UNIVERSITY OF MODENA

AND REGGIO EMILIA

PhD Program in Clinical and Experimental Medicine (CEM)

Curriculum: Translational Medicine

Cycle XXXIV

THE T-CELL PROJECT:

VALUE AND RELEVANCE OF THE T-CELL LYMPHOMA REGISTRIES

PhD Candidate:
Tetiana Skrypets

Supervisor:
Prof. Massimo Federico

PhD Program Coordinator:
Prof. Giuseppe Biagini

SUMMARY:

Abbreviations

AIC	Akaike's information criteria
AITL	Angioimmunoblastic T-cell lymphoma
ALCL	Anaplastic large cell lymphoma
ALK	Anaplastic lymphoma kinase
ALK+	Anaplastic lymphoma kinase positive
AlloSCT	Allogenic stem cell transplant
ALK-	Anaplastic lymphoma kinase negative
ATLL	Adult T-cell leukemia/lymphoma
AutoHSCT	Autologous Hematopoietic stem cell transplant
BIC	Bayesian information criteria
BM	Bone marrow
CAR	Chimeric antigen receptor
CI	Confidence interval
CR	Complete response
CRP	C-reactive protein
CTCL	Cutaneous T cell lymphoma
DLBCL	Diffuse Large B Cell Lymphoma
DNA	Deoxyribonucleic acid
eCRF	electronic Case Report Forms
EATL	Enteropathy-associated T-cell lymphoma
EBV	Epstein-Barr Virus
EATCL	Enteropathy-associated T-cell lymphoma
ECOG	Eastern Cooperative Oncology Group
EFS	Event Free Survival
ENKTCL	Extranodal natural killer NK/T-cell lymphoma
ENS	Extranodal sites
EPI	Enteropathy-associated T-cell lymphoma Prognostic Model
FISH	Fluorescence in situ hybridization
GTP	Guanosine triphosphate
HDAC	Histone deacetylase inhibitors
HDC	High-dose chemotherapy
HR	Hazard ratio
HSTCL	Hepatosplenic T-cell lymphoma
ICML	International Conference on Malignant Lymphoma
IPTCLP	International peripheral T-cell lymphoma Project score
IPI	International Prognostic Index
JAK	Janus kinase
LDH	Lactate dehydrogenase
LMR	Lymphocyte to monocyte ratio
MEITL	Monomorphic epitheliotropic intestinal T-cell lymphoma
MF	Mycosis fungoides
m-PIT	modified Prognostic Index for T-cell lymphoma

NCCN	National Comprehensive Cancer Network
NR	Not reached
NRM	Non-related mortality
NHL	Non-Hodgkin Lymphoma
NK	Natural Killer
NLR	Neutrophil to lymphocyte ratio.
WHO	World Health Organisation
OS	Overall survival
PCR	Polymerase chain reaction
PD	Progressive disease
PD-L1	Programmed death-ligand 1
PET	Positron emission tomography
pEBVd	plasma EBV-DNA
PFS	Progression-free Survival
PH	Proportional hazard
PIAI	Prognostic Index for AITL
PINK	Prognostic index of natural killer lymphoma
PI3K	Phosphatidylinositol 3-kinase
PIT	Prognostic Index for T-cell lymphoma
PLT	Thrombocytes level
POD24	Progression of disease within 24 months
PS	Performance status
PTCL	Peripheral T-cell lymphoma
PTCL-NOS	Peripheral T-cell lymphoma. Not otherwise specified
PTCL-u	Peripheral T-cell lymphoma – unspecified
qRT	quantitative real time
RCT	Randomized clinical trials
RNA	Ribonucleic acid
S-Alb	Serum albumin
SAP	Statistical analysis plan
SD	Stable disease
SPTCL	Subcutaneous panniculitis-like T-cell lymphoma
STAT	Signal transducer and activator of transcription proteins
SYK	Spleen tyrosine kinase
TCP	T-Cell Project
TCR	T-cell receptor
TFH	Follicular T helper
Th	T-cell helper type
T-LGLL	T-cell large granular lymphocytic leukemia
T-PLL	T-cell prolymphocytic leukemia
TCR	T-cell receptor
TCS	T-cell score
US	United States

WHO	World Health Organisation
18FDG	18Fluorodeoxyglucose
β2M	β2 microglobulin
γδ	gamma-delta

ABSCTRACT

Introduzione. I linfomi a cellule T periferiche (PTCL) sono un gruppo raro ed eterogeneo di neoplasie che hanno origine dalle cellule linfoidi post-timiche a diversi stadi di differenziazione. Differiscono tra di loro per caratteristiche morfologiche e fenotipiche, per la presentazione clinica, la risposta alle terapie e la prognosi. I PTCL rappresentano il 10-15% di tutti i disturbi linfoproliferativi nell'emisfero occidentale, con un'incidenza complessiva di 0,5-2 casi x100.000 persone/anno. La rarità ed eterogeneità dei PTCL ha reso estremamente difficile la loro conoscenza, e la ricerca è tuttora concentrata ad una maggiore comprensione del decorso clinico, della risposta al trattamento e della prognosi dei pazienti che ricevono una diagnosi di questo tipo. I PTCL colpiscono con maggiore frequenza i soggetti di sesso maschile, e l'età media alla diagnosi è di 62 anni. Secondo l'ultima classificazione dei linfomi pubblicata dalla nel 2016 (WHO2016) si possono distinguere più di 20 diversi sottotipi di PTCL, dei quali quelli più comuni sono: PTCL non altrimenti specificato (NOS), angioimmunoblastico (AITL), il linfoma nasale extranodale a cellule NK/T (ENKTCL), a cellule T dell'adulto leucemia/linfoma (ATLL), linfoma anaplastico a grandi cellule ALK positivo (ALCL, ALK+) e ALK negativo (ALCL, ALK-). Rispetto ai linfomi non-Hodgkin a cellule B, i PTCL sono associati a scarsa risposta alla terapia iniziale, ad alti tassi di recidiva e ad una prognosi sfavorevole, con un tasso di sopravvivenza a 5 anni inferiore al 40%.

Metodi: Il T-cell Project (TCP) è uno studio internazionale sulla prognosi dei linfomi a cellule T realizzato dall'International T Cell Lymphoma Project (IPTCLP) al quale aderiscono oltre 100 Centri in 17 diversi Paesi. I casi sono registrati su una piattaforma dedicata, e seguiti fino a 5 anni dalla diagnosi. L'endpoint primario dello studio è la sopravvivenza libera da progressione (progression-free survival).

Risultati. Dal 2006 sono stati registrati 1695 casi nello studio TCP 1.0, e 839 nel TCP 2.0. Con i dati raccolti nel TCP 1.0 sono stati realizzati e già pubblicati numerosi lavori sulle caratteristiche cliniche e sulla prognosi del PTCL-NOS, degli AITL, NKTCL, ALCL ALK-, ALCL ALK + ed altri tipi dei linfomi T.

Nel 2018 è stato avviato il TCP 2.0, con l'obiettivo di registrare ulteriori 1000 casi, classificandoli secondo la più recente classificazione WHO 2016. Allo studio TCP 2.0 hanno finora aderito 102 centri in 17 Paesi, in 4 Continenti. Di questi, 694 casi sono risultati attualmente valutabili per l'endpoint primario. Da una analisi preliminare, i sottotipi più frequenti sono risultati essere il PTCL-NOS, il ALCL ALK – e il linfoma AITL, che rappresentano rispettivamente il 31%, il 19% e il 13% dei casi. Più in dettaglio, i PTCL-NOS

rappresentano il sottotipo più frequente in tutte le arre geografiche, mentre la leucemia/linfoma a cellule T dell'adulto risulta la più frequente in Brasile, i sottotipi AITL e ALCL ALK- in Australia/India e gli ALCL ALK+ in Nord America ed Europa. Inoltre, si è registrata una frequenza relativamente alta di casi di linfoma extranodale a cellule NK/T in Brasile, ma non negli altri Paesi dell'America Latina. I restanti sottotipi infine rappresentano meno del 5% dei casi in tutte le aree geografiche.

Conclusioni. Data la rarità dei linfomi a cellule T periferiche, i TCP 1.0 e 2.0, nati da una collaborazione internazionale, rappresentano una importante fonte di dati, che fotografano la prognosi e la curabilità di queste malattie nella Real Life. Il TCP 2.0 inoltre consentirà di meglio valutare la rilevanza clinica della Classificazione WHO2016, approfondire il ruolo della PET nella stadiazione e nella valutazione della risposta, e infine indagare sulle strategie di trattamento più adeguate per queste neoplasie.

Background: 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 diverse morphological patterns, phenotypes, and clinical presentation. PTCLs account for 10–15% of all lymphoproliferative disorders in the Western hemisphere, with an overall incidence of 0.5–2/100,000 people/year, and have a striking epidemiological distribution, with higher incidence in Asia. The exceeding rarity (5–10% of all lymphoproliferative disorders) and the heterogeneity of PTCLs has made extremely difficult to investigate on them, and a satisfactory understanding of their clinical pictures, response to treatment and prognosis are still awaited. More commonly they appeared in male patients, and the median age at diagnosis is 62 years. In the last 2016 WHO classification there are more than 20 subtypes of PTCLs, where the most common subtypes are PTCL not otherwise specified (NOS), angioimmunoblastic (AITL), extranodal natural killer NK/T-cell lymphoma (ENKTCL), adult T-cell leukemia/lymphoma (ATLL), anaplastic large-cell lymphoma (ALCL) anaplastic lymphoma kinase positive and negative (ALK+ and ALK-). PTCLs are associated with high relapse rates and a poor prognosis compared to B-cell non-Hodgkin lymphomas with a 5-year-survival rate less than 40%.

Objectives:

In 2018, the International T-cell non-Hodgkin's Lymphoma Study Group launched the T-cell Project 2.0 (TCP 2.0), which adapts to changes made in diagnosis, classification, staging and response evaluation, in order to verify whether a prospective collection of data would allow to achieve more accurate information on T-cell lymphomas and search for more disease oriented prognostic models. In particular, the aim of the TCP 2.0 relied on the opportunity of contributing to a real-time understanding of the evolving landscape of T-cell lymphoma biology and treatment, together with the application of recently available new technologies to further identify new therapeutic targets.

Methods: The T-cell Project is an international study on the prognosis of T-cell lymphomas carried out by the International T Cell Lymphoma Project (IPTCLP). Today more than 100 clinical centers in 17 different countries are participating in the project. The cases are recorded on a dedicated platform, and followed up to 5 years from the diagnosis. The primary endpoint of the study is progression-free survival.

Results. From 2006 were registered 1695 cases in TCP 1.0, and 839 in TCP 2.0 With the data going from TCP 1.0 there have been already published numerous manuscripts on clinical and prognostic characteristics of PTCL-NOS, AITL, NKTCL, ALCL ALK-, ALCL ALK + and other PTCL subtypes

In 2018 a TCP 2.0 had been launched with the aim to register another 1000 cases due to a new classification WHO2016 of lymphoid neoplasms. Now in the TCP 2.0 there 102 centers in 17 different countries from 4 continents. Of these, 694 cases were currently evaluable for the primary endpoint. Overall, PTCL-NOS, ALCL ALK-, and AITL, represent the most frequent subtypes, accounting on 31%, 19% and 13% of cases, respectively. Moreover, PTCL-NOS represents the most frequent subtype worldwide, whereas Adult T-cell leukemia/lymphoma was more frequent in Brazil, AITL and ALCL ALK- in Australia/India, and ALCL ALK+ in North America and Europe. Of note, ENKTCL, was relatively frequent in Brazil and quite rare in the other Latin America Countries. Finally, many sub-types represent less than 5% of cases in all geographic areas.

Conclusions. Given the rarity of PTCLs, TCP 1.0 and TCP 2.0 were born from an international collaboration, represent an important source of data, which assessing the prognosis and treatment strategies in Real Lyfe. TCP 2.0 will also make it possible to better assess the clinical relevance of the WHO2016 classification, to investigate the role of PET in staging and response assessment, and finally to investigate the most appropriate treatment approaches for these neoplasms.

1. PERIPHERAL T-CELL LYMPHOMAS

1.1 General aspects.

Lymphomas are hematological malignancies caused by the overgrowth of specific cells of the immune system, the lymphocytes. Lymphomas are generally developing in the lymph nodes (which are clusters of lymphocytes and other immune cells) or other lymphoid organs (such as the spleen), but can affect all organs in the body. The B or T cells undergo a tumor transformation and so replicate without any control. The lymphocyte transformation is caused by genetic mutations that damage the DNA and interfere with mechanisms underlying cell growth and survival. The lymphocyte transformation is caused by genetic mutations that damage the DNA and interfere with mechanisms underlying cell growth and survival. The different subtypes of lymphoma are caused by different genetic mutations affecting the lymphocytes at various stages of their development: this is the reason why the characteristics of lymphomas are so variable from indolent to really aggressive.

There are two main subtypes of lymphoma: non-Hodgkin lymphomas (NHL) and Hodgkin lymphomas (HL). Peripheral T-cell lymphomas (PTCLs) are part of the NHL and collectively include neoplasms of mature (i.e., post-thymic) T or NK cells.[1] PTCLs comprise a heterogeneous group of neoplasms that are derived from post-thymic lymphoid cells at different stages of differentiation, with diverse morphological patterns, phenotypes, and clinical presentation. PTCLs account for 10–15% of all lymphoproliferative disorders in the Western hemisphere, with an overall incidence of 0.5–2/100,000 people/year, and have a striking epidemiological distribution, with higher incidence in Asia. All subtypes are found more commonly in male patients, and the median age at diagnosis is 62 years.[2] This disease is generally associated with high relapse rates and a poor prognosis, with inferior treatment outcomes compared with B-cell lymphomas, and have a 5-year-survival < 32%.[3,4]

The incidence and prevalence vary in different racial populations and geographical regions,[1,2] largely due to host genetic and environmental makeup and prevalence of risk factors, including diseases affecting immunity and virus epidemiology.[5,6]

1.2 Epidemiology

In the United States (US), the incidence of T cell lymphomas has been gradually increasing over the past two decades, whereas the incidence of B-cell lymphomas has plateaued.

According to a review of US surveillance, epidemiology and end results cancer database, over a 10-year period from 2007 to 2016, the incidence rate of T-cell lymphomas is 2.2 (2.2/1000 patients). Among the T cell lymphomas, PTCLs had the highest incidence (1.2), followed by Cutaneous T-cell lymphoma (CTCL) – 0.6. PTCL-not otherwise specified (NOS) was the most common subtype of PTCL (0.4), followed by Adult T-cell lymphoma/leukemia (ATLL) – 0.3, Anaplastic large cell lymphoma (ALCL) – 0.2, and Angioimmumoblastic T-cell lymphoma (AITL) – 0.2.[7]

In 2008, The International T-cell Lymphoma Project reported data on 1,314 cases of PTCL/natural killer (NK)-cell lymphomas from 22 centers worldwide with diagnoses between 1990 and 2002. The aim of this study, among others, was to determine the relative frequencies and geographic variation of the T-cell lymphoma subtypes. The most common subtype identified was PTCL-NOS (25.9%), with the second most common subtype being AITL (18.5%). Extranodal natural killer NK/T-cell lymphoma (ENKTCL) represented 10.4% and ATLL 9.6% of the cases. The next most common subtypes were ALCL ALK positive (ALK+; 6.6%); ALCL, ALK negative (ALK-; 5.5%); and Enteropathy-associated T-cell lymphoma (EATL; 4.7%). All the other specific subtypes of PTCLs represented less than 2% of the total.[2]

PTCLs showed a wide geographical heterogeneity with a consequence on the distribution of subtypes across several countries and on the overall incidence. PTCL-NOS was the most common subtype in both North America (34.3%) and Europe (34.3), whereas NKTCL and ATLL were common in Asia (22.4% and 25%, respectively). ATLL was frequent in Japan, but was not found in the other Asian countries, whereas NKTCL made up 44% of the cases in Asia excluding Japan. ALCL, ALK+, was most common in North America (16.0%), whereas EATL was most common in Europe (9.1%, mainly Norway). Interestingly, angioimmunoblastic type was most common in Europe (28.7%) compared with the other regions. Primary cutaneous ALCL was higher in North America than in Europe (5.4% vs. 0.8%), possibly because of referral of such cases to dermatologists in Europe, whereas systemic and cutaneous ALCL, enteropathy-type, and hepatosplenic PTCL were uncommon in Asia.[2]

1.3 T-cell and NK neoplasm's classification.

In 2008 the World Health Organization (WHO) classification for lymphoid neoplasm was published, and PTCL were grouped in 4 clinical categories (Table 1).[8]

Table 1. Practical Classification PTCL/NK/T-cell lymphoma.

NODAL - Peripheral T-cell lymphoma, not otherwise specified (PTCL-NOS) - Angioimmunoblastic T- cell lymphoma (AITL) - Anaplastic large cell lymphoma (ALCL), ALK+ - Anaplastic large cell lymphoma (ALCL), ALK-
CUTANEOUS - Mycosis fungoides - Sézary syndrome - Primary cutaneous CD30-positive T -cell lymphoproliferative disorders - Lymphomatoid papulosis - Primary cutaneous anaplastic large cell lymphoma - Primary cutaneous 8 T – cell lymphoma - Primary cutaneous CD8-positive aggressive epidermotropic cytotoxic T-cell lymphoma - Primary cutaneous CD4-positive small medium T- cell lymphoma
EXTRANODAL - Extranodal NK/T-cell lymphoma, nasal type - Enteropathy associated T -cell lymphoma - Hepatosplenic T -cell lymphoma - Subcutaneous panniculitis like T – cell lymphoma - Seroma associated ALCL of breast
PRIMARY LEUKEMIC - Aggressive NK leukemia- associated with hemophagocytic syndrome - T-cell prolymphocytic leukemia - T-cell large granular lymphocytic leukemia - Adult T-cell leukemia lymphoma
VARIED PRESENTATION - Chronic lymphoproliferative disorder of NK cells - Systemic Epstein-Barr virus (EBV) positive T- cell lymphoproliferative disease of childhood - Hydroa vacciniforme like lymphoma - Systemic EBV+ T-cell lymphoproliferative disease-associated with hemophagocytic syndrome

But after 8 years of information and experience that have emerged from scientific and clinical studies, an update of the diagnostic criteria was felt to be necessary and timely. As a result, the new WHO classification was published in 2016, which includes updates to current entities as well as the addition of a limited number of new provisional entities. The current classification recognizes about 30 biologically distinct subtypes of mature T and NK neoplasms, summarized in Table 2.

Table 2. WHO 2016 classification of mature T and NK neoplasms.

Mature T and NK neoplasms
T-cell prolymphocytic leukemia
T-cell large granular lymphocytic leukemia
Chronic lymphoproliferative disorder of NK cells
Aggressive NK-cell leukemia
Systemic EBV$^+$ T-cell lymphoma of childhood
Hydroa vacciniforme–like lymphoproliferative disorder*
Adult T-cell leukemia/lymphoma
Extranodal NK-/T-cell lymphoma, nasal type
Enteropathy-associated T-cell lymphoma
Monomorphic epitheliotropic intestinal T-cell lymphoma*
*Indolent T-cell lymphoproliferative disorder of the GI tract**
Hepatosplenic T-cell lymphoma
Subcutaneous panniculitis-like T-cell lymphoma
Mycosis fungoides
Sezary syndrome
Primary cutaneous CD30$^+$ T-cell lymphoproliferative disorder
Lymphomatoid papulosi
Primary cutaneous anaplastic large cell lymphoma
Primary cutaneous γδ T-cell lymphoma
Primary cutaneous CD8$^+$ aggressive epidermotropic cytotoxic T-cell lymphoma
*Primary cutaneous acral CD8$^+$ T-cell lymphoma **
Primary cutaneous CD4$^+$ small/medium T-cell lymphoproliferative disorder
Peripheral T-cell lymphoma, NOS
Angioimmunoblastic T-cell lymphoma
*Follicular T-cell lymphoma**
Nodal peripheral T-cell lymphoma with TFH phenotype*
Anaplastic large-cell lymphoma ALK+
Anaplastic large-cell lymphoma ALK-*
*Breast implant–associated anaplastic large-cell lymphoma**
Provisional entities are listed in italics ***** Changes from the 2008 Classification

All these types are various with respect to pathology, clinical presentation, response to therapy, and expression of surface markers.[1] Despite this, diagnostic accuracy and agreement with consensus diagnosis is still suboptimal due to several factors (the rarity of these tumors, the lack for detailed phenotype and an incomplete understanding of the biology of the disease) and still remains a matter of concern.

Among the most relevant changes, for example, it should be noted that AITL is now regarded as part of a broader category termed "nodal T-cell lymphomas with T-follicular helper phenotype", which also includes follicular T-cell lymphoma and nodal peripheral T-cell lymphoma with T-follicular helper phenotype. Moreover, ALCL ALK- is no longer conceived as a provisional subcategory, but now represents a distinct disease entity and a clearly defined subtype. Because of these changes in terminology, which reflect our deeper understanding of the biologic heterogeneity of PTCL, future studies in T-cell lymphomas will classify patients in a different way than even the most recent clinical trials have done so far.

1.4 Molecular mechanisms

PTCLs are characterized by the accumulation of mutations in genes that govern multiple epigenetic pathways, with some entities like PTCL-follicular helper T cell (TFH) and AITL, representing the subtypes most enriched for these genetic events.[9]

Mutation-induced activation of signaling pathways that play a key role in normal T and NK cell physiology, like the Janus kinase/signal transducers and activators of transcription pathway or T-cell receptor signaling, are highly recurrent and common to many entities. Extranodal NK/T-cell lymphoma and adult T-cell leukemia/lymphoma represent two remarkable models' lymphomas induced by viruses with superimposed genetic lesions. The tumor microenvironment, and the nature of its cellular milieu, plays an important role in PTLC lymphomagenesis, especially in AITL.[10]

Molecular analysis showed the diversity and hierarchy of genetic events linked to T-cell lymphomagenesis. In general, T-cell lymphoma development results from an accumulation of genetic hits targeting pathways which are critical for cell survival or proliferation and control of gene transcription (i.e. epigenetic modifiers, cell signaling and cell cycle). Notably, mutation-induced activation of signaling pathways that play a key role in normal T and NK-cell physiology ((i.e. the Janus kinase – signal transducer and activator of transcription proteins

(JAK–STAT) pathway or T-cell receptor (TCR) signaling)) are highly recurrent and common to many entities. ENKTL and ATLL represent two remarkable models of lymphomas induced by viruses with superimposed genetic lesions. The current challenge is to translate these novel data into more efficient therapeutic strategies to improve patient outcomes. The development of novel in vivo and in vitro pre-clinical models should help our understanding of the complexity of oncogenic mechanisms, and to identify promising candidates in the future. [11]

TCR signaling plays a critical physiologic role in T-cell function and its dysregulation has been proposed to be a major factor in PTCL pathogenesis. In T-cell lymphomas, an abnormal T lymphocyte grows and duplicate itself producing a large number of identical clones, so all monoclonal cells have the same rearrangement profile of TCR genes. Molecular analyses to detect clonal TCR gene rearrangements or other assessments of clonality (such as FISH, karyotype, genomic analysis) are useful tools not only for diagnosis, but also as markers to evaluate the therapy efficacy and any relapses.[12] Sequencing of PTCLs has revealed somatic mutations and genomic rearrangements in the TCR signaling pathway, bearing direct or indirect effects on Ras- and Rho-family guanosine triphosphatases (GTPases). These mutations include activating mutations and gene fusions involving the guanine nucleotide exchange factor, *VAV1*, as well as activating and dominant negative mutations in the GTPases *KRAS* and *RHOA*, respectively. In addition to mutations directly affecting the GTPase pathway, TCR signaling mutations indirectly affecting Ras- and Rho-family GTPases involving genes such as *CD28*, *FYN*, *LCK*, and *PLCG1* are also found.[13]

EBV is a ubiquitous lymph tropic gamma-herpesvirus associated with several lymphoma subtypes, including a subset of PTCLs. EBV-associated lymphomas are canonically defined by the presence of EBV-encoded RNAs (EBERs) in tumor tissue. Moreover, EBV-positive lymphomas, release of EBV DNA from tumor cells into the plasma might be useful for disease monitoring and prognostication.[14] Cell-free plasma EBV-DNA (pEBVd) can be detected and quantified by quantitative real time polymerase chain reaction (qRT PCR), providing an easily attainable candidate biomarker to assess tumor's linkage to EBV and disease burden.[15-18]

1.5 Diagnosis

The diagnosis of TCL should be made by histological and cytological examination of tissue. In the presence of adenopathy, an excisional biopsy of the lymph node must be performed. In the absence of adenopathy, a probability diagnosis can be performed by histological and

cytological examination of bone marrow (BM) biopsy. The criteria for making a diagnosis of PTCLs are defined by the WHO classification of hematopoietic malignancies and depend on histological subtype.[1,8]

1.6 Staging

As regards the staging of lymphomas, over the years several staging systems have been proposed. The following table (Table 3) shows the Ann Arbor staging system, which is the "standard" method of staging; its validity has been recognized over time in several studies.

Table 3. Ann Arbor staging system.

Stage	Involved sites
I	Involvement of a single lymph region (I); localized involvement of a single extra lymphatic organ or site (IE)
II	Involvement of two or more lymph regions from the same side of the diaphragm (II); localized involvement of a single extra lymphatic organ or site together to the interest of one or more lymph locations from the same side of the diaphragm (IIE)
III	Involvement of many lymph regions above and below the diaphragm (III), which can be accompanied by localized involvement of an extra lymphatic organ or site (IIIE).
IV	Diffuse or disseminated involvement of one or more organs or extra lymphatic sites with or without involvement of lymph locations. The affected organs are marked with a symbol: H (liver), L (lungs), M (bone marrow), P (pleura), O (bones), D (skin)

Each stage is also identified as A or B according to the absence or presence, respectively, of one or more of the following symptoms: night sweats, fever, weight loss greater than 10% in the previous six months (B symptoms).

Although, following the progress made, particularly in imaging techniques, the 11th International Conference on Malignant Lymphoma (ICML) in Lugano, Switzerland, June 2011 had the aim to develop universally accepted, unambiguous, improved staging criteria for HL

and NHL. Clinical and imaging subcommittees presented their conclusions at a subsequent workshop at the 12th International Conference on Malignant Lymphoma, leading to revised criteria for staging. As a result, [18F] fluorodeoxyglucose positron emission tomography (18F FDG-PET)-computed tomography (CT) was formally incorporated into standard staging for FDG- avid lymphomas. A modification of the Ann Arbor descriptive terminology will be used for anatomic distribution of disease extent, but the suffixes A or B for symptoms will only be included for HL. A BM biopsy is no longer indicated for the routine staging of HL and most DLBCL, while with PTCL this approach is still unclear. PET-CT is used to assess response in FDG-avid histologies using the 5-point scale. The product of the perpendicular diameters of a single node can be used to identify progressive disease. These recommendations should improve evaluation of patients with lymphoma and enhance the ability to compare outcomes of clinical trials.[19]

1.6.1 Prognosis

The prognosis of PTCLs remains poor in comparison to B-cell NHLs (median OS at 5 years of less than 40%), largely due to lower response rates and less durable responses to standard combination chemotherapy regimens such as CHOP.[8, 20-22]

The study conducted by Armitage et al. also assessed the outcome for the various subtypes of PTCL and NKTCL. The 5-year OS for PTCL-NOS, AITL, and all NKTCLs was 32% compared with only 14% for ATLL. ALCL, ALK positive, demonstrated the best 5-year OS (70%), with ALCL, ALK negative, having an intermediate 5-year OS (49%). Although rare, primary cutaneous ALCL had an excellent 5-year OS of 90%. The 5-year OS for subcutaneous panniculitis-like PTCL was also good (64%) compared with enteropathy-type (20%) and hepatosplenic PTCL (7%). The 5-year OS for nasal NKTCL was 42%, with an apparent plateau, compared with a 5-year OS of only 9% for extranasal NKTCL and aggressive or unclassifiable NK-cell leukemia/lymphoma.[2]

To better define the clinical outcome of patients with PTCLs, many prognostic models have been proposed over the years. The International Prognostic Index (IPI) derived for Diffuse Large B Cell Lymphomas (DLBCLs) has been used and was shown to be predictive of both OS and PFS for patients with PTCLs.[22-23] In 2004 the Intergruppo Italiano Linfomi performed a large study on 385 patients diagnosed and treated in the 1990s and defined a prognostic model (PIT).[23]

Among different clinical parameters assessed at the time of diagnosis, age (<60years), performance status (Eastern Cooperative Oncology Group [ECOG] 2 or higher), lactate dehydrogenase (LDH) level above upper normal range, and bone marrow involvement were independent predictors of inferior overall survival.[21] Overall, the Intergruppo Italiano Linfomi study confirmed the need to develop clinical trials specifically focused on the disease.

The PIT was slightly more effective than the IPI in stratifying patients. Finally, an updated version of the PIT (m-PIT) was proposed resulting in a more robust tool than the PIT.[24] These prognostic indices can be used to stratify patients in risk subgroups and in certain circumstances can guide treatment decisions for patients with PTCLs.

A new model, the T-cell score, has recently been defined by using the prospectively collected data registered in the T-cell Project.[25] More recently, novel prognostic indexes have been identified and validated for specific PTCL subtypes, including EATL and ENKTCL. As shown in Table 4, all available prognostic indexes share the same structure of categorical scores based on simple laboratory and clinical features. Although all of these indexes have been formally validated, the accuracy of prognostication in PTCL remains suboptimal; thus, more prognostic studies that take into account novel biomarkers and novel prognostic features are warranted. Among recent advances, a better definition of response by means of FDG-PET may play an important role in PTCL management and decision-making.[26] PTCLs are listed among FDG-avid diseases, and several studies have already confirmed the role of metabolic tumor volume and of interim and end-of-treatment FDG-PET to predict outcomes.[27-28] Although promising, data regarding the role of metabolic response in PTCLs are very preliminary and thus need to be confirmed by larger studies.[29]

Table 4. Available prognostic indices for PTCLs.

