



Allotransplant setting in CTCL European perspective

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T-Cell Lymphomas, Bologna April 27-29, 2015

Background

Allogeneic Stem Cell Transplantation for advanced CTCL

➤ **Duvic, JCO 2010: 19 MF/SS patients**

- Total skin electrontherapy + non-myeloablative conditioning
- Median follow-up: 19 months
- 6 deaths (median OS not reached), 8 relapses
- 2 year-OS: 79%, PFS: 53%

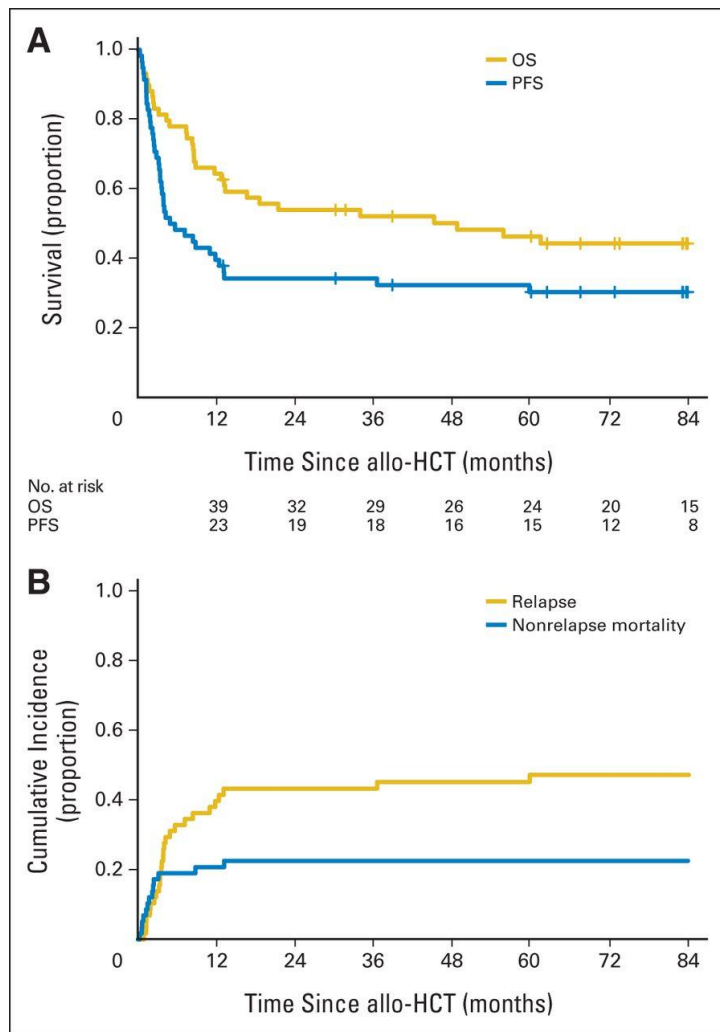
➤ **Duarte, JCO 2010: 60 MF/SS patients (36 MF/24 SS)**

- Median follow-up: 3 years
- 1 year OS: 66%
- 3 year-OS: 54% (median OS not reached), 3 year-PFS: 34%

➤ **Duarte, JCO 2014: 60 MF/SS patients (36 MF/24 SS)**

- Extended analysis with a median follow-up in survivors of 7 years
- 5 year OS: 46%, 7 year OS: 44%
- 5 year PFS: 32%, 7 year PFS: 30%
- Myeloablative conditioning associated with poorer NRM (non relapse mortality) and OS

(A) Long-term probability of overall survival (OS) and progression-free survival (PFS), and (B) cumulative incidence of nonrelapse mortality and disease relapse or progression after allogeneic hematopoietic cell transplantation in patients with mycosis fungoides



Background

Allogeneic Stem Cell Transplantation for advanced CTCL

➤ Lechowicz MJ, Bone Marrow Transplantation 2014:

- 129 MF/SS patients
- NRM at 1 year: 19%, at 5 years: 22%
- Risk of disease progression at 1 year: 50%, at 5 years: 61%
- PFS at 1 year: 31%, PFS at 5 year: 17%
- OS at 1 year: 54%, OS at 5 year: 32%

