Welcome to the Summer 2013 issue of the Stanford Cancer Institute Clinical Research Newsletter! 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 and research studies 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. In each issue we will highlight a number of our more than 300 clinical trials by focusing on three different disease areas. In addition, we will present early-phase clinical trials aimed at cancers that have failed other treatment from our Developmental Therapeutics Program. As the new Division Chief of Medical Oncology, I am delighted to have the opportunity to introduce myself to you along with our multi-disciplinary programs in Head and Neck Oncology, Neuro-Oncology, and Thoracic Oncology.

In January 2013, I took over as Division Chief of Medical Oncology from Ron Levy, MD, who is now focusing on translational research. As a former president of the American Society for Clinical Oncology and a clinician-scientist at Indiana University Simon Cancer Center focusing on innovative treatments for breast cancer, I am excited about the opportunity to bring new understanding about the biology and genomics of cancer together to help patients in the clinic. We are actively working to extend Stanford’s success rate with non-solid tumors. The programs showcased in this newsletter are examples of multi-disciplinary programs that offer cutting edge clinical trials for patients with tumors that can be challenging to treat with current routine care. The Head and Neck Oncology Program offers a breadth of trials including treatment of intermediate and advanced disease as well as hypoxia imaging. The Neuro-Oncology program offers Phase I through III trials for patients with tumors of the nervous system, including but not restricted to brain metastases, leptomeningeal cancer, glioblastomas and less aggressive gliomas, benign brain and spinal tumors, base of brain neoplasms including pituitary disorders, and neurological complications of cancer. Our Thoracic Oncology Program features a wide number of clinical trials incorporating novel treatments for both early and advanced stage non-small cell lung cancer, as well as for other thoracic malignancies. Stanford Cancer Institute is proud to lead a national clinical trial in early stage lung cancer using chemotherapy and a monoclonal antibody. We also offer advanced stage lung cancer trials focused on individualized treatment based on the molecular characteristics of tumors and overcoming drug resistance.

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. One of our many clinical trials may be the best treatment choice for your patient, especially for those with advanced stage disease, recurrent cancers, and cancers that are difficult to cure. We, in turn, will make every effort to deliver great care to your patient and keep you informed of the patient’s treatment and response.

George Sledge Jr., MD  
Professor of Medicine - Oncology  
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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.

**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 EGFR or KRAS mutations and ALK and ROS1 rearrangements.

- **Circulating Tumor Signatures:** Stanford physicians and basic scientists are developing methods to identify and isolate circulating cancer cells and circulating tumor DNA from blood.

- **Cancer Immunotherapy:** Stanford is at the forefront of discoveries in cancer immunotherapy, yielding exciting prospects of re-training the immune system to fight cancer.

- **Imaging:** Stanford has advanced imaging capabilities, including radiation planning with PET/CT scans and clinical trials with novel PET tracers.

**CURRENT RESEARCH HIGHLIGHTS FEATURE**

**Early stage disease national clinical trial on chemotherapy and monoclonal antibody.** In early stage disease, Stanford is the national principal investigator for one of the highest priority national clinical cancer trials—ECOG 1505—in which patients with surgically resected non-small cell lung cancer may be treated with chemotherapy plus bevacizumab. Bevacizumab is a monoclonal antibody against vascular endothelial growth factor (VEGF), which inhibits the formation of blood vessels in tumors. It is hoped that the addition of this drug will lead to more disease cures.

**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 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 LKD378.

- Small cell lung cancer patients who have failed prior chemotherapy can consider the clinical trial with dose-escalated desipramine.

- Upcoming clinical trials will use additional immunotherapeutic strategies to target advanced non-small cell lung cancer.

**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 will:

- reduce the need for invasive biopsies for patients with the disease, and
- allow for cutting edge molecular testing, bringing medicine closer to the personalized treatment of 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 soon to be published study, for example, has shown that Stanford’s novel approach to patients with multifocal adenocarcinoma in situ (formerly termed bronchioalveolar carcinoma, or “BAC”)—consisting of surgical resection of the dominant tumor and close monitoring of other smaller tumors—appears to be highly successful.

