Welcome to the Fall 2015 issue of the Stanford Cancer Institute Clinical Research Newsletter for Colleagues in the Community. This quarterly publication is designed to inform our colleagues in the medical community, and especially physicians who are considering treatment options for their patients with cancer, about current clinical trials available at the NCI-designated Stanford Cancer Institute. Many of these trials provide access to novel therapies including new “targeted” agents, often not available in the community.

As the faculty director of the Cancer Clinical Trials Office and co-leader of the Thoracic Oncology program, I am delighted to introduce this edition of the newsletter, as it focuses on Head and Neck Oncology, Neuro-Oncology, and Thoracic Oncology. Each of these programs offers cutting edge clinical trials for patients with tumors that can be challenging to treat with current routine care. Weekly multi-disciplinary tumor boards are available for each program. The articles on each program will introduce you to our programs, faculty researchers, and currently available clinical trials.

Our Developmental Therapeutics Program is profiled in each issue of this newsletter. Shivaani Kummar, MD, who joined Stanford from the National Cancer Institute earlier this year, leads the program which offers Phase I/II clinical trials designed to evaluate new treatments for cancer. Dr. Kummar is in the process of opening new trials and collaborating with other NCI designated cancer centers on promising anticancer therapies.

This issue also announces that Eben Rosenthal, MD, joined Stanford in August as the Medical Director of the Stanford Cancer Center. Dr. Rosenthal is board certified in otolaryngology and in facial plastic and reconstructive head and neck surgery.

We hope that you will consider a Stanford Cancer Institute clinical trial when you deem it appropriate to refer a patient to an academic medical facility.

Heather Wakelee, MD  
Associate Professor of Medicine (Oncology)  
Faculty Director, Cancer Clinical Trials Office  
Co-leader, Thoracic Oncology Program
The Stanford Thoracic Oncology Program features a variety of clinical trials incorporating novel treatments for both early and advanced stage non-small cell lung cancer and for other thoracic malignancies. In addition, the group provides high quality standard-of-care surgical, oncological, and radiotherapeutic approaches for lung cancer patients.
THORACIC ONCOLOGY PROGRAM UPDATES / HIGHLIGHTS

- Appointed a new Associate Professor, Leah Backhus, MD, a thoracic surgeon, who comes to Stanford from the University of Washington and has expertise in lung cancer and mesothelioma.

- Participates in and features Dr. Joseph Shrager as its National Principal Investigator of a new randomized study testing a new versus an old type of “PleurX” catheter to treat malignant pleural effusions. Dr. Shrager and his research team hypothesize that the new catheter is likely to be highly effective in achieving a rapid pleurodesis and will become the new standard of care.

- Sees many lung tumors on the “adenocarcinoma-in situ” spectrum. In addition, the Program has published one paper and is working on several others that seek to establish the standard of care approach to surgical therapy for these types of tumors.

- Established the Stanford Center for Minimally Invasive Thoracic Surgery (SMITS), co-directed by Drs. Mark Berry and Joseph Shrager. This Center solidifies Stanford’s leadership in minimally invasive approaches to all thoracic problems.

- Remains in the top quartile in all outcome measures in the Society of Thoracic Surgeon’s national database—a group that includes only the top institutions doing thoracic surgery in the country. In the most recent data collection, covering three years, Stanford had not a single death after more than 100 esophagectomies—an operation that nationally has an approximately 5 percent death rate.

- Continues to expand the interventional pulmonology (IP) program as a feature of its armamentarium in lung cancer management. Among the modalities offered is navigational bronchoscopy for biopsy of lung nodules. IP is an emerging field that uses minimally invasive diagnostic and staging techniques for potential lung cancers. Stanford’s lead interventional pulmonologist is Arthur Sung, MD, Clinical Associate Professor, Medicine—Pulmonary & Critical Care Medicine. The program has hired two additional IP experts.

INNOVATIVE RESEARCH INCLUDES

- Molecular Profiling of Lung Cancer: Stanford Cancer Institute investigators use minute quantities of tumor tissue to tailor personalized drug therapy against certain tumors, particularly non-small cell tumors with oncogenic driver mutations in EGFR, ALK, ROS1, BRAF, HER2, KRAS, and others.