Variable	IPI International NHL Prognostic Factors Project, 1993	PIT Gallamini et al., 2004	IPTCLP Vose et al., 2008	mPIT Went et al., 2006	TCS Federico et al., 2018	AITL Hong et al., 2018	PINK Kim et al., 2016	EPI de Baaij et al., 2015
Age > 60	**X**	**X**	**X**	**X**		**X**		**X**
ECOG ≥ 1	**X**	**X**	**X**	**X**	**X**			**X**
LDH (abn. Values)	**X**	**X**		**X**			**X**	**X**
Stage III-IV	**X**				**X**	**X**	**X**	**X**
ENS > 2	**X**					**X**		**X**
BM+		**X**						
Plt < 150K/mmc			**X**			**X**		
S-Alb					**X**			
Neutrophils					**X**			
KI-67 ≥ 80%				**X**				
Anemia (M<13, F<11g/dl)						**X**		
Serum IgA (>400 mg/dl)						**X**		
B symptoms							**X**	**X**
Regional Lymph nodes							**X**	
PTCL subset	*All*	*PTCL-NOS*	*PTCL-NOS*	*PTCL-NOS*	*PTCL-NOS*	*AITL*	*ENKTCL*	*EATCL*

2. TREATMENT APPROACHES

2.1 General aspects

The optimal management of patients with PTCL, which is disputed, is in any case limited to few options, all with unsatisfactory efficacy. None of the currently available recommendations are based on high-quality evidence, and few well-designed randomized clinical trials (RCT) have been conducted to support therapeutic choices. The currently recommended treatment strategy for PTCLs derives mostly from B-cell lymphoma treatment strategies, with the recommended use of an aggressive approach with anthracycline-based polychemotherapy (i.e. CHOP or CHOEP) and with autologous stem cell transplant (autoHSCT) to consolidate response to first-line therapy or to manage relapsed patients.[30]

2.2 First-line therapy

The limited size of the PTCL patient population and the subdivision of this disease into distinct clinical entities present major obstacles to obtaining the necessary data for particular subtypes in randomized clinical trials to inform treatment decisions. Consequently, no consensus regarding first-line therapy for PTCLs currently exists.

Regarding the role of anthracyclines in PTCL, while their role is still debated, anthracycline void regimens have so far failed to demonstrate their superiority to CHOP.[30] Based on a recent meta-analysis, the 5-year OS achieved with this approach was 36.6%. [31]

Several attempts have been made to improve the poor results achieved with CHOP. These include the addition of novel agents and the intensification of therapy. Some clinical studies on etoposide intensification of standard CHOP have shown conflicting results. However, the addition of etoposide has shown better PFS, especially in patients with ALCL, in those with favorable risk factors, and in patients age ≤ 60 years. [32-35]

The results of three randomized trials that evaluated the efficacy of adding a novel agent to the CHOP backbone are available. One prospective trial combined alemtuzumab, an anti-CD52 monoclonal antibody, with CHOP; it failed to show improved outcomes compared to chemotherapy alone.[36] Another randomized trial compared standard CHOP with CHP (cyclophosphamide, vincristine, prednisone) combined with the antiCD30 antibody-drug conjugate brentuximab vedotin (BV-CHP; ECHELON-2 trial).[37] This trial, which enrolled 452 treatment naïve CD30-positive PTCLs, demonstrated improved PFS and OS rates for the BV-CHP combination. Most of the patients included in this trial (about 75%) had ALCL, with

clearly positive results for this subtype. However, the scientific community was left without any clear demonstration of the efficacy of BV-CHP in non-ALCL CD30-positive subtypes.

A third trial compared CHOP with CHOP + the histone deacetylase inhibitor romidepsin, Showing promising single-agent activity in relapsed refractory patients (ROCHOP trial).[38] The ROCHOP randomized clinical trial conducted by the LYSA group enrolled 421 patients with PTCL who were not planned to receive autoHSCT or allogeneic SCT (alloSCT). The median PFS (mPFS) for patients in the experimental arm was 12 months (9–25.8), without significant difference compared to the reference arm (mPFS 10.2 months (7.4 – 13.2); HR 0.81; 95% CI 0.63–1.04). Although this study was not able to confirm the initial hypothesis of the superiority of Ro-CHOP, the subgroup analysis seems to suggest that the novel combination acts differently in different PTCL subtypes, with relatively higher activity observed for AITLs.[38]

In summary, even if associated with unsatisfactory results, CHOP chemotherapy should still be considered as the reference therapy for most PTCL subtypes with the main exception of ALCL for which BV-CHP is the preferred recommended option and of ENKTCL. The use of CHOEP is supported by low quality of evidence but can be considered as a reasonable option in young and fit subjects with non-ALCL PTCLs. The use of high-dose chemotherapy (HDC) followed by autoSCT in first complete remission (CR1) is recommended by most of the available guidelines (Table 5).[30,39]

Several groups have reported that achieving complete remission (CR) before autoHSCT is a significant independent predictor of improved survival in patients with PTCL receiving upfront autoHSCT.[40-42] However, there have been no RCTs specifically designed to evaluate upfront autoHSCT in comparison with observation in CR1 for PTCL.[43-45] Several retrospective studies and prospective single-arm phase II trials have reported encouraging results with this approach. The largest prospective phase II study, published by the Nordic Group (NLG-T-01), included 160 patients with PTCLs; 72% of patients underwent autoHSCT in first remission after 6 courses of CHOEP chemotherapy.[46] All nodal PTCL subtypes were included, with the exception of ALK+ ALCLs. One hundred and thirty patients achieved CR (63%) or partial response (37%), and 115 (88.5%) underwent ASCT. Overall, the 5-year OS and PFS for the intention-to-treat population were 51% and 44%, respectively. Considering subtype distribution, better outcomes were observed for ALK- ALCL than for other subtypes.[46] In a second study by Reimer et al., 83 patients with PTCL were enrolled, with the exclusion of CTCL and of ALK+ ALCL. Fifty-nine patients (71%) completed stem cell mobilization after CR (66%) or partial response (PR) (34%) and 55 underwent autoHSCT. The 3-year OS was 48%.[4]

Table 5. ESMO and NCCN clinical practice guidelines for auto-alloSCT in PTCLs.

PTCLs subtype	Primary diagnosed PTCLs		Relapsed/Refractory PTCLs	
	ESMO	***NCCN***	***ESMO***	***NCCN***
PTCL-NOS	PR, CR, transplant eligible – autoHSCT	Clinical trials, or ASCT, or observation if CR, or if PR – see rel/ref* settings	PR, CR, transplant eligible – alloSCT (or ASCT)	PR, CR, transplant eligible – alloSCT (or ASCT)
AITL	PR, CR, transplant eligible – autoHSCT	Clinical trials or ASCT or observation if CR, or if PR – see rel/ref settings	PR, CR, transplant eligible – alloSCT (or ASCT)	PR, CR, transplant eligible – alloSCT (or ASCT)
ALCL ALK-	PR, CR, transplant eligible – autoHSCT	Clinical trials, or ASCT, or observation if CR, or if PR – see rel/ref settings	PR, CR, transplant eligible – alloSCT (or ASCT)	PR, CR, transplant eligible – alloSCT (or ASCT)
ALCL ALK+	No further treatment, Or autoHSCT if high-risk profile	Only chemotherapy ± ISRT	PR, CR, transplant eligible – alloSCT (or ASCT)	PR, CR, transplant eligible – alloSCT (or ASCT)
EATL	AutoHSCT	Clinical trials, or ASCT, or observation if CR, or if PR – see rel/ref settings	PR, CR, transplant eligible – alloSCT (or ASCT)	PR, CR, transplant eligible – alloSCT (or ASCT)
HSCTL	ASCT or allo if donor available	CR or PR – preferred alloSCT	PR, CR, transplant eligible – alloSCT (or ASCT)	Preferred alloSCT if eligible
ENKTCL	ASCT	Stage IV if CR – allo or ASCT	PR, CR, transplant eligible – alloSCT (or ASCT)	AlloSCT (or ASCT)

*rel/ref – relapsed/refractory

Some recently published studies provide additional insights into the role of autoHSCT in CR1. A real-world data analysis from the Swedish Lymphoma Registry found prolonged OS and PFS for transplanted patients with PTCL-NOS, AITL, ALK- ALCL and EATCL after adjustment for confounding factors.[48] However, the selection of non-ASCT patients used as the control group may have been biased by early progressing patients after induction therapy. Another study was a large multicenter analysis conducted by the LYSA group. Among the 527 studied cases, a final cohort of 269 patients age < 65 years with a CR or PR after induction chemotherapy was identified: 78 cases of PTCL-NOS, 123 cases of AITL, and 68 cases of ALK- ALCL. Overall, 81% were in CR and 19% in PR; 50% of the final cohort was allocated to autoHSCT (134 patients). Neither the Cox multivariate model nor the propensity score analysis found any survival advantage in favor of autoHSCT as a consolidation procedure for

patients in response after induction therapy. Subgroup analyses did not reveal any further difference in terms of response status, disease stage, or risk category.[49] Recently, Park et al. published their first report of the large prospective observational COMPLETE study, conducted by 56 US academic centers.[50] This paper described the outcomes of 119 patients who achieved CR after induction therapy, including 54 PTCL-NOS, 35 AITL, and 30 ALK-ALCL. Thirty-six patients underwent autoHSCT; patients with AITL had significantly improved OS and PFS but patients with other PTCL subtypes did not. Finally, an exploratory of the ECHELON-2 trial was conducted, for the 82 patients with a declared intention to transplant out of the 177 patients randomized to BV-CHP arm (ALK+ ALCL were excluded). SCT was in fact performed in 38 patients (27 ALK- ALCL and 11 non-ALCL patients), most of whom were from non-Asian centers, suggesting regional practice differences. Despite the fact that the ECHELON-2 study was not designed to evaluate the role of upfront consolidation with ASCT, numerical PFS estimates favored the use of consolidative SCT in patients with ALK- ALCL and with non-ALCL who achieved a CR at the end of induction after frontline BV-CHP.[51]

Interpreting the results from these studies on the role of autoHSCT consolidation is complicated by the diverse eligibility criteria adopted, the suboptimal rates of transplantation among PTCL subtypes, and the differing rates of CR before autoHSCT. The decision to proceed to autoHSCT in a subject with PTCL who responds to first-line chemotherapy is difficult and should always be discussed with the individual patient. Researchers are strongly encouraged to run well-designed clinical trials that adopt the same up-to-date criteria for response definition (i.e. FDG-PET). These trials, which would necessarily require considerable international cooperation, would hopefully provide data by PTCL subtype.

AlloSCT could be identified as alternative option to autoHSCT as consolidation of CR1 patients. Schmitz et al. recently published data from the first randomized phase 3 trial of auto versus alloSCT as part of first-line therapy in poor-risk PTCLs excluding ALK+ ALCLs.[52] The trial enrolled 18 to 60 years old patients of all stages and IPI and was planned to detect an improvement of event-free survival (EFS) at three years from 35% achieved with autoHSCT to 60% by alloSCT in the intent-to-treat population. After the enrollment of 104 patient randomization and recruitment was prematurely stopped because a planned interim analysis had shown that it was highly unlikely to meet the primary endpoint. The transplant-related mortality observed contributed to this result. In conclusion alloSCT cannot be recommended as consolidation therapy for CR1 PTCL patients due to the lack of evidence and because of it toxicity profile. The only exception to this general statement might be represented by HSTCL

for whom a systematic review of 44 cases treated with alloSCT at first or second relapse demonstrated a 3-year relapse-free survival of 42% and OS of 56%.[53]

2.3 Relapsed/refractory PTCLs

Approximately 70% of patients with PTCL are expected to develop relapsed or refractory disease after first-line therapy.[54-55] A dismal outcome can be expected for these patients, with median OS of a few months, even for those who are able to proceed to salvage therapy.[54] Among the options available, the effectiveness of autoHSCT in relapsed disease is uncertain due to the frequent use of autoHSCT in CR1 in eligible patients, and because the salvage therapies available for relapsed PTCLs have very limited activity, thereby further reducing the feasibility of an autoHSCT program when planned. Available salvage regimens were previously developed as a first-line strategies mostly for B-cell malignancies, from them well-known ICE (ifosfamide, carboplatin, etoposide), DHAP (high-dose cytarabine, cisplatin, dexamethasone), GDP (gemcitabine, cisplatine, dexamethasone), and ESHAP (etoposide, cytarabine, cisplatin and methylprednisolone). Despite the fact that these regimens were previously studied for aggressive lymphomas, due to the rarity of PTCLs a small number of patients were included without independent subset analysis.[56-59] Even if limited by a low power due, a subset analysis of the Canadian Cancer Trials Group LY.12 randomized phase 3 study was not able to confirm DHAP superiority over GDP in PTCLs.[60] In relapsed/refractory PTCLs, alloSCT is also a feasible option in almost all subtypes after failing prior autoHSCT.[30,39, 61] However, non-relapse mortality (NRM) varies from 8.2% to 40%.[62-64] These scatter data suggest that it is necessary to carefully select possible candidates for alloSCT.
Several new agents have been tested in the relapsed refractory setting, and, while some have already received formal approval for clinical use, approval is not uniform across countries. These include the antiCD30 antibody-drug conjugate brentuximab vedotin (BV), pralatrexate (approved in the US only), and four histone deacetylase inhibitors (HDAC): romidepsin (US only), belinostat (US only), vorinostat (US only), and chidamide (China only). Results achieved with these agents are very similar with CR rates of 10%-25% and with a median PFS of less than one year.

2.4 Future perspectives for the use of SCT in PTCLs

We are currently living a time of big and quick changes in the study of PTCLs. Among recent acquisitions some may have an important role on PTCLs management and decision-making regarding the use SCT; these include a better definition of response by means of FDG-PET, and the role of new agents.

Over the last decade FDG-PET has been widely used for staging and restaging malignant lymphomas, and its use is now recommended by international guidelines.[26] PTCLs are listed among FDG avid disease and several studies have already confirmed the role of interim and end of treatment FDG-PET in PTCLs to predict outcomes.[27-28] Although very promising, data regarding the role of metabolic response in PTCLs are very preliminary and need confirmation in larger studies A better and more reproducible response definition however might significantly contribute to improve our understanding of consolidation therapies including the use of SCT, granting a better selection of truly responding patients to pre-ASCT induction.

A second contribution to a better definition of the use of ASCT in PTCLs may result from the use of novel agents. The final results of the first global, double-blind, randomized, phase III study – ECHELON-2 have correlated the addition of brentuximab vedotin to CHP (BV-CHP) showing higher response, PFS and OS rates compared to CHOP alone.[37] In this study consolidative SCT was allowed at physician discretion. In an exploratory analysis that excluded ALK+ ALCL patients, intent to transplant was declared for 82 out of 177 patients randomized to BV-CHP arm. SCT was actually performed in 38 patients (27 ALK- ALCL and 11 non ALCL patients) mostly from non-Asian centers suggesting regional practice differences. Even if this study was not designed to evaluate the role of upfront consolidation with SCT, numerical PFS estimates favored the use of consolidative SCT in patients with ALK- ALCL and with non-ALCL who achieve a CR at the end of induction after front line BV-CHP. [65]

Either the hypotheses that a better definition of response with FDG-PET or that availability of more active therapies might modify the role of SCT in PTCL represent two important questions for future well deigned clinical trials.

2.5 Novel agents

Pharmacology research is very active in PTCL, and therapeutic development is mainly driven by advances in the understanding of the biology of the disease **(Table 6).**

The frequent alteration of the epigenetic machinery in PTCL, mainly of the TFH phenotype, justifies strong rationale for the search of novel HDAC inhibitors and to test the efficacy of combining more than one epigenetic modifier. A recent phase I combination trial of 5-azacitidine and romidepsin reported very interesting OR and CR rates of 73% and 55%, respectively.[66]

Inhibition of spleen tyrosine kinase (SYK) signaling and of phosphatidylinositol 3-kinase (PI3K) pathways have also been investigated, with promising results from phase I-II studies. Cerdulatinib is an oral SYK, JAK1, JAK3, and Tyk2 inhibitor; in a phase Iia study on 41 PTCL patients, it was able to produce an overall response rate of 34%, with 27% CR rates.[67] Among PI3K inhibitors, the oral duvelisib was used in a phase I study with 16 PTCL and 19 CTCL patients. The overall response rate was 50% for the PTCL patients and the median PFS was 8.4 months.[60] The same agent has been evaluated in combination with romidepsin, showing greater activity in AITL and PTCL-NOS (Overall response rates 74% and 64%, respectively, CR rates 63% and 36%, respectively).[68]

A promising therapeutic strategy in PTCL is represented by targeting of tumor microenvironment. Blocking the PD1 interaction with its ligand is justified by the finding of an increased expression of PD-L1 in both malignant and stromal cells of several PTCL subtypes. Indeed, some activity of antiPD1 agents in PTCL has been described by phase I studies, and more convincing results have been achieved with NKTCL.[69] The use of PD1 blockers, however, has also been associated with cases of hyper progression, thus making further clarification of PD-1 inhibition in PTCL urgently needed.

Finally, cellular therapy based on the concept of chimeric antigen receptor (CAR) T-cells is also being developed for T-cell lymphomas, as is the use of bispecific antibodies targeting both CD30 and CD16A.[70-71]

Table 6. Clinical trials exploring novel agents in relapsed/refractory T-cell lymphoma.

Novel agents	Phase	ClinicalTrials.gov identifier
Romidepsin + tenalisib	I/II	NCT03770000
Romidepsin+ pembrolizumab	I/II	NCT03278782
Pembrolizumab + decitabine + pralatrexate	IB	NCT01947140
Durvalumab + different combinations of pralatrexate, Romidepsin and azaciditine	I/II	NCT03161223
Pembrolizumab + pralatrexate	I/II	NCT03598998
Pembrolizumab + copanlisib	I/II	NCT02535247
Brentuximab vedotin + gemcitabine	II	NCT02400627
Brentuximab vedotin + bendamustine	II	NCT02499627
AFM13	II	NCT04101331
Nivolumab + antagonistic CSF1R monoclonal antibody cabiralizumab (BMS-986227)	II	NCT03927105
IPH4102/lacutamab (anti-KIR3DL2) + GEMOX	II	NCT03902184
Chidamide + CPT	II	NCT02879526
Chidamide + PECM	II	NCT03321890
Chidamide+ lenalidomide	II	NCT04329130
Duvelisib	II	NCT03372057
GB226 (Genor Biopharma)	II	NCT03502629
AZD4205 (oral Janus kinase inhibitor)	I/II	NCT04105010
Tipifarnib	II	NCT02464228
Mitoxantrone hydrochloride liposome injection	II	NCT03776279
Durvalumab + lenalidomide	I/II	NCT03011814
Avelumab	Iia	NCT03046953
Avelumab +IL15	I	NCT03905135
Ixazomib	I/II	NCT03547700
Venetoclax	II	NCT03552692/NCT03534180
TTI-621 (SIRPαFc)	I	NCT02663518
OT-82 (Oncotartis, Inc.)	I	NCT03921879
Fenretinide (4-HPR) intravenous emulsion	II	NCT02495415
Anti-ICOS monoclonal antibody MEDI-570	I	NCT02520791

AFM13, bispecific chimeric anti-human CD30 x anti-human CD16A antibody; CPT, cyclophosphamide, prednisone, thalidomide; CSF1R, colony stimulating factor 1 receptor; GEMOX, gemcitabine, oxaliplatin; ICOS, inducible T-cell co-stimulator; IL, interleukin; PECM, prednisone, cyclophosphamide, etoposide, and methotrexate.

3. THE RELEVANCE OF T-CELL LYMPHOMA REGISTRIES [31]

3.1 T-CELL PROJECT 1.0

The Peripheral T-cell Lymphoma Registry (T-cell Project 1.0) was an observational study and was designed to complement clinical studies in PTCL. T-cell Project 1.0 aimed to verify whether a prospective collection of data provided more accurate information to better define prognosis newly diagnosed patients with the more frequent subtypes of PTCL (PTCL unspecified [PTCL-u] and AITL) and to better define clinical characteristics and outcome of the more uncommon subtypes (ENKTL); enteropathy-type TCL; gamma–delta hepatosplenic TCL [γδ HSTL]; subcutaneous panniculitis-like TCL; ALCL, T/null cell, primary systemic type). Its primary endpoint was five-year survival. The number of patients registered in T-cell Project 1.0 has provided information on the prevalence of adverse prognostic factors in the most frequent types (i.e., PTCL-u and AITL). Under these conditions, the sample size was represented by 460 cases of PTCL-u, 460 of AILT, and all cases of rarer histologies observed in the same time frame in which PTCL-u and AILT cases were accrued. The sample size for the 31 more uncommon PTCL subtypes was not possible because of their rarity. The T-cell Project was initiated in 2006 as a prospective registry of patients with PTCL. This study was designed as a prospective collection of information that could be used to define potentially prognostic features for newly diagnosed patients with the more frequent subtypes like PTCL-NOS and AITL and to better define clinical characteristics and outcome of the more uncommon subtypes (ENKTL, enteropathy-type TCL, γδ HSTL; subcutaneous panniculitis-like TCL; ALCL, T/null cell, primary systemic type). Thus far, this registry has provided several platforms to overcome previous challenges in collecting data. To that end, registration of patients in the study and data collection were performed online. Electronic case report forms were available. The adoption of SSL03 technology assured protection in web communications of clinical data. Data access and management was regulated by the use of pass-words with different levels of admittance, providing that subject confidentiality was respected.

OBJECTIVES AND ENDPOINTS

Five goals were outlined for the study: 1. To evaluate the ability of hematopathologists to apply the WHO classification to a large group of cases; 2. To evaluate the role of clinical data in the diagnosis of the T cell lymphoma subtypes; 3. To determine the relative frequencies and geographic variation of the subtypes; 4. To determine clinical correlations, including clinical features, treatment, and survival outcomes; and 5. 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.

Primary Endpoint was 5-year overall survival and Secondary Endpoint – 5-year event free survival. Additional Endpoints were highlighted as Remission rate with initially therapy and 5-year progression free survival.

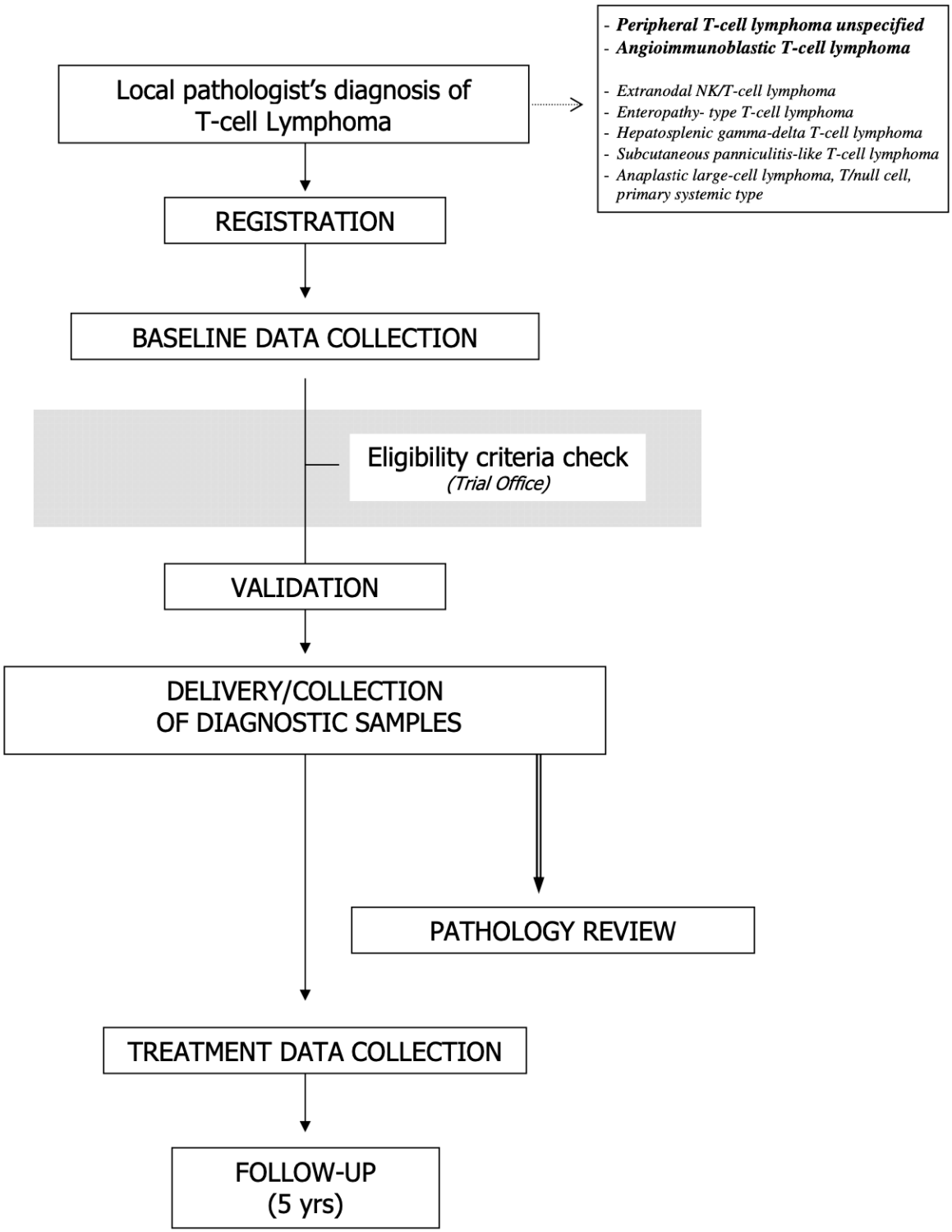
STUDY DESIGN

This is a prospective, longitudinal, international, observational study of patients with histological diagnosis of Peripheral T-cell lymphoma. Eligible patients will be identified from sites. No study specific visit or procedure will be required as part of patient participation in the study. Patients will be evaluated according to the physician's standard practice.

While patients may receive experimental interventions in the course of their care, the Registry is not designed to test any specific intervention. Patients enrolled in the Registry will undergo routine clinical assessments and receive therapy prescribed by their treating physicians.

After patient's registration, diagnosis review is planned for each patient registered in the Study. The samples are to be sent to the Trial Office in batches, and after request of the Trial Office.

Study Flow-chart



SUBJECT SELECTION

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 time;
- 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

STATISTICAL CONSIDERATIONS

Analysis of prognostic factors were 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.

3.2 TCP 1.0: CLINICAL SUBTYPES

In total, 1695 patients were registered by 74 sites from 13 countries worldwide. The main patient characteristics, including distribution of histologic subtypes and data on five-year overall and progression-free survival are shown in **Table 7** and Figure 1 (a-b). PTCL-NOS is the most frequent subtype, accounting for 546 cases (35%). Distribution of subtypes among different geographic areas is similar to prior reports, with AITL being more frequent in Europe and the United States (52% and 28%, respectively), ALK– ALCL in South America (33%), and NK cell in Asia (31.2%). Most patients were at low or low to intermediate risk according to the International Prognostic Index (IPI) and the Prognostic Index for PTCL-NOS (PIT; 59.5% and 59.4%, respectively). Chemotherapy alone or in combination with radiotherapy was the preferred choice in 89% of patients. Anthracycline and etoposide-containing regimens were adopted in 61% and 24% of patients, respectively. Stem-cell transplant was adopted as a consolidation strategy after initial response in 9% of patients.

Table 7. Frequency of lymphoma subtypes and available data on OS and PFS in TCP 1.0 and COMPLETE Registry [72].

	All cases (№)	**PTCL-NOS**	**AITL**	**ALCL ALK-**	**ALCL ALK+**	**NKTCL**	**EATCL**	**SPTCL**	**HSTCL**	**T-LGL γ/δ**
COMPLETE	273	51%	26%	18%	5%					
TCP 1.0	1506	35%	18%	15%	9%	11%	4%	2%	2%	1%
Available data on OS and PFS										
	All cases (№)	**PTCL-NOS**	**AITL**	**ALCL ALK-**	**ALCL ALK+**	**NKTCL**	**EATCL**	**SPTCL**	**HSTCL**	**T-LGL γ/δ**
COMPLETE										
4-yr OS		48%	39%							
TCP 1.0										
5-yr OS	44,2%	34,2%	44,1%	48,5%	77,9%	47,3%	29,6%	75,1%	45,5%	52,3%
5-yr PFS	34,6%	23,9%	31,6%	43,3%	64,1%	39,5%	43,8%	55%	42,7%	32,4%

Figure 1 (a). 5-year OS by different histological subtypes from TCP 1.0.

