
INTERNATIONAL T-CELL NON-HODGKIN'S LYMPHOMA STUDY GROUP

T-Cell Project:

PROSPECTIVE COLLECTION OF DATA IN PATIENTS WITH PERIPHERAL T-CELL LYMPHOMA (Peripheral T-cell lymphoma unspecified; Angioimmunoblastic T-cell lymphoma; Extranodal NK/T-cell lymphoma; Enteropathy- type T-cell lymphoma; Hepatosplenic gamma-delta T-cell lymphoma; Subcutaneous panniculitis-like T-cell lymphoma; Anaplastic large-cell lymphoma, T/null cell, primary systemic type).

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1.0 INTRODUCTION-RATIONALE

Peripheral T-cell lymphomas (PTCLs) comprise a heterogeneous group of neoplasms that are derived from post-thymic lymphoid cells at different stages of differentiation with different morphological patterns, phenotypes, and clinical presentations¹. PTCLs are highly diverse, reflecting the diverse cells from which they can originate¹⁻⁶. Peripheral T-Cell Lymphomas account for 5–10% of all lymphoproliferative disorders in the Western hemisphere^{7, 8}, with an overall incidence of 0.5–2 per 100,000 per year⁹, and have a striking epidemiological distribution, with higher incidence in Asia¹⁰.

Mature T-cell lymphomas are currently subclassified according to their clinical features, using World Health Organization (WHO) criteria, into leukemic, cutaneous, other extranodal, and nodal. The clinical subtypes of PTCL can be further divided into real and not real clinical entities based on the presence of distinguishing clinico-biologic features¹. Real entities, which include Mycosis Fungoides (MF), Anaplastic Large Cell Lymphoma (ALCL) and Adult T-cell Leukemia/Lymphoma (ATLL), along with NK-derived lymphomas, can be easily diagnosed on the basis of distinguishing features. All other entities which include nodal PTCL (i.e., PTCL unspecified and Angioimmunoblastic T-cell Lymphoma) together with all the other extra nodal PTCLs (i.e., Enteropathy Type T-cell Lymphoma, Hepatosplenic $\gamma\delta$ T-cell Lymphoma and Subcutaneous Panniculitis T-cell Lymphoma) are more difficult to diagnose and are generally included within the broad category of PTCL.

The clinical features of PTCL are extremely heterogeneous. PTCLs express even more clinical diversity than B-cell NHLs, and there is a close, though not absolute, relationship between some unusual clinical features and certain histological subtypes.

Despite efforts to transferring to patients with T-cell lymphomas the most recent advances in the treatment of other subtypes of B-cell lymphomas, the prognosis of patients with PTCL is still poor. Unfortunately, the optimal therapy for PTCL is still unknown. The complete response rate is rather low, ranging from 40% to 50% with a median Relapse Free Survival (RFS) of 2–3 years. As a consequence of the aggressiveness of the disease and of the low efficacy of available salvage treatments, Overall Survival (OS) is also short and the long-term survival rate is lower than 10% in many series.

Several studies have been performed to assess the contribution of a number of clinical and biological factors to the prognosis of PTCL^{8, 11-16}. In most of them, adverse prognostic features such as poor performance status, advanced stage, presence of extranodal sites, bulky disease, and high LDH levels were significantly correlated with shorter OS. The usefulness of the International Prognostic Index (IPI), defined for DLBCL, has also been investigated and confirmed by several authors.

To better define the clinical outcome of PTCL-u, the Intergruppo Italiano Linfomi (IIL) recently performed a large study on 385 patients diagnosed and treated in the 1990s and defined a prognostic model specifically devised for patients with this uncommon disease. Among different clinical parameters assessed at time of diagnosis age (<60 yr), Performance Status (ECOG PS 2 or higher), LDH level above upper normal range, and bone-marrow involvement were independent predictors of OS. In addition to defining a prognostic model specifically devised for PTCL-u, the IIL study confirms the relevance of research on series of clearly defined cases in order to the development of rationally designed and potentially more-efficacious treatment modalities.

More recently, the role of biological features of the disease is emerging as an important issue not only for understanding its pathogenesis but also for prognosis and for addressing specific biologic targets altered in the neoplasia. The expression of Th1- or Th2-associated antigens or activated T-cell receptor, for example, has been recently evaluated in a series of T-NHLs. The pattern of expression of such antigens was correlated with the specific subtype of nodal T-cell lymphoma (AILT, ALCL, and PTCL-u) and allowed the identification of subgroups

of PTCL-u patients with different probabilities of survival¹⁷. In particular, patients with PTCL-u expressing one of Th1 or Th2 antigens tended to show favorable prognosis as compared with cases not expressing Th1 or Th2 antigens.

Significant progress in the prognosis of PTCL can be expected from the novel, sophisticated, and powerful technologies of genomics and proteomics, which will allow more reliable subtyping of PTCL into distinct clinical groups characterized by different patterns of survival, as already demonstrated for some B-NHLs¹⁸.

One common limitation of existing studies on prognosis of PTCL is their retrospective nature. Currently available data are based on analysis performed on series collected over a long period of time. This aspect is very important as it may introduce relevant biases in the collected series. First classification systems have changed dramatically over time and cases may have been defined in differently based on diagnosis year. Second some clinical or laboratory data which now are considered as prognostic relevant may have not been determined in older series of patients. Third in a retrospective analysis there is no guarantee that collected series are based on real consecutive cases.

These are the reasons why we thought it would be useful to start a new study based on the prospective registration in a short period of time of patients with diagnosis of Peripheral T-cell lymphoma for whom it would be possible collect an exhaustive set of clinical data and biological information.

2.0 OBJECTIVES AND ENDPOINTS

2.1 Objectives

The designed study follows up the previous one by the International T-cell Non-Hodgkin's Lymphoma Study Group and its purpose is to verify whether a prognostic collection of data would allow to achieve more accurate information to better define prognosis and to investigate on most adequate treatment strategies for these neoplasms.