- Cancer Immunotherapy: Stanford is at the forefront of discoveries in cancer immunotherapy, yielding exciting prospects of re-training the immune system to fight cancer. Research includes the current investigation of...
Thoracic Oncology Program, continued

the anti-PD-L1 monoclonal antibody MEDI-4736 for metastatic non-small cell lung cancer as well as other upcoming lung cancer studies that focus on PD-1 and PD-L1 with nivolumab and pembrolizumab

• Imaging: Stanford has advanced imaging capabilities, including radiation planning with PET/CT scans and clinical trials with novel PET tracers. Stanford recently established a CT-screening program for patients at high risk for developing lung cancer

CURRENT RESEARCH FEATURES

Advanced stage NSCLC therapy study
- Erlotinib and momelotinib to treat epidermal growth factor receptor (EGFR) Mutated EGFR tyrosine kinase inhibitor (TKI) naïve metastatic NSCLC

Early stage therapy for patients with EGFR and ALK positive NSCLC
- Adjuvant therapy options following surgery (Adjuvant afatinib and the ALCHEMIST trial with adjuvant erlotinib or crizotinib).
- The RTOG 1306 trial, nationally chaired by Dr. Bill Loo, using neoadjuvant erlotinib or crizotinib prior to chemotherapy and radiation for stage III NSCLC.

Advanced stage lung cancer clinical trials focused on individualized treatment based on the molecular characteristics of tumors and overcoming drug resistance
- Patients with acquired resistance to the EGFR inhibitor erlotinib or afatinib may consider the CO-1686 clinical trial to overcome resistance.
- Patients with acquired resistance to the ALK inhibitor crizotinib may also have a clinical trial option with the agent X-396.
- Depending on line of therapy and tumor histology, patients may consider immunotherapeutic strategies to target advanced non-small cell lung cancer with anti-PDL1 and anti-PD1 drugs.

Studies to identify tumor cells or tumor DNA circulating in the blood
- In collaboration with basic science colleagues, members of the Thoracic Oncology Program are participating in innovative studies to identify circulating tumor factors in the blood. In the future, the ability to identify circulating tumor cells and DNA may:
  — Reduce the need for invasive biopsies for patients with the disease
  — Allow for cutting edge molecular testing, bringing Stanford closer to providing truly personalized treatments for lung cancer.

CLINICAL OUTCOMES RESEARCH

Stanford thoracic surgeons and oncologists are continuously reviewing their results with current and past patients to gather information that will help future patients. One such study, for example, has shown that Stanford’s novel approach to patients with multifocal adenocarcinoma in situ (formerly termed bronchioloalveolar carcinoma, or “BAC”)— consisting of surgical resection of the dominant tumor and close monitoring of other smaller tumors—appears to be highly successful.

ADVANCED TECHNIQUES FOR RESECTABLE LUNG CANCER

When a lung cancer is resectable, the thoracic surgery team offers advanced and minimally invasive techniques that are available in only a few centers in the United States. These methods allow resection of the smallest amount of lung tissue that will provide the optimal chance of cure, with the least risk. They include:

• VATS (thoracoscopic) lobectomy (and VATS segmentectomy for small Stage I tumors)
• Sleeve resections to avoid pneumonectomy for centrally located tumors
• Anterior, smaller-incision-based approaches to Pancoast tumors
• Endobronchial Ultrasound for biopsy of hilar and mediastinal lymph nodes
• Stereotactic Ablative Radiotherapy (SABR) for stage I lung cancers in surgically ineligible or high-risk surgical patients


All patients who have a question about whether surgery or radiation therapy would be best for them are encouraged to be seen by the multidisciplinary tumor board, which meets weekly.

