

Clinical Research

Newsletter for Colleagues in the Community

Welcome to the Fall 2014 issue of the Stanford Cancer Institute Clinical Research Newsletter! This quarterly publication is designed to inform our colleagues in the medical community 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 novel “targeted” agents and immunotherapeutic options not available in the community. As the co-leader of the Neuro-Oncology program, I am delighted to have the opportunity to introduce this issue which showcases our multi-disciplinary programs in Thoracic Oncology, Head and Neck Oncology, and Neuro-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 Thoracic Oncology Program features a wide number of clinical trials for both early and advanced stage lung cancer, including clinical trials focused on individualized treatment based on the molecular characteristics of tumors, overcoming drug resistance, and employing immunotherapeutics. The program now offers interventional pulmonology (IP) modalities, including navigational bronchoscopy for biopsy of lung nodules. IP is an emerging field that uses minimally invasive diagnostic and staging techniques for potential lung cancers.

The Head and Neck Oncology Program’s research studies and protocols include treatment of intermediate and advanced disease as well as hypoxia imaging. A breadth of treatment options are available including minimally invasive surgery, robotic surgery, stereotactic radiosurgery such as CyberKnife, microvascular reconstruction, intraoperative radiation therapy (IORT), along with new chemotherapy trials.

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. Clinical trials offered by our program include vaccine therapy, antibody therapy, novel chemotherapy agenda, radiation sensitizers and novel radiation therapy and radiosurgery techniques.

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.



Lawrence Recht, MD

*Professor of Neurology
Stanford Cancer Institute*

Thoracic Oncology Program

Novel Care for Non-small Cell Lung Cancer Patients: Individualized Treatment, Immunotherapy, and Cutting Edge Surg



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 such as thymic malignancies and mesothelioma. In addition, the group provides high quality standard-of-care surgical, oncological, and radiotherapeutic approaches for lung cancer patients.



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Phase I and II Studies for Multiple Cancers

Stanford's latest additions to its armamentarium in lung cancer management are interventional pulmonology (IP) modalities, including 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.

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, and KRAS.
- **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 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 to develop lung cancer.

CURRENT RESEARCH HIGHLIGHTS FEATURE

Early stage therapy for patients with EGFR and ALK positive NSCLC include

- 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 inhibitors 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 removable by surgery, 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

See more detail on surgical treatment of lung cancer at Stanford at http://thoracicsurgery.stanford.edu/patient_care/lung_cancer.html

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, First-in-Human, Dose-Escalation Study to Evaluate the Safety, Tolerability, and Pharmacokinetics of X-396 in Patients with Advanced Solid Tumors (VAR0098)
- Randomized Phase II Study of Pre-Operative Chemo-radiotherapy +/- 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

- 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 I/II, 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 I/II Study to Evaluate MEDI4736
- 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 I 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)

Mesothelioma

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

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

- 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)

- *highlighted studies are Stanford investigator initiated*

Head and Neck Oncology Program

Renowned Faculty Researchers, Innovative Patient-Centered Care



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, the 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 novel tracers 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 demonstrated 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.
- Normal tissue stem cell studies that led to the identification of adult salivary gland stem cells and their governing pathways that can be manipulated for preservation and/or restoration of salivary gland function from radiation damage.

- Work with the Stanford Clinical Laboratory to harmonize biomarker measurement/assessment for biomarker driven trials to test treatment intensification or de-intensification such as the use of circulating EBV DNA in nasopharyngeal carcinoma.

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 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 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.