Methods

- **Retrospective multicentric study: 18 centers**
(Paris, Créteil, Bordeaux, Marseille, Montpellier, Limoges, Besançon, Clermont-Ferrand, Lyon, Caen, Rennes, Rouen, Nantes, Angers, Tours, Poitiers, Lille, Liège)
- **Inclusion criteria**
 - Advanced CTCL
 - Allogeneic Stem Cell Transplantation
- **Study of**
 - Overall Survival (OS)
 - Progression Free Survival (PFS)
 - Relapse or Progression (REL)
 - Treatment Related Mortality (TRM)
- **Factors influencing** OS, PFS, REL and TRM

Patients, allogeneic stem cell transplant

- **Inclusion of 37 patients**
- **31 MF/SS**
 - 26 MF, including 20 transformed MF
 - 5 SS, not transformed

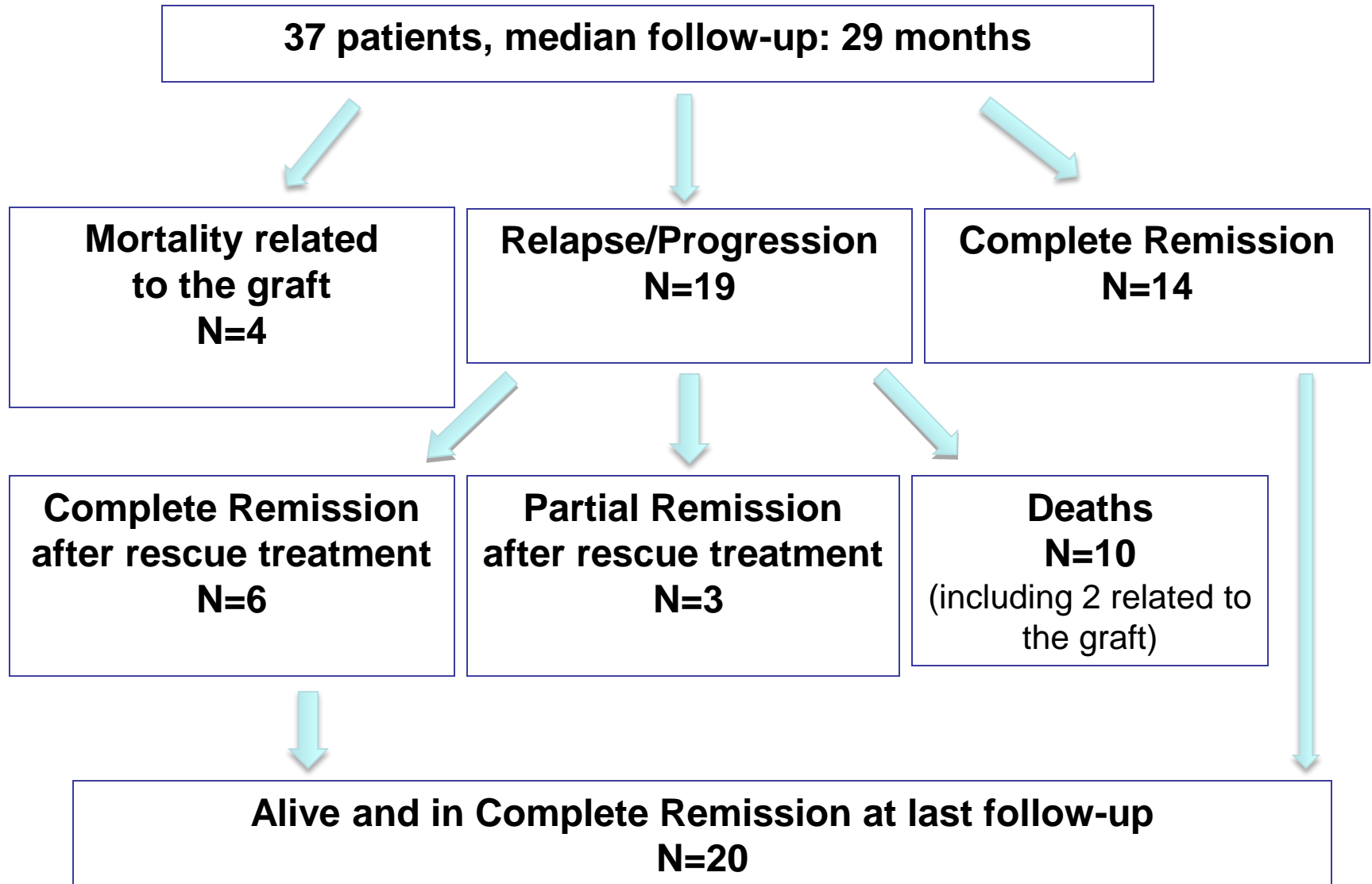
 - Stage II-III (n=13)
 - Stage IV (n=18)
- **6 Non MF/SS**
 - 5 CD30+ Large T-cell lymphomas with disseminated nodal/visceral involvement
 - 1 PCTCL-NOS

