Allotransplant setting in CTCL European perspective

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Background

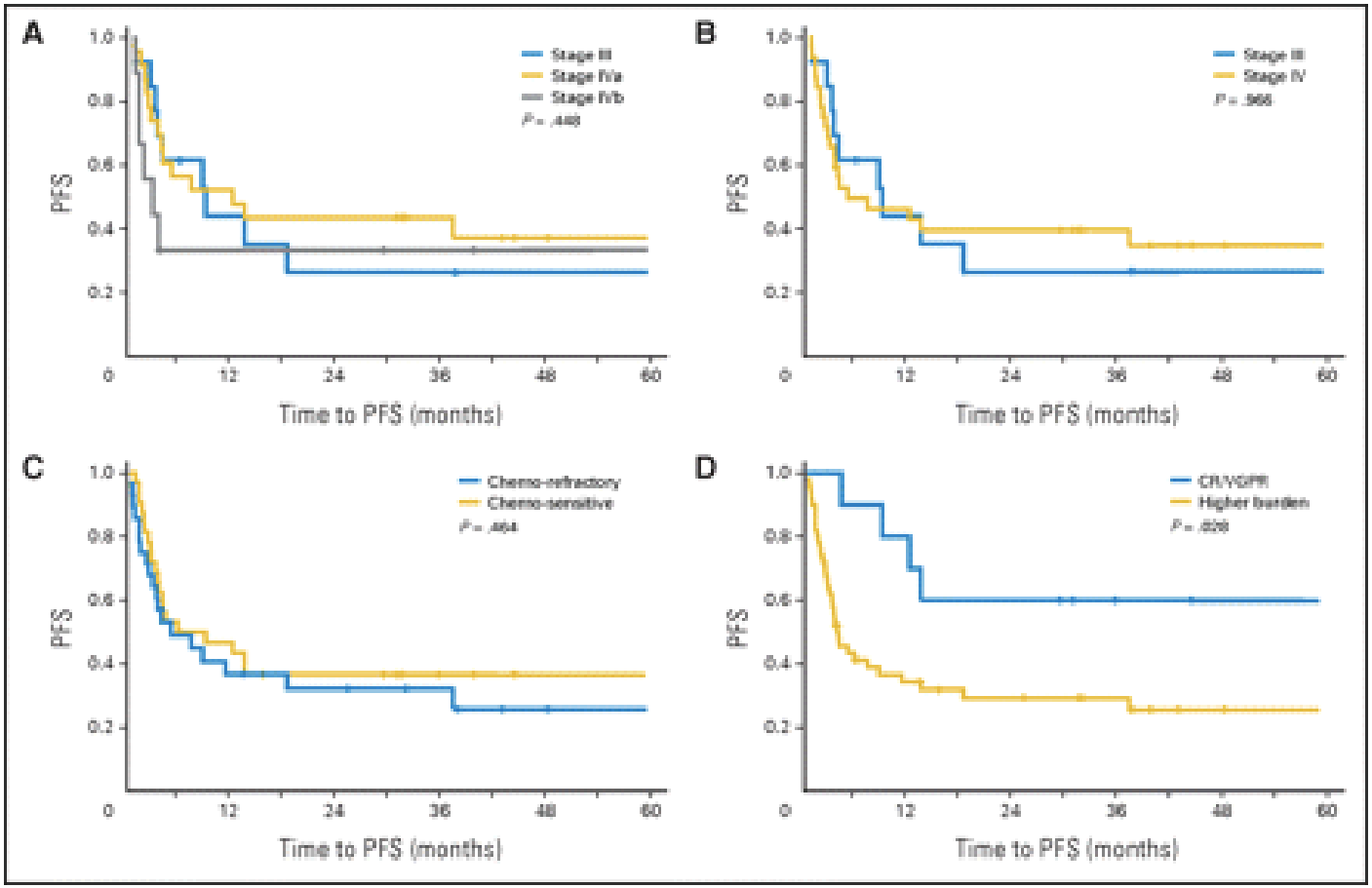
Allogeneic Stem Cell Transplantation for advanced CTCL

- **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%

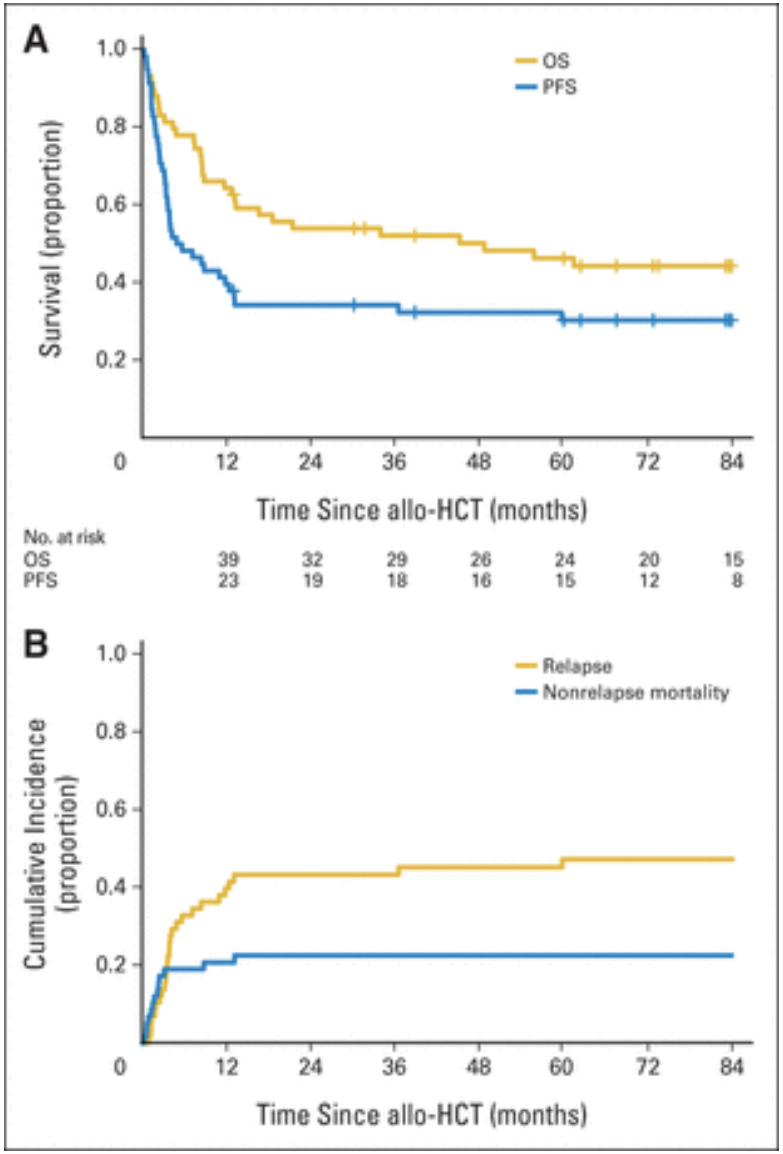
- **Duarte, JCO 2014:** 60 MF/SS patients (36 MF/24 SS)
  - Extended analysis with a median follow-up in survivors of 7 years
  - 5 year OS: 46%, 7 year OS: 44%
  - 5 year PFS: 32%, 7 year PFS: 30%
  - Myeloablative conditioning associated with poorer NRM (non relapse mortality) and OS

