Il management del linfoma primitivo cutaneo di derivazione T-linfocitaria nell'ambito della regione Emilia-Romagna

Bologna, Royal Hotel Carlton
17 gennaio 2023

Ematologia Modena

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Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
Novartis						x	
Abbvie						x	
MSD						x	
Gilead Sci						x	x Travel Grant
Jazz Pharma						x	
Daiichi-Sankyo						x	
Sanofi						x	
Grifols						x	

Accesso Pazienti con sospetto o provato linfoma cutaneo in Ematologia MO da

- UO-C Dermatologia
- PS Affido Onco-Ematologico lun-ven 8.00-20.00 e sab 8.00-13.00
- Ambulatorio di riferimento Ematologico per MMG e territorio AUSL MO, lun-ven 14.00-16.00

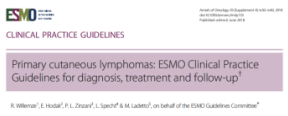
Diagnosi di neoplasie ematologiche in Ematologia MO si basa su

Piattaforma diagnostica avanzata che comprende esami di

- Cito-isto-immunoistochimica
- Biologia molecolare
- Citogenetica
- Citofluorimetria

e produce un referto integrato

PD1 for dd between Sèzary Syndrome and Erythrodermic Inflammatory Dermatoses



ESMO CLINICAL PRACTICE GUIDELINES

Primary cutaneous lymphomas: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up†

Criteria	Scoring system
Clinical	
Basic	2 points for basic criteria and 2 additional criteria
Persistent and/or progressive patches/thin plaques	1 point for basic criteria and 1 additional criterion
Additional	
(1) Non-sun-exposed location	
(2) Size/shape variation	
(3) Poikiloderma	
Histopathological	
Basic	2 points for basic criteria and 2 additional criteria
Superficial lymphoid infiltrate	1 point for basic criteria and 1 additional criterion
Additional	
(1) Epidermotropism without spongiosis	
(2) Lymphocytic atypia	
Molecular biological	
(1) Clonal T-cell receptor gene rearrangement	1 point for clonality
Immunopathological (immunohistochemical)	
(1) <50% CD2+, CD3+, and/or CD5+ T cells	1 point for one or more criteria
(2) <10% CD7+ T cells	
(3) Epidermal/dermal discordance of CD2, CD3, CD5, or CD7 (T-cell antigen deficiency confined to the epidermis)	

Early stage MF vs inflammatory benign dermatoses like eczema, parapsorisis, lichenoid dermatoses, drug eruptions etc.

Pimpinelli N, Olsen EA, Santucci M, Vonderheid E, Haeffner AC, Stevens S, et al. Defining early mycosis fungoides. J Am Acad Dermatol. 2005;53:1053–63.

International Society for Cutaneous Lymphoma Algorithm for diagnosis of Early MF

Table 2. Recommendations for staging evaluation in patients with MF/SS [6]

Complete physical examination including:
- Determination of type(s) of skin lesions
- Identification of any palpable lymph node, especially those ≥ 1.5 cm in largest diameter or firm, irregular, clustered or fixed
- Identification of any organomegaly

Skin biopsy
- Most indurated area if only one biopsy
- Routine histology and immunophenotyping
- Evaluation for clonality of *TCR* gene rearrangement (optional)

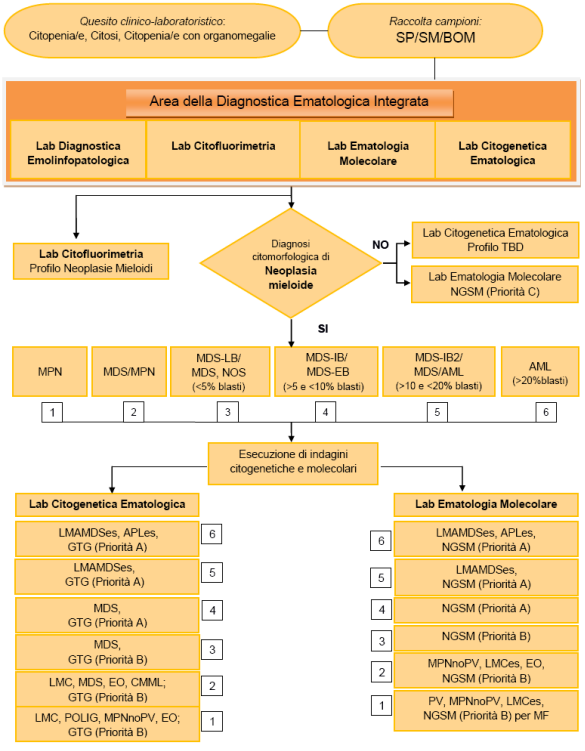
Blood tests
- CBC with manual differential, liver function tests, LDH, comprehensive chemistries
- *TCR* gene rearrangement and relatedness to any clone in skin (optional)
- Analysis for abnormal lymphocytes by either Sézary cell count with determination absolute number of Sézary cells and/or flow cytometry (including $CD4^+/CD7^-$ or $CD4^+/CD26^-$) (optional)

Radiological tests
- CT scans of chest, abdomen and pelvis alone ± FDG-PET (optional in patients with early-stage MF)

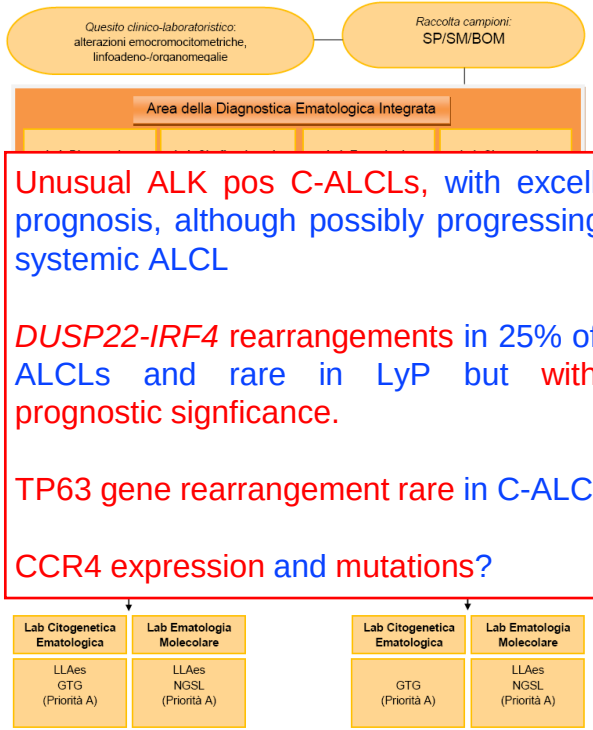
Lymph node biopsy
- Excisional biopsy in patients with a node that is either ≥ 1.5 cm in diameter and/or is firm, irregular, clustered or fixed
- Routine histology, immunohistochemistry and *TCR* gene rearrangement analysis

CBC, complete blood count; CT, computed tomography; FDG-PET, fluorodeoxyglucose-positron emission tomography; LDH, lactate dehydrogenase; MF, mycosis fungoides; SS, Sézary syndrome; TCR, T cell receptor
Adapted from [6] with permission from the American Society of Hematology; permission conveyed through Copyright Clearance Center, Inc.

Percorso Ematologia Diagnostica Neoplasie mieloidi



Percorso Ematologia Diagnostica delle Neoplasie dei Precursori Linfoidi



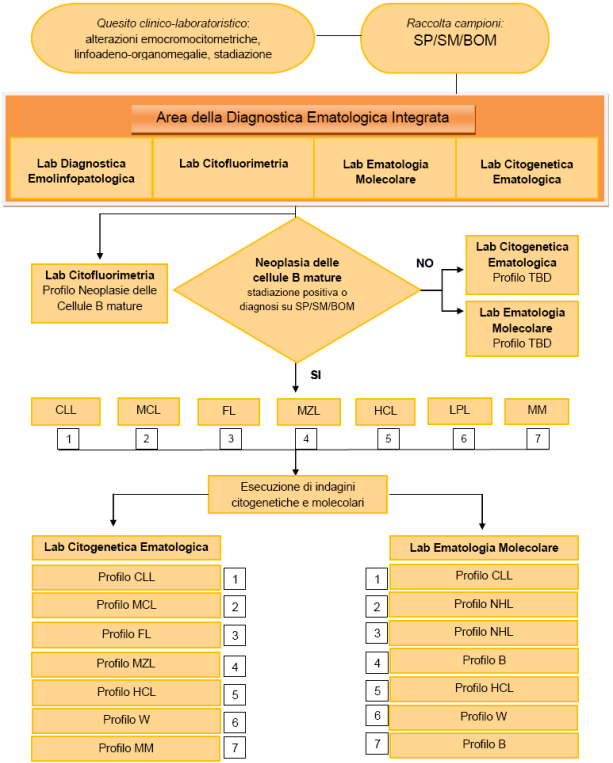
Unusual ALK pos C-ALCLs, with excellent prognosis, although possibly progressing to systemic ALCL

DUSP22-IRF4 rearrangements in 25% of C-ALCLs and rare in LyP but without prognostic signficance.

TP63 gene rearrangement rare in C-ALCLs.

CCR4 expression and mutations?

Percorso Ematologia Diagnostica Neoplasie delle cellule B mature ("Small B cell neoplasms")



Courtesy of A. Paolini and E. Tagliafico

Table 2. WHO Classification of Haematolymphoid Tumours, 5th edition: T-cell and NK-cell lymphoid proliferations and lymphomas.

