Welcome to the Winter 2015 issue of the Stanford Cancer Institute (SCI) 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 Physician Leader of the Cancer Care Program in Cutaneous Oncology, I am pleased to introduce this issue that showcases our multi-disciplinary programs in Gastrointestinal (GI) Oncology, Cutaneous Oncology - Skin Cancer, and Sarcoma. Each program offers weekly Tumor Boards that provide an ideal mechanism to present challenging cases and discuss treatment options with all relevant subspecialists. The newsletter also includes a listing of Phase I trials from our Developmental Therapeutics Program.

The Gastrointestinal Oncology Program is comprised of a multidisciplinary team of specialists who focus on malignancies of the GI tract, including both rare (e.g. GI stromal and neuroendocrine tumors) and common cancers (gastric, colon, and pancreas). This program currently offers 20 clinical trials that range from multimodality trials to new chemo- and molecularly-targeted therapies, including drugs that specifically bind to key molecules on or in the tumor cells, and immunotherapeutic antibodies capable of triggering an immune response against the cancer.

The Skin Cancer Program at the Stanford Cancer Institute is a leading innovator in the prevention and treatment of skin cancer, and offers novel therapies for melanoma, basal cell carcinoma, squamous cell carcinoma, Merkel cell carcinoma, and cutaneous lymphoma, as well as Supportive Dermato-Oncology. We have recently initiated several innovative clinical trials from the broad immunotherapy portfolio of the Cancer Immunotherapy Trials Network for cutaneous lymphoma, melanoma, and Merkel cell carcinoma. This article details our multi-faceted clinical offerings, research, and prevention efforts in “solid tumor” cutaneous oncology, along with introducing our physicians, specialty clinics, and research collaborators.

The Sarcoma Program’s clinical trials focus on targeted therapies and newer drugs such as aldoxorubicin and regorafenib. In addition, a novel hypoxia-activating agent, TH302, is under intense investigation for high-grade soft tissue sarcomas. The program includes specialists in sarcoma surgery, interventional radiology, stereotactic body radiation therapy, and intraoperative radiotherapy. We are an active participant in clinical trials conducted in collaboration with Dana Farber Cancer Institute, MD Anderson Sarcoma Center, and the University of Michigan Cancer Center through SARC (Sarcoma Alliance for Research through Collaboration).

We hope that you will consider a Stanford Cancer Institute clinical trial or novel treatment program when considering referral to an academic medical facility. We will strive to deliver state-of-the-art care, keep you informed during every phase of treatment, and would be glad to collaborate in ongoing cancer surveillance and screening for your patients.

Susan Swetter, MD
Professor of Dermatology
Director, Pigmented Lesion and Melanoma Program
Stanford Cancer Institute
Stanford’s Gastrointestinal (GI) Oncology Program integrates the latest laboratory discoveries, technological innovations, and support services into the care of cancer patients. As an NCI designated cancer center, Stanford is renowned for its contributions to cancer research and for the translation of research successes to the benefit of patients. Specialists work together to develop a personalized treatment strategy that offers the best chance of a favorable outcome, aiming for cure whenever possible.

**ACCESS TO NOVEL THERAPIES**

GI specific medical oncologists conduct studies on the most promising drugs that come from laboratory experimentation. For instance, drugs that are now standard for patients with colorectal cancer were available in clinical trials at Stanford and other cancer centers years before they were approved. Centers such as Stanford are poised to lead the field of new, targeted therapeutics specifically suited to the molecular features of an individual’s tumor, thereby ushering in the era of true personalized oncology care.

**Trials of Particular Interest**

- Randomized vaccine study of resected pancreas cancer in which the standard chemotherapy or chemoradiation can be administered by the patient’s local oncologist.
- Multicenter trial led by Stanford with Memorial Sloan Kettering and Johns Hopkins that is investigating the role of stereotactic radiosurgery for unresectable pancreas cancer. Again, the standard “chemo” can be administered by the patient’s local oncologist.
- Phase I/II trials using novel molecularly targeted agents for metastatic colorectal and gastro-esophageal cancers. Molecularly targeted therapies include drugs that specifically bind to key molecules on or in the tumor cells and immunotherapeutic antibodies that are capable of triggering an immune response against the cancer. These promising strategies are in their infancy in development yet are already showing encouraging clinical results in patients.
GI Oncology Multidisciplinary Team of Specialists

- This multidisciplinary team consists of specialists who focus on cancers of the GI tract. These include cancers of the esophagus, stomach, liver, pancreas, bile duct, gall bladder, small intestine, appendix, colon, rectum, and anus. In addition, rare tumors such as neuroendocrine (carcinoid), GI Stromal Tumors (GIST), and pseudomyxoma peritonei fall within the GI Oncology Program domain.

