MALATTIA «ADVANCED STAGE»: IL RUOLO DELLA TERAPIA DIRETTA ALLA CUTE

UNIVERSITÀ DEGLI STUDI FIRENZE

Nicola Pimpinelli

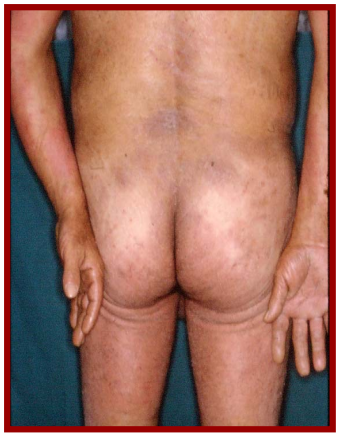
SST Azienda USL Toscana centro
Servizio Sanitario della Toscana

Dipartimento Scienze della Salute – sez. Dermatologia, *Università degli Studi di Firenze*
SS.CC. Dermatologia Firenze, *Azienda USL Toscana Centro*

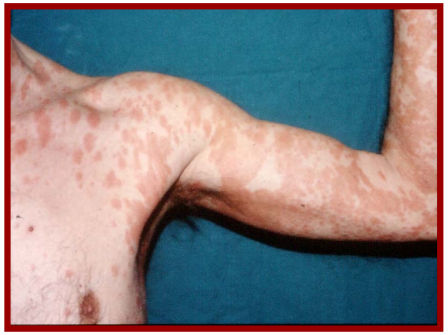
Dichiarazione conflitto di interessi

Nicola Pimpinelli dichiara di aver intrattenuto rapporti con le seguenti aziende farmaceutiche negli ultimi 2 anni:

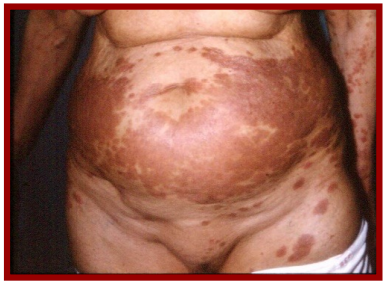
ALMIRALL, HELSINN, KYOWA KIRIN, MSD, NOVARTIS, PIERRE FABRE, RECORDATI RARE DISEASES, SANOFI, TAKEDA

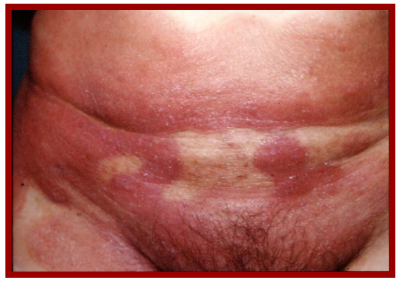


PATCH STAGE

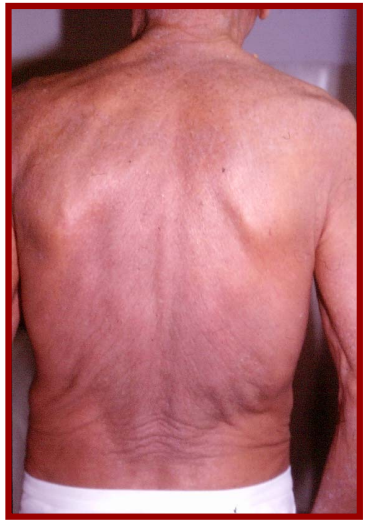


PLAQUE STAGE

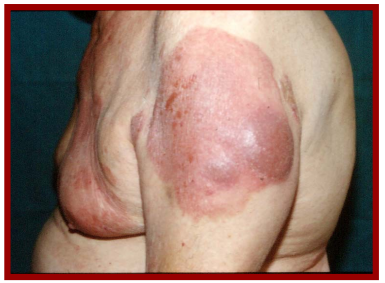


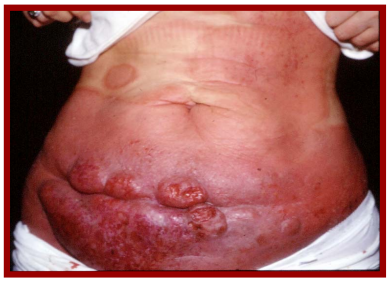


ERYTHRODERMA



TUMOR STAGE





Original Article **Cancer, 2012**

Time Course, Clinical Pathways, and Long-Term Hazards Risk Trends of Disease Progression in Patients With Classic Mycosis Fungoides

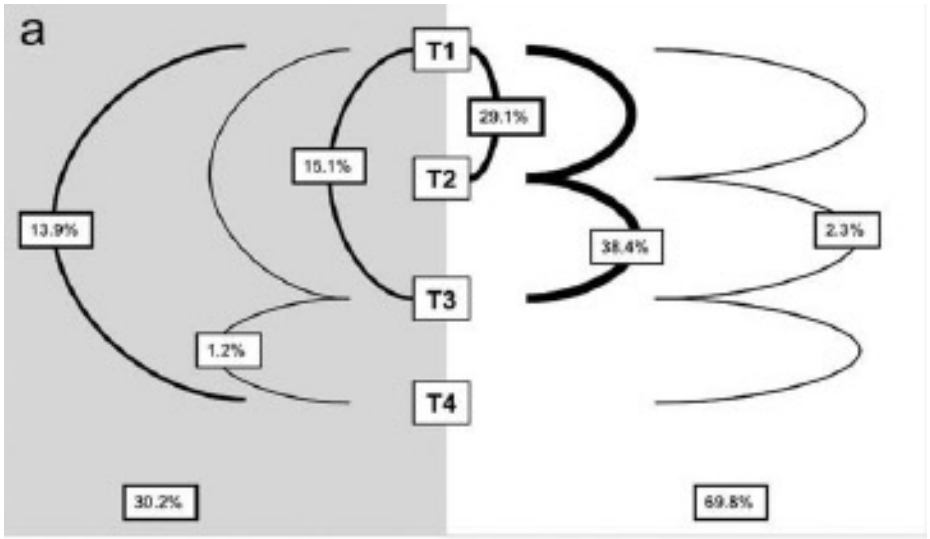
A Multicenter, Retrospective Follow-Up Study From the Italian Group of Cutaneous Lymphomas