STUDY OF VACCINE AS SUPPLEMENT TO SURGERY
Also for patients with completely resected disease, the MAGRIT study evaluates immunotherapy (lung cancer “vaccine”) as a supplement to surgery. Stanford recently completed accrual for this international study, in which patients whose tumors express the MAGE-A3 tumor protein may receive immunizations against this protein after surgery. The concept of this treatment is to train the patient’s own immune system to eradicate residual tumor cells that might remain in other parts of the body even following removal of the main tumor.

ADVANCED TECHNIQUES FOR RESECTABLE LUNG CANCER
When a lung cancer is resectable, the thoracic surgery team offers advanced 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 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 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
• A Randomized Phase II Study Comparing Concise (3 months) versus Prolonged (2 years) Afatinib as Adjuvant Therapy for Patients with Resected Stage I-II NSCLC with EGFR Mutation (LUN0058)
• A Phase III Randomized Trial of Adjuvant Chemotherapy with or without Bevacizumab for Patients with Completely Resected Stage IB (> 4 cm)-IIIA Non-Small Cell Lung Cancer (NSCLC) (ECOGE1505)
• A Phase II Study of L-BLP25 and Bevacizumab in Unresectable Stage IIIA and IIB Non-Squamous Non-Small Cell Lung Cancer after Definitive Chemoradiation (ECOGE6508)
• Randomized Phase II Study of Pre-Operative Chemoradiation +/- Panitumumab (IND #110152) Followed by Consolidation Chemotherapy in Potentially Operable Locally Advanced (Stage IIIA, N2+) Non-Small Cell Lung Cancer (RTOG0839)
• 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)

Stage IV NSCLC Previously Untreated
• A Phase I Trial of Vorinostat Concurrent with Stereotactic Radiotherapy in Treatment of Brain Metastases from Non-Small Cell Lung Cancer (LUN0036)
• A Randomized, Phase II, Multicenter, Double-Blind, Placebo Controlled Study Evaluating the Efficacy and Safety of MetMAb in Combination with Either Bevacizumab + Platinum + Paclitaxel Or Pemetrexed + Platinum As First-Line Treatment for Patients

• highlighted studies are Stanford investigator initiated
Clinical Research Newsletter for Colleagues in the Community

Stanford Thoracic Oncology Program continued

Stage IIIB or IV Non-Squamous Non–Small Cell Lung Cancer (NSCLC) (LUN0051)

- Randomized Phase III Study of Maintenance Therapy with Bevacizumab, Pemetrexed, or a Combination of Bevacizumab and Pemetrexed Following Carboplatin, Paclitaxel and Bevacizumab for Advanced Non-Squamous NSCLC (ECOG5508)

Stage IV NSCLC Previously Treated

- A Phase 1/2, Open-Label, Safety, Pharmacokinetic and Preliminary Efficacy Study of Oral CO-1686 in Patients with Previously Treated Mutant EGFR Non-Small Cell Lung Cancer (NSCLC) (LUN0052)

- A Phase II, Multicenter, Single-Arm Study of Oral LDK378 in Adult Patients with ALK-Activated Non-Small Cell Lung Cancer Previously Treated with Chemotherapy and Crizotinib (LUN0054)

- An Open Label, Multi-center, IRESSA™ Clinical Access Program of Gefitinib 250 mg (IRESSA™) for the Continued Treatment of Patients in the United States Who Are Currently Benefiting or Have Benefited from Gefitinib Treatment (VAR0069)

- A Phase 1 Study of Recombinant Human IL15 (rhIL15) in Adults with Advanced Solid Tumors: Melanoma, Renal Cell, Non-Small Cell Lung and Head and Neck Cancer (VAR0093)

- A Randomized Phase II Trial of Erlotinib, Cabozantinib, or Erlotinib plus Cabozantinib as 2nd or 3rd Line Therapy in Patients with EGFR Wild-Type NSCLC (ECOG1512)

Diagnostic – Thoracic Malignancy Previously Treated with SABR

- Pilot Study of FLT-PET/CT for Evaluation of Suspected Local Recurrence after Thoracic Stereotactic Ablative Radiotherapy (LUN0055)