CURRENTLY OPEN STUDIES INCLUDE

Stage I-III NSCLC
• Phase II Trial of Individualized Lung Tumor Stereotactic Ablative Radiotherapy (iSABR) (LUN0048)
• EF5-PET for Imaging of Tumor Hypoxia in Early Stage Lung Cancer Treated with SABR
• 4-D CT Based Regional Lung Ventilation Imaging in Patients Treated with RT for Lung Cancer (LUN0034)
• A Randomized Phase II Study Comparing Concise (3 months) versus Prolonged (2 years) Afatinib as Adjuvant Therapy for Patients with Resected Stage I-III NSCLC with EGFR Mutation (LUN0058)
• Phase I/II, First-in-Human, Dose-Escalation Study of X-396 in Patients with Advanced Solid Tumors and Expansion Phase in Patients with ALK+ Non-Small Cell Lung Cancer (VAR0098)
• Randomized Phase II Trial of Individualized Adaptive Radiotherapy Using During-Treatment FDG-PET/CT and Modern Technology in Locally Advanced Non-Small Cell Lung Cancer (NSCLC) (RTOG1106)
• A Randomized Phase II Study of Individualized Combined Modality Therapy for Stage III Non-Small Cell Lung Cancer (NSCLC) (RTOG1306)

Stage IV NSCLC Previously Untreated
• A Phase 1b Study of Erlotinib and Momelotinib for the Treatment of Epidermal Growth Factor Receptor (EGFR) Mutated EGFR Tyrosine Kinase Inhibitor (TKI) Naïve Metastatic Non-Small Cell Lung Cancer (NSCLC) (LUN0066)

Stage IV NSCLC Previously Treated
• A Phase 1/2 Study to Evaluate the Safety, Tolerability, and Pharmacokinetics of MEDI4736 in Subjects with Advanced Solid Tumors (LUN0063)

Mesothelioma
• Randomized Phase II Study of Maintenance Pemetrexed versus Observation for Patients with Malignant Pleural Mesothelioma without Progression after First-Line Chemotherapy (ECOGC30901)

Small Cell
• A Phase II Study of Etirinotecan Pegol (NKTR 102) in Patients with Refractory Brain Metastases and Advanced Lung Cancer or Metastatic Breast Cancer (MBC) (LUN0067)
• Phase III Comparison of Thoracic Radiotherapy Regimens in Patients with Limited Small Cell Lung Cancer also Receiving Cisplatin and Etoposide (RTOG0538)

• highlighted studies are Stanford investigator initiated
The Stanford Cancer Institute Neuro-Oncology Program runs national and Stanford-originated clinical trials and offers multidisciplinary, collaborative evaluation and treatment of patients with tumors of the nervous system. This includes but is not restricted to brain metastases, leptomeningeal cancer, glioblastomas and less aggressive gliomas, benign brain and spinal tumors, and base of brain neoplasms including pituitary disorders.

The Neuro-Oncology medical team also treats neurological complications of cancer including treating chemotherapy and radiation complications that effect the nervous system as well as cancer related immune diseases (paraneoplastic syndromes). The participating faculty includes representatives from the Departments of Neurosurgery, Radiation Oncology, Neurology, Radiology, and Pathology.

**Clinical Trials Have Focused On**
- vaccine therapy
- antibody therapy
- novel chemotherapy agents
- radiation sensitizers
- novel radiation therapy and radiosurgery techniques

**FEATURES OF THE ADULT NEURO-ONCOLOGY SERVICE**
- Weekly Multidisciplinary Tumor Boards.
- CyberKnife stereotactic radiosurgery.
- Advanced radiation techniques such as Intensity Modulated Radiotherapy (IMRT) and Rapid Arc Volumetric Modulated Arc Therapy (VMAT).
- Expertise in base of brain surgery for tumors such as pituitary adenomas, meningiomas, acoustic neuromas, chordomas, and chondrosarcomas.
- Close working relationships between center members as well as other physicians and services within the Stanford Cancer Institute.
• Strong links to developmental therapeutics scientists within Stanford that facilitate advancement of new treatment strategies.

• Full range of treatment options including minimally invasive surgery, CyberKnife stereotactic radiosurgery, and individualized immunotherapy and chemotherapy based on molecular analysis of tumor in the Tumor Tissue Bank.

• Coordination of patient care for medical, social, and referral needs.

