired leading medical experts to create the organization known as the International Thyroid Oncology Group.