SELECTED TRIALS PRESENTLY OPEN

Chemotherapy, Radiation Therapy, and Chemoradiation

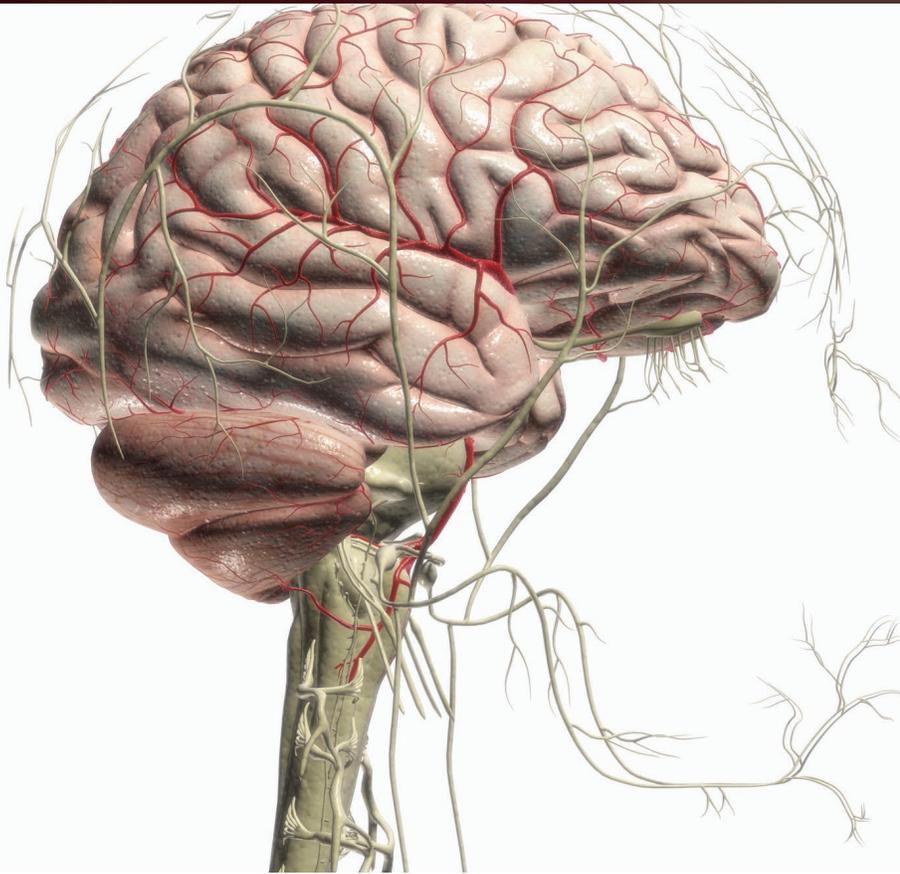
- A Phase II Study of Sequential and Concurrent Chemoradiation for Patients with Advanced Nasopharyngeal Carcinoma (NPC) (ENT0025)
- Phase I Trial of Metabolic Reprogramming Therapy for Treatment of Recurrent Head and Neck Cancers (ENT0031)
- A Phase III Randomized Trial of Chemotherapy with or without Bevacizumab in Patients with Recurrent or Metastatic Head and Neck Cancer (ECOG1305)
- Phase II Randomized Trial of Transoral Surgical Resection Followed by Low-dose or Standard-dose IMRT in Resectable p16+ Locally Advanced Oropharynx Cancer (ECOG13311)
- 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)
- Randomized Phase II Trial of Transoral Endoscopic Head and Neck Surgery followed by Risk-based IMRT and Weekly Cisplatin versus IMRT and Weekly Cisplatin for HPV Negative Oropharynx Cancer (RTOG1221)
- Randomized Phase II and Phase III Studies of Individualized Treatment for Nasopharyngeal Carcinoma Based on Epstein Barr Virus (EBV) Deoxyribonucleic Acid (DNA) (NRG-HN001) (The Stanford Lab is central for this international trial.)

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- *highlighted studies are Stanford investigator initiated*

Adult Neuro-Oncology Program

Multidisciplinary, Collaborative Evaluation and Treatment of Nervous System Tumors



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 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)