Primary cutaneous T-cell lymphomas	
Primary cutaneous CD4-positive small or medium T-cell lymphoproliferative disorder	(Same)
Primary cutaneous acral CD8-positive lymphoproliferative disorder	Primary cutaneous acral CD8-positive T-cell lymphoma
Mycosis fungoides	(Same)
Primary cutaneous CD30-positive T-cell lymphoproliferative disorder: Lymphomatoid papulosis	(Same)
Primary cutaneous CD30-positive T-cell lymphoproliferative disorder: Primary cutaneous anaplastic large cell lymphoma	(Same)
Subcutaneous panniculitis-like T-cell lymphoma	(Same)
Primary cutaneous gamma/delta T-cell lymphoma	(Same)
Primary cutaneous CD8-positive aggressive epidermotropic cytotoxic T-cell lymphoma	(Same)
Primary cutaneous peripheral T-cell lymphoma, NOS	*Not previously included*

SEPARATE ENTITIES

The 5th edition of the World Health Organization Classification of Haematolymphoid Tumours: Lymphoid Neoplasms

Rita Alaggio[1], Catalina Amador[2], Ioannis Anagnostopoulos[3], Ayoma D. Attygalle[4], Iguaracyra Barreto de Oliveira Araujo[5], Emilio Berti[6], Govind Bhagat[7], Anita Maria Borges[8], Daniel Boyer[9], Mariarita Calaminici[10], Amy Chadburn[11], John K. C. Chan[12], Wah Cheuk[12], Wee-Joo Chng[13], John K. Choi[14], Shih-Sung Chuang[15], Sarah E. Coupland[16], Magdalena Czader[17], Sandeep S. Dave[18], Daphne de Jong[19], Ming-Qing Du[20✉], Kojo S. Elenitoba-Johnson[21], Judith Ferry[22✉], Julia Geyer[11], Dita Gratzinger[23], Joan Guitart[24], Sumeet Gujral[25], Marian Harris[26], Christine J. Harrison[27], Sylvia Hartmann[28], Andreas Hochhaus[29], Patty M. Jansen[30], Kennosuke Karube[31], Werner Kempf[32], Joseph Khoury[33], Hiroshi Kimura[34], Wolfram Klapper[35], Alexandra E. Kovach[36], Shaji Kumar[37], Alexander J. Lazar[38], Stefano Lazzi[39], Lorenzo Leoncini[39], Nelson Leung[40], Vasiliki Leventaki[41], Xiao-Qiu Li[42], Megan S. Lim[21], Wei-Ping Liu[43], Abner Louissaint Jr.[22], Andrea Marcogliese[44], L. Jeffrey Medeiros[33], Michael Michal[45], Roberto N. Miranda[33], Christina Mitteldorf[46], Santiago Montes-Moreno[47], William Morice[48], Valentina Nardi[22], Kikkeri N. Naresh[49], Yasodha Natkunam[23], Siok-Bian Ng[50], Ilske Oschlies[35], German Ott[51✉], Marie Parrens[52], Melissa Pulitzer[53], S. Vincent Rajkumar[54], Andrew C. Rawstron[55], Karen Rech[48], Andreas Rosenwald[3], Jonathan Said[56], Clémentine Sarkozy[57], Shahin Sayed[58], Caner Saygin[59], Anna Schuh[60], William Sewell[61], Reiner Siebert[62✉], Aliyah R. Sohani[22], Reuben Tooze[63], Alexandra Traverse-Glehen[64], Francisco Vega[33], Beatrice Vergier[65], Ashutosh D. Wechalekar[66], Brent Wood[36], Luc Xerri[67] and Wenbin Xiao[53]

Leukemia (2022) 36:1720 – 1748

MEDICAL DERMATOLOGY

BJD
British Journal of Dermatology

Clinical, histopathological and prognostic features of primary cutaneous acral CD8⁺ T-cell lymphoma and other dermal CD8⁺ cutaneous lymphoproliferations: results of an EORTC Cutaneous Lymphoma Group workshop*

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British Journal of Dermatology (2022) **186**, pp887–897

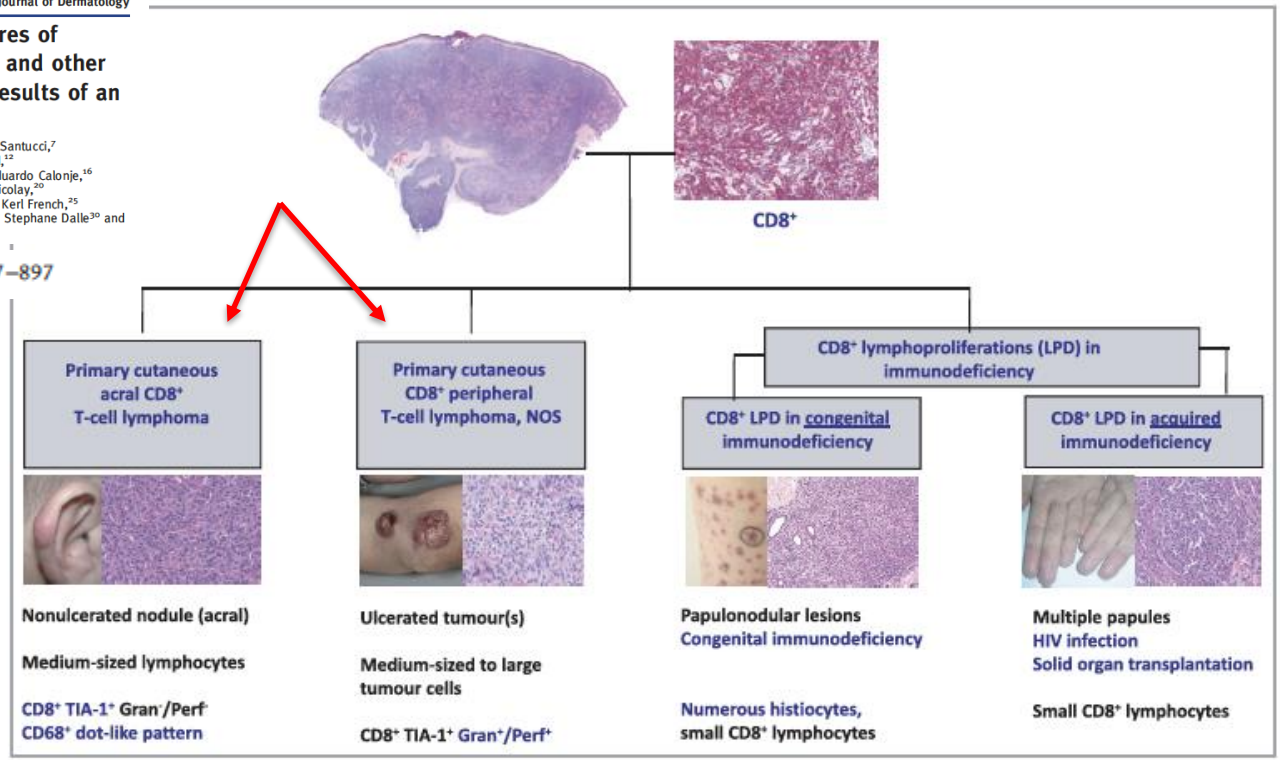


Figure 5 Differentiation of dermal small- to medium-sized CD8⁺ infiltrates. Summary of the most relevant clinical, histological and immunophenotypic features for the differentiation of dermal CD8⁺ infiltrates. Gran, granzyme B; NOS, not otherwise specified; Perf, perforin.

Primary cutaneous T-cell lymphoid proliferations and lymphomas (CTCL): rare subtypes become entities

Primary cutaneous T-cell lymphoid proliferations and lymphomas (CTCL) comprise a dedicated family within the mature T/NK-cell neoplasms chapter in WHO-HAEM5, and include nine entities.

In WHO-HAEM4R, primary cutaneous gamma/delta T-cell lymphoma, CD8-positive aggressive epidermotropic cytotoxic T-cell lymphoma, acral CD8-positive T-cell lymphoproliferative disorder and CD4-positive small or medium T-cell lymphoproliferative disorder were grouped together under the term 'cutaneous peripheral T-cell lymphoma, rare subtypes', but are now each listed as separate entities in WHO-HAEM5 acknowledging their specific clinicopathological and genetic characteristics. The variants of mycosis fungoides from WHO-HAEM4R remain in place as subtypes; however, within the folliculotropic category, clinical early versus advanced stage patterns are described, and should be distinguished, to acknowledge differing clinical outcomes. There still remain rare cases that do not fit into the other known CTCL entities, and that are grouped into the newly coined entity "primary cutaneous peripheral T-cell lymphoma, NOS", awaiting further studies to clarify their nature [224].

As there is morphologic and immunophenotypic overlap among the various forms of primary CTCL, correlation with clinical history, signs and symptoms is a key element of the diagnostic work-up. Thus, dermatological examination and clinical photographic documentation are indispensable in reaching the correct diagnosis [224, 225].

FMF

NOS

Leukemia (2022) 36:1720–1748

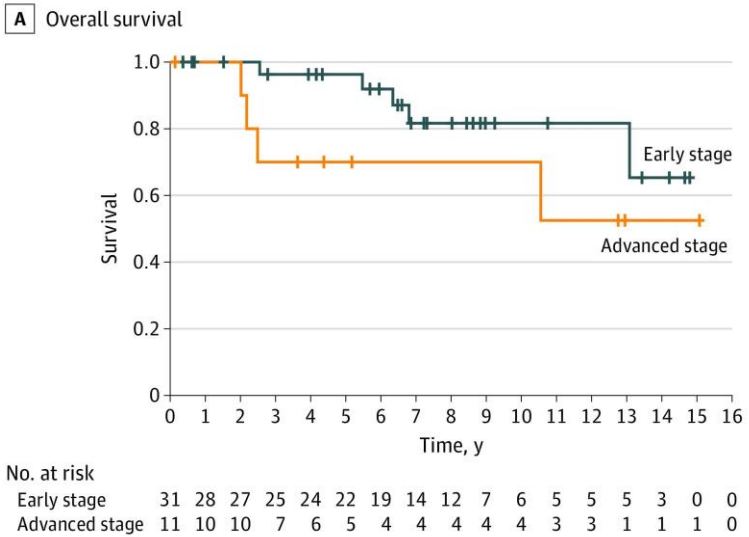
The 5th edition of the World Health Organization Classification of Haematolymphoid Tumours: Lymphoid Neoplasms