- Team members work under one roof enabling seamless transitions among specialties and often same-day appointments with cancer surgeons, radiation oncologists, and medical oncologists. The GI Oncology Program also meets weekly with interventional and diagnostic radiologists, nuclear medicine specialists, gastroenterologists, and pathologists to review complex cases and newly diagnosed patients who would benefit from multidisciplinary expertise.

OTHER KEY ATTRIBUTES

- **Weekly GI and Liver Tumor Boards:** Newly diagnosed patients with GI cancers who might benefit from multidisciplinary consultation are seen in the weekly GI Tumor Board or in the weekly Liver Tumor Board. Anyone with localized pancreas, gastric, or rectal cancer may bring their family or close friends to a tumor board appointment where the entire GI Tumor Board reviews their medical history, pathology, and radiographic studies followed by a face-to-face discussion and consultation with the cancer surgeon, the medical oncologist, and the radiation oncologist. The advantage of meeting all relevant subspecialists to address patient and family questions and concerns is a unique feature of the tumor boards and an immense source of satisfaction for patients and their families.

- **World Renowned Expertise in Radiation Oncology:** Stanford is the birthplace of modern radiation therapy with contributions such as the first linear accelerator and the first CyberKnife. SCI also has the first Trilogy and TrueBeam systems for clinical use in the Western U.S. Many of the stereotactic radiotherapy techniques used routinely around the world were developed here. The first clinical trials investigating single fraction stereotactic body radiotherapy (SBRT) or stereotactic ablative radiotherapy (SABR) in liver and pancreas were from Stanford. GI radiation oncologists continue to improve the precision with which they radiate tumors while sparing adjacent normal tissues.
Minimally Invasive Laparoscopic and Robotic Surgeries:
Specialists in surgical oncology can sometimes remove cancers using a laparoscope, which can result in equally successful outcomes while limiting the size of the incision (and scar) and improving the recovery time following surgery. Surgeons offer laparoscopic procedures routinely for colon cancer and for selected cancers involving the stomach, pancreas, liver, and rectum. For selected patients with rectal cancer, Stanford can now offer “robotic” surgeries, a technological innovation that has been proven to be successful for prostate cancer and is now being applied to rectal cancers.

State of the Art Imaging Modalities and Regional Therapies: GI diagnostic and interventional radiologists as well as nuclear medicine specialists collaborate to provide the highest resolution images of tumors. Identifying the full anatomic extent of an individual cancer is key to determining the optimal treatment of the patient. For example, for selected patients whose cancer is limited to the liver, interventional radiologists can administer treatments directly through the blood vessels that feed the tumors in the liver, thus minimizing side effects of drugs to the rest of the body. Furthermore, high resolution MRIs determine which rectal cancer patients might benefit from radiation and which ones might be able to avoid a colostomy.

The Stanford GI Oncology Program feels that there are no “simple” GI cancers and that each newly diagnosed patient deserves the expertise that only a multidisciplinary team of GI-focused specialists can bring to bear. The best time to cure a cancer is the first time.

Clinical Studies Include

Colon/Rectal Adenocarcinoma

Neoadjuvant Rectal

- A Phase II/III Trial of Neoadjuvant FOLFOX with Selective Use of Combined Modality Chemoradiation versus Preoperative Combined Modality Chemoradiation for Locally Advanced Rectal Cancer Patients Undergoing Low Anterior Resection with Total Mesorectal Excision (ECOGN1048)
Neuroendocrine/Carcinoid Tumors

Metastatic Pancreatic NET

• A Phase II Study of Capecitabine, Temozolomide and Bevacizumab for Metastatic or Unresectable Pancreatic Neuroendocrine Tumors (NET0012)
• A Randomized Phase II Study of Temozolomide or Temozolomide and Capecitabine in Patients with Advanced Pancreatic Neuroendocrine Tumors (ECOGE2211)

Metastatic Pancreatic NET-Resected

• A Randomized, Double-Blinded, Placebo-Controlled Phase II Study of Adjuvant Everolimus Following the Resection of Metastatic Pancreatic Neuroendocrine Tumors to the Liver (ECOGE2212)

Metastatic Small Bowel NET

• A Multicenter, Stratified, Open, Randomized, Comparator-Controlled, Parallel-Group Phase III Study Comparing Treatment with 177Lu-DOTA0-Tyr3-Octreotate to Octreotide LAR in Patients with Inoperable, Progressive, Somatostatin Receptor Positive Midgut Carcinoid Tumours (NET0014)

Carcinoid Syndrome

• A Multicenter, Long-term Extension Study to Further Evaluate the Safety and Tolerability of Telotristat Etiprate (LX1606) (NET0019EXT)
• A Phase 3, Randomized, Placebo-controlled, Parallel-group, Multicenter, Double-blind Study to Evaluate the Efficacy and Safety of Telotristat Etiprate (LX1606) in Patients with Carcinoid Syndrome Refractory to Somatostatin Analog (SSA) Therapy (NET0016)
• SOON TO OPEN: A Phase 3, Randomized, Placebo-controlled, Multicenter, Doubleblind Study to Evaluate the Safety and Efficacy of Telotristat Etiprate (LX1606) in Patients with Carcinoid Syndrome (NET0018)