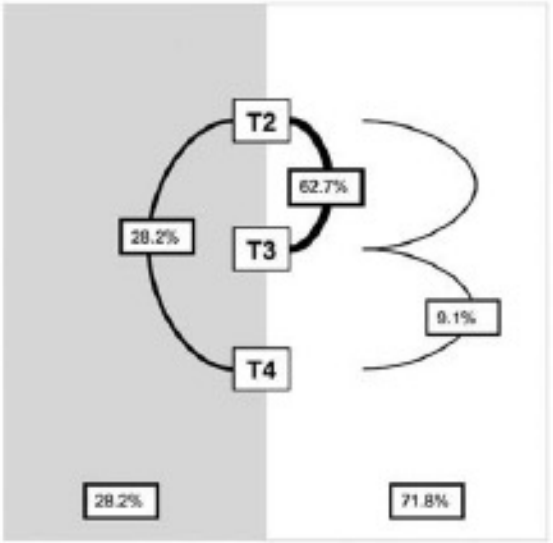
Pietro Quaglino, MD[1]; Nicola Pimpinelli, MD[2]; Emilio Berti, MD[3]; Piergiacomo Calzavara-Pinton, MD[4]; Giuseppe Alfonso Lombardo, MD[5]; Serena Rupoli, MD[6]; Mauro Alaibac, MD[7]; Ugo Bottoni, MD[8,9]; Angelo Carbone, MD[10]; Paolo Fava, MD[1]; Michele Fimiani, MD[11]; Angela Maria Mamusa, MD[12]; Stefano Titli, MD[1]; Pier Luigi Zinzani, MD[13]; Maria Grazia Bernengo, MD[1]; and On behalf of the Gruppo Italiano Linfomi Cutanei (GILC)

G ITAL DERMATOL VENEREOL 2012;147:523-31

Mycosis fungoides: disease evolution of the "lion queen" revisited

P. QUAGLINO [1], N. PIMPINELLI [2], E. BERTI [3], P. CALZAVARA-PINTON [4], G. A. LOMBARDO [5] S. RUPOLI [6] M. ALAIBAC [7], L. ARCAINI [8], S. BAGNATO [9], A. BALDO [10], U. BOTTONI [11], A. CARBONE [12], R. CESTARI [13] R. CLERICO [14], A. DE RENZO [15], P. FAVA [1], M. T. FIERRO [1], R. FILOTICO [16], M. FIMIANI [17], M. FRONTANI [5] V. GIRGENTI [18], G. GOTERI [19], C. LEALI [4], A. M. MAMUSA [20], G. MARIOTTI [2], V. MASTRANDREA [21] C. PELLEGRINI [22], E. PENNESE [23], A. PILERI [24], P. SAVOIA [1], C. STELITANO [25], S. TITLI [1] A. VIRGILI [26], L. ZICHICHI [27], P. L. ZINZANI [22], M. G. BERNENGO [1]





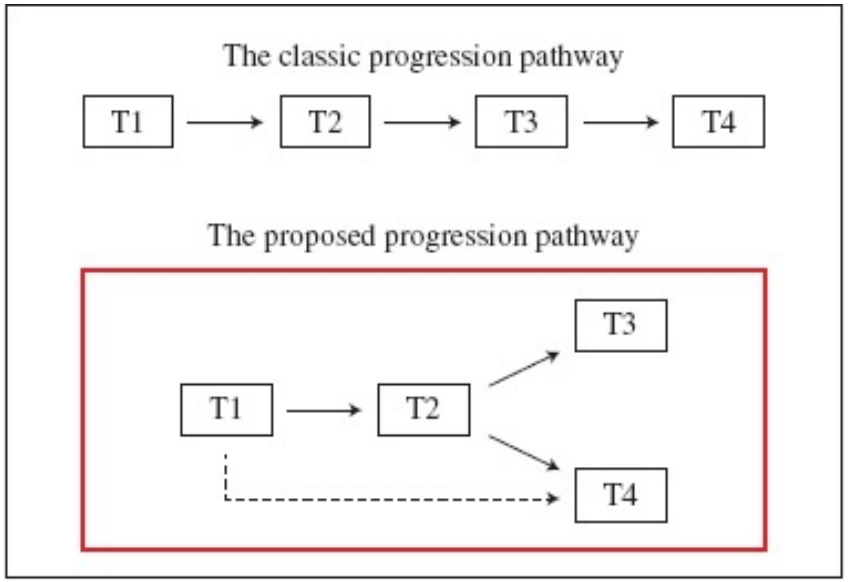


Figure 3.—Old and new potential disease evolution pathway interpretations.

Figure 2. T score evolution of patients with (a) T1 lesions and (b) T2 lesions at the time of initial diagnosis is shown. The number represents the percentage of patients who developed disease progression calculated based on the total number of patients whose disease progressed from either T1 or T2. Gray-shaded areas at the left of each figure include those patients whose cutaneous disease evolution spared $\geq$ 1 consecutive stages. The thickness of each line is proportional to the number of patients who developed disease progression after this specific evolution.

Revisions to the staging and classification of mycosis fungoides and Sézary syndrome: a proposal of the International Society for Cutaneous Lymphomas (ISCL) and the cutaneous lymphoma task force of the European Organization of Research and Treatment of Cancer (EORTC)

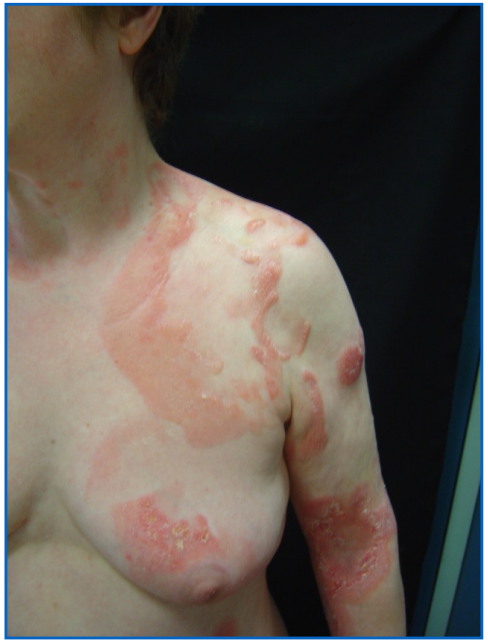
Elise Olsen,[1] Eric Vonderheid,[2] Nicola Pimpinelli,[3] Rein Willemze,[4] Youn Kim,[5] Robert Knobler,[6] Herschel Zackheim,[7] Madeleine Duvic,[8] Teresa Estrach,[9] Stanford Lamberg,[2] Gary Wood,[10] Reinhard Dummer,[11] Annamari Ranki,[12] Gunter Burg,[11] Peter Heald,[13] Mark Pittelkow,[14] Maria-Grazia Bernengo,[15] Wolfram Sterry,[16] Liliane Laroche,[17] Franz Trautinger,[6] and Sean Whittaker,[18] for the ISCL/EORTC