Small Cell, Thymoma, Supportive Care

- Intervention Development for Anxiety in Metastatic NSCLC Patients and Their Caregivers (LUN0053)

- A Randomized, Double-Blind, Placebo-Controlled Multi-Center Study of BYM338 for Treatment of Cachexia in Patients with Stage IV Non-Small Cell Lung Cancer or Stage III/IV Adenocarcinoma of the Pancreas (VAR0067)

- A Phase Ila Intrapatient Dose Escalation Study of Desipramine in Small Cell Lung Cancer and other High-Grade Neuroendocrine Tumors (VAR0087)

- Phase III Comparison of Thoracic Radiotherapy Regimens in Patients with Limited Small Cell Lung Cancer also Receiving Cisplatin and Etoposide (RTOG0538)

- Randomized Phase II Study Comparing Prophylactic Cranial Irradiation Alone to Prophylactic Cranial Irradiation and Consolidative Extra-Cranial Irradiation for Extensive Disease Small Cell Lung Cancer (ED-SCLC) (RTOG0937)

- A Phase II Study of Amrubicin in Relapsed or Refractory Thymic Malignancies (THOR0003)
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, base of brain neoplasms including pituitary disorders, and neurological complications of cancer.

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 INCLUDE**

- 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 Fractionated Stereotactic Radiosurgery for Large Brain Metastases (BRN0010)
- An International, Randomized, Double-Blind, Controlled Study of Rindopepimut/GM-CSF with Adjuvant Temozolomide for Newly Diagnosed, Surgically Resected, EGFRvIII-positive Glioblastoma (The "ACT IV" Study) (BRN0016)
- A Phase II Study of Rindopepimut/GM-CSF for Relapsed EGFRvIII-Positive Glioblastoma (BRN0017)
- A Phase I Trial of Vorinostat Concurrent with Stereotactic Radiotherapy for Brain Metastases from Non-Small Cell Lung Cancer (LUN0036)
- Effect of the Novel Somatostatin Analog Pasireotide in Rare Tumors of Neuroendocrine Origin (END0010)
- Phase II/III Study of Image-guided Radiosurgery/SBRT for Localized Spine Metastasis (RTOG0631)

*highlighted studies are Stanford investigator initiated*
The Stanford Cancer Institute Head and Neck Oncology Program (HNOP) participates in both national and Stanford-originated clinical trials as well as translational and basic research. In addition, HNOP offers multi-disciplinary, collaborative and integrated evaluation and care for patients with head and neck cancers.

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

- Organ preservation approaches to head and neck cancer.
- New drugs for head and neck squamous cell carcinoma (HNSCC) and extending uses of existing drugs to HNSCC and nasopharyngeal carcinoma (NPC).
- Advanced radiation therapy techniques that limit toxicity and improve outcomes.
- A cutting edge method to synthesize EF5 tracer for hypoxia imaging that is now applied to patients.
- Bench to bedside approaches such as a Phase I dichloroacetate (DCA) study on modulating tumor cell activity.
- Stem cell work that extends the findings of the first paper, demonstrating the existence of “cancer stem cells” in HNSCC by researchers from Stanford and Michigan in 2007; and a 2009 Stanford study establishing that stem cell properties of patients’ malignancies correlate with prognosis. This work led to subsequent stem cell papers in 2011 and 2012.
- Normal tissue stem cell studies to identify salivary gland stem cells and to manipulate them for preservation and/or restoration of salivary gland function from radiation damage.
- HNOP’s breadth of research studies and protocols including treatment of intermediate and advanced disease as well as hypoxia imaging.

**INNOVATIONS AND FEATURES AT THE HNOP INCLUDE**

- Creation of the first head and neck multidisciplinary tumor patient conference (tumor board) in the U.S.
- Introduction of the first use of chemotherapy with irradiation for head and neck squamous cell carcinoma (HNSCC), which is the basis of organ-preservation chemoradiation in the U.S.
• 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 in the treatment of advanced skin cancers.
• Innovative research by physicians now at Stanford that demonstrates the utility of the FDA-approved Mobetron for intraoperative radiation therapy.
• Contributing research in a Phase II trial of immunotherapy in intermediate and advanced surgically-treated HNSCC. A Phase III trial is now planned.
• Leadership in the head and neck disease site committee of the Radiation Therapy 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.