2.2 Primary Endpoint

- 5-year overall survival

2.3 Secondary Endpoint

- 5-year event free survival

2.4 Additional Endpoints

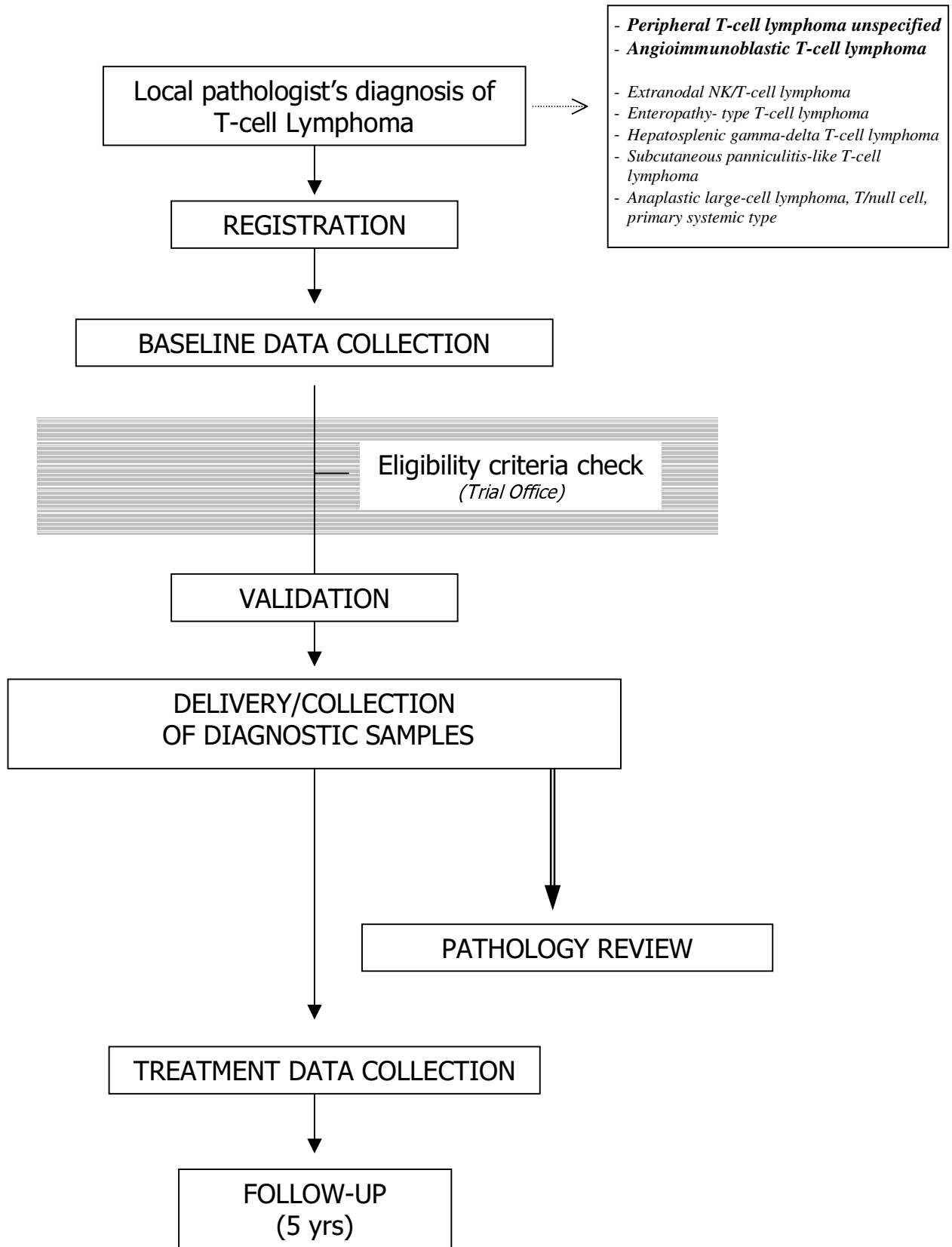
- Remission rate with initial therapy
- 5-year progression free survival

3.0 STUDY DESIGN

3.1 Study Design

The present study is designed as a prospective collection of information potentially useful to predict the prognosis of newly diagnosed patients with the more frequent subtypes of Peripheral T-cell lymphoma (*Peripheral T-cell lymphoma unspecified* and *Angioimmunoblastic T-cell lymphoma*) and to better define clinical characteristics and outcome of the more uncommon subtypes (*Extranodal NK/T-cell lymphoma; Enteropathy-type T-cell lymphoma; Hepatosplenic gamma-delta T-cell lymphoma; Subcutaneous panniculitis-like T-cell lymphoma; Anaplastic large-cell lymphoma, T/null cell, primary systemic type*).

3.2 Study Flow Chart



4.0 SUBJECT SELECTION

4.1 Inclusion Criteria

1. Previously-untreated patients with *de novo* diagnosis of peripheral T-cell or NK/T-cell lymphoma:
 - Peripheral T-cell lymphoma unspecified;
 - Peripheral T-cell lymphoma, lymphoepitelioid variant;
 - Peripheral T-cell lymphoma, T-zone variant ;
 - Peripheral T-cell lymphoma, parafollicular variant ;
 - Angioimmunoblastic T-cell lymphoma;
 - Nasal NK/T-cell lymphoma;
 - NK/T-cell lymphoma, nasal type;
 - Anaplastic large-cell lymphoma, T/null cell, ALK+, primary systemic type
 - Anaplastic large-cell lymphoma, T/null cell, ALK-, primary systemic type
 - Anaplastic large cell lymphoma, small cell variant, ALK+
 - Anaplastic large cell lymphoma, lymphohistiocytic variant, ALK+
 - Enteropathy- type T-cell lymphoma;
 - Hepatosplenic T-cell lymphoma;
 - Peripheral gamma-delta T-cell lymphoma;
 - Subcutaneous panniculitis-like T-cell lymphoma;
 - Unclassifiable peripheral T-cell Lymphoma
 - Unclassifiable NK-cell lymphoma

2. Age over 18

3. Tissue biopsies adequate for diagnosis and classification and available for centralized review

4. Clinical data including baseline information on disease localization and laboratory parameters at staging, features of treatment adopted and assurance of follow-up updating for at least 5 years are requested

5. Written informed consent

4.2 Exclusion Criteria

1. Age < 18

2. Diagnosis of T-cell or NK-cell leukemia or proliferation and other than mature types including:
 - Adult T-cell leukemia/lymphoma;
 - Blastic NK-cell leukemia/lymphoma;
 - Aggressive NK-cell leukemia
 - T-cell large granular lymphocytic leukemia
 - T-cell large granular lymphocytic proliferation
 - NK-cell large granular lymphocytic proliferation
 - T-cell prolymphocytic leukemia
 - Precursor T-cell lymphoblastic leukemia/lymphoma
 - Mycosis fungoides;
 - Sézary syndrome;
 - Primary cutaneous ALCL

5.0 STUDY PROCEDURES

5.1 Trial Office Location

The T-Cell Project Trial Office will check for coherence of data and will monitor the study. The Trial Office is located at:

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5.2 Patients Enrollment

Patients with histologically confirmed T-cell or NK-cell lymphoma are registered in the study despite their planned treatment, observation only included. Registration is based on locally established histological diagnosis.

Registration will be made on-line on a key restricted accessible web-database: the Investigator must complete the on-line registration forms after obtaining the informed consent dated and signed by the patient.

Investigators are requested to register consecutive cases diagnosed at each participant Institution (all patients satisfying Inclusion criteria without selection).

Inclusion criteria will be checked at the Trial Office: a patient number (**Patient ID**) will be assigned strictly sequentially in ascending order as patient's eligibility is verified. In case patient's eligibility is not confirmed by the Trial office and the patient withdrawn from the study, the patient number will not be reused. The assigned number together with patient's initial will be used as the identification code recognizing the subject. A space will be provided for the Clinician to enter a local alphanumeric code to better identify the patient. Every registered patient has as well to undergo a central histopathology review by a panel of experts.

The referring pathologist will collect and review the pathologic material sent by the participating centers, without knowing the clinical outcome of the patient.

The reviewed material will refer to both onset and eventual relapse.

The classification scheme in use is the World Health Organization recently published¹⁹.

The pathologic criteria will be strictly applied.

Guidelines for tissue handling and processing are summarized in Appendix E.

We encourage the collection and the storage at local centers of fresh frozen samples - tumor, serum and mononuclear peripheral cells - for possible further analyses to be defined.

Validated cases have to be supplied of information regarding treatment procedures and follow-up updating for at least 5 years.

5.3 Data Collection List

The following variables will be recorded at time of diagnosis:

1. Baseline Data

- Patient's Initials
- Gender
- Year of birth
- Date of diagnostic biopsy
- Histologic diagnosis
- Prior diseases involving autoimmune system or lymphoproliferative disorders and use of immunosuppressive drugs
- Initial disease presentation type

2. Clinical Data

- Systemic symptoms in details (absence/presence):
 - Fever
 - Weight loss
 - Night sweats
- Other symptoms:
 - Erythroderma
 - Raised rash
 - Pruritis
 - Purpura
 - Adenopathy
 - Fatigue/weakness
 - Infection
 - Headache
 - Neurologic symptoms
 - Cough
 - Chest pain
 - Dyspnea
 - Hemoptysis
 - Anorexia
 - Abdominal pain
 - Dysphagia
 - Hematochezia
 - ...
- ECOG performance status (Appendix D)

2. Sites of Disease

- Nodal and/or extranodal sites of involvement in detail, with indication of major lesion, as detailed in the electronic case report form through the use of the EasyStage[®] adapted for T-cell Lymphomas
- Ann Arbor Stage (Appendix C)

3. Laboratory Data

- Haemoglobin
- Total white blood count & differential (absolute values)
- Platelets
- Serum LDH, β 2-microglobulin, Erythrocyte Sedimentation Rate, C-Reactive Protein levels, with laboratory maximum admissible values
- Total serum protein and electrophoresis

- Calcium level
- Results of serologic assessment for HbsAg, HCV, HIV, HTLV-1, EBV
- Serum Monoclonal component presence
- Presence of hemolytic anemia and/or hemophagocytic syndrome

4. Planned Approach Data

- Planned Radiotherapy
- Planned Chemotherapy
- Planned High dose therapy
- Other planned treatment

The following variables will be recorded at the end of initial therapy (that is, at the end of all the treatments indicated in the planned approach form):

- Detailed information on type of treatment adopted and drugs used as part of initial chemotherapy regimen
- Date of treatment started and finished
- Response to initial therapy

The following variables will be recorded during Follow-up of alive patients (Every six months during first two years and once a year afterward)

- Date of last contact
- Disease status at last contact
- Evidence of second malignancy or concomitant diseases.