Allogeneic SCT for CTCL: Duarte et al, JCO 2010



- PFS is better in patients with **Complete Remission or Very Good Partial Remission**

Allogeneic SCT for CTCL: Duarte et al, JCO 2014



National French Study (2014)

- **Retrospective french multicentric study: 18 centers**

- **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

National French Study (2014)

- **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**

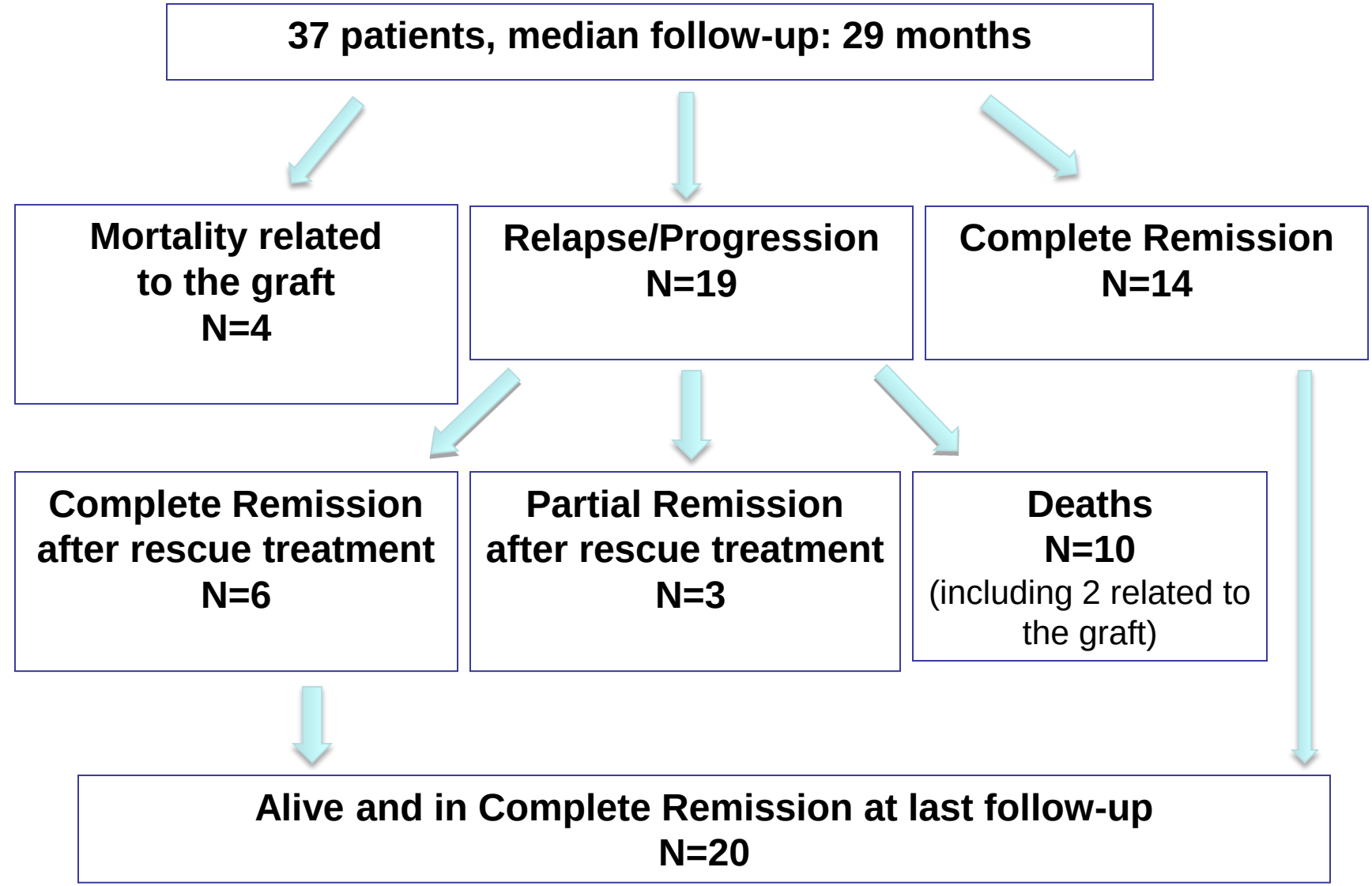
  - 5 CD30+ Large T-cell lymphomas with disseminated nodal/visceral involvement
  - 1 PCTCL-NOS

  - 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
  - Phenoidentical unrelated donor: n=20
- **In vivo T-cell depletion with Antithymocyte globulin:**
  16 patients