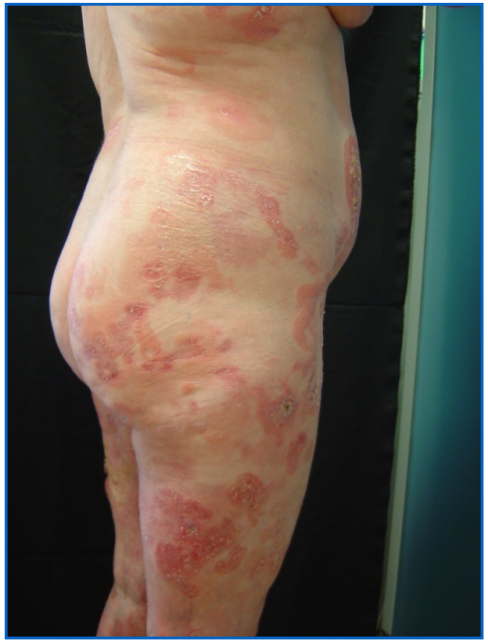
[1]Department of Medicine, Divisions of Dermatology and Oncology, Duke University Medical Center, Durham, NC; [2]Department of Dermatology, Johns Hopkins University, Baltimore, MD; [3]Department of Dermatological Sciences, University of Florence, Florence, Italy; [4]Department of Dermatology, Leiden University Medical Center, Leiden, The Netherlands; [5]Department of Dermatology, Stanford University Medical Center, Stanford, CA; [6]Department of Dermatology, University of Vienna, Vienna, Austria; [7]Department of Dermatology, University of California at San Francisco; [8]Department of Dermatology, University of Texas at Houston; [9]Department of Dermatology, University of Barcelona, Barcelona, Spain; [10]Department of Dermatology, University of Wisconsin, Madison; [11]Department of Dermatology, University Hospital Zurich, Zurich, Switzerland; [12]Department of Dermatology and Venereal Diseases, Helsinki University Hospital, Helsinki, Finland; [13]Department of Dermatology, Yale University, New Haven, CT; [14]Department of Dermatology, Mayo Clinic, Rochester, MN; [15]Department of Dermatology, University of Turin, Turin, Italy; [16]Department of Dermatology, Charité, Humboldt University, Berlin, Germany; [17]Department of Immuno-Dermatology, Hospital Avicenne–University of Paris XIII, Paris, France; [18]St John's Institute of Dermatology, Skin Tumour Unit, St Thomas' Hospital, London, United Kingdom

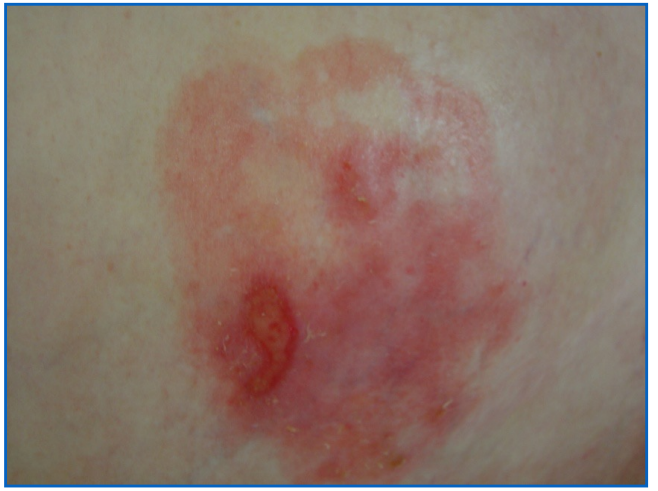
The ISCL/EORTC recommends revisions to the Mycosis Fungoides Cooperative Group classification and staging system for cutaneous T-cell lymphoma (CTCL). These revisions are made to incorporate advances related to tumor cell biology and diagnostic techniques as pertains to mycosis fungoides (MF) and Sézary syndrome (SS) since the 1979 publication of the original guidelines, to clarify certain variables that currently impede effective interinstitution and interinvestigator communication and/or the development of standardized clinical trials in MF and SS, and to provide a platform for tracking other variables of potential prognostic significance. Moreover, given the difference in prognosis and clinical characteristics of the non-MF/non-SS subtypes of cutaneous lymphoma, this revision pertains specifically to MF and SS. The evidence supporting the revisions is discussed as well as recommendations for evaluation and staging procedures based on these revisions. (Blood. 2007;110: 1713-1722)

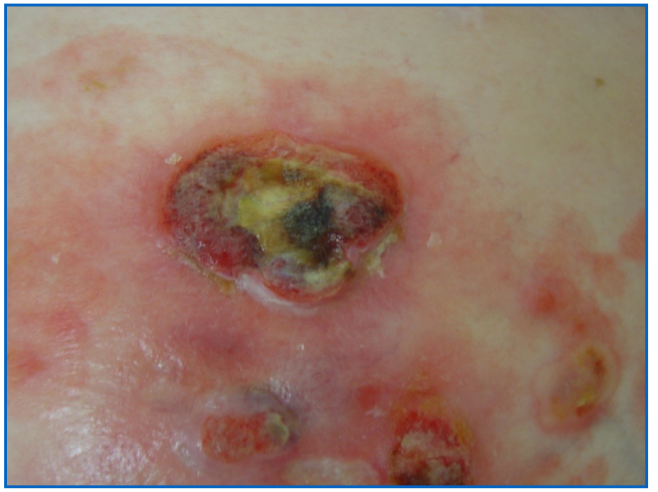
Table 4. ISCL/EORTC revision to the classification of mycosis fungoides and Sézary syndrome