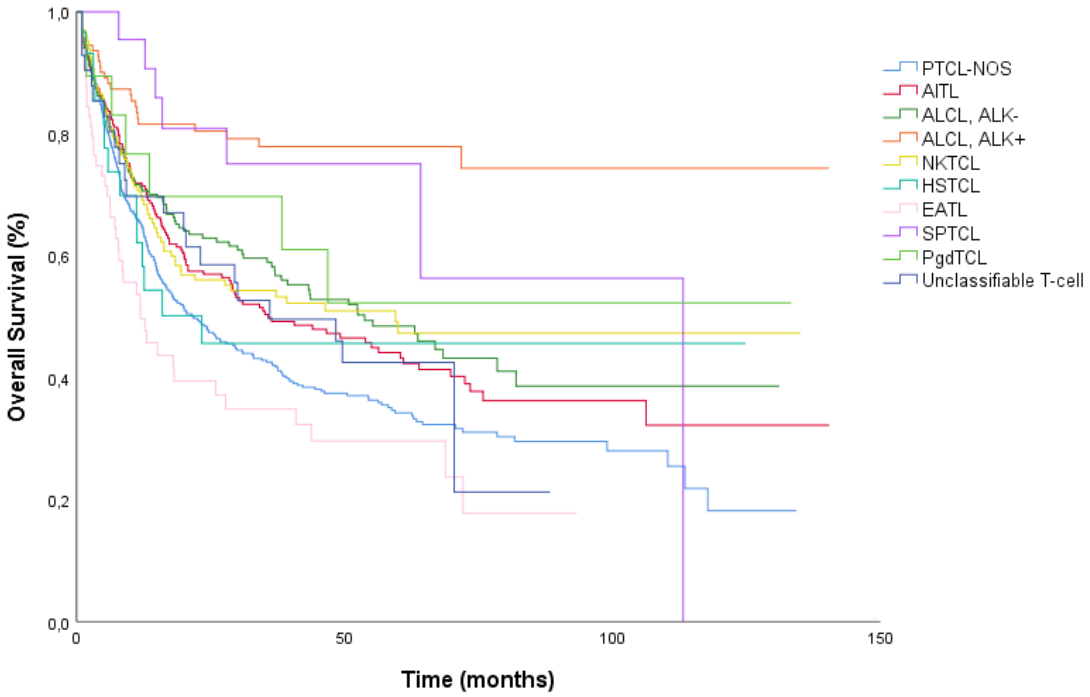
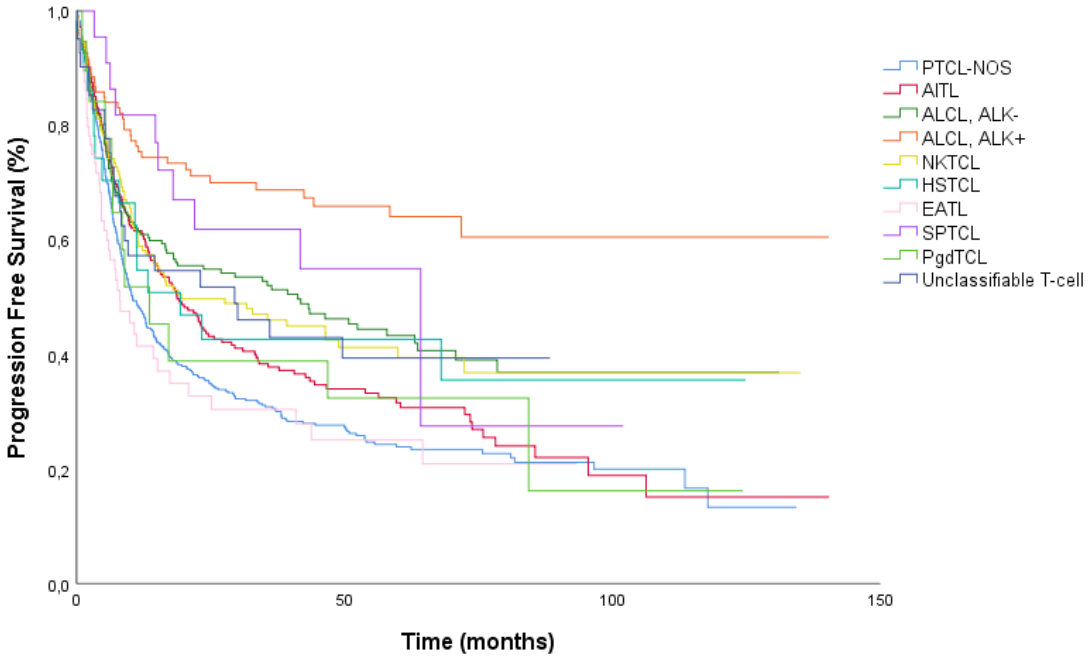


Figure 1 (b). 5-year PFS by different histological subtypes from TCP 1.0.



3.2.1 TCP 1.0: Peripheral T cell lymphoma, not otherwise specified (PTCL-NOS). A new prognostic model developed by the International T cell Project Network [25]

Different models to investigate the prognosis of peripheral T cell lymphoma not otherwise specified (PTCL-NOS) have been developed by means of retrospective analyses. Here we report on a new model designed on data from the prospective T Cell Project. Twelve covariates collected by the T Cell Project were analyzed and a new model (T cell score), based on four covariates (serum albumin, performance status, stage and absolute neutrophil count) that maintained their prognostic value in multiple Cox proportional hazards regression analysis was proposed. Among patients registered in the T Cell Project, 311 PTCL-NOS were retained for study. At a median follow-up of 46 months, the median overall survival (OS) and progression-free survival (PFS) was 20 and 10 months, respectively. Three groups were identified at low risk (LR, 48 patients, 15%, score 0), intermediate risk (IR, 189 patients, 61%, score 1–2), and high risk (HiR, 74 patients, 24%, score 3–4), having a 3-year OS of 76% [95% confidence interval 61–88], 43% [35–51], and 11% [4–21], respectively ($P < 0.001$, Log-rank). Comparing the performance of the T cell score on OS to that of each of the previously developed models, it emerged that the new score had the best discriminant power. The new T cell score, based on clinical variables, identifies a group with very unfavorable outcomes.

The many studies performed to assess the contribution of clinical and biological factors in influencing the prognosis of PTCL-NOS reported that poor Eastern Cooperative Oncology Group performance status (ECOG-PS), advanced stage, presence of extranodal sites, bulky disease, LDH levels and Ki-67 rate were significantly correlated with shorter OS.[22-24]

The usefulness of the International Prognostic Index (IPI), developed for DLBCL, has also been investigated and confirmed for PTCL-NOS.[22-23]

To better define the clinical outcome of PTCL-NOS, the Intergruppo Italiano Linfomi (now Fondazione Italiana linfomi, FIL) performed a large study on 385 patients diagnosed and treated in the 1990s and defined a prognostic model, the Prognostic Index for PTCL-unspecified (PIT), in which age (<60 years), ECOG PS 2 or higher, LDH level above upper normal range, and bone-marrow involvement were independent predictors of OS.[23]

The PIT stratified the patients into four distinct groups with differing risk: low (no adverse factors), intermediate (1 adverse factor) intermediate-high (2 adverse factors) and high (3–4

adverse factors), with a 5-year OS of 62·3%, 52·9%, 32·9% and 18·3%, respectively ($P < 0.0001$, Log-rank).

The PIT was slightly more effective than the IPI in stratifying patients.[23]

An updated version of the PIT (m-PIT) was proposed, in which bone marrow involvement was replaced by Ki67 rate of expression, resulting in a more robust tool than the PIT.[25]

The most recent efforts to improve the understanding of clinical prognostic factors in PTCL-NOS were undertaken by the International Peripheral T cell Lymphoma Project (IPTCLP) on a sample of 340 cases diagnosed between 1990 and 2002: both the PIT and the IPI remained highly significant for both OS and progression-free survival (PFS) ($P < 0.001$).[22] In univariate analysis, the presence of B-symptoms, bulky disease ≥10 cm, elevated serum C-reactive protein, a high number of transformed tumor cells, and platelet count less than 150×10^9/l adversely affected both OS and PFS; in multiple Cox proportional hazards (PH) regression analysis controlled for IPI, only bulky disease remained predictive for both OS and PFS, and thrombocytopenia for PFS.[22]

A common limitation of the latter studies is their retrospective nature. As a result, data have spanned several years, not been collected on consecutive cases, and do not account for changes in the classification systems.[22-23]

To evaluate prognosis prospectively, the IPTCLP established the T Cell Project, which collects an exhaustive set of clinical data and biological information. Herein we report on the analysis of prognostic factors performed on a cohort of 506 cases of PTCL-NOS collected in the prospective T Cell Project.

Patients and methods

The T Cell Project (NCT01142674) was incepted in September 2006 as a prospective registry of patients with PTCL-NOS, AITL, ALCL and all of the rarer subtypes of nodal and extranodal aggressive histologies of PTCL.

Data collection was accomplished via electronic case report forms using a dedicated website (http://www.tcellproject.org) with adoption of the proper technology to ensure protection of the data of individual subjects in web communications.

The study was conducted in compliance with the Helsinki Declaration, was approved by the appropriate research Ethics Committees/Institutional Review Boards and required each patient to consent in written prior to registration.

Most of the cases from the T Cell Project and the COMPLETE Registry (NCT01110733) underwent a central review of initial diagnosis, as per protocol.

Patient characteristics and treatment

Between September 2006 and October 2015, 506 cases of potentially assessable PTCL-NOS were registered, and a total of 311 PTCL-NOS patients (61%) were retained for developing the prognostic model; the list of the investigated covariates and their characteristics in the study cohort are summarized in Table 8.

Table 8. Baseline characteristics of the patients of the training sample (n = 311) including variables with possible impact on survival analyzed.

Factor	N	%
Median age, years (range)	63 (23-83)	
Age > 60 years	170	55
Sex, male	192	62
Stage III-IV	237	76
B-symptoms presence	136	44
Extra nodal sites >1	88	28
ECOG PS >1	81	26
LDH>ULN	164	53
HGB<120 g/l	122	39
Albumin 35 g/l	118	38
Platelet count $<150x10^9$ cells/l	65	21
NLR > 6.5	64	21
ANC > $6.5x10^9$ /l	73	23
LMR $\leq$ 2.1	129	41

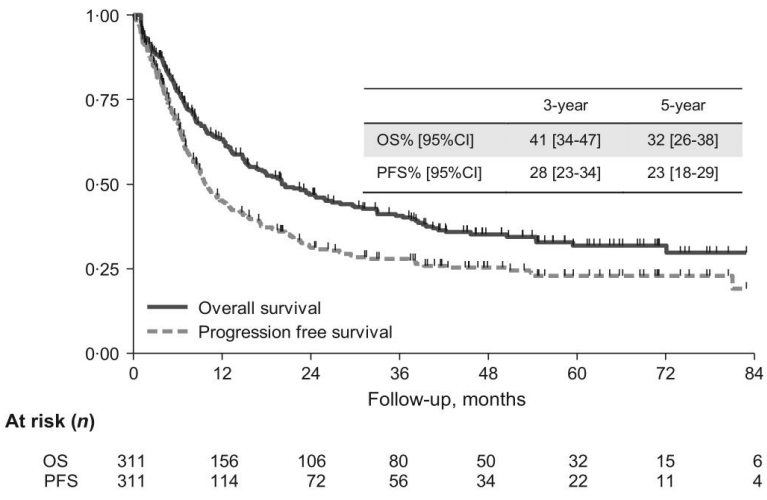
ANC, absolute neutrophil count; ECOG-PS, Eastern Cooperative Oncology Group performance status; HGB, hemoglobin; LDH, lactate dehydrogenase; LMR, lymphocyte to monocyte ratio; NLR, neutrophil to lymphocyte ratio.

The median age was 63 years (range 23–83), 62% of patients were male, and advanced stage disease was found in 76%.

Most patients of the study sample were from Europe (*n* = 157, 50%), followed by South America (*n* = 70, 23%), United States (*n* = 59, 19%) and Asia (*n* = 25, 8%).

The majority of patients were classified as low/low-intermediate risk according to each of the indices previously reported that were applied: IPI 53%, PIT 53%, IPTCLP 75% and m-PIT 88%, respectively. [22-24]Overall, 246 patients (79%) received systemic therapy with curative intent: of these 246 patients, 182 (74%) were treated with CHOP (cyclophosphamide, doxorubicin, vincristine, prednisolone)/CHOP-like and 31 patients (13%) 43 (18%) with etoposide-containing (CHOEP/CHOEP-like) regimens; and 21 (9%) patients received other different regimens; Ten patients (4%) had a satisfactory initial response and were consolidated by stem cell transplant, with some geographical variations (Europe 4·6%, USA 8·9%, South America 1·8%, Asia 0·0%). At a median follow-up of 46 months (range 1–99), 170 deaths were recorded, most due to lymphoma (70%), followed by infection (9%), treatment toxicity (8%) or other (13%). The 3-year and 5-year OS was 41% [95 CI 34–47] and 32% [95 CI 26–38], respectively, with a median OS of 20 months; the OS of the 189 cases excluded due to missing covariates was superimposable to that of study sample, suggesting a lack of selection bias (*P* = 0.431). The 3-year and 5-year PFS was 28% [95 CI 23–34] and 23% [95 CI 18–29], respectively, with a median PFS of 10 months (Figure 2).

Figure 2. Kaplan–Meier curves of overall survival and progression-free survival (for all patients in the training sample (n = 311). 95% CI, 95% confidence interval; OS, overall survival; PFS, progression-free survival.



Prognostic model development

In univariate analysis, all the analyzed variables had a statistically significant impact on OS (Table 9).

Table 9. Univariate and multivariate Cox PH regression in the training sample (n = 311).

		5-year OS [95 CI]	Univariate	Multivariate*	
Overall (n = 311)		32 [26–38]			
Factor	Status		HR [95 CI]	HR [95 CI]	P-value
Stage	I–II	52 [37–65]	1·00	1·00	
	III–IV	25 [18–33]	2·16 [1·43–3·27]	1·74 [1·14–2·65]	0·010
ECOG PS	0–1	38 [30–46]	1·00	1·00	
	2–4	15 [7–25]	2·62 [1·91–3·61]	2·12 [1·52–2·94]	<0·001
Albumin, g/l	≥35	42 [34–52]	1·00	1·00	
	<35	15 [8–24]	2·66 [1·96–3·61]	2·03 [1·47–2·81]	<0·001
ANC, $\times 10^9$/l	≤6·5	38 [30–45]	1·00	1·00	
	>6·5	13 [5–26]	2·05 [1·48–2·85]	1·85 [1·33–2·58]	<0·001
NLR	≤6·5	37 [30–45]	1·00		
	>6·5	13 [5–24]	2·23 [1·60–3·12]		
Age, years	≤60	39 [30–48]	1·00		
	>60	26 [18–35]	1·25 [0·92–1·70]		
Sex	Female	43 [31–54]	1·00		
	Male	26 [19–34]	1·54 [1·11–2·14]		
B-symptoms	No	42 [33–51]	1·00		
	Yes	18 [11–27]	1·79 [1·32–2·43]		
ENS, n	0–1	32 [24–40]	1·00		
	>1	31 [21–42]	1·19 [0·86–1·65]		
LDH	≤ULN	44 [34–54]	1·00		
	>ULN	21 [14–29]	1·99 [1·46–2·73]		
Hb, g/l	≥120	37 [28–45]	1·00		
	<120	26 [17–35]	1·43 [1·06–1·95]		
Platelet count, $\times 10^9$/l	≥150	34 [27–42]	1·00		
	<150	23 [12–36]	1·54 [1·08–2·20]		
LMR	>2·1	37 [28–46]	1·00		
	≤2·1	25 [16–34]	1·53 [1·13–2·08]		

Slope shrinkage 0·955 (overfitting 0·045). c-Harrell 0·706 (corrected 0·700). Log-likelihood test final model *versus* full model, P = 0·273. Final model included 310 cases: one subject removed because of an influential point on the coefficient vector. Slope shrinkage and corrected c-Harrell over 250 bootstrap replicates. 95 CI, 95% confidence interval; Cox PH, cox proportional hazard regression, Efron method for ties; ECOG-PS, Eastern Cooperative Oncology Group performance status; ENS, extranodal sites; Hb, hemoglobin; HR, hazard ratio; LDH, lactated dehydrogenase; LMR, lymphocyte monocyte ratio; NLR, neutrophil lymphocyte ratio; PS, performance status; ULN, upper limit of normality.
*Final model estimated in sample of 310 patients, one excluded because it was an outlier. Median follow-up 46 months (range 1–99 months).

The 170 reported events correspond to an event/variable ratio of 14/1, which was acceptable to perform the multivariate analysis; risk groups were defined by comparing the relative risk of death in patients with each possible number of presenting risk factors and combining the categories with a similar relative risk.

From multiple Cox PH regression analysis four factors were predictive of OS: stage, ECOG-PS, serum albumin level and absolute neutrophil count (ANC) (Table 9).

The prognostic model (T cell score) was developed considering each adverse factor as having weight = 1, and identified three groups at different risk: low-risk (LR, 48 patients, 15%, score

zero), intermediate risk (IR, 189 patients, 61%, score one or two), and high-risk (HiR, 74 patients, 24%, score three or four).

The three risk groups had a 3-year and 5-year OS of 76% [95 CI 61–88] and 69% [95 CI 49–83], 43% [95 CI 35–51] and 31% [95 CI 23–40], 11% [95 CI 4–21] and 8% [95 CI 2–18] for patients at LR, IR and HiR respectively ($P < 0.001$).

The model also proved to be a robust tool for PFS: the 5-year PFS was 52% [95 CI 33–67], 22% [95 CI 16–30] and 7% [95 CI 2–16] in LR, IR and HiR, respectively ($P < 0{\cdot}001$; data not shown).

External validation

In view of the fact that some US Institutions participated in both the T Cell Project and the COMPLETE registry, a preliminary crosscheck was performed to exclude the COMPLETE registry cases that were used for the T cell score development from the validation sample: 98 patients remained available for the validation, with a median age of 61 years (range 24–90), 65% male, 76% presented with advanced stage.

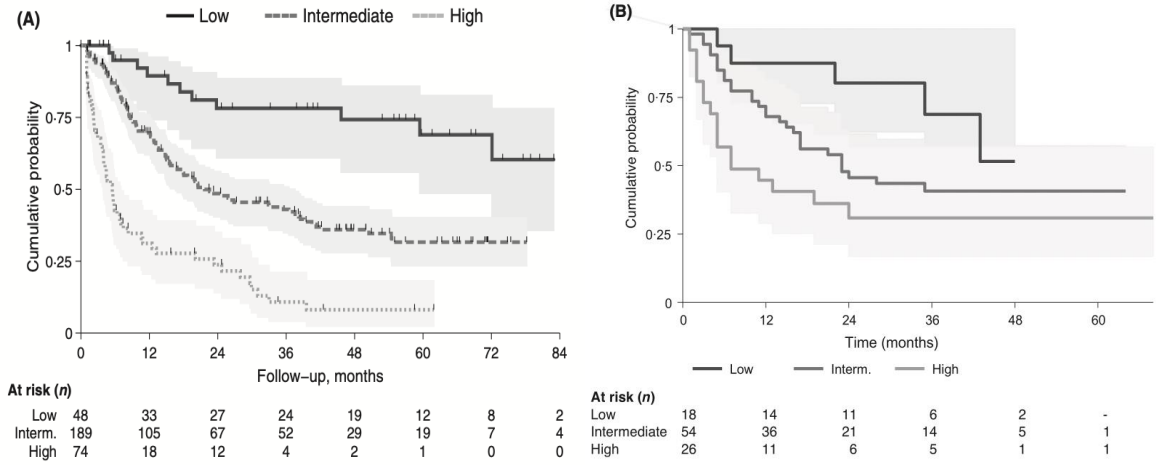
The median follow-up of the validation cohort was 18 months (range 0–68), and 52 events for survival (53% of patients) were recorded: due to the shorter follow-up of the validation sample, 3-year OS is presented, which was 43% [95 CI 33–55] for the entire cohort, with a median OS of 23 months.

Applying the model in the validation sample, multiple Cox PH regression analysis stratified the patients as follows: LR, 18 patients (18%); IR, 54 patients (55%); HiR, 26 patients (27%): the 3-year OS of the three groups was 69% [95 CI 46–100], 41% [95 CI 29–57] and 31% [95 CI 17–57] for the LR, IR and HiR, respectively ($P = 0.02$).

Notably, the distribution of the different risk groups was superimposable in the training and validation samples, being 15% and 18% in LR, 61% and 55% in IR, and 24% and 27% in HiR, respectively, and the discriminant power between the two groups was also comparable, with c-Harrell 0.674 and 0.631 in the training and validation samples, respectively.

The Kaplan-Meier curves for LR and IR were similar in the two cohorts. However, HiR patients had an apparent better survival in the external validation cohort (3-year OS 27% vs. 11% and HR = 3.80 vs. 8.88) (Figure 3).

Figure 3. Kaplan–Meier curves of overall survival by risk groups identified by the model in the training sample (n = 311) (Panel A) and in the validation sample (n = 98) (Panel B). Interm., intermediate.



Conclusions

The prognosis of PTCL-NOS is poor, for both the first line and salvage settings. There is consequently an urgent need to risk stratify the affected patients through accurate prognostic models. Among all the previously reported indices, IPI and PIT are the most commonly used. Notably, there is a considerable overlap in parameters used to build all the various models, all developed based on retrospective data collections.

The present study proposes a new model (T cell score) that is able to stratify patients into three groups with differing risk, which was developed in a subset of 311 patients with PTCL-NOS prospectively registered in the T Cell Project starting from 12 covariates with a significant impact on OS in univariate analysis, and based on the four covariates that maintained their impact in multivariate analysis (serum albumin level, (ANC), ECOG-PS and stage).

ECOG-PS and stage were previously well recognized as having a prognostic impact in PTCL by a series of authors,[41-43] and indeed they were already included in previously reported indices, showing them to be highly significant predictors for both OS and PFS.[22-24]

In recent years, low serum albumin was reported to have an adverse prognostic impact on OS in PTCL, both in univariate analysis and as an independent predictor.[76-78]

There is increasing and consistent evidence in recent literature that cancer-associated inflammation is a key determinant of outcome in patients with cancer.[76-78] One routinely

available marker of the systemic inflammatory response is the NLR. A single institution experience reported on 119 mycosis fungoides (MF) patients having a NLR of 2.07 ± 1.17 compared to 1.76 ± 0.53 for the control group ($p < 0.05$), confirming that a high NLR at MF diagnosis represents a simple, poor prognostic factor for identifying high-risk patients with MF.[79] Recently, Beltran *et al* (2016) retrospectively evaluated 83 PTCL-unspecified patients in terms of NLR, and reported that in multivariate analyses, a NLR ≥ 4 was independently associated with worse OS after adjustment for the IPI and the PIT scores.[80]

Our analyses demonstrated that ANC strongly correlated with NLR, with 92% of the cases in our cohort classified into the same risk group (K statistics 0·854; $P < 0.001$) when using either the NLR or ANC; thus, ANC was retained instead of NLR in the analysis.

To date, the innate mechanisms of tumor pathogenesis and progression remains unclear. However, several studies have indicated that tumor pathogenesis and progression are closely associated with the tumor microenvironment. Recent studies have suggested that a systemic inflammatory state is associated with the malignant biological behavior of the tumor. In particular, elevated ANC has been found as a predictor of poor prognosis in various types of tumors, including gastric, colorectal, pancreatic, breast and lung cancers and Hodgkin Lymphoma.

Considering the OS of the different risk groups identified by the T cell score, patients with a score zero, i.e. none of the four adverse prognostic factors (15% of the cohort) had a 5-year OS of 69%, i.e. a better outcome with respect to patients reported at low-risk by previous indices. The T cell score also identified a group with very unfavorable risk, with a score of 3–4 (24% of the patients), and a 5-year OS of 8%.

The external validation was performed on 98 patients with PTCL-NOS registered in the COMPLETE registry: the validation and training samples had similar patient characteristics, showed a homogeneous distribution of risk groups, and had a superimposable discriminant power, as suggested by the c-Harrell values and by a $P = 0.02$.

Outcomes for the LR and the IR groups were superimposable in the training and the external validation sample, while in the latter a better OS for HiR group was recorded; this might be due to the large differences between the training and the external validation sample in median follow-up (49 vs. 18 months, respectively) and the numeric difference (331 vs. 98 patients, respectively).

Frontline therapy was homogeneous in our cohort with >80% receiving anthracycline-based therapy; however, given that therapy influences significantly prognostic factors, the score will need to be validated as new therapies evolve.

In the analysis conducted by the IPTCLP, Ki67 proliferation index, transformed tumor cells, EBV-encoded small RNA-positive T cells, CD56 and CD30 expression were also found to be adverse prognostic factors both for OS and PFS in univariate analysis, while multivariate analysis controlling for the IPI, only transformed cells >70% was predictive for OS, and no pathological feature was predictive for PFS; in the 311 patients used as training sample for the T cell score, CD30 expression was available in 43% of our patients, thus precluding its incorporation in the model development; however, the analysis performed regarding the impact of CD30 expression on OS in the available cases did not lead to a significant difference ($P = 0.428$).[22]

The pattern of expression of T cell helper type 1 (Th1)- or type 2 (Th2)-associated antigens or activated T-cell receptor evaluated in a series of T cell Non-Hodgkin lymphoma patients allowed the identification of subgroups of PTCL-NOS patients with different probabilities of survival: in particular, patients with PTCL-NOS expressing one of Th1 or Th2 antigens tended to show favorable prognosis as compared with cases not expressing Th1 or Th2 antigens; moreover, the recently revised 2016 WHO classification recognizes a category with a T follicular helper type phenotype that includes prior cases of PTCL-NOS as defined by the WHO 2008 classification. [1,8,81]

Finally, gene expression profiling studies have reported reclassification of 37% morphologically diagnosed PTCL-NOS cases into other subtypes; in the remainder of the cases two major subgroups were identified by either high expression of *GATA3* or *TBX21* with the former associated with a poor OS, and high expression of a cytotoxic gene-signature within the *TBX21* subgroup showing poor clinical outcome. [14]

Like previous models, the new T cell score it is also based only on clinical variables, and does not account for differences bought about by the new molecular and genotypic findings, which could have potential clinical relevance.

In conclusion, although the IPI, PIT, IPTCLP and m-PIT still remain useful in defining risk for PTCL-NOS, the T cell score, developed on a prospectively collected data set, better stratifies patients and has the best performance compared to the other indices; further studies implementing some of the emerging biological variables to clinical factors, need to be

performed to determine if clinical risk can be further refined and allow for better risk stratification.

3.2.2 TCP 1.0: Outcomes and prognostic factors in angioimmunoblastic T-cell lymphoma: final report from the international T-cell Project [82]

Patients

We performed a subset analysis of patients with AITL enrolled between September 2006 and February 2018 in the TCP (registered at clinicaltrials.gov under NCT01142674). Seventy-four institutions in 13 countries (Argentina, Brazil, Chile, France, Israel, Italy, South Korea, Slovakia, Spain, Switzerland, England, United States, and Uruguay) served as enrolment sites. The study was conducted in compliance with the Helsinki Declaration, and approval was obtained from the institutional review board at the coordinating center (Modena Cancer Center, University of Modena and Reggio Emilia, Italy) and at each participating center per institutional standards, with all patients signing informed consent prior to registration. Consecutive patients with mature T-cell or NK-cell lymphomas diagnosed according to the WHO classification of tumors of hematopoietic and lymphoid tissues (editions 2001, 2008 or 2017) were registered into the TCP at initial diagnosis before initiation of treatment. Eligible patients were adults (age ≥18 years) with adequate tissue biopsies for diagnosis and available clinical data including baseline information on disease staging, laboratory parameters at diagnosis, treatment regimens received, and follow-up for at least 5 years.

The TCP used a central dedicated database (http://www.tcellproject.org). Data were collected on baseline clinical and disease characteristics, first-line treatment, and response evaluation as assessed by the local investigators following standard institutional imaging protocols. Survival follow-up was updated until database lock on March 30, 2019. Data on radiotherapy dose and field and EBV viral load were not routinely collected.

Study endpoints

The primary endpoint of the study was OS at 5 years, measured from the date of diagnosis until death from any cause or the date of the last known contact for living patients. The key secondary endpoint was PFS at 5 years, measured from the time of diagnosis to the date of progressive disease assessment or death from any cause. We also compared outcomes between patients with early progression of disease within 24 months (POD24) after diagnosis and those

without POD24.[83] Patients were not evaluable for POD24 if they were censored or had died within 24 months without POD.

Results

Patient characteristics

Of 1,553 patients eligible for analysis in the TCP, 282 patients (18%) had a diagnosis of AITL. Biopsy specimens were centrally reviewed in 231 cases (82%), and pathology reports were centrally reviewed for all patients. AITL comprised 7% (22/299), 21% (80/384), 21% (147/689), and 18% (33/181) of all T-cell lymphoma cases registered in South America, North America, Europe, and Asia, respectively, with significantly fewer cases reported in South America compared to the other geographic regions (p=0.002). Additional demographic features and patients' characteristics are summarized in **Table 10**. The median age at diagnosis was 64 years (range 22-88 years) with a male predominance (60%). Ninety percent of patients had advanced stage disease. Lymphadenopathy was present in 74% of patients while splenomegaly and hepatomegaly were reported in 31% and 22%, respectively. Polyclonal hypergammaglobulinemia was present in 30% of patients. Skin rash, hemolytic anemia, and other autoimmune phenomena occurred in 14%, 12%, and 10% of patients, respectively.

Table 10. Patient's characteristics (AITL N=282)

Parameters	**N total**	**N**	**%**
Age ≥ 60 years	282	177	63
Age ≥ 70 years	282	107	38
Male sex	282	170	60
Stage III-IV	282	254	90
ECOG performance status > 2	262	80	31
B symptoms	268	172	64
Bulky disease > 5 cm	282	30	11
Extranodal sites ≥ 2	268	88	33

Bone marrow involvement	268	36	13
LDH > ULN	240	139	58
Hemoglobin < 12g/dL	261	158	61
Platelets < 150,000/mm^3	262	73	28
Monocytes < 800/mm^3	237	179	76
ANC > 6,500/mm^3	251	88	35
β2 microglobulin > ULN	125	99	79
CRP > ULN	151	108	82
IPI ≥ 3	183	102	56
PIT ≥ 2	183	113	62
PIAI ≥ 2	183	115	63

Treatment regimens and outcomes

Complete treatment details were available in 216 patients, the majority of whom (81%) received anthracycline containing chemotherapy regimens with or without etoposide (16% and 65%, respectively). The remaining patients received other chemotherapy regimens without anthracyclines (11%) or supportive care (8%). One hundred and six patients treated with curative intent achieved a CR (51%), and 37 had a partial response (18%), for an overall response rate (ORR) of 69%. Thirteen percent of patients (N=27) underwent consolidative ASCT in CR1. The decision to undergo ASCT in CR1 was pre-planned and varied according to institutional practice. Only 3% of patients received consolidative radiotherapy.

