EMERGING MULTI-KINASE INHIBITORS IN ADVANCED THYROID CARCINOMA
Dear Colleagues,

It is my honor to present the 2015 Penn Otorhinolaryngology–Head and Neck Surgery Newsletter. This issue features groundbreaking advances in thyroid cancer treatment, a retrospective review of the department’s focused efforts to deintensify head and neck cancer treatment for HPV positive patients, an expanded FDA approval for TransOral Robotic Surgery (TORS), and other department developments over the past year.

The pioneering work of world-renowned researcher Marcia Brose, MD, PhD has dramatically altered the outlook for thyroid cancer patients. An Associate Professor at Penn Medicine, Dr. Brose was instrumental in the development and 2013 FDA approval of the multi-kinase inhibitor sorafenib for the treatment of metastatic and advanced RAI-refractory differentiated thyroid carcinoma. That story, and Dr. Brose’s recent research on expanded multi-kinase inhibitor treatment are reported in this issue.

TORS — a surgical approach developed at Penn Medicine — has been used in the context of diagnosed oropharyngeal squamous cell cancers (OPSCC), with a focus on HPV positive patients. In research performed at Penn, TORS has been found to be highly effective in the management of OPSCC independent of HPV status. Generally these HPV positive patients are younger, much less likely to have the traditional risk factors associated with OPSCC and much more likely to respond to treatment. Clinical trials are underway at Penn to investigate deintensified treatments including TORS in patients with OPSCC caused by p16+ human papilloma virus infection.

You will also find updates about recent and newsworthy events in this issue: developments in TORS for obstructive sleep apnea, recent expansions for our department at Penn Medicine Washington Square, the Perelman Center for Advanced Medicine and Penn Medicine University City, and new faculty profiles.

For more news about our research, objectives and future, please visit us at PennMedicine.org/ent.

Best Regards,

Bert W. O’Malley, Jr., MD
Gabriel Tucker Professor and Chair, Department of Otorhinolaryngology - Head and Neck Surgery
Associate Vice President, University of Pennsylvania Health System
Thyroid Cancer Treatment Success Continues at Penn Medicine

Marcia Brose, MD, PhD, a medical oncologist for Penn Otorhinolaryngology - Head and Neck Surgery, was among the first investigators in the world to recognize the potential of the multi-kinase inhibitor (MKI) sorafenib for the treatment of thyroid cancer. Following a series of clinical trials for which Dr. Brose was the primary investigator, sorafenib was FDA approved for the treatment of metastatic and advanced radioactive iodine (RAI)-refractory differentiated thyroid carcinoma (DTC) in 2013, becoming the first approved treatment for the disease since 1974. At Penn Medicine, the sorafenib trials marked the initiation of a progressive and continuing series of investigations into MKIs for the treatment of thyroid cancer.

Targeting Cell Signaling in Thyroid Cancer

Radioactive iodine (RAI) is used to kill thyroid cancer cells that are not cured by surgery alone. RAI can be curative in the majority of patients with the disease. Of patients with residual disease, however, up to 50% will become refractory to RAI. This occurs either because their cells can no longer absorb RAI or are no longer inhibited by RAI. Patients with RAI-refractory differentiated thyroid carcinoma (DTC) were essentially beyond the scope of standard treatment, and had an average lifespan of 2.5 to 3.5 years. Their disease was defined by continuous progression, resulting in pulmonary, bone and brain complications, among other concerns.

Treatment of RAI-Refractory Differentiated Thyroid Cancer

The search for new options for the treatment of RAI-refractory DTC was initiated by need and a greater understanding of thyroid carcinogenesis and the role of targeted therapies. For the latter part of the twentieth century, the only drug approved to treat the condition was doxorubicin, a toxic, ineffective and thus little-used chemotherapeutic. The development of targeted cancer therapies at the turn of the 21st century, however, allowed for a far more efficacious therapy to be found for RAI-refractory DTC.

Sorafenib was an early and likely prospect for this role. Developed in 1999 as a multi-kinase inhibitor (MKI), sorafenib inhibits a number of somatic mutations, including the angiogenic kinases VEGFR2, VEGFR3 and mVEGFR2 as well as B-RAF, mutant B-RAF.
V600E, and platelet-derived growth factor receptor (PDGFR).

That the VEGF gene is over-expressed in renal cell carcinoma (RCC) has been known since 1992; a decade later, the B-RAF mutation was identified in melanoma. By 2003, sorafenib was in clinical trials for both diseases.

