Welcome to the Summer 2017 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 therapies, including the latest “targeted” agents and immunotherapeutic options only available in the academic realm.

As the Physician Leader of the Cutaneous Oncology Program, Professor of Dermatology, and Director of the Pigmented Lesion and Melanoma Program, I am pleased to introduce this issue that showcases our multidisciplinary programs: 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 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 and atypical melanocytic neoplasms (both adult and pediatric), high-risk and solid organ transplant-associated squamous cell carcinoma, advanced basal cell carcinoma, Merkel cell carcinoma, and rarer cutaneous malignancies. It encompasses several distinct clinical programs, including a unique Supportive Dermato-Oncology clinic that addresses cutaneous side effects from treatment, across the cancer spectrum. Clinics are held in the Stanford Cancer Center in Palo Alto and Cancer Center South Bay (CCSB) in San Jose.

The Sarcoma Program’s clinical trials focus includes tyrosine kinase inhibitors for gastrointestinal stromal tumors and other sarcomas. The program offers access to newer drugs such as aldoxorubicin and regorafenib. In addition, a novel hypoxia-activating agent, TH302, is under investigation for high-grade soft tissue sarcomas.

The program features specialists in sarcoma surgery, interventional radiology, stereotactic body radiation therapy, and intraoperative radiotherapy. Stanford is 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 the Sarcoma Alliance for Research through Collaboration (SARC).

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.

Susan M. Swetter, MD
Professor of Dermatology
Director, Pigmented Lesion and Melanoma Program
Physician Leader, Cutaneous Oncology Program
The Cutaneous Oncology Program at the Stanford Cancer Institute, led by Professor of Dermatology and Director of the Pigmented Lesion and Melanoma Program Dr. Susan Swetter, continues to lead in the research and treatment of all skin cancer types, including melanoma and atypical melanocytic neoplasms (both adult and pediatric), high-risk and solid organ transplant-associated squamous cell carcinoma, advanced basal cell carcinoma, Merkel cell carcinoma, and rarer cutaneous malignancies. Cutaneous Oncology – Skin Cancer and Supportive Dermato-Oncology clinics are held in the Stanford Cancer Center in Palo Alto (900 Blake Wilbur, 3rd floor [BW-3]) and the Cancer Center South Bay (CCSB) in San Jose.
RECENT CUTANEOUS ONCOLOGY PROGRAM EXPANSION HIGHLIGHTS

New Faculty, Program Development, and Community Outreach

The Cutaneous Oncology Program welcomed Clinical Assistant Professor of Dermatology Dr. Kathryn Martires in August 2016. She specializes in graft-versus-host disease (GVHD) and sees patients at both BW-3 and CCSB. Dr. Martires has established a new GVHD Clinic that focuses on cutaneous complications following hematopoietic stem cell (e.g. bone marrow) transplantation. Dr. Martires also co-attends in the Pigmented Lesion and Melanoma Clinic (PLMC) at BW-3 and runs a satellite PLMC at CCSB for new and established patients. She continues the Supportive Dermato-Oncology efforts at CCSB as well.

Clinical Assistant Professor of Dermatology Dr. Teresa Fu directs the Post-Transplant/High Risk Skin Cancer Clinic at both Palo Alto and CCSB locations, specializing in the multidisciplinary care of patients with Merkel cell carcinoma and high-risk and solid organ transplant-associated squamous cell carcinoma (SCC).

Clinical Assistant Professor of Surgery Dr. Dana Lin specializes in sentinel lymph node biopsy and lymphadenectomy for trunk and extremity melanomas, and other skin cancers. Dr. Lin is exploring collaborative research opportunities for neoadjuvant therapy in melanoma with surgical oncologists nationwide.

Dr. Kavita Sarin, Assistant Professor of Dermatology, directs a Skin Cancer Genetic Clinic in BW-3 to evaluate and treat patients at high risk of skin cancer due to strong family history or positive genetic test results. This clinic provides diagnostic evaluation, genetic testing, preventive care, skin surveillance, and education to at-risk patients, in conjunction with Stanford Cancer Genetics faculty and counselors. Patients include those with the p16/CDKN2A mutation associated with melanoma and pancreatic cancer, as well as inherited cancer syndromes such as Li-Fraumeni, familial melanoma and pancreatic cancer, BRCA1 and BRCA2, neurofibromatosis, and Lynch Syndrome.

Dr. John Yost, Clinical Assistant Professor of Dermatology, directs a weekly Nail Disorders Clinic in BW-3 that is focused on treating nail-related side effects due to cancer therapy and improving diagnosis and treatment of skin cancers that arise within the nail unit, including melanoma. Conditions treated include paronychia and onychocryptosis (ingrown toenails) resulting from EGFR-inhibitor therapy, onycholysis associated with chemotherapeutic agents, secondary bacterial and fungal infections of the nail unit from therapy-related immunosuppression, and treatment and monitoring of longitudinal melanonychia and other neoplastic onychodystrophies.