Metastatic Carcinoid

• A021202 Prospective Randomized Phase II Trial of Pazopanib (NSC # 737754, IND 75648) versus Placebo in Patients with Progressive Carcinoid Tumors (ECOGA021202)

• A Phase 2 Study to Investigate the Safety and Activity of Fosfretabulin Tromethamine (CA4P) in the Treatment of Well-Differentiated, Low-to-Intermediate-Grade Unresectable, Recurrent or Metastatic Gastrointestinal Neuroendocrine Tumors/Carcinoid (GI-NET) with Elevated Biomarkers (NET0020)

Pancreatic Adenocarcinoma

Locally Advanced

• A Randomized Phase III Study Evaluating Modified FOLFIRINOX (mFFX) with or without Stereotactic Body Radiotherapy (SBRT) in the Treatment of Locally Advanced Pancreatic Cancer (PANC0015)
The Skin Cancer Program at the Stanford Cancer Institute is a leading innovator in the research and treatment of all types of skin cancer, including melanoma, basal cell carcinoma, squamous cell carcinoma, Merkel cell carcinoma, and cutaneous lymphoma. The “solid tumor” Cutaneous Oncology Program relocated to the Stanford Cancer Center Blake Wilbur 3rd Floor (BW-3) location in February 2014 along with the Head and Neck Oncology Program, in an effort to expand clinical services, interdisciplinary care, and collaborative research in both melanoma and nonmelanoma skin cancers.

**MELANOMA: NEW FACULTY, CLINICAL-EPIDEMIÓLOGICAL RESEARCH AND PROGRAM DEVELOPMENT**

Dr. Justin Ko, Clinical Assistant Professor of Dermatology, joined the Stanford PLMP in December 2013 to enhance the care of patients with atypical nevi and melanoma. Dr. Ko is a vital link in Stanford’s community outreach expansion efforts that provide Stanford Dermatology expertise and clinical presence embedded within primary care practices in the East Bay (San Pablo and Alameda), Hayward, Portola Valley and Los Altos with sites in Oakland and Santa Clara soon to come. He has a clinical and research interest in new models of delivering care that leverage technology to support screening, triage and follow-up care of patients. Dr. Ko works closely with Dr. Swetter and Dr. Jennifer Boldrick, Adjunct Clinical Assistant Professor of Dermatology, to provide care in the Pigmented Lesion and Melanoma Clinic in BW-3.

The Stanford PLMP continues its longstanding research focus on melanoma epidemiology, prevention and survivorship under the direction of Dr. Swetter and other faculty colleagues, research epidemiologists at the Cancer Prevention Institute of California (CPIC), and Dr. Robert Haile, Professor in the Department of Medicine and Associate Director of Population Sciences at the Stanford Cancer Institute.

Collaborative work with CPIC researchers (Drs. Christina Clarke and Theresa Keegan) that demonstrated markedly
worse survival in young men compared with young women has prompted further study of patient factors related to early versus delayed detection in the adolescent and young adult population in California as well as potential biologic sex differences in melanoma tumor biology that may be immune-mediated, genetically distinct, and/or hormone-related.

Dr. John Sunwoo, Assistant Professor of Otolaryngology—Head and Neck Surgery, and Dr. Swetter are co-principal investigators of a recently awarded two-year Stanford Cancer Institute grant, funding a multi-disciplinary project focused on understanding these biologic differences.

Additional large-scale epidemiologic research lead by Jean Tang, MD, PhD, Associate Professor of Dermatology, Marcia Stefanick, PhD, Professor of Medicine at the Stanford Prevention Research Center, and Dr. Swetter utilized the Women’s Health Initiative Observational Study data and demonstrated that regular use of nonsteroidal anti-inflammatory agents (NSAIDs) was associated with an 18% lower odds of developing nonmelanoma skin cancer in women who had a history of skin cancer, suggesting the value of future studies to assess potential chemopreventative effects of NSAIDs in this subgroup. This study was published in 2014 in Preventive Medicine. In addition, Dr. Tang conducted the first trial of high dose vitamin D (4,000 IU) on precursor melanoma cells in women to investigate the global effects of vitamin D on the skin.

Further prevention efforts have been directed to Stanford’s outdoor student-athletes and the entire Stanford community through a novel program entitled SUNSPORT™, which stands for Stanford University Network for Sun Protection, Outreach, Research, and Teamwork. This unique initiative involves collaboration among Stanford Dermatology, Stanford Athletics (including Sports Medicine and Athletic Trainers), Stanford Cancer Institute, and Stanford Health Care to create an integrated research, education and intervention program dedicated to providing skin cancer risk awareness and sun protection education to student athletes, fans and supporters, and the Stanford community at large.