 - Stage N2/N3 (n=3)
 - Stage M1 (n=3)

Allogeneic stem cell transplant

- **Median number of systemic treatments before allograft:**
5 (2-11)
- **Status of disease before the graft:**
 - Complete Response (CR) or Very Good Partial Response (VGPR):
n=18
 - Partial Response (PR), Stable Disease (SD) or Progressive Disease):
n=19
- **Conditioning:**
 - Reduced Intensity Conditioning (RIC): n=25
 - Myeloablative Conditioning (MAC): n=12
- **Donor:**
 - Sibling donor: n=17
 - Phenotypical unrelated donor: n=20
- **In vivo T-cell depletion with Antithymocyte globulin:**
16 patients

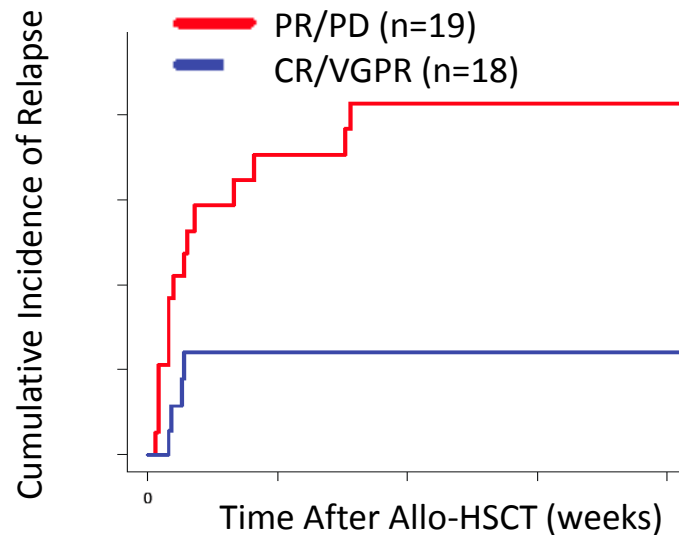
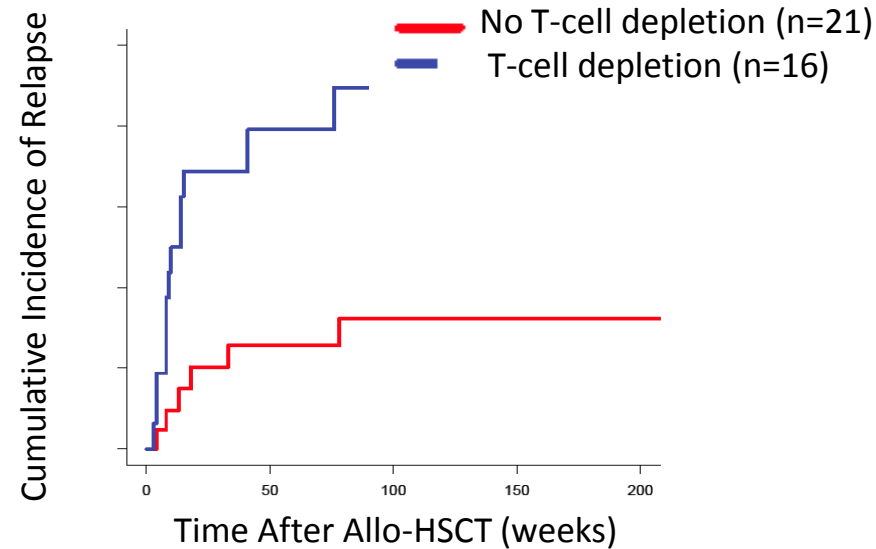
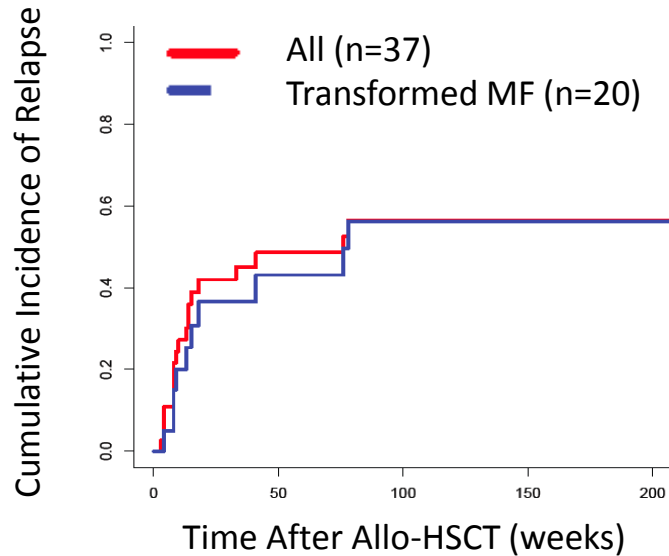
Evolution after allo-SCT