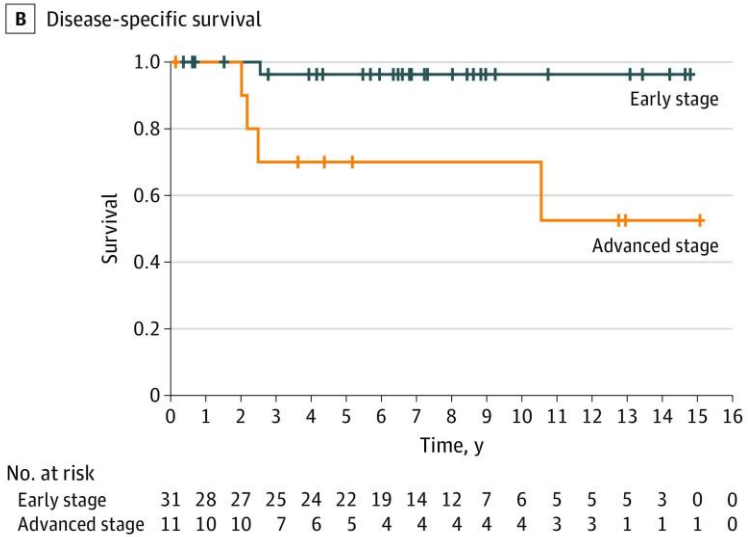
Rita Alaggio[1], Catalina Amador[2], Ioannis Anagnostopoulos[3], Ayoma D. Attygalle[4], Iguaracyra Barreto de Oliveira Araujo[5], Emilio Berti[6], Govind Bhagat[7], Anita Maria Borges[8], Daniel Boyer[9], Mariarita Calaminici[10], Amy Chadburn[11], John K. C. Chan[12], Wah Cheuk[12], Wee-Joo Chng[13], John K. Choi[14], Shih-Sung Chuang[15], Sarah E. Coupland[16], Magdalena Czader[17], Sandeep S. Dave[18], Daphne de Jong[19], Ming-Qing Du[20]✉, Kojo S. Elenitoba-Johnson[21], Judith Ferry[22]✉, Julia Geyer[11], Dita Gratzinger[23], Joan Guitart[24], Sumeet Gujral[25], Marian Harris[26], Christine J. Harrison[27], Sylvia Hartmann[28], Andreas Hochhaus[29], Patty M. Jansen[30], Kennosuke Karube[31], Werner Kempf[32], Joseph Khoury[33], Hiroshi Kimura[34], Wolfram Klapper[35], Alexandra E. Kovach[36], Shaji Kumar[37], Alexander J. Lazar[38], Stefano Lazzi[39], Lorenzo Leoncini[39], Nelson Leung[40], Vasiliki Leventaki[41], Xiao-Qiu Li[42], Megan S. Lim[21], Wei-Ping Liu[43], Abner Louissaint Jr.[22], Andrea Marcogliese[44], L. Jeffrey Medeiros[33], Michael Michal[45], Roberto N. Miranda[33], Christina Mitteldorf[46], Santiago Montes-Moreno[47], William Morice[48], Valentina Nardi[22], Kikkeri N. Naresh[49], Yasodha Natkunam[23], Siok-Bian Ng[50], Ilske Oschlies[35], German Ott[51]✉, Marie Parrens[52], Melissa Pulitzer[53], S. Vincent Rajkumar[54], Andrew C. Rawstron[55], Karen Rech[48], Andreas Rosenwald[3], Jonathan Said[56], Clémentine Sarkozy[57], Shahin Sayed[58], Caner Saygin[59], Anna Schuh[60], William Sewell[61], Reiner Siebert[62]✉, Aliyah R. Sohani[22], Reuben Tooze[63], Alexandra Traverse-Glehen[64], Francisco Vega[33], Beatrice Vergier[65], Ashutosh D. Wechalekar[66], Brent Wood[36], Luc Xerri[67] and Wenbin Xiao[53]

3 clinical subgroups of Folliculoptropic Mycosis fungoides with significantly different survival data were distinguished:

early skin-limited FMF (group A; n = 84; **5-year and 10-year OS, 92% and 72%**);
advanced skin-limited FMF (group B; n = 102**; 5-year and 10-year OS, 55% and 28%**);
FMF presenting with extracutaneous disease (group C; n = 17; 5-year and 10-year OS, 23% and 2%).

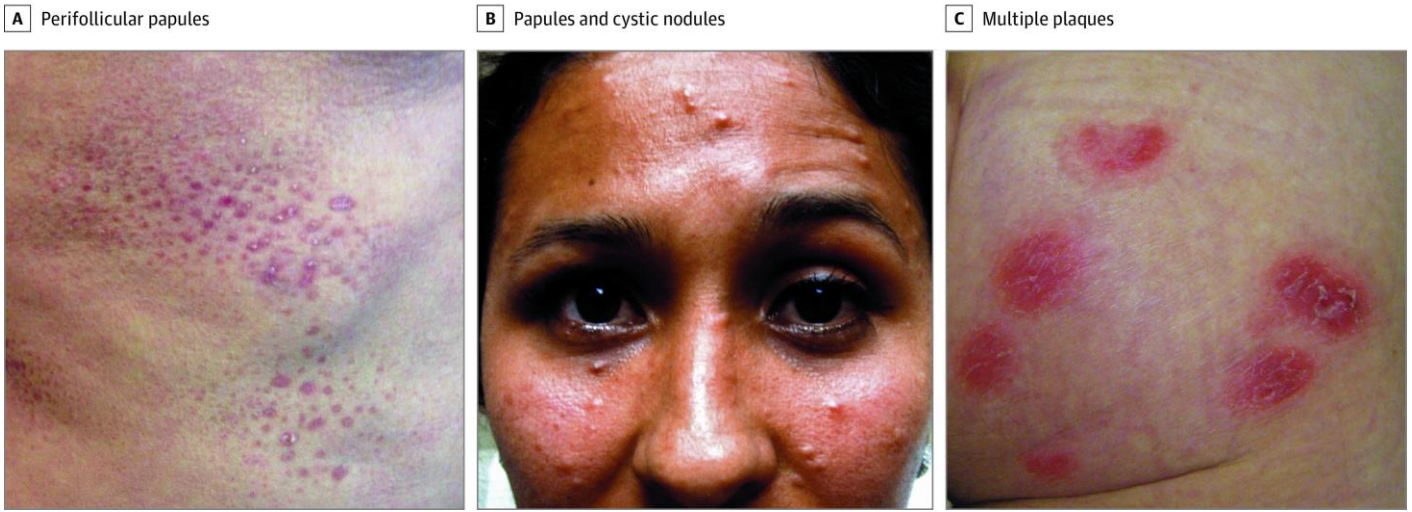
Age at diagnosis, large cell transformation and secondary bacterial infection were independent risk factors for disease progression and/or poor survival *Charli-Joseph et al., JAMA Dermatol. 2021 Feb; 157(2): 1–9.*

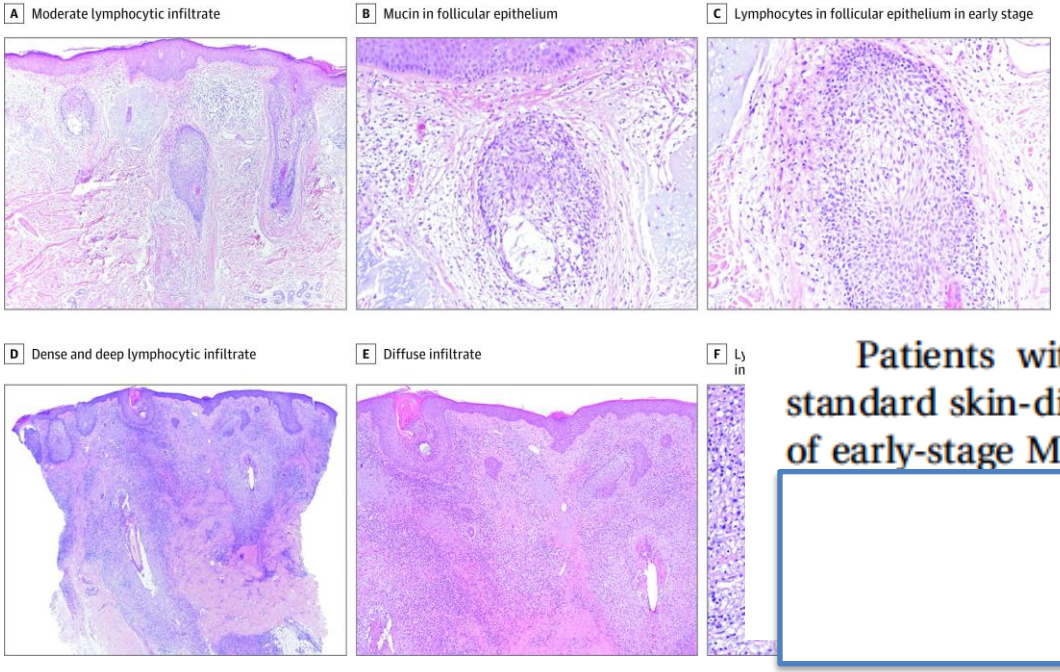




Clinical Morphologic Features in Folliculotropic Mycosis Fungoides

A, Perifollicular papules coalescing into plaques on the flank in a patient with early-stage cutaneous disease.
B, Comedone-like papules and cystic nodules on the face of a patient with early-stage cutaneous disease.
C, Multiple plaques without follicular prominence on buttocks in a patient with advanced-stage cutaneous disease.
Charli-Joseph et al., JAMA Dermatol. 2021 Feb; 157(2): 1–9.



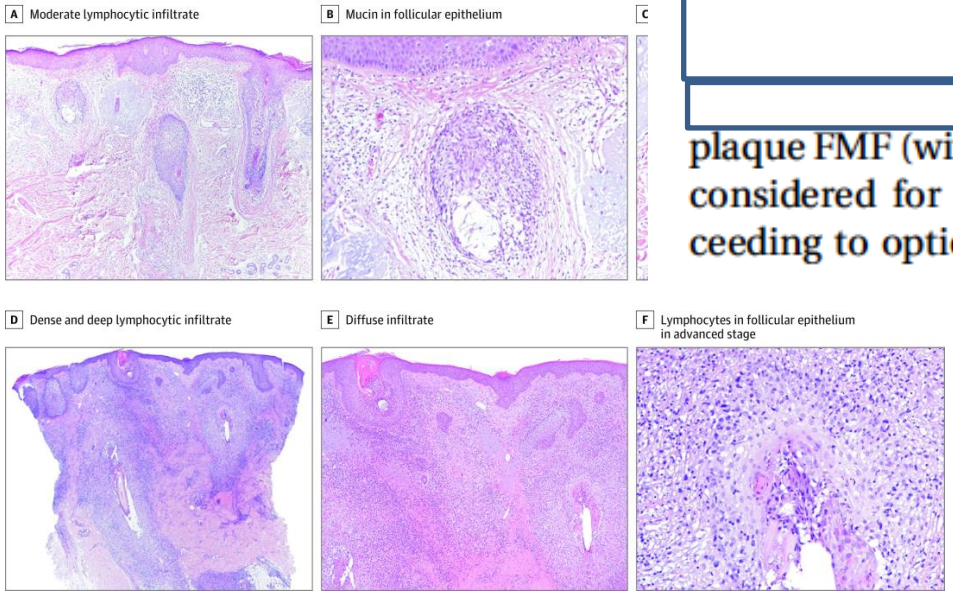


Patients with early-stage FMF may benefit from standard skin-directed therapies used for the treatment of early-stage MF

Histopathologic Features Seen in Folliculotropic Mycosis Fungoides (FMF)

A, Low-power image of early-stage cutaneous FMF with perifollicular and intrafollicular sparse to moderate lymphocytic infiltrate (hematoxylin-eosin, original magnification ×40). B, Medium-power image of early-stage cutaneous FMF demonstrating mucin within follicular epithelium (hematoxylin-eosin, original magnification ×200). C, High-power image of early-stage cutaneous FMF demonstrating penetration of lymphocytes into follicular epithelium (hematoxylin-eosin, original magnification ×400).

