Società Italiana di Ematologia

FORMAZIONE SIE

I linfomi: un nome con almeno 40 sfaccettature!

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Bologna
Royal Hotel
Carlton

CTCL

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Disclosures of Francesco Onida

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
Kyowa kirin					√		
Takeda					√	√	
Menarini StemLine					√		
Johnson & Johnson					√		

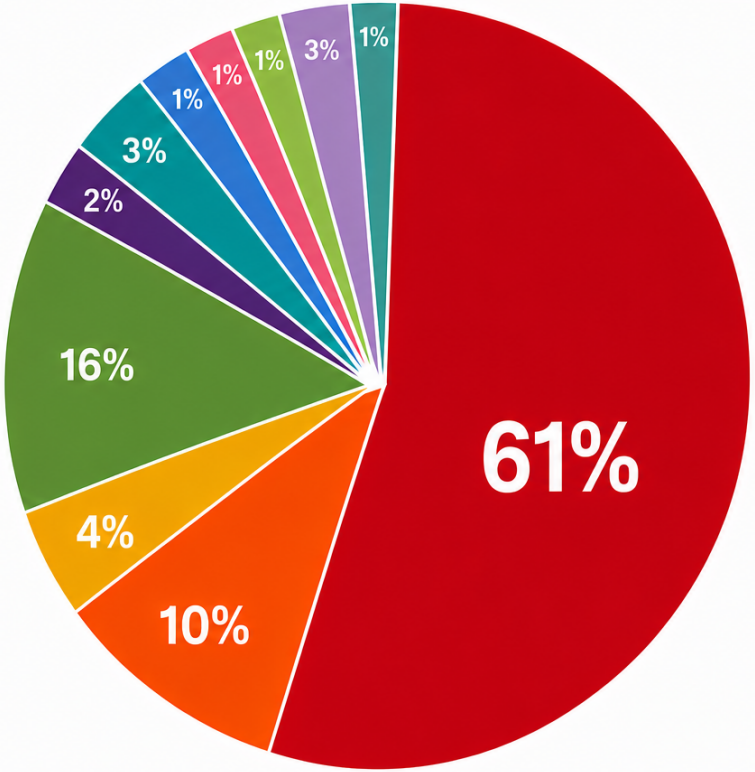
LINFOMI CUTANEI A CELLULE T (CTCL)

- Gruppo eterogeneo di linfomi non Hodgkin a primitività cutanea
- I CTCL costituiscono il 75-80% dei linfomi cutanei
- Incidenza: 6.4 casi per milione

Subtype	Frequency (%)	5-year survival rate (%)
CTCL – indolent clinical behaviour:		
Mycosis fungoides (MF)	44	88
Folliculotropic MF	4	80
Pagetoid reticulosis	< 1	100
Granulomatous slack skin	< 1	100
Lymphomatoid papulosis (LyP)	12	100
Primary cutaneous anaplastic large cell lymphoma (C-ALCL)	8	95
Subcutaneous panniculitis-like T-cell lymphoma (SPTCL)	1	82
Primary cutaneous small/medium pleomorphic T-cell lymphoma	2	72
CTCL – aggressive clinical behaviour:		
Sézary syndrome (SS)	3	24
Primary cutaneous peripheral T-cell lymphoma, unspecified	2	16
Primary cutaneous aggressive epidermotropic CD8 T-cell lymphoma (AECTCL)	< 1	18
Primary cutaneous γ/δ T-cell lymphoma (PCGD-TCL)	< 1	–
Primary cutaneous (extra-nodal) NK/T-cell lymphoma, nasal-type	< 1	–

Relative frequency of different subtypes of CTCL

MF, FMF and SS account for approximately 75% of all CTCL cases



61%	Mycosis fungoides (MF)
10%	Folliculotropic MF
4%	Sézary syndrome (SS)
16%	*Lymphomatoid papulosis* (LyP)
2%	Primary cutaneous anaplastic large cell lymphoma (C-ALCL)
3%	Primary cutaneous small/medium pleomorphic T-cell lymphoma
1%	Subcutaneous panniculitis-like T-cell lymphoma (SPTCL)
1%	Primary cutaneous peripheral T-cell lymphoma, unspecified
1%	Primary cutaneous aggressive epidermotropic CD8 T-cell lymphoma (AECTCL)
3%	Primary cutaneous γ/δ T-cell lymphoma (PCGD-TCL)
1%	Primary cutaneous (extra-nodal) NK/T-cell lymphoma, nasal-type

WHO 2022 Classification of CTCL

Mature T-cell and NK-cell neoplasms

- ***Mature T-cell and NK-cell leukaemias***
  - T-prolymphocytic leukaemia
  - T-large granular lymphocytic leukaemia
  - NK-large granular lymphocytic leukaemia
  - Adult T-cell leukaemia/lymphoma
  - **Sezary syndrome**

- ***Primary cutaneous T-cell lymphomas***
  - Primary cutaneous CD4+ small or medium T-cell lymphoproliferative disorder (LPD)
  - Primary cutaneous acral CD8+ LPD
  - **Mycosis fungoides**
  - Primary cutaneous CD30+ T-cell LPD
    - Lymphomatoid papulosis
    - Anaplastic large cell lymphoma
  - Subcutaneous panniculitis-like T-cell lymphoma
  - Primary cutaneous γ/δ T-cell lymphoma
  - Primary cutaneous CD8+ aggressive epidermotropic cytotoxic T-cell lymphoma
  - Primary cutaneous PTCL, NOS

Alaggio R et al. Leukemia (2022) 36:1720-1748

TNMB Staging of MF/SS (ISCL/EORTC consensus)

Skin (T)	**T1**	Patches, plaques, or papules <10% BSA	**T1A**	Patch/papule only	**Patch** = Any size skin lesion without significant elevation or induration. **Plaque** = Any size skin lesion that is elevated or indurated. **Papule** = Small, circumscribed, elevated solid skin lesion, typically <1 cm in diameter **Tumor** = at least one ≥1 cm diameter solid or nodular lesion with evidence of depth and/or vertical growth.
			T1B	Plaque ± patch	
	T2	Patches, plaques, or papules, ≥ 10% BSA	**T2A**	Patch/papule only	
			T2B	Plaque ± patch	
	T3	One or more tumors ≥ 1 cm in diameter			
	T4	Confluence of erythema covering ≥ 80% BSA			
Node (N)	**N0**	No clinically abnormal LN (no biopsy necessary)			**NCI-VA Lymph Node Classification** LN0: no atypical lymphocytes LN1: occasional and isolated atypical lymphocytes LN2: many atypical lymphocytes or in 3–6 cell clusters LN3: aggregates of atypical lymphocytes; nodal architecture preserved LN4: partial/complete effacement of nodal architecture **Dutch Criteria for Lymph Nodes** Grade 1: Dermatopathic lymphadenopathy Grade 2: Early involvement by mycosis fungoides Grade 3: Partial effacement of lymph node architecture Grade 4: Complete effacement of lymph node architecture
	N1	Dutch grade 1 or NCI LN 0-2			
	N2	Dutch grade 2 or NCI LN3			
	N3	Dutch grade 3-4 or NCI LN4			
	Nx	Clinically abnormal node but no pathologic determination of representative LN			
Visceral (M)	**M0**	No visceral involvement			**Bone marrow** involvement is considered visceral involvement, and is defined as a nodular, diffuse, or interstitial involvement (>5% of BM cellularity) with immunophenotype and clonal TCR consistent with the skin.
	M1	Visceral involvement	**M1a**	BM only involvement	
			M1b	Non-BM visceral involvement	
	Mx	Visceral involvement is neither confirmed nor refuted			
Blood (B)	**B0**	Absence of significant blood involvement			**B0** = 250/μL of CD4+/CD26- or CD4+/CD7- **B1** = does not meet criteria for B0 or B2 **B2** = ≥1000/μL of CD4+/ CD26- or CD4+/CD7- cells Note: In patients with marked lymphopenia, absolute counts of aberrant T cells may underestimate blood involvement and should be interpreted in the context of overall lymphocyte counts and flow cytometry results.
	B1	Low blood tumor burden			
	B2	High blood tumor burden			
	Bx	Unable to quantify blood involvement			

TNMB Staging of MF/SS

Early stages

Clinical Stage		T	N	M	B
IA	Limited skin involvement	T1	N0	M0	B0-1
IB	Skin-only disease	T2	N0	M0	B0-1
IIA		T1-2	N1-2	M0	B0-1
IIB	Tumor stage disease	T3	N0-2	M0	B0-1
IIIA	Erythrodermic disease	T4	N0-2	M0	B0
IIIB		T4	N0-2	M0	B1
IVA1	Sezary	T1-4	N0-2	M0	B2
IVA2	Sezary and non-Sezary	T1-4	N3	M0	B0-2
IVB	Visceral	T1-4	N0-3	M1	B0-2

Advanced stages

Stage IA-IB

	T	N	M	B
IA	1	0	0	0,1
IB	2	0	0	0,1
II	1,2	1,2	0	0,1
IIB	3	0-2	0	0,1
III	4	0-2	0	0,1
IIIA	4	0-2	0	0
IIIB	4	0-2	0	1
IVA_1	1-4	0-2	0	2
IVA_2	1-4	3	0	0-2
IVB	1-4	0-3	1	0-2






Stage IB-IIA

T2a

T2b

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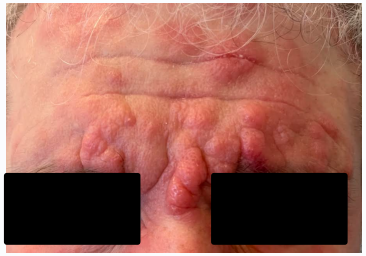
Courtesy of P. Quaglino

Stage IIB

	T	N	M	B
IA	1	0	0	0,1
IB	2	0	0	0,1
II	1,2	1,2	0	0,1
IIB	3	0-2	0	0,1
III	4	0-2	0	0,1
IIIA	4	0-2	0	0
IIIB	4	0-2	0	1
IVA_1	1-4	0-2	0	2
IVA_2	1-4	3	0	0-2
IVB	1-4	0-3	1	0-2



