Prospective Study to Establish a CL International Prognostic Index Model and Impact of Systemic Therapies in Advanced Mycosis Fungoides & Sézary Syndrome (PROCLIIPI)

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Collaborative Networks in CTCL

Bringing it all together for greater impact

• Collaborative networks as conduit for large-scale studies
  – Collectively validate scientific discoveries for meaningful translation to the clinics
    • Assess diagnostic/prognostic relevance and actionable targets
    • Identify biomarkers that correlate with outcome
  – Enable large-scale prospective data collection for consistency and completeness
  – Federated Biobank with SOP for consistent collection/processing/storage, as foundation for future basic discovery or translational projects
    – Cooperative clinical trials for greater sample size, multi-arm

• Networks for research collaboration
  – EORTC CLTF, USCLC, other regional networks
  – CL International Consortium, CLIC
Prognostic index models in CTCL

Integration of multifaceted prognostic information to generate meaningful risk groups

Do we need one?

• MF/SS TNMB/staging system is not adequate for prognostication
  – Wide range of clinical outcome within clinical stage

• Prognostic model that can integrate newer markers and augment current TNMB/staging, enable precision, risk-stratified management would improve clinical outcome

• Allows clinical trials design by risk groups
  – More meaningful safety, efficacy, biomarker data
  – Better assessment of risk/benefit and unmet need
Cutaneous Lymphoma International Consortium Study of Outcome in Advanced Stages of Mycosis Fungoides and Sézary Syndrome: Effect of Specific Prognostic Markers on Survival and Development of a Prognostic Model

- CLIC investigators, demonstrated feasibility of large-scale collaboration
- Retrospective study of 10 parameters in advanced stage MF/SS, dx from 2007
- 29 CL sites (EU, US, Israel, Australia, Japan, S America) => 1,275
  - 4 of 10 variables => independent factors
  - Combined into prognostic index model => 3 risk groups
Initial Collaborative Project

PROCLIPI and Correlative Treatment Impact (PROSYST) in Advanced MF and SS (Stages IIB-IV)
PROCLIPI study as initial collaborative project

Steps

• Feasibility studies (retrospective) that show CLIC can be productive, *led by Julia Scarisbrick and Pietro Quaglino*
  – Highlight problems with retrospective study

• Set ground work for prospective study
  – **PROCLIPI work groups** to identify candidate parameters and establish well-defined criteria for consistency
  – Investigator meetings (Paris/EORTC, Stanford/ASH, Turin/EORTC)
  – Bridge funding towards securing larger grants

• **CLIC Biobank (federated) SOP development**
Specific Aims

1. Determination of prognostic factors in advanced MF and SS in a prospective design

2. Development of Cutaneous Lymphoma International Prognostic Index (CLIPI) towards improved prognostication and stratification for management in advanced MF and SS

3. Characterization of geographic pattern of treatment utilization and CLIPI-based differential clinical outcome of major systemic treatments in advanced MF and SS
Study Design

Site requirements for participation in the PROCLIP study

1. Each participating site must aim to complete and capture 100% of the minimum (required) dataset and encouraged to complete and capture information in the exploratory dataset.

2. Each participating site will have at least one dedicated pathologist to review the pathology data (derm and hematopath) prior to transfer to the primary data center for upload. The site pathologist will ensure that the path data meets the definition and criteria specified in the PROCLIP protocol.

3. Each site will have at least one designated data coordinator for effective resolution of any data queries or maintenance of the site’s regulatory binder.

Federated Biobank SOP encouraged at all participating sites
PROCLIPPI & PROSYST

Study Plan and Procedures

Inclusion criteria

- Advanced stage MF or SS (Stages IIB – IVB) within 6 months of presentation to the participating center
- 5 year study from enrollment to follow-up data collection
  - Target accrual of 2,000 over 4 year period
  - Analysis at end of 5th year
- Minimum (required) and Exploratory (Optional) Datasets
- Patient data at diagnosis and initial staging
- Patient data at scheduled follow-up (at least annually) and/or occurrence of disease progression (as determined by TNMB/clinical stage) or adverse prognostic event (e.g., folliculotrophic or transformed disease)
Federated ("Virtual") Biobank establishment, optional: biomaterial kept at site, site ICF, data tracked by CLIC

Sample collection registration, and handling per SOP

- Date, type, method of sample collection
  - Skin biopsy ≥ 4 mm, store as FFPE (if poss adjacent snap frozen issue); encouraged to sample >1 site/type of lesion
  - PBMC 10-20 ml
  - Germline DNA (granulocytes)
  - Serum 10-20 ml

- Time points for collection
  - At diagnosis
  - Disease progression and/or occurrence of adverse prognostic events (e.g., F-MF, LCT)
  - Start of new systemic therapy
PROCLIPI & PROSYST

Regulatory & quality assurance considerations

- CLIC Regulatory and Data Management Workgroup (CLIC RDMW), meet at least annually (EORTC/AAD/WCCL) to review compliance and quality of study
- Regulatory plan
  - IRB and data share compliance
- PROCLIPI database and data management
  - Database platform and data upload modalities
  - Data management and quality assurance checks
- **Pathology data quality assurance**
  - Participating site (local) pathology data
  - Protocol for histopathologic training
  - *Central pathology review process SOP in development (pilot project, led by A Gru)*
PROCLIPI & PROSYST

**Outcome Measurement**

- **Primary outcome and measurement**
  - Overall survival (OS)

- **Secondary outcome and measurement**
  - Disease-specific survival (DSS)
  - Progression-free survival (PFS): event defined by progression to higher T, N, M, or B or clinical stage or death due to MF or SS
  - Type and number of significant primary therapies
  - Time-to-next significant treatment (TTNT)

- **Exploratory outcome and measurement**
  - Clinical response
Ultimate goal is to build and validate a prognostic index model that will help us better predict the survival probability

- **Observational study w/o interim analysis**, but if overall enrollment not optimal and/or anticipated death events not occurring, consider more sites or extend time line

- Randomly select 75% from each center for main analyses to build index model; 25% for validation
  - **Training set: n = 1,500 ; Validation set: n = 500**

- Prognostic model development: multivariate model constructed via 2 procedures
  - Cox regression with lasso regularization
  - Adaptive index model (AIM) procedure

- Cross-validation method used to select optimal model
Data Flow

USCLC (US Registry) -> Import App -> Advanced MF Disease

PROCLIPPI -> Import App

European Data Capture -> Import App

Application

Advanced MF and SS

Site uses its own MF management database or any other management app like CL-Tacker

Region: USA

Application

Advanced MF and SS

Site uses the CLIC CL app hosted locally on the site’s server

Region: Europe

Region: Japan

Region: Brazil

Region: Australia

Region: Canada
Data Capture: CLIC CL Application
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