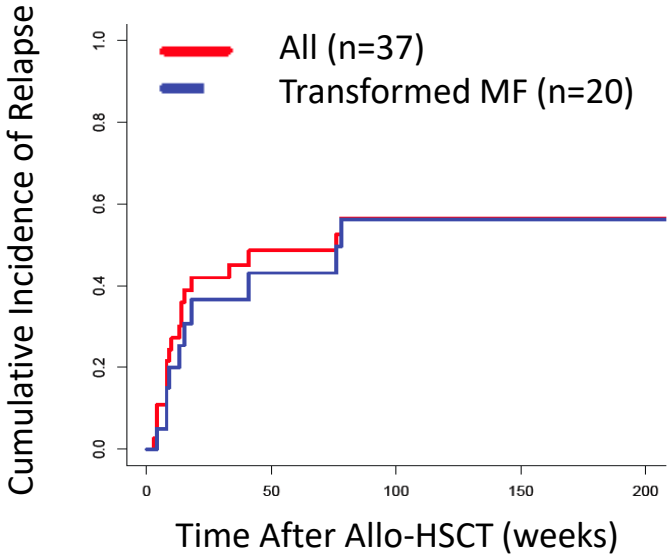
Evolution after allo-SCT

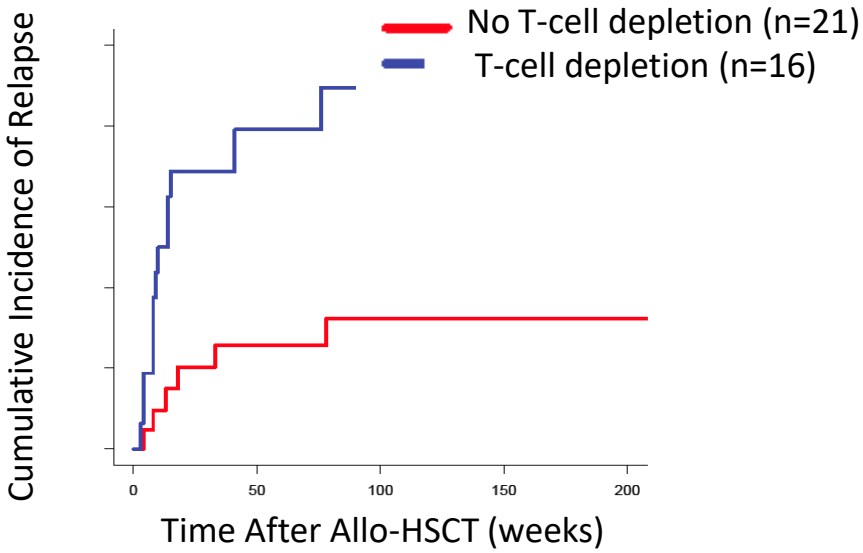


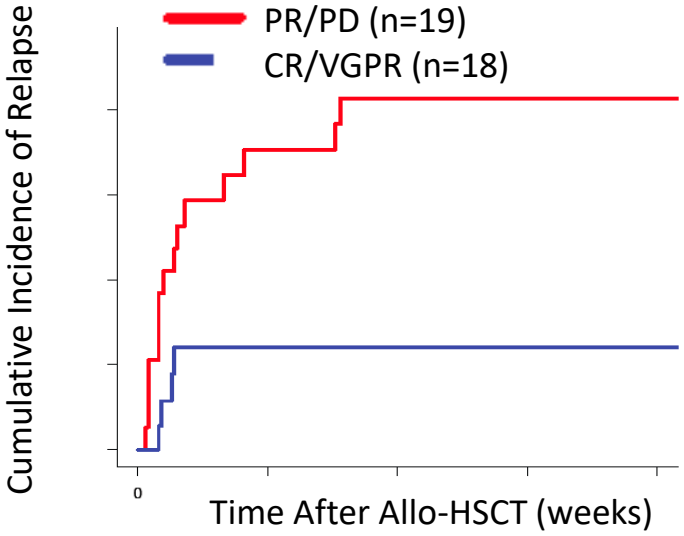
Uni and multivariate analyses

	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	

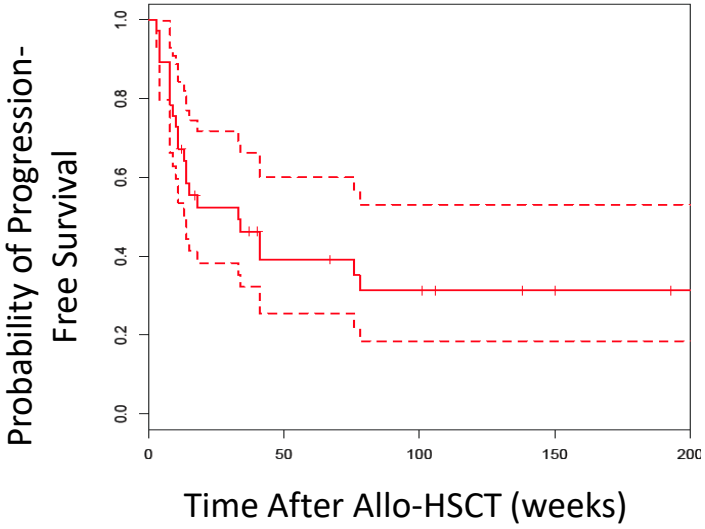
Cumulative incidence curves of TRM

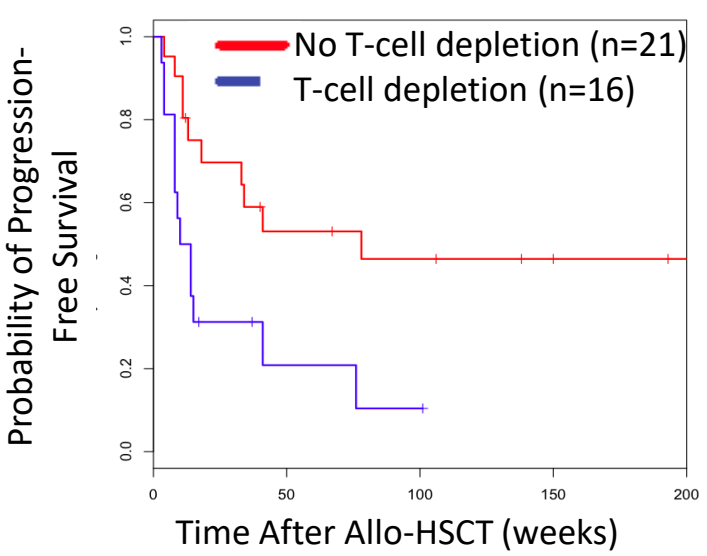


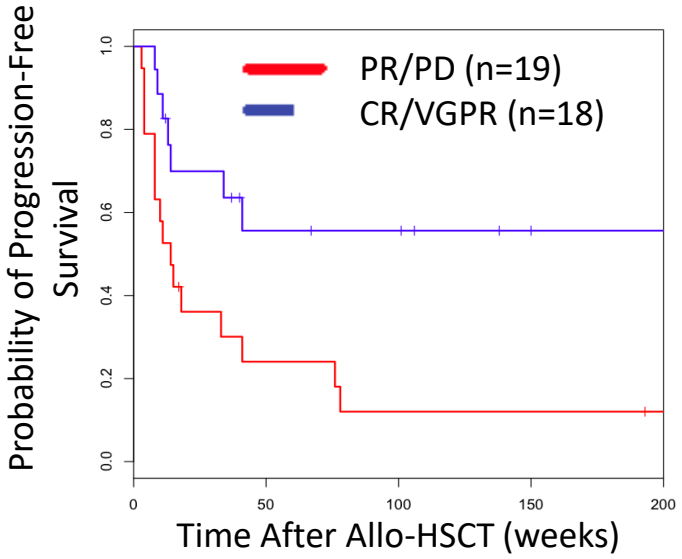




Progression Free Survival (PFS)

