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CLIC Prognostic and Treatment Outcome Studies in Advanced Mycosis Fungoides and Sézary Syndrome: Biobank Establishment for Biomarkers/Translation Research (CLIC Year 2)

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Lead US Collaborators: Alejandro Gru (U of Virginia), Jinah Kim (Stanford), Joan Guitart (Northwestern U), Richard Hoppe (Stanford)

OVERVIEW:
Over the course of the year the prospective international prognostic index modeling in advanced MF/SS (PROCLIPI) project and the complementary project on systemic treatment patterns and outcomes (PROSYST) have made noteworthy progress with respect to clinical implementation of both the protocol and the CLIC CL application platform. Moreover, we have been able to provide additional support for the early stage PROCLIPI project (Appendix B), as a companion study led by our UK co-leader, Julia Scarisbrick. The early stage project is able to utilize the same CL application platform with which all CLIC project participants that hosts the application can use. It is our vision that the success of the CLIC's leadership in the global linkage of expert institutions will serve as a model of large-scale collaborative platform implementation for other rare/orphadsfzdfn disease groups.

Ongoing milestones discussed in the progress report for the year 2015 were met in the expected timeframe and many essential works were added. Furthermore, a number of abstracts were accepted for oral and/or poster presentations (Appendix D), which will be translated into manuscripts for publications. The retrospective study on systemic treatment, led by Pietro Quaglino, was completed and will be submitted to the Journal of Clinical Oncology (Appendix D). This retrospective treatment study served as a foundation for development of the prospective project by evaluating the pattern and impact of systemic therapies in advanced MF/SS.

The year also marked the unexpected passing of Stanford's software developer, John Allen, our long-time, colleague and dear friend. John had decades of experience with lymphoma databases and was truly dedicated to the success of our vision; thus, his passing was not only a great loss of a brilliant software developer, but an irreplaceable loss of a unique individual who was passionate about connecting an international community of clinical and research experts through interactive, intelligent data systems. Moving forward without the breadth of both his technical expertise and institutional knowledge posed a great challenge, but we were able to circumvent this predicament with increased effort by contracted software developer, Robert Ivens, a friend of John's and co-designer of the Stanford's CL application and CLIC PROCLIPI repository. Robert Ivens has thus served as the primary developer of CLIC CL application from the time of John Allen's passing, taking on the additional role of implementing disease specific logic. Lastly, with John's passing, the Stanford Data Coordinating Center (DCC) has modified its requirements for secure data transfer from external sources to our PROCLIPI repository, thus requiring additional solutions, all which have been successfully implemented.

Specific Aim I: Infrastructure development and implementation for CLIC alliance projects, PROCLIPI as a model

Aim IA: Complete infrastructure development for CLIC/PROCLIPI

Refinement of Datasets and Regulatory Processes
Completed: Additional refinement of the PROCLIPI data dictionary and glossary was needed for the minimum (required) and exploratory datasets to optimize quality and clarity of data collection; updated datasets were distributed to participating sites (Appendix A). Special attention was paid to variables related to Pathology. Lead members of the Pathology Working Group, Jinah Kim, MD (Stanford) and Alejandro Gru, MD (University of Virginia) were regularly consulted to refine the data dictionary, thereby ensuring efficient and consistent data capture from all sites (Appendix A). Pathology data form was created as a tool to facilitate consistency. The PROCLIPI protocol was updated to address recent modifications to data capture, and to include the enrollment of participating centers (Appendix B). The protocol and ICF were sent to participating institutions for translation and local IRB approval. Case report forms were developed and distributed to enable sites to collect data from each patient with enhanced accuracy. A site initiation visit protocol and presentation was developed to familiarize institutions with the required elements of the PROCLIPI

project including pathology and clinical data to be recorded, regulatory processes and methods for data capture and transmission (Appendix C).

Planned: We will register the PROCLIPI data dictionary and datasets as part of a national NIH database. To this end, the PROCLIPI datasets will not only serve to catalyze clinical and translational research in cutaneous lymphoma, but will also set the groundwork for rigorous and extensive data capture in a wide range of other cancer groups. Moreover, we are planning a manuscript detailing not only the structure and design on the PROCLIPI datasets, but also describing the process with which the CLIC institutions and investigators have built a mechanism for large-scale collaboration with rigorous clinical, pathology, and molecular data linked with a federated biobank.