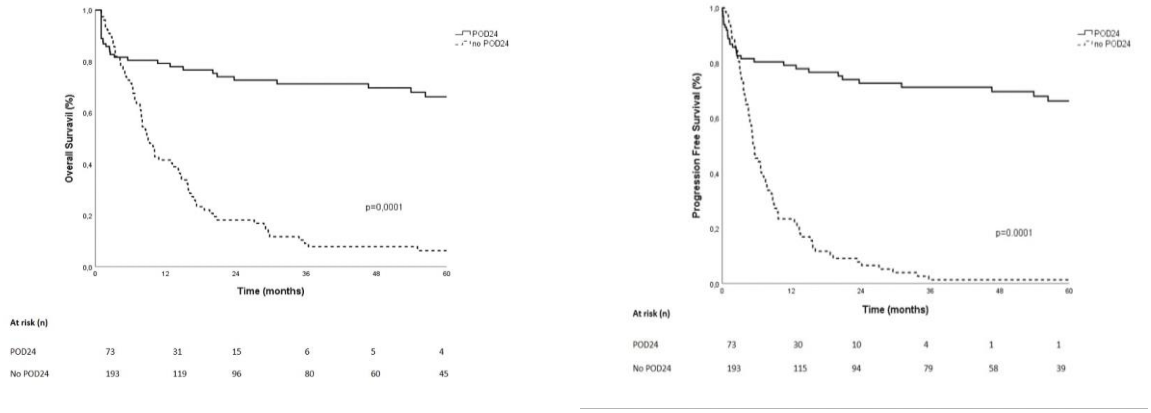
At a median follow-up of 58 months, the 5-year OS and PFS estimates for the entire patient cohort were 44% (95% CI 15-54%) and 32% (95% CI 17-39%), respectively. For patients receiving chemotherapy regimens with and without etoposide, the 5-year OS estimates were 50% (95% CI 18-68%) and 43% (95% CI 22-62%), respectively (p=0.769). Patients who underwent consolidative ASCT in CR1 (N=27) had superior outcomes compared to transplant-eligible patients (age <65, ECOG <2, adequate renal and hepatic function) who did not undergo ASCT (N=56) with 5-year OS estimates of 89% and 52%, respectively (p=0.05), and 5-year

PFS estimates of 79% and 31%, respectively (p=0.022). In total, 128 deaths were recorded, with 48% of deaths occurring within 1 year from diagnosis and 84% occurring within 2 years from diagnosis. The most common cause of death was progressive disease (69%) followed by infection (16%), second malignancies (1%), and other treatment-related toxicities (3%).

POD24

POD24 occurred in 73 patients (27%), while 193 patients were without disease progression within the first 24 months (73%). Of the 73 patients with POD24, 65 died within 24 months while only 8 were alive at the last follow-up. POD24 was a powerful prognostic factor with 5-year OS and PFS estimates of 63% and 48%, respectively for patients without POD24 versus only 6% and 2%, respectively for patients with POD24 (p<0.0001 for both comparisons, **Figure 4).**

Figure 4. Overall Survival and Progression-Free Survival stratified by POD24. Kaplan-Meier estimates of OS (3a) and PFS (3b) are shown for patients experiencing POD24 (red) or without POD24 (blue). The number of patients under follow up is listed under the x-axis. Outcomes were superior for patients without POD24 (log rank p value <0.0001 for both comparisons).



Prognostic indices

Of the 282 patients in this study, 183 had complete laboratory data to calculate previously reported prognostic indices including the IPI, PIT, and PIAI (**Table 4**). All prognostic indices identified high-risk subgroups with inferior OS and PFS compared to low-risk patients (**Table 11**). Patients with high-risk IPI, PIT, and PIAI scores (56%, 62%, and 63% of patients, respectively) had 5-year PFS estimates of 25%, 27%, and 24%, respectively. Patients with low-risk IPI, PIT, and PIAI scores had 5-year PFS estimates of 40%, 37% and 44%, respectively.

In 96 patients, additional laboratory data were available including baseline β2 microglobulin (β2M) and C-reactive protein (CRP) levels. In univariate analysis, factors associated with inferior OS and PFS included age ≥60 years, ECOG performance status >2, multiple extranodal sites, B symptoms, hemoglobin <12 g/dl, elevated β2M, and elevated CRP **(Table 12).** In multivariate analysis, only four factors retained an independent prognostic value for PFS: age ≥60 years, ECOG performance status >2, elevated β2M, and elevated CRP. Combining these four covariates, we developed a novel prognostic score (AITL score), which stratified patients into low (17%), intermediate (23%), or high-risk (60%) groups. Patients with low, intermediate, and high-risk AITL scores had 5-year PFS estimates of 41%, 37%, and 13%, respectively (p=0.003) and 5-year OS estimates of 63%, 54%, and 21%, respectively (p=0.0003).

In comparison to the IPI, PIT, and PIAI, the AITL score demonstrated the greatest discriminant power with a lower AIC (524.0) and higher Harrell C-statistic (0.785) than the other prognostic indices (**Table 11**).

Table 11. Comparison of AITL score with established prognostic indices

Prognostic index	**IPI**		**PIT**		**PIAI**		**AITL score**		
Risk group (score)	***Low risk (0-2)***	***High risk (3-5)***	***Low risk (0-1)***	***High risk (2-4)***	***Low risk (0-1)***	***High risk (2-5)***	***Low risk (0-1)***	***Intermediate (2)***	***High risk (3-4)***
N (%)	81/183 (44%)	102/183 (56%)	70/183 (38%)	113/183 (62%)	68/183 (37%)	115/183 (63%)	16/96 (17%)	22/96 (23%)	58/96 (60%)
Median PFS (95% CI)	34 mo. (12-57)	8 mo. (5-11)	29 mo. (18-41)	9 mo. (4-14)	46 mo. (13-59)	13 mo. (7-19)	31 mo. (13-NR)	12 mo. (8-16)	9 mo. (4-15)
5-year PFS (95% CI)	40% (21-65%)	25% (9-48%)	37% (17-52%)	27% (9-41%)	44% (14-66%)	24% (8-36%)	41% (17-62%)	37% (9-41%)	13% (7-26%)
P value	**P = 0.0006**		**P = 0.03**		**P = 0.0006**		**P=0.003**		
Median OS (95% CI)	NR	16 mo.	NR	17 mo. (4-31)	NR	24 mo. (1-48)	NR	35 mo. (14-44)	20 mo. (6-30)
5-year OS (95% CI)	61% (23-79%)	32% (11-51%)	64% (21-81%)	29% (10-50%)	61% (14-72%)	36% (14-49%)	63% (20-68%)	54% (10-67%)	21% (11-32%)
P value	**P = 0.0005**		**P = 0.0002**		**P = 0.001**		**P=0.0003**		
Harrell C-statistic	0.697		0.648		0.711		0.785		
AIC global fit	566.4		575.3		543.4		524.0		

IPI = International Prognostic Index; PIT = Prognostic Index for T-cell lymphoma; PIAI = Prognostic Index for AITL; AITL = angioimmunoblastic T-cell lymphoma; PFS = progression-free survival; OS = overall survival; CI = confidence interval; NR = not reached, AIC = Akaike's information criteria

Table 12. Univariate and multivariate analysis for progression-free survival.

Parameters	**N_{TOT}**	**N**	**%**
Median age (yrs)	235	54 (18-89)	
Age ≥60 yrs	235	92	**39%**
Gender (Male)	218	146	**62%**
ECOG >1	217	53	**24%**
B-symptoms	221	99	**45%**
Discomfort disease-related	195	136	**70%**
Stage III-IV	187	133	**71%**
Nodal only disease	163	53	**32%**
Extranodal involvement	235	112	**48%**
Bulky disease (≥ 10 cm)	235	13	**6%**
Number of extranodal sites >1	163	42	**26%**
BM involvement	194	16	**8%**
LDH > ULN	195	92	**47%**
HB < 12 g/dL	212	89	**42%**
Platelets < 150K/mm^3	211	21	**10%**
Monocytes ≥ 800/mm^3	197	53	**27%**
ANC > 6.5 · 10^3/mm^3	209	76	**36%**
β2M > ULN	88	50	**57%**
CRP > ULN	89	61	**69%**

Conclusions

To our knowledge, this study represents the largest prospective international cohort of AITL patients reported to date, allowing for an assessment of real-world treatment approaches, outcomes, and prognostic factors of patients treated in the contemporary era. Constituting 18% of patients in the TCP database, AITL represents the second most common subtype of PTCL globally, with a lower incidence in South America as previously published.[50] Consistent with prior reports, AITL was more frequently diagnosed in older adults (median age 64 years) and typically presented with advanced stage disease, B symptoms, elevated LDH, and high-risk disease as defined by multiple prognostic indices including the IPI, PIT, and PIAI.[84-87]

Most patients were treated with anthracycline-based regimens such as CHOP, and only a small proportion also received etoposide (16%), which may in part reflect the older age of our cohort (63% of patients ≥60 years old). There was no significant difference in outcomes with or without etoposide, although statistical power is limited due to the relatively small number of patients. An even smaller proportion of patients underwent consolidative ASCT in CR1 (13%). This may also reflect the older age of our cohort as well as geographic variations in practice patterns. Comparing outcomes between patients who underwent ASCT in CR1 with those who did not (but who were transplant eligible), ASCT was associated with superior outcomes with favorable 5-year OS and PFS estimates of 89% and 79%, respectively. However, the intrinsic selection bias and lack of a randomized comparison are important limitations. Notably, the benefit of ASCT in CR1 observed in this cohort is consistent with prior studies, including a prospective study from the United States COMPLETE registry, and a recent systematic review and meta-analysis of 16 retrospective studies.[88] Cumulatively, these data suggest that consolidative ASCT should be considered in CR1 for transplant-eligible patients with AITL.

Our study validated the prognostic value of the IPI, PIT, and PIAI in a large prospective AITL cohort, and in a limited data set of 96 patients enabled identification of novel prognostic factors and a new prognostic score (AITL score). We identified β2M and CRP as independent prognostic factors associated with PFS, consistent with a prior retrospective study.[89] The AITL score combining four covariates (age, performance status, β2M, and CRP) stratified patients into low, intermediate, and high-risk groups and demonstrated greater discriminant power than the IPI, PIT, and PIAI, although due to limited sample size validation in a larger cohort is required. We also identified POD24 as a powerful prognostic factor, consistent with a recent retrospective study in PTCL.[90]

Overall, treatment of AITL with standard chemotherapy regimens in the contemporary era was associated with disappointing outcomes with 5-year OS and PFS estimates of 44% and 32%, respectively. Recently, several trials have attempted to improve upon standard CHOP-based therapy by using alternative chemotherapy backbones or incorporating novel agents such as brentuximab vedotin (BV) or romidepsin into frontline therapy. A randomized phase 2 trial in the United Kingdom compared CHOP with a non-anthracycline-based regimen (gemcitabine, cisplatin, and methylprednisolone) to mitigate multidrug resistance efflux pumps but was closed early for lack of efficacy.[91] More recently, the international, randomized phase 3 ECHELON-2 trial demonstrated superior outcomes in patients with CD30+ PTCL (defined as ≥10% CD30 expression) receiving BV-CHP versus CHOP chemotherapy.[92] However, only 12% of patients on the ECHLEON-2 trial had AITL, and the benefit of BV-CHP in CD30+ AITL remains unclear (hazard ratio for PFS: 1.40, 95% CI 0.64-3.07; hazard ratio for OS: 0.87, 95% CI 0.29-2.58).

Improvements in our understanding of AITL biology over the past decade, including the identification of recurrent somatic mutations in *RHOA*, *TET2*, *DNMT3A*, and *IDH2*, have led to novel therapeutic strategies such as epigenetic modifying therapies.[93-96] Recent studies suggest that AITL and other TFH PTCLs may have higher response rates to histone deacetylase (HDAC) inhibitors, such as romidepsin and belinostat, compared to non-TFH PTCLs, which may reflect the higher frequency of mutations in *TET2* and *DNMT3A*, which perturb epigenetic regulation.[66, 97] Azacitidine, a hypomethylating agent, has also demonstrated high response rates in AITL as a single agent and in combination with romidepsin, further supporting the role of epigenetic dysregulation in AITL.[98] A randomized phase 3 trial comparing CHOP with or without romidepsin as frontline therapy for PTCL is currently ongoing (NCT01796002) based on favorable results from a phase 1b/2 study.[99]

In conclusion, we demonstrate in this international prospective study that outcomes remain suboptimal for patients with AITL treated in the contemporary era, with particularly poor outcomes for high-risk patients and for those experiencing POD24. Elevated β2M and CRP at initial diagnosis had an independent prognostic impact associated with inferior PFS. In transplant eligible patients, superior outcomes were observed among patients consolidated with ASCT in CR1. These findings are hypothesis generating and lay the framework for future studies. Optimal treatment of AITL remains an unmet need. Novel therapeutic approaches and better understanding of disease biology are required to improve outcomes.

3.2.3 TCP 1.0: ALK-negative anaplastic large cell lymphoma: features and outcomes of 235 patients from the International T-Cell Project [100]

Between September 2006 and February 2018, a total of 1695 patients with newly diagnosed PTCLs were registered in the T-Cell Project database by 74 institutions in 13 countries; of these patients, 1553 were confirmed eligible for enrollment and included in the analyses. A diagnosis of ALK– ALCL was reported in 235 cases (15%), with significant differences in geographical distribution: ALK⁻ ALCL comprised 26% (71 of 271), 14% (50 of 368), 14% (89 of 644), and 4.5% (8 of 176) of cases registered in South America, the United States, Europe, and Asia, respectively.

Patient characteristics and treatment

Table 13 summarizes the main demographic and clinical characteristics of this cohort of patients. The median age at diagnosis was 54 years (range, 18-89 years), with a male predominance (62%). More than 27% of patients were aged >65 years, and 16% were aged >70 years. Stage III to IV disease was identified in 71% of patients, and disease-related discomfort was present in 70%; bulky disease and bone marrow involvement were uncommon (6% and 8%, respectively). Elevations of β2M and CRP were reported in 57% and 69% of patients. IPI and Prognostic Index for T-cell Lymphoma (PIT) scores were assessed in 150 cases. According to IPI, 99 patients (66%) had a low/intermediate score (0-2), and 51 patients (34%) had an intermediate/high score (3-5). Similar distribution of patients with higher prevalence of low/intermediate scores (0-1) compared with intermediate/high scores (2-4) was found in the PIT score analysis, with 95 (63%) vs 55 (37%) patients.

Treatment details were available in 220 patients, of whom 15 (6.8%) received only best supportive care. Of the remaining 205 patients, 168 (82%) were treated with anthracycline-containing regimens, 31 (15%) with anthracycline/etoposide–containing regimens, and 6 (3%) with other regimens. Sixteen patients (8%) underwent high-dose chemotherapy with autologous stem cell support as consolidation of first-line therapy. Finally, 4 patients were treated with radiotherapy alone (2%).

Table 13. Patient clinical and demographic characteristics.

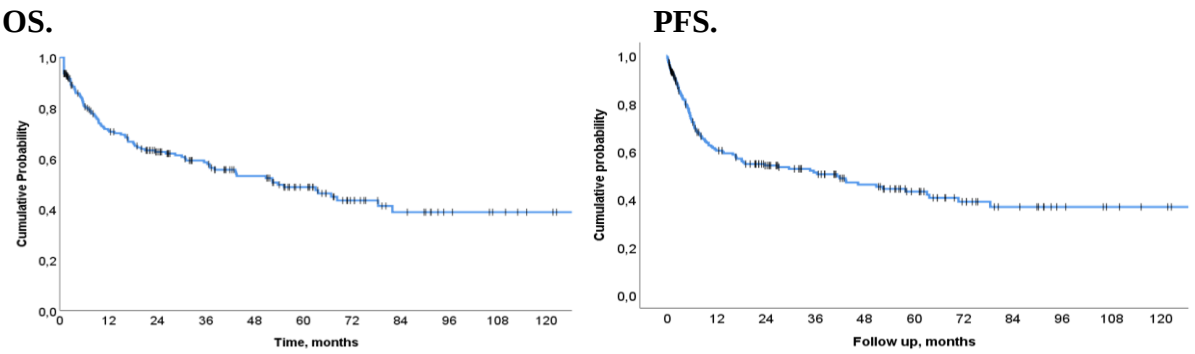
Parameters	**N_{TOT}**	**N**	**%**
Median age (yrs)	235	54 (18-89)	
Age ≥60 yrs	235	92	**39%**
Gender (Male)	218	146	**62%**
ECOG >1	217	53	**24%**
B-symptoms	221	99	**45%**
Discomfort disease-related	195	136	**70%**
Stage III-IV	187	133	**71%**
Nodal only disease	163	53	**32%**
Extranodal involvement	235	112	**48%**
Bulky disease (≥ 10 cm)	235	13	**6%**
Number of extranodal sites >1	163	42	**26%**
BM involvement	194	16	**8%**
LDH > ULN	195	92	**47%**
HB < 12 g/dL	212	89	**42%**
Platelets < 150K/mm^3	211	21	**10%**
Monocytes ≥ 800/mm^3	197	53	**27%**
ANC > 6.5 · 10^3/mm^3	209	76	**36%**
β2M > ULN	88	50	**57%**
CRP > ULN	89	61	**69%**

Response to treatment and survival

Of 205 patients who were treated with curative intent, 129 (63%) achieved a complete response, and 29 (14%) had a partial response, with an overall response rate of 77%. In the remaining 47 patients (23%), the response was recorded as stable or progressive disease.
The median follow-up for the entire cohort of 235 patients was 52 months (95% confidence interval [CI], 36-75). Seven patients (3%) were lost to follow-up after a median time of 21 months. The minimum and median follow-up times for surviving patients were 48 months and 70.3 months, respectively. The median OS was 55 months. The 3- and 5-year OS rates were 60% (95% CI, 48-72) and 49% (95% CI, 35-59). The 3- and 5-year PFS rates were 52% (95% CI, 43-69) and 43% (95% CI, 20-69) (Figure 5).

At the time of data lock, 102 deaths were recorded: 72 (70%) due to lymphoma, 9 (9%) due to infection, 2 (2%) due to organ failure, 2 (2%) due to treatment-related toxicity, and 4 (4%) due to second malignancies. For 13 patients (13%), the cause of death was unknown. Overall, 103 patients (50%) experienced progression or relapse.

Figure 5. Overall survival (OS) and Progression-free Survival (PFS).



Treatment with anthracycline and etoposide was associated with a superior outcome: 3-year and 5-year OS rates were 56% and 44% in the anthracycline-based treatment group, and 76% and 69% in the anthracycline/etoposide–based treatment group, and the differences were statistically significant (P = 0.05). Similar results were also observed in PFS. The 3-year and 5-year PFS rates were 47% (95% CI, 32-59) and 39% (95% CI, 29-48) for those treated with

anthracycline-only regimens vs 65% (95% CI, 32-87) and 50% (95% CI, 36-89) for those treated with anthracycline/etoposide–containing regimens; the differences were not statistically significant (P = 0.186).

In 150 patients, sufficient data allowed for IPI and PIT score calculations. As expected, patients with high IPI and PIT scores had a worse prognosis, as summarized in **Table 14**.

In a univariate analysis, several clinical and laboratory features had a significant negative impact on OS, including age >60 years (p=0.025), Eastern Cooperative Group performance status (ECOG-PS) ≥2 (p=0.007), presence of B symptoms (P = .002), elevated LDH levels (p=0.001), and a platelet count $<150 \times 10^9$ (p=0.014). Moreover, stage III to IV disease (p =0.01), ECOG-PS ≥2 (p=0.001), presence of B symptoms (p=0.001), and an elevated LDH level (P = .001) were also predictive of inferior PFS (Table 3). In the multivariate analysis, the presence of B symptoms (p=0.008), elevated LDH level (p=0.001), ECOG-PS ≥2 (p=0.001), and a platelet count $<150 \times 10^9$ (p=0.05) carried significance for OS (Table 4). The presence of B symptoms (p=0.02), elevated LDH level (p=0.001), and ECOG-PS ≥2 (p=0.001) maintained their prognostic significance for PFS.

Table 14. OS and PFS rates by IPI and PIT scores.

IPI	**5-yr OS**	**5-yr PFS**	**Median OS**	**Median PFS**	**P**
Low (0-2)	62%	53%	Not Reached	64 (95CI 37-90)	<.001
High (2-4)	27%	21%	9 (95CI 5-13)	7 (95CI 3-11)	
PIT	**5-yr OS**	**5-yr PFS**	**Median OS**	**Median PFS**	**P**
Low (0-2)	60%	51%	Not reached	64 (95CI 34-93)	<.001
High (2-4)	24%	21%	9 (95CI 6-13)	7 (95CI 2-11)	

Conclusions.

The T-Cell Project is the largest, to date, prospective cohort study with a centralized computer database allowing for uniform analysis of PTCL patients enrolled at numerous independent global sites. Collection of the large number of cases created a unique opportunity to analyze the rare subtypes of these non-Hodgkin lymphomas with sufficient statistical power and without interference from other biologically distinct entities. Although the absence of a particular defined treatment protocol might seem as a limitation of the study, it also has the benefit of presenting a real-life scenario and outcomes in patients with a particular malignancy.

ALK– ALCL comprised 15% of the diagnoses reported to the T-Cell Project by the investigators. This frequency among PTCLs is higher than the 5.5% that was previously recorded in the retrospective International Peripheral T-cell Lymphoma Project.[2] The reason for such a discrepancy is not entirely clear but might involve the demographic differences in the 2 study populations. It might also be supported by a report from the Surveillance, Epidemiology, and End Results registry showing demographic predilection of this entity, with a higher incidence in Black and non-Hispanic White subjects and a very low incidence in Asian, Hispanic, American Native, and Pacific Islander subjects.[101]

We also admit to a limitation of our study in the lack of central pathology review and diagnostic validation. Despite the planned expert review in the study design, investigators encountered unsurmountable challenges related to secure shipments of hundreds of tissue specimens from 74 countries with varying regulatory requirements. However, with rare exceptions, the patients in the study were enrolled by academic centers around the globe with recognized expertise in hematopathology, which partially negates this limitation in the opinion of study investigators. In addition, the authors acknowledge the missing data for several patient and disease characteristics, as well as treatment and outcome details, as another weakness of the study. Despite the colossal effort by the study executive team and investigators, the hurdles of conducting a global prospective data collection of this magnitude imposed these limitations.

Anthracycline-containing multiagent chemotherapy has long been a standard initial therapy for patients with ALCL approached with curative intent.[6,14] In our study, 97% of patients were treated with CHOP(-like) therapy, including 15% who received both an anthracycline and etoposide. This is consistent with findings in the retrospective international project in which 93% of ALK– ALCL patients received multiagent chemotherapy with curative intent. The very high rate of curative intent multiagent chemotherapy in both registries despite the patients'

advanced median age (ie, >60 years) underscores the curative potential of aggressive front-line therapies in ALK– ALCL. In both studies, the rate of consolidative high-dose therapy and autologous stem cell transplantation was low at 8% and 7%, respectively. The latter finding might reflect the lack of randomized trial data showing clear benefit with a consolidative approach or access to advanced-level oncologic facilities equipped to perform the transplant procedure. Furthermore, our results recapitulate the findings from the retrospective study of superior outcomes in ALK– ALCL compared with PTCL not otherwise specified or in most other histologic subtypes.

The proximity in the range of major clinical end points (ie, OS, PFS) between previously published retrospective and current prospective registries is important in that it solidifies the benchmark against which future clinical trials of novel combinations and agents should be compared. It should also be noted that our results represent outcomes in real-life environments as opposed to highly standardized clinical trials conducted at expert academic institutions. As such, our results might provide an appropriate lens through which to extrapolate the results of either successful or failed academic trials. To validate our point, in the recently reported randomized, double-blind controlled clinical trial that compared novel brentuximab vedotin plus CHP combination with standard CHOP therapy, the 5-year rate of OS in the control group was ~65%, whereas in our study and in the retrospective registry study, the 5-year OS rates were both 49%.[10] If we assume that this sizable difference represents the inherent selection bias in academic clinical trials toward lower risk patients (eg, able to travel, younger, higher socioeconomic status, less rapidly progressive or lower burden disease to afford delay of care for screening periods), then we should also be cautious about overinterpreting an unusually high OS rate of ~80% in the experimental arm that was not previously seen in PTCL or ALCL after the front-line therapy when applying these results to real-life oncology practice. We would therefore argue that prospective registry studies provide a unique perspective of disease outcomes that is compromised by the scrutiny of therapeutic academic and/or registrational studies.

It should be noted that since the data cutoff date in our study, the standard of care for ALCL patients has changed with the report of ECHELON-2 (Brentuximab Vedotin With Chemotherapy for CD30-Positive Peripheral T-Cell Lymphoma) clinical trial results, confirming clinical benefit of brentuximab vedotin and CHP combination over standard CHOP for $CD30^+$ PTCL in which the majority of the study patients had an ALK+ and ALK– ALCL

diagnosis.[37] It is noteworthy that the superiority of the novel combination has not been shown over anthracycline/etoposide–containing regimens (ie, etoposide phosphate, prednisone, vincristine sulfate, cyclophosphamide, and doxorubicin hydrochloride [CHOEP]), and the addition of etoposide to CHOP-like regimens has shown a trend toward better survival outcomes (both, OS and PFS), at least in a retrospective meta-analysis of patients enrolled in clinical trials of the DSHNHL.[32] It is also hard to dismiss the favorable results of the prospective single-institution phase 2 study in which 12-year PFS in high-risk ALCL patients was >70%.[102] Resonating with these results, our study also indicates superior OS ($p = 0.05$) and a trend toward higher PFS ($p = 0.186$) in patients who received treatments that contained both anthracycline and etoposide. However, the authors acknowledge that there are significant limitations to this analysis, given the lack of randomization to a particular therapy; there is an inherent bias by the treating physicians to use more intensive therapies in younger fit patients with fewer comorbidities or disease-associated sequelae, potentially selecting for a better prognosis cohort. It should also be considered that such patients would be more likely to use aggressive curative intent therapies upon relapse that would further affect OS.

In addition, while brentuximab vedotin was approved by the US Food and Drug Administration in the midst of study enrollment, it has not been available and therefore not used in several participating countries, further confounding the analysis. It is therefore impossible to make strong recommendations regarding the benefits of etoposide when added to CHOP based on these data. Conversely, our results still raise the question of whether standard CHOP is an adequate control arm in indicating superiority of new treatment regimens over a standard-of-care approach. Finally, if we consider a 5-year failure rate of 60% by the current multidrug regimens to cure ALK^- ALCL and sizable treatment-related morbidities, especially in light of numerous emerging novel biologic agents, we should then ask the provocative question of whether traditional “add-on” strategies in clinical trials should give way to developing new therapeutic platforms consisting entirely or mostly of rationally developed PTCL-specific drugs.

We also observed that the rates of OS and PFS in our study are in close proximity at both the 3- and 5-year cutoffs, indicating low rescue rates with current salvage strategies and underscoring the need for novel first-line platforms. We should bear in mind that brentuximab vedotin was available only through the second half of the study enrollment, and for many study locations only for small fraction of the enrollment period. Therefore, the full impact of this

novel and highly effective agent was not captured. Recent studies of composite epigenetic-targeted therapy, combinations of phosphatidylinositol 3–kinase inhibitors + proteasome inhibitors, phosphatidylinositol 3–kinase inhibitors + histone deacetylase inhibitors, antifolate + histone deacetylase inhibitor, and others reported very promising levels of clinical responses comparable to the rates observed in front-line therapies with multiagent cytotoxic combinations.[66,103] Combined with better toxicity profiles of novel agents compared with traditional cytotoxic drugs, it is likely only a matter of time that we will see a major shift from established CHOP-based platforms in ALK$^-$ ALCL and other PTCL subtypes.

Recent advances in genomic characterization of hematologic malignancies challenged traditional clinical prognostic scales (eg, IPI, PIT, PINK-E). Two specific recurrent genetic alterations have defined biologically distinct ALCL subtypes. The *DUSP22-IRF4* translocation is found in ~30% of patients with ALCL and portends excellent prognosis, with 5-year OS rates of >80% with traditional therapies.[66] Mutations or cryptic translocations in *TP63* can be identified in 5% to 6% of ALCLs and are predictive of the early treatment failures and a dismal overall prognosis, with <10% of patients being cured of their lymphoma.[66,104] Based on some reports, even early application of high-dose therapy and autologous stem cell transplantation does not overcome the negative impact of these genomic lesions.[12] These new molecular markers seem to be independent of clinical risk models and will most likely replace traditional models in disease stratification. Uneven distribution of the genomic subtypes of ALCL might account for some discrepancies in the results of therapeutic and cohort studies. These new findings are in urgent need of validation in prospective clinical trials, including prospective registry trials. The second stage of the T-Cell Project that was recently initiated will focus on molecular characterization of PTCLs as well as on further clinical and epidemiologic studies, and it will hopefully better define the role of new genomic markers in driving future therapies and risk stratification.

3.2.4 TCP 1.0: Characteristics and Clinical Outcomes of Patients with ALK-positive Anaplastic Large Cell Lymphoma: Report from the Prospective International T-Cell Lymphoma Project

The T-Cell Project (NCT01142674), sponsored by the International T-Cell Lymphoma Project (ITCLP), was incepted in 2006, and builds on the retrospective study carried on by the network, which evaluated a cohort of 1553 cases of PTCL and NKTCL, representing the largest retrospective study to date in this subset of patients. Patients with aggressive, mature, nodal, and extranodal PTCL subtypes as from the WHO 2001 or WHO 2008 were registered in the T-Cell Project at initial diagnosis. [8,105] The study is devised as a prospective collection of information potentially relevant to better define prognosis for the more frequent subtypes of PTCL - i.e. PTCL-NOS and AITL and ALCL- and to outline clinical characteristics and outcome of the more uncommon PTCL subtypes. Additional eligibility criteria included age ≥ 18, tissue biopsies adequate for diagnosis and classification and available for centralized review, clinical data including baseline information on disease localization and laboratory parameters at staging. Data were collected on front-line treatment, response evaluation at the end of the treatment, and updated follow-up for at least 5 years for living patients. Participating Institutions were asked to provide information about a consecutive series of cases, without any selection. Patients who did not receive any kind of treatment were also registered. Data collection was performed with a web-based platform via electronic Case Report Forms (eCRFs) at a dedicated website (www.tcellproject.org), adopting proper technology assuring protection in web communications of the subject's clinical data. Data access and management were regulated by the use of passwords with different levels of admittance, providing that subject confidentiality was respected. Data and study management were performed at the study Trial Office in Modena, Italy. Registration was based on locally established histological diagnosis; a panel of expert hematopathologists was planned to review the diagnosis of all patients entered in the study.