Charli-Joseph et al., JAMA Dermatol. 2021 Feb; 157(2): 1–9.



those with generalized indolent/ plaque FMF (without evidence of LCT) should initially be considered for options under SYST-CAT A before proceeding to options listed under SYST-CAT B.

Histopathologic Features Seen in Folliculotropic Mycosis Fungoides (FMF)

D, Low-power image of advanced-stage cutaneous FMF with a dense and deep perifollicular and intrafollicular lymphocytic infiltrate (hematoxylin-eosin, original magnification ×40). E, Medium-power image of advanced-stage cutaneous FMF demonstrating follicular prominence of the infiltrate despite the diffuse configuration (hematoxylin-eosin, original magnification ×200). F, High-power image of advanced-stage cutaneous FMF demonstrating penetration of lesional lymphocytes into the follicular epithelium and follicular distortion (hematoxylin-eosin, original magnification ×400).

Charli-Joseph et al., JAMA Dermatol. 2021 Feb; 157(2): 1–9.

SYST-CAT A includes regimens that can often be tolerated for longer periods with less cumulative toxicity, less immunosuppression, and/or higher efficacy. In a patient with stage IIB disease with limited tumor lesions or stage IIB generalized tumor stage disease we would consider a SYST-CAT A regimen, often following initial RT.

	Preferred Regimens (alphabetical order)
SYST-CAT A	• Brentuximab vedotin[i,j,k] • Bexarotene[n] • Extracorporeal photopheresis (ECP)[l] • Interferons (IFN-alfa-2b[m] or IFN-gamma 1b) • Methotrexate (≤50 mg q week) • Mogamulizumab[n] • Romidepsin[n] • Vorinostat[h]

SYST-CAT B includes regimens that can have more significant cumulative toxicity, but in our experience, can be effective for stage IIB generalized tumor disease stage III erythrodermic disease, or stage IV disease

SYST-CAT B	• Brentuximab vedotin[i,j,k] • Gemcitabine • Liposomal doxorubicin • Pralatrexate (low-dose or standard dose)

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LCT of MF

LCT is diagnosed when large cells are present in >25% of lymphoid/tumor cell infiltrates in a skin lesion biopsy, and the incidence of LCT is strongly dependent on the disease stage at diagnosis (1% in early-stage disease vs 27% for stage IIB and 56% to 67% for stage IV disease).[7–9] LCT is often, but not always, aggressive. CD30 expression is associated with LCT in MF or SS in 30% to 50% of cases and this finding may have potential implications for CD30-directed therapies.[7–9] However, it should be noted that CD30 expression is variable in MF and SS, with the leukemic Sézary cells typically being CD30–.

Systemic therapy (brentuximab vedotin, gemcitabine, liposomal doxorubicin, pralatrexate, or romidepsin) with or without skin-directed therapies is the initial treatment of generalized cutaneous or extracutaneous lesions with LCT

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SKIN-DIRECTED THERAPY

SYSTEMIC THERAPY

Clinical Staging of MF and SS[l]

Clinical Stage[r]	T (Skin)	N (Node)	M (Visceral)	B (Blood Involvement)	Guidelines Page
IA (Limited skin involvement)	T1 (patches, papules, and/or plaques covering <10% body surface area [BSA])	N0	M0	B0 or B1	MFSS-6
IB (Skin only disease)	T2 (patches, papules, and/or plaques covering ≥10% BSA)	N0	M0	B0 or B1	MFSS-7
IIA	T1–2	N1–2	M0	B0 or B1	MFSS-7
IIB (Tumor stage disease)	T3 (One or more tumors [≥1 cm in diameter])	N0–2	M0	B0 or B1	MFSS-8
IIIA (Erythrodermic disease)	T4 (Confluence of erythema ≥80% BSA)	N0–2	M0	B0	MFSS-10
IIIB (Erythrodermic disease)	T4 (Confluence of erythema ≥80% BSA)	N0–2	M0	B1	MFSS-10
IVA_1	T1-4	N0–2	M0	B2	MFSS-11
IVA_2	T1-4	N3	M0	B0 or B1 or B2	MFSS-11
IVB	T1-4	N0–3	M1	B0 or B1 or B2	MFSS-11
	Large-cell transformation (LCT)[s]				MFSS-12

[l] Olsen E, Vonderheid E, Pimpinelli N, et al. Blood 2007;110:1713-1722.
[r] Folliculotropism is a histologic feature that can occur irrespective of stage. Histologic evidence of folliculotropic MF is associated with higher risk of disease progression. In selected cases or inadequate response, consider primary treatment for stage IIB (tumor stage disease).
[s] LCT is a histologic feature that can occur irrespective of clinical stage. LCT often but not always corresponds to a more aggressive growth rate requiring systemic therapies.

Terapia sistemica di pazienti con linfoma T cutaneo in Ematologia MO offerta a

- Pazienti in stadio IIB-IV (MF), SS, linfomi cutanei anaplastici CD30+
- Terapie sistemiche: bexarotene, MTX, ECP, brentuximab (*Alcanza* e *real life*), mogamulizumab (*MAVORIC*), (allo-tx)
- Tossicità vs Progressione (mogamulizumab)
- Resistenza (mogamulizumab)
- Progressione dopo vaccino Sars CoV2
- Terapia Supportiva/Palliativa Precoce, integrata a terapia sistemica *standard* emato-oncologica

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Extracorporeal photopheresis (ECP) is an immunomodulatory therapy in which patient's leukocytes are removed by leukapheresis, treated extracorporeally with 8-methoxypsoralen and UVA, and then returned to the patient.[53–55] ECP may be a more appropriate systemic therapy for patients with some level of blood involvement (B1 or B2).

Blood	B0	Absence of significant blood involvement: ≤5% of peripheral blood lymphocytes or <250/mcL are atypical (Sézary) cells or <15% CD4+/CD26- or CD4+/CD7- cells of total lymphocytes
	B1	Low blood tumor burden: >5% of peripheral blood lymphocytes are atypical (Sézary) cells or >15% CD4+CD26- or CD4+CD7- of total lymphocytes but do not meet the criteria of B0 or B2
	B2	High blood tumor burden: ≥1000/mcL Sézary cells[n] determined by cytopathology or ≥1000 CD4+CD26- or CD4+CD7- cells/uL or other abnormal subset of T lymphocytes by flow cytometry with clone in blood same as that in skin. Other criteria for documenting high blood tumor burden in CD4+ MF/SS include CD4+/CD7- cells ≥40% and CD4+CD26- cells ≥30%.

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Phase II and III[82]	Bexarotene	300 mg/m²/d	Stage IA–IIA (n=28)	54%
		>300 mg/m²/d	Stage IA–IIA (n=15)	67%
Phase II and III[83]	Bexarotene	300 mg/m²/d	Stage IIB–IVB (n=56)	45%
		>300 mg/m²/d	Stage IIB–IVB (n=38)	55% (13% CR)

ORR

favorable tolerability profile without significant cumulative toxicity, the NCCN Guidelines recommend consideration of bexarotene for patients with early-stage MF who have insufficient disease control with skin-directed therapy. Bexarotene is also used in combination with phototherapy or ECP for early-stage disease with inadequate response to single-agent therapy and in patients with advanced-stage disease.[65–68] It is important to note that bexarotene is associated with hypertriglyceridemia and central hypothyroidism, which necessitates laboratory monitoring for triglycerides, and serum levels of free thyroxine (T4), often requiring additional management.

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JOURNAL OF CLINICAL ONCOLOGY SPECIAL ARTICLE

Clinical End Points and Response Criteria in Mycosis Fungoides and Sézary Syndrome: A Consensus Statement of the International Society for Cutaneous Lymphomas, the United States Cutaneous Lymphoma Consortium, and the Cutaneous Lymphoma Task Force of the European Organisation for Research and Treatment of Cancer

Elise A. Olsen, Sean Whittaker, Youn H. Kim, Madeleine Duvic, H. Miles Prince, Stuart R. Lessin, Gary S. Wood, Rein Willemze, Marie-France Demierre, Nicola Pimpinelli, Maria Grazia Bernengo, Pablo L. Ortiz-Romero, Martine Bagot, Teresa Estrach, Joan Guitart, Robert Knobler, José Antonio Sanches, Keiji Iwatsuki, Makoto Sugaya, Reinhard Dummer, Mark Pittelkow, Richard Hoppe, Sareena Parker, Larisa Geskin, Lauren Pinter-Brown, Michael Girardi, Günter Burg, Annamari Ranki, Maarran Vermeer, Steven Horwitz, Peter Heald, Steve Rosen, Lorenzo Cerroni, Brigette Dreno, and Eric C. Vonderheid

How We Treat Mycosis Fungoides and Sézary Syndrome

Niloufer Khan, MD[1], Sarah J. Noor, MD[2], Steven Horwitz, MD[1]