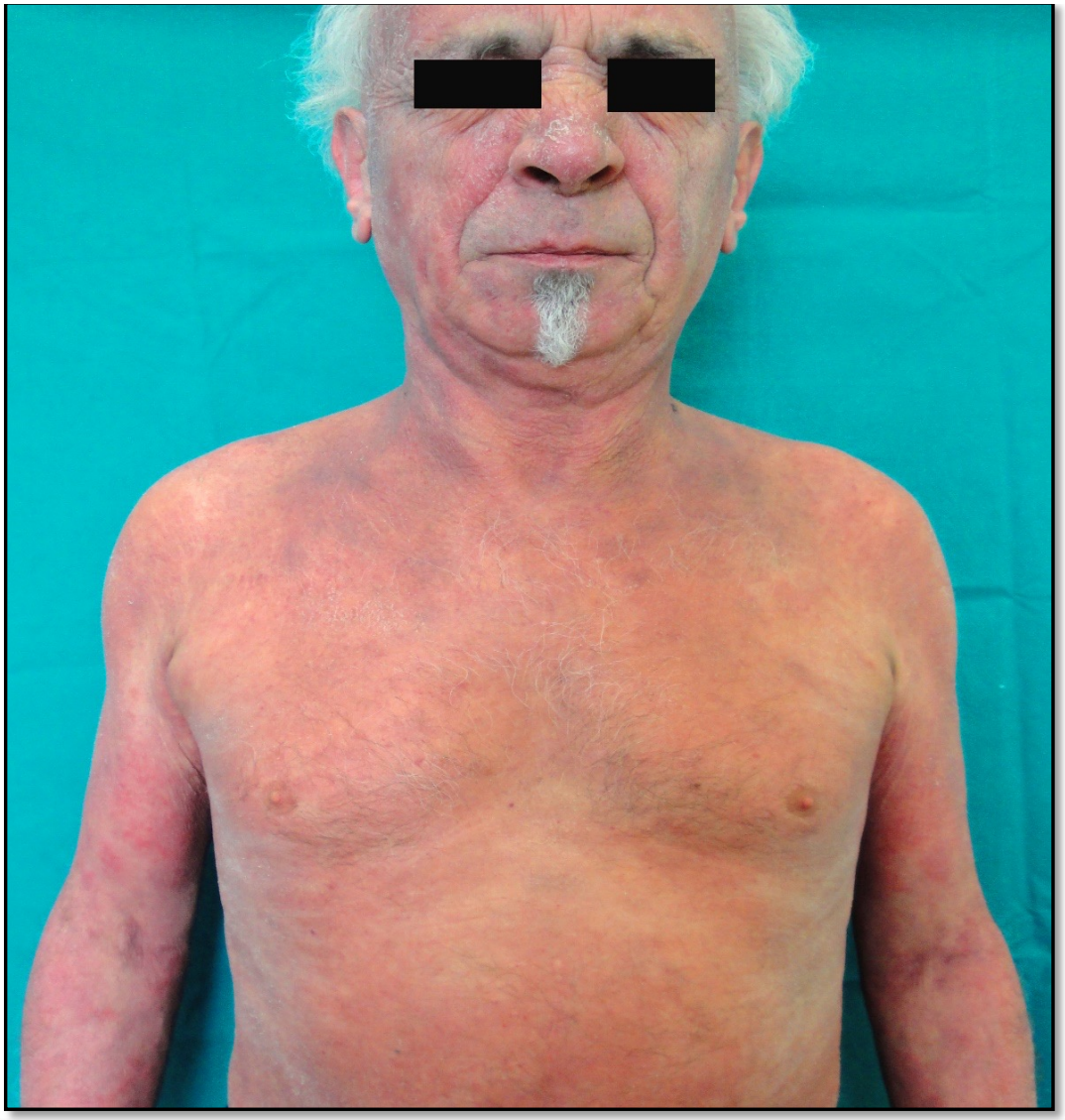
TNMB stages	
Skin	
T_1	Limited patches,* papules, and/or plaques† covering < 10% of the skin surface. May further stratify into T_{1a} (patch only) vs T_{1b} (plaque ± patch).
T_2	Patches, papules or plaques covering ≥ 10% of the skin surface. May further stratify into T_{2a} (patch only) vs T_{2b} (plaque ± patch).
T_3	One or more tumors‡ (≥ 1-cm diameter)
T_4	Confluence of erythema covering ≥ 80% body surface area
Node	
N_0	No clinically abnormal peripheral lymph nodes§; biopsy not required
N_1	Clinically abnormal peripheral lymph nodes; histopathology Dutch grade 1 or NCI LN_{0-2}
N_{1a}	Clone negative#
N_{1b}	Clone positive#
N_2	Clinically abnormal peripheral lymph nodes; histopathology Dutch grade 2 or NCI LN_3
N_{2a}	Clone negative#
N_{2b}	Clone positive#
N_3	Clinically abnormal peripheral lymph nodes; histopathology Dutch grades 3-4 or NCI LN_4; clone positive or negative
N_x	Clinically abnormal peripheral lymph nodes; no histologic confirmation
Visceral	
M_0	No visceral organ involvement
M_1	Visceral involvement (must have pathology confirmation¶ and organ involved should be specified)
Blood	
B0	Absence of significant blood involvement: ≤ 5% of peripheral blood lymphocytes are atypical (Sézary) cells‖
B_{0a}	Clone negative#
B_{0b}	Clone positive#
B1	Low blood tumor burden: > 5% of peripheral blood lymphocytes are atypical (Sézary) cells but does not meet the criteria of B_2
B_{1a}	Clone negative#
B_{1b}	Clone positive#
B2	High blood tumor burden: ≥ 1000/μL Sézary cells‖ with positive clone#











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Review

European Organisation for Research and Treatment of Cancer consensus recommendations for the treatment of mycosis fungoides/Sézary syndrome – Update 2017

Franz Trautinger [a,b,*], Johanna Eder [a,b], Chalid Assaf [c], Martine Bagot [d], Antonio Cozzio [e], Reinhard Dummer [f], Robert Gniadecki [g,h], Claus-Detlev Klemke [i], Pablo L. Ortiz-Romero [j], Evangelia Papadavid [k], Nicola Pimpinelli [l], Pietro Quaglino [m], Annamari Ranki [n], Julia Scarisbrick [o], Rudolf Stadler [p], Liisa Väkevä [n], Maarten H. Vermeer [q], Sean Whittaker [r], Rein Willemze [q], Robert Knobler [s]

Stage IIB

Recommendations for first-line treatment of MF stage IIB.