The T-Cell Project was conducted in compliance with the Helsinki Declaration. It was approved by the appropriate research Ethics Committees or Institutional Review Boards at each participating Institution. It required each patient to provide written informed consent before registration.

RESULTS

In a period of 12 years, between September 2006 and February 2018, 1553 reports were analyzed by TCP project. They were collected from 74 institutions in 13 countries around Europe, South America, United State of America (USA) and Asia. The majority (689/1553) were obtained from European sites.

Patient's characteristics.

Out of 1553 patients registered in the study, a diagnosis of ALCL, ALK+ was centrally confirmed for 131 patients. Patients' characteristics are described in Table 15. ALCL ALK+ represented 8% of all cases, with similar distribution around the world, except for Asia, where the incidence was just 5% (Figure 6). The median age of ALCL, ALK+ patients was 39 years (range, 18-84). Only 13 patients (10%) aged >60 years, and there was a slight male predominance (78 vs. 53 patients).

Even though the majority of patients (66%) presented with advanced stage disease, only 16% had high-risk IPI score [>2 (IPI 3:10 patients; IPI 4:3 patients)] and the bone marrow involvement was found in only 15%. Other non-IPI defining high-risk features included elevated C-reactive protein (CRP) in 72%, elevated β2M in 47%, and bulky disease (>10 cm) in 7% of patients. Extranodal involvement was observed 37 % of patients. The most common hematologic abnormalities were anemia [Hb<12g/ dL (32%)] and elevated absolute neutrophil count [ANC > $6.5x10^3/mm^3$ (58%)]. Thrombocytopenia and leucopenia were uncommon.

Treatment characteristics

The data on treatment was available for 99 patients and 2 patients received the best supportive care only. The majority of the patients (82%, 81/99) received chemotherapy alone and 10% combined modality treatments (chemotherapy + radiotherapy). Only 6% of patients received consolidative autologous steam cell transplantation (ASCT) in the first remission. Chemotherapy regimen included anthracycline in the majority of the cases (80/99) and etoposide was added to intensify treatment in 11% of the cases (11/99).

Table 15. Clinical characteristics of patients included in the analysis

Parameter	**N_{tot}**	**N (%)**
Median follow-up		35 mo (18-84mo)
Median age (y)	131	39 (18-84y)
Age ≥60 y	131	13 (10)
Gender (Male)	131	78 (60)
ECOG >1	113	25 (22)
B-symptoms	117	69 (59)
Bone marrow involvement	99	15 (15)
Stage I-II **Stage III-IV**	98	33 (34) 65 (66)
Extranodal involvement	131	49 (37)
LDH> ULN	111	41 (37)
HB <12g/dL	112	42 (32)
Platelets <150K/mm3	111	9 (8)
Bulky disease (>10 cm)	131	9 (7)
Monocyte >800/ mm3	103	37 (36)
ANC> 6.5 x 103/ mm3	109	63 (58)
β2M >ULN	58	27 (47)
CRP> ULN	57	41 (72)
IPI **0-1** **2-3** **4-5**	83	 45 (54) 35 (42) 3 (4)
PIT **0-1** **2-4**	79	 64 (81) 15 (19)
Chemotherapy **Combined modality** **Radiotherapy alone**	99	 81 (82) 9 (10)
ASCT	99	6 (6)

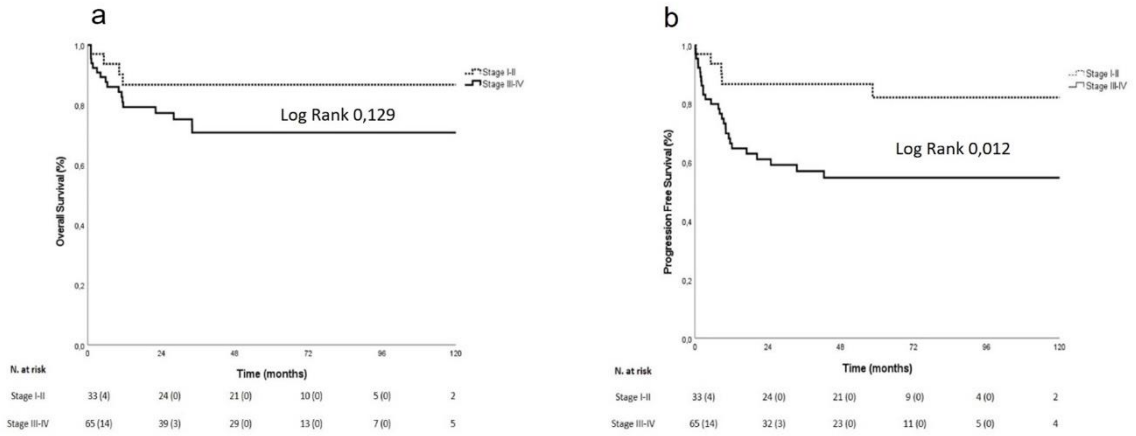
Patient outcomes

The overall response rate (ORR) in this study was 81%, with 70% (69/131) of complete responses. The median follow-up time was 49 months (95% - CI 36-62 months), and 101 patients (78%) were alive at time of this study, 27 (20%) died, and 3 patients were lost along follow-up. The main causes of death were progressive lymphoma (79%), followed by infection (11%) and solid tumor (4%). Treatment toxicity-related death was reported in 4 cases (3%).

The median OS and PFS for ALK+ ALCL of the entire cohort were not reached. Although, OS and PFS estimated in 3 years were 77% (95% CI 51-94) and 68% (95CI 46-89), respectively. Results estimated in 5 years were very similar 77% of OS (95%CI 62-98) and 64% of PFS (95%CI 39-94).

Patients with localized disease (stage I-II) had higher OS – 87% (95% CI 77-98) and PFS – 82% (95CI 69-104) than advanced stage disease, at 5-years. OS of 71 % (95CI 51-92) and PFS of 55% (95CI 39-61) – Figure 7 a-b).

Figure 7 a-b. Overall survival (OS) and Progression-free Survival (PFS) by stages



Outcomes in low vs. high-risk disease

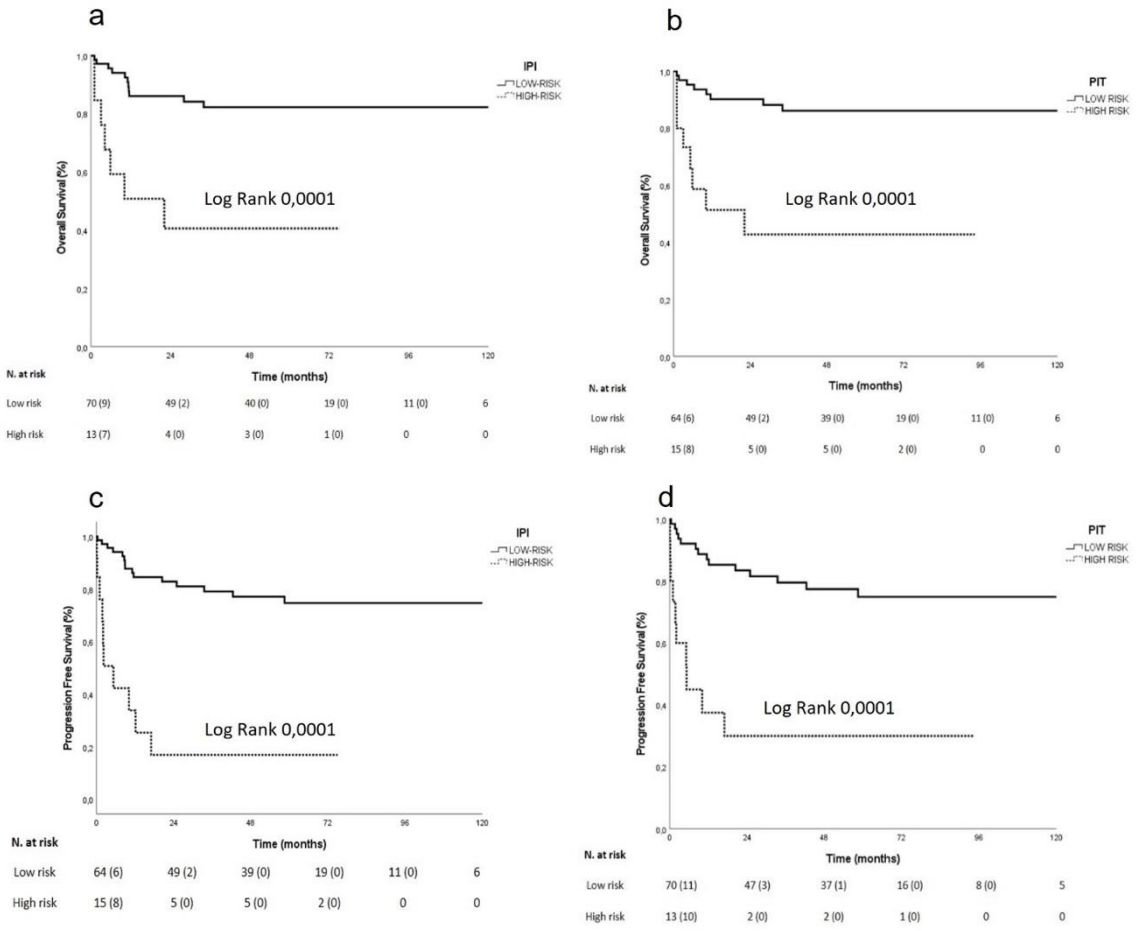
Eighty-three patients were stratified using International Prognostic Index (IPI), while 79 by Prognostic Index for T-cell lymphoma (PIT). Sixteen percent of patients were at high-risk IPI (IPI>2) and 19% at high risk by PIT (PIT>2).

Median PFS in high risk IPI and PIT patients was 5 months and an estimated 22 months in low risk IPI and PIT, both 3 and 5 years (95%CI 0-48 and 95%CI 0-49), respectively.

Comparing high-risk versus low-risk patients using both IPI and PIT, high risk patients had a worst OS (not-reached, estimated in 43% vs 75% in 5 years). Figure 8 a-b.

Most patients (80/99) received anthracycline-based chemotherapy in first-line treatment, from that 16% (16/99) combined with etoposide. Median OS and PFS was not reached when comparing anthracycline and anthracycline/etoposide regimens.

Figure 8 a-b. OS by IPI and PIT; **8 c-d.** PFS by IPI and PIT



Univariate analyses have been done to assess different clinical and laboratory features and consequently evaluate an impact on OS and PFS. Significantly predictive values in univariate analysis for OS were ECOG-PS $\leq$2 (p=0.008), elevated LDH (p=0.001), and PTL>150x10^9 rate (p=0.006). Independent predictors for PFS were advanced stage (III-IV) (p=0.012), ECOG-PS $\leq$2 (p=0.005), elevated LDH (p=0.001), and PTL>150x10^9 rate (p=0.007).

Multivariate analysis showed, that the presence of B symptoms (P=0.008), elevated LDH (p=0.001), ECOG-PS $\leq$2 (p=0.001) and PTL>150x10^9 (p=0.05), were significant for OS. The rate of B symptoms (p=0.02), elevated LDH rate (p=0.001) and ECOG-PS$\leq$2 (p=0.001) maintained their prognostic value for PFS.

Conclusions.

ALCL, ALK+ for the past three decades remains a sufficiently favorable disease. In the last edition of WHO classification 2017 ALCL, ALK + are recognized as independent entity within other types with ALCL (ALCL ALK-negative primary cutaneous ALCL and breast implant-associated ALCL).[1] Compared to other aggressive types of T-cell lymphomas, there is a good tendency to achieve a tumor response with first-line standard treatment, although ALCL, ALK+ should be identified as a separate disorder from more aggressive types of PTCL.

Results of our prospective study reaffirmed the difference of ALCL, ALK + in age distribution, outcomes, and clinical behavior compared to ALCL, ALK-negative, and PTCL NOS. Several prior studies also confirmed a higher percentage of young patients (median age 39 years) and a good prognosis of the disease. We have also established a male predominance and a high rate of advanced disease stage, as previously reported. [32, 37, 106]

According to several studies from 70 to 90% of patients respond well for anthracycline-based regimens, when approximately 60-70% of patients are disease-free in 5 years. This data confirms a favorable outcome for this group of patients. For example, The German High-Grade Non-Hodgkin's Lymphoma Study Group retrospectively analyzed 289 ALCL patients; between them 78 patients had ALK+ status. 3-year OS and EFS were 89,8% and 75,8%, respectively. [32] In 2012, the GELA group presented a retrospective analysis with a long-time follow-up, in which 138 patients with systemic ALCL and 46% had ALCL, ALK+ were included. In this study the median follow-up was 8 years. Results showed that this group of patients had excellent results of OS and PFS (82% and 72%, respectively).[107]

Despite bright prospects in first-line treatment, up to 30-40% of ALCL, ALK+ patients undergo relapsed/refractory disease and belong to an unfavorable group. So, we still do not know a specific group of patients who will benefit from the improvement of treatment strategies.

Regarding the consolidation in the first remission, due to good outcomes, the ASCT remains an option for those individuals with high risk, and IPI >2. [108]

In our analysis 5-year OS and PFS for patients with advanced-stage ALCL, ALK+ were 75% vs 55%, respectively. However, interesting results were received after assessing patients with IPI and PIT. Historically, IPI has been done for diffuse large B-cell lymphoma, while PIT has been proposed for PTCL. [23, 32] Our results showed an effective influence for risk group identification with IPI and PIT. The 5-year OS and PFS in high-risk IPI and PIT groups are approximately the same (Figure 4a-d) compared to those with more aggressive types, such as PTCL (NOS) or ALCL ALK-negative. This data is comparable with previous results (5-year

FFS only 25% to 30%).[107] CHOP remains the backbone of the induction regimen for different subtypes of PTCL; even thus different entities have distinct outcomes. Moreover, based on the current data we can postulate that this regiment is not satisfactory even for ALCL ALK+ patients with high risk IPI or PIT. Toward this end, the addition of the etoposide (CHOEP) was tested, although there was no benefit in OS with only a slightly improved PFS in young patients, despite high toxicities. [32] In our analysis, we have registered 18 patients (19%) who received CHOEP, without improving in OS and PFS rates, a finding may be due to the relatively small number of patients in our study.

Nevertheless, multiple studies have proven a high activity in ALCL ALK + patients of novel agents targeting the CD30 or ALK. The phase 3 ECHELON-II study showed encouraging results for the treatment patients with CD30-expression PTCL, mainly in systemic ALCL in the combination brentuximab-vedotin with CHP (BV+CHP) vs CHOP as a first-line, with manageable security, without excessive toxicities. In this study, 22% of patients had diagnosis of ALCL, ALK +. The data showed superior results in OS and PFS in the arm of BV-CHP.[65]

At the 5 years follow-up, the brenturixmab group continued to provide a superiority compared to CHOP, for the ALCL ALK+ subgroup and the HR was 0.4 (95% CI: 0.17-0.98).[51]

To improve the inferior outcome of ALCL, ALK+, the crizotinib, a selective ALK inhibitor, has been introduced, demonstrating a good response value in patients with relapsed/refractory ALCL, ALK +. The down-regulation of BCL2, after crizotinib treatment, leading to autophagy and tumor cell death, confirms the ALK experiments models. Toward this end, the ALK-driven activation of STAT3 and PI3K signaling supports novel regiments. New clinical trials and the entry of selective STAT3 degraders are expected to shortly assess new regiments in refractory/relapsed patients. [109-114]

Due to the improvement in efficacy therapy is expected that occurs a growth in ASCT rate as consolidation, because the number of patients with overall response will growth too.

Considering the low incidence of PTCL and its heterogenicity between subgroups diagnosis steps and therapeutic still a challenge. For this reason, huge studies, with high among is essential to improve our knowledge about this kind of lymphoproliferative diseases.

CHOP-like regimens still the backbone of ALCL ALK+ ‘s treatment, despite its favorable outcomes, around 30% of patients will need a second line therapy (refractory or relapse patients), which makes necessary the development of more specific therapies with better long-term response rates, preserving safety profile.

3.2.5 TCP 1.0: Survival outcomes of patients with extranodal natural-killer T-cell lymphoma: a prospective cohort study from the international T-cell Project. [115]

We did a substudy of patients with ENKTL who had been enrolled in the T-cell Project, a global prospective cohort study initiated in 2006 that builds on the retrospective study previously undertaken by the International Peripheral T-Cell Lymphoma Project Group.[2] Throughout the T-cell Project, 74 hospitals in 13 countries (Argentina, Brazil, Chile, France, Israel, Italy, South Korea, Slovakia, Spain, Switzerland, the UK, the USA, and Uruguay) served as enrolment sites. Consecutively diagnosed patients at the participating institutions, with newly diagnosed, previously untreated, mature T-cell or NK lymphomas according to WHO 2001 or WHO 2008 classifications (peripheral T-cell lymphoma, not otherwise specified; angioimmunoblastic T-cell lymphoma; ENKTL; enteropathy-type T-cell lymphoma; hepatosplenic γδ T-cell lymphoma; subcutaneous panniculitis-like T-cell lymphoma; anaplastic large-cell lymphoma [all sub- categories]; and unclassifiable peripheral T-cell or NK lymphoma) were registered into the T-cell Project at initial diagnosis before initiation of treatment. Eligible patients were aged 18 years and older, had adequate tissue biopsies for diagnosis and classification by central review, and had clinical data including baseline information on disease staging and laboratory para-meters at diagnosis, types of treatment received, and follow-up for at least 5 years. Some patients were included on the basis of local diagnosis and central review of histology reports if centralization of samples was not possible. No upper age limit nor other exclusions related to performance status or other clinical parameters were applied. The study was done in compliance with the Declaration of Helsinki and approved by research ethics committees and institutional review boards at each participating institution. All patients provided written informed consent before study entry.

Procedures

The first patient was enrolled on the T-cell Project on Oct 12, 2006, and the last patient on Feb 28, 2018, constituting a total of 1695 patients. The first patient with ENKTL was enrolled on Feb 15, 2007, and the last patient on May 26, 2017. The T-cell Project used a central dedicated database (http://www.tcellproject.org; now inactive) to store all patient data, hosted at the University of Modena and Reggio Emilia, Modena, Italy, which was locked for analysis on March 30, 2019.

Patient registration onto the study was based on local histological diagnosis. A central panel of expert haemato-pathologists based at the University of Modena and Reggio Emilia

subsequently undertook histopathological reviews when possible, for registered patients. Patients were removed from the study if deemed ineligible on histology review or if consent was withdrawn. Staging (Ann Arbor system) and evaluation of treatment response were undertaken by local investigators following institutional imaging protocols at times according to local standard practice and following completion of first-line therapy.

Data were collected on baseline clinical and disease characteristics, first-line treatment, and response evaluation, and updated with survival follow-up until database lock. Data on radiotherapy dose and field and Epstein-Barr viral load were not routinely collected.

Additionally, we analyzed the ENKTL cohort according to the prognostic index of NK lymphoma (PINK), a prognostic index for ENKTL first published in 2016.[18] This index comprises four risk factors: age >60 years, stage III or IV disease, distant lymph-node involvement, and non-nasal type disease.[116] According to the established PINK categories, we stratified patients as low risk (0 factors), intermediate risk (1 factor), and high risk (≥2 factors).

Results

At the data cut off (March 30, 2019), 1695 patients were registered for the T-cell Project, of whom 1553 were eligible for analysis. Of the 74 participating centers, 40 centers from the 13 participating countries across four continents registered patients with ENKTL for the study. Of the 181 cases locally registered as ENKTL, 98 (54%) underwent central pathological review. The diagnostic concordance of local pathological diagnosis with the international histopathology panel was 94% (n=92 concordant cases), with the six discordant cases deemed to be ineligible. For 81 (45%) registered ENKTL cases, diagnostic samples were not centralized and were evaluated based on the local diagnosis, with central review of the histology report. Two (1%) cases could not be adequately classified by central reviewers and were retained in the study based on local diagnosis and central review. Four cases were registered as other peripheral T-cell lymphoma subtypes by local pathology review and subsequently recategorized as ENKTL by the central review panel. In total, 166 cases (11%) of the 1553 eligible cases were categorized as ENKTL, of which 98 (59%) were designated as nasal, and 68 (41%) as extranasal. Figure 1 shows the study profile.

The frequency of ENKTL among the 1553 evaluable cases was significantly higher in Asian countries than in Europe and the USA (54 [31%] of 175 patients *vs* 82 (8%) of 1053, p=0·0008),

with Asian cases across the T-cell Project predominantly registered in South Korea (n=118). Interestingly, the frequency of nasal ENKTL versus extranasal ENKTL differed across continents.

The key baseline clinical characteristics of patients are shown in the table 16. As expected, patients with extranasal disease presented with more adverse clinical characteristics than those with nasal disease, particularly with regard to stage III–IV disease, involvement of more than one extranodal site, and high serum lactate dehydrogenase.

Table 16. Clinical characteristics and treatment details of patients with ENKTL (n=166)

	Total	Nasal-type	Extranasal-type
Median age, years*	53 (18–90)	53 (21–89)	51·5 (18–82)
Age >60 years	52/166 (31%)	30/98 (31%)	22/68 (32%)
Gender			
Male	108/166 (65%)	65/98 (66%)	43/68 (63%)
Female	58/166 (35%)	33/98 (34%)	25/68 (37%)
ECOG performance status			
0	65/149 (44%)	31/87 (36%)	34/62 (55%)
1	60/149 (40%)	46/87 (53%)	14/62 (23%)
2	18/149 (12%)	8/87 (9%)	10/62 (16%)
>2	6/149 (4%)	2/87 (2%)	4/62 (6%)
B symptoms†	60/152 (39%)	30/89 (34%)	30/63 (48%)
>1 extranodal site	80/166 (48%)	68/98 (69%)	56/68 (82%)
Bone marrow involvement	9/134 (7%)	4/77 (5%)	5/57 (9%)
Ann Arbor stage			
I	74/153 (48%)	43/91 (47%)	31/62 (50%)
II	30/153 (20%)	21/91 (23%)	9/62 (15%)
III	7/153 (5%)	4/91 (4%)	3/62 (5%)
IV	42/153 (27%)	23/91 (25%)	19/62 (31%)
Lactate dehydrogenase > upper limit of normal	55/141 (39%)	23/81 (28%)	32/60 (53%)
Bulky disease >10 cm	7/166 (4%)	3/98 (3%)	4/68 (6%)
Distant lymph node involvement	76/140 (54%)	56/85 (66%)	20/55 (36%)
First-line treatment			
Chemotherapy alone	43/130 (33%)	14/75 (19%)	24/55 (44%)
Radiotherapy alone	5/130 (4%)	4/75 (5%)	1/55 (2%)
Chemotherapy and radiotherapy	73/130 (56%)	52/75 (69%)	21/55 (38%)
Chemotherapy and consolidation high-dose treatment	14/130 (11%)	5 (7%)	9 (16%)
Chemotherapy regimen			
L-asparaginase+, anthracycline–, platinum– (SMILE, VIDL, MIDLE, PEGS, other)	54/130 (42%)	30/75 (40%)	24/55 (44%)
L-asparaginase–, anthracycline–, platinum+ (VIPD, DEVIC, ICE, ESHAP, other)	21/130 (16%)	16/75 (21%)	5/55 (9%)
L-asparaginase–, anthracyline+, platinum–	50/130 (38%)	27/75 (36%)	23/55 (42%)
L-asparaginase+, anthracycline–, platinum+	5/130 (4%)	2/75 (3%)	3/55 (5%)

Data are n/total cases (%) or median (IQR) of available data. Percentages do not always add up to 100% due to rounding. ENKTL=extranodal natural killer T-cell lymphoma. ECOG=Eastern Cooperative Oncology Group. SMILE=dexamethasone, methotrexate, ifosfamide, L-asparaginase, and etoposide. VIDL=etoposide, ifosfamide, dexamethasone, and L-asparaginase. MIDLE=methotrexate, ifosfamide, etoposide, dexamethasone, and L-asparaginase. PEGS=cisplatin, etoposide, gemcitabine, and methylprednisolone. VIPD=etoposide, ifosfamide, cisplatin, and dexamethasone. DEVIC=dexamethasone, etoposide, ifosfamide, and carboplatin. ICE=ifosfamide, carboplatin, and etoposide. ESHAP=etoposide, methylprednisolone, cisplatin, and cytarabine. *Total cases, n=166; nasal-type, n=98; extranasal-type, n=68. †Fever, weight loss, and night sweats.

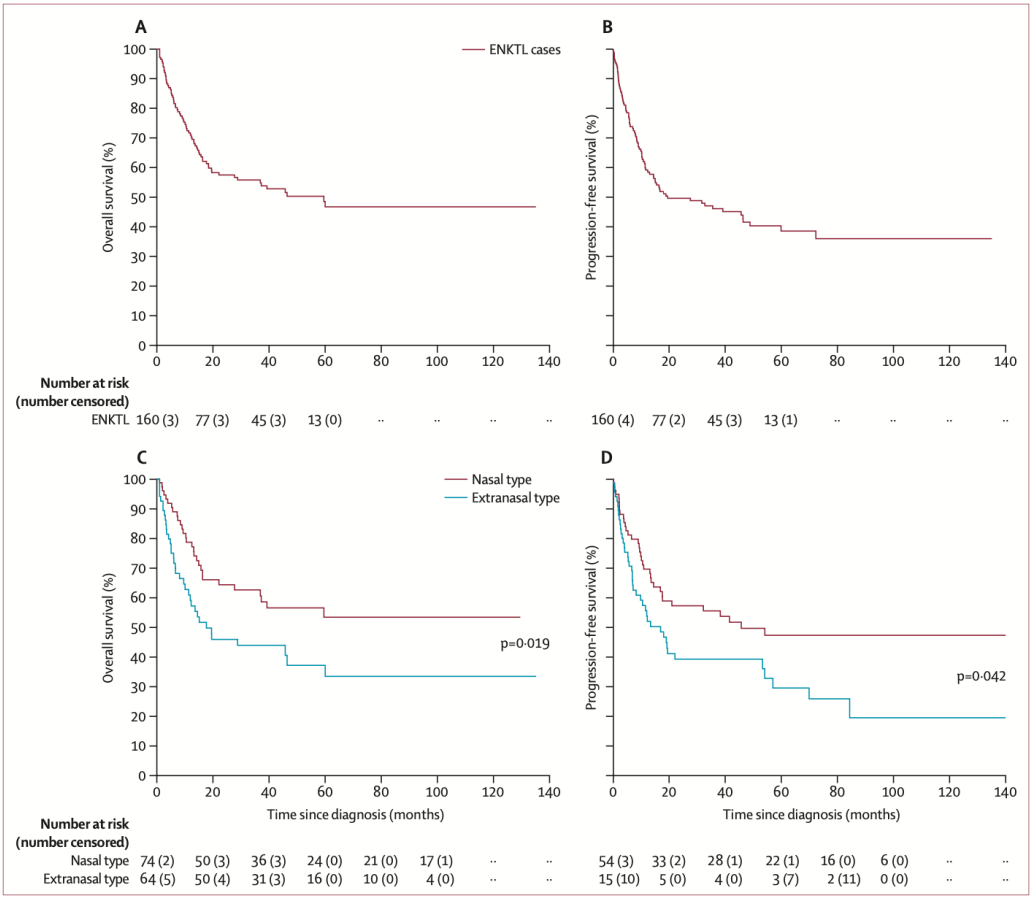
With a median follow-up of 44 months (IQR 20–61), we estimated a median overall survival of 59 months (95% CI 41–86) and a median progression-free survival of 20 months (1–39) for the whole ENKTL cohort (figure 9A and 9B).

The median overall survival of patients with nasal involvement (not reached [95% CI not reached–not reached]) was significantly higher than that in patients with extranasal disease (18 months [9–32]; HR 9·6 [95% CI 9·2–32·4]; p=0·019; figure 9C). In patients with nasal disease, overall survival at 3 years was 63% (45–77) and at 5 years was 54% (44–63). In patients with extranasal disease, overall survival at 3 years was 44% (27–87) and at 5 years was 34% (27–46; figure 2C). 71 deaths were registered, comprising 43% of the evaluable cohort. 46 (65%) deaths were due to lymphoma. Of the remaining deaths, 9 (13%) were attributed to infection, 3 (4%) to treatment toxicity, and 1 (1%) to a second primary malignancy. For 12 (17%) patients, the cause of death was not available. Median progression-free survival in patients with nasal disease was significantly improved compared with that of patients with extranasal disease (39 months [21–59]) *vs* 14 months [5–29]; HR 5·7 [5·1–28·9]; p=0·042; figure 9D). Progression-free survival at 3 years was 51% (29–69) and at 5 years was 47% (36–57) for patients with nasal disease, compared with 39% (19–58) and 26% (17–38) for those with extranasal disease **(figure 9D).** For the whole ENKTL cohort, the cumulative incidence of disease progression or relapse was 41% (33–50) at 3 years and 44% (35–52) at 5 years. The cumulative risk of non- relapse mortality was 9% (5–14) at 3 years and 13% (7–20%) at 5 years (data not shown).