At about this time, Marcia Brose, MD, PhD was investigating the B-RAF pathway in melanoma and lung cancer at Penn Medicine. Familiar with sorafenib, Dr. Brose suspected that the drug would be effective against RAI-refractory DTC. In recent studies, the B-RAF V600E somatic mutation had been identified as the most common genetic change in papillary thyroid cancers; an association between thyroid cancer and the VEGF pathway had long been known. Yet for patients with RAI-refractory DTC, sorafenib was available only through clinical trials for other indications.

Unexpectedly, researchers in the existing RCC trial expanded the study to examine hypertension in patients taking sorafenib, whether or not they had renal cell carcinoma. Given this opportunity, Dr. Brose and her colleagues at Penn treated a patient with RAI-refractory DTC with sorafenib. The patient’s response was remarkable, and based on this result, Dr. Brose initiated a Phase II trial at Penn.

This open-label study involved up to 60 patients with metastatic RAI-refractory DTC, and resulted in clinical benefit for 82% of patients. About a third of patients saw regression in tumor size of at least 30%. The average time to progression was ~18 months. On the basis of clear evidence of efficacy, the Phase II study was published early and Dr. Brose was invited to become the principal investigator for the DECISION trial. This was a Phase III, double-blind, randomized study of sorafenib versus placebo in locally advanced or metastatic patients with RAI-refractory DTC. The DECISION trial demonstrated significantly extended progression-free survival (PFS) for patients taking sorafenib compared to placebo. The median PFS was 10.8 months among patients treated with sorafenib, compared to 5.8 months among patients receiving placebo (HR=0.587 [95% CI, 0.454-0.758]; p<0.0001).

In 2013, sorafenib was approved by the FDA for the first-line treatment of metastatic and RAI-refractory differentiated thyroid cancer.

Dr. Brose continues to investigate sorafenib and other new MKIs for patients with all types and stages of thyroid cancer. Her work has contributed to the FDA approval of the multi-kinase inhibitor cabozantinib (an inhibitor of MET, VEGFR2 and RET) for the treatment of advanced medullary thyroid cancer, and the completion of SELECT, a Phase 3 study of lenvatinib (another highly effective kinase inhibitor) for RAI-refractory DTC.

At this time, Penn Medicine is a global leader in the development of novel therapies for patients with thyroid cancer.
A Phase II Trial of Cabozantinib for the Treatment of Radioactive Iodine (RAI)-Refractory Differentiated Thyroid Carcinoma (DTC) in the First-line Setting

This is a phase II, non-randomized, open-label study to determine the efficacy of cabozantinib as a firstline treatment for patients with RAI-refractory differentiated thyroid cancer. Subjects will receive the drug at a starting dose of 60mg orally, daily. Subjects can receive the drug as long as they continue to derive clinical benefit or until they experience unacceptable drug-related toxicity. As a first-line treatment for RAI-refractory DTC, cabozantinib might offer a treatment option for patients in addition to sorafenib.

A Phase II Study of Everolimus and Sorafenib in Patients with Metastatic Differentiated Thyroid Cancer (DTC) Who Progressed on Sorafenib Alone

The primary objective of this study is to determine the effect of combining the mTOR (mammalian target of rapamycin) inhibitor everolimus and sorafenib in patients with metastatic DTC who have progressed on sorafenib alone. mTOR is a kinase that regulates many cellular processes in cancer, including metabolism, proliferation and angiogenesis.

Secondary outcome measures include the performance of correlative scientific studies to determine the relationship between clinical response to everolimus and sorafenib and multiple parameters including:

- The mutational status of BRAF, N-RAS and other relevant cancer genes in the tumor
- Time to disease progression in patients receiving everolimus and sorafenib
- An evaluation of the activity of additional signaling pathways in surrogate tissue and tumor samples and their relevance to outcome measures

Study Comparing Complete Remission After Treatment with Selumetinib/Placebo in Patients with Differentiated Thyroid Cancer (ASTRA)

This randomized, double-blind study is designed to evaluate the clinical efficacy, safety and tolerability of selumetinib (an orally active, small molecule ATP-independent inhibitor of mitogen-activated protein kinase (MEK or MAPK/ERK kinase) 1 and 2) over a five week period prior to radioactive iodine (RAI). Patients will be randomized to receive one of the following:

- 1) Selumetinib plus radioactive iodine (RAI) therapy with thyrogen (recombinant human TSH) to stimulate iodine uptake
- 2) Placebo plus RAI

The dose of selumetinib is three 25 mg capsules orally twice daily. The primary objective of the trial is to compare the complete remission rate in the overall study population.