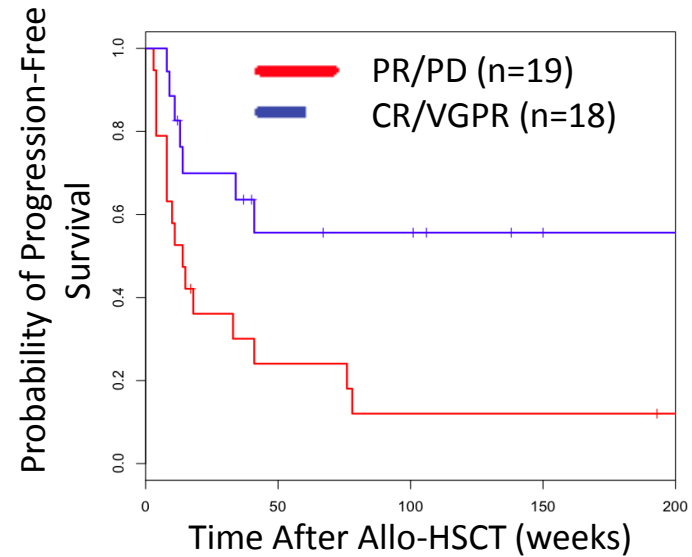
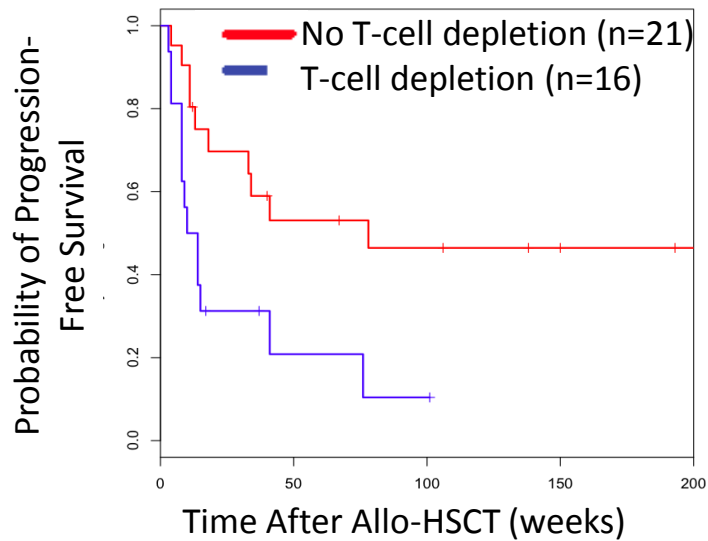
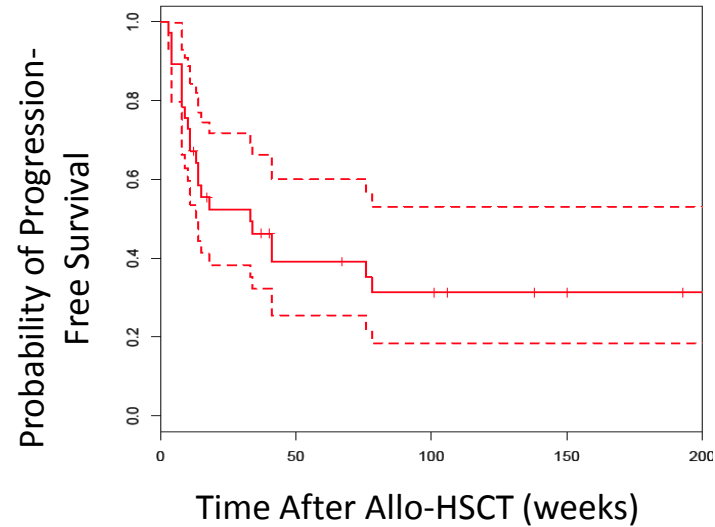
Uni and multivariate analyses