The following variables will be recorded in case of disease progression or relapse:

- Date of progression or relapse
- Salvage treatment modalities
- Date salvage treatment started

The following variables will be collected in case of death:

- Date of death
- Cause of death
- Disease status at time of death

5.4 Data Collection Modalities

Registration of patients in the study and data collection will be performed on-line. Electronic Case Report Forms (ECRFs) will be available at the Internet address:

www.tcellproject.org

ECRFs must be reviewed and verified for accuracy by the local Investigator. Patients registered into the study will not be identified by name on any study documents to be collected, but will be identified by a Subject Identification Number (Patient ID).

The adoption of SSL03 technology will assure protection in web communications of subject's clinical data (Appendix B).

Data access and management will be regulated by the use of passwords with different level of admittance, providing that subject confidentiality is respected.

Data will be divided into different electronic forms, each regarding a particular set of information.

After completion of a single form, data will be locked and it won't be possible to modify them anymore, unless a specific and documented written query is submitted to the Trial Office.

The timing for completion of patient's forms is summarized in the Schedule of Events (Appendix I). The ECRFs will automatically generate e-mails to remind subject's updating.

5.5 Retention and Availability of Records

A file for each subject must be maintained by the Clinician that includes the signed Subject Information Sheet/Informed Consent form and copies of all source documentation related to that subject. The Investigator must ensure the reliability and availability of source documents from which the information on the CRF was derived.

5.6 Monitoring and Compliance

Data Managers will monitor the study at the Trial Office. They are responsible for performing reviews of ECRFs at regular intervals throughout the study to verify adherence to the protocol, completeness, accuracy and consistency of the data.

The Investigator agrees to cooperate with the Trial Office to ensure that any problem detected during reviews is resolved.

6.0 STATISTICAL CONSIDERATIONS

6.1 Sample Size

Sample size is a very crucial issue in every clinical trial, but especially in such a study is particularly difficult to define an exact number of cases to enroll. Due to the fact that prognosis has to be studied in the two more frequent subtypes of PTCLs – i.e. Peripheral T-cell lymphoma unspecified (PTCL-U) and Angioimmunoblastic lymphoma (AILD) – the sample size is calculated basing on characteristics of these two subtypes. Since the definition of a sample size for more uncommon PTCLs subtypes is not possible due to their rarity, the study is designed only to prospective collecting all cases of rarer histologies in the same time frame PTCL-U and AILD are planned to be accrued.

Sample size definition for PTCL-U:

If the risk factor has a prevalence of almost 10%, the 5 year survival of the remaining subjects is 45%, and the hazard ratio is 2 for death with the risk factor compared to that without, then there will be 80% power to detect a statistically significant effect of the risk factor on survival with a total sample size of 460 patients, allowing interrelationship between risk factors and 10% of the patients to be ineligible.

Sample size definition for AILD:

Given that AILD have a prognosis similar to that of PTCL-U, the same assumptions can be made also for this subtype, having a total sample size of 460 patients with AILD necessary to detect a statistically significant effect of the risk factor on survival.

6.2 Analysis of Outcome

Analysis of prognostic factors will be performed on all validated cases. Difference in remission rates between groups will be analyzed by the Pearson's X^2 test (or Fisher exact test) for contingency tables. Overall survival, event-free survival and progression-free survival will be estimated by the method of Kaplan-Meier. The Log-rank test will be used to compare different groups.

A *P* value of 0.05 (two-sided) will be considered the limit of significance for each analysis.

6.3 Estimated Study Duration

Based on the final accrual of the former retrospective International PTCL study, the success of the F2-study (that prospectively collected 1093 patients with follicular lymphoma in 2 years) and the interest in the project expressed by participants to both these previous studies, it is planned to complete accrual in 2 years; furthermore, a minimum follow-up of 5 years is required for the final analysis of primary and secondary endpoints.

6.4 Endpoints Definition

The endpoints of interest in the present study have been adapted from the Standardize Response Criteria for Non-Hodgkin's Lymphoma²⁰ and from Recommendations for Revised Response Criteria for Malignant Lymphoma²¹ (Appendix G). In particular:

- Overall Survival (OS) is measured from date of diagnosis until death from any cause.
- Event-free survival (EFS) is measured from date of diagnosis until date of event (treatment failure; progression/relapse; second-line treatment start; death from any cause).
- Complete Response (CR), Partial Response (PR) rates.
- Progression-free survival (PFS) is measured from date of diagnosis until date of disease progression or death from T-cell Lymphoma.

7.0 WITHDRAWAL OF PATIENTS

Patients can be withdrawn in case of:

- Lack of eligibility criteria
- Histological revision assessing diagnosis other than follicular lymphoma
- Missing data; warnings will be periodically sent to the Investigators. In case of persistent missing data the patient will be rejected from the study

8.0 PUBLICATION RULES

All publication will be signed as "International T-cell Non-Hodgkin's Lymphoma Study Group".

9.0 ETHICAL CONSIDERATIONS

9.1 Subject Informed Consent

Prior to any study-related procedure, a subject information sheet/informed-consent form must be signed and personally dated by the subject or a legally acceptable representative. The local Investigator(s) and appropriate IEC must agree upon the format and content of the subject information sheet/informed-consent form, if requested.

The Subject Information Sheet/Informed Consent form documents the study-specific information the Investigator provides to the subject and the subject's agreement to participate. Among other things, the Investigator will fully explain in layman's terms the nature of the study, along with the aims, methods and any discomfort participation may entail. The Subject Information Sheet/Informed Consent form must be appropriately signed and dated before entering the study. The original and any amended signed and dated Subject Information Sheet/Informed Consent forms must be retained by the Investigator in the subject's file at the study site; and a copy must be given to the subject.

Every participating center will develop its own Subject Information Sheet/Informed Consent form according to directories of its own IEC.

9.2 Subject Confidentiality

The Investigator must ensure that the subject's anonymity is maintained. On the CRFs or other documents submitted, subjects are identified exclusively by a Subject Identification Code (Patient ID).

The Investigator in compliance with privacy statements should keep documents that are not for submission, (e.g. signed Subject Information Sheet/Informed Consent forms) in strict confidence.

It is required that the Investigator and Institution permit authorized representatives of the study (Chairpersons, Hystopatholgy Review Panel, Data Managers) direct access to review the subject's original medical records for verification of study-related procedures and data.

Direct access includes examining, analyzing, verifying and reproducing any records and reports that are important to the evaluation of the study. The Investigator is obligated to inform the subject that the above named representatives will review his/her study-related records, although the confidentiality of his/her records will be maintained as much as reasonably possible.

9.3 Ethical Conduct of the Study

The study will conform to Good Clinical Practice Guidelines and to the Declaration of Helsinki 1964, as modified by the 52nd WMA General Assembly, Edinburgh, Scotland, October 2000 (Appendix A).

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APPENDIX A: DECLARATION OF HELSINKY

ETHICAL GUIDELINES: THE DECLARATION OF HELSINKI

World Medical Association Declaration of Helsinki Recommendations guiding physicians in biomedical research involving human subjects.

Adopted by the 18th World Medical Assembly, Helsinki, Finland, June 1964, and amended by the 29th World Medical assembly, Tokyo, Japan, October 1975, 35th World Medical Assembly, Venice, Italy, October 1983 and the 41st World medical Assembly Hong Kong, September 1989.