Low-dose methotrexate, an oral antifolate agent (<50 mg/wk orally), is also a treatment option for those with patch/plaque MF. In retrospective studies, methotrexate has shown a 33% ORR in 60 patients with stage T2 disease. Time to treatment failure was approximately 15 months (95% CI, 9–20).[30] The ORR was 58% in another, similar retrospective study of 29 patients who had erythrodermic CTCL, with 12 CRs (41%) and 5 PRs (17%). The median time of freedom from treatment failure was 31 months.[31] Of note, the initial trials for bexarotene and methotrexate were conducted before implementation of the global response criteria. These consensus criteria for disease assessment incorporate a detailed assessment of the CTCL burden in lymph nodes and blood, as well as in skin, and provide a uniform method for staging disease response in clinical trials.[32] When bexarotene and methotrexate were used as controls in prospective randomized trials, response rates were lower than previously reported

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Table 1. Systemic Therapy for MF and SS

Trial	Regimen/Dose		Disease Stage and Number of Patients	ORR	Median PFS
ALCANZA trial (phase III RCT)[a,30]	Brentuximab vedotin (1.8 mg/kg every 3 weeks; up to 16 3-week cycles)		Stage IA–IVB MF (n=48)	65% (10% CR)	17 mo
	Oral methotrexate (5–50 mg once per week) for up to 48 weeks or Oral bexarotene (300 mg/m² once per day) for up to 48 weeks		Stage IA–IVB MF (n=49)	16%	4 mo
MAVORIC trial (phase III RCT)[b,31]	Mogamulizumab (1 mg/kg intravenously on a weekly basis for the first 28-day cycle, then on days 1 and 15 of subsequent cycles)		Stage IB–IVA (n=186)	28% (23% by IR)	8 mo (7 mo by IR)
	Vorinostat (400 mg daily)		Stage IB–IVA (n=186)	5% (4% by IR)	3 mo (4 mo by IR)
Phase II and III[32]	Bexarotene	300 mg/m²/d	Stage IA–IIA (n=28)	54%	
		>300 mg/m²/d	Stage IA–IIA (n=15)	67%	
Phase II and III[33]	Bexarotene	300 mg/m²/d	Stage IIB–IVB (n=56)	45%	
		>300 mg/m²/d	Stage IIB–IVB (n=38)	55% (13% CR)	
Phase IIB[35]	Vorinostat (400 mg daily)		Stage IB–IVA (n=74)	30%	
Phase II[38]	Romidepsin (14 mg/m² as a 4-hour IV infusion on days 1, 8, and 15 of each 28-day cycle for up to 6 cycles)		Stage IB–IVA (n=96)	34% (6% CR)	

blood advances 14 DECEMBER 2021 • VOLUME 5, NUMBER 23

Randomized phase 3 ALCANZA study of brentuximab vedotin vs physician's choice in cutaneous T-cell lymphoma: final data

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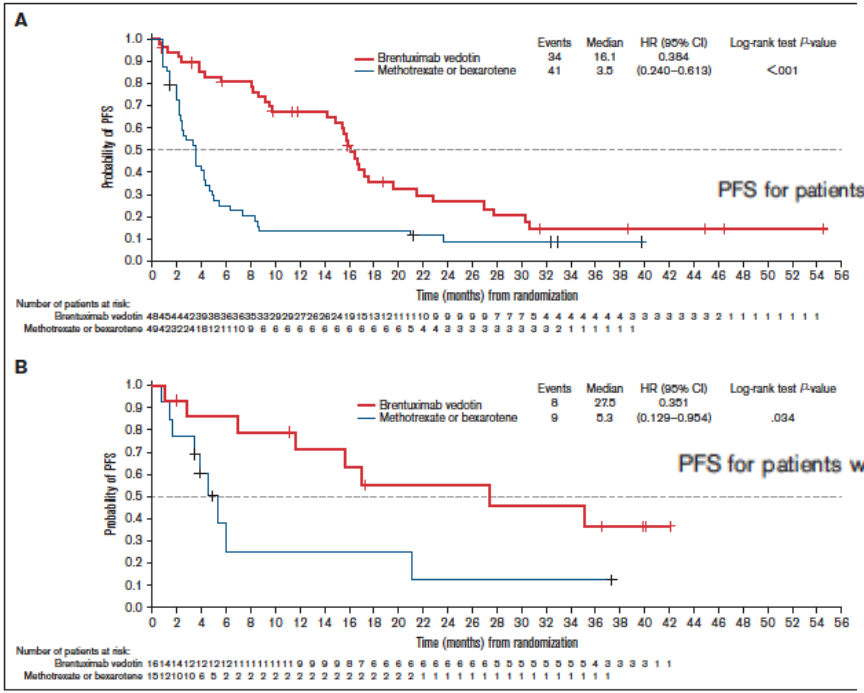


PFS for patients with MF.

PFS for patients with C-ALCL.

Table 1. Summary of efficacy in the ITT population

	Brentuximab vedotin (n = 64)	Physician's choice (n = 64)	P
ORR4 per IRF, n (%)	35 (54.7)*	8 (12.5)	<.001
Best response per IRF, n (%)			
ORR (CR+PR)	42 (65.6)	13 (20.3)	<.001
CR	11 (17.2)	1 (1.6)	.002
PR	31 (48.4)	12 (18.8)	
SD	10 (15.6)	18 (28.1)	
PD	5 (7.8)	22 (34.4)	
Median PFS per IRF, months (95% CI)†	16.7 (15.4-21.6)	3.5 (2.4-4.6)	
HR for PFS (95% CI)	0.38 (0.25-0.58)		<.001
3-y OS rate, % (95% CI)	64.4 (50.7-75.2)	61.9 (47.3-73.6)‡	
HR for OS (95% CI)	0.75 (0.42-1.32)		.310

PD, progressive disease; PR, partial response; SD, stable disease.
*Based on additional information provided to the IRF after the 31 May 2016 data cutoff, the IRF determined that 1 patient had not achieved ORR4 as was originally reported; the change in status was determined through a standard IRF adjudication process.
†Median follow-up for OS in the brentuximab vedotin arm was 48.4 mo.
‡Median follow-up for OS in the physician's choice arm was 42.9 mo.

Median follow up, 45,9 months

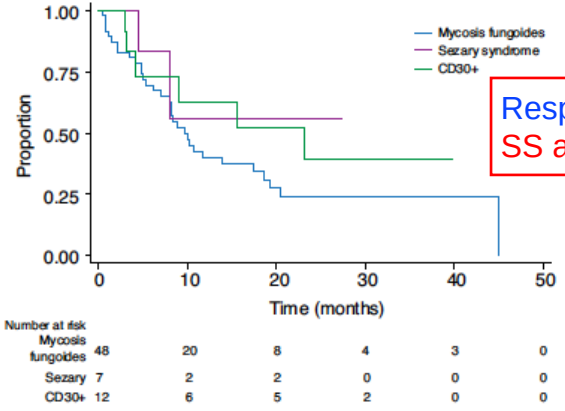
Median PFS for BV vs physician's choice was 16,7 vs 3,5 months

ORIGINAL ARTICLE

Brentuximab vedotin in the treatment of cutaneous T-cell lymphomas: Data from the Spanish Primary Cutaneous Lymphoma Registry

Cristina Muniesa[1,2] | Fernando Gallardo[3] | Ignacio García-Doval[4] | M. Teresa Estrach[5] | Andrea Combalia[6] | Mercedes Murillo-Andújar[6] | Fátima De la Cruz-Vicente[7] | Salma Machan[8] | Cristina Moya-Martínez[9] | Roger Rovira[7] | Blanca Sanchez-Gonzalez[9] | Elvira Acebo[10] | Elena Amutio[11] | Yeray Peñate[12] | María del Carmen Losada-Castillo[13] | M. Pilar García-Muret[14] | Helena Iznardo[15] | Concepción Román-Curto[16] | Javier Cañueto[15] | Ricardo Fernández-de-Misa[16] | Ángeles Flórez[17] | Rosa María Izu[18] | Ignacio Torres-Navarro[19] | Ana Zayas[20] | Gema Pérez-Paredes[21] | Mar Blanes[22] | J. Ignacio Tanguas[23] | Amparo Pérez-Ferriols[24] | Marta Callejas-Charavia[25] | Pablo Luis Ortiz-Romero[26] | Amalia Pérez-Gil[27] | Lucía Prieto-Torres[28] | Eva González-Barca[29] | Octavio Servitje[1]

PFS of 10,3 vs 16,7 months in the ALCANZA study



Response in SS and LyP

FIGURE 1 Kaplan–Meier curve for progression free survival in patients with mycosis fungoides, Sézary syndrome and CD30+ lymphoproliferative disorders treated with Brentuximab Vedotin.

TABLE 1 Clinical characteristics, responses, and adverse events in cutaneous T-cell lymphoma patients treated with Brentuximab Vedotin

	Total, *N* (%)	MF, *N* (%)	SS, *N* (%)	CD30 LPD, *N* (%)
Clinical characteristics				
Number	67 (100)	48 (72)	7 (10)	12 (18)
Sex				
Male	41 (61)	31 (65)	4 (57)	6 (50)
Female	26 (39)	17 (35)	3 (43)	6 (50)
Age at BV initiation (years)[a]	59 (24–92)	58 (24–92)	65 (43–80)	59 (36–76)
Previous systemic treatments[a]	4 (1–11)	4 (2–9)	5 (2–11)	2 (1–5)
Time from diagnosis to BV (years), mean	5.7	6.3	4.4	4.2
CD30 expressing cells				
<10%	26 (39)	21 (44)	4 (57)	1 (8)
>10%	30 (45)	21 (44)	3 (43)	6 (50)
Unknown	11 (16)	6 (12)	0 (0)	5 (42)
BV cycles, median (p25–p75)	7 (4–12)	8 (4–12)	4 (2–7)	7 (5–16)
Retreatment with BV	13 (20)	8 (17)	1 (17)	4 (33)
Response to BV retreatment				
Complete response	3 (23)	1 (12)	0 (0)	2 (50)
Partial response	4 (31)	2 (25)	1 (100)	1 (25)
Stable disease	4 (31)	4 (50)	0 (0)	0 (0)
Progression disease	2 (15)	1 (12)	0 (0)	1 (25)
HSCT after BV	8 (12)	5 (10)	2 (33)	1 (9)
Follow-up (months), median (p25–p75)	18.4 (5.8–29.1)	17.3 (5.7–31.1)	10.3 (3.9–22.8)	23.6 (14.7–29.5)
Current status				
Alive without disease	16 (24)	8 (17)	3 (43)	5 (42)