	TRM (%)		REL (%)		PFS (%)		OS (%)	
	1 Year	2 Years	1 Year	2 Years	1 Year	2 Years	1 Year	2 Years
All	18	18	49	56	39	31	65	57
Age of the recipient								
<50 yrs	15	15	43	49	47	41	76	68
>50 yrs	23	23	59	67	25	16	46	39
p	NS		NS (p=0.06)		0.03 (0.1*)		NS (p=0.05)	
Disease type								
T-MF	22	22	43	56	39	26	66	60
Other PCTCL	13	13	55	55	39	39	63	52
p	NS		NS		NS		NS	
Disease status at allo-HSCT								
VGPR or CR	26	26	24	24	56	56	74	74
PR, SD or PD	11	11	71	83	24	12	56	43
p	NS		0.004 (0.03*)		0.01 (0.2*)		NS (p=0.1)	
T-cell depletion								
Yes	0	0	79	79	21	10	66	44
No	32	32	26	32	53	46	63	63
p	0.02		0.002 (0.02*)		0.01 (0.04*)		NS	

Cumulative incidence curves of TRM

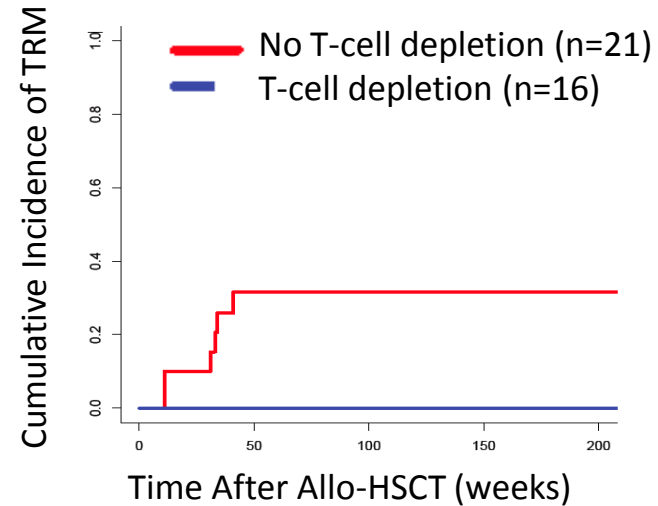
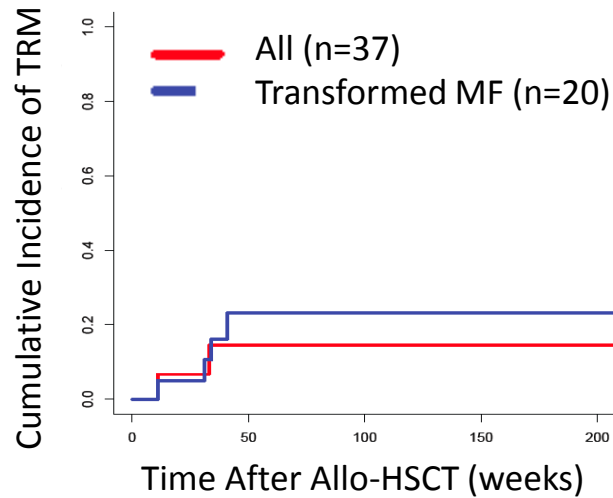