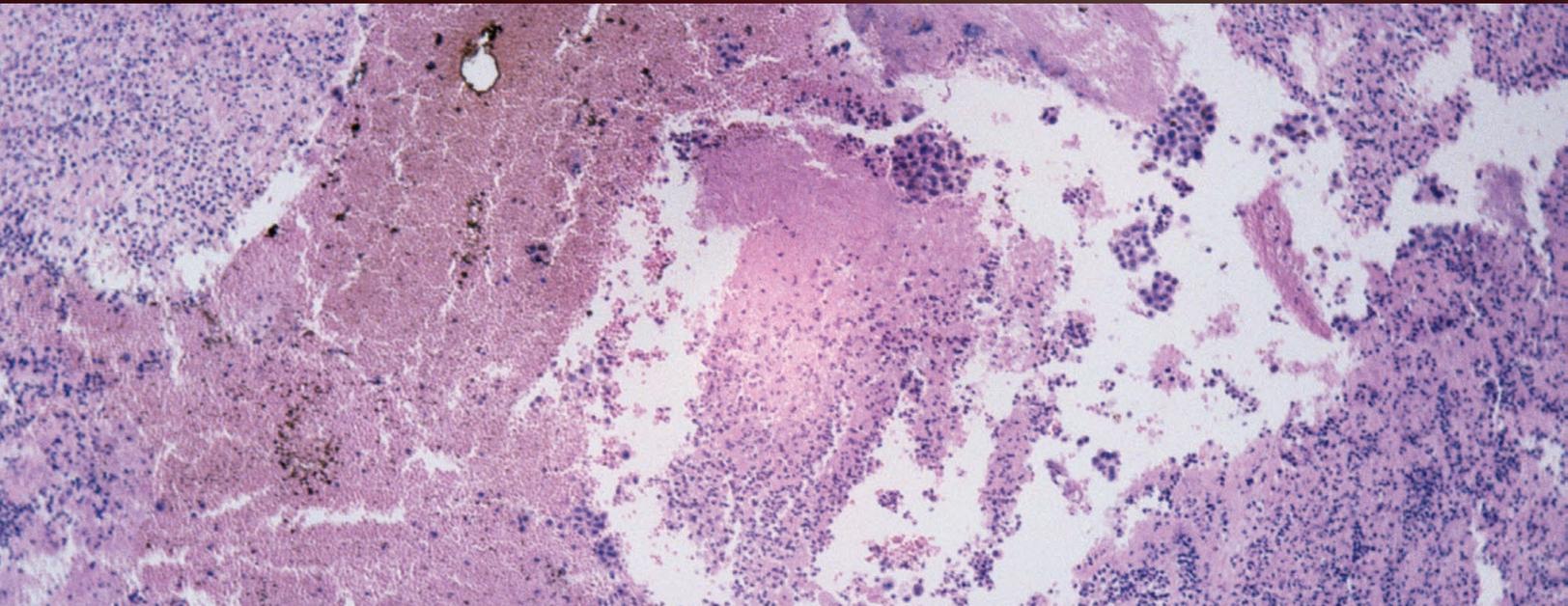
- An International, Randomized, Double-Blind, Controlled Study of Rindopepimut/GM-CSF with Adjuvant Temozolomide for Newly Diagnosed, Surgically Resected, EGFRvIII-positive Glioblastoma (The “ACT IV” Study) (BRN0016)
- A Phase I/Ib, Multicenter, Open-label, Dose-Escalation and Expansion Study to Evaluate the Safety and Antitumor Activity of MEDI3617, a Human Monoclonal Antibody Directed Against ANG2, as a Single-Agent or in Combination Therapy in Adult Subjects with Advanced Solid Tumors (BRN0020)
- 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 Phase I Trial of Vorinostat Concurrent with Stereotactic Radiotherapy for Brain Metastases from Non-Small Cell Lung Cancer (LUN0036)
- A Phase I Study to Evaluate the Safety, Tolerability, and Pharmacokinetics of MEDI4736 in Subjects with Advanced Solid Tumors (LUN0063)
- Phase I Ad-RTS-hIL-12 in Recurrent/Progressive Glioblastoma or Grade III Malignant Glioma (BRN0025)
- Natural History of Postoperative Cognitive Function, Quality of Life, and Seizure Control in Patients With Supratentorial Low-Risk Grade II Glioma (RTOG0925)

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- *highlighted studies are Stanford investigator initiated*

Developmental Therapeutics

Phase I and II Studies for Multiple Cancers



Stanford Cancer Center's Developmental Therapeutics Program, led by A. Dimitrios Colevas, MD, offers Phase I and II clinical trials using novel therapeutics. Dr. Colevas' clinical interests are mainly in head and neck cancers. Other faculty participating in this effort include Drs. Heather Wakelee and Joel Neal (lung cancers), George Fisher and Pamela Kunz (GI cancers), Mark Pegram and Melinda Telli (breast cancers), Sunil Reddy (melanoma), Ranjana Advani and Holbrook Kohrt (lymphomas), and Branimir I. Sikic (sarcoma).

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 I studies.

PHASE I STUDIES

Multiple Solid Tumor Sites

- 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 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)
- Phase I, First-in-Human, Dose-Escalation Study to Evaluate the Safety, Tolerability, and Pharmacokinetics of X-396 in Patients with Advanced Solid Tumors (VAR0098)

Targeted and Immune Based Treatment

- A Phase I 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)

Advanced Disease

- A Phase Ib, Open-Label, Multicenter Study of Urelumab (BMS-663513) in Combination with Cetuximab in Subjects with Advanced/ Metastatic Colorectal Cancer or Advanced/ Metastatic Squamous Cell Carcinoma of the Head and Neck (VAR0106)

- A Phase II Study of Capecitabine in Patients with Advanced or Recurrent Squamous Cell Carcinoma of the Skin (SKIN0016)
- An Open Label, Randomized Phase III Clinical Trial of Nivolumab (anti-PD-1 antibody) vs Therapy of Investigator's Choice in Recurrent or Metastatic Platinum-refractory Squamous Cell Carcinoma of the Head and Neck (ENT0041)

Palliative Treatment

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

- Phase II Randomized Study of Whole Brain Radiotherapy in Combination with Concurrent Lapatinib in Patients with Brain Metastasis from HER2-Positive Breast Cancer (RTOG1119)
- 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)

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