SUNSPORT co-founder, Dr. Justin Gordon, Clinical Assistant Professor of Dermatology, joined the Stanford Dermatology Department in September 2014 to continue to lead the program efforts, including skin screening for incoming freshman athletes and working with Stanford coaches and trainers to provide direct education to athletes to promote sun protection practices. Dr. Gordon plans to expand the educational messages to younger, school-age athletes, including those participating in Stanford youth sports camps, and outdoor enthusiasts alike.

- Improved survival in patients with advanced melanoma has only recently been demonstrated, following decades of new drug failures. Promising and effective novel immunotherapy and molecularly-targeted therapies continue to be approved by the FDA, including pembrolizumab, nivolumab, and the combination of dabrafenib and trametinib, both powerful inhibitors of components of the MAP kinase pathway that drives the aggressive biology of 50% of melanomas. These agents have been associated with improved patient outcomes and lower toxicity profiles than previously available drugs. Equally important is the use of systemic therapies to prevent melanoma recurrence in patients at high risk of relapse.

— Under the direction of medical oncologist, Dr. Sunil Reddy, Clinical Assistant Professor in Medicine, the Stanford PLMP continues to assess the use of adjuvant vemurafenib (a BRAF inhibitor) in patients with surgically removed high risk cutaneous melanoma (stage IIC) and resected stage III (lymph node) melanoma. A randomized adjuvant therapy trial assessing the use of both low and high-dose ipilimumab versus high-dose interferon in patients with surgically resected stage IIIB, IIIC, and IV melanoma was recently completed in the adult population and remains open to pediatric and adolescent age groups. The study results may change
the landscape of adjuvant therapy and provide further data for the design of future trials directed at lowering the risk of relapse and enhancing the lifespan of patients with high-risk melanoma.

Studies to watch for will include a multi-institution trial of nivolumab (a PD-1 inhibitor) and ipilimumab in patients with brain metastases, adjuvant trials comparing one of the PD-1-directed immune checkpoint blockers with either interferon or ipilimumab, cooperative group trials of intermittent versus continuous MAP kinase pathway inhibitors for advanced BRAF mutant melanoma, and comparisons of the sequences of combined checkpoint inhibitors with combined MAP kinase inhibitors for advanced BRAF mutant melanoma. Other studies in development will revisit the role of high-dose interleukin-2 with other immunomodulatory therapies for advanced melanoma patients.

Other trials of molecularly-guided therapy, particularly important in patients whose tumors do not have a BRAF mutation, and novel immunotherapies will follow, and we expect to see a surge in patient referrals once these trials are in place at Stanford.

Over one million Americans are currently living with a melanoma diagnosis. As melanoma becomes a more treatable disease in patients with advanced stages, attention to survivorship issues is even more critical. Stanford melanoma surgeon Ralph Greco, MD, Professor of Surgery, Dr. Swetter, Oxana Palesh, PhD, Assistant Professor of Psychiatry and Behavior Science (Psychosocial), and Kelly Bugos, MS, NP, Manager of the Stanford Cancer Survivorship Program, recently published the results of a needs assessment survey in Supportive Care in Cancer, which showed that both short- and long-term melanoma survivors report ongoing psychosocial symptoms years after treatment, especially anxiety, and express a need for education regarding long-term melanoma effects, family risk, protection from future sun damage, and prevention of additional skin cancer. Given these results, the Stanford PLMP is establishing a formal Melanoma Survivorship Clinic, along with conducting more research to improve the quality of life for melanoma survivors.

NEW PROGRAM DEVELOPMENT AND FACULTY IN SUPPORTIVE DERMATO-ONCOLOGY AND CUTANEOUS MALIGNANCIES DERMATOLOGY AND SURGICAL PROGRAMS

Supportive Dermato-Oncology (SDO): In August 2014, Dr. Silvina Pugliese, Clinical Assistant Professor of Dermatology, joined colleague Dr. Bernice Kwong, Clinical Assistant Professor of Dermatology, to expand the clinical efforts of the Stanford Supportive Dermato-Oncology Program. This unique program allows for same-day, on-site dermatology evaluation of patients undergoing cancer therapy to address cutaneous complications related to cancer diagnosis and skin side effects of cancer treatment. Patients are seen at the Stanford Cancer Center (SCC), Blake Wilbur, and the Infusion Treatment Area (ITA), with plans to expand to the Redwood City Infusion Therapy Center (ITC) and South Bay Cancer Center.

The SDO program, directed by Dr. Kwong, has improved quality of life for patients by treating debilitating skin conditions and allowing cancer patients to continue treatment in many cases. Dr. Pugliese, a recent graduate from Loma Linda Dermatology residency, has a longstanding interest in cutaneous oncology and provides much needed assistance for the rapidly-expanding SDO program at Stanford. She will also lead the South Bay Cancer Center SDO clinic efforts in the coming year.