Stage III

	T	N	M	B
IA	1	0	0	0,1
IB	2	0	0	0,1
II	1,2	1,2	0	0,1
IIB	3	0-2	0	0,1
III	4	0-2	0	0,1
IIIA	4	0-2	0	0
IIIB	4	0-2	0	1
IVA_1	1-4	0-2	0	2
IVA_2	1-4	3	0	0-2
IVB	1-4	0-3	1	0-2

Stadio B2

THE OFFICIAL JOURNAL OF THE INTERNATIONAL CLINICAL CYTOMETRY SOCIETY
CLINICAL CYTOMETRY

ORIGINAL ARTICLE | Free Access

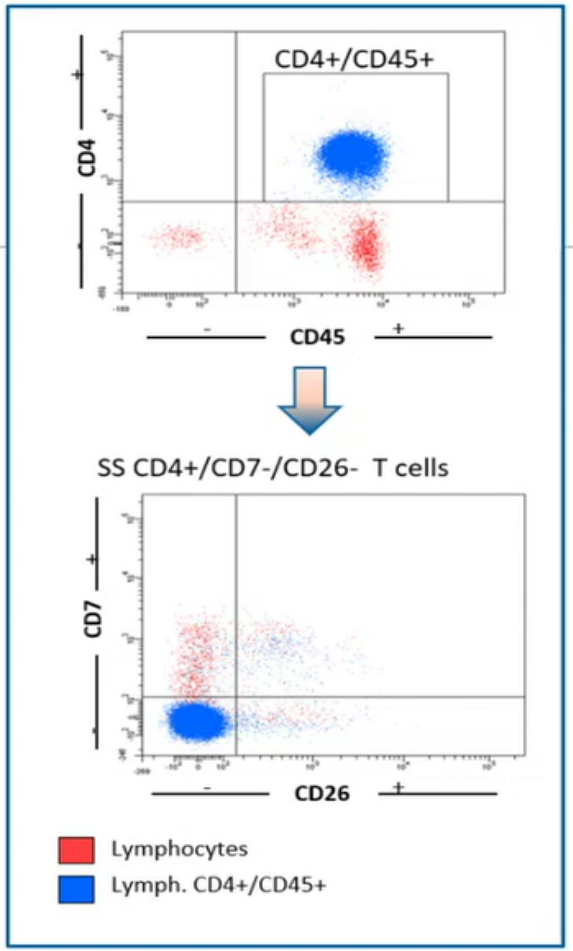
Flow cytometric evaluation of peripheral blood for suspected Sézary syndrome or mycosis fungoides: International guidelines for assay characteristics

Pedro Horna, Sa A. Wang, Kristy L. Wolniak, Katherina Psarra, Julia Almeida, Andrea J. Illingworth, Ulrika Johansson, Fiona E. Craig, Richard Torres

First published: 22 April 2020 | https://doi.org/10.1002/cyto.b.21878 | Citations: 12

TABLE 1 Recommended flow cytometry markers for the detection of Sezary cells in peripheral blood

Marker	Normal expression	Sézary cells	Utility	Clone(s) tested
CD3	Bright positivity on T-cells. Negative on other cells	Positive. Slight dim expression in 40–80% of cases. Rare partial or complete negativity	Gating of all T-cells Detection of Sézary cells	UCHT1, SK7
CD4	Bright positivity on a subset of T-cells. Some CD4/CD8 double-positive T-cells might be dim for CD4. Positive on monocytes	Positive. Slight dim expression inconsistently reported in 30–50% of cases. Rare partial or complete negativity	Gating of major T-cell subsets along with CD8 Detection of Sézary cells	SK3, T4, 13B8.2
CD7	Positive on CD4 T-cells, with variable loss in minor subsets and in reactive conditions. Bright positive on essentially all NK cells	Partially or completely negative in 50–80% of cases	Detection of Sézary cells in combination with CD26 Detection of NK cells	M-T701, 4H9, 3A1E-12H7, 6B7
CD8	Bright positivity on a subset of T-cells. Some CD4/CD8 double-positive T-cells and CD4/CD8 double-negative T-cells might be dim for CD8	Almost always negative	Gating of major T-cells subsets along with CD4	RPA-T8, SK1, B9.11
CD26	Variably positive on CD4 T-cells, with variable loss in minor subsets and in reactive conditions	Partially or completely negative in 70–100% of cases	Detection of Sézary cells in combination with CD7	4EL-1C7, L272
CD45	Bright positive on all lymphocytes	Bright positive, rare dim expression	Accurate gating and quantification of lymphocytes	J33, 2D1, HI30



Clinical features of SS

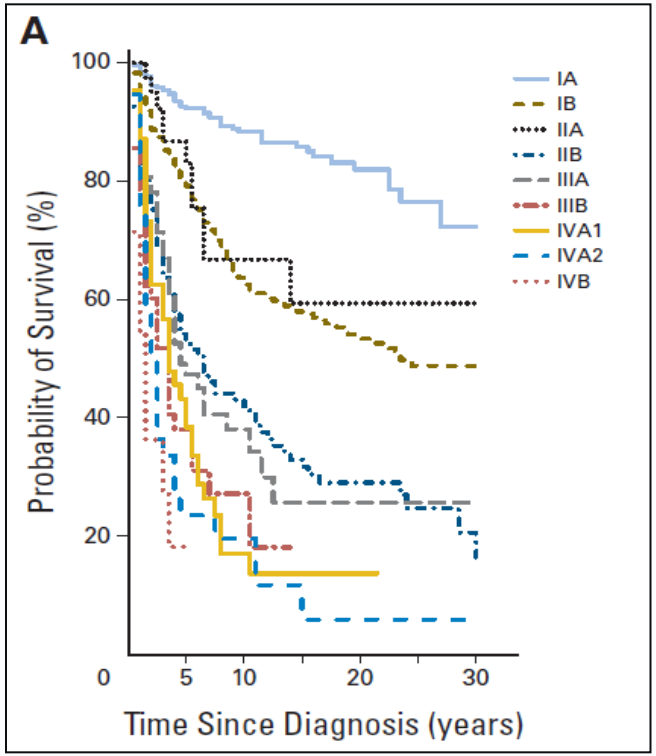
Clinical features

- **Lymphocytosis**
- **Generalized erythroderma**
- **Superficial lymphoadenopathies**
- Palmo-plantar keratosis
- Onychodystrophy
- Alopecia

Sézary syndrome need to be differentiated from other kind of erythroderma (benign and malignant):

- **Erythrodermic MF (stage III MF)**
- Erythrodermic psoriasis (and other psoriasiform skin diseases)
- Erythrodermic atopic dermatitis
- Drug induced erythroderma

Life expectation in MF and in SS



1502 pts

Characteristic	No.	%	Median Survival (years)	OS (%) 5 Years	10 Years	20 Years
Clinical stage						
IA	438	29.2	35.5	94	88	73
IB	583	38.8	21.5	84	70	52
IIA	40	2.7	15.8	78	52	47
IIB	167	11.1	4.7	47	34	21
IIIA	100	6.7	4.7	47	37	25
IIIB	56	3.7	3.4	40	25	NR
IVA1	67	4.5	3.8	37	18	15
IVA2	37	2.5	2.1	18	15	3
IVB	14	0.9	1.4	18	NR	NR

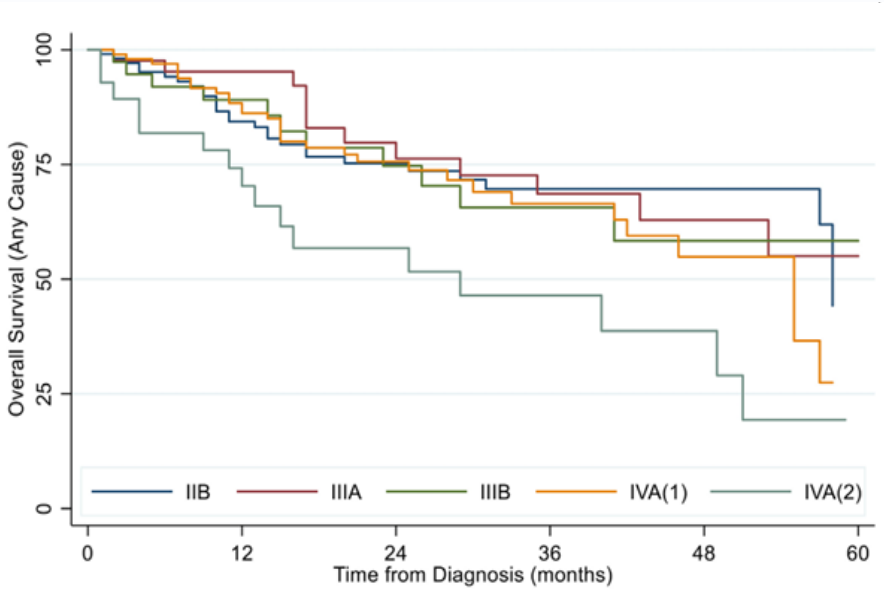
The overall survival rate at 5 years in pts with SS is 24%.