ORR 53%
CR 23%

ESMO
CLINICAL PRACTICE GUIDELINES

Primary cutaneous lymphomas: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up†

R. Willemze[1], E. Hodak[2], P. L. Zinzani[3], L. Specht[4] & M. Ladetto[5], on behalf of the ESMO Guidelines Committee*

Personalised medicine

- BV is used for the treatment of advanced stage refractory or relapsed CD30$^+$ CTCL, including both patients with C-ALCL and patients with MF/SS, also with the purpose of bridging eligible patients with MF/SS to an alloSCT

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SS excluded

PFS of about 10 months in real life

LCT MF excluded
ORR 68% blood, 42% skin, 19% lymph nodes

Response lasting > 12 months in 11% patients

Gemcitabine
1000 mg/m2 day 1,8,15, every 4 weeks

IFN-alpha
3x106 UI
3 times a week

JAMA Network

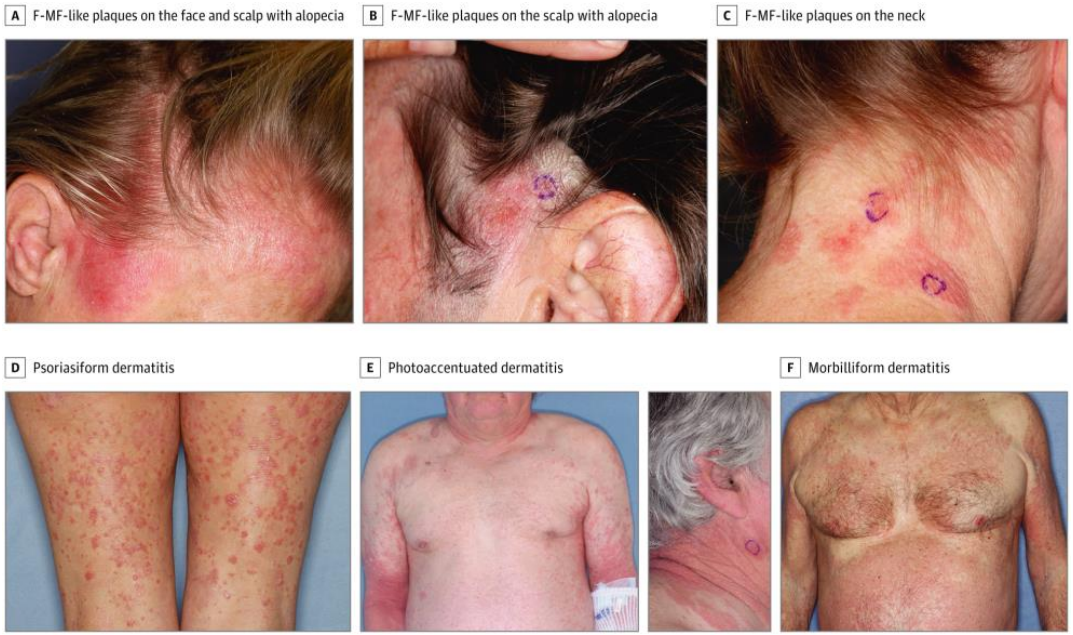
From: **Clinical Characterization of Mogamulizumab-Associated Rash During Treatment of Mycosis Fungoides or Sézary Syndrome**

JAMA Dermatol. 2021;157(6):700-707. doi:10.1001/jamadermatol.2021.0877

- MAR onset in 1/3 cases (56 days to 3,8 ys-median time 119 days-).
- Discontinuation, topical and systemic corticosteroids, low dose MTX
- MAR does not preclude retreatment

Clinical Characteristics of Patients With Mogamulizumab-Associated Rash (MAR)

Patients with MAR exhibit 4 predominant clinical presentations, including (1) folliculotropic mycosis fungoides (F-MF)–like plaques with alopecia on the head and neck, including the scalp (A-C); (2) papules and/or plaques, often with lichenoid or psoriasiform features (D); (3) photoaccentuated dermatitis (E); and (4) morbilliform or erythrodermic dermatitis (F).



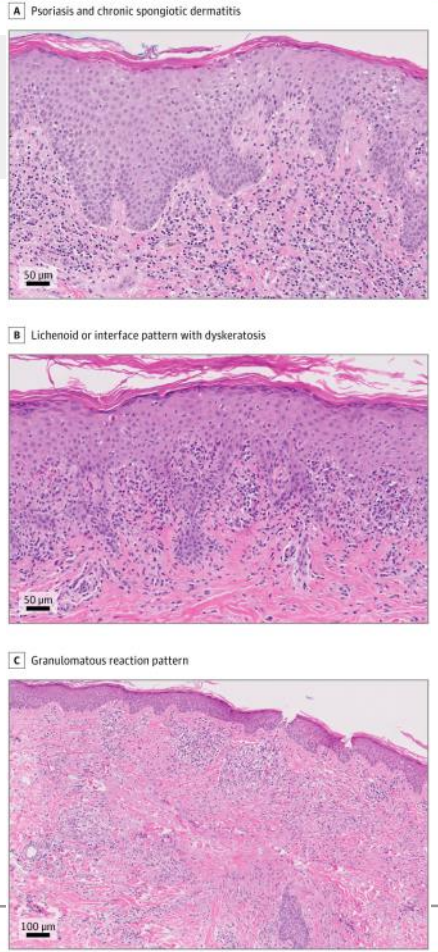
JAMA Network™

From: **Clinical Characterization of Mogamulizumab-Associated Rash During Treatment of Mycosis Fungoides or Sézary Syndrome**

JAMA Dermatol. 2021;157(6):700-707. doi:10.1001/jamadermatol.2021.0877

Histopathologic Features of Mogamulizumab-Associated Rash (MAR)

Three major histopathologic reaction patterns of MAR were identified. The most common pattern showed overlapping features of psoriasis and a chronic spongiotic dermatitis (hematoxylin-eosin, original magnification ×20) (A). Other cases showed a lichenoid or interface pattern with dyskeratosis (hematoxylin-eosin, original magnification ×10) (B). A smaller subset of cases had a granulomatous reaction pattern with moderately to well-formed granulomas. (hematoxylin-eosin, original magnification ×20) (C).



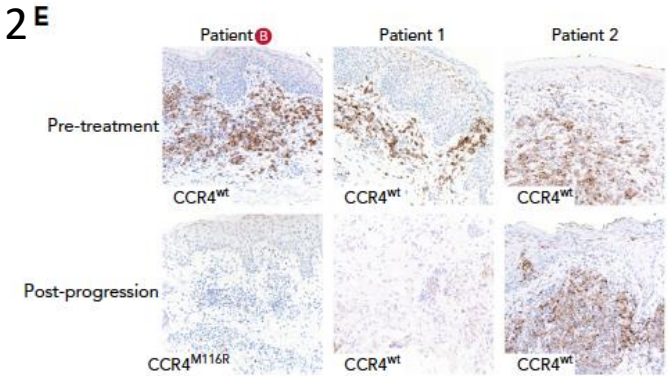
Low CCR4 expression in 65% of resistant pts

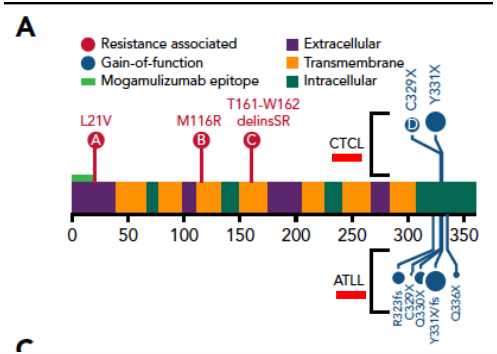
Thus, we find that patients with resistance to mogamulizumab fall into 3 categories: (1) CCR4 antigen loss associated with genomic events disrupting *CCR4* (Figure 2E, left), (2) loss of CCR4 expression in the absence of detectable genomic events (Figure 2E, middle), and (3) an as-of-yet undetermined mechanism of mogamulizumab resistance with retained high CCR4 expression (Figure 2E, right). Low CCR4 expression was identified in 10 of 14 patients with Sézary syndrome and 1 of 3 patients with mycosis fungoides. Additional studies of mycosis fungoides are needed to determine if CCR4 loss is common among mogamulizumab-treated patients. These findings have practical implications for the development and use of the next generation of CCR4-targeting therapies, such as cellular therapies currently in development. Our results suggest that CCR4-targeted therapies may only be effective in less than half of patients previously treated with mogamulizumab and that screening for CCR4 expression should be considered to select patients more likely to respond to second-line therapies.

Resistance to mogamulizumab is associated with loss of CCR4 in cutaneous T-cell lymphoma

Sara Beygi,[1,*] George E. Duran,[1,2,*] Sebastian Fernandez-Pol,[3] Alain H. Rook,[4] Youn H. Kim,[1,2] and Michael S. Khodadoust[1,2]

blood® 30 JUNE 2022 | VOLUME 139, NUMBER 26





GoF
Favorable response?