Nonmelanoma Skin Cancer (NMSC): Stanford Dermatology surgeon Dr. Sumaira Aasi, Clinical Professor of Dermatology and Director of the Dermatologic Surgery Program, and Dr. Vasu Divi, Assistant Professor of Otolaryngology—Head and Neck Surgery, recently established a multi-specialty Nonmelanoma Skin Cancer Working Group, which includes over 20 Stanford faculty members in the departments of medical and surgical dermatology, dermatopathology, head and neck and plastic/reconstructive surgery, medical and radiation oncology, as well as basic science and translational researchers. This Tumor Board examines optimal treatment for patients with advanced basal cell carcinoma (BCC), high-risk squamous cell carcinoma (SCC), as well as other rare skin tumors and promotes translational research and clinical trials to improve patient outcomes.
— **Dr. S. Tyler Hollmig**, Clinical Assistant Professor of Dermatology and Director of Laser and Aesthetic Dermatology, joined Dr. Aasi in September 2014 as a Stanford Dermatology surgeon, following completion of his procedural dermatology fellowship at the Medical University of South Carolina. Dr. Hollmig’s clinical focus is on Mohs Micrographic Surgery and complex reconstruction, rare and high-risk NMSC, as well as cosmetic dermatology. In addition to his role as a member of the multidisciplinary high-risk nonmelanoma skin cancer team, Dr. Hollmig provides support to an even broader platform of cancer patients through his new “Aesthetic Oncology” practice. This clinic provides care for cancer patients with aesthetic concerns arising from systemic, surgical, and/or radiation-related treatment, including laser treatment for hypertrophic scars and radiation-induced telangiectasias, fillers for atrophic skin, and other techniques that can improve the well-being of the cancer patient both during and following treatment.

— **Dr. Anne Chang**, Assistant Professor of Dermatology, offers a multidisciplinary Advanced Basal Cell Carcinoma (BCC) Clinic at BW-3 in conjunction with medical oncology colleague Dr. Dimitri Colevas and head and neck surgeon Dr. Divi. Together, they collaborate in the care of patients with complex and difficult-to-treat BCCs referred from the surrounding region and other states. Dr. Chang supervises cutting-edge clinical trials for the management of advanced BCC, as well as a multi-year registry to study outcomes of this condition.

— **Dr. Carolyn Lee**, Clinical Instructor in Dermatology, established a Post-Transplant / High Risk Skin Cancer Clinic in Stanford Dermatology, which focuses on patients at increased risk of developing skin cancer (especially squamous cell carcinoma) due to various causes, including immune suppression therapy following a solid organ or bone marrow transplant. Dr. Lee recently identified KNSTRN, a new oncogene in human cancer, while investigating genetic causes of squamous cell carcinoma in the lab of Dr. Paul Khavari, Professor and Chair of Dermatology. This work, published in *Nature Genetics*, showed that a single base substitution arising during the cell’s attempt to repair ultraviolet-associated DNA damage promotes aneuploidy and subsequent tumor growth. Dr. Lee has transitioned the High-Risk Skin Cancer Clinic to BW-3 to increase the interaction with surgical and medical oncology experts involved in the care of these patients. Stanford dermatologists plan to add a second NMSC screening clinic in BW-3 focusing on both at-risk adults and the adolescent and young adult (AYA) population with immunosuppression resulting from organ and bone marrow transplantation. Cancer screening in both younger and older transplant recipients is critical as skin cancer risks dramatically increase with longer duration of immunosuppression.

— **Dr. Kavita Sarin**, Clinical Assistant Professor of Dermatology, is spearheading a new Skin Cancer Genetics Clinic in BW-3 to identify patients at a high risk of skin cancer due to strong family history or positive genetic test results and to provide preventive skin surveillance and education to these individuals. Patients include those with inherited cancer syndromes such as Li-Fraumeni, familial melanoma and pancreatic cancer, BRCA1 and BRCA2, neurofibromatosis, and Lynch Syndrome. Dr. Sarin will conduct clinical care and research efforts in conjunction with Stanford Cancer Genetics faculty and counselors. We are pleased to provide this novel approach to improving the lives of cancer patients and their relatives who may also benefit from early intervention to provide skin screening and enhanced prevention efforts.

— The PLMP and NMSC Program are fortunate to have two Stanford surgeons specializing in head and neck surgical oncology, Drs. Sunwoo and Divi, as well as *Subhro Sen, MD*, Clinical Assistant Professor of Plastic and Reconstructive Surgery, who specializes in complex surgical reconstruction on the head/neck, trunk, and extremities. One of Dr. Sunwoo’s main clinical interests is melanoma of the head and neck. His laboratory research interests include the study of natural killer...
cells and the immune response to cancer stem cells to improve understanding of host immune surveillance in malignant transformation and cancer development.

Dr. Sunwoo is also working with Lei Xing, PhD, Director of the Physics Division of Radiation Oncology, and Andrew Quon, MD, Co-Director of Nuclear Medicine, to develop novel uses of photoacoustic imaging to aid the detection of melanoma metastases to lymph nodes. He also manages a clinical database of head and neck sentinel lymph node biopsy cases that will be used to improve the understanding of this approach in the broad context of melanoma surgical management.