Agar NS et al. JCO 2010, 28 (29): 4730-4739

The PROCLIPI international registry

The study opened in 2015 and recruitment has been strong with to date 1916 patients recruited from 52 Centres from 19 countries across 6 continents

Overall Stage	Number of Patients	%
IA	762	39.8%
IB	602	31.4%
IIA	122	6.4%
Early Stage Disease	**1486**	**77.6%**
IIB	146	7.6%
IIIA	45	2.3%
IIIB	48	2.5%
IVA(1)	140	7.3%
IVA(2)	37	1.9%
IVB	14	0.7%
Advanced Stage Disease	**430**	**22.4%**

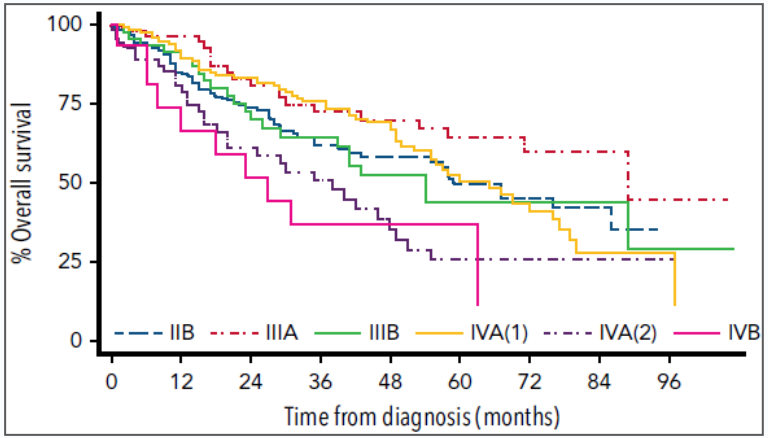


Scarisbrick J. Press Med 2022

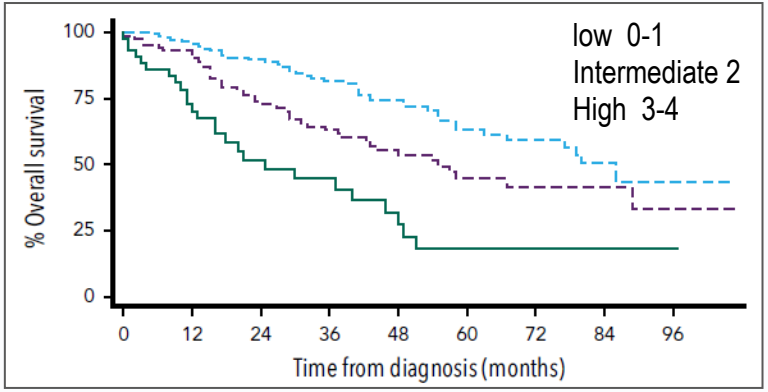
PROCLIPI Registry – New CLIPI (prognostic index)

Overall stage	Number of pts	%
IIB	184	7.6%
IIIA	64	2.5%
IIIB	56	2.3%
IVA(1)	172	7.3%
IVA(2)	60	2.4%
IVB	16	0.7%
Advanced phase	**552**	**23%**

Overall stage	5-y OS%
IIB	50%
IIIA	64.8%
IIIB	43.9%
IVA(1)	50.8%
IVA(2)	25.9%
IVB	36.9%



Prognostic Factor	Hazard Ratio (95% CI)	P value
Age > 60 years	2.39 (1.65-3.47)	< .001
LDH above upper limit	1.43 (1.04-1.96)	.029
Large Cell Transformation	1.58 (1.06-2.37)	.025
N3 (Stage IV)	1.98 (1.29-2.04)	.002



Risk group	5-y OS%
Low	63.3%
Intermediate	44.7%
High	18.3%

Scarisbrick JJ et al, Blood 2025

THERAPEUTIC OPTIONS FOR MYCOSIS FUNGOIDES / SÉZARY SYNDROME

Overview of Available Therapeutic Modalities

1. SKIN-DIRECTED THERAPIES

- Topical corticosteroids
- Topical clormethine
- Bexarotene gel
- P-UVA
- UVBnb (narrowband UVB)
- Local RT (radiotherapy)
- TSEB (Total Skin Electron Beam Therapy)

Effective in localized or early-stage disease and in combination with systemic therapies for disease control.

2. IMMUNOMODULATORY THERAPIES

- Peg-α-Interferon
- Acitretin
- Bexarotene (oral)
- Lenalidomide
- Extracorporeal photopheresis (ECP)

Preferred backbone for most patients with advanced CTCL; useful for long-term disease control and symptom management.

3. TARGETED THERAPIES

- Mogamulizumab (anti-CCR4)
- Brentuximab vedotin (anti-CD30)
- Alemtuzumab (anti-CD52)
- HDAC inhibitors (vorinostat, romidepsin, belinostat)

Effective options for patients with relapsed/refractory disease or ineligible for other systemic therapies.

4. CYTOTOXIC THERAPIES

- Chlorambucil or Cyclophosphamide + Prednisone
- Low-dose methotrexate (10–25 mg/week)
- Purine analogues (pentostatin, fludarabine)
- Gemcitabine
- Liposomal doxorubicin
- CHOP, CHOP-like

Indicated for selected patients with aggressive, refractory or rapidly progressive disease, or as a bridge to transplant.

TREATMENT INDIVIDUALIZATION IS KEY

Choice depends on disease stage, skin/blood involvement, prior therapies, comorbidities, patient preferences and treatment goals (disease control vs. long-term cytoreduction).

MULTIDISCIPLINARY MANAGEMENT

Optimal care requires collaboration between dermatologists, hematologists and transplant specialists.

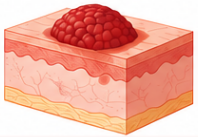
RT = Radiotherapy; TSEB = Total Skin Electron Beam Therapy; P-UVA = Psoralen + UVA; UVBnb = Narrowband UVB; HDAC = Histone Deacetylase Inhibitors; ECP = Extracorporeal Photopheresis.

ADVANCED MYCOSIS FUNGOIDES (STAGE IIB–IV)

FIRST-LINE THERAPEUTIC APPROACH: TREAT THE DOMINANT DISEASE COMPARTMENT

TREATMENT SELECTION SHOULD BE DRIVEN BY THE DOMINANT DISEASE COMPARTMENT (SKIN, BLOOD, NODES) AND TRANSPLANT ELIGIBILITY.

1. TUMOUR-STAGE MF (T3)



LOCAL THERAPY
- Local Radiotherapy (RT) 8–12 Gy

+

SYSTEMIC THERAPY
- Bexarotene (or acitretin*)
- Peg-IFN-α
- Low-dose Methotrexate
- Combination with SDT

Goal: local control and prevent progression

2. ERYTHRODERMIC MF (STAGE III)

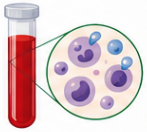
PREFERRED FIRST-LINE
- ECP*-based regimen

+

COMBINATIONS
- IFN-α
- Bexarotene (or acitretin*)
- Low-dose Methotrexate

Goal: control symptoms, reduce skin inflammation

3. BLOOD INVOLVEMENT (B1–B2)



PREFERRED FIRST-LINE
- ECP-based regimen

+

COMBINATIONS
- Peg-IFN-α
- Bexarotene (or acitretin*)
- Low-dose Methotrexate

Goal: control Sézary cells and disease burden

4. SYSTEMIC DISEASE CONTROL (ALL PATIENTS)

IMMUNOMODULATORY SYSTEMIC THERAPIES
- Bexarotene (or acitretin*)
- Peg-IFN-α
- Low-dose Methotrexate

+

CONSIDER COMBINATIONS WITH SDT
- ECP
- Phototherapy
- Topical treatments

Goal: durable disease control and quality of life

IMMUNOMODULATORY THERAPIES – KEY DRUGS

BEXAROTENE (or acitretin*)
300 mg/m²/day PO
Monitor lipids, thyroid function, liver enzymes

PEG-IFN-α2a
45–180 µg/week SC (or up to 180–360 µg/week in dose-escalation studies)
Monitor blood counts, thyroid function, mood

LOW-DOSE METHOTREXATE
5–35 mg/week PO or SC
Monitor blood counts, liver function, renal function

EXTRACORPOREAL PHOTOPHERESIS (ECP)
ECP-based regimen
Adjust according to response and tolerance

COMBINATIONS WITH SDT
- Enhance efficacy
- Allow dose reduction
- Improve disease control
- Manage toxicity

SELECTED HIGH-BURDEN DISEASE: GEMCITABINE OR PEGLYLATED LIPOSOMAL DOXORUBICIN

For selected patients with stage IIB (T3 extensive) or stage IVB (N3/M1b) disease or in special clinical situations*

GEMCITABINE
1000–1200 mg/m² IV on days 1, 8, 15 every 28 days (various schedules reported)
Monitor myelosuppression and infections

PEGLYLATED LIPOSOMAL DOXORUBICIN
20–40 mg/m² IV every 2–4 weeks
Monitor cardiotoxicity, infusion reactions, mucositis

EARLY TRANSPLANT REFERRAL IN ELIGIBLE HIGH-RISK PATIENTS

Assessment for allogeneic hematopoietic cell transplantation (allo-HCT) should be performed early in the disease course in appropriate candidates.

- Potentially curative option
- Discuss in experienced centers
- Individualize based on age, comorbidities, donor availability and patient preference

* Acitretin is not specifically approved for MF/SS and may be used off-label according to local practice and regulatory policies.

* Special clinical situations include rapid disease progression, need for rapid cytoreduction, bridge to allo-HCT, or contraindications to immunomodulatory therapies.

SDT = skin-directed therapies (topical corticosteroids, phototherapy, local RT/TSEBI, etc.)
RT = Radiotherapy ECP = Extracorporeal Photopheresis IFN = Interferon

Therapies are presented in alphabetical order and do not reflect a hierarchy of efficacy or clinical preference.

THERAPEUTIC OPTIONS FOR RELAPSED / REFRACTORY MF

Treatment Approaches After Failure of First-Line Therapy

Treatment selection should be driven by dominant disease compartment (skin, blood, nodes), prior therapies, comorbidities, performance status, and transplant eligibility.

1. IMMUNOMODULATORY THERAPIES

Extracorporeal photopheresis (ECP)
- Effective in blood and skin disease

Peg-α-Interferon
- Particularly useful for blood involvement

Bexarotene (oral)
- Active in skin and blood compartments

Lenalidomide
- Immunomodulatory and anti-angiogenic effects

Acitretin
- Useful for hyperkeratotic skin lesions

Can be used as single agents or in combination with other modalities.

2. TARGETED THERAPIES

Mogamulizumab (anti-CCR4)
- Active in MF and SS
- Particularly effective in blood involvement

Brentuximab vedotin (anti-CD30)
- For CD30+ MF
- Skin, nodal and systemic activity

HDAC inhibitors (vorinostat, romidepsin, belinostat)
- Oral and IV options
- Active in skin and blood disease

Appropriate for patients progressing on or intolerant to prior therapies.

3. CYTOTOXIC THERAPIES

Purine analogues (pentostatin, fludarabine)
- Particularly active in blood disease

Gemcitabine
- Active in advanced MF/SS

Liposomal doxorubicin
- Active in advanced MF/SS

Other regimens (e.g., CHOP, CHOP-like)
- Consider for aggressive disease

Chlorambucil or Cyclophosphamide + Prednisone
- Option for indolent or elderly patients

Consider for rapid disease control or visceral involvement.

4. LOCALLY DIRECTED APPROACHES (AS PART OF SYSTEMIC STRATEGY)

Local Radiotherapy (RT)
- For isolated or symptomatic lesions or nodes

TSEB (Total Skin Electron Beam Therapy)
- For extensive skin involvement

Useful for symptom control and compartment-directed management.