INTRODUCTION

It is the mission of the physician to safeguard the health of the people. His or her knowledge and conscience are dedicated to the fulfilment of this mission.

The Declaration of Geneva of the World Medical Association binds the physician with the words, "The health of my patient will be my first consideration", and the International Code of Medical Ethics declares that, "A physician shall act only in the patient's interest when providing medical care which might have the effect of weakening the physical and mental condition of the patient".

The purpose of biomedical research involving human subjects must be to improve diagnostic, therapeutic and prophylactic procedures and the understanding of the aetiology and pathogenesis of disease.

In current medical practice most diagnostic, therapeutic or prophylactic procedures involve hazards: this applies especially to biomedical research.

Medical progress is based on research which ultimately must rest in part on experimentation involving human subjects.

In the field of biomedical research a fundamental distinction must be recognised between medical research in which the aim is essentially diagnostic or therapeutic for a patient, and medical research, the essential object of which is purely scientific and without implying direct diagnostic or therapeutic value to the person subjected to the research.

Special caution must be exercised in the conduct of research which may affect the environment, and the welfare of animals used for research must be respected. Because it is essential that the results of laboratory experiments be applied to human beings to further scientific knowledge and to help suffering humanity, the World Medical Association has prepared the following recommendations as a guide to every physician in biomedical research involving human subjects. They should be kept under review in the future. It must be stressed that the standards as drafted are only a guide to physicians all over the world. Physicians are not relieved from criminal, civil and ethical responsibilities under the laws of their own countries.

1) Basic Principles

- a) Biomedical research involving human subjects must conform to generally accepted scientific principles and should be based on adequately performed laboratory and animal experimentation and on a thorough knowledge of the scientific literature.
- b) The design and performance of each experimental procedure involving human subjects should be clearly formulated in an experimental protocol which should be transmitted to a specially appointed independent committee for consideration, comment and guidance.
- c) Biomedical research involving human subjects should be conducted only by scientifically qualified persons and under the supervision of a clinically competent medical person. The responsibility for the human subject must always rest with a medically qualified person and never rest on the subject of the research, even though the subject has given his or her consent.

- d) Biomedical research involving human subjects cannot legitimately be carried out unless the importance of the objective is in proportion to the inherent risk to the subject.
- e) Every biomedical research project involving human subjects should be preceded by careful assessment of predictable risks in comparison with foreseeable benefits to the subject or to others. Concern for the interests of the subject must always prevail over the interests of science and society.
- f) The right of the research subject to safeguard his or her integrity must always be respected. Every precaution should be taken to respect the privacy of the subject and to minimise the impact of the study on the subject's physical and mental integrity and on the personality of the subject.
- g) Physicians should abstain from engaging in research projects involving human subjects unless they are satisfied that the hazards involved are believed to be predictable. Physicians should cease any investigations if the hazards are found to outweigh the potential benefits.
- h) In publication of the results of his or her research, the physician is obliged to preserve the accuracy of the results. Reports of experimentation not in accordance with the principles laid down in this Declaration should not be accepted for publication.
- i) In any research on human beings, each potential subject must be adequately informed of the aims, methods, anticipated benefits and potential hazards of the study and the discomfort it may entail. He or she should be informed that he or she is at liberty to abstain from participation in the study and that he or she is free to withdraw his or her consent to participation at any time. The physician should then obtain the subject's freely-given informed consent, preferably in writing.
- j) When obtaining informed consent for the research project, the physician should be particularly cautious if the subject is in a dependent relationship to him or her or may consent under duress. In that case the informed consent should be obtained by a physician who is not engaged in the investigation and who is completely independent of this official relationship.
- k) In case of legal incompetence, informed consent should be obtained from the legal guardian in accordance with national legislation. Where physical or mental incapacity makes it impossible to obtain informed consent, or when the subject is a minor, permission from the responsible relative replaces that of the subject in accordance with national legislation. Whenever the minor child is in fact able to give a consent, the minor's consent must be obtained in addition to the consent of the minor's legal guardian.
- l) The research protocol should always contain a statement of the ethical considerations involved and should indicate that the principles enunciated in the present Declaration are complied with.

2) Medical Research Combined With Professional Care (Clinical Research)

- a) In the treatment of the sick person, the physician must be free to use a new diagnostic and therapeutic measure, if in his or her judgement it offers hope of saving life, re-establishing health or alleviating suffering.
- b) The potential benefits, hazards and discomfort of a new method should be weighed against the advantages of the best current diagnostic and therapeutic methods.
- c) In any medical study, every patient – including those of a control group, if any – should be assured of the best proven diagnostic and therapeutic method.
- d) The refusal of the patient to participate in a study must never interfere with the physician-patient relationship.
- e) If the physician considers it essential not to obtain informed consent, the specific reason for this proposal should be stated in the experimental protocol for transmission to the independent committee (see Section 2.b).
- f) The physician can combine medical research with professional care, the objective being the acquisition of new medical knowledge, only to the extent that medical research is justified by its potential diagnostic or therapeutic value for the patient.

3) Non-Therapeutic Biomedical Research Involving Human Subjects (non-clinical biomedical research)

- a) In the purely scientific application of medical research carried out on a human being, it is the duty of the physician to remain the protector of the life and health of that person on whom biomedical research is being carried out.
- b) The subjects should be volunteers – either healthy person or patients for whom the experimental design is not related to the patient's illness.
- c) The investigator or the investigating team should discontinue the research if in his/her or their judgement it may, if continued, be harmful to the individual.
- d) In research on man, the interest of science and society should never take precedence over considerations related to the well-being of the subject.

APPENDIX B: AUTHENTICATION AND CONFIDENTIALITY

The standard that will be adopted in the T-cell Project to assure patient's confidentiality is the SSL (Secure Sockets Layer) technology that guarantees data cryptography through the employment of Digital Certificates. Characteristics of these protocols are summarized in the following sections.

1. *Cryptography*

In the physical world, there are many proven techniques for safeguarding information. A number of means, including photo ID cards or passwords currently provide authentication; access is controlled by locks, keys and badges; confidentiality is ensured through private conversations or sealed letters.

In the virtual world, however, safeguards are more complex. The solution to the problems of identification, authentication, and privacy in computer-based systems lies in cryptography, digital certificates technology and biometrics, that are important building blocks in the implementation of all the security services introduced above.

Encryption techniques for protecting valuable information is through a virtual *key* system, in which information is coded according to an algorithm and can only be shared among users who hold a key or the uncoding algorithm.

The USA government-sponsored *Data Encryption Standard (DES)* is an example of such a key system. With DES, secret encryption keys are shared among parties who wish to exchange information. While this technique is easy and effective in small networks with limited access requirements, it has serious drawbacks in today's larger enterprise environments. Today's RSA public-key/private-key cryptosystems provide a better solution.

RSA public key cryptography is widely used for authentication and encryption in the computer industry. Public key encryption is a technique that uses a pair of asymmetric keys for encryption and decryption. Each pair of keys consists of a public key and a private key. The public key is made public by distributing it widely and can be seen by all users. The corresponding unique private key is never distributed; it is always kept secret and not shared among users, thereby ensuring privacy and verifying the identity of the sender.

The public key and private key perform inverse operations and are used together. For example data that is encrypted with the public key can be decrypted only with the private key. Conversely, data encrypted with the private key can be decrypted only with the public key. This asymmetry is the property that makes public key cryptography so useful.

To make the public/private key system (*PKI*) more effective for providing authentication and privacy protection in large networks, the RSA algorithm makes use of a number called the public modulus, which is obtained by multiplying two prime numbers and which thereby makes breaking the mathematical code all but impossible. That is why the RSA algorithm is now standard in most public-key cryptographic systems.

2. *Digital Certificates*

Digital certificates let you securely exchange sensitive information online by giving your users confidence that their transactions are safe, all that by simply installing a digital certificate and turning on the SSL (Secure Sockets Layer) capabilities built into web servers and web browsers.