Dr. Divi has a strong clinical interest in the surgical management of head and neck cutaneous malignancies, including melanoma, Merkel cell carcinoma, and high-risk squamous cell carcinoma. His research interests include clinical outcomes for high-risk cutaneous head and neck squamous cell carcinoma and examining tumor biomarkers associated with high-risk disease. Dr. Divi is currently focused on determining the optimal imaging and treatment strategies in high-risk SCC, including the use of sentinel lymph node biopsy and adjuvant radiation therapy for appropriate patients. Dr. Sen has a particular clinical interest in reconstruction following melanoma and nonmelanoma skin cancer resection utilizing state-of-the-art graft, flap and microsurgical techniques.

Collaborative Cutaneous Oncology Surgical Team Expands Research to Improve Skin Cancer Surgery
Stanford melanoma surgeons perform surgery for all stages of melanoma, from early disease to the most advanced. Dermatologic surgeons operate on patients with melanoma in situ and thinner tumors that do not require simultaneous staging with the sentinel lymph node biopsy procedure. Surgical Oncologists specialize in melanoma surgery for patients with head and neck tumors (Otolaryngology, Head & Neck Surgery) or for melanoma elsewhere on the body (General Surgery/Surgical Oncology).

— The Stanford PLMP features a collaborative team of dermatologic and melanoma surgeons who perform wide local excision, sentinel lymph node biopsy (SLNB) for melanoma staging, as well as resection of more advanced disease.
— Mohs and Dermatologic Surgeons Dr. Aasi and Dr. Hollmig continue to expand cutaneous surgical treatment of melanoma and nonmelanoma skin cancers in the Dermatology Department.
— The Skin Cancer Program uses SLNB to detect microscopic spread of melanoma and Merkel cell carcinoma in regional lymph nodes with novel imaging modalities to improve accuracy. Significant advances in localizing sentinel lymph nodes have occurred over the years, and the Stanford melanoma surgeons work closely with the Stanford Division of Nuclear Medicine and Molecular Imaging during the preoperative assessment and lymphatic mapping.
— Newer imaging techniques, such as SPECT/CT, have dramatically improved Stanford surgeons’ ability to assess the location of the sentinel lymph node in the setting of complex anatomy. Stanford surgeon Dr. Greco and Dr. Swetter recently published a study assessing the role of indocyanine green dye for improved localization of sentinel lymph nodes during the sentinel node biopsy. The article was published in 2014 in the *Journal of Surgical Oncology*.

**MELANOMA TRANSLATIONAL RESEARCH HIGHLIGHTS**

- **Studies of the innate immune response** to melanoma cancer stem cells and what regulates this response are being conducted in the laboratory of Dr. Sunwoo. He and Dr. Swetter are co-principal investigators of a two-year Stanford Cancer Institute-funded project, focused on understanding potential immune-related mechanisms underlying differences in clinical outcomes between men and women with melanoma. This multi-disciplinary project involves a number of Stanford collaborators, including Drs. Haile, Holden Maecker, Howard Chang, Michelle Longmire, Serena Chang, Mark Davis, and Holbrook Kohrt, as well as collaborators at the Cancer Prevention Institute of California, Drs. Keegan and Clarke.

- Dr. Sunwoo was also recently awarded a grant from the National Institutes of Health through the National Cancer Institute “Provocative Questions” initiative to identify signals that activate the immune system at the earliest stages.
of malignant transformation in melanoma. This project represents a collaborative effort between Jinah Kim, MD, PhD, Assistant Professor of Pathology and Dermatology and Director of Stanford Dermatopathology, and Dr. Swetter.

- **Identification of genetic alterations and pathways of melanoma development** continue in the laboratory of Dr. Paul Khavari, Professor and Chair of Dermatology, and will provide powerful therapeutic options for patients diagnosed with all stages of melanoma.

- **New immunotherapy trials**
  - The first potentially curative immunotherapy, ipilimumab, has become a standard of care for patients with advanced melanoma by stimulating the immune response against cancer. A novel immunotherapy agent targeting PD-1 appears even more promising and will be tested at Stanford as a treatment for Merkel cell carcinoma.
  - Stanford Professor of Radiation Oncology Susan Knox, MD, PhD, continues to lead a trial of ipilimumab and palliative radiation therapy, for patients with metastatic melanoma. This study tests whether ipilimumab combined with radiation therapy enhances the body’s ability to attack melanoma—even outside of the radiation field. Significant clinical responses in disease sites outside the radiation therapy field have been observed in a subset of patients, and work is ongoing to study potential immune response biomarkers that correlate with response in these patients. This study has helped to provide a compelling rationale for a phase II trial at Stanford and other collaborating institutions that will open in 2015. This new randomized study will evaluate the efficacy of combining nivolumab and ipilimumab with different doses/schedules of external beam radiotherapy and will specifically address how best to deliver radiation therapy in combination with immunotherapy.