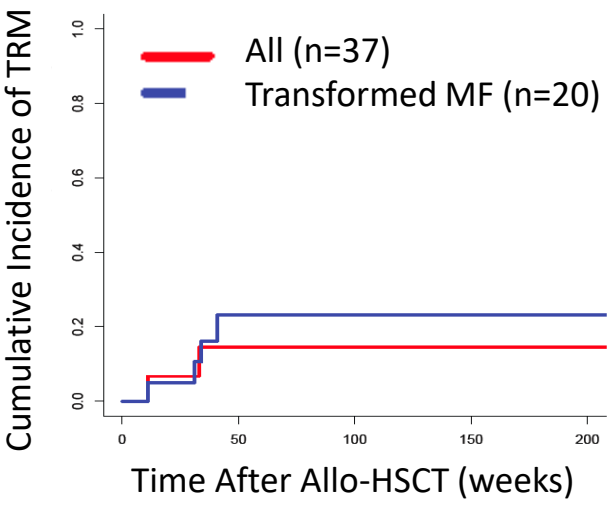


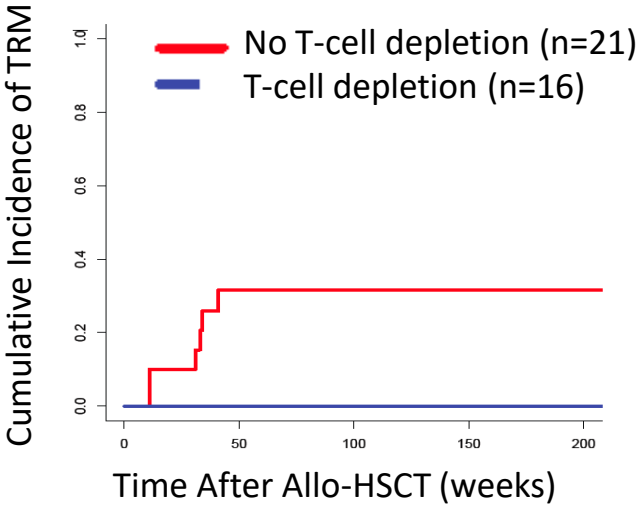




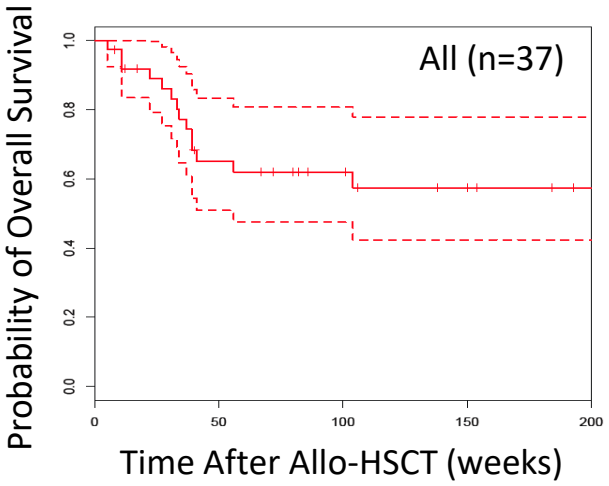
Treatment Related Mortality / Overall Survival

TRM





OS



Conclusions of this study

- 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

de Masson et al, Haematologica 2014: 99; 2-9

Limits and Perspectives

- Limits of the study
  - Retrospective
  - Small patient number
  - Insufficient follow-up (Chronic GVH ?)

- Remaining questions

  - Improvement of Overall Survival ?
  - Improvement of Quality of Life ?
  - Best patients and optimal timing of allogeneic transplantation

- 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
- Search for an allogeneic BMT donor in progress or realized

And at least one poor prognostic 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