Evaluation of Efficacy, Safety of Vandetanib in Patients with Differentiated Thyroid Cancer (VERIFY)

This randomized, double-blind, placebo-controlled, multi-center Phase III study will assess the efficacy, safety and tolerability of the VEGFR inhibitor vandetanib, 300 mg daily, versus placebo in patients with locally advanced or metastatic differentiated thyroid cancer who are refractory or unsuitable for radioactive iodine therapy. The primary outcome is to determine the efficacy (as assessed by progression-free survival) of vandetanib when compared to placebo in the patient population.

Patients and investigators wishing to contact Dr. Brose or the thyroid cancer clinical research team at Penn Medicine may call 215-615-5858, or make an appointment at PCAM4ACCIntake@uphs.upenn.edu.
In September 2014, The Food and Drug Administration expanded its indication for the use of transoral robotic surgery (TORS) for benign base of tongue resection procedures. The clinical trials for this indication originated at Penn Medicine under the direction of Erica Thaler, MD in which benign tongue base resection was used for the treatment of obstructive sleep apnea.

The treatment of obstructive sleep apnea (OSA) often combines two procedures, uvulopalatopharyngoplasty (UPPP) and lingual tonsillectomy, that address the separate contributory factors of the condition. UPPP is used to remove all or part of the soft tissues at the rear of the mouth, including the uvula, soft palate and tonsils, while lingual tonsillectomy trims lymphatic tissue from the surface of the tongue. While neither procedure is particularly effective as treatment alone, in combination the surgeries have been shown to ameliorate OSA in a majority of patients.

Tongue base surgery generally presents a variety of challenges, however, including the difficulty of manipulating surgical instruments in a limited operative field, visualization with endoscopic instruments and the occasional need for concomitant tracheotomy and/or other external incisions during surgery. Transoral robotic surgery (TORS) was developed at Penn Medicine by Bert O’Malley Jr., MD and Gregory Weinstein, MD, FACS to provide an alternative to open surgery in head and neck procedures. Recently, Dr. O’Malley, Dr. Weinstein, and a colleague at Penn Medicine, otorhinolaryngologist Erica Thaler, MD, conducted a clinical trial to evaluate standard UPPP coupled with TORS tongue base resection in patients with obstructive sleep apnea complicated by tongue base obstruction. Preliminary findings of this trial were published in the Annals of Otology, Rhinology and Laryngology in 2012.

At this time, 65% of patients had responded to surgery. A significant decline in apnea-hypopnea index occurred (56.7%; p < 0.001) and there were significant improvements in mean preoperative to postoperative minimum arterial oxygen saturation values (75.8% to 81.7%; p = 0.013). In addition, a significant improvement in the Epworth Sleepiness Scale score occurred, from 13.4 to 5.9 (p = 0.003).

The division is also exploring other methods and approaches to the treatment of OSA and will be reporting on these developments in the near future.

Erica Thaler, MD
In the developed world, more than half of newly diagnosed oropharyngeal squamous cell cancers (OPSCC) will test positive for p16, a marker for the human papilloma virus (HPV).

The recent history of oropharyngeal cancers has been defined by an etiologic paradox: a decrease in the incidence of oral cancers coincident with an increased incidence of oropharyngeal cancers (more than 90% of which are squamous cell malignancies). The drop in oral cancers has been attributed to a 50-year long decline in tobacco use, which paired with alcohol abuse, had once comprised the traditional pathology of mouth and throat cancers. The rise in oropharyngeal squamous cell cancers owes its origin to the human papilloma virus (HPV), an etiologic agent previously recognized in cervical cancer.

HPV belongs to a family of non-enveloped DNA viruses with more than 100 genotypes. Of these, the variant HPV-16 is strongly identified with both oropharyngeal squamous cell cancers (OPSCC) and overexpression of the P16 tumor suppression protein. An expanding literature has defined the correlation between p16-positivity and high-risk HPV, as well as the characteristics of the subpopulation of patients with oropharyngeal cancer for which p16+ HPV (HPV+ OPSCC) is the primary etiology. By contrast to the previously described traditional patient with OPSCC—a middle-aged man with a history of alcohol and tobacco abuse—patients with HPV+ OPSCC are usually younger and much less likely to smoke and drink. In clinical trials, these patients have demonstrated better tumor control than their HPV-negative counterparts, with significantly improved overall survival at five years with standard therapy despite the tendency to be diagnosed with a relatively small primary but prominent neck nodes and hence they almost uniformly present as advanced stage disease.

At present, treatment regimens for patients with OPSCC do not distinguish between patients with, and those without, HPV. This means, at many centers, patients with a demonstrably milder course of disease commonly receive the same regimen—high dose chemotherapy and radiation—administered to patients with severe and aggressive OPSCC, but must live much longer with the functional and psychological magnitude of treatment.