5. ALLOGENEIC HEMATOPOIETIC CELL TRANSPLANTATION (allo-HCT)

Only potentially curative option
- Consider early in eligible patients with advanced, high-risk disease
- Best outcomes with lower disease burden and chemosensitive disease

INDIVIDUALIZE THERAPY

Tailor treatment based on disease biology, prior therapies, patient goals, and toxicity profile.

SEQUENTIAL & COMBINATION APPROACHES

Use sequential or combination strategies to maximize response depth and duration while minimizing toxicity.

EARLY TRANSPLANT REFERRAL

Early referral to transplant centers is recommended for eligible patients, ideally before multiple lines of therapy.

MF = Mycosis Fungoides; SS = Sézary Syndrome; RT = Radiotherapy; TSEB = Total Skin Electron Beam Therapy; HDAC = Histone Deacetylase Inhibitors; ECP = Extracorporeal Photopheresis; allo-HCT = Allogeneic Hematopoietic Cell Transplantation.

Clinical trial enrollment should be considered at every stage of relapsed/refractory disease.

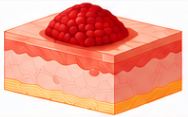
ADVANCED MYCOSIS FUNGOIDES (STAGE IIB–IV)

THERAPEUTIC APPROACHES AFTER FAILURE OF FIRST-LINE THERAPY

TREAT THE DOMINANT DISEASE COMPARTMENT

TREATMENT SELECTION SHOULD BE DRIVEN BY THE DOMINANT DISEASE COMPARTMENT (SKIN, BLOOD, NODES) AND PRIOR THERAPIES, COMORBIDITIES, PERFORMANCE STATUS AND TRANSPLANT ELIGIBILITY.

1. TUMOUR-STAGE MF (T3)



LOCAL THERAPY (PREFERRED)
- Local Radiotherapy (RT) 8–12 Gy (isolated/symptomatic lesions)
- TSEB (extensive skin involvement)

+

SYSTEMIC THERAPY OPTIONS (BY PRIORITY)
1. Brentuximab vedotin (anti-CD30)*
2. Mogamulizumab (anti-CCR4)
3. Switch to/optimize immunomodulatory therapy (bexarotene, IFN, ECP, lenalidomide)
4. Low-dose methotrexate
5. Acitretin or Bexarotene (oral)
6. Consider combination strategies

Goal: achieve skin disease control and improve quality of life

2. ERYTHRODERMIC MF (STAGE III)

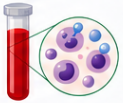
PREFERRED SYSTEMIC OPTIONS (BY PRIORITY)
1. Mogamulizumab (anti-CCR4)
2. ECP (as single agent or in combination)
3. Bexarotene (oral) ± IFN-α

+

OTHER SYSTEMIC OPTIONS
1. Brentuximab vedotin (anti-CD30)*
2. Peg-IFN-α
3. Low-dose methotrexate
4. Acitretin
5. Consider combination strategies

Goal: control symptoms, restore quality of life and reduce skin inflammation

3. BLOOD INVOLVEMENT (B1–B2)



PREFERRED SYSTEMIC OPTIONS (BY PRIORITY)
1. Mogamulizumab (anti-CCR4)
2. ECP (as single agent or in combination)
3. Peg-IFN-α

+

OTHER SYSTEMIC OPTIONS
1. Bexarotene (oral)
2. Low-dose methotrexate
3. Acitretin
4. Consider combination strategies

Goal: control Sézary cells, improve blood parameters and reduce symptoms

4. SYSTEMIC DISEASE CONTROL (ALL PATIENTS)

SEQUENCING SYSTEMIC THERAPY
- Use agents with different mechanisms after progression
- Consider combinations for rapid or incomplete responses

+

KEY OPTIONS AFTER PROGRESSION
1. Mogamulizumab (if not used)
2. Brentuximab vedotin*
3. Peg-IFN-α
4. Bexarotene (oral)
5. Low-dose methotrexate
6. Gemcitabine
7. Liposomal doxorubicin
8. CHOP or CHOP-like regimens (selected patients)
9. Allogeneic transplant evaluation
10. **Consider clinical trial, if available**

Goal: durable disease control and prolong survival

KEY SYSTEMIC THERAPIES – DETAILS

MOGAMULIZUMAB (anti-CCR4)
- 1.0 mg/kg IV
- Once weekly for 4 weeks then every 2 weeks
- Active in skin, blood and nodal disease

BRENTUXIMAB VEDOTIN (anti-CD30)*
- 1.8 mg/kg IV
- Every 3 weeks
- For CD30+ MF/SS (skin, nodal, systemic)
- Confirm CD30 expression before use

PEG-IFN-α
- 90–180 µg/week SC
- Active in skin and blood disease

BEXAROTENE (oral)
- 300 mg/m²/day PO
- Monitor lipids, thyroid function, liver enzymes

LOW-DOSE METHOTREXATE
- 5–25 mg/week PO or SC
- Monitor blood counts, liver function, renal function

TSEB (Total Skin Electron Beam Therapy)
- 12–15 Gy in 15–20 fractions
- For extensive skin involvement

RT LOCALE (Radiotherapy)
- 8–12 Gy
- For isolated or symptomatic lesions

WHEN TO CONSIDER ALLOGENEIC HEMATOPOIETIC CELL TRANSPLANTATION (allo-HCT)

- Relapsed/refractory disease after ≥2 lines of therapy
- High-risk features (e.g., large cell transformation, bulky nodal disease, aggressive course)
- Medically fit patients with suitable donor

Best outcomes with lower disease burden
Consider referral early

INDIVIDUALIZE AND SEQUENCE THERAPY

Tailor treatment based on disease biology, depth of response, toxicity, patient preference and goals of care.

MONITOR AND REASSESS

Regularly assess clinical response, blood counts, Sézary cell burden, skin scores and quality of life. Adjust therapy accordingly.

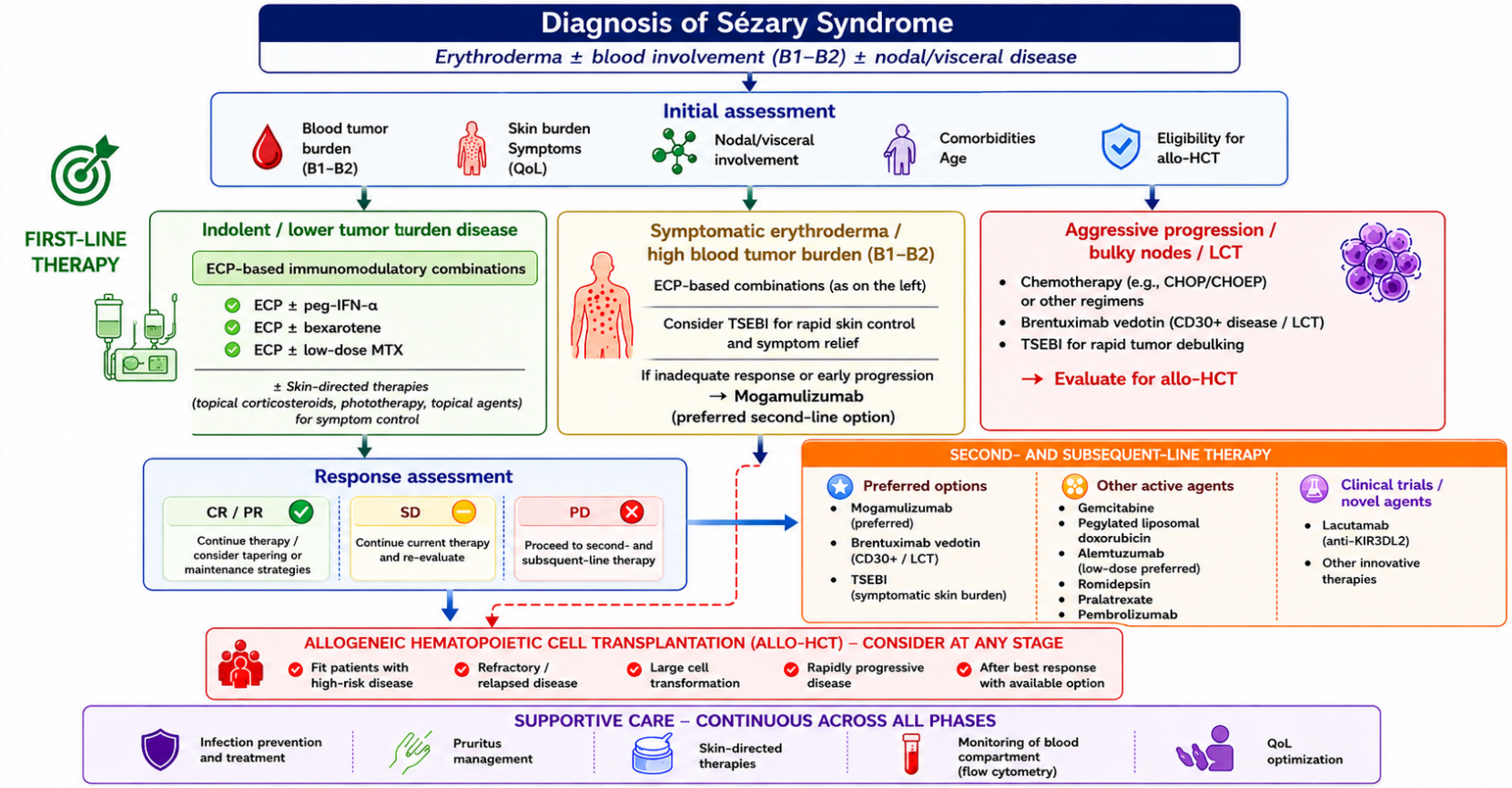
EARLY TRANSPLANT REFERRAL

Early referral to transplant centers should be considered in eligible patients, ideally before multiple lines of therapy.

* CD30 expression should be confirmed before Brentuximab vedotin.

MF = Mycosis Fungoides; SS = Sézary Syndrome; RT = Radiotherapy; TSEB = Total Skin Electron Beam Therapy; ECP = Extracorporeal Photopheresis; IFN = Interferon.

Therapies are presented in order of priority within each category and do not reflect a hierarchy of efficacy or clinical preference.