Progression Free Survival (PFS)

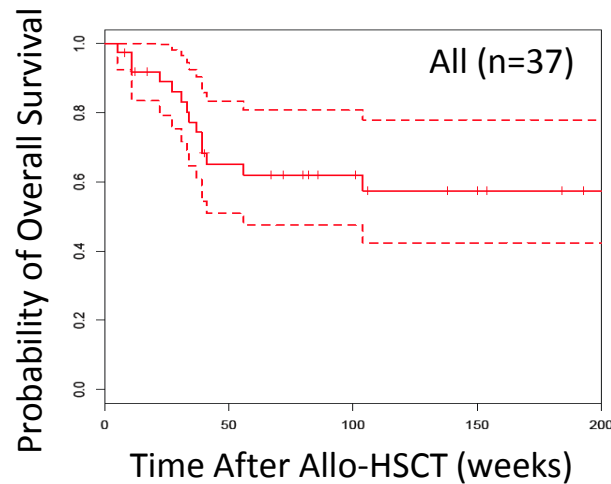


Treatment Related Mortality / Overall Survival

TRM



OS



Conclusions

- Interesting results of allogeneic SCT for the treatment of advanced CTCL: Graft versus Leukemia effect
- After a median follow-up of 29 months, 19 patients relapsed, leading to a 2-year incidence of relapse of 56%
- Estimated 2-year OS was 57% and PFS 31%
- 3-year PFS higher
 - in patients with pre-transplant CR or VGPR (56%)
 - in patients who did not receive T-cell depletion with ATG (46%)
- 6 of 19 patients with post-transplant relapse achieved subsequent CR after salvage therapy, with a median duration of 41 months

Limits and Perspectives

- **Limits of the study**
 - Retrospective
 - Small patient numbers
 - Insufficient follow-up (Chronic GVH ?)
- **Remaining questions**
 - Improvement of Overall Survival ?
 - Improvement of Quality of Life ?
 - Best patients and optimal timing of allogeneic transplantation
- **Perspective: National prospective controlled study**
 - Patients included at the time of donor search
 - Comparison of patients treated with reduced intensity allo-SCT and patients treated with chemotherapy

Inclusion criteria

Patients eligibility criteria

- Age ≥ 18 and ≤ 65 ans
- Histopathologically confirmed diagnosis of ISCL-EORTC stage IIB-IVB CTCL
- Complete or very good partial response of the lymphoma disease (as defined by the international ISCL/EORTC criteria) at the time of registration
- Written informed consent given by the patient
- Contraception in women of childbearing age
- Search for an allogeneic BMT donor in progress or realized

And at least one of the following criteria

- Refractoriness or early relapse (i.e., within one year) after at least one line of systemic chemotherapy (PUVA, ECP, MTX, IFN, and retinoids)
- Early histological large-cell transformation, *i.e.*, within 2 years following diagnosis
- Histologically proven nodal (ISCL-EORTC N3) or extracutaneous visceral involvement by the lymphoma

Exclusion criteria

- Prior allogeneic HSCT
- Other evolutive neoplastic disease or evolutive psychotic disease
- Left ventricular ejection fraction < 50% (as determined by trans-thoracic echocardiography)
- Carbone monoxide diffusion capacity < 50% of the theoretical value
- Creatinine clearance <50 ml/min
- Transaminases or bilirubin >2-fold the normal value in the absence of liver involvement by the lymphoma
- Patient with no health coverage
- Patient under guardianship or curatorship
- HTLV-1 associated lymphoma