Analysis according to Ann Arbor stage revealed a median progression-free survival of 46 months (11–81) and a median overall survival of 59 months (not estimable–not estimable) for patients with stage I or II ENKTL, compared with 15 months (9–20; HR 7.2 [5.4–19.9]; p=0.021) and 19 months (4–34; p=0.042) for those with stage III or IV disease. Notably, we observed significant differences in progression-free survival and overall survival between stage I and stage II disease (median progression-free survival, not reached [not- reached–not-reached] *vs* 13 months [1–16]; HR 3.2 [0–21]; p=0.012); and median overall survival, not reached [not- reached–not-reached] *vs* 29 months [2–34]**;** HR 3.1 [1–62]; p=0.067). Overall survival at 3 years was 69% (40–81) and at 5 years was 55% (21–79) in patients with stage I disease, compared with 48% (17–58) and 42% (17–58) in those with stage II disease (figure 3A and 3B). In patients with stage III–IV disease, median progression-free survival was 8 months (3–13; *vs* stage I disease, HR 2.7 [2.1–14.2]) and median overall survival was 10

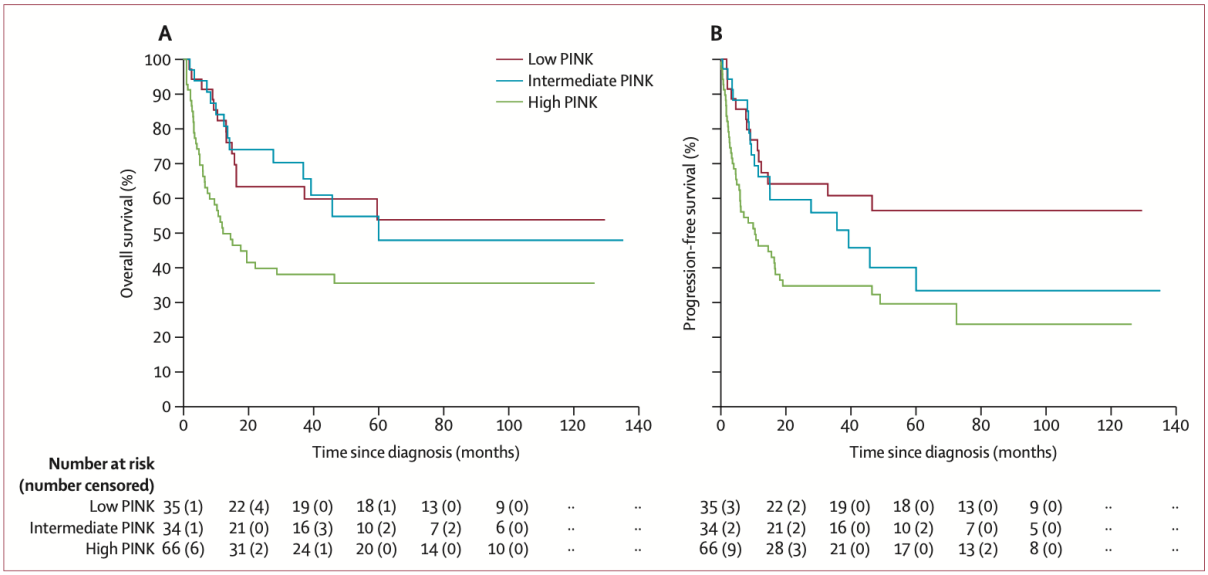
months (4–15; *vs* stage I disease, HR 2.9 [2.4–16.1]); overall survival at 3 years was 33% (9-38) and at 5 years was 24% (8–29).

Figure 9 A-D. Survival analyses in all patients and by ENKTL subtype
Overall survival (A) and progression-free survival (B) in the total ENKTL cohort. Overall survival (C) and progression-free survival (D) by ENKTL presentation (nasal or extranasal). Log-rank p values are shown.



From the available data, calculation of PINK score was possible in 144 cases. Of these, 34 (24%) were classified as low-risk, 41 (28%) as intermediate-risk, and 69 (48%) as high-risk cases in terms of prognosis. 5-year overall survival was 54% (31–70) in patients of low risk, 51% (21–64) in patients of intermediate risk, and 35% (10–41) in patients of high risk (p=0.0021; figure 10A). Progression-free survival at 5 years was 56% (29–60) in low-risk cases, 34% (17–49) in intermediate-risk cases, and 28% (9–34) in high-risk cases (p=0.0082; figure 10B). The appendix (p 45) reports the predictive value of the individual PINK variables with respect to 5-year overall survival and progression-free survival.

Figure 10 A-B. Survival analyses by PINK score
Overall survival (A) and progression-free survival (B) according PINK score (low PINK, 0 prognostic factors; intermediate PINK, 1 factor; and high PINK, ≥2 factors). Log-rank p values are shown. PINK = prognostic index of natural killer lymphoma



Of the 166 patients with ENKTL, treatment details were not available for 32 (19%) patients and a further four patients (2%) received best supportive care only; thus, 36 patients were excluded from treatment analyses. Of the 130 patients analyzed, 75 had nasal disease and 55 extranasal. 73 (56%) patients underwent chemo- therapy plus radiotherapy as a first-line treatment (table). Among the 59 regimens incorporating L-asparaginase, the SMILE protocol (dexamethasone, methotrexate, ifosfamide, L-asparaginase, and etoposide), administered in 23 (39%) patients, was the most commonly used. 14 (11%) of the 130 patients analyzed underwent high- dose chemotherapy with autologous stem cell support as first-line consolidation.

In patients with early-stage (I and II) disease receiving chemotherapy alone (n=11), overall survival at 3 years was 12% (not estimable–not estimable) and at 5 years was 12% (not estimable–not estimable), compared with 70% (41–91) and 59% (31–78) in those receiving chemotherapy and radiotherapy (n=48; p=0.0091**).** In patients with advanced-stage (III and IV) disease receiving chemo- therapy alone (n=27), overall survival at 3 years was 24% (8–32) and at 5 years was 24% (7–33), compared with 66% (33–87) and 58% (39–76) in patients receiving chemotherapy and radiotherapy (n=27; p=0.0006). Progression-free survival at 3 years was 0% (not estimable–not estimable) and at 5 years was 0% (not estimable–not estimable) in early-stage patients receiving chemotherapy alone, compared with 66% (40–87) and 53% (33–69) in those receiving chemotherapy and radiotherapy; the progression-free survival difference was

significant (log-rank p=0.0003. In patients with advanced-stage (III or IV) disease receiving chemotherapy alone, progression-free survival at 3 years was 14% (7–25) and at 5 years was 0% (not estimable–not estimable), compared with 59% (31–72) and 40% (27–69) in patients receiving chemotherapy and radiotherapy (p=0.0009).

We subsequently explored the effects of different chemotherapeutic regimens on survival outcomes in ENKTL. On analysis by treatment type, 5-year progression- free survival was 42% (11–64) and 5-year overall survival was 50% (32–74) in patients receiving an L-asparaginase-based regimen, compared with 26% (9–40) and 31% (11–58) in those receiving an anthracycline-based regimen, and 59% (30–77) and 66% (31–94) in those not receiving either drug (largely platinum-based regimens).

Overall, a response to first-line therapy was observed in 93 (72%) of 130 patients, with 84 (65%) patients (54 with nasal disease and 30 with extranasal disease) achieving a complete response and nine (7%; two with nasal disease and seven with extranasal disease) a partial response. In patients who achieved complete response, 5-year overall survival was 63% (48–77; 68% [41–79] for nasal-type and 54% [38–60] for extranasal type [not shown]) and 5-year progression-free survival was 61% (40–74; figure 5D; 66% [40–74] for nasal-type and 46% [37–56] for extranasal-type [not shown]). By contrast, patients who achieved only partial response had notably poor outcomes: 5-year overall survival was 32% (12–39) and 5-year progression- free survival was not estimable (not estimable–not estimable.

In patients with stage I or II disease, response to therapy by treatment group (chemotherapy alone, radiotherapy alone, and chemotherapy plus radiotherapy) was evaluable in 60 patients. Of these, complete remission was achieved in 1 (13%) of 8 patients receiving only chemotherapy, 1 (25%) of 4 patients receiving only radiotherapy, and 38 (79%) of 48 patients receiving chemotherapy plus radiotherapy. In patients with stage III or IV disease, we analyzed response to therapy in three treatment groups: L-asparaginase-based therapy, anthracycline-based therapy, and non-anthracyline, non-asparaginase protocols. In 60 evaluable patients, complete remission rates were 67% (n=40), 30% (n=18), and 1% (n=2). We also did an exploratory analysis of response to therapy and overall survival by geographical region. Although no significant differences were observed, response and survival outcomes appeared to be superior in ENKTL patients enrolled at Asian centers (data not shown).

Conclusions

To our knowledge, this Article presents the largest prospective international study of patients with ENKTL done to date.[116, 117] Initiated in 2006, the T-cell Project registered a total of 1695 patients with mature T-cell and NK cell lymphomas, with 166 cases classified as ENKTL, comprising 11% of eligible cases in the T-cell Project cohort. Compared with the previous International Peripheral T-Cell Lymphoma Project, we identified notable improvements in the survival of patients with ENKTL, representing the largest change in clinical outcomes in the past decade among all of the T-cell lymphoma subtypes studied.[118] This improvement is possibly attributable to an evolution in clinical management, including a move away from anthracycline- based therapy and towards asparaginase-based and platinum-based protocols, and increasing use of radiation therapy. In this study, improved survival was markedly associated with stage I disease, a low-risk PINK score, achievement of complete remission, and the use of radiation therapy.

We recognize the potential limitation in the 46% of cases that were not classified centrally, which were included on the basis of local pathology diagnosis alone, in line with the WHO pathological classification for ENKTL.[1] However, of cases centrally reviewed within the T-cell Project, concordance was high between local and centrally assigned diagnosis. This high diagnostic concordance is likely to reflect the high sensitivity and specificity of Epstein-Barr encoding region in-situ hybridization, as the standard clinical method for diagnosis of ENKTL in this clinicopathological context. The registered ENKTL cases were distributed widely across Asia, Europe, and North and South America. Notably, cases from Europe and North America constituted almost half (82 [49%] of 166 cases) of the entire ENKTL cohort, compared with 32 (24%) of 136 cases in the previous T-cell project report.[118] As expected, ENKTL cases represented a higher proportion of all T-cell and NK lymphoma cases in Asia, compared with in the USA and countries in Europe. Interestingly, for the whole ENKTL cohort, we observed a higher proportion of extranasal cases (68 [41%]) than previously reported in population-based studies (35 [26%] of 136 cases and 47 [13%] of 362); this was particularly notable in cases from Europe (24 [47%] of 51 European cases).[117-118] Given that the T-cell Project protocol required participating institutions to register consecutively diagnosed patients with T-cell or NK lymphoma, we consider the risk of selection bias to be low. Interestingly, we noted differences in overall survival by geographical region, although the numbers are too small to

be conclusive (data not shown). Although speculative, the more frequent use of both radiotherapy and L-asparaginase in Asia (data not shown) might be relevant factors.

As anticipated, patients with extranasal disease had significantly worse survival outcomes than those with nasal disease. Consistent with this result, advanced-stage (III and IV) disease conferred significantly worse outcomes over stage I and II ENKTL. However, this difference appeared to be explained by the favorable prognosis of stage I disease. This observation was unexpected, although patients with stage II disease comprised a relatively small subgroup (n=30; table), and only 10 patients (43%) with stage II disease received radiotherapy as part of first-line treatment (data not shown).The reasons for this low use of radio therapy are not clear, but might reflect heterogeneity within the stage II group. Furthermore, the unexpectedly poorer outcomes with stage II versus stage I disease highlights inherent limitations of both the Ann Arbor staging system for ENKTL, and the use of staging by CT imaging.

The T-cell Project was initiated in 2006, before the incorporation of PET-CT imaging into lymphoma staging and response assessment criteria, and thus PET-CT might have altered the staging of some patients in the study. Similarly, we recognize the limitations of CT as a response assessment method for ENKTL, being less sensitive than PET for identifying extranodal disease, and acknowledge that our dataset did not capture the imaging modality (ie, PET-CT versus CT or MRI) used for each patient.

In their study from the previous retrospective International Peripheral T-Cell Lymphoma Project, Au and colleagues reported outcomes on a large inter- national series of ENKTL cases, largely including patients from east Asian countries. [118] More than a decade after, we report significant improvements in progression-free survival and overall survival for both nasal and extranasal disease. We acknowledge that, consistent with this previous study, progression-free survival and overall survival were calculated from date of diagnosis rather than date of treatment initiation. The median overall survival reported in the retrospective Peripheral T-Cell Lymphoma Project series of patients with extranasal disease was 4 months, and in those with nasal disease was 19 months, compared with 18 months [95% CI 9–32] and not reached (not reached–not reached) in the present study. This magnitude of improvement exceeds that of any other T-cell lymphoma subtypes studied, and represents a paradigm shift in the clinical management of patients with ENKTL. Notable differences in patterns of treatment in the past decade include a large reduction in the proportion of patients receiving anthracycline-based

therapy and, accordingly, an increase in those receiving either platinum-based or asparaginase-based protocols. Several prospective clinical studies have shown the prognostic value of asparaginase in treatment regimens for ENKTL.[116, 119, 120] However, we were unable to show a definitive advantage of asparaginase within treatment protocols, even in advanced-stage disease. This lack of apparent benefit in the present study could be confounded by a number of factors, including treatment selection bias and geographical variation in treatment approaches.

The important role of radiotherapy in the management of ENKTL was highlighted by our study. In patients with early-stage disease, combined modality therapy with chemotherapy plus radiotherapy was associated with improved survival; chemotherapy alone was associated with poor outcomes (12% survival at 5 years). Unfortunately, further details on the radiotherapy dose, schedule, and anatomical field were not available in the T-cell Project database. Furthermore, the potential influence of different chemotherapy regimens on the effect and dose requirement of radiotherapy remains to be clarified. Anthracycline-based chemotherapy was used in a substantial proportion of patients in this study; however, reduced radiotherapy doses or fields might be feasible with non-anthracycline regimens, given the potential superior efficacy of such regimens. Interestingly, the addition of radiotherapy in patients with stage III or IV disease was associated with a highly significant improvement in overall survival. We believe such a strong abscopal effect to be unlikely in this disease, although the potential effect of radiation therapy on antigen presentation might be relevant in a lymphoma that expresses antigens encoded by Epstein-Barr virus.[121] We also recognize the potential for treatment bias, given that patients responsive to chemotherapy might be more likely to undergo radiation therapy than those with early disease progression or early mortality after diagnosis. However, given the apparent size of effect associated with radiotherapy, this observation warrants further study.

Differentiating early-stage from advanced-stage disease is essential for both treatment planning and predicting treatment outcome, although outcome prediction has not been straightforward in ENKTL.[122] In 2016, the ENKTL-specific prognostic index, PINK, was described, which showed improved prognostic delineation in the context of non-anthracycline based therapy.[116] This score was further refined in advanced-stage disease by including EBV DNA when detectable in peripheral blood as an additional parameter (PINK-E).[116] We validated the PINK score in our international ENKTL cohort of patients treated with anthracycline-based and non-anthracycline-based protocols, confirming that a high-risk PINK score identifies patients with

a particularly poor prognosis. For these patients, investigational therapies are warranted. Unfortunately, longitudinal data on Epstein-Barr virus DNA values, recognized to be a useful monitoring tool in ENKTL, were not routinely collected in this study. [122]

Prospective global studies for rare malignancies such as T-cell and NK lymphomas are crucial to improve understanding of epidemiological and clinical factors affecting the disease course and to provide information on treatment patterns and survival outcomes. Such studies are particularly required for very rare subtypes such as ENKTL, for which treatment algorithms have been largely derived from small non-randomized studies in restricted geographical areas. Our ENKTL dataset, as a planned sub study of the T-cell Project, has both strengths and limitations. The prospective design, with the registering of data centrally on consecutively diagnosed patients with ENKTL from 40 centers in 13 countries across 4 continents, permits substantial insight into the clinical characteristics of ENKTL, and offers a truly international picture of its modern-day clinical management. Furthermore, the long follow-up of the study allowed for confident interpretation of survival outcomes. However, an international study of this size and scope is inherently limited by the granularity of data that are routinely collected on patients. Similarly, correlative biological studies were not feasible within the main study.

Further therapeutic progress will require an improved understanding of the pathobiology of ENKTL, as a rare clinicopathological entity, to allow the development of rationally designed, biologically driven treatment approaches for those patients who do not respond to modern chemoradiation protocols. Examples of such a strategy have been reported in recent years, and several academic and commercial prospective studies are underway, including the T-cell Project 2.0, initiated in 2019 (NCT03964480). [123,124] The complementary role of such prospective cohort studies, alongside interventional clinical studies, remains vital to understanding rare lymphomas and improving outcomes.

3.3 COMPLETE

COMPLETE is a prospective multicenter cohort study of patients with newly diagnosed PTCL in the United States. The main objectives of the study were (i) to describe patterns of care for patients with PTCL, and (ii) to document outcomes, identify factors influencing treatment decisions, determine incidence and severity of selected treatment toxicities and identify supportive care received. [125]

This registry has been designed to provide information on a population of patients treated in a real-world setting in North America, to augment institution-based registries and to build a broad knowledge base for the disease. The COMPLETE registry is an observational study where no specific treatment is dictated in the protocol. Compared with SEER and the European Network of Cancer Registries, which principally focus on incidence and survival, the COMPLETE registry is directed at providing detailed information on patient characteristics, treatments, and outcomes. COMPLETE includes practitioners in all settings, including academic and community practices, and provides data directly to individual healthcare providers. This allows participating physicians to compare, confidentially, the findings from their individual practices to that of the aggregate dataset on an ongoing basis. So far, 499 patients with a newly diagnosed histologically confirmed PTCL have been enrolled in 40 academic and 15 community- based centers, and are now on continuous follow-up.

The COMPLETE database was used for analyzing the diagnostic work-up of PTCLs in US clinical practice. [126-128] Baseline assessment forms were available for 489 patients, of which 339 (69%) were available for analysis. The three most common diagnoses, accounting for two-thirds of all diagnoses, were PTCL-NOS, ALCL, both ALK+ and ALK–, and AITL. A mean of 10 markers (range: 0–21) were assessed per patient. Most patients were evaluated for 6–15 markers. There was no difference between academic and community settings in the mean number of markers assessed. CD30 was assessed frequently but not uniformly in non-ALCL. Gene rearrangement tests were done in 43% of patients; the two most common loci tested were TCR gamma and TCR beta. This analysis suggests that the diagnostic work-up for PTCL in the United States is widely variable, often lacking important phenotypic information required to fully characterize the lymphoma and maximize diagnostic accuracy. [129]

One more contribution coming from the COMPLETE registry was the analysis on the role of autologous stem-cell transplantation (ASCT) in patients with newly diagnosed PTCL and in first complete remission. A total of 213 patients with PTCL achieved first complete remission, and 119 patients with nodal PTCL, defined as ALK− ALCL, AITL, or PTCL-NOS, were identified. Some 83 patients did not undergo ASCT, whereas 36 underwent consolidative ASCT in first complete remission. ASCT was associated with superior survival for patients with advanced-stage disease or intermediate-to-high IPI scores. In a multivariable analysis, ASCT was independently associated with improved survival. [130]

3.4 T-CELL PROJECT 2.0

Since the prospective T-cell Project 1.0 was started, several new findings have contributed to improved understanding of biological, clinical, and therapeutic aspects of PTCL. The identification of unique biomarkers through techniques of gene expression analysis and next generation sequencing significantly improved the information of the genetic/molecular landscape of numerous lymphoid neoplasms. This made it necessary to update the WHO classification. As a result, the new WHO classification of lymphoid neoplasms was published in 2016. [1] This revised classification incorporates new insights into the biology and genetics of these disorders, with the addition of new provisional entities. The most relevant changes are as follows: the provisional entity "nodal T-cell lymphomas with T-follicular helper phenotype" is an umbrella category that highlights the similarities between AITL, follicular T-cell lymphoma, and PTCL with TFH phenotype; ALK– ALCL has been moved from a provisional to a definitive entity; addition of a new provisional entity "breast implant-associated ALCL" distinguishes it from other cases of ALK− ALCL because of its unique presentation and clinical course; indolent T-cell proliferations have also been identified, warranting the addition of indolent T-cell lymphoproliferative disorder of the gastrointestinal tract and primary cutaneous acral CD8+ T-cell lymphoma as provisional entities. [38] Moreover, the introduction of new and more effective therapies and the availability of better technologies for disease assessment led the major international lymphoma clinical trials groups and cancer centers to provide updated patient evaluation, staging, and response criteria. [19] Despite the positive contribution of new information arising from a number of clinical studies in recent years, there remain a number of key issues to be addressed. The International T-cell non-Hodgkin's Lymphoma Study Group launched T-cell Project 2.0, which adapts to changes made in diagnosis, classification, staging and response evaluation, in order to have a contemporary, real-time understanding of the evolving landscape of T-cell lymphoma biology and treatment, together with the application of contemporary technologies to further identify of new therapeutic targets.

The current web platform is compliant with National Institutes of Health, Health Insurance Portability and Accountability Act, Code of Federal Regulations Title 21 Part 11 requirements and other regulatory guidelines, and guarantees a careful management of security and confidentiality of data. The platform allows to collect details on patient relapses/progressions and related treatments.

OBJECTIVES AND ENDPOINTS

The designed study follows up the previous one T-Cell Lymphoma Project 1.0 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. In particular, to better define the clinical relevance of the new WHO Classification, the role of FDG-PET in staging and response assessment, the prognosis of different entities, the genomic landscape of different subtypes, and to investigate on most adequate treatment strategies for these neoplasms in the real-world population. Moreover, from a molecular point of view, one key objective of the study is to estimate prospectively the frequency of pEBVd detection in our cohort of PTCL patients at baseline and at the end of initial therapy, to characterize agreement between pEBVd and EBER in tumor tissue, and to explore the prognostic or predictive implications of detectable pEBVd in PTCL. Finally, to investigate the genetics and pathogenic mechanisms of aggressive PTCLs on an international scale.

Primary Endpoint is 2-year progression Free survival**, while there are more Secondary Endpoints:** 3 and 5-year Overall Survival; 3 and 5-year Progression Free Survival; Event Free Survival at 24 months (EFS 24)**;** Complete Response Rate at 30 months (CR30)

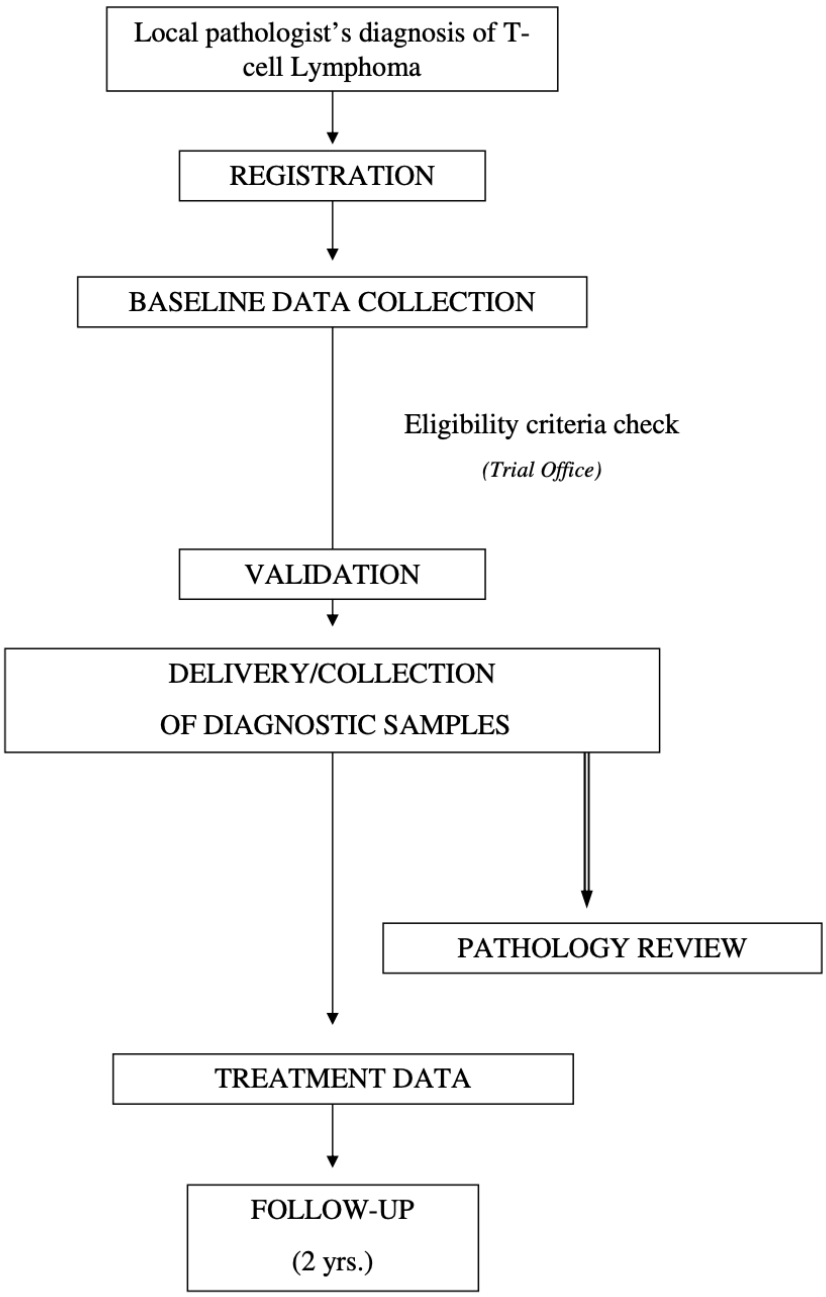
STUDY DESIGN

This is a prospective, longitudinal, international, observational study of patients with histological diagnosis of Peripheral T-cell lymphoma. Eligible patients will be identified from sites. No study specific visit or procedure will be required as part of patient participation in the study. Patients will be evaluated according to the physician's standard practice.

While patients may receive experimental interventions in the course of their care, the Registry is not designed to test any specific intervention. Patients enrolled in the Registry will undergo routine clinical assessments and receive therapy prescribed by their treating physicians.

After patient's registration, diagnosis review is planned for each patient registered in the Study. The samples are to be sent to the Trial Office in batches, and after request of the Trial Office.

Study Flow-chart



SUBJECT SELECTION

INCLUSION CRITERIA

1. Previously-untreated patients with *de novo* diagnosis of peripheral T-cell or NK/T-cell lymphoma:

- T-cell large granular lymphocytic leukemia;
- Chronic lymphoproliferative disorder of NK cells;
- Aggressive NK-cell leukemia;
- Adult T-cell leukemia/lymphoma;
- Extranodal NK/T-cell lymphoma, nasal type;
- Intestinal T-cell lymphoma;
- Hepatosplenic T-cell lymphoma;
- Subcutaneous panniculitis-like T-cell lymphoma;
- Peripheral T-cell lymphoma, not otherwise specified;
- Angioimmunoblastic T-cell lymphoma and other nodal lymphomas of T follicular helper cell origin;
- Anaplastic large cell lymphoma, ALK-positive;
- Anaplastic large cell lymphoma, ALK-negative;
- Breast implant-associated anaplastic large 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

STATISTICAL CONSIDERATION

Sample size

Sample size was defined using an empirical approach, as no formal hypothesis on the final prognostic model is possible before study start. Sample size was calculated to define a prognostic score for PTCL-NOS using a Cox proportional hazard regression and considering Overall Survival (OS) as principal endpoint. To estimate the number of observed events we hypothesized that OS has a risk function which follows Weibull distribution with time parameter (in year) λ of 0.369 and form parameter p of 0.773, and a censored distribution with lambda parameter of 0.104 and form parameter of 1.393. The Weibull parameters were

estimated from the OS of PTCL-NOS observed from T-Cell project 1.0. After 10,000 Monte Carlo simulations, we calculated that with 1000 cases enrolled in 2 years and followed up for at least 2 years, we would observe 570 events at the end of the study. We plan to separate along the registration the sample in training (2/3) and external validation (1/3); 670 cases with about 380 events and 330 cases with about 190 events will be in training and test sample, respectively. The test sample will be frozen until to the external validation analysis. Based on the assumption that to the develop a prognostic model we would need an excess of 10/15 events for each binary covariate with a prevalence of worst prognosis group of 20-25% (or for degree of freedom for continuous covariate), in these conditions it is possible to develop a model starting from about 15-17 regressors in the training sample.[79, 80] The test sample will be used to check the calibration and discrimination ability of prognostic index obtained from Cox model.

An initial estimate of primary endpoint will be performed when the follow-up of last enrolled patient reaches 2 years.

It is expected that approximately 100 sites will participate in the Registry although no limit on site participation has been set. Both academic and community practices are expected to contribute patients to the Registry.

Statistical analysis plan (SAP)

- Descriptive analysis. Continuous variables will be summarized as median, interquartile distance, or mean and standard deviation. Categorical variables will be expressed as absolute and percentage frequencies.

- Comparison of continuous between two or more groups. Continuous covariates will be compared by means of Mann-Whitney test (between two groups) or Kruskal-Wallis test (between more than two groups).

- Comparison of categorical covariates between groups. Categorical covariates will be compared using the Fisher's exact test or Chi2 test, if appropriate.

- Survival analysis. The survival functions will be calculated and plotted using the Kaplan-Meier method, and the survival rate at 3 and 5 years of follow-up will be reported with the estimated 95% confidence interval (95%CI, standard error from Greenwood's formula).

- Covariate effect: The prognostic effect of covariate will be estimated using the Cox proportional hazard (PH) regression model, reported as hazard ratio (HR) with 95%CI. The proportionality of the hazard by means of the analysis of Schoenfeld residuals will be checked.

- Model developing. The prognostic model will be developed following the step-by-step likelihood ratio test, controlled by Akaike's information criterion (AIC) and Bayesian information criterion (BIC). The covariates will be selected according to statistical and clinical consideration.

The model will be diagnosed graphically, evaluating the residuals influence by means of the analysis of the likelihood displacement as function of martingala residuals.

- Internal validation. Will be calculated the shrinkage factor (check for overfitting) and the calibration of the prognostic index obtained from the Cox PH model, using bootstrap techniques as suggested by Harrell FE.[81] The discrimination power of the model will be estimated using c-Harrell and D-Royston.[83]

- External validation. The reproducibility of PI and of risk groups (risk score), obtained from Cox PH model, will be checked in the external sample (test sample), evaluating:

a) The intercept and slope of PI;

b) The discriminant power of PI and risk score in the test sample, using c-Harrell and D-Royston.