CURRENTLY OPEN STUDIES INCLUDE

• A Phase I/II Trial of Temozolomide and Hypofractionated Radiotherapy in Treatment of Supratentorial Glioblastoma Multiforme (BRN0012)

• A Phase I/II Study of Local Field Irradiation and Temozolomide Followed by Continuous Infusion Plerixafor as an Upfront Therapy for Newly Diagnosed Glioblastoma GBM (BRN0023)

• A Multi-Center Phase 2 Open-Label Study to Evaluate Safety and Efficacy in Subjects with Melanoma Metastatic to the Brain treated with Nivolumab in Combination with Ipilimumab followed by Nivolumab Monotherapy (BRN0027)

• A Phase II Study of Etirinotecan Pegol (NKTR 102) in Patients with Refractory Brain Metastases and Advanced Lung Cancer or Metastatic Breast Cancer (MBC) (LUN0067)

• Phase I Ad-RTS-hIL-12 in Recurrent/Progressive Glioblastoma or Grade III Malignant Glioma (BRN0025)

• A Phase II Randomized Trial Comparing the Efficacy of Heat Shock Protein-Peptide Complex-96 (HSPPC-96) Vaccine Given with Bevacizumab versus Bevacizumab alone in the Treatment of Surgically Resectable Recurrent Glioblastoma Multiforme (GBM) (NRGA071101)

To register for this course, please visit: cme.stanford.edu/multicancers

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• highlighted studies are Stanford investigator initiated
The Stanford Head & Neck Oncology Program (HNOP) provides leading-edge multi-disciplinary, collaborative and integrated treatment and evaluation for patients with head and neck cancer. World-renown specialists in each discipline (surgery, radiation oncology, medical oncology, and speech and swallowing rehabilitation) lead and participate in both national and Stanford-initiated clinical trials. Physician and surgeon-scientists at Stanford bring the latest discoveries in basic and translational science to the bedside and clinic.

**HNOP IS A PIONEER OF MAJOR SCIENTIFIC BREAKTHROUGHS THAT HELP PATIENTS THROUGH**

- Organ preservation approaches to head and neck cancer, using minimally invasive surgery and state-of-the-art radiation.
- New drugs for head and neck squamous cell carcinoma (HNSCC) and extending uses of existing drugs to HNSCC.
- Advanced radiation therapy techniques that limit toxicity and improve outcomes.
- A cutting edge method to synthesize novel tracers for hypoxia imaging.
- Robotic head and neck surgery, using minimally invasive techniques to preserve speech and swallowing function.
- Bench to bedside approaches such as a Phase I dichloroacetate (DCA) study on modulating tumor cell metabolic activity.
- Stem cell work that demonstrated the existence of “cancer stem cells” in HNSCC that correlated with worse prognosis.
- Identification of adult salivary gland stem cells and their governing pathways that can be manipulated for preservation and/or restoration of salivary function from radiation damage.
- Collaboration with the Stanford Clinical Laboratory to harmonize biomarker measurement for biomarker driven trials to test treatment intensification or de-intensification such as the use of circulating EBV DNA in nasopharyngeal carcinoma.
- Genetic sequencing to identify key driver mutation in ameloblastoma, leading to a clinical trial targeting BRAF in these tumors.
• Developing novel imaging approaches for intraoperative assessment of tumor margins to maximize tumor resection and organ preservation.

• Collaboration with basic scientists to define the best combination of immunotherapy in head and neck cancer.

FEATURES AT THE HNOP INCLUDE
• Close working relationships with:
  — Neurosurgery, Interventional Radiology, and Neuroradiology, which are critical for complex open and endonasal endoscopic skull base surgery.
  — Endocrinology in the treatment of thyroid cancer.
  — Dermatology and Cutaneous Oncology in the treatment of advanced skin cancers.
• Innovative research by physicians now at Stanford that demonstrates the utility of the Mobetron for intraoperative radiation therapy.
• Leadership in the head and neck disease site committee of the NRG Oncology Group to develop new nation-wide clinical trials in head and neck cancer.
• Biomarker studies to identify novel circulating biomarkers for prognostication and post-treatment surveillance in head and neck cancer.
• Strong links to developmental therapeutics such as the advancement of new drugs to treat cancer.
• Provision of a full range of treatment options that include minimally invasive surgery, robotic surgery, stereotactic radiosurgery such as CyberKnife, microvascular reconstruction, intraoperative radiation therapy (IORT), and new chemotherapy trials.