Abbreviations: allo-HCT, allogeneic hematopoietic cell transplantation; B1–B2, blood involvement classification; CHOP, cyclophosphamide, doxorubicin, vincristine, prednisone; CHOEP, CHOP + etoposide; ECP, extracorporeal photopheresis; IFN, interferon; LCT, large cell transformation; MTX, methotrexate; PD, progressive disease; PR, partial response; QoL, quality of life; SD, stable disease; TSEBI, total skin electron beam irradiation.

NOVEL SYSTEMIC THERAPEUTIC APPROACHES FOR ADVANCED CTCL

Investigational Agents in Clinical Development

The following agents and strategies are investigational or in early-phase clinical development for patients with relapsed/refractory mycosis fungoides (MF) or Sézary syndrome (SS). Available data are limited and not yet mature. Their role in routine clinical practice remains to be defined.

AGENT / TARGET	CLASS / MECHANISM OF ACTION	CLINICAL DATA IN CTCL	DEVELOPMENT STATUS / REFERENCES
Lacutamab (anti-KIR3DL2 mAb)	Humanized monoclonal antibody targeting KIR3DL2, expressed in ~85% of SS patients.	In RR MF/SS after ≥2 prior lines (incl. mogamulizumab in SS): ORR in SS 42.9% with median DOR 25.6 months; manageable safety profile.	Phase I/II (TELLOMAK study) [118]
CTX-130 (anti-CD70 CAR T)	Allogeneic CRISPR-Cas9–engineered CAR T cells targeting CD70.	Phase 1 COBALT-LYM study: 10 CTCL pts among 39. ORR 40% (CR 10%). Manageable safety; CRS in 67% (mostly grade 1–2); infections most common AE.	Phase I [119]
Fenretinide (ST-001 nanoFenretinide)	Retinoic acid receptor (RAR) and retinoid X receptor (RXR) agonist; nanoformulation improves tolerability.	Ongoing phase 1a/1b study in relapsed/refractory T-cell lymphomas including CTCL.	Phase 1a/1b [120,121]
JAK/STAT inhibitors (e.g., ruxolitinib)	Inhibition of JAK/STAT signaling pathway.	Phase II ruxolitinib study in CTCL: ORR 40% in enriched cohort, but only 1/7 PR, no CR. Modest activity overall.	Phase II and beyond [122–125]
EZH2 inhibitors (oral agents)	Inhibition of enhancer of zeste homolog 2 (EZH2), overexpressed in T-cell lymphomas.	EZH2 inhibitors have shown efficacy in T-cell lymphomas with a very favorable safety profile.	Early phase / Phase I–II [126–128]
PI3K inhibitors (delta isoform) (e.g., duvelisib, tenalisib, linperlisib)	Inhibition of PI3K delta isoform.	Duvelisib: ORR ~31% in CTCL in early-phase studies. Other agents (tenalisib, linperlisib) show preliminary signals of activity (mono or combination). Durability remains under investigation.	Early phase / Phase I–II [129–133]
CCR4 antagonists (e.g., C021, AZD2098)	Small-molecule antagonists of CCR4, highly expressed in CTCL cells.	Preclinical in vitro and in vivo activity demonstrated.	Preclinical / Early clinical [134]
CCR8 monoclonal antibodies (e.g., JS005, DT-7012)	Target CCR8 expressed on intratumoral regulatory T cells in CTCL skin.	One agent: acceptable safety and preliminary antitumor activity in CTCL. DT-7012 entering phase 1.	Early clinical / Phase I [135–137]
CD47/SIRPα inhibitors (e.g., TTI-621)	Blockade of CD47–SIRPα axis to restore anti-tumor immunity.	Intralesional: ≥50% CAILS reduction in 34% (RR CTCL/SS). Systemic (phase I, 29 CTCL pts): ORR ~20%.	Phase I / Completed (IL) and ongoing (systemic) [138,139]
CDK9 inhibitors	Inhibition of cyclin dependent kinase 9 (CDK9), a driver of CTCL.	Initial single-agent results modest; combination strategies may be promising.	Early phase [140]
CD74 ADC (STRO-001)	Anti-CD74 antibody–drug conjugate with dual non-cleavable maytansinoid payloads.	Efficiently kills CTCL cell lines and eradicates murine xenografts in vivo.	Preclinical [141]
Denileukin Diftitox (DD-cxdl)	Reformulated IL-2 receptor–targeting immunotoxin.	Phase III (n=69): ORR 36.2% (CR 8.7%); median DOR 8.9 months; median TTR 1.4 months; capillary leak syndrome in 20% (grade ≥3: 5.8%).	FDA approved (2024) for R/R stage I–III CTCL after ≥1 prior systemic therapy [142]
PTX-100 (GGTase-I inhibitor)	Inhibitor of geranylgeranyl transferase-I, modulating Rho/Ras signaling.	Early-phase studies in relapsed/refractory T-cell lymphomas (incl. CTCL) show preliminary antitumor activity with manageable toxicity.	Early clinical (Fast Track Designation by FDA) [143]

Clinical trial participation should be considered whenever possible.

AE = Adverse Event; CR = Complete Response; CTCL = Cutaneous T-Cell Lymphoma; DOR = Duration of Response; MF = Mycosis Fungoides; ORR = Overall Response Rate; PR = Partial Response; RR = Relapsed/Refractory; SS = Sézary Syndrome.

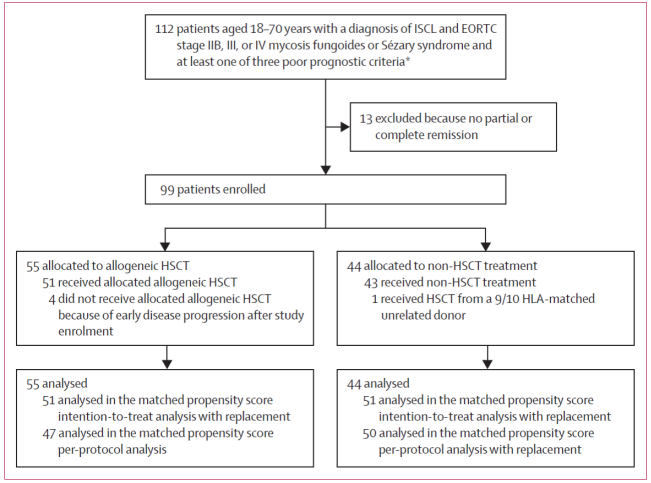
Allo-HCT in CTCL

Reference	Subtype N° of patients	Prospective/ retrospective/ Phase	Treatment/ conditioning	NRM	PFS	OS
Duarte et al. 2010	36 MF/24 SS	Retrospective	44 RIC/25 TCD	2y; 22%	3y; 34%	3y; 54%
Duvic et al. 2010	19	Prospective	RIC	NA	NA	Median not reached at 19 mo
Delioukina et al. 2012	11	Prospective	RIC	2y; 22%	2y; 47%	2y; 55%
Lechowicz et al. 2014	MF/SS 129	Retrospective	83 RIC/46 MAC	5y; 22%	5y; 17%	5y; 32%
De Masson et al. 2014	37	Retrospective	25 RIC/12 MAC	2y; 18%	2y; 31%	2y; 57%
Hosing et al. 2015	MF 30 SS 17	Prospective	RIC	3y; 17%	4y; 26%	4y; 51%
Weng et al. 2020	MF 13 SS 22	Prospective Phase II	TSEB/TLI/ ATG	2y; 14%	3y; 41%	3y; 26%
Ritchie et al 2020	SS:4 MF:11	Retrospective	TSEB/ TLI/ATG	2y; 7%	-	1y; 87% 2y; 79%
Domingo-Domenech et al. 2021	113	Retrospective	76% RIC	5y; 28%	5y; 26%	5y; 38%
Stamouli et al 2021	MF 8 SS 2	Retrospective	Low-dose TBI fludarabine-Cy	12% (mFU 20 mo)	51 mo	51 mo
Elliott et al. 2021	MF 17 SS 9	Retrospective	2 MAC 24 RIC	17%	-	-
De Masson et al. 2023	MF 37 SS 18	Prospective	RIC	10%	Median 9 mo	Median not reached at 12 mo
Morris SL et al. 2024	MF 34 SS 7	Prospective	RIC	5 y 23.4%	5 y 37.1%	5 y 37.7%
Onida et al 2024 (5WCCL)	MF 40 SS 23	Retrospective	Low-dose TBI+pentostatin, fludarabine-melphalan	5y 14%	5y DFS 33%	5y 53%

Allogeneic transplantation in advanced cutaneous T-cell lymphomas (CUTALLO): a propensity score matched controlled prospective study

Adèle de Masson, Marie Beylot-Barry, Caroline Ram-Wolff, Jean-Baptiste Mear, Stéphane Dalle, Michel d'Incan, Saskia Ingen-Housz-Oro, Corentin Orvain, Julie Abraham, Olivier Dereure, Amandine Charbonnier, Jérôme Cornillon, Christine Longvert, Stéphane Barete, Serge Boulinguez, Ewa Wierzbicka-Hainaut, François Aubin, Marie-Thérèse Rubio, Marc Bernard, Aline Schmidt-Tanguy, Roch Houot, Anne Pham-Ledard, David Michonneau, Pauline Brice, Hélène Labussière-Wallet, Jean-David Bouaziz, Florent Grange, Hélène Moins-Teisserenc, Katayoun Jondeau, Laurence Michel, Samia Mourah, Maxime Battistella, Etienne Daguindau, Michael Loschi, Alexandra Picard, Nathalie Franck, Natacha Maillard, Anne Huynh, Stéphanie Nguyen, Ambroise Marçais, Guillaume Chaby, Patrice Ceballos, Yannick Le Corre, Sébastien Maury, Jacques-Olivier Bay, Henri Adamski, Emmanuel Bachy, Edouard Forcade, Gérard Socié, Martine Bagot*, Sylvie Chevret†, Régis Peffault de Latour†, on behalf of the CUTALLO Investigators, Groupe Français d'Etude des Lymphomes Cutanés, Société Française de Greffe de Moëlle et Thérapie Cellulaire*