Our busy Supportive Dermato-Oncology (SDO) clinics take place at BW-3 and CCSB. This unique service was developed by Stanford Clinical Associate Professor Dr. Bernice Kwong in 2012 to provide urgent, on-site dermatology evaluation of cutaneous complications related to cancer diagnosis and treatment, allowing for improved quality of life during therapy. The SDO program is run by Dr. Kwong and Clinical Assistant Professor of Dermatology Dr. Silvina Pugliese at BW-3, and by Dr. Martires at CCSB. Dr. Kwong is spearheading a new Dermatology-Oncology Consult Service (DOCS) to provide dedicated SDO services to cancer inpatients at Stanford Hospital, slated to begin in July 2018. As part of the SDO program, Dr. Tyler Hollmig, Clinical Assistant Professor of Dermatology/Dermatologic Surgery and Director of Laser and Aesthetic Dermatology is
working with Stanford cancer patients to provide “aesthetic oncology” treatments related to prior or current cancer therapy, such as scar revision of port sites and removal of radiation-related telangiectasias or tattoos.

In January 2017, a new Photodynamic Therapy (PDT) Clinic was launched at Stanford Cancer Center in BW-3 to deliver treatment for patients at high risk for developing precancerous skin lesions and superficial skin cancers such as basal cell carcinoma, and also to study new applications of PDT for conditions such as cutaneous metastasis. It is anticipated that PDT services will be expanded to CCSB as well.

Stanford Professor of Dermatology Dr. Sumaira Aasi continues to co-lead the Nonmelanoma Skin Cancer Working Group, along with Dr. Vasu Divi, Assistant Professor of Otolaryngology, Head and Neck Surgery. This multi-specialty “dry” tumor board features 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.

The monthly Tumor Board examines optimal treatment for patients with advanced basal cell carcinoma (BCC), high-risk SCC, and other rare skin tumors, and promotes translational research to improve patient outcomes.

Drs. Hollmig and Aasi use state-of-the-art surgical techniques for melanoma in situ, lentigo maligna type, on cosmetically-sensitive areas, such as the face. The Mohs surgical approach is combined with real-time immunohistochemical stains (melan-A) for melanoma to allow for more precise intra-operative determination of peripheral tumor margins to preserve as much normal skin as possible.

Associate Professor of Dermatology Dr. Anne Chang works closely with Stanford medical and surgical oncology specialists to provide a weekly multidisciplinary BCC at BW-3. Together they collaborate in the care of patients with complex and difficult-to-treat BCCs referred from the surrounding region and other states, and have spearheaded progress in immune checkpoint blockade for advanced nonmelanoma skin cancers. Several research trials are enrolling for patients with BCC and cutaneous squamous cell carcinomas.

**CUTANEOUS MALIGNANCIES — CLINICAL AND TRANSLATIONAL RESEARCH HIGHLIGHTS**

- **Viral oncolytic immunotherapy with Talimogene Laherparepvec (T-VEC)**
  This novel oncolytic immunotherapy is based on the herpes simplex virus and injected directly into cutaneous and nodal metastasis to induce viral lysis of melanoma cells, followed by stimulation of a tumor-specific immune response. The administration of T-VEC requires special handling and is available through the Stanford Cutaneous Oncology Program for appropriate patients, offering an exciting new approach to treatment.

- **Novel Approaches to Uveal Melanoma**
A randomized, controlled phase 3 study is planned at Stanford for patients with ocular melanoma with liver metastasis, under the direction of Clinical Assistant Professor of Medicine-Oncology Dr. Sunil Reddy and Associate Professor of Ophthalmology and new Director of Ocular Oncology at the Byers Eye Institute, Dr. Prithvi Mruthyunjaya. This trial will evaluate the efficacy, safety, and pharmacokinetics of the chemotherapeutic agent melphalan with the Delcath Hepatic Delivery System (HDS) for uveal melanoma with hepatic metastasis. Dr. Mruthyunjaya brings valuable expertise to research and treatment of ocular melanoma, which has been poorly responsive to most therapies.

**New Immunotherapy Trials**

Immune checkpoint blockade has revolutionized cancer treatment and was first studied in melanoma, where anti PD-1 and CTLA-4 antibodies are now first-line therapy, along with combined inhibitors of the MAP kinase pathway (e.g. targeted therapy). Numerous studies are in progress or slated to open at the Stanford Cancer Center involving PD-1, PD-L1, and/or CTLA-4 inhibitors in combination with other systemic therapies or radiation therapy. Key highlights of ongoing and novel research are listed.

