Multidisciplinary Cutaneous and T-Cell Lymphoma Program

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STANFORD MULTIDISCIPLINARY CUTANEOUS AND T-CELL LYMPHOMA PROGRAM (MCTLP)

The Stanford Multidisciplinary Cutaneous and T-cell Lymphoma team offers expert treatment for patients with cutaneous or systemic T-cell lymphomas, including mycosis fungoides (MF), Sézary syndrome (SS), CD30+ lymphoproliferative disorders (lymphomatoid papulosis and anaplastic large cell lymphoma), subcutaneous panniculitis-like T-cell lymphoma, gamma-delta T-cell lymphoma, CD8+ aggressive epidermotropic T-cell lymphoma, NK/T-cell lymphoma, systemic peripheral T-cell lymphomas, and cutaneous B-cell lymphomas. Our physicians subspecialize in treating these types of cancers, and have extensive expertise in handling the most complicated cases. In fact, we serve as the consultants to the experts. Consultations are comprehensive and clinic visits are coordinated to allow joint evaluations by our multidisciplinary team.

Innovative Discoveries and Treatments Available at Stanford

The Stanford team continues its leadership in bringing cutting-edge technology platforms to the clinics, testing new diagnostic and prognosticating tools and establishing biomarkers to guide selection of therapies that best align with patient’s lymphoma profile. Our multidisciplinary approach allows the most comprehensive and personalized management for each patient. Moreover, we offer the newest in novel targeted and immune therapies, including treatments that attack newly discovered tumor surface proteins, genetic and epigenetic alterations that affect cell signaling, proliferation, or survival pathways and/or microenvironment elements, to eliminate cancer cells. Here are examples of the new therapies available at Stanford and highlights of the clinical and translational development:

- Mogamulizumab (KW-0761) is a bioengineered, humanized monoclonal antibody against CCR4, highly expressed on tumor cells. Stanford’s leadership has led to the successful completion of the phase 3 trial and the FDA approval. We are now exploring combination therapies with mogamulizumab to improve the overall clinical benefit including strategies with radiation therapy or other immune therapies that can result in synergistic activity with mogamulizumab.

- Brentuximab vedotin is an antibody-drug-conjugate that targets CD30, commonly expressed on tumor cells in cutaneous T-cell lymphoma (CTCL). Stanford-led clinical trial in CTCL has shown impressive activity, allowing brentuximab vedotin as a standard of care option in the NCCN guidelines. Stanford’s trial, along with the phase 3 clinical trial data, was instrumental in the official FDA approval in CTCL, and we have demonstrated that brentuximab can clear CTCL even with minimal amount of CD30 target molecule.

- Immune checkpoint blockade, such as anti-PD-1 monoclonal antibody, unleashes the antitumor effector T cells that fight off malignant T cells in mycosis fungoides and Sézary syndrome. Promising clinical activity in CTCL with durable responses were observed with pembrolizumab. Comprehensive translational studies are ongoing to further characterize biomarkers predictive of clinical response or resistance to pembrolizumab and to identify optimal combination therapy strategies.
Novel macrophage checkpoint blockade, anti-CD47 monoclonal antibody, specifically discovered by Stanford investigators, is undergoing clinical development in solid tumors and lymphomas including CTCL. Blocking the checkpoint (“don’t eat me” signal) with the antibody allows effective phagocytosis of the malignant cells by patient’s own macrophages. Combination therapy with mogamulizumab (anti-CCR4 antibody) may enhance the “eat-me” signal and provide clinical immune synergy with improved results. Stanford is leading a multicenter ETCTN trial exploring this novel combination approach.

Anti-KIR3DL2 monoclonal antibody (lacutamab) therapy in cutaneous T-cell lymphoma. KIR3DL2 is highly and selectively expressed on neoplastic T cells, including mycosis fungoides and Sézary syndrome. This antibody works by stimulating the patient’s own immune system to attack the KIR3DL2-expressing cancer cells. In the phase 1 study, patients tolerated the humanized antibody very well and experienced significant clinical benefit, especially in those with Sézary syndrome. The early promising results has led to the development of the currently ongoing phase 2 pivotal study.