Systemic therapies[a]	
Retinoids[b]	Level 2
IFN-α	Level 2
TSEB	Level 2
Monochemotherapy (gemcitabine, pegylated liposomal doxorubicine)	Level 4
Low dose MTX	Level 4
Localised RT[c]	Level 4

Recommendations for second-line treatment of MF stage IIB.

Polychemotherapy[a]	level 3
Allogeneic stem cell transplantation[b]	level 3

[a] CHOP is the most widely used regimen with a number of variants and other combinations available.
[b] Should be restricted to exceptional patients, see text for details.

Stage IIIA/B

Recommendations for first-line treatment of MF stage IIIA and B.	
Systemic therapies[a]	
Retinoids[b]	Level 2
IFN-α	Level 2
ECP[c]	Level 3
Low dose MTX	Level 4
TSEB	Level 2

Recommendations for second-line treatment of MF stage IIIA and B.	
Monochemotherapy (gemcitabine, pegylated liposomal doxorubicine)	Level 3
Allogeneic stem cell transplantation[a]	Level 3

[a] Should be restricted to exceptional patients, see text for details.

MF/SS THERAPY AT A GLANCE: FIRST LINE

European Organisation for Research and Treatment of Cancer consensus recommendations for the treatment of mycosis fungoides/Sézary syndrome - Update 2017.

F. Trautinger, J. Eder, C. Assaf, M. Bagot, A. Cozzio, R. Dummer, R. Gniadecki, C.D. Klemke, P.L. Ortiz-Romero, E. Papadavid, N. Pimpinelli, P Quaglino, A. Ranki, J. Scarisbrick, R. Stadler, L. Väkevä, M.H. Vermeer, S. Whittaker, R. Willemze, R. Knobler

European Journal of Cancer (2017) 77: pp57-74

CORTESIA Prof. P. Quaglino

EORTC
European Organisation for Research and Treatment of Cancer

	Wait & see	Topical steroids	Photo therapy	Local RT	TSET	Interferon	Bexarotene	Mono-CT	MTX	PoliCT	ECP
IA	■	■	■	■							
IB	■	■	■	■							
IIA		■	■	■							
IIB				■	■	■	■	■	■		
III					■	■	■		■		■
SS						■	■	■	■		■
IVA - IVB								■		■	

MF/SS THERAPY AT A GLANCE: SECOND LINE

CORTESIA Prof. P. Quaglino

European Organisation for Research and Treatment of Cancer consensus recommendations for the treatment of mycosis fungoides/Sézary syndrome - Update 2017.

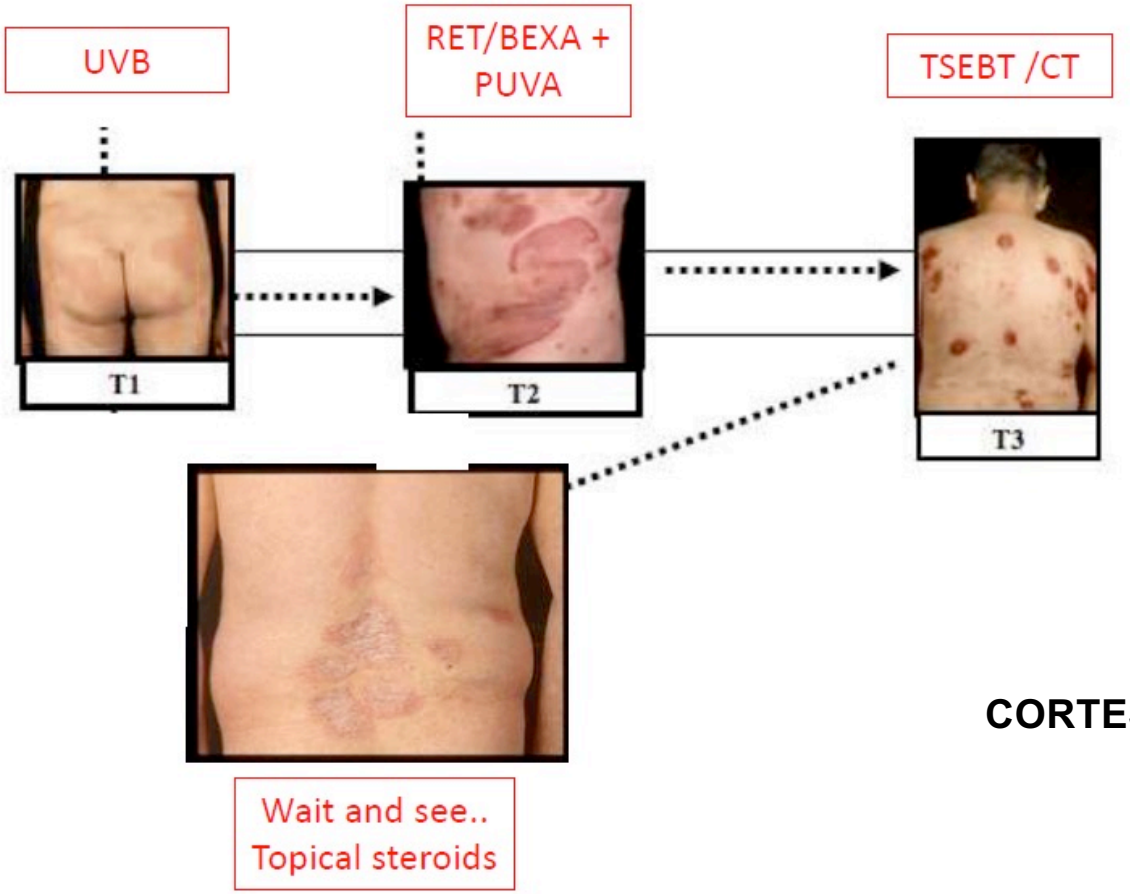
F. Trautinger, J. Eder, C. Assaf, M. Bagot, A. Cozzio, R. Dummer, R. Gniadecki, C.D. Klemke, P.L. Ortiz-Romero, E. Papadavid, N. Pimpinelli, P Quaglino, A. Ranki, J. Scarisbrick, R. Stadler, L. Väkevä, M.H. Vermeer, S. Whittaker, R. Willemze, R. Knobler