GoF
Favorable response

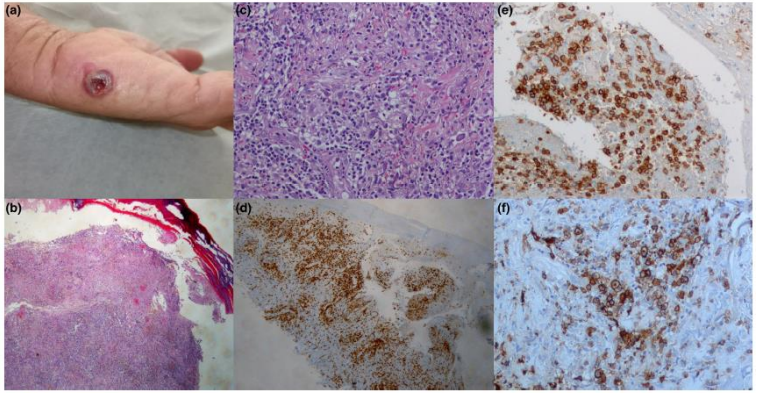


Figure 1 (a) a crusted ulcerated violaceous nodule on the left palm of the patient (1b) following BioNTech, Pfizer (BNT162b2) COVID-19 mRNA vaccine. (b) Diffuse, polymorphic infiltration of the dermis by small and scattered large lymphocytes and histiocytes with red cell extravasation. The epidermis is dissociated from the dermis and ulcerated (Hematoxylin and eosin, ×10). (c) Diffuse, polymorphic infiltration of the dermis by small and scattered large lymphocytes and histiocytes with red cell extravasation (Hematoxylin and eosin, ×20). (d) CD3 expression by all lymphocytes (CD3 antibody stain, ×10). (e) Significant predominant expression of CD8 by small and large lymphocytes (CD8 antibody stain, ×40). (f) CD30 expression by the large lymphocytes (CD30 antibody stain, ×40)

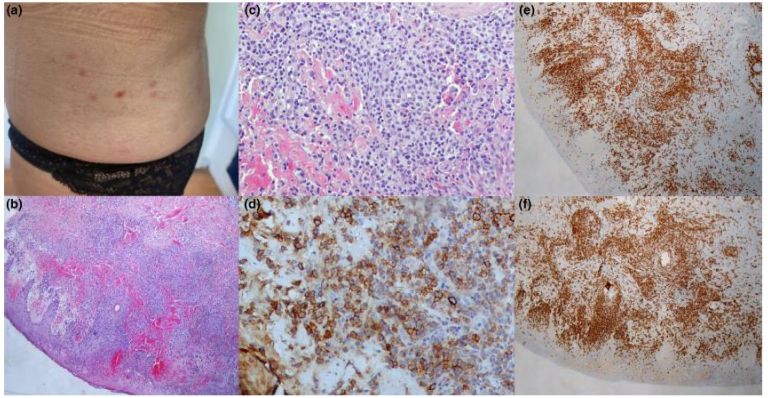


Figure 2 (a) Several violaceous papules on the abdomen of the second patient. (b and c) Diffuse, heavy infiltration of the dermis and epidermis by variably sized (small, medium, large) lymphocytes accompanied by extensive erythrocytic extravasation (hematoxylin and eosin staining, ×10 and ×20, respectively. (d) CD30 expression by the majority of mostly large lymphocytes (CD30 staining, ×40). (e) CD3 expression on all T-lymphocytes (CD3 staining, ×10). (f) Predominant CD8 expression by the lymphocytic population (CD8 staining, ×10)

Lymphomatoid papulosis (LyP) after AZD1222 and BNT162b2 COVID-19 vaccines

International Journal of Dermatology 2022, **61**, 900–902

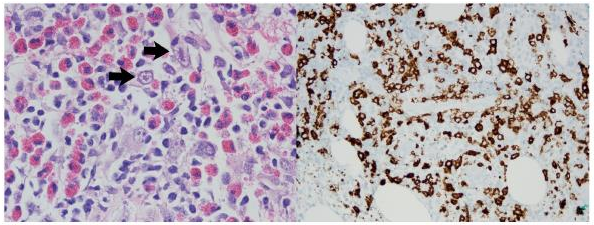


Figure 2. Histopathologic Findings. (A): Large Reed-Sternberg-like cells (arrows) scattered among numerous eosinophils (hematoxylin-eosin; original magnification: x600). (B): Immunohistochemical staining showing atypical CD30+ lymphocytes.

LEUKEMIA & LYMPHOMA
2021, VOL. 62, NO. 10, 2554–2555
https://doi.org/10.1080/10428194.2021.1924371

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LETTER TO THE EDITOR

Recurrence of primary cutaneous CD30-positive lymphoproliferative disorder following COVID-19 vaccination

Caitlin M. Brumfiel[a], Meera H. Patel[a], David J. DiCaudo[a], Allison C. Rosenthal[b], Mark R. Pittelkow[a] and Aaron R. Mangold[a]

[a]Department of Dermatology, Mayo Clinic Arizona, Scottsdale, USA; Department of Medicine, Division Hematology-Oncology, Phoenix, USA

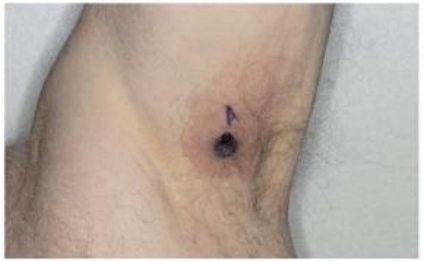


Figure 1. Biopsy-proven CD30+ lymphoproliferative disorder. A 3-centimeter ulcerated tumor with surrounding erythema in the left axilla. Photo taken 6 days after COVID-19 vaccination.

Bone Marrow Transplantation (2021) 56:1391–1401
https://doi.org/10.1038/s41409-020-01197-3

ARTICLE

Allogeneic hematopoietic stem cell transplantation for advanced mycosis fungoides and Sézary syndrome. An updated experience of the Lymphoma Working Party of the European Society for Blood and Marrow Transplantation

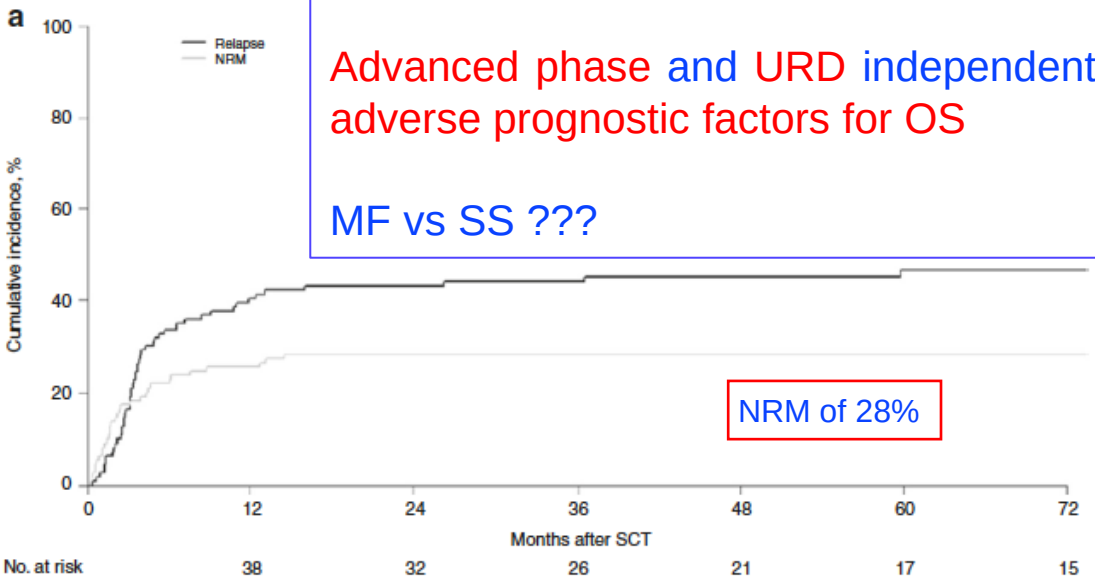
E. Domingo-Domenech[1] · R. F. Duarte[2] · A. Boumedil[3] · F. Onida[4] · I. Gabriel[5] · H. Finel[3] · W. Arcese[6] · P. Browne[7] · D. Beelen[8] · G. Kobbe[9] · H. Veelken[10] · R. Arranz[11] · H. Greinix[12] · S. Lenhoff[13] · X. Poiré[14] · J. M. Ribera[15] · J. Thompson[16] · T. Zuckerman[17] · G. J. Mufti[18] · A. Cortelezzi[4] · E. Olavarria[5] · P. Dreger[19] · A. Sureda[1] · S. Montoto[20]

Use of TBI associated with lower incidence of relapse

Advanced phase and URD independent adverse prognostic factors for OS

MF vs SS ???

BV before allo-tx (and Mogamulizumab in trials? despite high rates of III-IV aGVHD in ATL, due to donor-derived Tregs depletion)



NRM of 28%

Results 113 patients were included [77 MF (68%)]; 61 (54%) were in complete or partial remission, 86 (76%) received reduced-intensity protocols and 44 (39%) an URD allo-HSCT. With a median follow up for surviving patients of 73 months, allo-HSCT resulted in an estimated overall survival (OS) of 38% at 5 years, and a progression-free survival (PFS) of 26% at 5 years.

Bone Marrow Transplantation (2014) 49, 1360–1365

www.nature.com/bmt

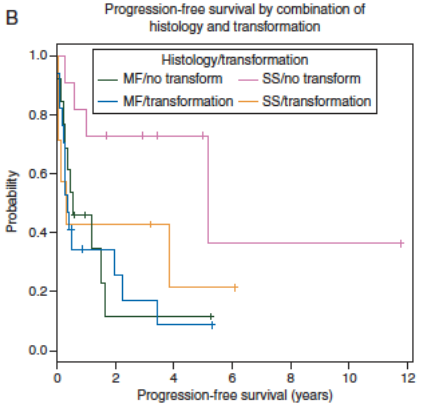
ORIGINAL ARTICLE

Allogeneic hematopoietic cell transplantation for mycosis fungoides and Sezary syndrome

MJ Lechowicz[1], HM Lazarus[2], J Carreras[3], GG Laport[4], CS Cutler[5], PH Wiernik[6], GA Hale[7], D Maharaj[8], RP Gale[9], PA Rowlings[10], CO Freytes[11], AM Miller[12], JM Vose[13], RT Maziarz[14], S Montoto[15], DG Maloney[16] and PN Hari[3]

CIBMTR: 129 MF/SS pts with PFS 17% and OS 32% at 5 yrs

4-year PFS of 11,4 % in MF and 73% in SS
In 5-year DFS of 27,5% in MF and 56% in SS in the 2019 update of Milan experience



Flu/Mel +- ATG

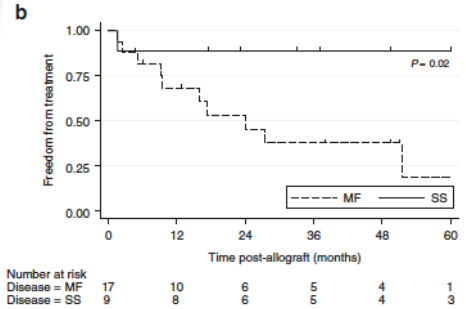
Allogeneic stem-cell transplantation in patients with cutaneous lymphoma: updated results from a single institution

C. Hosing[1*], R. Bassett[2], B. Dabaja[3], R. Talpur[4], A. Aloui[1], S. Ciurea[1], U. Popat[1], M. Qazilbash[1], E. J. Shpall[1], Y. Oki[5], Y. Nieto[1], C. Pinnix[3], M. Fanale[3], F. Maadani[1], M. Donato[3], R. Champlin[1] & M. Dovic[4]