CURRENTLY OPEN STUDIES INCLUDE

Chemotherapy, Radiation Therapy, and Chemoirradiation

• A Phase II Study of Sequential and Concurrent Chemoradiation for Patients with Advanced Nasopharyngeal Carcinoma (NPC) (ENT0025)
• Phase I Trial of Metabolic Reprogramming Therapy for Treatment of Recurrent Head and Neck Cancers (ENT0031)
• A Feasibility Study of IMRT Modulation to Account for Scattered Radiation from Dental Fillings in Head and Neck Cancer Patients (ENT0032)

Targeted and Immune Based Treatment

• A Pilot Study of Electronic Administration of Short Form Quality of Life Assessments During and After Treatment of Head and Neck Cancers (ENT0036)
• A Phase III Randomized Trial of Chemotherapy with or without Bevacizumab in Patients with Recurrent or Metastatic Head and Neck Cancer (ECOGE1305)
• A Phase III Study of Post-Operative Radiation Therapy (IMRT) +/- Cetuximab for Locally-Advanced Head and Neck Cancer (CIRB) (RTOG0920)
• A Randomized Phase II Study of Adjuvant Concurrent Radiation and Chemotherapy versus Radiation Alone in Resected High-Risk Malignant Salivary Gland Tumors (RTOG1008)
• Phase III Trial of Radiotherapy plus Cetuximab versus Chemotherapy in HPV-associated Oropharynx Cancer (RTOG1016)
• 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)

Palliative Treatment

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

highlighted studies are Stanford investigator initiated
Stanford Cancer Center’s Developmental Therapeutics Program, led by Branimir I. Sikic, MD, offers Phase 1 and 2 clinical trials using novel therapeutics. Dr. Sikic’s clinical interests are mainly in ovarian cancers and cancers of unknown primary. Other faculty participating in this effort include Drs. Heather Wakelee and Joel Neal (lung cancers), Dimitri Colevas (head and neck cancers), George Fisher and Pamela Kunz (GI cancers), Mark Pegram and Melinda Telli (breast cancers), Sunil Reddy (melanoma), and Ranjana Advani and Holbrook Kohrt (lymphomas).

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. This research focuses on early clinical studies, investigator-initiated trials, the development of analytic approaches to enhancing the discovery of drugs and targets, and the analysis of clinical trials.

Below is a sampling of currently available Phase 1 and 2 studies.

**PHASE 1 STUDIES**

**Multiple Solid Tumor Sites**

- A Phase I, Open-label, Dose-escalation Study of the Safety and Pharmacokinetics of MPDL3280A Administered Intravenously as a Single Agent to Patients with Locally Advanced or Metastatic Solid Tumors (VAR0082)

- A Phase I, Open-label, Dose-escalation, Safety and Pharmacokinetic Study of CDX-1127 in Patients with Selected Refractory or Relapsed Hematologic Malignancies or Solid Tumors (VAR0081)

- 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)

- A Phase I/II Study of Intratumoral Injection of Ipilimumab in Combination with Local Radiation in Melanoma, Non-Hodgkin Lymphoma and Colorectal Carcinoma (VAR0090)

**Lymphomas**

- A Phase I Study of PF-05082566 as a Single Agent in Patients with Advanced Cancer, and in Combination with Rituximab in Patients with Non-Hodgkin’s Lymphoma (NHL) (LYMNHL0092)

**PHASE 2 STUDIES**

**Thymic Cancers**

- A Phase 2 Study of Amrubicin in Relapsed or Refractory Thymic Malignancies (THOR0003)

**Small Cell Lung Cancer and Other High-Grade Neuroendocrine Tumors**

- A Phase Ia Intrapatient Dose Escalation Study of Desipramine in Small Cell Lung Cancer and other High-Grade Neuroendocrine Tumors (VAR0087)