Evaluation criteria

- **Primary endpoint : 3-year PFS**

  Death or Progression in Skin (mSWAT), Lymph nodes, Blood, Viscera

- **Secondary endpoints :**

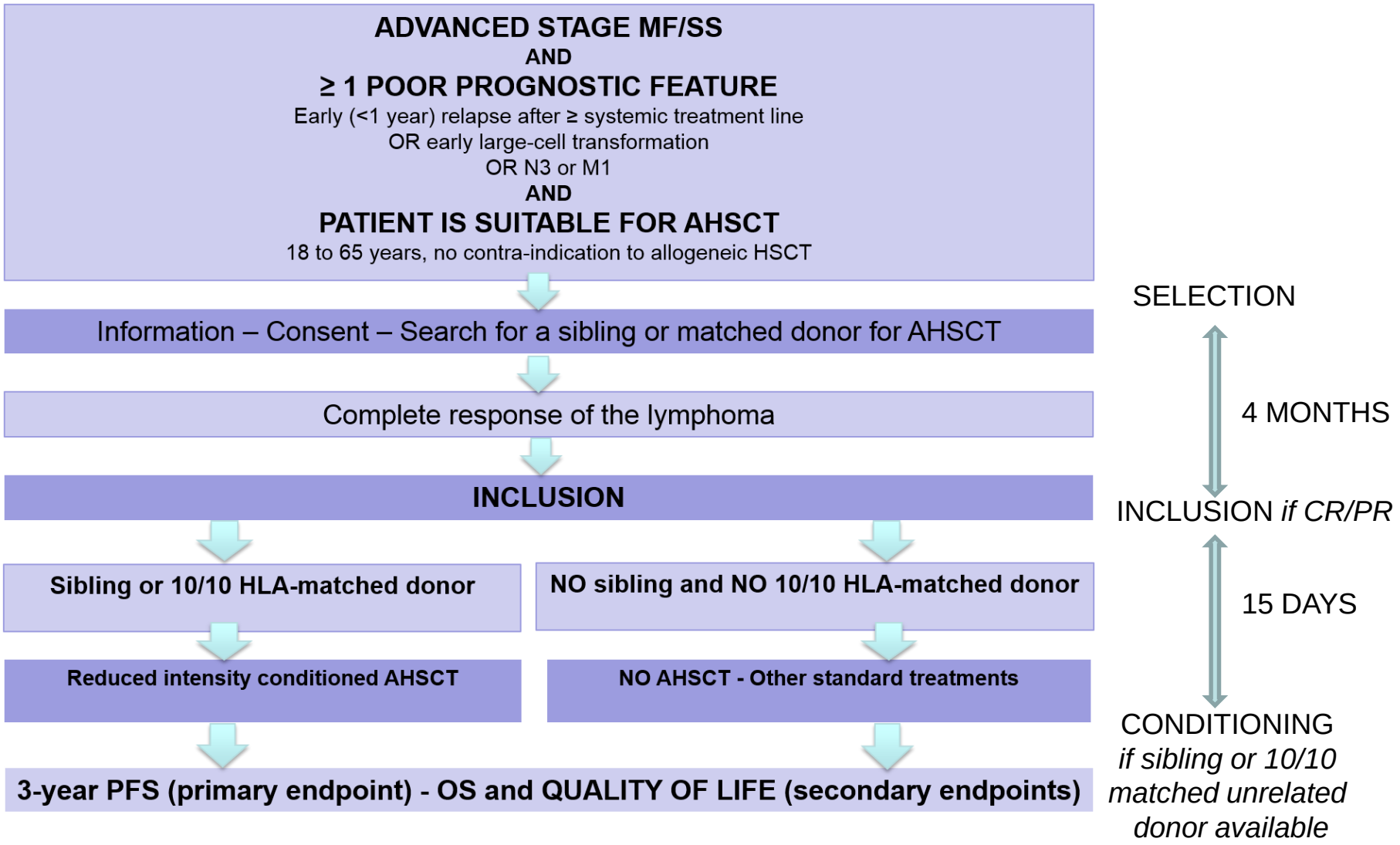
- Comparative endpoints:

- Incidence of **disease relapse**.
- **Non-relapse mortality**
- **Overall survival**
- Evaluation of the **quality of life**
- Evaluation of the **medical costs** (number of hospital days)

- In the alloHSCT group only:

- Incidence of neutrophil **engraftment**
- Incidence and severity of **acute GVHD**
- Incidence and severity of **chronic GVHD**

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

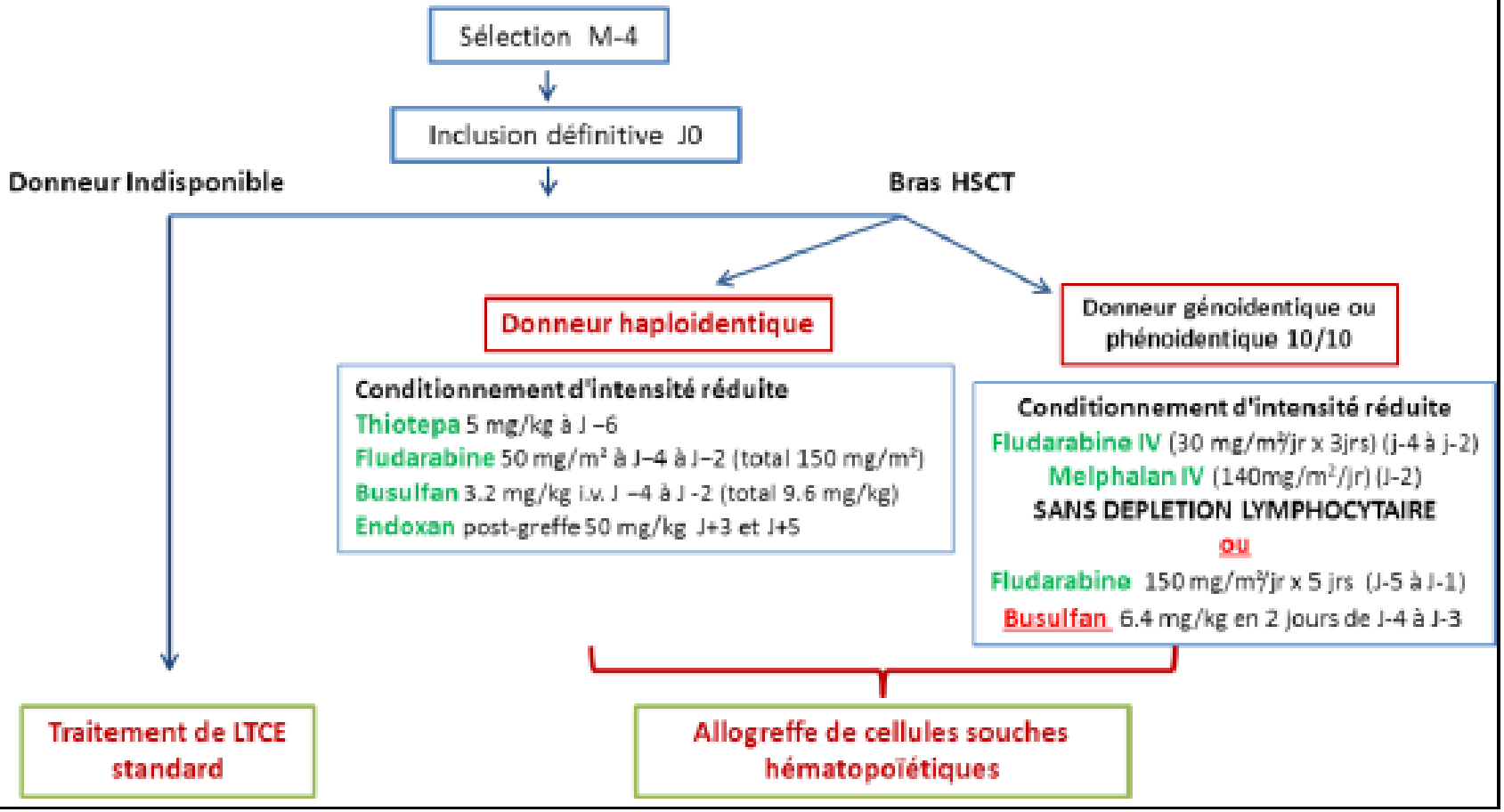
Flow chart	Selection M-4	Inclusion <15 days before start of the conditioning DAY 0	M1	M2	M3	M6	M12	M24	M36	Progression
HLA typing and donor search	x									
Informed consent	x									
Medical history	x									
Physical exam	x	x	x	x	x	x	x	x	x	x
Pregnancy test	x									
WBC, liver and renal function	x	x	x	x	x	x	x	x	x	x
Chest Xrays, lung function tests (HSCT group)	x									
ECG and echocardiography (HSCT group)	x									
Inclusion criteria validation		x								
CRF	x	x	x	x	x	x	x	x	x	x
Skin disease (mSWAT)	x	x	x	x	x	x	x	x	x	x
Quality of life (Skindex-29)	x	x			x		x	x	x	
Thoracoabdopelvic CT scan	x	x			x		x	x	x	x
Sezary cells	x	x	x	x	x	x	x	x	x	x
Chimerism (HSCT group)					x					x
Immune reconstitution (HSCT group)					x					
Blood biomarkers		x						x		
Number of hospital days since the last follow-up point			x	x	x	x	x	x	x	