HEAD & NECK PROGRAM UPDATES / HIGHLIGHTS, 2014-2015
• Lisa Orloff, MD, FACS, joined in 2014 to create the Stanford Program in Endocrine Head and Neck Surgery. Professor of Otolaryngology—Head & Neck Surgery, Dr. Orloff brings years of experience as an endocrine surgeon with particular expertise in head and neck ultrasound. Her clinical practice focuses on the surgical management of thyroid and parathyroid tumors. She launched the Thyroid Cancer Care Collaborative Registry and hosted the first Stanford Head and Neck Ultrasound Course in June 2015.

• In January 2015, Heather Starmer, M.A. joined Stanford from Johns Hopkins School of Medicine. Ms. Starmer serves as Director of the Head and Neck Speech and Swallowing Rehabilitation Center. She is a board certified specialist in swallowing disorders with a focus on the rehabilitation of speech, voice, and swallowing in patients with head and neck cancer. She has a strong interest in head and neck cancer survivorship and in helping patients to accomplish their personal goals and to optimize their quality of life. Ms. Starmer is Clinical Assistant Professor of Otolaryngology—Head and Neck Surgery.

• In August, 2015, the Head and Neck Program welcomed Eben Rosenthal, MD, as Medical Director of the Stanford Cancer Center. Dr. Rosenthal is Professor of Otolaryngology and is also board certified in facial plastic and reconstructive head and neck surgery. His research and clinical interests include head and neck oncology and microvascular reconstruction, targeted cancer therapies, and novel surgical imaging technologies. Dr. Rosenthal will see patients in the Head and Neck Cancer Practice while also serving as the new Associate Director of Clinical Care of the Stanford Cancer Institute.

CURRENTLY OPEN SELECTED TRIALS:
• Minimally Invasive Surgery (Transoral Robotic Surgery)
• Randomized Trial of Transoral Surgical Resection Followed by Low-dose or Standard-dose IMRT in Resectable p16+ Oropharynx Cancer (ECOGE3311)
Chemotherapy, Radiation Therapy, and Chemoradiation

• A Phase II Study of Sequential and Concurrent Chemoradiation for Patients with Advanced Nasopharyngeal Carcinoma (NPC) (ENT0025) This protocol is for patients with high risk locally advanced NPC or metastatic disease at presentation who may benefit from an initial approach of chemotherapy followed by chemoradiation.

• A Randomized Phase II Trial for Patients with p16 Positive, Non-Smoking Associated, Locoregionally Advanced Oropharyngeal Cancer (NRGHN002) This trial represents an innovative patient-specific approach to overall treatment reduction, by either using accelerated radiation techniques or lower chemotherapy doses for patients with very good prognosis HPV related cancer.

• Randomized Phase II/III Trial of Surgery and Postoperative Radiation Delivered with Concurrent Cisplatin versus Docetaxel versus Docetaxel and Cetuximab for High-Risk Squamous Cell Cancer of the Head and Neck (RTOG1216) This trial is asking whether non-platinum containing chemoradiation can be substituted for the historical cisplatin-based chemoradiation after surgery in patients with high risk for relapse.

• Randomized Phase II and Phase III Studies of Individualized Treatment for Nasopharyngeal Carcinoma Based on Epstein Barr Virus (EBV) Deoxyribonucleic Acid (DNA) (NRGHN001) This trial, the largest ever conducted in NPC, will both explore whether a patient specific biomarker can help select patients who will not benefit from adjuvant chemotherapy and whether an alternative chemotherapy will benefit patients at highest risk of relapse. Dr. Quynh Le is the translational science co-chair and Dr. Dimitrios Colevas is the medical oncology co-chair of this collaborative international trial.