Completion of Database and Repository Establishment:

The ability to connect the world with a user-friendly, intelligent communication platform is central to future clinical and translational research. Without it, we will be left with varying databases and worksheets that cannot be easily shared and analyzed collectively. We have now completed the software application (CLIC CL App) and have tested its ability to transfer data in real-time from international sites that are locally hosting the application to Stanford's PROCLIPI repository. The same mode of data share and transfer will be used for participating US sites as well.

Completed: The PROCLIPI/PROSYST data interface, which is a HIPAA-secure, web-based application with EMR/EPIC integration, has been under development for the last 3 years by software developers John Allen and Robert Ivens. Following John Allen's passing, Robert Ivens has worked extensively with the Data Coordinating Center (DCC), which is part of the Stanford Cancer Center, to meet the new requirements by the DCC and continue to build and refine the application and house both the database and data on Stanford servers. The PROCLIPI REST endpoint (central repository) was built this year, which will enable all external sites to electronically send data using their own database or the CLIC CL Application. This feature will serve to streamline the process of data transfer with appropriate quality assurance checks in place. Additionally, a detailed JavaScript Object Notation (JSON) template was built to enable institutions with their own databases to structure their data in a standardized format that is capable of being electronically transmitted to the repository located at Stanford.

Ongoing: Because the interface must communicate with a growing number of software systems, ongoing resolution is imperative. Furthermore, a comprehensive user manual is under development to facilitate data entry. The JSON template is currently being implemented at City of Hope and University of Utah. Additional centers will implement the JSON template on a rolling basis.

Planned: Additional software intelligence is essential to data management and quality control, therefore refinement of the CLIC CL Application is continually necessary. Bug fixes will be required throughout the early phases of the project, and IT support from Stanford and Robert Ivens will be necessary to facilitate data transfer from all participating institutions. The IT and DCC support at Stanford is a free-of-charge service for Stanford faculty with investigative leadership.

Development of Central Pathology Review Process

Completed: Many of our candidate prognostic parameters are features established by pathologic review; thus it is essential to establish a mechanism of optimizing pathology data capture and interpretation. In our retrospective CLIPI (Retro-CLIPI) paper (Appendix D), we found that majority of missing data are of pathologic features. Thus means to facilitate complete and consistent pathology data is critical for the success of PROCLIPI. Furthermore, we have learned from the National Cancer Institute advisors that incorporating a central pathology review to optimize data quality and consistency of our pathologic prognostic parameters is key to a favorable evaluation of

future grant application and scientific publications. Upon considering methods of central review, namely sharing of distributed photomicrographs versus review of scanned glass slides, it was determined that a comprehensive review of scanned slides performed concurrently by a panel of pathologists provides the highest quality data. This is particularly relevant to the advanced stage project where the pathologic parameters are complex including immunohistochemical stain data. The Central Pathology Review Pilot was completed in the summer of 2016. An abstract entitled *Validation of Central Pathology Review in the Diagnosis of Advanced-Stage Cutaneous T-cell Lymphomas, a Multi-Institutional and International Pathology Pilot Study* (Appendix D) was accepted as an oral presentation at the 3rd World Congress for Cutaneous Lymphomas. The purpose of this pathology project was to analyze inter-observer pathology agreement using a retrospective approach in the diagnosis of advanced stage cutaneous T-cell lymphoma. Given the complexity of coordinating an efficient process for pathology to be reviewed by an international panel of experts, this pilot project was implemented to demonstrate the feasibility of the central review process with scanned glass slides. The pilot utilized the scanning of glass slides at a central site to share images via a web-interface with the panel of experts. Led by Alejandro Gru, MD, (University of Virginia), the pilot reviewed 31 cases from 11 different institutions in the US and United Kingdom. Excellent inter-observer agreement (>95%) was achieved upon 'live' revision of the slides using webinars as means of communication. Pathology central review using expert consensus is essential for an adequate evaluation of prognostic biomarkers in advanced stage cutaneous T-cell lymphomas.