European Journal of Cancer (2017) 77: pp57-74

EORTC
European Organisation for Research and Treatment of Cancer

	Topical steroids	Photo therapy	Local RT	TSET	Interferon	Bexarotene	Mono-CT	MTX	PoliCT	ECP	HSCT
IA											
IB											
IIA											
IIB											
III											
SS											
IVA - IVB											

TREATMENT DOWN GRADE



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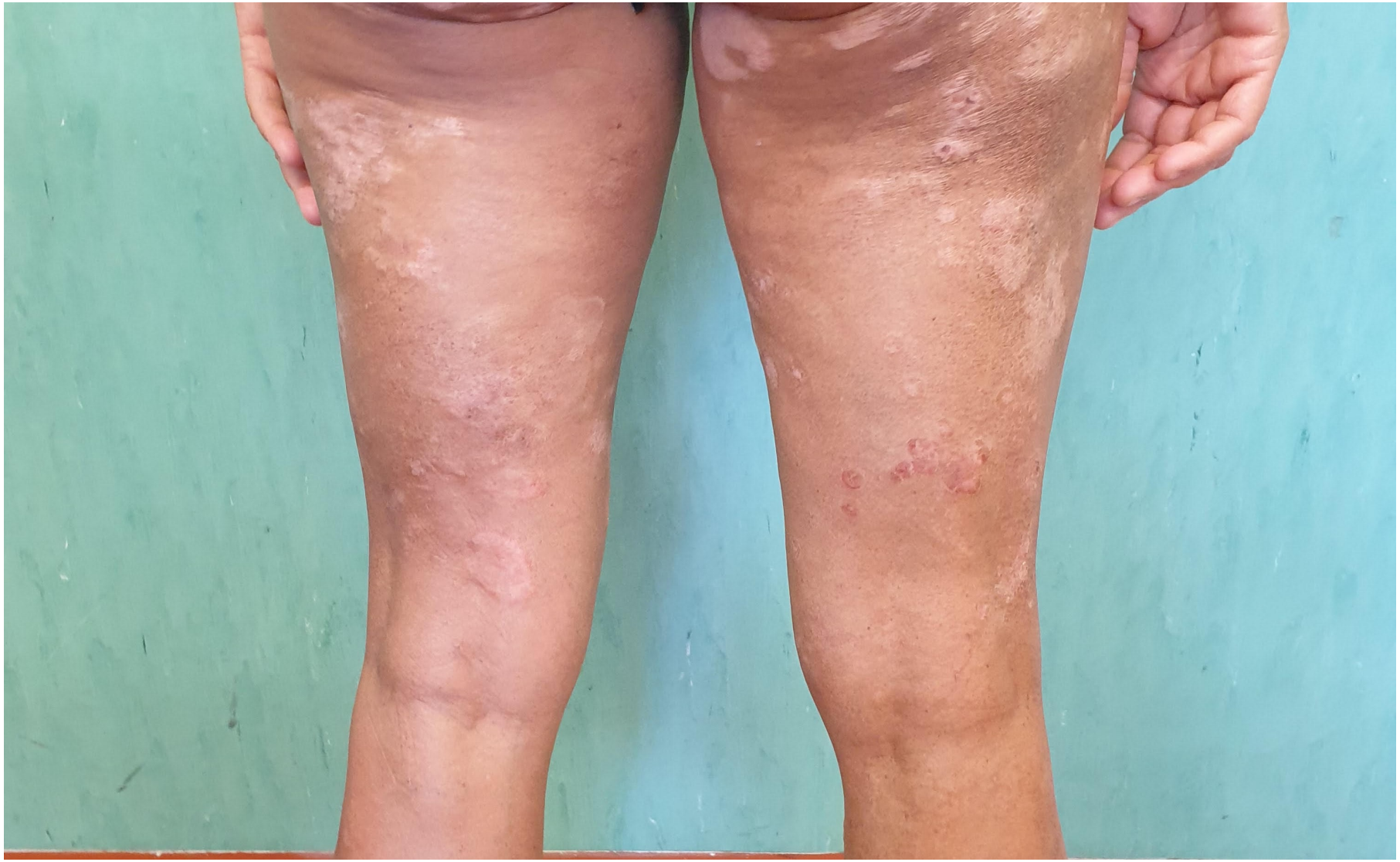
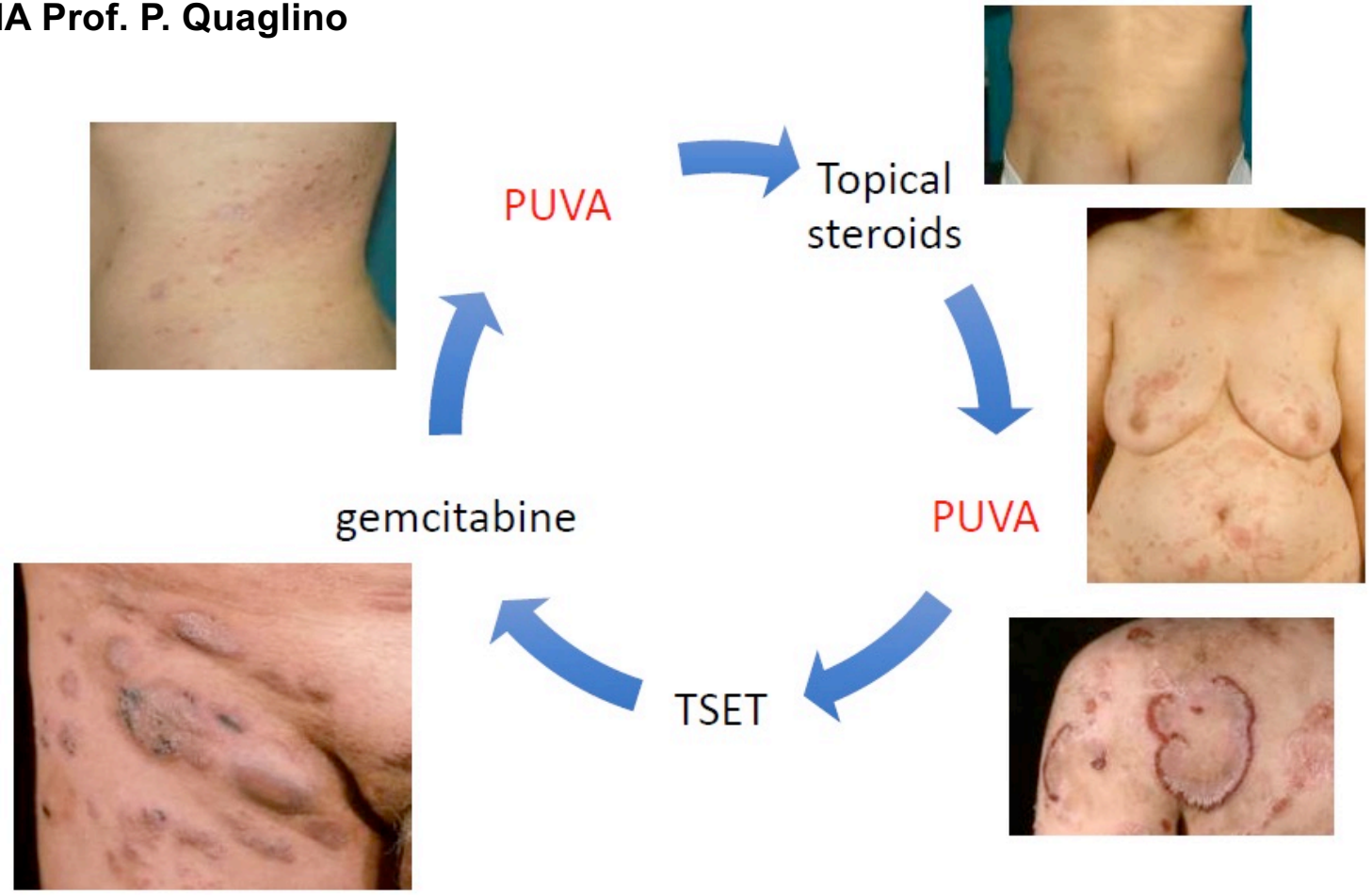