3.4.1 T-Cell Project 2.0: General aspects

Since the prospective T-cell Project was started, several new findings have contributed to improved understanding of biological, clinical, and therapeutic aspects of PTCL. The identification of unique biomarkers through techniques of gene expression analysis and next-generation sequencing significantly improved the information of the genetic/molecular landscape of numerous lymphoid neoplasms. This made it necessary to update the WHO classification. As a result, the new WHO classification of lymphoid neoplasms was published in 2016.[1] This revised classification incorporates new insights into the biology and genetics of

these disorders, with the addition of new provisional entities. The most relevant changes are as follows: the provisional entity “nodal T-cell lymphomas with T-follicular helper phenotype” is an umbrella category that highlights the similarities between AITL, follicular T-cell lymphoma, and PTCL with TFH phenotype; ALK– ALCL has been moved from a provisional to a definitive entity; addition of a new provisional entity “breast implant-associated ALCL” distinguishes it from other cases of ALK− ALCL because of its unique presentation and clinical course; indolent T-cell proliferations have also been identified, warranting the addition of indolent T-cell lymphoproliferative disorder of the gastrointestinal tract and primary cutaneous acral CD8+ T-cell lymphoma as provisional entities. Moreover, the introduction of new and more effective therapies and the availability of better technologies for disease assessment led the major international lymphoma clinical trials groups and cancer centers to pro- vide updated patient evaluation, staging, and response criteria.[19] Despite the positive contribution of new information arising from a number of clinical studies in recent years, there remain a number of key issues to be addressed. The International T-cell non-Hodgkin’s Lymphoma Study Group launched T-cell Project 2.0, which adapts to changes made in diagnosis, classification, staging and response evaluation, in order to have a contemporary, real-time understanding of the evolving landscape of T-cell lymphoma biology and treatment, together with the application of contemporary technologies to further identify of new therapeutic targets.

By expert pathology committee were defined minimal revision criteria to provide a centralized review (Table 17 and table 18).

Table 17. Specific markers for minimal revision criteria.

T-cell markers	CD2, CD3, CD4, CD5, CD7, CD8, βF1, TCRγ/δ; optional but useful CD43, CD52, TH1, TH2: GATA3, TBX21
Cytotoxic markers	TIA1, granzyme B, perforin
TFH-markers	PD1, ICOS, CXCL13, CD10, SAP, CCR5, BCL6
T-Reg markers:	FoxP3
NK-cell markers:	CD16, CD56, CD57
Activation markers:	CD25, CD30
Others:	ALK, EMA, CD45, IRF4, PD-L1, TCL1, MATK, CD95, CD103
Proliferation:	MIB1/Ki-67
B-cell markers:	CD20, BSAP/PAX5
Follicular dendritic cells:	CD21, CD23
Histiocytes and epithelioid elements:	CD68/PG-M1
EBV:	EBER ISH
Optional, but useful in the recognition of the majority of the nodal PTCL disorders	TCR Beta and Gamma PCR, RHOA and IDH2

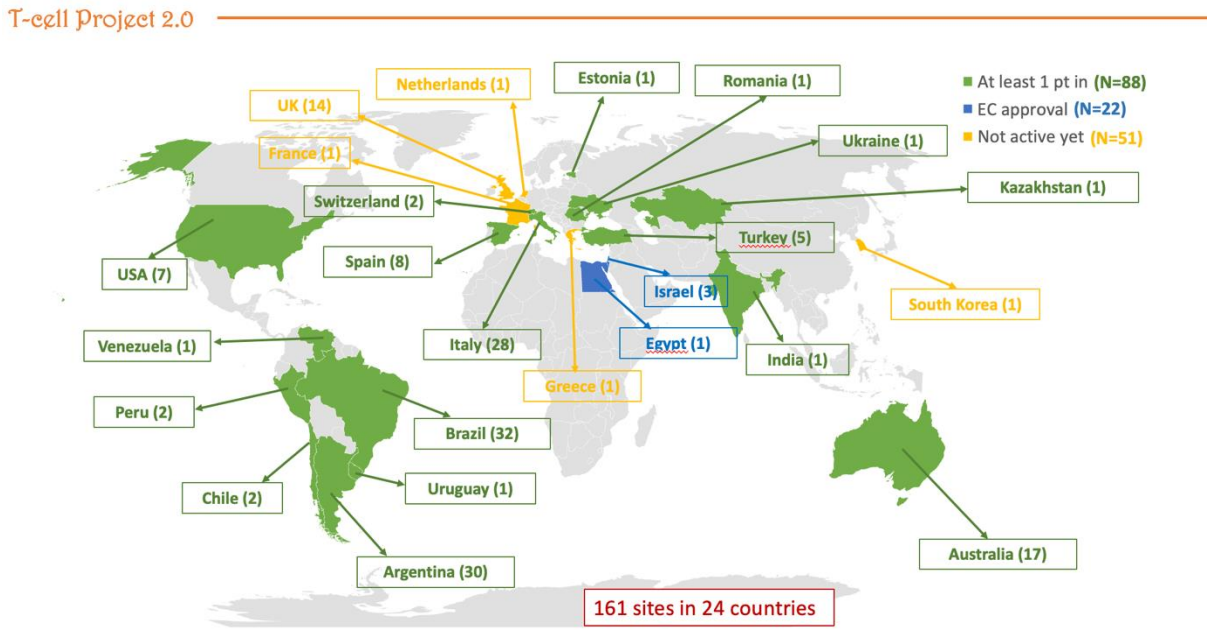
Minimal panel: Ki-67, PAX5 and T-cell markers (CD2-CD8) in any case, to assess the defectivity of the phenotypic profile, which is distinctive of PTCLs. In addition, the staining for CD3 allows distinguishing between CD3 surface and cytoplasmic.

Table 18. Further and optional required markers in different PTCLs subtypes

T-cell large granular lymphocytic leukaemia	further required = CD52, TCL1
Chronic lymphoproliferative disorder of NK cells	further required = CD56, cytotoxic markers.
Aggressive NK-cell leukaemia:	further required = CD56, cytotoxic markers, EBER ISH
Adult T-cell leukaemia/lymphoma:	further required = CD25, FoxP3; optional but useful: CCR4, CD30
Extranodal NK/T-cell lymphoma, nasal type:	further required = EBER ISH, CD56, cytotoxic markers; optional but useful: CD95, MATK, CD30
Intestinal T-cell lymphoma:	further required = βF1, TCRγ/δ, cytotoxic markers, CD56; optional but useful: CD30, CD103, MATK
Hepatosplenic T-cell lymphoma:	further required = βF1, TCRγ/δ, CD56, cytotoxic markers (only TIA1+)
Subcutaneous panniculitis-like T-cell lymphoma:	further required = βF1, cytotoxic markers, CD56 (should be negative)
Peripheral T-cell lymphoma, not otherwise specified	further required = exclusion of TFH phenotype; optional but useful GATA3, TBX21, CD30 and cytotoxic markers. At times, CD20 is aberrantly expressed.
Angioimmunoblastic T-cell lymphoma and other nodal lymphomas of T follicular helper cell origin:	further required = simultaneous expression of at least two, preferably three TFH markers, CD20, CD21 or CD23, EBER ISH. Optional but useful: CD30.
Anaplastic large cell lymphoma, ALK-positive:	further required = CD30, ALK, CD45, CD43, CD4, perforin, IRF4; optional but useful: further cytotoxic markers, PD-L1.
Anaplastic large cell lymphoma, ALK-negative:	ditto.
Breast implant-associated anaplastic large cell lymphoma:	ditto.

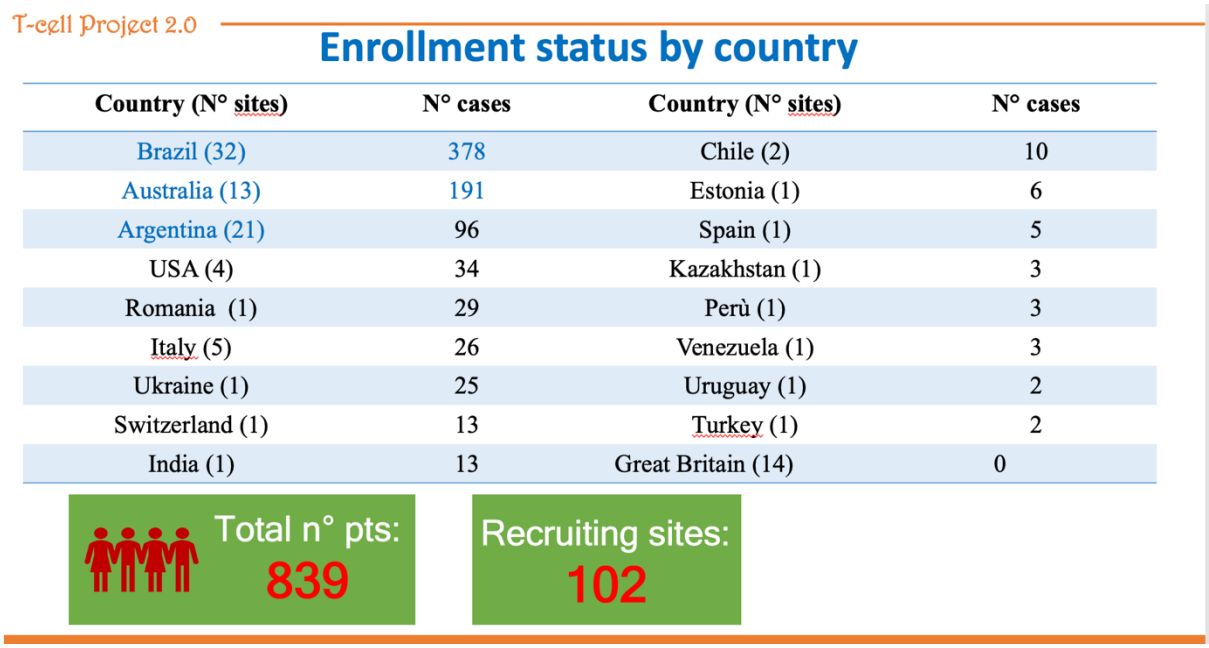
The most recent updated data on the status of the T-cell Project 2.0 at the time of writing (January, 2022) revealed that more than 161 sites in 24 different countries have expressed interest in participating (Figure 11).

Figure 11. Current status of TCP 2.0



Currently, 102 centers received ethics committee approval by the local competent authorities and 839 are included (Figure 11). In less than 18 months from activation, 452 new cases have been registered from 65 sites active all over the world, with an accrual rate double compared with T-cell Project 1.0. The current web platform is compliant with National Institutes of Health, Health Insurance Portability and Accountability Act, Code of Federal Regulations Title 21 Part 11 requirements and other regulatory guidelines, and guarantees a careful management of security and confidentiality of data. The platform allows to collect details on patient relapses/progressions and related treatments.

Figure 12. Enrolment status by country



We analysed some baseline patients' characteristics. The median age at diagnosis was 56 years (range 18-93). Stage III-IV had 70% of patients and 58% were males. Additionally, 20% of patients received auto SCT in first-line treatment as consolidation. All patients' characteristics are shown in **Table 19**.

As the TCP2.0 adapts to changes made in the new WHO2016 classification, additionally we did a preliminary analysis of patients for whom the diagnosis made by the local pathologist was reported in the electronic CRFs.

Of these data, 714 patients with median age of 56 years (18-93) have been validated by the centralized trial office. Overall, PTCL-NOS, ALCL ALK-negative, and AITL, represent the most frequent subtypes, representing 31,2%, 19,2% and 13,9% of cases, respectively.

As reported in **Table 20** and **Figure 13**, PTCL-NOS represents the most frequent subtype worldwide, whereas Adult T-cell leukemia/lymphoma was more frequent in Brazil, ALCL ALK-negative in Australia/India, AITL and ALCL ALK-positive in North America and Europe. ENKTCL, nasal type was relatively frequent in Brazil and quite rare in the other Latin America Countries. Finally, many sub-types represent less than 5% of cases in all geographic areas.

Table 19. Baseline patients' characteristics (N=766)

Parameters	**N total**	**N**	**%**
Age	**766**	**56 (18-93)**	
Gender male	**780**	**455**	**58**
Stage III-IV	**695**	**488**	**70**
ECOG PS **2** **3** **4**	**723**	**111** **44** **14**	 **15** **6** **2**
B symptoms **Fever ≥ 38** **Night sweats** **Weight loss**	**760**	 **191** **213** **196**	 **25** **28** **26**
Extranodal involvement	**747**	**447**	**60**
BM involvement	**718**	**187**	**26**
LDH > ULN	**665**	**382**	**57**
Hemoglobin < 12g/dL	**721**	**324**	**45**
Platelets < 150,000/mm^3	**718**	**146**	**20**
β2M > ULN	**304**	**169**	**56**
ASCT as consolidation	**548**	**110**	**20**

Figure 13. Subtypes distribution of mature T and NK cell lymphomas according to 2016 WHO classification by geographic area (n=714).

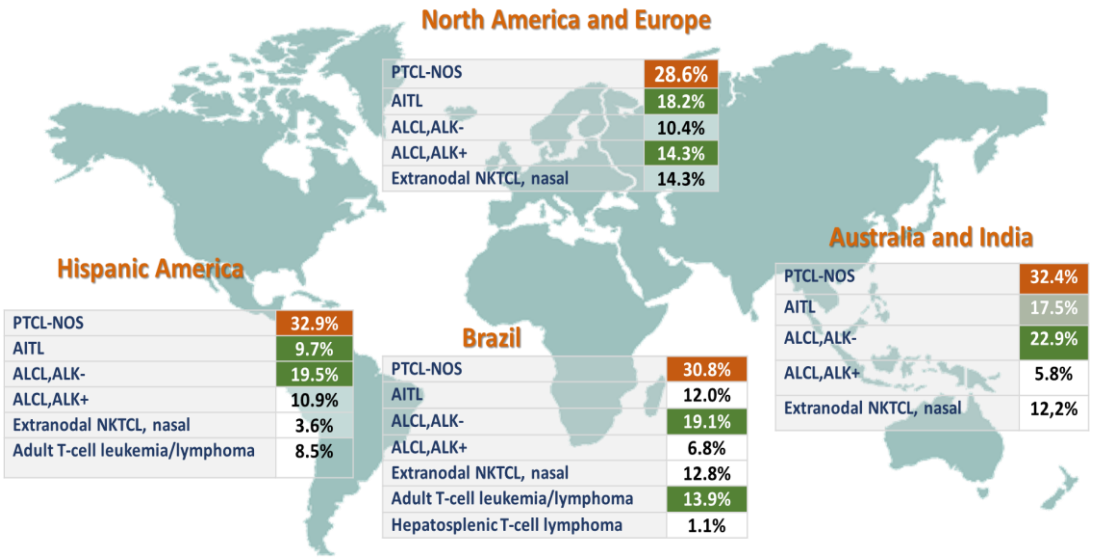


Table 20. Subtypes distribution of mature T and NK cell lymphomas according to 2016 WHO classification by geographic area (n=714).

Subtypes	Total N (%)	Australia/India	Brazil	Hispanic America	North America/Europe
PTCL (NOS)	**223 (31,2)**	**61 (32,4)**	**113 (30,8)**	**27 (32,9)**	**22 (28,6)**
Lymphoepitelioid lymphoma	3 (0,4)	0 (0,0)	0 (0,0)	3 (3,6)	0 (0,0)
ALCL, ALK-	**137 (19,2)**	**43 (22,9)**	**70 (19,1)**	**16 (19,5)**	8 (10,4)
Breast-implant ALCL	3 (0,4)	0 (0,0)	2 (0,5)	1 (1,3)	0 (0,0)
AITL	**99 (13,9)**	**33 (17,5)**	44 (12,0)	**8 (9,7)**	**14 (18,2)**
PTCL-TFH	1 (0,1)	0 (0,0)	0 (0,0)	0 (0,0)	1 (1,3)
ENKTCL, nasal type	**84 (11,8)**	23 (12,2)	47 (12,8)	3 (3,6)	11 (14,3)
ATLL	**67 (9,4)**	6 (3,2)	**51 (13,9)**	7 (8,5)	3 (3,9)
ALCL, ALK+	**56 (7,8)**	11 (5,8)	25 (6,8)	9 (10,9)	**11 (14,3)**
HSTCL	10 (1,4)	5 (2,7)	4 (1,1)	1 (1,3)	0 (0,0)
SPTCL	10 (1,4)	6 (3,2)	2 (0,5)	0 (0,0)	2 (2,6)
EATL	7 (1,0)	0 (0,0)	2 (0,5)	4 (4,9)	1 (1,3)
MEITL	3 (0,4)	0 (0,0)	0 (0,0)	2 (2,4)	1 (1,3)
T-LGL	9 (1,3)	0 (0,0)	6 (1,6)	1 (1,3)	2 (2,6)
CLPD-NK	1 (0,1)	0 (0,0)	0 (0,0)	0 (0.0)	1 (1,3)
ANKL	1 (0,1)	0 (0,0)	1 (0,3)	0 (0.0)	0 (0,0)
TOTAL	**714**	**188**	**367**	**82**	**77**

As a diagnosis review is planned for each patient registered in the TCP 2.0, the expert pathologists will review the pathological material by strictly applying criteria of the most recent edition of the WHO2016 Classification. Since the beginning of this sub study, there were included 115 patients from 9 centres **(Table 21).**

Table 21. Centres included in centralized pathology review sub study

Center	**N° cases uploaded or in progress**
Cluj Napoca-TCELL	29
Italy (5 sites)	26
Kiev National Cancer Instutute	25
Buenos Aires - FUNDALEU	19
Philadelphia_T Jefferson U	11
Salamanca - HU	5
TOTAL	**115**

4 Conclusions

TCLs are rightfully an orphan group of lymphoproliferative disorders that need more care. In addition to the opportunity to extract even more accurate information on clinical outcomes of different subtypes of PTCLs, prospective collection of data as proposed by T-cell Project 2.0 may help in better define the clinical relevance of the new WHO classification, the role of fluorine-18-fluorodeoxyglucose positron emission tomography in staging and response assessment, the prognosis of different entities, the genomic landscape of different subtypes, and to investigate on most adequate treatment strategies for these neoplasms in the real-world population. Moreover, from a molecular point of view, one goal of the study is to estimate

prospectively the frequency of cell-free plasma EBV DNA (pEBVd) detection in our cohort of patients with PTCL at baseline and at the end of initial therapy, to characterize agreement between pEBVd and EBV-encoded RNA in tumor tissue, and to explore the prognostic or predictive implications of detectable pEBVd in PTCL. Finally, to investigate the genetics and pathogenic mechanisms of aggressive PTCLs on an international scale.

Another important outcome is the opportunity of assessing new methods of response to therapy. In recent years, advances have been made in circulating tumor DNA, which can be detected with allele-specific polymerase chain reaction, or with next-generation sequencing techniques. The search for ctDNA in PTCL may be a useful analysis to assess disease response and to predict relapse. This approach could in the future become a new tool for routine clinical practice, thus assisting clinicians in ultimately better tailoring the most appropriate treatment to be offered to patients with PTCL.

Acknowledgements

During my PhD program, I had the opportunity to meet many fantastic and amazing people, whom I want to express my gratitude for all their support during this period. First of all, I would like to thank to our legend and my supervisor, **Professor Massimo Federico**, for giving me all my opportunities I had, have and will have, and of course, for my chance to be enrolled in the PhD program of Clinical and Experimental Medicine at the University of Modena and Reggio Emilia (Modena, Italy). I am deeply grateful to him that he showed what is real research, how to be a person with a huge soul and of course, how to work in team and achieve successful results. His school of life and work does not have analogues all over the world. I am completely satisfied that he became my real-life coach. I would like to thank you for all the precious advice and for putting so much faith in my abilities as a young researcher.

Moreover, I would like to thank to **Associazione Angela Serra Per La Ricerca Sul Cancro**, for their financial support. Thanks to **Giovanna, Silvia and Paola** from Associazione Angela Serra for their support and always positive attitude. I am thankful for **Professor Giuseppe Biagini** who followed us during these years of PhD Program, to his organization and availability to us.

I am deeply thankful to **Dr. Attilio Guarini** for welcoming me in department of hematology in Istituto Tumori "Giovanni Paolo II" in Bari. I am grateful to **Dr. Carla Minoia** for all her enormous help, patients visits and fruitful discussions, as well as for translating me everything during my first year from Italian to English before give me responsibilities to follow visits with Italian patients without any barriers. Of course, I would like to add my gratitude to **all my colleagues from Bari** for having shared with me these exciting years.

I would also like to thank **Professor Pier Luigi Zinzani** and **Professor Maurizio Martelli** for accepting the task of revising this work. Also, I would like to thank the members of the jury for agreeing to participate in my PhD dissertation.

I would also thank **Dr. Chiara Gabbi** and **Dr. Davide Mazzi** for their impressive and very interesting courses of "Communicate Science", "Come scrivere e comunicare la scienza" and "Technical English", during our **PhD in Clinical and Experimental Medicine**.

I also would like to thank to **Dr. Martina Manni** for having shared with me her experience, for being always joyful and a super pleasant person to work with. It was extremely amazing to work with you on all our projects with our **Professor Massimo Federico**.

This work is dedicated to my **family**, my Mom, Dad, my grandmother and my grandfather (unfortunately he passed away 13 years ago, but he would be proud of me) and my brother. My family is my cornerstone, they are helping and continuously supporting me during my life.

Also, this work I would like to dedicate to my country Ukraine and to all citizens who are fighting for our future.

"Success is not final, failure is not fatal,
it is the courage to continue that counts". – Winston Churchill

"Nothing is impossible…" – Prof. Massimo Federico

REFERENCES.

1. Swerdlow SH, Campo E, Pileri SA, et al. The 2016 revision of the World Health Organization classification of lymphoid neoplasms. *Blood*. 2016;127(20):2375-2390.
2. Vose J, Armitage J, Weisenburger D: International peripheral T-cell and natural killer/T-cell lymphoma study: pathology findings and clinical outcomes. J Clin Oncol 26:4124–4130, 2008
3. A clinical evaluation of the International Lymphoma Study Group classification of non-Hodgkin's lymphoma. The Non-Hodgkin's Lymphoma Classification Project. Blood 89:3909–18, 1997
4. Savage KJ: Peripheral T-cell lymphomas. Blood Rev 21:201–16, 2007
5. Non-Hodgkin's Lymphoma Classification Project (1997). A clinical evaluation of the International Lymphoma Study Group classification of non-Hodgkin's lymphoma. *Blood* 89: 3909–3918.
6. Rüdiger, T., Weisenburger, D.D., Anderson, J.R. et al. (2002). Peripheral T-cell lymphoma (excluding anaplastic large-cell lymphoma): results from the Non-Hodgkin's Lymphoma Classification Project. *Ann Oncol* 13 (1): 140–149.
7. Howlader N, Noone AM, Krapcho M, Miller D, Brest A, Yu M, Ruhl J, Tatalovich Z, Mariotto A, Lewis DR, Chen HS, Feuer EJ, Cronin KA (eds). SEER Cancer Statistics Review, 1975-2018, National Cancer Institute. Bethesda, MD, https://seer.cancer.gov/csr/1975_2018/, based on November 2020 SEER data submission, posted to the SEER web site, April 2021.
8. Swerdlow, SH ; Campo, E; Harris N et al., Swerdlow E.; Harris N.L.; Jaffe E.S.; Pileri S.A.; Stein H.; Thiele J.; Vardiman J.W. SH. C: WHO Classification of Tumors of Haematopoietic and Lymphoid Tissues. (ed 4th). Lyon, France, IARC Press, 2008
9. de Leval, L., Rickman, D.S., Thielen, C. et al. (2007). The gene expression profile of nodal peripheral T-cell lymphoma demonstrates a molecular link between angioimmunoblastic T-cell lymphoma (AITL) and follicular helper T (TFH) cells. *Blood* 109 (11): 4952–4963.
10. de Leval, L., Rickman, D.S., Thielen, C. et al. (2007). The gene expression profile of nodal peripheral T-cell lymphoma demonstrates a molecular link between angioimmunoblastic T-cell lymphoma (AITL) and follicular helper T (TFH) cells. *Blood* 109 (11): 4952–4963.
11. Seif, F., Khoshmirsafa, M., Aazami, H. et al. (2017). The role of JAK-STAT signaling pathway and its regulators in the fate of T helper cells. *Cell Commun Signal* 15 (1): 23.
12. Iqbal J, Wright G, Wang C, et al: Gene expression signatures delineate biological and prognostic subgroups in peripheral T-cell lymphoma. Blood 123:2915–2923, 2014
13. Luchtel, R.A., Zimmermann, M.T., Hu, G. et al. (2019). Recurrent MSCE116K mutations in ALK-negative anaplastic large cell lymphoma. *Blood* 133 (26): 2776–2789.
14. Kataoka, K., Miyoshi, H., Sakata, S. et al. (2019). Frequent structural variations involving programmed death ligands in Epstein-Barr virus-associated lymphomas. *Leukemia* 33 (7): 1687–1699.
15. Cristofoletti, C., Picchio, M.C., Lazzeri, C. et al. (2013). Comprehensive analysis of PTEN status in Sézary syndrome. *Blood* 122 (20): 3511–3520.
16. Wartewig, T., Kurgyis, Z., Keppler, S. et al. (2017). PD-1 is a haploinsufficient suppressor of T cell lymphomagenesis. *Nature* 552 (7683): 121–125.
17. Kataoka, K., Nagata, Y., Kitanaka, A. et al. (2015). Integrated molecular analysis of adult T cell leukemia/ lymphoma. *Nat Genet* 47 (11): 1304–1315.

18. The-Peripheral T-cell Lymphomas. Owen A. O'Connor (Editor), Won Seog Kim (Editor), Pier L. Zinzani (Editor). Book ISBN 978-1-119-67131-2 May 2021 Wiley-Blackwell 416 Pages. Chapter 2. Mechanisms of T-cell lympomagenesis. T *François Lemonnier, Philippe Gaulard and Laurence de Leval* Pages 9-26
19. Cheson BD, Fisher RI, Barrington SF, et al. Recommendations for Initial Evaluation, Staging, and Response Assessment of Hodgkin and Non-Hodgkin Lymphoma: The Lugano Classification. *J Clin Oncol*. 2014;32(27):3059-3067. doi:10.1200/JCO.2013.54.8800.
20. Horwitz, S Ansell SWZ et al.: NCCN Clinical Practice Guidelines in Oncology [Internet], 2018Available from: www.nccn.org
21. Foss FM, Zinzani PL, Vose JM, et al: Peripheral T-cell lymphoma. Blood 117:6756–67, 2011
22. Weisenburger DD, Savage KJ, Harris NL, et al: Peripheral T-cell lymphoma, not otherwise specified: a report of 340 cases from the International Peripheral T-cell Lymphoma Project. Blood 117:3402–3408, 2011
23. Gallamini A, Stelitano C, Calvi R, et al: Peripheral T-cell lymphoma unspecified (PTCL-U): a new prognostic model from a retrospective multicentric clinical study. Blood 103:2474–9, 2004
24. Went, P., Agostinelli, C., Gallamini, A., Piccaluga, P.P., Ascani, S., Sabattini, E., Bacci, F., Falini, B., Motta, T., Paulli, M., Artusi, T., Piccioli, M., Zinzani, P.L. & Pileri, S.A. (2006) Marker expression in peripheral T-cell lymphoma: a proposed clinical-pathologic prognostic score. Journal of Clinical Oncology, 24, 2472–2479.
25. Federico, M., Bellei, M., Marcheselli, L., et al. (2018). *Peripheral T cell lymphoma, not otherwise specified (PTCL-NOS). A new prognostic model developed by the International T cell Project Network. British Journal of Haematology, 181(6), 760–769.*doi:10.1111/bjh.15258
26. Cheson BD. PET/CT in Lymphoma: Current Overview and Future Directions. *Semin Nucl Med*. 2018;48(1):76-81. doi:10.1053/j.semnuclmed.2017.09.007
27. Pellegrini C, Argnani L, Broccoli A, Stefoni V, Derenzini E, Gandolfi L, Casadei B, Maglie R, Pileri S, Zinzani PL (2014) Prognostic value of interim positron emission tomography in patients with peripheral T-cell lymphoma. Oncologist 19:746–750.
28. El-Galaly TC, Pedersen MB, Hutchings M, Mylam KJ, Madsen J, Gang AO, Bogsted M, de Nully BP, Loft A, Nielsen AL, Hendel HW, Iyer V, Gormsen LC (2015) Utility of interim and end-of-treatment PET/CT in peripheral T-cell lymphomas: a review of 124 patients. Am J Hematol 90:975–980.
29. Luminari S, Skrypets T. What's new in peripheral T-cell lymphomas. Hematol Oncol. 2021 Jun;39 Suppl 1(Suppl 1):52-60. doi: 10.1002/hon.2846. PMID: 34105820; PMCID: PMC8251564.
30. d'Amore, F., Gaulard, P., Trumper, L., Corradini, P., Kim, W.S., Specht, L., Bjerregaard Pedersen, M. & Ladetto, M. (2015) Peripheral T-cell lymphomas: ESMO Clinical Practice Guidelines for diagnosis
31. Abouyabis AN, Shenoy PJ, Sinha R, Flowers CR, Lechowicz MJ. A Systematic Review and Meta-Analysis of Front-line Anthracycline-Based Chemotherapy Regimens for Peripheral T-Cell Lymphoma. *ISRN Hematol*. 2011;2011:623924. doi:10.5402/2011/623924
32. Schmitz N, Trumper L, Ziepert M,et al.Treatment and prognosis of matureT-cell and NK cell lymphoma: ananalysis of patients with T-cell lymphoma treated in studies of the German High-Grade Non-Hodgkin Lymphoma Study Group. Blood. 2010;116(18):3418-3425.