- PD-1 inhibitors have been successfully tested in a phase 2 trial at Stanford as a treatment for advanced Merkel cell carcinoma, with ongoing investigation of these agents planned.
- Stanford radiation and medical oncologists have analyzed the first cohort of patients in a prospective trial of ipilimumab and palliative radiation therapy for metastatic melanoma, in which significant clinical responses in disease sites outside the radiation therapy field were observed in a subset of patients, with ongoing complete responses at over 152 weeks. As a result, a phase 1 trial of combination checkpoint blockade (ipilimumab and nivolumab) and radiation therapy has been initiated at Stanford under the direction of Dr. Susan Knox, Associate Professor of
Radiation Oncology, in collaboration with Memorial Sloan Kettering Cancer Center. This will be followed by a randomized Phase II trial of this immunotherapy with 2 different radiation dose/fractionation regimens.

— A phase 2 trial is being led by Stanford neuro-oncologists of nivolumab (PD-1 inhibitor) and ipilimumab for melanoma with brain metastasis.

— Additional early phase trials of PD-1 inhibitors as in combination with other agents are also being studied at Stanford for melanoma and other skin cancer types, under the direction of Dr. Shivaani Kummar, Professor of Medicine and Director, Phase I Clinical Research Program, in the Division of Oncology at Stanford.

— Dr. John Sunwoo, Associate Professor of Otolaryngology (Head and Neck Surgery), in collaboration with Dr. Swetter and Dr. Holden Maecker, Research Professor of Immunology and Microbiology and Director, Human Immune Monitoring Center, continues his translational research to explore differences in cancer immune responses to cancer between males and females.

• **Novel Medical Therapy for Basal Cell Carcinomas**

The **Basal Cell Carcinoma Research Group** at Stanford is conducting ongoing clinical studies to assess novel therapies for patients with aggressive and/or inoperable BCC and SCC as part of the **Nonmelanoma Skin Cancer Program**. This research includes testing chemoresistant BCCs with combination therapies and studying ways to improve quality of life of patients while on long term targeted chemotherapy.

Numerous high-impact scientific publications have resulted from the collaborative research efforts of the Stanford Cutaneous Oncology faculty and staff that will advance the care and survivorship of cancer patients.
• A Phase 1 Study to Evaluate the Safety and Efficacy of Combination Checkpoint Blockade (Ipilimumab and Nivolumab) Plus External Beam Radiotherapy in Subjects with Stage IV Melanoma (MEL0015)
• Randomized Phase 2/3 Study of Nivolumab plus Ipilimumab plus Sargramostim versus Nivolumab plus Ipilimumab in Patients with Unresectable Stage III or Stage IV Melanoma (ECOG-ACRIN-EA6141)
• A Phase 3 Randomized Trial Comparing Physician/Patient Choice of Either High Dose Interferon or Ipilimumab to MK-3475 (Pembrolizumab) in Patients with High Risk Resected Melanoma (ECOG-ACRIN-S1404)
• A Randomized, Controlled, Phase 3 Study to Evaluate the Efficacy, Safety and Pharmacokinetics of Melphalan/HDS Treatment in Patients with Hepatic-Dominant Ocular Melanoma (SKIN0036) (SOON TO OPEN)
• A Phase 3, Double-Blinded, Randomized, Placebo-Controlled Study of Atezolizumab Plus Cobimetinib and Vemurafenib Versus Placebo Plus Cobimetinib and Vemurafenib in Previously Untreated BRAF (V600) Mutation-Positive Patients with Unresectable Locally Advanced or Metastatic Melanoma (MELMTS0006) (SOON TO OPEN)
• A Phase 1/1b, Open-Label, Multicenter, Repeat-Dose, Dose-Selection Study of CPI-444 as Single Agent and in Combination with Atezolizumab in Patients with Selected Incurable Cancers (VAR0141)
• A Phase 1/2 Multicenter Trial of ICOS Agonist Monoclonal Antibody (mAb) JTX-2011 Alone or in Combination with Nivolumab in Adult Subjects with Advanced Refractory Solid Tumor Malignancies (VAR0143)
• A Phase 2 Basket Study of the Oral TRK Inhibitor LOXO-101 in Subjects with NTRK Fusion Positive Tumors (VAR0136)

Nonmelanoma (Keratinocyte) Skin Cancer
• A Case Study of the Effects of Topical Itraconazole on Pharmacodynamic Modulation of Hedgehog Target Gene Expression in BCC in Patients (SKIN0030)