**NON-MELANOMA SKIN CANCER EXPERTISE**

**Stanford Leadership in Novel Medical Therapy for Basal Cell Carcinomas**

- The **Basal Cell Carcinoma Research Group** at Stanford is conducting several clinical studies to assess novel therapies for non-melanoma skin cancers, including basal cell carcinoma (BCC). Stanford Dermatology clinical-investigators and basic scientists conducted pivotal research in the use of the recently FDA-approved drug, vismodegib, for patients with advanced BCC, including those with inoperable tumors and metastatic disease. This drug stems from basic research on the hedgehog pathway at Stanford over the past 15 years and is the first drug in a new class of anti-tumor agents.

  — Stanford Dermatology researchers Anthony Oro, MD, PhD (Professor of Dermatology), Dr. Chang, and Dr. Tang have pioneered the study of this agent in patients with locally aggressive and metastatic BCCs, as well as those BCCs that derive from patients with basal cell nevus syndrome, a genetic disorder than results in the formation of hundreds of skin cancers. Along with Dr. Aasi, they recently published their study of this drug as pretreatment prior to skin cancer surgery (Mohs) to shrink tumors and reduce scarring in the *Journal of the American Academy of Dermatology*.

  — Ongoing research involving this class of drugs, termed hedgehog pathway inhibitors, is in progress at Stanford for locally advanced tumors that are not curable with surgery or in whom surgery would lead to loss of vital function or unacceptable morbidity or for metastatic BCC. Dr. Sarin continues her research to assess germline and somatic genetic variants that influence BCC risk, prognosis, and response to therapy. Dr. Chang completed a multicenter study of erismodegib for advanced BCC and has several studies to address resistance to smoothened inhibitor monotherapy. Dr. Tang has also tested new drugs (itraconazole, arsenic trioxide) for resistant BCCs and recently published this data in the *Journal of Clinical Oncology*. In addition, studies to address advanced SCC using immunotherapy are in the planning stages.

- **Merkel Cell Carcinoma**

Merkel cell carcinoma, also called neuroendocrine cancer of the skin, is a rare skin cancer, although incidence is on the rise in the US. Merkel cell carcinoma (MCC) is usually found on the sun-exposed areas of the head, neck, arms, and legs of older, fair-complexioned individuals but can occur in people of other races and ages. MCC grows rapidly...
and often metastasizes to other parts of the body. When the disease spreads, it tends to spread to the regional (nearby) lymph nodes and may also spread to the liver, bone, lungs, and brain.

The Stanford Merkel Cell Program offers a multidisciplinary approach to the treatment of MCC, utilizing the expertise of Stanford surgeons for wide local excision and SLNB staging. MCC is very sensitive to radiation therapy, and thus, most patients will benefit from adjuvant radiation to the primary tumor site following resection, as well as to the regional lymph node basin in the event that the SLNB is positive for metastasis. The Multidisciplinary MCC Program at Stanford is pursuing research of newer immunotherapies, including PD-1 inhibitors, to treat advanced disease.

**CLINICAL TRIALS INCLUDE**

**Melanoma**

- A Pilot Study of Ipilimumab in Subjects with Stage IV Melanoma Receiving Palliative Radiation Therapy (MEL0005)

- A Phase III, Randomized, Double-blind, Placebo-controlled Study of Vemurafenib (RO5185426) Adjuvant Therapy in Patients with Surgically Resected, Cutaneous BRAF-Mutant Melanoma at High Risk for Recurrence (MEL0006)

- The NEMO Trial (NRAS Melanoma and MEK Inhibitor): A Randomized Phase III, Open Label, Multicenter, Two-Arm Study Comparing the Efficacy of MEK162 versus Dacarbazine in Patients with Advanced Unresectable or Metastatic NRAS Mutation-Positive Melanoma (MEL0008)

- SOON TO OPEN: A Phase 1 Study of the Clinical and Immunologic Effects of ALT-803, a Novel Recombinant IL-15 Complex in Patients with Advanced Melanoma (MEL0011)

- SOON TO OPEN: A Phase II Randomized Study to Evaluate the Efficacy of the Combination of Nivolumab and Ipilimumab with Different Doses/Schedules of External Beam Radiation Therapy (MEL0009)

- SOON TO OPEN: A Phase III Randomized, Double-blind Study of Adjuvant Immunotherapy with Nivolumab vs Ipilimumab after Complete Resection of Stage IIIB/C or IV Melanoma in Subjects at High Risk for Recurrence

**Nonmelanoma Skin Cancer**

- A Prospective Observational Study of Treatment Patterns and Effectiveness and Safety Outcomes in Advanced Basal Cell Carcinoma and Basal Cell Carcinoma Nevus Syndrome Patients (SKIN0013)