Long-term outcomes for allogeneic bone marrow transplantation in Sezary syndrome and mycosis fungoides

Bone Marrow Transplantation (2022) 57:1724–1726; https://doi.org/10.1038/s41409-022-01787-3

Jessica Elliott[1✉], Shalini Ahlawat[1], H. Miles Prince[1,2], Glen Kennedy[3], Jillian Wells[4], Gillian Huang[4], Jenny Collins[1], Peter Bardy[5], Carrie Van Der Weyden[1], David Ritchie[1] and Amit Khot[1,2]



NO AVAILABLE RCT STUDIES

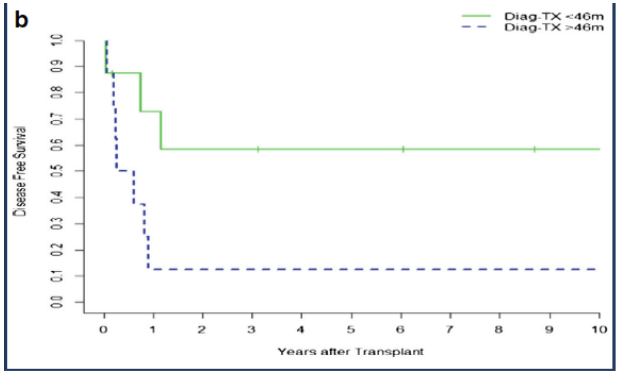
Annals of Hematology (2018) 97:1041–1048
https://doi.org/10.1007/s00277-018-3275-z

ORIGINAL ARTICLE

Allogeneic hematopoietic stem cell transplantation in Primary Cutaneous T Cell Lymphoma

Laura Cudillo[1] · Raffaella Cerretti[1] · Alessandra Picardi[1] · Benedetta Mariotti[1] · Gottardo De Angelis[1] · Maria Cantonetti[1] · Massimiliano Postorino[1] · Eleonora Ceresoli[1] · Giovanna De Santis[1] · Daniela Nasso[1] · Francesco Pisani[2] · Enrico Scala[3] · Fabio Di Piazza[1] · Alessandro Lanti[4] · William Arcese for the Rome Transplant Network

DFS of 34% at 10 yrs. Pre-transplant follow up adverse factor

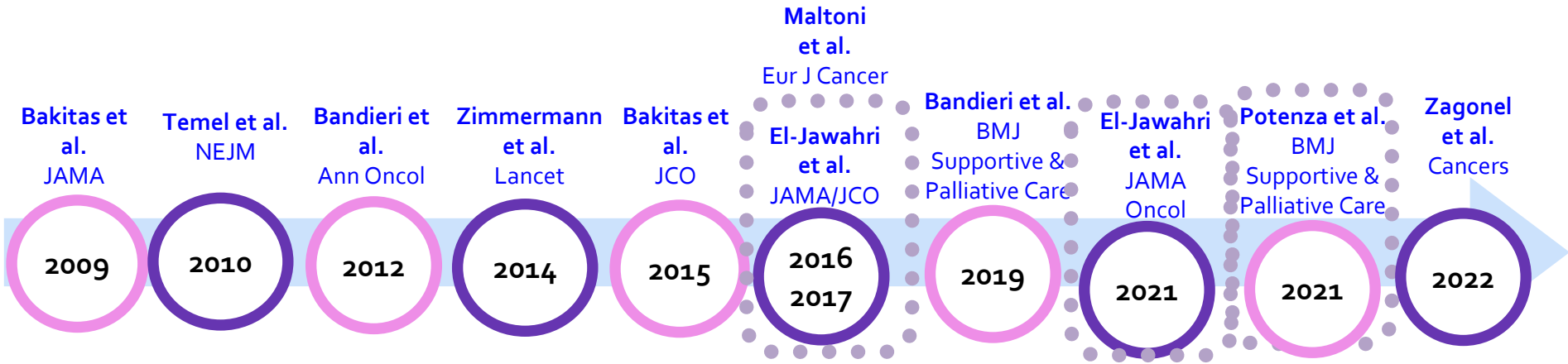


MAC: TBF; BuCy
RIC: Thiotepa/Cy/Flu

Terapia sistemica di pazienti con linfoma T cutaneo in Ematologia MO offerta a

- Pazienti in stadio IIB-IV (MF), SS, linfomi cutanei anaplastici CD30+
- Terapie sistemiche: bexarotene, MTX, ECP, brentuximab (*Alcanza* e *real life*), mogamulizumab (*MAVORIC*), (allo-tx)
- Tossicità vs Progressione (mogamulizumab)
- Resistenza (mogamulizumab)
- Progressione dopo vaccino Sars CoV2
- Terapia Supportiva/Palliativa Precoce, integrata a terapia sistemica *standard* emato-oncologica

Benefici delle Cure Palliative Precoci in Pazienti Emato-Oncologici



Miglioramento del **controllo dei sintomi**
Miglioramento **della qualità di vita**
Riduzione **dei sintomi depressivi**
Maggiore **consapevolezza della prognosi e obiettivi di cura**
Riduzione della **aggressività di cura nel fine vita**
Maggiore **sopravvivenza mediana**

Accesso alle cure palliative era definito **PRECOCE**
Quando iniziava **entro 8 settimane dalla diagnosi di malattia**

ASCO statements
2013
2017

EPC solo in ematologia

Early palliative/supportive care in acute myeloid leukaemia allows low aggression end-of-life interventions: observational outpatient study

Leonardo Potenza,[1] Miki Scaravaglio,[1] Daniela Fortuna,[2] Davide Giusti,[1] Elisabetta Colaci,[1] Valeria Pioli,[1] Monica Morselli,[1] Fabio Forghieri,[1] Francesca Bettelli,[1] Andrea Messerotti,[1] Hillary Catellani,[1] Andrea Gilioli,[1] Roberto Marasca,[1] Eleonora Borelli,[3] Sarah Bigi,[4] Giuseppe Longo,[5] Federico Banchelli,[6] Roberto D'Amico,[6] Anthony L Back,[7] Fabio Efficace,[8] Eduardo Bruera,[9] Mario Luppi,[1] Elena Bandieri[10]

BMJ Potenza L, *et al. BMJ Supportive & Palliative Care* 2021;0:1–8. doi:10.1136/bmjspcare-2021-002898

5. Il panel raccomanda, laddove fattibile, il precoce coinvolgimento del team di cure palliative e l'eventuale servizio di Assistenza Psicologica (istituzionale o supportato dalle Organizzazioni di Volontariato) nell'ottica di promuovere un simultaneo intervento dell'ematologo e del medico palliativista.

- I benefici delle EPC sono stati dimostrati in studi randomizzati di pazienti con neoplasia ematologica, sottoposti a regimi intensivi come la chemioterapia di induzione o il trapianto di cellule staminali emopoietiche *(El-Jawahri A et al, JAMA 2016, JAMA Oncol. 2021).*
- In uno studio nella nostra Regione di piu' di 215 pazienti con leucemia mieloide acuta, un intervento di EPC riduce i sintomi fisici, aumenta la consapevolezza della prognosi di malattia e degli obiettivi di cure riducendo l' accanimento terapeutico *(Potenza et al, BMJ Supp & Pall Care 2021).*

Table 4. Triggers for specialty palliative care consultation for patients with lymphoma

High or refractory symptom burden
Psychological distress
Difficulty coping with illness
Misperceptions about illness understanding despite goals-of-care discussions
Complex goals-of-care discussions
Complicated family dynamics
Planned hematopoietic stem cell transplant
Recurrent unplanned hospital admissions
Surprise question (You would not be surprised if the patient died in the next 1 y.)

Ruolo EPC in Linfomi T Cutanei?

Strategies for introducing palliative care in the management of relapsed or refractory aggressive lymphomas

| Hematology 2020 | ASH Education Program

Oreofe O. Odejide
Dana-Farber Cancer Institute, Boston, MA; and Harvard Medical School, Boston, MA

Table 1
Relative frequency and prognosis of primary cutaneous lymphomas included in the 2018 update of the WHO-EORTC classification [5].

WHO-EORTC Classification 2018	Frequency (%)#	5-year DSS (%)#
Cutaneous T-cell lymphomas		
Mycosis fungoides	39	88
Mycosis fungoides variants		
• Folliculotropic MF	5	75
• Pagetoid reticulosis	<1	100
• Granulomatous slack skin	<1	100
Sézary syndrome	2	36
Adult T-cell leukemia/lymphoma	<1	NDA
Primary cutaneous CD30-positive lympho-proliferative disorders		
• Primary cutaneous anaplastic large cell lymphoma	8	95
• Lymphomatoid papulosis	12	99
Subcutaneous panniculitis-like T-cell lymphoma	1	87
Extranodal NK/T-cell lymphoma, nasal type	<1	16
Chronic active EBV infection	<1	NDA
Primary cutaneous peripheral T-cell lymphoma, rare subtypes		
• Primary cutaneous γ/δ T-cell lymphoma	<1	11
• Primary cutaneous aggressive epidermotropic CD8-positive T-cell lymphoma (provisional)	<1	31
• Primary cutaneous CD4+ small/medium T-cell LPD (provisional)	6	100
• Primary cutaneous acral CD8+ T-cell lymphoma (provisional)	<1	100
Primary cutaneous peripheral T-cell lymphoma, NOS	2	15

Primary cutaneous lymphoma: the 2018 update of the WHO-EORTC classification
Presse Med 51 (2022) 104126

Rein Willemze*

Based on data included in Dutch and Austrian cutaneous lymphoma registries between 2002 and 2017.

Treatment Considerations

Although MF and SS are treatable, they are not curable with conventional systemic therapy, and symptoms have significant impact on quality of life.

Optimal treatment of any patient at any given time should be individualized based on overall goals of therapy (improve disease burden and quality of life, attain adequate response to reduce/control symptoms, and minimize the risk of progression), route of administration, and toxicity profile. Discussions regarding cumulative toxicity of therapy, impact of therapy on quality of life, and supportive care for symptom control are a key part of management of patients with MF and SS.

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Si, Ricerca sul Ruolo EPC in Linfomi T Cutanei