Ongoing/Planned: Rein Willemze, MD, (Leiden University Medical Center, Netherlands) will be presenting the results of the Pathology Central Review for the early stage project conducted in the EU and Alejandro Gru, MD, will be presenting results of the Pathology Central Review for the advanced stage pilot study at the CLIC Meeting to be held during the 3rd World Congress of Cutaneous Lymphomas held October 26-28, 2016 at Columbia University, in New York City (Appendix E). Each of these will be translated into manuscripts for publication.
Given the success of the pilot study, Alejandro Gru, MD, and CLIC partners will implement the Central Review for the advanced stage in continuity with PROCLIPI implementation at US and international sites, provided necessary funding is secured.

Aim IB: Implementation and Initiation of PROCLIPI

Legal Reviews and Data Use Agreement

Completed: To receive data, the Stanford Privacy Office requires entry into a data use agreement (DUA) between Stanford and all institutions sending data to the PROCLIPI repository. The Stanford Office of Sponsored Research drafted a DUA (Appendix F) to lawfully receive data from University Hospitals Birmingham (UHB). The DUA was fully executed with UHB in June of 2016, allowing UHB to transfer advanced stage patient data to the Stanford repository from all participating EU sites. This DUA serves as the template for all data use agreements issued to participating sites. UHB has executed DUA with participating EU sites, 33 sites to date, as a lead EU site to collect data and transfer them to Stanford, rather than Stanford executing DUAs with individual EU sites. Using this model template with UHB, separate DUAs were reviewed and fully executed by 5 United States and 2 non-EU international centers to date (Appendix G).

Ongoing/Planned: The DUA is currently under review at 10 domestic and international centers (Appendix G). The DUA will be shared with sites interested in participating in the PROCLIPI project, who also meet the minimum necessary requirements, on a rolling basis. We plan to establish a similar agreement with the US Cutaneous Lymphoma Consortium (USCLC), so the US institutions that prefer to send data through USCLC will be able to participate in the PROCLIPI projects.

Site Recruitment and Institutional Review Board Approvals

Completed: 69 sites have confirmed participation in the Advanced Stage MF/SS PROCLIPI project

All centers must obtain institutional review board approval prior to data collection. Ten US and 49 international centers have obtained IRB approval. Approvals were submitted to the Stanford IRB, which recognized these sites for inclusion in the project.

Ongoing/Planned: 10 US and international centers are in the process of obtaining IRB approval (Appendix G). Additionally, the CLIC meeting to be held at 3rd World Congress Cutaneous Lymphomas (WCCL) in New York will demonstrate the progress thus far and also encourage more sites to participate (Appendix E). The PROCLIPI protocol and ICF will be shared with sites interested in participating in the PROCLIPI project, who also meet the minimum necessary requirements, on a rolling basis.

CLIC CL Application Installation: added essential work

Completed: The CLIC CL Application (CL App) was successfully installed at two international centers: Peter MacCallum Center in Melbourne, Australia and the University of Sao Paulo, Brazil. Robert Ivens has implemented upgrades and bug fixes at both centers. A protocol for CLIC CL App Installation was developed which includes technical requirements for installation and a detailed description of the CLIC CL App functionality (Appendix H).

Ongoing/Planned: 8 centers have confirmed that they will download the application (Appendix G). The next centers to locally install the application this year will be Hospital Italiano de Buenos Aires in Argentina and Peking University First Hospital in China. Policies in the US regarding external application installation require the completion of intensive data security assessments as required by institutional IT security. A comprehensive manual is being developed and will be provided to all CLIC CL App users.

Data Flow

Completed: The mechanism for data flow has been further refined. All data from Europe will come from the EU lead site, led by Julia Scarisbrick at University Hospitals Birmingham (UHB). UHB has successfully sustained the PROCLIPI project in the EU, collecting early and advanced stage data from 33 sites in 16 EU countries thus far. Additionally, for the early stage PROCLIPI project, a central pathology review (using photomicrographs and not scanned slides), led by Rein Willemze, MD, (Leiden University Medical Center, Netherlands), was initiated and implemented within the EU to build a large cohort of centrally reviewed patients for future studies. For the early stage project, photomicrographs were felt to be sufficient as the pathology data is simpler.