33. Lage LA de PC, Cabral TCDS, Costa R de O, et al: Primary nodal peripheral T-cell lymphomas: diagnosis and therapeutic considerations. Rev Bras Hematol Hemoter 37:277–84
34. Dearden CE, Johnson R, Pettengell R, et al: Guidelines for the management of mature T-cell and NK-cell neoplasms (excluding cutaneous T-cell lymphoma). Br J Haematol 153:451–85, 2011
35. Karakas T, Bergmann L, Stutte HJ, et al: Peripheral T-cell lymphomas respond well to vincristine, adriamycin, cyclophosphamide, prednisone and etoposide (VACPE) and have a similar outcome as high-grade B-cell lymphomas. Leuk Lymphoma 24:121–9, 1996
36. Wulf GG, Altmann B, Ziepert M, D'Amore F, Held G, Greil R, Tournilhac O, Relander T, Viardot A, Wilhelm M, Wilhelm C, Pezzutto A, Zijlstra JM, Neste EVD, Lugtenburg PJ, Doorduijn JK, Gelder MV, van Imhoff GW, Zettl F, Braulke F, Nickelsen M, Glass B, Rosenwald A, Gaulard P, Loeffler M, Pfreundschuh M, Schmitz N, Trümper L; ACT-2 study investigators. Alemtuzumab plus CHOP versus CHOP in elderly patients with peripheral T-cell lymphoma: the DSHNHL2006-1B/ACT-2 trial. Leukemia. 2021 Jan;35(1):143-155. doi: 10.1038/s41375-020-0838-5. Epub 2020 May 7. PMID: 32382083.
37. Horwitz S, O'Connor OA, Pro B, et al. Brentuximab vedotin with chemotherapy for CD30-positive peripheral T-cell lymphoma (ECHELON-2): a global, double-blind, randomised, phase 3 trial. *Lancet*. 2019;393(10168):229–240.
38. Bachy E, Camus V, Thieblemont C, et al. Final analysis of the Ro-CHOP Phase III (conducted by LYSA): Romidepsin plus CHOP in patients with peripheral T-cell lymphoma. Presented at: 62nd American Society of Hematology (ASH) Annual Meeting and Exposition; December 5-9, 2020. Abstract 39.
39. https://www.nccn.org/professionals/physician_gls/pdf/t-cell_blocks.pdf
40. Corradini P, Tarella C, Zallio F, et al. Long-term follow-up of patients with peripheral T-cell lymphomas treated up-front with high-dose chemotherapy followed by autologous stem cell transplantation. *Leukemia*. 2006; **20**: 1533- 1538.
41. Kyriakou C, Canals C, Goldstone A, et al. High-dose therapy and autologous stem-cell transplantation in angioimmunoblastic lymphoma: complete remission at transplantation is the major determinant of Outcome-Lymphoma Working Party of the European Group for Blood and Marrow Transplantation. J Clin Oncol 2008;26(2):218–24.
42. Rodriguez J, Conde E, Gutierrez A, et al. The adjusted International Prognostic Index and beta-2-microglobulin predict the outcome after autologous stem cell transplantation in relapsing/refractory peripheral T-cell lymphoma. *Haematologica*. 2007; **92**: 1067- 1074.
43. Stiff PJ, Unger JM, Cook JR, et al. Autologous transplantation as consolidation for aggressive non-Hodgkin's lymphoma. *N Engl J Med*. 2013; **369**: 1681- 1690.
44. Mounier N, Gisselbrecht C, Briere J, et al. Prognostic factors in patients with aggressive non-Hodgkin's lymphoma treated by front-line autotransplantation after complete remission: a cohort study by the Groupe d'Etude des Lymphomes de l'Adulte. *J Clin Oncol*. 2004; **22**: 2826- 2834.
45. Mounier N, Gisselbrecht C, Briere J, et al. All aggressive lymphoma subtypes do not share similar outcome after front-line autotransplantation: a matched-control analysis by the Groupe d'Etude des Lymphomes de l'Adulte (GELA). *Ann Oncol*. 2004; **15**: 1790- 1797.
46. d'Amore, F., Relander, T., Lauritzsen, G.F., Jantunen, E., Hagberg, H., Anderson, H., Holte, H., Osterborg, A., Merup, M., Brown, P., Kuittinen, O., Erlanson, M., Ostenstad,

B., Fagerli, U.M., Gadeberg, O.V., Sundstrom, C., Delabie, J., Ralfkiaer, E., Vornanen, M. & Toldbod, H.E.(2012) Up-front autologous stem-cell transplantation in peripheral T-cell lymphoma: NLG-T- 01. Journal of Clinical Oncology, 30, 3093–3099.

47. Reimer P, Schertlin T, Rüdiger T, et al. Myeloablative radiochemotherapy followed by autologous peripheral blood stem cell transplantation as first-line therapy in peripheral T-cell lymphomas: first results of a prospective multicenter study. *Hematol J*. 2004;5(4):304-311. doi:10.1038/sj.thj.6200359
48. Ellin F, Landström J, Jerkeman M, Relander T. Real-world data on prognostic factors and treatment in peripheral T-cell lymphomas: a study from the Swedish Lymphoma Registry. Blood. 2014 Sep 4;124(10):1570–7.
49. Fossard G, Broussais F, Coelho I, et al. Role of up-front autologous stem-cell transplantation in peripheral T-cell lymphoma for patients in response after induction: an analysis of patients from LYSA centers. *Ann Oncol*. 2018;29(3):715-723. doi:10.1093/annonc/mdx787
50. Park, S.I., Horwitz, S.M., Foss, F.M. et al. (2019). The role of autologous stem cell transplantation in patients with nodal peripheral T-cell lymphomas in first complete remission: report from COMPLETE, a prospective, multicenter cohort study. *Cancer* 125 (9): 1507–1517.
51. Horwitz S, O'Connor OA, Pro B, et al. The ECHELON-2 Trial: 5-year results of a randomized, phase III study of brentuximab vedotin with chemotherapy for CD30-positive peripheral T-cell lymphoma. Ann Oncol 2021.
52. Schmitz N, Truemper LH, Bouabdallah K, Ziepert M, Leclerc M, Cartron G, Jaccard A, Reimer P, Wagner-Drouet EM, Wilhelm M, Sanhes L, Lamy T, de Leval L, Rosenwald A, Roussel M, Kroschinsky FP, Lindemann WW, Dreger P, Viardot A, Milpied NJ, Gisselbrecht C, Wulf GG, Gyan E, Gaulard P, Bay JO, Glass B, Poeschel V, Damaj G, Sibon D, Delmer AJ, Bilger K, Banos A, Haenel M, Dreyling M, Metzner B, Keller U, Braulke F, Friedrichs B, Nickelsen M, Altmann B, Tournilhac O. A randomized phase 3 trial of auto vs. allo transplantation as part of first-line therapy in poor-risk peripheral T-NHL. Blood. 2020 Dec 17:blood.2020008825. doi: 10.1182/blood.2020008825. Epub ahead of print. PMID: 33512419.
53. Rashidi A, Cashen AF. Outcomes of allogeneic stem cell transplantation in hepatosplenic T-cell lymphoma. *Blood Cancer J*. 2015;5(6):e318. Published 2015 Jun 5. doi:10.1038/bcj.2015.43
54. Mak V, Hamm J, Chhanabhai M, et al. Survival of patients with peripheral T-cell lymphoma after first relapse or progression: spectrum of disease and rare long-term survivors. *J Clin Oncol*. 2013;31(16):1970-1976. doi:10.1200/JCO.2012.44.7524
55. Dreyling M, Thieblemont C, Gallamini A, et al: ESMO Consensus conferences: guidelines on malignant lymphoma. part 2: marginal zone lymphoma, mantle cell lymphoma, peripheral T-cell lymphoma. Ann Oncol Off J Eur Soc Med Oncol 24:857–77, 2013
56. Jerkeman M, Leppä S, Kvaløy S, et al. ICE (ifosfamide, carboplatin, etoposide) as second-line chemotherapy in relapsed or primary progressive aggressive lymphoma: The Nordic Lymphoma Group experience. *Eur J Haematol*. 2004;73:179–182
57. Philip T, Chauvin F, Armitage J, et al. Parma international protocol: Pilot study of DHAP followed by involved-field radiotherapy and BEAC with autologous bone marrow transplantation. *Blood*. 1991;77:1587–1592.
58. Zelenetz AD, Hamlin P, Kewalramani T, et al. Ifosfamide, carboplatin, etoposide (ICE)-based second-line chemotherapy for the management of relapsed and refractory aggressive non-Hodgkin's lymphoma. *Ann Oncol*. 2003;14(suppl 1):i5–i10.

59. Velasquez WS, McLaughlin P, Tucker S, et al. ESHAP: An effective chemotherapy regimen in refractory and relapsing lymphoma—A 4-year follow-up study. *J Clin Oncol*. 1994;12:1169–1176.
60. Skamene T, Crump M, Savage KJ, Reiman T, Kuruvilla J, Good D, LeBrun D, Meyer RM, Sehn LH, Soulières D, Stakiw J, Laferriere N, Luminari S, Shepherd LE, Djurfeldt M, Zhu L, Chen BE, Hay AE. Salvage chemotherapy and autologous stem cell transplantation for peripheral T-cell lymphoma: a subset analysis of the Canadian Cancer Trials Group LY.12 randomized phase 3 study. Leuk Lymphoma. 2017 Oct;58(10):2319-2327. doi: 10.1080/10428194.2017.1312379. Epub 2017 May 15. PMID: 28504033.
61. Kharfan-Dabaja MA, Kumar A, Ayala E, et al. Clinical Practice Recommendations on Indication and Timing of Hematopoietic Cell Transplantation in Mature T Cell and NK/T Cell Lymphomas: An International Collaborative Effort on Behalf of the Guidelines Committee of the American Society for Blood and Marrow Transplantation. *Biol Blood Marrow Transplant*. 2017;23(11):1826-1838. doi:10.1016/j.bbmt.2017.07.027
62. Kyriakou C, Canals C, Goldstone A, et al. High-dose therapy and autologous stem-cell transplantation in angioimmunoblastic lymphoma: complete remission at transplantation is the major determinant of Outcome-Lymphoma Working Party of the European Group for Blood and Marrow Transplantation. J Clin Oncol 2008;26(2):218–24.
63. Loirat M, ChevallierP, Leux C, et al. Upfront allogeneic stem-cell transplantation for patients with nonlocalized untreated peripheral T-cell lymphoma: an intention to treat analysis from a single center. Ann Oncol 2015;26(2):386–92
64. Smith SM, Burns LJ, van Besien K, et al. Hematopoietic cell transplantation for systemic mature T-cell non-Hodgkin lymphoma. J Clin Oncol 2013;31(25): 3100–9.
65. Exploratory analysis of brentuximab vedotin plus chp (a+chp) as frontline treatment for patients with cd30-expressing peripheral t-cell lymphomas (echelon-2): impact of consolidative stem cell transplant. E-poster, 46th Annual Meeting of the European Society for Blood and Marrow Transplantation (EBMT), 2020
66. 'Connor OA, Falchi L, Lue JK, et al. Oral 5-azacytidine and romidepsin exhibit marked activity in patients with PTCL: A multicenter phase 1 study. *Blood*. 2019;134(17):1395–1405.
67. Steven M. Horwitz, Tatyana A. Feldman, Brian T. Hess, Michael S Khodadoust, Youn H. Kim, Javier Munoz, Manish R Patel, Tycel J. Phillips, Stephen D. Smith, Sonali M. Smith, Ryan A. Wilcox, Andrew Steele, Anjali Pandey, Matt R Birrell, Janet M. Leeds, Pamela B. Conley, Glenn Michelson, Gregory P. Coffey, John T Curnutte, Paul A. Hamlin; The Novel SYK/JAK Inhibitor Cerdulatinib Demonstrates Good Tolerability and Clinical Response in a Phase 2a Study in Relapsed/Refractory Peripheral T-Cell Lymphoma and Cutaneous T-Cell Lymphoma. *Blood*2018; 132 (Supplement 1): 1001. doi: https://doi.org/10.1182/blood-2018-99-119944
68. Horwitz SM, Koch R, Porcu P, et al. Activity of the PI3K-delta,gamma inhibitor duvelisib in a phase 1 trial and preclinical models of T-cell lymphoma. Blood 2018;131:888-98.
69. Lesokhin AM, Ansell SM, Armand P, Scott EC, Halwani A, Gutierrez M, Millenson MM, Cohen AD, Schuster SJ, Lebovic D, Dhodapkar M, Avigan D, Chapuy B, Ligon AH, Freeman GJ, Rodig SJ, Cattry D, Zhu L, Grosso JF, Bradley Garelik MB, Shipp MA, Borrello I, Timmerman J. Nivolumab in Patients With Relapsed or Refractory Hematologic Malignancy: Preliminary Results of a Phase Ib Study. J Clin Oncol. 2016

Aug 10;34(23):2698-704. doi: 10.1200/JCO.2015.65.9789. Epub 2016 Jun 6. PMID: 27269947; PMCID: PMC5019749.
70. Maciocia PM, Wawrzyniecka PA, Philip B, Ricciardelli I, Akarca AU, Onuoha SC, Legut M, Cole DK, Sewell AK, Gritti G, Somja J, Piris MA, Peggs KS, Linch DC, Marafioti T, Pule MA. Targeting the T cell receptor β-chain constant region for immunotherapy of T cell malignancies. Nat Med. 2017 Dec;23(12):1416-1423. doi: 10.1038/nm.4444. Epub 2017 Nov 13. PMID: 29131157.
71. Ahmed Sawas et al., ASH 2020. Abstract 2971 Title: Clinical and Biological Evaluation of the Novel CD30/CD16A Tetravalent Bispecific Antibody (AFM13) in Relapsed or Refractory CD30-Positive Lymphoma with Cutaneous Presentation: A Biomarker Phase Ib/IIa Study (NCT03192202)
72. The-Peripheral T-cell Lymphomas. Owen A. O'Connor (Editor), Won Seog Kim (Editor), Pier L. Zinzani (Editor). Book ISBN 978-1-119-67131-2 May 2021 Wiley-Blackwell 416 Pages. Chapter 26. The value and relevance of T-cell lymphoma registries. T. Skrypets, M. Manni, M. Ciavarella, I. Kriachok, M. Federico. Pages 353-365
73. Watanabe, T., Kinoshita, T., Itoh, K., Yoshimura, K., Ogura, M., Kagami, Y., Yamaguchi, M., Kurosawa, M., Tsukasaki, K., Kasai, M., Tobinai, K., Kaba, H., Mukai, K., Nakamura, S., Ohshima, K., Hotta, T. & Shimoyama, M. (2010) Pretreatment total serum protein is a sig- nificant prognostic factor for the outcome of patients with peripheral T/natural killer-cell lymphomas. Leukemia & Lymphoma, 51, 813– 821.
74. Chihara, D., Oki, Y., Ine, S., Yamamoto, K., Kato, H., Taji, H., Kagami, Y., Yatabe, Y., Nakamura, S. & Morishima, Y. (2009) Analysis of prognos- tic factors in peripheral T-cell lymphoma: prog- nostic value of serum albumin and mediastinal lymphadenopathy. Leukemia & Lymphoma, 50, 1999–2004.
75. Raina, V., Singhal, M.K., Sharma, A., Kumar, L., Kumar, R., Duttagupta, S., Kumar, B. & Das, P. (2010) Clinical characteristics, prognostic fac- tors, and treatment outcomes of 139 patients of peripheral T-cell lymphomas from AIIMS, New Delhi, India. Journal of Clinical Oncology, 28, e18549–e18549.
76. Mantovani, A., Allavena, P., Sica, A. & Balkwill, F. (2008) Cancer-related inflammation. Nature, 454, 436–444.
77. Grivennikov, S.I., Greten, F.R. & Karin, M. (2010) Immunity, inflammation, and cancer. Cell, 140, 883–899.
78. Gu, L., Li, H., Chen, L., Ma, X., Li, X., Gao, Y., Zhang, Y., Xie, Y. & Zhang, X. (2016) Prognos- tic role of lymphocyte to monocyte ratio for patients with cancer: evidence from a systematic review and meta-analysis. Oncotarget, 7, 31926– 31942.
79. Cengiz, F.P., Emiroglu, N., Ozkaya, D.B., Bahali, A.G., Su, O. & Onsun, N. (2017) Prognostic evaluation of neutrophil/lymphocyte ratio in patients with mycosis fungoides. Annals of Clini- cal and Laboratory Science, 47, 25–28.
80. Beltran, B.E., Aguilar, C., Quin~ones, P., Morales, D., Chavez, J.C., Sotomayor, E.M. & Castillo, J.J. (2016) The neutrophil-to-lymphocyte ratio is an independent prognostic factor in patients with peripheral T-cell lymphoma, unspecified. Leukemia & Lymphoma, 57, 58–62.
81. Tsuchiya, T., Ohshima, K., Karube, K., Yamaguchi, T., Suefuji, H., Hamasaki, M., Kawasaki, C., Suzumiya, J., Tomonaga, M. & Kikuchi, M. (2004) Th1, Th2, and activated T-cell marker and clinical prognosis in peripheral T-cell lym- phoma, unspecified: comparison with AILD, ALCL, lymphoblastic lymphoma, and ATLL. Blood, 103, 236–241.
82. Advani RH, Skrypets T, Civallero M, Spinner MA, Manni M, Kim WS, Shustov AR, Horwitz SM, Hitz F, Cabrera ME, Dlouhy I, Vassallo J, Pileri SA, Inghirami G, Montoto

S, Vitolo U, Radford J, Vose JM, Federico M. Outcomes and prognostic factors in angioimmunoblastic T-cell lymphoma: final report from the international T-cell Project. Blood. 2021 Jul 22;138(3):213-220. doi: 10.1182/blood.2020010387. PMID: 34292324; PMCID: PMC8493974.
83. Shipp MA, Harrington DP, Anderson JR, et al. A Predictive Model for Aggressive Non-Hodgkin's Lymphoma. *N Engl J Med.* 1993;329(14):987–994.
84. Federico M, Rudiger T, Bellei M, et al. Clinicopathologic characteristics of angioimmunoblastic T-cell lymphoma: Analysis of the International Peripheral T-cell Lymphoma Project. *J Clin Oncol.* 2013;31(2):240–246.
85. Lunning MA, Vose JM. Angioimmunoblastic T-cell lymphoma: The many-faced lymphoma. *Blood*. 2017;129(9):1095–1102.
86. Yabe M, Dogan A, Horwitz SM, Moskowitz AJ. Angioimmunoblastic T-Cell lymphoma. *Cancer Treat Res.* 2019;176:99–126.
87. Mourad N, Mounier N, Brière J, et al. Clinical, biologic, and pathologic features in 157 patients with angioimmunoblastic T-cell lymphoma treated within the Groupe d'Etude des Lymphomes de l'Adulte (GELA) trials. *Blood*. 2008;111(9):4463–4470.
88. El-Asmar J, Reljic T, Ayala E, et al. Efficacy of High-Dose Therapy and Autologous Hematopoietic Cell Transplantation in Peripheral T Cell Lymphomas as Front-Line Consolidation or in the Relapsed/Refractory Setting: A Systematic Review/Meta-Analysis. *Biol Blood Marrow Transplant.* 2016;22(5):802–814.
89. Shang Y, Fu X, Chang Y, Li Y, Zhang M. B2 microglobulin is a novel prognostic marker of Angioimmunoblastic T-cell lymphoma. *Sci Rep.* 2018;8(1):12907.
90. Wudhikarn K, Bunworasate U, Julamanee J, et al. Event free survival at 24 months is a strong surrogate prognostic endpoint of peripheral T cell lymphoma. *Hematol Oncol.* 2019;37(5):578–585.
91. Gleeson M, Peckitt C, To YM, et al. CHOP versus GEM-P in previously untreated patients with peripheral T-cell lymphoma (CHEMO-T): a phase 2, multicentre, randomised, open-label trial. *Lancet Haematol.* 2018;5:e190-200.
92. Horwitz S, O'Connor OA, Pro B, et al. Brentuximab vedotin with chemotherapy for CD30-positive peripheral T-cell lymphoma (ECHELON-2): a global, double-blind, randomised, phase 3 trial. *Lancet*. 2019;393(10168):229–240.
93. Cairns RA, Iqbal J, Lemonnier F, et al. IDH2 mutations are frequent in angioimmunoblastic T-cell lymphoma. *Blood*. 2012;119(8):1901–1903.
94. Sakata-Yanagimoto M, Enami T, Yoshida K, et al. Somatic RHOA mutation in angioimmunoblastic T cell lymphoma. *Nat Genet.* 2014;46(2):171–175.
95. Odejide O, Weigert O, Lane AA, et al. A targeted mutational landscape of angioimmunoblastic T-cell lymphoma. *Blood*. 2014;123(9):1293–1296.
96. Ghione P, Faruque P, Mehta-Shah N, et al. T follicular helper phenotype predicts response to histone deacetylase inhibitors in relapsed/refractory peripheral T-cell lymphoma. *Blood Adv.* 2020;4(19):4640–4647.
97. Ahmed N, Feldman AL. Targeting epigenetic regulators in the treatment of T-cell lymphoma. *Expert Rev Hematol.* 2020;13(2):127–139.
98. Lemonnier F, Dupuis J, Sujobert P, et al. Treatment with 5-azacytidine induces a sustained response in patients with angioimmunoblastic T-cell lymphoma. *Blood.* 2018;132(21):2305–2309.
99. Dupuis J, Morschhauser F, Ghesquières H, et al. Combination of romidepsin with cyclophosphamide, doxorubicin, vincristine, and prednisone in previously untreated patients with peripheral T-cell lymphoma: A non-randomised, phase 1b/2 study. *Lancet Haematol.* 2015;2(4):e160–e165.

100. Shustov A, Cabrera ME, Civallero M, Bellei M, Ko YH, Manni M, Skrypets T, Horwitz SM, De Souza CA, Radford JA, Bobillo S, Prates MV, Ferreri AJM, Chiattone C, Spina M, Vose JM, Chiappella A, Laszlo D, Marino D, Stelitano C, Federico M. ALK-negative anaplastic large cell lymphoma: features and outcomes of 235 patients from the International T-Cell Project. Blood Adv. 2021 Feb 9;5(3):640-648. doi: 10.1182/bloodadvances.2020001581. PMID: 33560375; PMCID: PMC7876884.
101. Adams SV, Newcomb PA, Shustov AR. Racial patterns of peripheral T-cell lymphoma incidence and survival in the UnitedStates. J Clin Oncol. 2016; 34(9):963-971.
102. Dunleavy K, Pittaluga S, Shovlin M, et al. Phase II trial of dose-adjusted EPOCH in untreated systemic anaplastic large cell lymphoma. Haematologica. 2016;101(1):e27-e29.
103. Parrilla Castellar ER, Jaffe ES, Said JW, et al. ALK-negative anaplastic large cell lymphoma is a genetically heterogeneousdisease with widely disparate clinical outcomes. Blood. 2014;124(9):1473-1480.
104. Vasmatzis G, Johnson SH, Knudson RA, et al. Genome-wide analysis reveals recurrent structural abnormalities of TP63and other p53-related genes in peripheral T-cell lymphomas. Blood. 2012;120(11):2280-2289.
105. Jaffe ES HN, Stein H, Vardiman JW. WHO classification of Tumours of Haematopoietic and Lymphoid Tissues: Pathology and Genetics. Lyon, France. IARC Press 2001.
106. Savage KJ, Harris NL, Vose JM, et al. ALK- anaplastic large-cell lymphoma is clinically and immunophenotypically different from both ALK+ ALCL and peripheral T-cell lymphoma, not otherwise specified: report from the International Peripheral T-Cell Lymphoma Project. Blood 2008;111:5496-504.
107. Sibon D, Fournier M, Briere J, et al. Long-term outcome of adults with systemic anaplastic large-cell lymphoma treated within the Groupe d'Etude des Lymphomes de l'Adulte trials. J Clin Oncol 2012;30:3939-46.
108. Zing NPC, Fischer T, Zain J, Federico M, Rosen ST. Peripheral T-Cell Lymphomas: Incorporating New Developments in Diagnostics, Prognostication, and Treatment Into Clinical Practice-PART 1: PTCL-NOS, FTCL, AITL, ALCL. Oncology (Williston Park) 2018;32:e74-e82.
109. Gambacorti Passerini C, Farina F, Stasia A, et al. Crizotinib in advanced, chemoresistant anaplastic lymphoma kinase-positive lymphoma patients. J Natl Cancer Inst 2014;106:djt378.
110. Werner MT, Zhang Q, Wasik MA. From Pathology to Precision Medicine in Anaplastic Large Cell Lymphoma Expressing Anaplastic Lymphoma Kinase (ALK+ ALCL). Cancers (Basel) 2017;9.
111. Chiarle R, Voena C, Ambrogio C, Piva R, Inghirami G. The anaplastic lymphoma kinase in the pathogenesis of cancer. Nat Rev Cancer 2008;8:11-23.
112. Astone G CL, Chiu W, Kayembe C, Wang R, Yang B, Sharma K, Dey J, Karnik R, Brambilla L, Levy D, Yoffe L, Boccalatte F, Hernaez JR, Tsirigos A, Zumbo P, Betel D, Verma A, Elemento O, Cumerlato M, Piva R, Horwitz SM, Epstein-Peterson ZD, Gollob J, DeSavi C, Liu PCC, Inghirami G. Selective STAT3 Degraders Dissect Peripheral T-Cell Lymphomas Vulnerabilities Empowering Personalized Regimens. Blood 2021;138 865.
113. Horwitz SM, Koch R, Porcu P, et al. Activity of the PI3K-delta,gamma inhibitor duvelisib in a phase 1 trial and preclinical models of T-cell lymphoma. Blood 2018;131:888-98.
114. Bai L, Zhou H, Xu R, et al. A Potent and Selective Small-Molecule Degrader of STAT3 Achieves Complete Tumor Regression In Vivo. Cancer Cell 2019;36:498-511 e17.

115.Fox CP, Civallero M, Ko YH, Manni M, Skrypets T, Pileri S, Kim SJ, Cabrera ME, Shustov AR, Chiattone CS, Horwitz SM, Dlouhy I, Spina M, Hitz F, Montoto S, Nagler A, Martinez V, De Souza CA, Fernandez-Alvarez R, Ballova V, Gabús R, Inghirami G, Federico M, Kim WS. Survival outcomes of patients with extranodal natural-killer T-cell lymphoma: a prospective cohort study from the international T-cell Project. Lancet Haematol. 2020 Apr;7(4):e284-e294. doi: 10.1016/S2352-3026(19)30283-2. Epub 2020 Feb 24. PMID: 32105608.
116. Kim SJ, Yoon DH, Jaccard A, et al. A prognostic index for natural killer cell lymphoma after non-anthracycline-based treatment:a multicentre, retrospective analysis. *Lancet Oncol* 2016; **17:** 389–400.
117. Yamaguchi M, Suzuki R, Oguchi M, et al. Treatments and outcomes of patients with extranodal natural killer/T-cell lymphoma diagnosed between 2000 and 2013: a cooperative study in Japan. *J Clin Oncol* 2017; **35:** 32–39.
118. Au WY, Weisenburger DD, Intragumtornchai T, et al. Clinical differences between nasal and extranasal natural killer/T-cell lymphoma: a study of 136 cases from the International Peripheral T-Cell Lymphoma Project. *Blood* 2009; **113:**393137.
119. Yamaguchi M, Kwong Y-L, Kim WS, et al. Phase II study of SMILE chemotherapy for newly diagnosed stage IV, relapsed, or refractory extranodal natural killer (NK)/T-cell lymphoma, nasal type:the NK-Cell Tumor Study Group study. *J Clin Oncol* 2011; **29:** 4410–16.
120.Jaccard A, Gachard N, Marin B, et al. Efficacy of L-asparaginase with methotrexate and dexamethasone (AspaMetDex regimen) in patients with refractory or relapsing extranodal NK/T-cell lymphoma, a phase 2 study. *Blood* 2011; **117:** 1834–39.
121. Lai J, Zhu YY, Ruan M, Chen L, Zhang QY. Local irradiation sensitized tumors to adoptive T cell therapy via enhancing the cross-priming, homing, and cytotoxicity of antigen-specific CD8 T cells. *Front Immunol* 2019; **10:** 2857.
122.Yamaguchi M, Suzuki R, Miyazaki K, et al. Improved prognosis of extranodal NK/T cell lymphoma, nasal type of nasal origin but not extranasal origin. *Ann Hematol* 2019; **98:** 1647–55.
123. Chan TSY, Li J, Loong F, Khong P-L, Tse E, Kwong Y-L. PD1 blockade with low-dose nivolumab in NK/T cell lymphoma failing L-asparaginase: efficacy and safety. *Ann Hematol* 2018; **97:** 193–96.
124.Reck M, Rodríguez-Abreu D, Robinson AG, et al. Pembrolizumab versus chemotherapy for PD-L1-positive non-small-cell lung cancer. *N Engl J Med* 2016; **375:** 1823–33.
125.Carson, K.,.R., Horwitz, S.M., Pinter-Brown, L.C. et al. (2017). A prospective cohort study of patients with peripheral T-cell lymphoma in the United States. *Cancer* 123 (7): 1174–1183.
126. Stuver, R.N., Khan, N., Schwartz, M. et al. (2019). Single agents vs combination chemotherapy in relapsed and refractory peripheral T-cell lymphoma: results from the Comprehensive Oncology Measures for Peripheral T-Cell Lymphoma Treatment (COMPLETE) registry. *Am J Hematol* 94 (6): 641–649.
127.Lansigan, F., Horwitz, S.M., Pinter-Brown, L.C. et al. (2020). Outcomes for relapsed and refractory peripheral T-cell lymphoma patients after front-line therapy from the COMPLETE registry. *Acta Haematol* 143 (1): 40–50.
128.Bellei, M., Nabhan, C., Pesce, E.A. et al. (2015). The value and relevance of the T cell lymphoma registries and international collaborations: the case of COMPLETE and the T-cell project. *Curr Hematol Malig Rep* 10 (4): 448–455.

129. Hsi, E.D., Horwitz, S.M., Carson, K.R. et al. (2017). Analysis of peripheral T-cell lymphoma diagnostic workup in the United States. *Clin Lymphoma Myeloma Leuk* 17 (4): 193–200.
130. Park, S.I., Horwitz, S.M., Foss, F.M. et al. (2019). The role of autologous stem cell transplantation in patients with nodal peripheral T-cell lymphomas in first complete remission: report from COMPLETE, a prospective, multicenter cohort study. *Cancer* 125 (9): 1507–1517.