Clinical trials at Penn Medicine and elsewhere are thus investigating the potential for deintensification of therapy in patients with HPV+ OPSCC. In this context, deintensification generally implies a reduction in the intensity or duration of radiotherapy and/or chemotherapy. Transoral robotic surgery (TORS), which was invented at Penn Medicine in 2004, became FDA cleared for benign and malignant T1 and T2 tumors in 2009. Research at Penn has demonstrated that TORS is highly effective in the management of OPSCC independent of HPV status. Moreover, TORS has been used with great success as a primary therapy in OPSCC not followed by adjuvant radiotherapy, and in the diagnosis and treatment of head and neck cancers of unknown primary origin.

The authors of the ongoing ECOG trial 3311 (Phase II Randomized Trial of Transoral Surgical Resection Followed by Low-Dose or Standard-Dose IMRT in Resectable p16+ Locally Advanced Oropharynx Cancer) have described the potential of TORS in HPV+ oropharyngeal cancer succinctly: TORS allows more appropriate use of postoperative adjuvant therapy based on pathologic staging. This valuable information has the potential to spare or diminish substantially the need for high-dose radiation or concurrent chemoradiation in patients who are expected to do well. Moreover such benefits are increased if the resection can be accomplished with low morbidity, which is the case with TORS.

TORS continues to be the impetus for new directions in research at Penn Medicine for HPV+ patients, as well as in other areas of treatment.
Human papilloma virus (HPV)-related squamous cell cancer of the oropharynx (OPSCC) accounts for ~25% of all squamous cell cancers of the head and neck.

In the developed world, greater than 50% of newly diagnosed OPSCC will test positive for HPV.

Incidence increasing 5% per year.

In the US more than 11,000 HPV-related OPSCC are now diagnosed annually.

Of the 100 HPV types, about 40 types are sexually transmitted and are drawn to the body’s mucous membranes. The other ~60 types of HPV cause warts on areas such as the hands or feet.
Steven B. Cannady, MD joined Penn Otorhinolaryngology – Head and Neck Surgery and is practicing at Pennsylvania Hospital and the Hospital of the University of Pennsylvania.

Dr. Cannady received his medical degree from the Ohio State University College of Medicine and Public Health. He completed his otorhinolaryngology residency program at the Head & Neck Institute — Cleveland Clinic and subsequently completed a microvascular and head & neck surgery fellowship at Oregon Health Sciences University. He is board certified in otolaryngology.

He is the author/coauthor of numerous scientific publications and textbook chapters on head and neck cancer and reconstructive surgery. His advanced training and passion for improving patient outcomes through reconstruction allow him to offer the most up-to-date rehabilitative options after cancer surgery. These techniques and advances have improved speech, swallowing and appearance for patients undergoing cancer surgery.

Dr. Cannady’s ongoing patient-centered outcome studies and innovative new surgical techniques are research focuses that lead to optimal patient satisfaction and quality of life after tumor surgery. High success rates with microvascular surgical procedures have allowed for expanded tumor removal and reconstruction options for previously unresectable tumors. Conversely, new techniques in reconstruction after minimally invasive tumor surgery have led to improved swallowing and speech after head and neck surgery. In addition, Dr. Cannady performs nerve, muscle and bone reconstructions in the head and neck for prior surgery or radiation resulting in numbness, scarring, pain, poor cosmetic outcomes, or muscle weakness.

Dr. Cannady’s focus on patient functional outcomes helps individual patients achieve satisfaction and the best possible results after cancer or other major head and neck surgery.

Jonathan M. Lee, MD joined Penn Otorhinolaryngology – Head and Neck Surgery and is practicing at Penn Presbyterian Medical Center and Penn Medicine Radnor.

Dr. Lee received his medical degree from the Perelman School of Medicine at the University of Pennsylvania. He completed both his internship in general surgery and his residency in Otorhinolaryngology – Head and Neck Surgery at the Hospital of the University of Pennsylvania.

His clinical interests include: endoscopic sinus surgery, nasal airway obstruction, thyroid and parathyroid surgery, obstructive sleep apnea, and salivary gland disorders. Dr. Lee focuses on a number of clinical research projects. He is currently investigating the use of TransOral Robotic Surgery (TORS) as a novel technique for the surgical management of obstructive sleep apnea.

Steven J. Eliades, MD, PhD joined Penn Otorhinolaryngology – Head and Neck Surgery and is practicing at the Hospital of the University of Pennsylvania.