Stanford investigators have shown that low-dose (12 Gy) total skin electron beam therapy (LD-TSEBT) can be highly effective in clearing the skin disease in patients with CTCL. We are exploring various combination approaches with LD-TSEBT, to not only clear lymphoma in all compartments including the blood and lymph nodes but also to provide sustaining response by partnering with immune therapies. We have successfully combined LD-TSEBT with pembrolizumab or immune cytokines such as interleukin-12. Currently, we are exploring the combination of LD-TSEBT with mogamulizumab in a clinical trial.

Clinical trial based on Stanford’s genomics research targeting the molecules and pathways that allow survival advantage of malignant T-cells is ongoing in collaboration with Memorial Sloan Kettering Cancer Center. An oral PI3K dual inhibitor, duvelisib, is combined with histone deacetylase inhibitor, romidepsin. Targeted sequencing and other translational studies are ongoing. Other trials targeting cancer cell signaling and survival pathways, including a dual SYK-JAK inhibitor (cerdulatinib) and selected ITK inhibitor (CPI-818), are also ongoing in partnerships with industry.

Non-myeloablative allogeneic hematopoietic stem cell transplantation (HSCT) using total skin electron beam therapy (TSEBT), total lymphoid irradiation (TLI), and anti-thymocyte globulin (ATG) as novel preparatory regimen for patients with mycosis fungoides and Sézary syndrome. Stanford’s "protective" conditioning regimen allows patients to have long-lasting or curative results with much improved safety profile compared to conventional HSCT regimens. Given the safety advantage, we are also able to reduce risks for our older patients. This novel Stanford regimen is now being adopted at multiple expert centers, globally. Patients referred for consideration of allogeneic HSCT will be managed jointly with our multidisciplinary group.

Chimeric antigen receptor T-cells (CAR-T) technology equips the activated T-cells with the ability to target specific molecules on the cancer cells, resulting in potent killing of cancer cells by super-charged T-cells. With the discovery of gene editing tools, we now are able to utilize the CAR-T therapy to fight T-cell lymphoma cells specifically without the good T-cells killing each other. In partnership with CRISPR Therapeutics, CD70 targeting CAR-T therapy in cutaneous and systemic T-cell lymphomas have been initiated and early results show promising efficacy and safety results.

Newer photodynamic therapy using topical hypericin and non-UV light source, similar to fluorescent light, is being explored as a safer, non-skin damaging option for those seeking light type of therapy. A multi-center clinical trial in early-stage CTCL has been completed and data is published and being reviewed by the FDA. The goal of this treatment is to enable patients to use this well-tolerated light source at the comfort and safety of their home.

Newer molecular diagnostic methods including T-cell receptor (TCR) high throughput sequencing that offers superior sensitivity and specificity over conventional tools for the identification and monitoring of clonal malignant T cells. This type of technology is actively used to follow cancer activity that is not measurable by conventional methods, thus better defining and predicting if patients can be in long-term remission. The same method is also used to establish patient’s distinct malignant TCR sequence, thus differentiating lymphoma from benign or inflammatory mimics, leading to early and/or more definitive diagnosis. Furthermore, in the era of immune therapies that cause significant skin rashes, this highly specific method can best distinguish CTCL from rashes associated with the newer CTCL therapies, thus allowing us to optimize our management.

Stanford investigators have also shown that the clonal TCR sequence unique to each CTCL patient is a potential great target for immune therapy. In each patient, their lymphoma TCR target is present on every CTCL cell and uniformly absent on normal cells, thus allowing highly specific immune therapy. We are exploring methods to train the patient’s immune system to better recognize and target the lymphoma TCR and effectively kill the CTCL cells by enhanced anti-tumor immune activity. Pre-clinical studies of patient-specific anti-TCR immune response have been promising and we hope to launch a clinical trial in the next year.