- Double-Blind, Randomized, Placebo-Controlled Two-Period Crossover Study to Assess the Effect of L-Carnitine on Vismodegib-Associated Muscle Spasms (SKIN0018)

- An Open-Label Pilot Study to Evaluate the Efficacy and Safety of a Combination Treatment of LDE225 and BKM120 for the Treatment of Advanced Basal Cell Carcinomas (SKIN0020)

- SOON TO OPEN: A Phase II Study of MK-3475 in Patients with Advanced Merkel Cell Carcinoma (MCC) (SKIN0025)
The Stanford Sarcoma Program participates in a variety of sarcoma clinical trials, plays an active role in SARC (Sarcoma Alliance for Research through Collaboration), and offers a multidisciplinary, collaborative approach to treatment, diagnostics, and prevention.

**STANFORD SARCOMA CLINICAL TRIALS FOCUS ON**
- Targeted therapies such as tyrosine kinase inhibitors for gastrointestinal stromal tumors (GIST) and other sarcomas.
- Newer drugs such as aldoxorubicin and regorafenib. In addition, a novel hypoxia-activating agent, TH302, is under intense investigation for high grade soft tissue sarcomas.
- Collaborations with:
  1. Dana Farber Cancer Institute
  2. MD Anderson Sarcoma Center
  3. University of Michigan Cancer Center in cooperative trials through SARC. SARC is an international organization facilitating research partnership among sarcoma researchers, physicians, and medical institutions to establish new models in sarcoma treatment, education, and prevention.

**THE PROGRAM FEATURES**
1. Surgical, radiation, and medical oncologists.
2. Sarcoma focused experts from pathology, interventional and diagnostic radiology, nuclear medicine, and genetics.
3. Nurse coordinators, nurse practitioners, physician assistants, social workers, and dietitians.

Among the experienced specialists are surgeons Jeffrey A. Norton, MD, The Robert L. and Mary Ellenburg Professor in Surgery, and David G. Mohler, MD, Clinical Professor, Orthopaedic Surgery; and pathologists Jan Matthijs van de Rijn, MD, PhD, Professor of Pathology, and Robert West, MD, Associate Professor of Pathology, both of whom research gene profiling.

**STANFORD SARCOMA PROGRAM HIGHLIGHTS**
- **Sarcoma Tumor Board That Meets on a Weekly Basis.** New patients, as well as other challenging cases, are presented to this multidisciplinary team. The patient’s radiographs are reviewed by expert radiologists, including the nuclear medicine team. The pathology slides are reviewed in tumor board by pathologists specializing
specifically in sarcoma histology. The team of medical oncologists, surgeons, and radiation oncologists then discuss the best treatment course for the patient.

- **Sarcoma Subspecialty Surgeons** who perform innovative surgical techniques in treating the most difficult sarcoma cases with complex surgical problems.

- **Multidisciplinary Sarcoma Clinics** that enable patients to undergo concurrent consultations from multiple disciplines such as a medical oncologist, oncological surgeon, and radiation oncologist, often at the same appointment.

- **Interventional Radiology Service** that offers chemoembolization, radiofrequency ablation, and radioembolization of primary liver sarcomas as well as limited metastases to the liver.

- **Stereotactic Body Radiation Therapy** that provides targeted delivery of radiotherapy for more localized lesions or limited metastatic foci.

- Intraoperative Radiotherapy that allows delivery of high dose radiation therapy in the operating room after removal of the tumor mass, leading to better local control.

**CLINICAL TRIALS INCLUDE**

- A Multicenter, Randomized, Open-Label Phase 3 Study to Investigate the Efficacy and Safety of Aldoxorubicin Compared to Investigator’s Choice in Subjects with Metastatic, Locally Advanced, or Unresectable Soft Tissue Sarcomas Who Either Relapsed or Were Refractory to Prior Non-Adjuvant Chemotherapy (SARCOMA0013)

- A Blanket Protocol to Study Oral Regorafenib in Patients with Refractory Liposarcoma, Osteogenic Sarcoma, and Ewing/Ewing-Like Sarcomas (SARC-024)

- A Feasibility Study to Evaluate the Safety and Initial Effectiveness of ExAblate MR Guided Focused Ultrasound Surgery in the Treatment of Pain Resulting from Metastatic Bone Tumors with the ExAblate 2100 Conformal Bone System (BONE0007)
Developmental Therapeutics
Phase 1 and 2 Studies for Multiple Cancers

Stanford Cancer Center’s Developmental Therapeutics Program, led by A. Dimitrios Colevas, MD, offers Phase 1 and 2 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.

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 studies.

**PHASE 1 STUDIES**

*Multiple Solid Tumor Sites*

- A Phase 1, 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 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)
- Phase 1, First-in-Human, Dose-Escalation Study to Evaluate the Safety, Tolerability, and Pharmacokinetics of X-396 in Patients with Advanced Solid Tumors (VAR0098)
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