- highlighted studies are Stanford investigator initiated
The Stanford Sarcoma Program participates in a variety of sarcoma clinical trials, plays an active role in Sarcoma Alliance for Research through Collaboration (SARC), 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 and other sarcomas.
- Newer drugs such as aldoxorubicin and regorafenib. In addition, a novel hypoxia-activating agent, TH302, is under investigation for high grade soft tissue sarcomas.
- TRC105 is human/murine chimeric monoclonal antibody directed against endoglin (CD105) with potential antiangiogenic and antineoplastic activities. TRC105 in combination with standard dose pazopanib compared to single agent pazopanib in patients with angiosarcoma that targets those patients who 1) are not amenable to curative intent surgery (e.g., metastatic or bulky disease, and disease for which surgical resection would carry an unacceptable risk) and 2) have not received pazopanib or TRC105 previously. 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, 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
• Pilot Study to Explore the Role of Circulating Tumor DNA in the Management of Patients with Soft Tissue Sarcoma (SARCOMA0016)
• A Phase 1/2 Study of FPA008, an Anti-CSF1 Receptor Antibody, in Patients with Pigmented Villonodular Synovitis (PVNS)/Diffuse Type Tenosynovial Giant Cell Tumor (dt-TGCT) (SARCOMA0019)
• A Blanket Protocol to Study Oral Regorafenib in Patients with Refractory Liposarcoma, Osteogenic Sarcoma, and Ewing/Ewing-Like Sarcomas (SARC-024)
• A Phase 2 Multi-Center Investigation of Efficacy of ABI-009 (Nab-Rapamycin) in Patients with Advanced Malignant Perivascular Epithelioid Cell Tumors (PEComa) (SARCOMA0020)
• A Randomized, Open-Label, Phase 2 Trial of CMB305 (Sequentially Administered LV305 and G305) and Atezolizumab in Patients with Locally Advanced, Relapsed, or Metastatic Sarcoma Expressing NY-ESO-1 (SARCOMA0022)
• A Randomized Phase 3 Trial of TRC105 and Pazopanib Versus Pazopanib Alone in Patients with Advanced Angiosarcoma (TAPPAS) (SARCOMA0027)
Stanford Cancer Center’s Developmental Therapeutics Program, led by director Shivaani Kummar, MD, offers Phase 1 and 2 clinical trials designed to evaluate new treatments 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 (lymphomas), and Branimir I. Sikic.

Developmental Therapeutics 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. Her research interests focus on developing novel therapies for cancer. Dr. Kummar 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. Dr. Kummar 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 1 and 2 studies.

PHASE 1 AND 2 STUDIES

Multiple Solid Tumor Sites

- An Open-label Phase I Dose-escalation Study to Evaluate the Safety, Tolerability, Maximum Tolerated Dose, Pharmacokinetics, and Pharmacodynamics of the Anti-C4.4a Antibody Drug Conjugate BAY 1129980 in Subjects with Advanced Solid Tumors Known to Express C4.4a (VAR0146)
- Phase 1/2 Multicenter Trial of ICOS Agonist Monoclonal Antibody (mAb) JTX-2011 Alone or in Combination with Nivolumab in Adult Subjects with Advanced Refractory Solid Tumor Malignancies (VAR0143)
- A Phase 1b, Open-Label, Multicenter, Repeat-Dose, Dose-Selection Study of CPI-444 as Single Agent and in Combination with Atezolizumab in Patients with Selected Incurable Cancers (VAR0141)
- A Phase 1b/2, Open-label, Multicenter, Dose-escalation Trial of Intratumoral Injections of SD-101 in Combination with Pembrolizumab in Patients with Metastatic Melanoma (METS0003)
- A Phase 1/2 Dose Escalation and Cohort Expansion Study of the Safety and Tolerability of Urelumab Administered in Combination with Nivolumab in Advanced/Metastatic Solid Tumors and B Cell Non-Hodgkins Lymphoma (VAR0126)
- Phase 1/2, 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)
- A Phase 2 Basket Study of the Oral TRK Inhibitor LOXO-101 in Subjects with NTRK Fusion-Positive Tumors (VAR0136)
- NCI 9938: Phase I Clinical Trial of VX-970 in Combination with the Topoisomerase I Inhibitor Irinotecan in Patients with Advanced Solid Tumors (VAR0144)

Opening Soon

- A Phase I, First-in-Human, Open Label, Dose Escalation Study of MGD009, A Humanized B7-H3 x CD3 Dual-Affinity Re-Targeting (DART®) Protein in Patients with Unresectable or Metastatic B7-H3-Expressing Neoplasms and Neoplasms Whose Vasculature Expresses B7-H3 (VAR0148)
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