Sophisticated in-depth next generation sequencing (NGS) methods have allowed Stanford investigators to identify key signaling and survival pathways and molecules used by CTCL cells for their growth and spread of cancer. These early discoveries have led us to have develop a targeted NGS panel for hematologic malignancies that can be utilized to identify actionable (“druggable”) targets in cutaneous and systemic T-cell lymphomas. These actionable NGS panels also help us identify the molecular mechanisms driving the patient’s lymphoma, allowing improved precision in prioritizing therapy.
International Leadership

The Stanford MCTLP team led the effort in establishing the Cutaneous Lymphoma International Consortium (CLIC), an international collaborative network of CL expert centers committed to partnering in large-scale research that is essential in generating meaningful data in rare disease groups such as CTCL. The CLIC Steering Committee was established to optimize the global representation of leadership. Collectively, we recognized the potential challenges of building and sustaining an ambitious international platform, thus we identified initial objectives with stepwise build towards the ultimate goal to prepare the CLIC alliance for translational discoveries with large-scale testing and validation for optimal clinical applicability. More than 60 international expert centers have joined to partake in the CLIC collaborative effort. Stanford and the UK co-lead center (UHB) serve as CLIC’s coordinating data center for the collection and management of clinical, pathology, and molecular data linked with a federated (“virtual”) Biobank establishment at each participating center. This CLIC Biobank and digitized pathology databank serve as an invaluable repository of clinical samples linked with prospectively collected clinical and pathology annotation for translational research in CL. Through this mechanism, key scientific discoveries reported from an expert center can be efficiently validated in a larger study at an international level.

CUTANEOUS AND T-CELL LYMPHOMA CLINICAL TRIALS

To learn more about active Lymphoma clinical trials, please visit: cancer.stanford.edu/trials or cutaneoulymphoma.stanford.edu

- Prospective Multicenter International Observational Study for Determination of a Cutaneous Lymphoma International Prognostic Index Model and Impact of Major Therapies in Patients with Advanced Mycosis Fungoides and Sézary Syndrome
- A Phase 2 Single-Center, Single-Arm, Open-Label Mogamulizumab Combined Upfront with Low-dose Total Skin Electron Beam Therapy (LD-TSEBT) in Patients with Mycosis Fungoides and Sézary Syndrome
- A Phase 1b/2 Study of Hu5F9-G4 (Magrolimab) in Combination with Mogamulizumab in Relapsed/Refractory T-cell Lymphoma
- Open-Label, Phase 2 Study to Assess the Safety of Mogamulizumab Given Every 4 Weeks Following Induction in Participants with Relapsed/Refractory Cutaneous T-cell Lymphoma (CTCL)
- An Open-Label, Multi-Cohort, Multi-Center Phase II Study Evaluating the Efficacy and Safety of IPH4102 Alone or in Combination with Chemotherapy in Patients with T-cell lymphoma: TELLOMAK study
- Optimizing Dosing of Brentuximab Vedotin for Mycosis Fungoides, Sezary Syndrome, and Lymphomatoid Papulosis
- A Phase 1/1b Dose-Escalation Trial Evaluating CPI-818, an Oral Interleukin-2-Inducible T-Cell Kinase Inhibitor, in Subjects With Relapsed/Refractory T-cell Lymphoma
- A Phase 1/2A Open-Label, Multi-Dose, Multi-Center Escalation and Exploratory Study of Cerdulatinib (PRT062070) in Patients with Relapsed/Refractory Chronic Lymphocytic Leukemia (CLL)/Small Lymphocytic Lymphoma (SLL) OR B-Cell or T-Cell Non-Hodgkin Lymphoma (NHL)
- A Phase 1/2 Trial of Duvelisib (IPI-145) in Combination with Either Romidepsin or Bortezomib in Relapsed/Refractory T cell Lymphomas
- Phase 3 Study to Demonstrate Safety and Efficacy of E7777 (Denileukin Diftitox) in Persistent or Recurrent Cutaneous T Cell Lymphoma
- A Phase 1, Open-Label, Multicenter, Dose Escalation and Cohort Expansion Study of the Safety and Efficacy or Anti-CD70 Allogeneic CRISPR-Cas9-Engineered T Cells (CTX130) in Adult Subjects with Relapsed or Refractory T or B Cell Malignancies

SELECTED PUBLICATIONS BY STANFORD MCLP AND COLLABORATORS

- Fong S, Hong EK, Khodadoust MS, Shufeng L, Hoppe RH, Kim YH, Hiniker SM. Low-dose total skin electron beam therapy combined with mogamulizumab for refractory mycosis fungoides and Sezary syndrome. Adv Radiat Oncol. 2020, Nov; available online D-20-00319R1