Digital certificates are in effect virtual fingerprints that authenticate the identity of a person or a thing absolutely, positively. The certificate itself is simply a collection of information to which a digital signature is attached. The digital signature is attached by a Certification Authority (CA), a third-party authority that is trusted by the community of certificate users.

The digital certificate usually includes:

- The name of the holder and other identification information, such as email address.
- A public key, which can be used to verify the digital signature of a message sender previously, signed with the matching mathematically unique private key.
- The name of the issuer, or Certification Authority.
- The certificate's validity period.

All this information is digitally signed and sealed by the CA and can be verified by anyone.

Digital certificates must be issued by that trusted entity known as a Certification Authority (CA). A CA's role is analogous to that of a Department of Motor Vehicles (DMV), which issues driver's licenses and is broadly acknowledged and accepted as a trustworthy means of personal identification. Certification Authorities typically offer a combination of cryptography technology, an infrastructure of highly secure facilities, and a specification of practices and liability that establish its ability to operate as a trusted third party.

In today's dynamic information climate, many companies want to take advantage of the peace of mind of working with a CA, but also want to maintain strict control over the issuance and revocation of digital certificates. It's possible to contract with the CA (like for example Verisign in USA, InfoCamere or PosteCom in Italy) a purchasing of a server certificate (usually a per-year fee), or to handle routine certificate administration tasks by installing its own CA, electing to assume responsibility for certificate issuance and revocation themselves, thereby maintaining a higher level of control.

3. *Secure Sockets Layer (SSL)*

The Secure Sockets Layer (SSL) technology, the industry-standard method for protecting web communications developed by Netscape Communications Corporation, adds sessions security to web sites. SSL can be used to protect the data exchange of any application protocol that normally operates over TCP/IP, for example, HTTP, FTP, or Telnet. The most common use of SSL is in protecting HTTP communications: for example, any URL beginning with ***https://*** indicates the use of HTTP protected by SSL.

SSL provides a range of security services for client/server sessions, including:

- ***Server authentication***: the server is authenticated to the client by demonstrating possession of a digital certificate. This proves to the originator that he or she is actually communicating with the intended web site and not with a fraudulent site stealing personal information or sensitive data.

- **Client authentication:** this service authenticates to the server that the client is who he or she claims to be, protecting the data from fraudulent users and over non-repudiation protection. If visitors to your site use *personal digital certificates*, your server can instantly recognize them, facilitating instant log-in (and preventing later repudiation of the web transaction). Of course in our application that solution it's not suggested for the standard user which inserts the data, but this could be a strong method to control the access of the operators and administrators to our system, instead of simple Username and Password.
- **Message integrity:** data items transferred are protected against attempts to modify them, digital certificates, using SSL technology, encrypt the data that visitors exchange with the site to keep them safe from interception or tampering.
- **Confidentiality:** users are assured that no unauthorized entity has access to the information being shared at the web site. This protects sensitive information such as account numbers, credit card numbers or data inherent clinical experimentation, as in our case, against eavesdroppers. SSL preserves the integrity of every transaction, generating a warning if so much as one character of information is changed between your server and your user's browser. Users are assured that no unauthorized entity has intercepted data en rout to the intended destination.

Server certificates are designed to protect the visitors to the site. Installing a digital certificate on the web server lets you taking advantage of the SSL technology to work seamlessly between your site and your visitor's web browsers. Because all major browsers and web servers are optimized and ready for SSL, all you need to activate SSL sessions with visitors to your site is simply installing a digital certificate on your server and configure it properly.

Here's how the process works:

1. A customer contacts your site, accessing a secured URL (indicated by a URL that begins with "https:" instead of just "http:" or by a message from the browser).
2. Your server responds, automatically sending the customer your site's digital certificate, which authenticates your site.
3. Your customer's web browser generates a unique *session key* (DES) to encrypt all communications with the site.
4. The user's browser encrypts the session key itself with the site's public key so only the site can read the session key.
5. A *secure session* is now established. It all takes only seconds and requires no action by the user. Depending on the browser, the user may see a key icon becoming whole or a padlock closing, indicating that the session is secure.

If your site doesn't have a digital certificate, visitors will see a warning message when they attempt to offer personal information.

SSL comes in two strengths, 40-bit and 128-bit, which refer to the length of the session key (DES) generated by every encrypted transaction. The longer the key, the more difficult it is to break the encryption code. Most browsers support 40-bit SSL sessions, and the latest browsers enable users to encrypt transactions in 128-bit sessions - trillions of times stronger than 40-bit sessions. In our system we will force 128-bit session key and SSL v3.0 for the transactions.

Digital certificates encrypt data using Secure Sockets Layer (SSL) protocol. SSL uses RSA public key cryptography for Internet security, to negotiate each time the session key: 1024-bit RSA key digital certificate for the web server is suggested, for a suitable security level.

APPENDIX C: ANN ARBOR STAGING SYSTEM

Stage I	Involvement of a single lymphatic region (I), or localized involvement of a single extra-lymphatic organ or site (IE)
Stage II	Involvement of two or more lymphatic regions on the same side of the diaphragm (II), or localized involvement of a single extra-lymphatic organ or site and of one or more lymphatic regions on the same side of diaphragm (IIE). An optional recommendation is that the number of lymphatic regions involved should be indicated by a subscript (e.g. II3)
Stage III	Involvement of lymphatic regions on both sides of the diaphragm (III), which may also be accompanied either by localized involvement of an extra-lymphatic organ or site (IIIE), or by involvement of spleen (IIIS), or by both (IIIE+S)
Stage IV	Diffuse or disseminated involvement of one or more extra-lymphatic organs with or without associated lymphatic involvement. The organ involved should be identified by a symbol: H for liver, L for lung, M for bone marrow, P for pleura, O for bone, D for skin

The absence or presence of unexplained fever, night sweats, and/or unexplained weight loss of more than 10% of the usual body weight in the 6 months prior the diagnosis is denoted by the suffix letters A or B, respectively.

APPENDIX D: ECOG PERFORMANCE STATUS SCALE

ECOG Scale	ECOG Status
0	Fully active, able to carry on all pre-disease performance without restriction.
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature (e.g. light house work, office work).
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	Completely disabled, Cannot carry on any self-care. Totally confined to bed or chair.

APPENDIX E: PATHOLOGY

Guidelines for tissue handling and processing

The tissue handling and the role of the pathologist are very crucial in the T-cell project prospective study as the correct manipulation of the bioptic sample provides clinicians and pathologists with material of highly precious potential value in terms of applicability of the most update techniques, including the gene profiling and tissue microarray ones.

In the suspicion of a lymphoma the lymph node should be immediately sent to the local pathologist without any fixative, preferably wrapped in a gauze, soaked in physiologic solution.

From the biopsy the following samples are recommended:

1. for **ordinary fixation** (10% buffered formalin is recommended, preferably buffered according to Lillie's recipe (volume 1 page 146 Histochemistry, Pearse A.G.E.) If it is possible and the sample size allows it, we would advise you to make one additional block, so that the latter could be more easily sent somewhere, if necessary.
2. for **cryopreservation** (liquid nitrogen, then stored in an -80°C ultrafreezer)
3. for **routine tumor cytogenetics** if available, send a 5 mm square piece of fresh tumor in tissue culture media to local lab

Material to be sent to the referring pathologist

1. One H&E or giemsa stained slide from each block, all immunostains performed, and one formalin- fixed block.
2. copy of the diagnostic report or, preferably, an English-translated version of it (provided it contains the description, the final diagnosis and the immunohistochemical and/or molecular results if done) and a copy of positive flow cytometry results.
3. Investigators are warmly encouraged to provide referring pathologist a formalin-fixed block; only in the case a formalin block is absolutely unavailable, please provide 20 unstained slides (preferably 2 μm -thick, coated on electrically charged slides; if available DAKO ChemMate, Capillary Gap Microscope slides are appreciated for use with a TechMate 500/1000)

Referring pathologists

Chairmen of the Histopathology Review Panel will locate Regional sites where expert hematopathologists will review the material and perform a panel of immunostains (T-cell panel + CD20) and marker not assessed at local site. Each Institution will be assigned a Regional site to contact for study materials shipment.