Evaluation criteria

- **Primary endpoint : 3-year PFS using international criteria**
Death or Progression in Skin (mSWAT), Lymph nodes, Blood, Viscera
- **Secondary endpoints :**
 - **Comparative endpoints:**
 - Incidence of **disease relapse**. Relapse in skin, blood or lymph nodes is defined according to ISCL/ EORTC consensus criteria for the assessment of clinical endpoints and response criteria
 - **Non-relapse mortality**, defined as any death not attributable to progression of the lymphoma disease
 - **Overall survival** (time from inclusion to death from any cause).
 - **Biomarkers** at inclusion and 1 year
 - Evaluation of the **quality of life** using the French versions of the Skindex 29 and EORTC-QLQ-C30
 - Evaluation of the **medical costs** (number of hospital days)
 - **In the alloHSCT group only:**
 - Incidence of neutrophil **engraftment** (day and proportion of patients reaching neutrophils $>0.5 \times 10^9/L$); and platelets recovery (day and proportion of patients reaching platelets $> 20 \times 10^9/L$ without transfusion) after transplantation.
 - Incidence and severity of **acute GVHD** (diagnosed and graded according to standard criteria).
 - Incidence and severity of **chronic GVHD** (diagnosed and graded according to NIH criteria).

Plan

ADVANCED STAGE MF/SS
AND
≥ 1 POOR PROGNOSTIC FEATURE
Early (<1 year) relapse after ≥ systemic treatment line
OR early large-cell transformation
OR N3 or M1
AND
PATIENT IS SUITABLE FOR AHSCT
18 to 65 years, no contra-indication to allogeneic HSCT

Information – Consent – Search for a sibling or matched donor for AHSCT

Complete response of the lymphoma

INCLUSION

Sibling or 10/10 HLA-matched donor

NO sibling and NO 10/10 HLA-matched donor

Reduced intensity conditioned AHSCT

NO AHSCT - Other standard treatments

3-year PFS (primary endpoint) - OS and QUALITY OF LIFE (secondary endpoints)

SELECTION
4 MONTHS
INCLUSION *if CR/PR*
15 DAYS
CONDITIONING
if sibling or 10/10 matched unrelated donor available

Name	Surname	Town
BAGOT SOCIE	Martine Gérard	Paris
BARETE NGUYEN	Stéphane Stéphanie	Paris – Pitié
BOCCARA SUAREZ	Olivia Felipe	Paris -Necker
FRANCK MAUBEC	Nathalie Eve	Paris -Cochin
SAIAG	Philippe	Boulogne
ORO CORDONNIER	Saskia Catherine	Créteil
LAROCHE	Liliane	Bobigny
BEYLOT-BARRY MILPIED	Marie Noël	Bordeaux
DEREURE CEBALLOS	Olivier Patrice	Montpellier
JOLY JARDIN	Pascal Fabrice	Rouen
LE CORRE FRANCOIS	Yannick Sylvie	Angers
BLAISE BONNET	Didier Nathalie	Marseille
MORTIER YAKOUB-AGHA	Laurent Ibrahim	Lille
VERNEUIL OUMEDALY	Laurence Reman	Caen
ADAMSKI BERNARD	Henri Marc	Rennes

Name	Surname	Town
MACHET LISSANDRE	Laurent Séverine	Tours
QUEREUX CHEVALLIER	Gaëlle Patrice	Nantes
HAINAUT MAILLARD	Ewa Natacha	Poitiers
MEYER HUYNH	Nicolas Anne	Toulouse
D'INCAN BAY	Michel Jacques Olivier	Clermont-Ferrand
GRANGE DELMER	Florent Alain	Reims
MITCOV LIOURE	Mona Bruno	Strasbourg
AUBIN DECONINCK	François Eric	Besançon
DALLE SALLES	Stéphane Gilles	Lyon
TEMPLIER CAHN	Isabelle Jean-Yves	Grenoble
GIACCHERO ROHRLICH	Damien Pierre-Simon	Nice
CHABY CHARBONNIER	Guillaume Amandine	Amiens
DALAC	Sophie	Dijon



Thank you for your attention