	HSCT (n=55)	Non-HSCT (n=44)
Diagnosis		
Mycosis fungoides	37 (67%)	24 (55%)
Sézary syndrome	18 (33%)	20 (45%)
Large-cell transformation	31 (56%)	20 (45%)
Maximum WHO disease stage		
IIB	23 (42%)	15 (34%)
IIIA	1 (2%)	3 (7%)
IIIB	3 (5%)	2 (5%)
IVA1	11 (20%)	14 (32%)
IVA2	12 (22%)	10 (23%)
IVB	5 (9%)	0
Age at diagnosis, years	46·1 (36·3–53·6)	53·6 (47·7–59·7)



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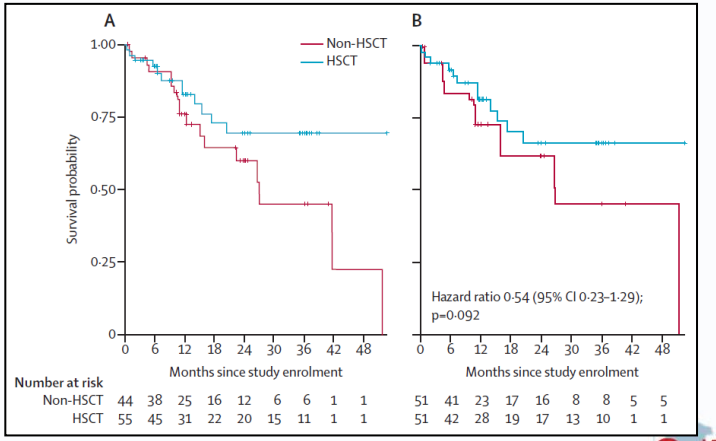
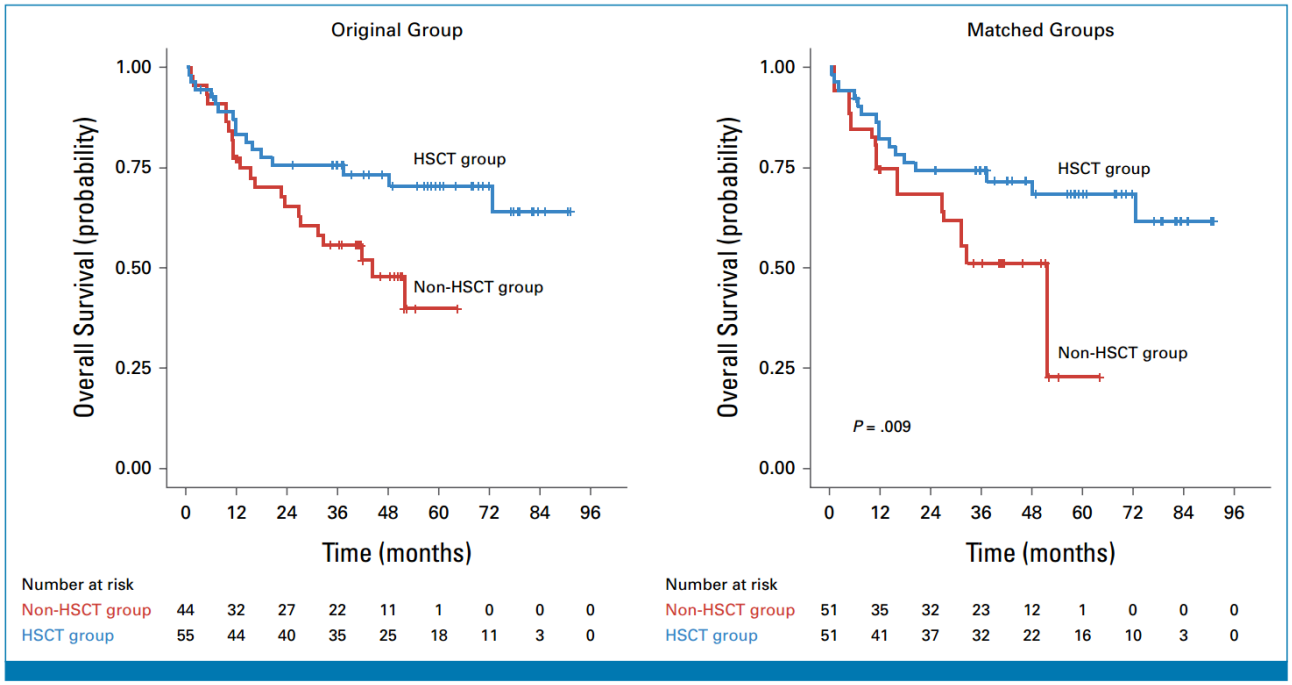


Società Italiana di Ematologia

De Masson A et al. Lancet 2023

Overall Survival After Allogeneic Transplantation in Advanced Cutaneous T-Cell Lymphomas (CUTALLO): A Propensity Score–Matched Controlled Prospective Study



De Masson A et al. JCO 2025

Milan Experience (updated March 2026)

Patients characteristics (N=76)	
Gender, N (%) male / female	48 (63%) / 28 (37%)
Diagnosis, N (%) MF / SS	50 (66%) / 26 (34%)
Stage at transplant indications IIb-III / IV	19 (25%) / 57 (75%)
Previous treatment lines, median (range)	6 (2-11)
Time to diagnosis to HSCT, months, median (range)	64 (10-274)
Disease status at allo-HCT CR, N (%) PR, N (%)	 19 (25%) 57 (75%)
Age at HSCT, years, median (range)	52 (20-72)
HCT-CI, median (range)	1 (0-6)
HSCT characteristics	
Donor type, N (%) HLA-id sib MUD mMUD Haplo	 23 (30%) 20 (27%) 17 (22%) 16 (21%)

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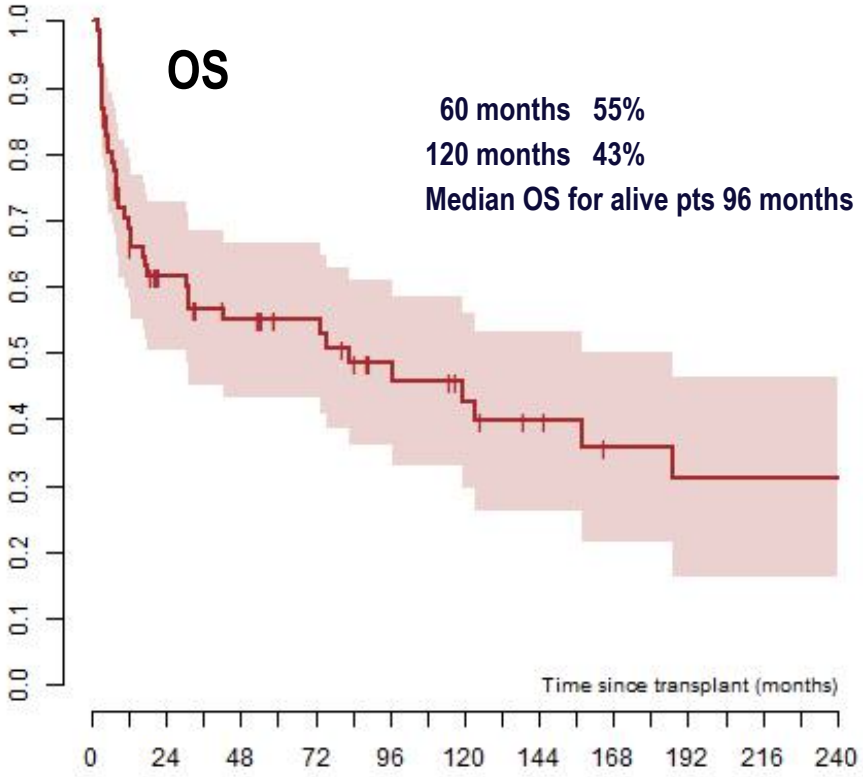
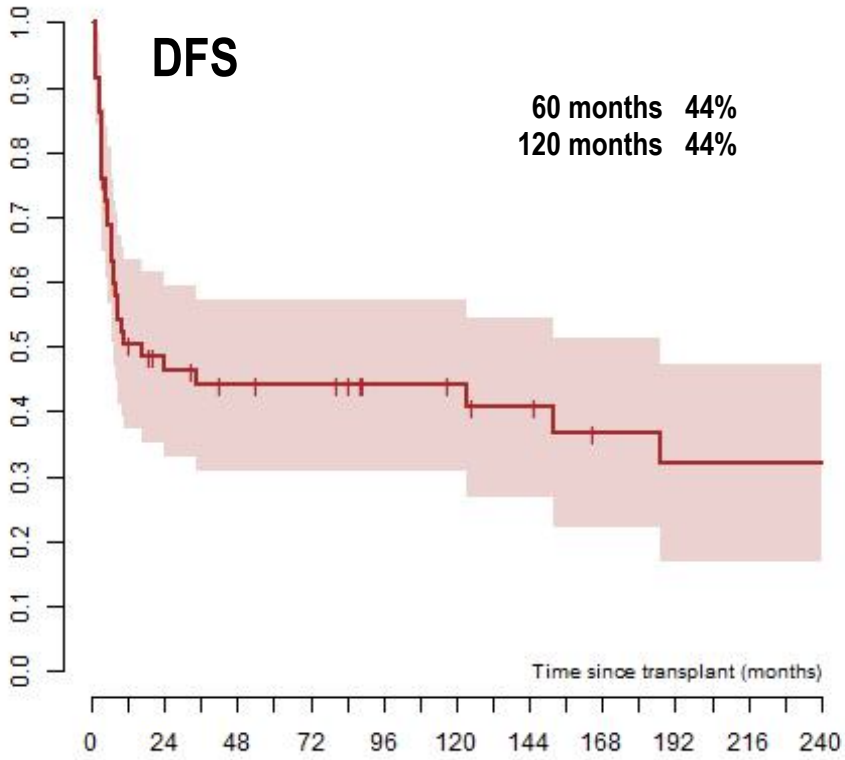
By courtesy of Giorgia Saporiti

Milan Experience (updated March 2026)