The re-challenge paradigm of CTCL therapy

CORTESIA Prof. P. Quaglino



PROCLIPI is an international prospective database in which all the new cases of mycosis fungoides(MF)/Sézary syndrome are registered after central clinico-pathological review to confirm diagnosis.


GENERAL DERMATOLOGY

BJD British Journal of Dermatology

The PROCLIPI international registry of early-stage mycosis fungoides identifies substantial diagnostic delay in most patients

J.J. Scarisbrick, P. Quaglino, H.M. Prince, E. Papadavid, E. Hodak, M. Bagot, O. Servitje, E. Berti, P. Ortiz-Romero, R. Stadler, A. Patsatsi, R. Knobler, E. Guenova, F. Child, S. Whittaker, V. Nikolaou, C. Tomasini, I. Amitay, H. Prag Naveh, C. Ram-Wolff, M Battistella, S. Alberti-Violetti, R. Stranzenbach, V. Gargallo, C. Muniesa, T. Koletsa, C. Jonak, S. Porkert, C. Mitteldorf, T. Estrach, A. Comballa, M. Marschalko, J. Csomor, A. Szepesi, A. Cozzio, R. Dummer, N. Pimpinelli, V. Grandi, M. Beylot-Barry, A. Pham-Ledard, M. Wobser, E. Geissinger, U. Wehkamp, M. Weichenthal, R. Cowan, E. Parry, J. Harris, R. Wachsmuth, D. Turner, A. Bates, E. Healy, F. Trautinger, J. Latzka, J. Yoo, B. Vydianath, R. Amel-Kashipaz, L. Marinos, A. Oikonomidi, A. Stratigos, M.-O. Vignon-Pennamen, M. Battistella, F. Climent, E. Gonzalez-Barca, E. Georgiou, R. Senetta, P. Zinzani, L. Vakeva, A. Ranki, A.-M. Busschots, E. Hauben, A. Bervoets, F.J.S.H. Woei-A-Jin, R. Matin, G. Collins, S. Weatherhead, J. Frew, M. Bayne, G. Dunnill, P. McKay, A. Arumainathan, R. Azurdia, K. Benstead, R. Twigger, K. Rieger, R. Brown, J.A. Sanches, D. Miyashiro, O. Akilov, S. McCann, H. Sahi, F.M. Damasco, C. Querfeld, A. Folkes, C. Bur, C.-O. Klemke, P. Enz, R. Pujol, K. Quint, L. Geskin, E. Hong, F. Evison, M. Vermeer, L. Cerroni, W. Kempf, Y. Kim and R. Willemze

the PROCLIPI (PROspective InternationalCutaneous Lymphoma Prognostic Index) study for early-stageMF is a prototype study for international collaborations in rare disease and present our initial findings and central reviewprocess.

Treatment of early-stage mycosis fungoides: results from the PROspective Cutaneous Lymphoma International Study (PROCLIPI study)