The referring pathologist will collect and review the pathological material sent by the participating centres, without knowing the clinical outcome of the patient.

The reviewed material will refer to both onset and eventual relapse.

The classification scheme in use is the World Health Organization recently published¹⁹.

The pathological criteria will be strictly applied.

List of molecules to be searched (in case a diagnosis of peripheral T-cell lymphoma is made)

The immunochemistry markers to be performed are summarized in the enclosed Table.

The T-cell receptors gene analysis will be performed according to the BIOMED protocol.

Source (mark one) <input type="checkbox"/> Initial biopsy site <input type="checkbox"/> Blood <input type="checkbox"/> Bone marrow <input type="checkbox"/> Other site (specify) _____ Frozen tissue <input type="checkbox"/> Frozen tissue available for study		Phenotype (mark one) <input type="checkbox"/> T-cell <input type="checkbox"/> NK-cell <input type="checkbox"/> B-cell <input type="checkbox"/> Hodgkin's disease <input type="checkbox"/> Indeterminant Phenotype Methods (mark all that apply) <input type="checkbox"/> Paraffin <input type="checkbox"/> Frozen <input type="checkbox"/> Flow Other (specify) <input type="checkbox"/> _____ <input type="checkbox"/> _____		Genotype (mark one) <input type="checkbox"/> T-cell <input type="checkbox"/> B-cell <input type="checkbox"/> Germline <input type="checkbox"/> Indeterminant (I) Molecular Methods (mark all that apply) <input type="checkbox"/> PCR <input type="checkbox"/> Southern <input type="checkbox"/> FISH <input type="checkbox"/> Cytogenetics (include report) <input type="checkbox"/> Other (specify) _____		Molecular Markers (mark all that apply) <input type="checkbox"/> TCR-gamma-RA <input type="checkbox"/> TCR-beta-RA <input type="checkbox"/> IgH-RA <input type="checkbox"/> IgK-RA <input type="checkbox"/> ALK-RA <input type="checkbox"/> iso 7q <input type="checkbox"/> del(5q) <input type="checkbox"/> HTLV1+ <input type="checkbox"/> HTLV1- Other (specify) <input type="checkbox"/> _____ <input type="checkbox"/> _____ <input type="checkbox"/> _____										
T-Cell Panel	CD2	+	-	I	CD4	+	-	I	CD56	+	-	I	EBER	+	-	I
	CD3E	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	CD8	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	TCR-beta	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	Ki67	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
	CD5	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	CD30	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	TIA1	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>		<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
T-Cell Markers	C1a	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	CD43	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	TCR-gamma	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	_____	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
	CD3s	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	CD27	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	TCR-delta	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	_____	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
	CD7	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	CD45RO	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	ALK	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	_____	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
	CD10	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	CD45RA	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	_____	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	_____	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
B-cell Markers	CD19	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	CD79a	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	sKappa	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	_____	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
	CD20	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	cKappa	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	sLambda	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	_____	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
	CD22	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	cLambda	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	EBER	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	_____	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Other Markers	CD11b	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	CD34	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	Granzyme B	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	_____	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
	CD15	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	CD45	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	Perforin	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	_____	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
	CD16	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	CD57	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	EMA	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	_____	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
	CD21	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	CD68	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	EBV-LMP	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	_____	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
	CD23	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	CD103	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	Tdt	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	_____	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
	CD25	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	HHV8	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	_____	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	_____	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Cell Counts	CD4+ T-cells:	<input type="text"/>	<input type="text"/>	⊕	CD30+ T-cells:	<input type="text"/>	<input type="text"/>	⊕	EBER+ T/NK- cells:	<input type="text"/>	+					
	CD8+ T-cells:	<input type="text"/>	<input type="text"/>	⊕	Ki67+ cells:	<input type="text"/>	<input type="text"/>	⊕	EBER+ B-cells:	<input type="text"/>	+					

APPENDIX F: SUGGESTED STAGING PROCEDURES

Procedures required at Baseline and at Restaging

- Adequate diagnostic surgical biopsy of lymph node, or any available tissue sample
- Clinical history and complete physical examination
- Complete blood count, complete biochemistry and virology
- Radiologic studies: chest X-ray, CT-scan of chest and abdomen/pelvis and/or other radiological studies, if clinically indicated
- Bone marrow biopsy
- Lumbar puncture for patients at risk : bone marrow and/or testis and/or peridural spaces and/or paranasal sinuses involvement at presentation (to omit for leucocytes > 15x10⁹/L or for platelets < 50 x10⁹/L, and to reconsider when values will be normalized)
- A bone marrow aspirate aliquot should be frozen for molecular analysis
- A serum aliquot (10 mL) should be frozen for parallel studies

Procedures required under Certain Circumstances

- Gastroscopy if Waldayer ring is involved or in presence of gastric symptoms
- Spinal CT scan and cerebrospinal fluid evaluation by lumbar puncture for neurologic signs or symptoms
- Biopsy of suspicious extranodal sites, if clinically indicated (for staging or scoring)
- Peripheral blood immunophenotyping in case of suspicious leukemic dissemination

Ancillary procedures Not Mandatory for Staging

The following procedures are not mandatory but strongly recommended:

- ⁶⁷Gallium scintigraphy (Ga-scans)
- ¹⁸F-Fluorodeoxyglucose (¹⁸F-FDG) positron emission tomography (PET)
- Cytogenetics analysis on bone marrow aspirate sample

APPENDIX G: CLINICAL EVALUATION

We strongly suggest to evaluate response of patients undergoing any kind of treatment by using the Recommendations for Revised Response Criteria for Malignant Lymphoma²¹ below summarized.

Assuming that PTCLs are predictably PET avid histologies, pretreatment PET is strongly encouraged to better define sites of disease, but is not required.

Complete Response (CR) requires the following:

1. the absence of signs and symptoms of disease
2. a negative PET scan in both patients PET+ and PET- prior to treatment
3. bone marrow must be normal by morphology, or if indeterminate, negative by immunohistochemistry, flow and/or molecular genetic studies

Note that CR unconfirmed (Cru) is no longer included

Partial Response (PR) requires the following:

1. $\geq 50\%$ decrease in tumor size, but PET+ at prior PET avid sites
or
2. $\geq 50\%$ decrease tumor size and PET- in the setting of a positive CT and PET- prior to treatment.

The bone marrow is not relevant.

Stable Disease (SD) is defined as neither PR nor progressive disease, PET+ only at prior sites of disease.

Progressive Disease (PD)/Relapsed Disease (from CR) requires the following:

1. $\geq 50\%$ increase in disease
or
2. new PET+ lesions

For PET- prior to therapy patients PET does not replace a biopsy before initiating new therapy.

APPENDIX H: CLINICAL CASE REPORT FORMS

Identification

Center/Institution.....

Date of Registration (dd/mm/yyyy)

Patient's Initials..... Gender Year of Birth.....

Diagnostic biopsy date (dd/mm/yyyy)

Institution Patient Code (assigned by local Clinician).....

Eligibility

Patient with newly diagnosed T-cell Lymphoma Yes No

Patient with histologically confirmed diagnosis
of T-cell Lymphoma Yes No

Age over 18 Yes No

APPENDIX H: CASE REPORT CLINICAL FORMS

1. BASELINE DATA

Histologic diagnosis

Diagnostic pathology #.....