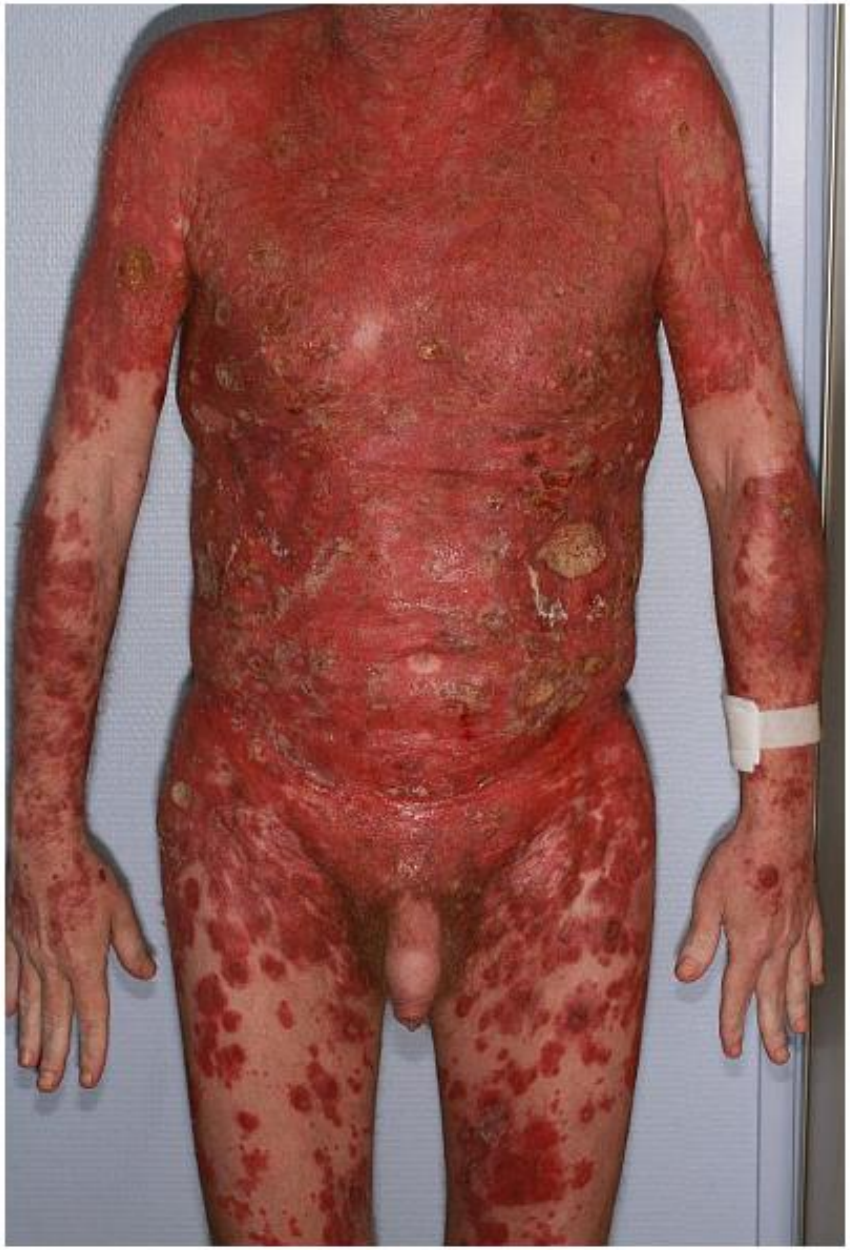
Update of the study

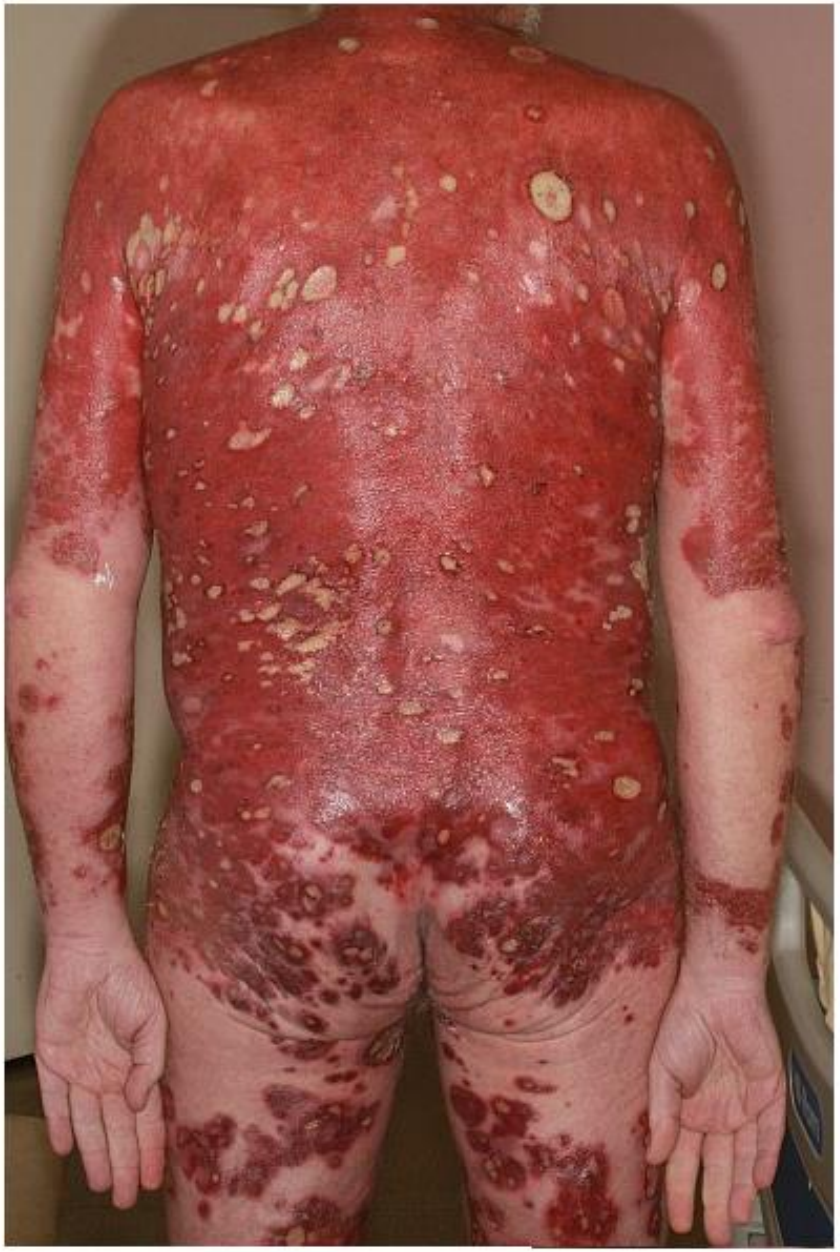
- 15 patients prospectively included in the study