Dr. Eliades received his medical degree and completed his residency at The Johns Hopkins University. His clinical interests include hearing loss and its treatment, cochlear implants, chronic ear disease, and disorders of balance including dizziness, vertigo, and Meniere’s disease.

Dr. Eliades has a strong focus on both basic science and translational research in hearing. His primary research interests are auditory-vocal integration, studying how the auditory system processes complex sound inputs (e.g. speech or vocalization), and how the brain interprets the sound of our own voice and then uses this information to help control our speech. His research interests also include central auditory processing and cochlear implant-related auditory plasticity.
Penn Medicine University City

Penn Medicine University City is an advanced treatment and outpatient facility that brings a multitude of specialties together, all under one roof. It strives to provide seamless, integrated care to patients.

Located at 3737 Market Street, Penn Medicine University City includes 200,000 square feet of exam rooms, outpatient operating rooms for same-day surgeries, as well as an outpatient radiology center.

Penn Otorhinolaryngology – Head and Neck Surgery moved into Penn Medicine University City from its previous clinic space across the street at Penn Presbyterian Medical Center in August 2014. The new clinic space offers five exam rooms, one procedure room, and a wheelchair-accessible audiology suite. Initially, this site will offer general otorhinolaryngology services but has the space necessary to expand into more subspecialized patient care.

Penn Medicine Washington Square

Serving as the main outpatient center for Pennsylvania Hospital, Penn Medicine Washington Square is home to more than 100 health care providers for a wide range of services, including cardiology, otorhinolaryngology (ear, nose, and throat), endocrinology, primary care, surgery, urology and women’s health. Together, in one convenient location, these practices enhance our ability to provide comprehensive, patient-centered care to optimize outcomes.

Penn Otorhinolaryngology – Head and Neck Surgery moved to Penn Medicine Washington Square, located at 800 Walnut Street, in October 2013. This site offers 12 exam rooms, two audiology booths, and one Aesthetician treatment room, and provides General Otolaryngology services with subspecialty care in Head and Neck Cancer, Voice and Swallowing Disorders, Sleep Surgery, Facial Plastic and Reconstructive Surgery, Audiology, and Aesthetician skincare.

Perelman Center for Advanced Medicine South Pavilion Extension

The New Perelman Center for Advanced Medicine South Pavilion Extension is the most recent expansion for this state-of-the-art, outpatient facility adjacent to the Hospital of the University of Pennsylvania. This expansion will allow for a comfortable and easy-to-navigate environment for patients and provides the most comprehensive, patient-centered care available in the region.

Penn Otorhinolaryngology - Head & Neck Surgery will move to this new center in March, 2015. The new space has 31 exam rooms, one procedure room, a dedicated allergy treatment room, an onsite CT machine, and a separate Audiology suite that includes five audiology booths. This new location will treat Head and Neck Cancer, Sinus, Ear, Throat and Vestibular disorders, Allergies, Hearing Loss, Cochlear Implantation, Benign Tumors of Head and Neck, Thyroid and Skull Base, and offer Facial Plastic and Reconstructive Surgery services.
Founded in 1870, Penn Otorhinolaryngology is one of the oldest departments and residency programs in the country. The legacy and tradition of excellence in patient care, education, and research continues to grow and flourish today.

Penn's multidisciplinary team of board-certified otolaryngologists specializes in the evaluation, diagnosis and treatment of a spectrum of ear, nose and throat disorders, as well as areas within the head and neck.

SERVICES INCLUDE:

- Audiology
- Balance Center
- Center for Head and Neck Cancer
- Center for Implantable Hearing Devices
- Cranial Base Surgery/Skull Base Surgery
- Facial Plastic and Reconstructive Surgery
- General Otolaryngology
- Head and Neck Surgery
- Hearing Aid Dispensing
- Otology/Neurotology
- Rhinology
- Smell and Taste Center
- Speech-Language Pathology and Rehabilitation
- Thyroid Program
- Tinnitus
- TransOral Robotic Surgery (TORS)
- Voice, Speech and Swallowing Disorders

Penn PhysicianLink provides facilitated access to, and simplifies the lines of communication between referring physicians and Penn Medicine. This comprehensive, coordinated collection of support services expedites and facilitates both direct physician communication as well as patient transfers.

Exclusive, Physician-Only Telephone Line:
877.937.PENN (7366)

This dedicated, physician-only telephone line offers direct access to facilitate:

- Emergent and non-urgent transfers to Penn Medicine
- Physician consults and referrals
- Information about medical education and clinical programs

Physician Liaison Services:
Penn Medicine physician liaisons will facilitate meetings between and among referring physicians and Penn providers for Grand Rounds, CME and education programs and other professional meetings.

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