Diagnostic biopsy site

Initial disease presentation: Nodal Extranodal Both

Prior immunosuppressive drugs? Yes No

If Yes, specify

History of autoimmune disease or antibodies? Yes No

If Yes, specify

History of other disorders of the immune system? Yes No

If Yes, specify

History of lymphoproliferative disease? Yes No

If Yes, specify

History of sprue/enteropathy? Yes No

If Yes, specify

Comments

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APPENDIX H: CASE REPORT CLINICAL FORMS

2. CLINICAL DATA

Systemic symptoms

Fever: No ≤ 38°C > 38°C

Weight loss: No ≤ 10% > 10%

Night Sweats: No Yes

ECOG 0 1 2 3 4

Other symptoms (mark all that apply)

- | | |
|--|---|
| <input type="checkbox"/> Erythroderma | <input type="checkbox"/> Chest pain |
| <input type="checkbox"/> Raised rash | <input type="checkbox"/> Dyspnea |
| <input type="checkbox"/> Pruritis | <input type="checkbox"/> Hemoptysis |
| <input type="checkbox"/> Purpura | <input type="checkbox"/> Anorexia |
| <input type="checkbox"/> Adenopathy | <input type="checkbox"/> Abdominal pain |
| <input type="checkbox"/> Fatigue/weakness | <input type="checkbox"/> Dysphagia |
| <input type="checkbox"/> Infection | <input type="checkbox"/> Hematochezia |
| <input type="checkbox"/> Headache | <input type="checkbox"/> Other |
| <input type="checkbox"/> Neurologic symptoms | If other, specify |
| <input type="checkbox"/> Cough | |

Comments

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APPENDIX H: CASE REPORT CLINICAL FORMS**3. EASY STAGE (DISEASE LOCALIZATION)****NODAL**

Waldeyer's ring	No	<input type="checkbox"/>	Yes	<input type="checkbox"/>	Max Ø (cm)	_____		
Submandibular	Right	<input type="checkbox"/>	Max Ø (cm)	_____	Left	<input type="checkbox"/>	Max Ø (cm)	_____
Laterocervical	Right	<input type="checkbox"/>	Max Ø (cm)	_____	Left	<input type="checkbox"/>	Max Ø (cm)	_____
Supraclavicular	Right	<input type="checkbox"/>	Max Ø (cm)	_____	Left	<input type="checkbox"/>	Max Ø (cm)	_____
Axillary	Right	<input type="checkbox"/>	Max Ø (cm)	_____	Left	<input type="checkbox"/>	Max Ø (cm)	_____
Lung hilum	Right	<input type="checkbox"/>	Max Ø (cm)	_____	Left	<input type="checkbox"/>	Max Ø (cm)	_____
Mediastinum	No	<input type="checkbox"/>	Yes	<input type="checkbox"/>	Max Ø (cm)	_____		
Celiac	No	<input type="checkbox"/>	Yes	<input type="checkbox"/>	Max Ø (cm)	_____		
Lomboaortic	No	<input type="checkbox"/>	Yes	<input type="checkbox"/>	Max Ø (cm)	_____		
Mesenteric	No	<input type="checkbox"/>	Yes	<input type="checkbox"/>	Max Ø (cm)	_____		
Iliac	Right	<input type="checkbox"/>	Max Ø (cm)	_____	Left	<input type="checkbox"/>	Max Ø (cm)	_____
Inguinal	Right	<input type="checkbox"/>	Max Ø (cm)	_____	Left	<input type="checkbox"/>	Max Ø (cm)	_____
Crural	Right	<input type="checkbox"/>	Max Ø (cm)	_____	Left	<input type="checkbox"/>	Max Ø (cm)	_____

EXTRANODAL

(code **0**=not involved; **1**=localized, 1 site (give max Ø); **2**=localized, more than 1 site (give max Ø); **3**=diffuse)

Head/Neck**Central Nervous System**

Brain	<input type="checkbox"/>	0	<input type="checkbox"/>	1	<input type="checkbox"/>	2	<input type="checkbox"/>	3	Max Ø (cm)	_____
Meninges	<input type="checkbox"/>	0	<input type="checkbox"/>	1	<input type="checkbox"/>	2	<input type="checkbox"/>	3	Max Ø (cm)	_____
Epidural	<input type="checkbox"/>	0	<input type="checkbox"/>	1	<input type="checkbox"/>	2	<input type="checkbox"/>	3	Max Ø (cm)	_____
Eye and Lacrimal glands										
Lacrimal glands	<input type="checkbox"/>	0	<input type="checkbox"/>	1	<input type="checkbox"/>	2	<input type="checkbox"/>	3	Max Ø (cm)	_____
Intraocular	<input type="checkbox"/>	0	<input type="checkbox"/>	1	<input type="checkbox"/>	2	<input type="checkbox"/>	3	Max Ø (cm)	_____
Conjunctiva	<input type="checkbox"/>	0	<input type="checkbox"/>	1	<input type="checkbox"/>	2	<input type="checkbox"/>	3	Max Ø (cm)	_____
Rhino-oro-pharinx										
Nose/Nasal cavity	<input type="checkbox"/>	0	<input type="checkbox"/>	1	<input type="checkbox"/>	2	<input type="checkbox"/>	3	Max Ø (cm)	_____
Paranasal sinus	<input type="checkbox"/>	0	<input type="checkbox"/>	1	<input type="checkbox"/>	2	<input type="checkbox"/>	3	Max Ø (cm)	_____
Oral cavity	<input type="checkbox"/>	0	<input type="checkbox"/>	1	<input type="checkbox"/>	2	<input type="checkbox"/>	3	Max Ø (cm)	_____
Tongue	<input type="checkbox"/>	0	<input type="checkbox"/>	1	<input type="checkbox"/>	2	<input type="checkbox"/>	3	Max Ø (cm)	_____
Parotid/Salivary glands	<input type="checkbox"/>	0	<input type="checkbox"/>	1	<input type="checkbox"/>	2	<input type="checkbox"/>	3	Max Ø (cm)	_____
Thyroid	<input type="checkbox"/>	0	<input type="checkbox"/>	1	<input type="checkbox"/>	2	<input type="checkbox"/>	3	Max Ø (cm)	_____

Thorax

Heart/Vascular system	<input type="checkbox"/>	0	<input type="checkbox"/>	1	<input type="checkbox"/>	2	<input type="checkbox"/>	3	Max Ø (cm)	_____
Pericardium	<input type="checkbox"/>	0	<input type="checkbox"/>	1	<input type="checkbox"/>	2	<input type="checkbox"/>	3	Max Ø (cm)	_____
Thymus	<input type="checkbox"/>	0	<input type="checkbox"/>	1	<input type="checkbox"/>	2	<input type="checkbox"/>	3	Max Ø (cm)	_____
Lungs/Bronchi	<input type="checkbox"/>	0	<input type="checkbox"/>	1	<input type="checkbox"/>	2	<input type="checkbox"/>	3	Max Ø (cm)	_____
Pleura	<input type="checkbox"/>	0	<input type="checkbox"/>	1	<input type="checkbox"/>	2	<input type="checkbox"/>	3	Max Ø (cm)	_____

Abdomen/Pelvis

Stomach	<input type="checkbox"/>	0	<input type="checkbox"/>	1	<input type="checkbox"/>	2	<input type="checkbox"/>	3	Max Ø (cm)	_____
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Liver/Biliar system	<input type="checkbox"/> 0	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	Max Ø (cm) _____
Pancreas	<input type="checkbox"/> 0	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	Max Ø (cm) _____
Adrenal glands	<input type="checkbox"/> 0	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	Max Ø (cm) _____
Ileum	<input type="checkbox"/> 0	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	Max Ø (cm) _____
Colon/Rectum	<input type="checkbox"/> 0	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	Max Ø (cm) _____
Kidneys	<input type="checkbox"/> 0	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	Max Ø (cm) _____
Peritoneum	<input type="checkbox"/> 0	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	Max Ø (cm) _____
Genital system	<input type="checkbox"/> 0	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	Max Ø (cm) _____
Spleen (code 0=not involved; 1=nodular; 2=enlargement; 3=both)					
	<input type="checkbox"/> 0	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	

Max spleen Ø (cm), in any case _____ Max nodule Ø (cm), if code 1 or 3 _____

Other Sites

(code 0=not involved; 1=localized, 1 site (give max Ø); 2=localized, more than 1 site (give max Ø); 3=diffuse)