Advanced Disease

• Weekly Docetaxel, Cisplatin, and Cetuximab (TPC) in Palliative Treatment of Patients with SCCHN (ENT0033)

• A Randomized Study of Topical Dilute Hypochlorite (Modified Dakin's Solution) Treatment for the Prevention of Radiation Dermatitis in Head and Neck Cancer (ENT0042)

• A Randomized Phase 2 Trial of Neoadjuvant and Adjuvant Therapy with the IRX-2 Regimen in Patients with Newly Diagnosed Stage III or IVA Squamous Cell Carcinoma of the Oral Cavity (ENT0045) (SOON TO OPEN)

Diagnostic

• NBI to Characterize Patterns of Vascular Supply within Lymphoepithelial Mucosa in Oropharyngeal Cancer (ENT0044) The purpose of this study is to characterize the blood supply at the base of the tongue and within the tonsil region. We hypothesize that high-resolution Narrow Band Imaging (NBI) will improve the diagnosis of oropharyngeal carcinoma (OPC). The goal is to provide better tumor assessment, thus providing better preoperative expectations to patients with OPC or tumor extent prior to radiation therapy.

• Identification of Infectious versus Noninfectious HPV in Saliva of Oropharynx Cancer Patients (ENT0040) This research will explore to what extent patients with HPV-related cancers are persistently infectious versus merely infected in the past but no longer infectious.

Image Guided Intervention

• Phase I, Open-label Study Evaluating the Safety and Pharmacokinetics of Escalating Doses of Cetuximab-IRDye800 as an Optical Imaging Agent to Detect Cancer During Surgical Procedures (ENT0049) (SOON TO OPEN)

• Phase I, Open-label Study Evaluating the Safety and Pharmacokinetics of Escalating Doses of Panitumumab-IRDye800 as an Optical Imaging Agent to Detect Head and Neck Cancer during Surgical Procedures (ENT0050) (SOON TO OPEN)
Stanford Cancer Center’s Developmental Therapeutics (DT) Program, led by director Shivaani Kummar, MD, offers Phase I/2 clinical trials designed to evaluate new treatment for cancer. Other faculty participating in this effort include Drs. Heather Wakelee and Joel Neal (lung cancers), A. Dimitrios Colevas (head and neck cancers), George Fisher and Pamela Kunz (GI cancers), George Sledge, Suleiman Massarweh, Mark Pegram and Melinda Telli (breast cancers), Sunil Reddy (melanoma), Ranjana Advani and Holbrook Kohrt (lymphomas), and Branimir I. Sikic.

DT Program Director Dr. Kummar is a Professor of Medicine in the Stanford Division of Oncology and former leader of the National Cancer Institute’s Developmental Therapeutics Clinic and Early Clinical Trials Development Program. Dr. Kummar’s research interests focus on developing novel therapies for cancer. She specializes in conducting pharmacokinetic and pharmacodynamic driven first-in-human trials tailored to make early, informed decisions regarding the suitability of novel molecular agents for further clinical investigation. Her studies integrate genomics and laboratory correlates into early phase trials, establishing the proof of mechanism and proof-of-concept in these trials. She has published numerous articles in medical journals and serves on a number of national and international scientific committees.

As a translational clinical studies program, Developmental Therapeutics brings together outstanding physicians with internationally regarded scientists to develop novel therapies and diagnostic modalities that utilize cutting-edge science and technologies. The program offers the opportunity for patients to enroll in clinical trials evaluating novel anticancer therapies. The overall goal of the program is to facilitate the development of promising, new treatments for cancer while ensuring the highest standards of patient safety.

Below is a sampling of currently available Phase I and II studies.

**PHASE I AND II STUDIES**

**Multiple Solid Tumor Sites**

- A Phase I Study of the Safety, Tolerability, Pharmacokinetics and Immunoregulatory Activity of BMS-663513 (Anti-CD137) in Subjects with Advanced and/or Metastatic Solid Tumors (VAR0071)
- Phase I/II, First-in-Human, Dose-Escalation Study of X-396 in Patients with Advanced Solid Tumors and Expansion Phase in Patients with ALK+ Non-Small Cell Lung Cancer (VAR0098)
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