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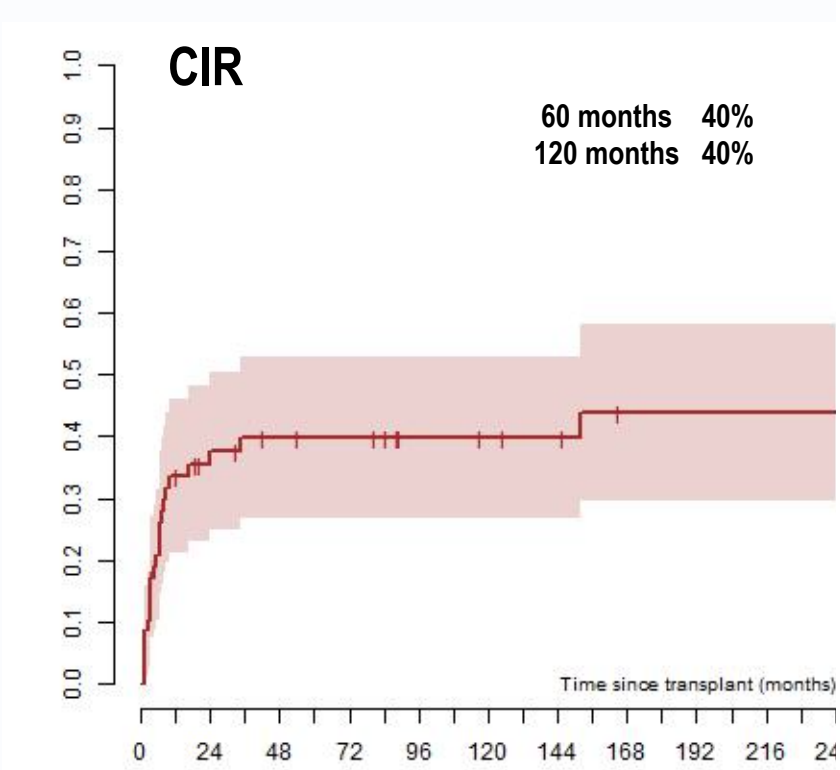
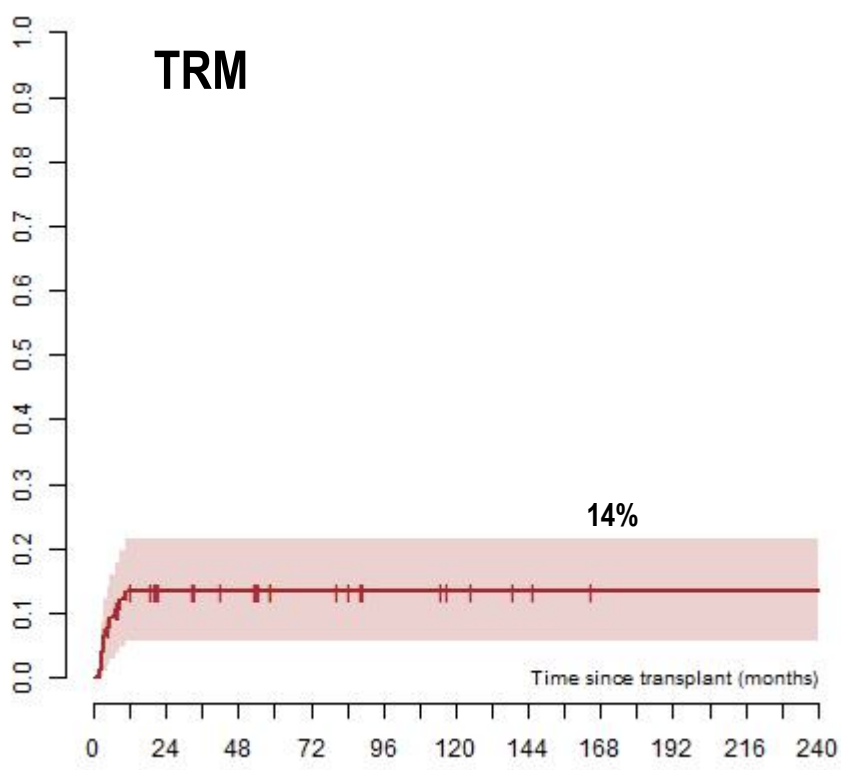
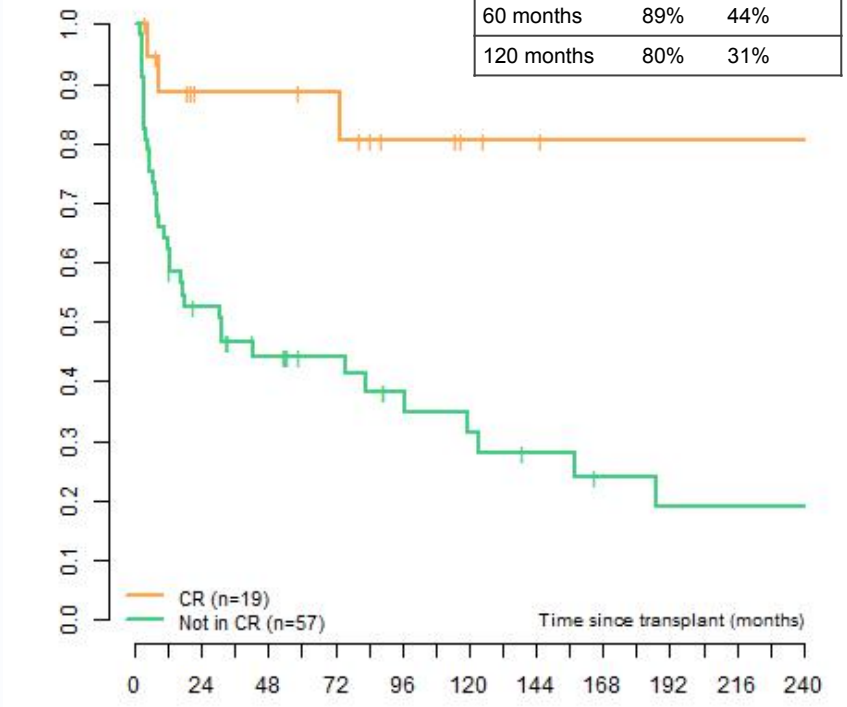




Overall and Progression-free Survival by disease status at HCT

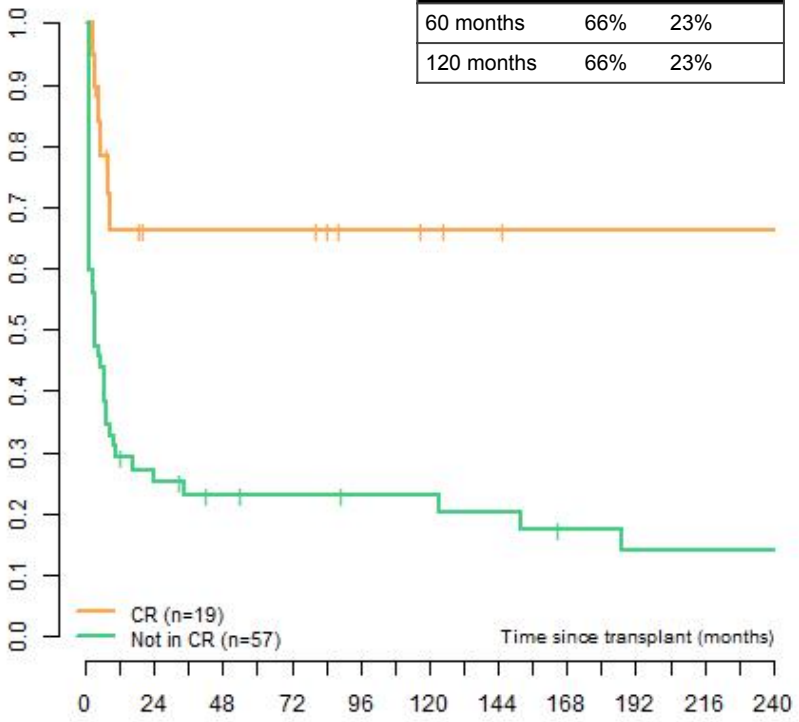
OS

Time	CR	Not CR
60 months	89%	44%
120 months	80%	31%

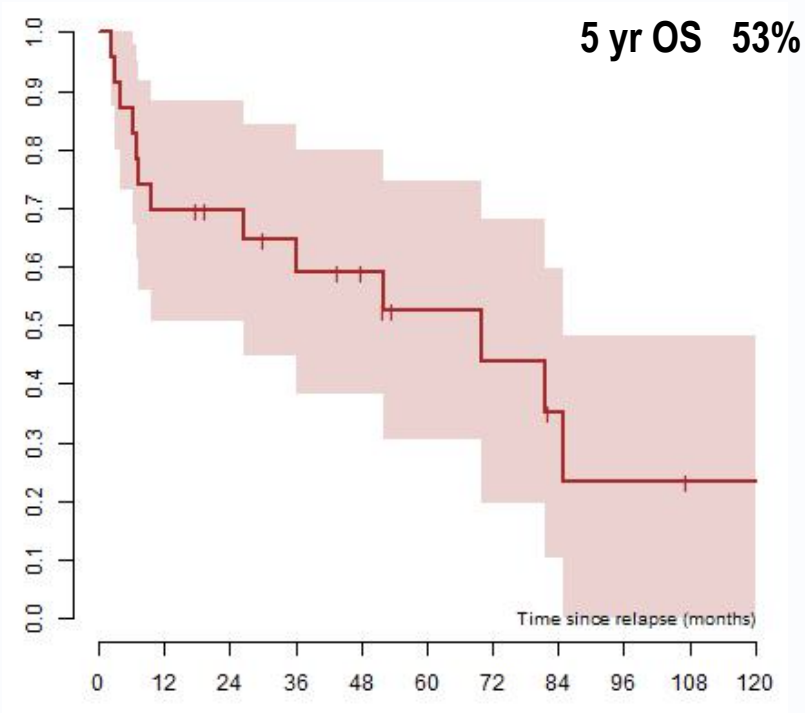


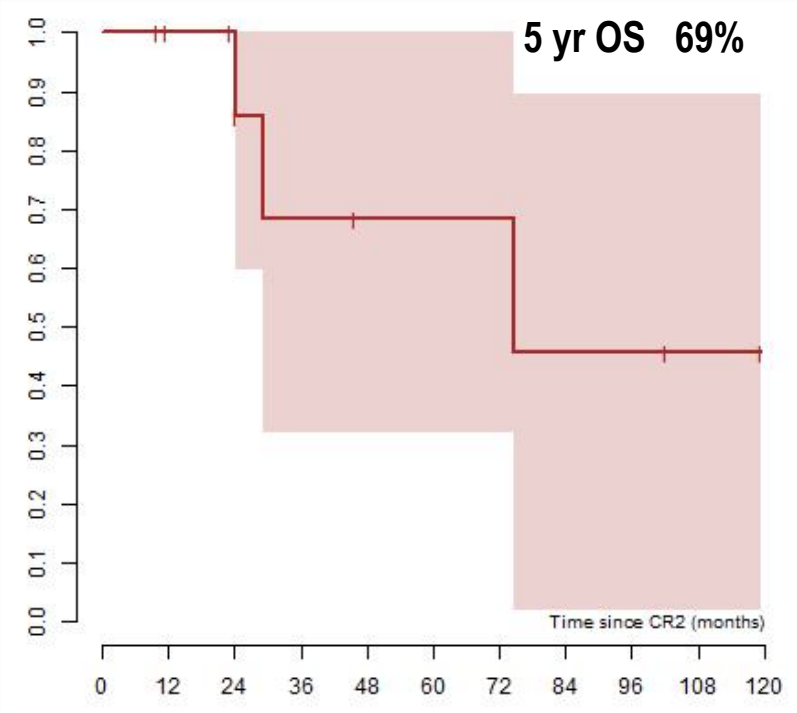
PFS

Time	CR	Not CR
60 months	66%	23%
120 months	66%	23%



Overall Survival after relapse and in CR2





REVIEW ARTICLE OPEN

Allogeneic hematopoietic cell transplant in cutaneous T-cell lymphomas: recommendations from the EBMT PH&G Committee