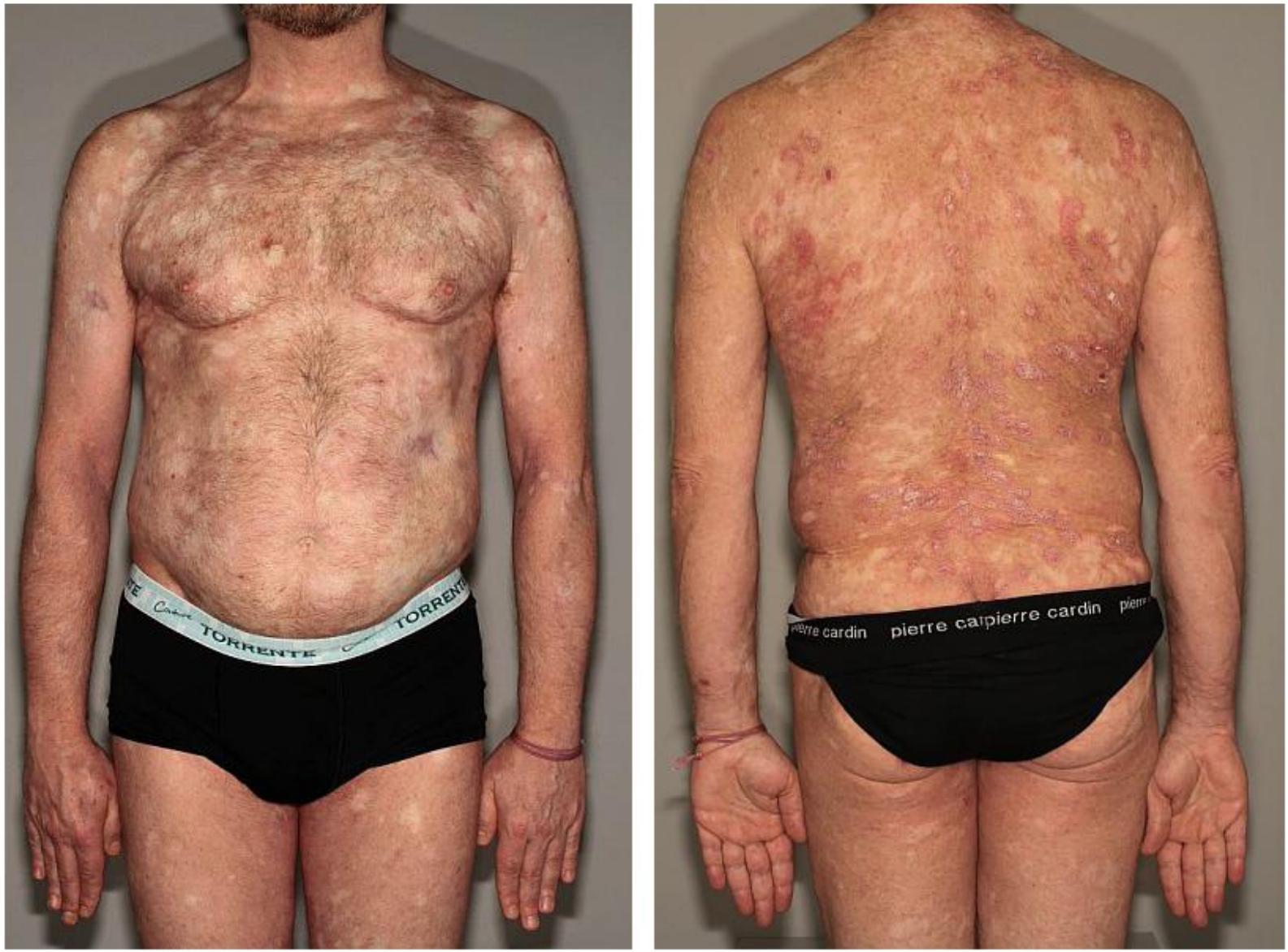
- Amendments (2018):
  - Inclusion age > 65
  - Haploidentical grafts allowed