Bone	<input type="checkbox"/> 0	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	Max Ø (cm) _____
Skin	<input type="checkbox"/> 0	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	Max Ø (cm) _____
Subcutaneous	<input type="checkbox"/> 0	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	Max Ø (cm) _____
Muscle	<input type="checkbox"/> 0	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	Max Ø (cm) _____
Breast (code 0=not involved; 1=monolateral; 2=bilateral)					
	<input type="checkbox"/> 0	<input type="checkbox"/> 1	<input type="checkbox"/> 2		Max Ø (cm) _____

Bone marrow (code 0=not involved; 1=nodular; 2=interstitial; 3=paratrabecular; 4=mixed; 5=diffuse; 6=unknown)

0 1 2 3 4 5

Infiltration _____ %

STAGE I Ie II IIe III IIIe IIIs IIIes IV

Comments

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APPENDIX H: CASE REPORT CLINICAL FORMS

4. LABORATORY

Hemoglobin (g/dL) _____

White Blood Cells ($\times 10^9/L$) _____

Neutrophils ($\times 10^9/L$) _____

Lymphocytes ($\times 10^9/L$) _____

Basophils ($\times 10^9/L$) _____

Eosinophils ($\times 10^9/L$) _____

Monocytes ($\times 10^9/L$) _____

Circulating Lymphoma cells ($\times 10^9/L$) _____

Platelet count ($\times 10^9/L$) _____

Serum LDH (U/L) _____

Upper normal value _____

Beta2 microglobulin (mg/L) _____

Upper normal value _____

Erythrocyte Sedimentation Rate (mm/h) _____

Upper normal value _____

C-Reactive Protein (mg/dL) _____

Upper normal value _____

Total serum protein (g/dL) _____

Serum albumin (g/dL) _____

Serum gammaglobulines (g/dL) _____

Calcium (mg/dL) _____

HBs-Antigen _____ (0=not assessed; 1=negative; 2=positive)

HCV- Antibody _____ (0=not assessed; 1=negative; 2=positive)

HIV _____ (0=not assessed; 1=negative; 2=positive)

HTLV-1 _____ (0=not assessed; 1=negative; 2=positive)

EBV _____ (0=not assessed; 1=negative; 2=positive)

Serum M-component Yes No Not assessed

If yes, g/dL _____

If yes, type of clone :

IgG κ IgG λ IgA κ IgA λ IgM κ IgM λ IgD κ IgD λ IgG κ
 κ light chain λ light chain

Hemolytic anemia? Yes No Not assessed

Hemophagocytic syndrome? Yes No Not assessed

Comments

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APPENDIX H: CASE REPORT CLINICAL FORMS

5. PLANNED THERAPY

Radiotherapy:

no IF EF Total skin Other

If Other, specify _____

Chemotherapy:

no single agent combination CHT without ADM combination CHT with ADM

In any case, specify regimen used and number of courses (mandatory) _____

High Dose Therapy:

Yes No

Other treatment:

Yes No

Specify type of treatment (mandatory) _____

Comments

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APPENDIX H: CASE REPORT CLINICAL FORMS

6. ACTUAL THERAPY

CHEMOTHERAPY

Biological Response Modifiers (BRMs) (e.g. α -IFN, retinoids, steroids, etc.)

Yes No Not assessed If Yes, specify _____

Single agent CHT

Yes No Not assessed If Yes, specify _____

Combination CHT without an anthracycline

Yes No Not assessed If Yes, specify _____

Combination CHT with an anthracycline (*mitoxantrone is considered equivalent to an anthracycline*)

Yes No Not assessed If Yes, specify _____

Date chemotherapy began (dd/mm/yyyy) _____

Date chemotherapy ended (dd/mm/yyyy) _____

Indicate drugs used as part of initial chemotherapy regimen (mark all that apply):

- | | |
|--|--|
| <input type="checkbox"/> None | |
| <input type="checkbox"/> Bleomycin | <input type="checkbox"/> Metotrexate |
| <input type="checkbox"/> Cisplatin | <input type="checkbox"/> Mitoxantrone |
| <input type="checkbox"/> Cyclophosphamide | <input type="checkbox"/> Prednisone |
| <input type="checkbox"/> Cytarabine | <input type="checkbox"/> Vincristine |
| <input type="checkbox"/> Doxorubicine | <input type="checkbox"/> Other |
| <input type="checkbox"/> Epirubicine/Epidoxorubicine | <input type="checkbox"/> If other, specify _____ |
| <input type="checkbox"/> Etoposide | _____ |

RADIOTHERAPY

no IF EF Total skin Other

If Other, specify _____

Date of radiotherapy began (dd/mm/yyyy) _____

Date of radiotherapy ended (dd/mm/yyyy) _____

Best Response to Initial treatment:

- Complete Response
- Complete Response, unconfirmed
- Partial Response
- No response / Progressive Disease
- Indeterminate (specify)
-
-
-
-

HIGH DOSE THERAPY

Type of transplant

- Autologous
- Syngenic
- Allogeneic, myeloablative
- Allogeneic, non-myeloablative

Type of product

- Bone marrow
- Cord blood
- Peripheral blood

Date of transplant (dd/mm/yyyy) _____

Response to Transplant:

- Complete Response
- Complete Response, unconfirmed
- Partial Response
- No response / Progressive Disease
- Indeterminate (specify)
-
-
-
-

Comments

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APPENDIX H: CASE REPORT CLINICAL FORMS

7. FOLLOW-UP

Date of form's Completion (dd/mm/yyyy) _____

Date of last contact (dd/mm/yyyy) _____

Disease status at last contact:

- No evidence of disease
- Evidence of disease
- Stable disease
- Progressive disease

Patient status at last contact:

Alive

Dead

Date of death (dd/mm/yyyy) _____

Cause of death

- Lymphoma
- Treatment toxicity
- Infection (specify)
- Solid tumor (specify)
- Myelodysplastic syndrome/Acute leukaemia
- Unknown
- Other (specify)

More details on cause of death.....
.....
.....
.....

Lost to follow-up

Disease relapse or progression:

no

Relapse

Progression

Date of relapse (dd/mm/yyyy) _____

Date of progression (dd/mm/yyyy) _____

Evidence of Second malignancy

- No
- Yes
- Not assessed

If yes, specify
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.....

Evidence of concomitant disease

- No
- Yes
- Not assessed

If yes, specify
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Comments

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APPENDIX I: SCHEDULE OF EVENTS

	Baseline	Restaging	Follow-up updating	PD or relapse^k	End of the study
Informed consent	X				
Demographics	X				
Relevant clinical history	X				
Complete physical examination	X			X	
Orientating physical examination		X	X		X
Complete blood count	X				
Complete biochemistry	X				
Urinalysis	X				
Virology	X				
Chest X-ray	X	X	X	X	X
CT-scan ^a	X	X	X	X	X
Bone marrow biopsy	X				
Lumbar puncture for pts at risk ^b	X				
Diagnostic surgical biopsy ^c	X				
Biopsy of suspicious extranodal sites ^d	X				
Gastroscopy ^e	X				
Spinal CT scan and cerebrospinal fluid evaluation by lumbar puncture ^f	X				
Peripheral blood immunophenotyping ^g	X				
Information on therapy ^h		X			
Follow-up information ⁱ			X		X
Diagnostic material ^j	X				

^a of chest and abdomen/pelvis

^b bone marrow and/or testis and/or peridural spaces and/or paranasal sinuses involvement at presentation

^c of lymph node or any available tissue sample

^d if clinically indicated

^e if Waldayer ring is involved or in presence of gastric symptoms

^f for neurologic signs or symptoms

^g in case of suspicious leukemic dissemination

^h not required in W & W patients

ⁱ once a year for 5 years

^j for histopathologic review

^k also in case of progression from a W & W policy

APPENDIX J: CALENDAR

Expected accrual time:	24 months
Database definition:	February 2006
Database circulation:	April 2006
Final approval:	July 2006
Commence of registrations:	August 2006
Minimum follow-up for alive patients:	5 years