Gandhi Damaj[1,26], Adèle de Masson[2,26], Peter Dreger[3], Ali Bazarbachi[4], Philipp Berning[5], Rafael F. Duarte[6], Christopher P. Fox[7], Emmanuella Guenova[8], Olivier Hermine[9], Charalampia Kyriakou[10], Alina Tanase[11], Olivier Tournilhac[12], Wojiech Jurczak[13], Imke E. Karsten[5], Stéphanie Nguyen Quoc[14], Yasmina Serroukh[15], Federico Stella[16], Gerald Wulf[17], Anna Sureda[18], Evangelia Papadavid[19], Pablo L. Ortiz-Romero[20], Annalisa Ruggeri[21], Isabel Sánchez-Ortega[22], Julia J. Scarisbrick[23], Ibrahim Yakoub-Agha[24], Francesco Onida[25,27] ✉ and Norbert Schmitz[5,27] ✉

DOI: 10.1111/jdv.70042

REVIEW ARTICLE

JEADV JOURNAL OF THE EUROPEAN ACADEMY OF DERMATOLOGY & VENEREOLOGY

Allogeneic haematopoietic cell transplant in cutaneous T-cell lymphomas: Recommendations from the EBMT PH&G Committee

Gandhi Damaj[1] | Adèle de Masson[2] | Peter Dreger[3] | Ali Bazarbachi[4] | Philipp Berning[5] | Rafael F. Duarte[6] | Christopher P. Fox[7] | Emmanuella Guenova[8] | Olivier Hermine[9] | Charalampia Kyriakou[10] | Alina Tanase[11] | Olivier Tournilhac[12] | Wojiech Jurczak[13] | Imke E. Karsten[5] | Stéphanie Nguyen Quoc[14] | Yasmina Serroukh[15] | Federico Stella[16] | Gerald Wulf[17] | Anna Sureda[18] | Evangelia Papadavid[19] | Pablo L. Ortiz-Romero[20] | Annalisa Ruggeri[21] | Isabel Sánchez-Ortega[22] | Julia J. Scarisbrick[23] | Ibrahim Yakoub-Agha[24] | Francesco Onida[25] | Norbert Schmitz[5]

EBMT: PH&G workshop (Lille 30/9-1/10/2024)

- Which CTCL patients are candidates for allo-HCT?
- What is the optimal timing for allo-HCT?
- How should allo-HCT be performed in CTCL patients?
- How should CTCL patients be managed post-allo-HCT

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Which CTCL patients are candidates for allo-HCT?

- **For patients with early-stage** MF (IA–IIA), **allo-HCT** is generally **not indicated** (it may be considered on an individual basis for patients with stage IB/IIA MF who have relapsed or are refractory after multiple lines of systemic therapy)
- Patients with **large cell transformation**, **stage IV MF and patients with SS**, should be considered for **allo-HCT regardless of the treatment line**.
- Eligible patients with **relapsed or refractory stage IIB and III** should be considered for **allo-HCT, as soon as response is achieved**.
- **For refractory cases**, including those post-TSEB, allo-HCT is **not recommended.**

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What is the optimal timing for allo-HCT?

- Patients with **high-risk advanced CTCL*** (both MF and SS) meeting the indication for allo-HCT, **should undergo transplantation as soon as they reach CR**.

- For patients not reaching CR after salvage therapy, **VGPR or PR with limited residual disease** are also considered **acceptable conditions.**

- There are no specific recommendations regarding the optimal number and modalities of prior therapies before allo-HCT.

* According to CLIPI

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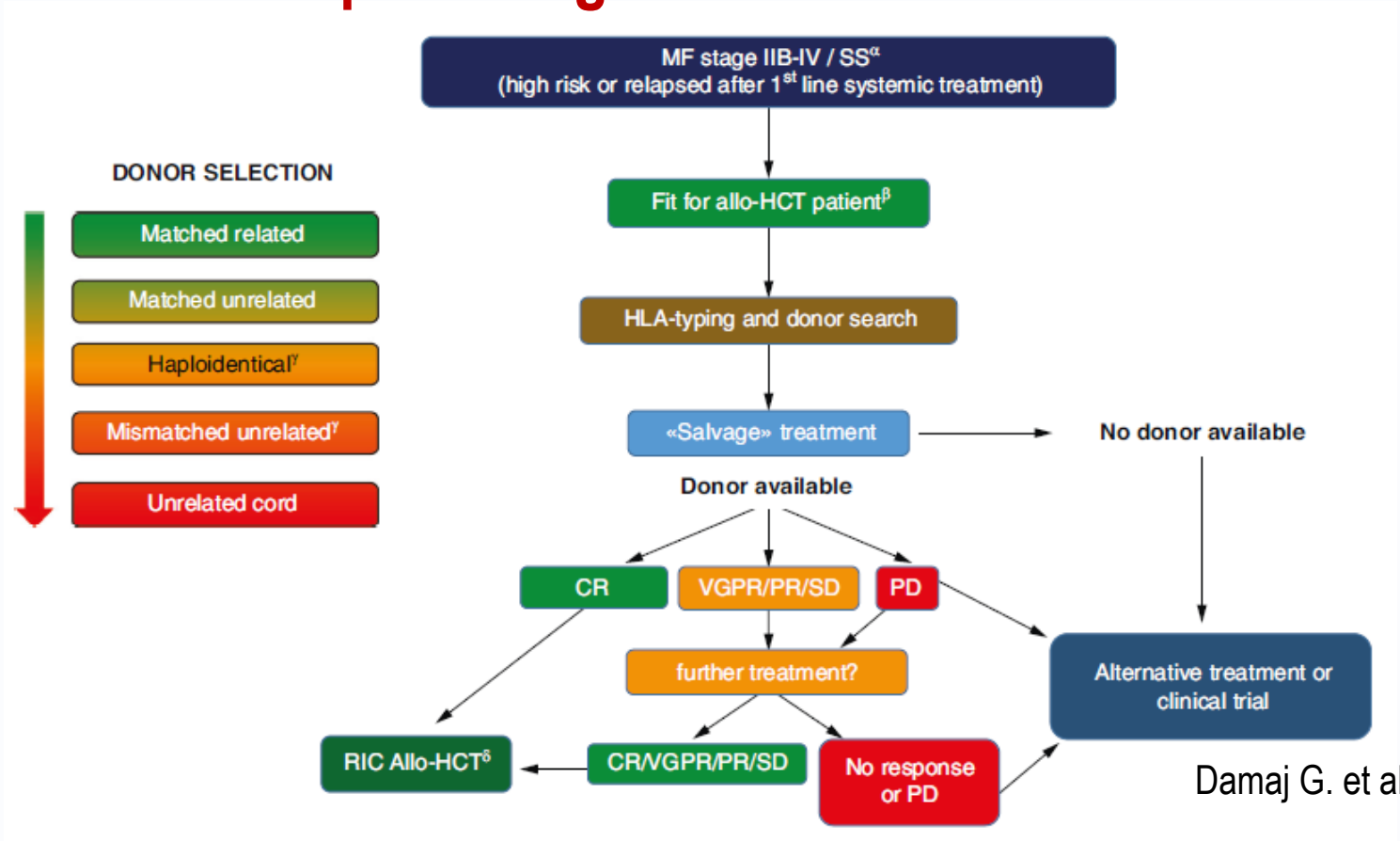
Proposed algorithm for allo-HCT in CTCL



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TAKE-HOME MESSAGES

1 TREATMENT SHOULD BE COMPARTMENT-DRIVEN

The dominant disease compartment should guide therapeutic selection.

2 IMMUNOMODULATORY APPROACHES REMAIN THE BACKBONE OF THERAPY

- ECP
- Bexarotene
- Peg-IFNα
- Low-dose methotrexate

Particularly in erythrodermic MF and Sézary syndrome.

3 TARGETED THERAPIES HAVE CHANGED THE TREATMENT LANDSCAPE

- Mogamulizumab (anti-CCR4)
- Brentuximab vedotin (anti-CD30)
- Alemtuzumab (anti-CD52) (selected patients)

Improved disease control with reduced reliance on conventional chemotherapy.

4 COMBINATION STRATEGIES ARE INCREASINGLY USED

- ECP + Bexarotene
- ECP + Peg-IFN
- Mogamulizumab + ECP
- TSEB-based combinations

Aim: maximize efficacy while minimizing cumulative toxicity.

5 EARLY TRANSPLANT REFERRAL IS ESSENTIAL

Allogeneic HCT remains the only potentially curative option.

Referral should occur before multiple treatment failures and before loss of disease control.

The goal is not simply to treat advanced CTCL, but to integrate skin-directed, systemic and transplant strategies within a personalized multidisciplinary pathway.

EHA EUROPEAN HEMATOLOGY ASSOCIATION | EORTC-CLTG Cutaneous Lymphoma Task Force | ISCL INTERNATIONAL SOCIETY FOR CUTANEOUS LYMPHOMAS | EBMT European Society for Blood and Marrow Transplantation

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