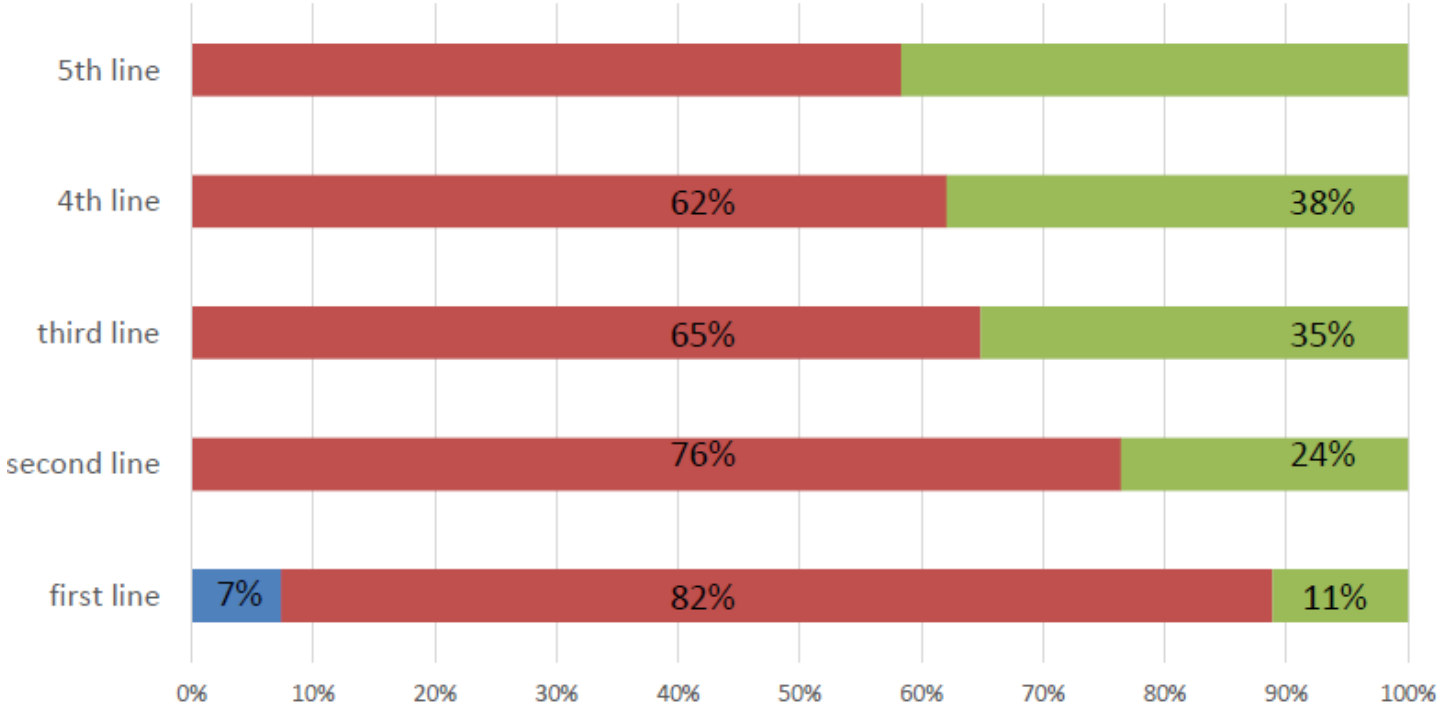
Running title: Treatment of early-stage Mycosis fungoides

P. Quaglino,[1] H.M. Prince,[2] R. Cowan,[3] M. Vermeer,[4] L. Papadavid,[5] M. Bagot,[6] O. Servitjie,[7] E. Berti,[8] E. Guenova,[9] R. Stadler,[10] C. Querfeld,[11] A.M. Busschots,[12] E. Hodak,[13] A. Patsatsi,[14] J. Sanches,[15] M. Maule,[16] J. Yoo,[31] M. Kevin,[31] P. Fava,[1] S. Ribero,[1] L. Zocchi,[1] M. Rubatto,[1] M.T. Fierro,[1] U. Wehkamp,[17] M. Marshalko,[18] C. Mitteldorf,[19] O. Akilov,[20] P. Ortiz-Romero,[21] T. Estrach,[22] L. Vakeva,[23] P.A. Enz,[24] M. Wobser,[25] M. Bayne,[26] C. Jonak,[27] M. Rubeta,[28] A. Forbes,[29] A. Bates,[30] M. Battistella,[6] R. Amel-Kashipaz,[31] B. Vydianath,[31] A. Combalia,[22] E. Georgiou,[14] E. Hauben,[12] E.K. Hong,[32] M. Jost,[17] R. Knobler [27] I. Amitay-Laish,[13] D. Miyashiro,[15] J. Cury-Martins,[15] X. Martinez,[11] C. Muniesa,[7] H. Prag-Naveh,[13] V. Nikolaou,[5] K. Quint,[4] C. Ram-Wolff,[6] K. Rieger,[32] R. Stranzenbach,[10] Á. Szepesi,[18] S. Alberti-Violetti,[8] E. Felicity,[31] L. Cerroni,[33] W. Kempf,[34] S. Whittaker,[35] R. Willemze,[4] Y. Kim[32] and J.J. Scarisbrick[31*]

Br J Dermatol . 2020 Jun 1. doi: 10.1111/bjd.19252. Online

Summary of treatments according to the therapy line

CORTESIA Prof. P. Quaglino



1st vs 2nd line
Chi square: 11,188
P<0.001

CTCLs are generally treated using a multimodal approach involving hematologists, dermatologists and radiation therapists.

Goals of therapy are to control symptoms, maintain cosmesis and improve survival by maximally reducing the tumor burden.

Maintenance treatments with skin directed or systemic therapy once remission has been achieved with the aim to maintain response and prevent relapse should be always considered particularly in advanced disease phases.

Critical concepts and management recommendations for cutaneous T-cell lymphoma: a consensus-based position paper from the Italian Group of Cutaneous Lymphoma

Pier Luigi Zinzani[1,2], Pietro Quaglino[3], Silvia Alberti Violetti[4], Maria Cantonetti[5], Gaia Goteri[6], Francesco Onida[7], Marco Paulli[8], Serena Rupoli[9], Giovanni Barosi[10], Nicola Pimpinelli[11]

SKIN-DIRECTED THERAPIES

- Skin-directed therapy (SDT) should be considered for early stages of disease and at disease relapse with early lesions after CR in advanced stages.

- SDT associated with immunomodulating agents should be considered both for early stages refractory to/relapsing after SDT alone and for disease relapse with early lesions after CR in advanced stages.

INTERNATIONAL SOCIETY FOR CUTANEOUS LYMPHOMAS

EORTC European Organisation for Research and Treatment of Cancer

Cutaneous Lymphoma Task Force

GRUPPO ITALIANO gilc LINFOMI CUTANEI

FONDAZIONE FIL ITALIANA LINFOMI

Gruppo Multidisciplinare LINFOMI CUTANEI Firenze

Vieri GRANDI, Irene LASTRUCCI, Isabella CIARDETTI, Marta BARZACCHI, *Pimpi*

Marco SANTUCCI, Vincenza MAIO, Raffaella SANTI (Anatomia Patologica)

Luca NASSI, Benedetta PUCCINI (Ematologia)

Gabriele SIMONTACCHI, Laura P. Ciccone (Radioterapia)