Plan expérimental








TORRENTE
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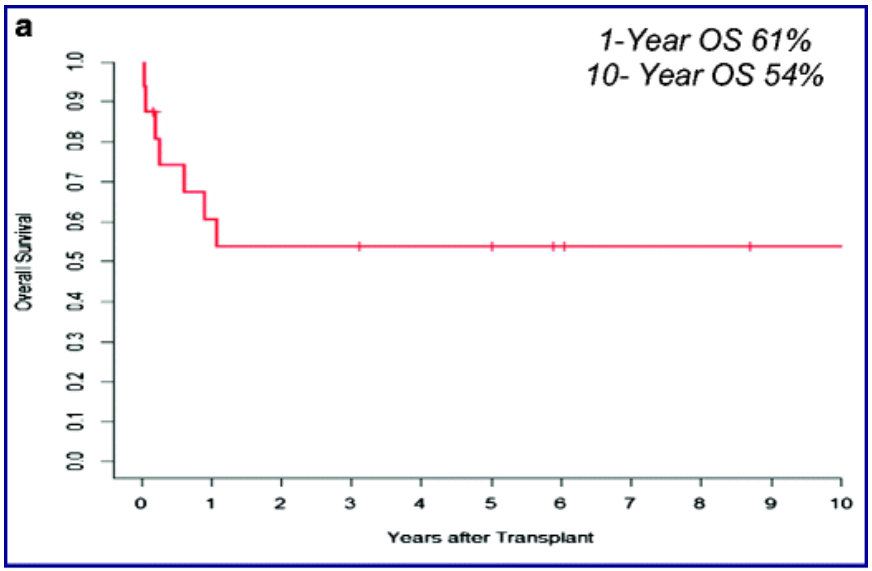
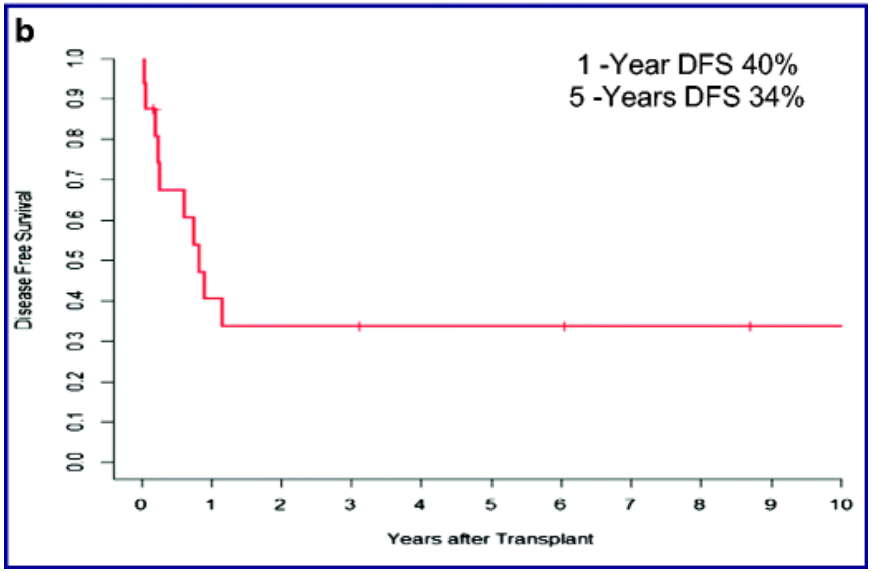
Cudillo L et al, Annals of Hematology 2018

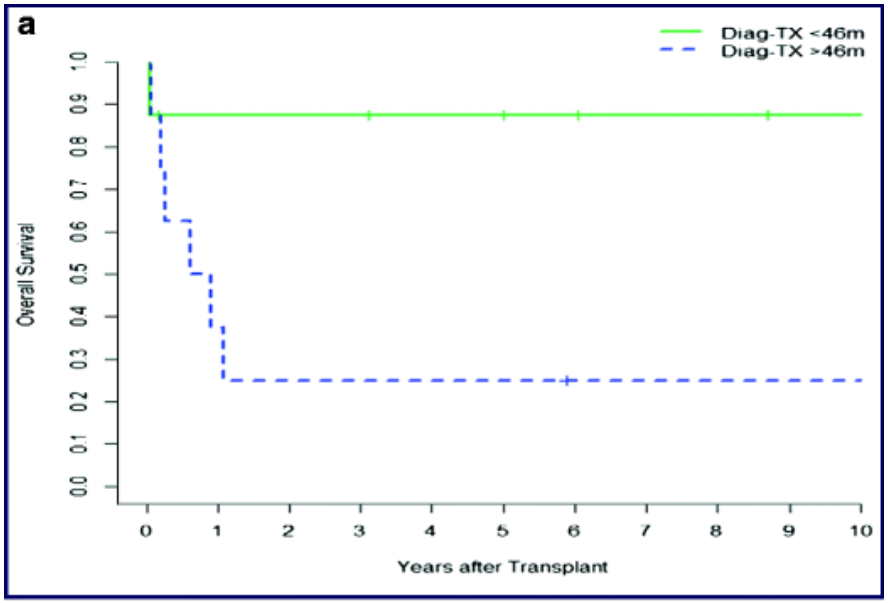


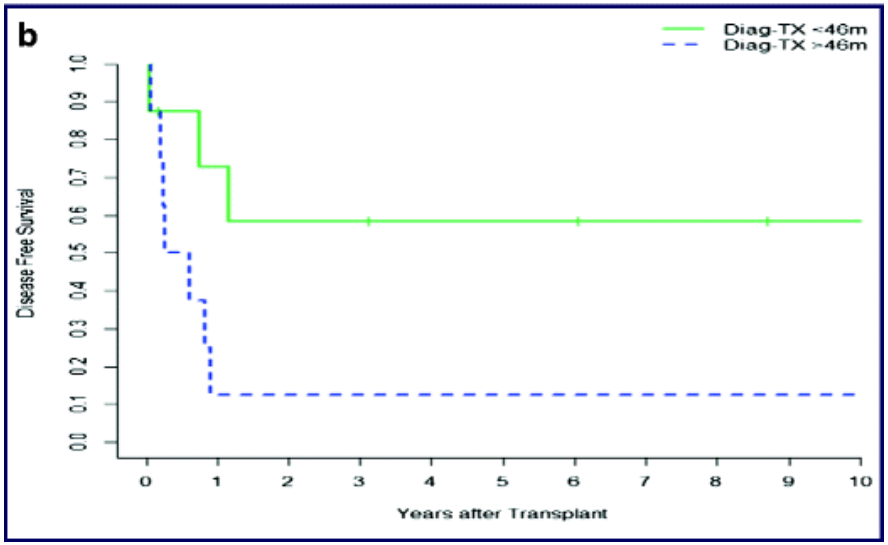


- 16 patients

- HLA-identical sibling : 8
- Matched unrelated donor : 5
- Haploidentical: 1
- Cord blood : 2

Cudillo L et al, Annals of Hematology 2018





Time from diagnosis to transplant influences negatively both OS and DFS