Ongoing: UHB has collected data from more than 92 patients with advanced staged cutaneous lymphoma. UHB's data collection was initiated prior to the completion of the CLIC CL App. Thus, UHB is developing the interface to electronically push this advanced stage patient data to the repository located at Stanford. This method will allow for expedient and efficient data transfer moving forward. The building of this interface will require dedicated time and resources on the parts of University Hospitals Birmingham (UHB), the Stanford PROCLIPI team and software developer, Robert Ivens. The cost from this ongoing added support will be reflected in the detailed budget for the grant extension. Our co-leader for PROCLIPI projects, Julia Scarisbrick, will be giving a combined presentation on the global status of the early and advanced stage PROCLIPI projects at the 3rd WCCL, October 26, 2016. (Appendix G).

Planned: Advanced stage cutaneous lymphoma data will flow directly from all international centers to the PROCLIPI repository located at Stanford. Participating sites in the US will either send data directly to the Stanford's PROCLIPI repository if they are CL App users or send data through USCLC. Stanford will enter into a data use/share agreement with USCLC and data will then be sent from USCLC to Stanford. USCLC has experienced delays with their registry construct and

regulatory processes, which has further slowed the implementation of the PROCLIPI project within the US.

Specific Aim II. Characterization of geographic pattern of systemic treatment utilization and determination of CLIPI-based differential clinical outcome of systemic treatments

Aim IIA: Completion of retrospective project on treatment outcome to refine design for PROSYST

Completed: Utilizing the established CLIC alliance network and clinical data annotation from the retrospective prognostic project in advanced MF/SS patients, the retrospective project on treatment outcome, led by Pietro Quaglino (Turin, Italy) and the Treatment Working Group (WG), has been completed. Preliminary data was presented at the 2015 EOTRC CLTF Meeting in Turin examining the difference in treatment approaches between US and non-US centers and its impact on geography specific survival outcomes. The abstract entitled *Global patterns of care in advances stage mycosis fungoides/Sézary syndrome: A Multicenter retrospective follow-up study from the Cutaneous Lymphoma International Consortium* was accepted as an oral presentation at the World Cutaneous Lymphomas Congress, October 26, 2016. The manuscript version of this retrospective treatment outcome project has been completed and submitted to the Journal of Clinical Oncology (Appendix D).

Aim IIB: Implementation and initiation of PROSYST (prospective treatment outcome project)

Ongoing/planned: Now that the final results have been obtained from the retrospective treatment study we are amending the study design for the prospective study (PROSYST) prior to implementation. There were significant missing data and lack of clarify of treatment types/duration and responses to therapy given the retrospective nature of this study, thus reinforcing the necessity of a prospective project. The refined Aims and Study Design will be incorporated into future grant applications. Furthermore, in the prospective project, the treatment data will be collected in parallel to the prospective prognostic data, therefore enabling the CLIC investigators to study a CLIPI-based treatment outcome.

Specific Aim III. Biobank establishment and management for CLIC alliance projects

Completed: SOP was established for the collection, handling, and storage of biomaterial (Appendix I). Our software developers completed the biobank data entry process to optimize tracking and to link samples with clinical/pathology data annotation. Participating centers will locally procure, store and track biobank samples for the use of future CLIC translational studies.

Ongoing/Planned: CLIC Biobank WG leader, Maarten Vermeer MD, has completed a paper on biomarkers in Sezary syndrome, which demonstrates how to use biomaterial in translational projects. The Journal of Investigative Dermatology published the manuscript entitled *Evaluation of immunophenotypic and molecular biomarkers for Sézary syndrome using standard operating procedures: multicenter study of 59 cases* in July of 2016. Dr. Vermeer will be presenting EU biobank results and opportunities for translation research at the upcoming CLIC Meeting at the 3rd World Congress of Cutaneous Lymphomas. Maarten Vermeer will be using his experience in EU collaborations to expand to a larger international platform through CLIC. CLIC Steering Committee approved the proposal for the process of review and approval of new projects prepared by Emmie Hodak (Tel Aviv University, Israel) (Appendix J). This will be distributed to all CLIC participating members/institutions to encourage and facilitate submissions of new/innovative clinical and translational project proposals.

In order to review the progress and discuss future projects, CLIC investigators will meet in conjunction with the 3rd WCCL, October 28, 2016 (Appendix E). We remain immensely grateful for our invaluable partnership with the Spatz Foundation as this historic scale of achievement and realization of our vision would not be possible without the Foundation's trust and support.