La terapia nel paziente ricaduto/refrattario con CTCL

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IL PARADIGMA DEL MELANOMA METASTATICO

	BRAF mutato	BRAF wild type
1 linea	BRAF i o anti-PD1	Anti-PD1
2 linea	Anti-PD1 o BRAFi	Anti-CTLA4
3 linea	Anti-CTLA4	Altri target o CT o BSC
4 linea	Altri target (cKit) o CT o BSC	Altri target (cKit) o CT o BSC

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

WHO-EORTC Classification 2018	Frequency, %*	5-y DSS, %*
CTCL		
MF	39	88
MF variants		
Folliculotropic MF	5	75
Pagetoid reticulosis	<1	100
Granulomatous slack skin	<1	100
SS	2	36
Adult T-cell leukemia/lymphoma	<1	NDA
Primary cutaneous CD30$^+$ LPDs		
C-ALCL	8	95
LyP	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
CD8$^+$ AECTCL (provisional)	<1	31
Primary cutaneous CD4$^+$ small/medium T-cell lymphoproliferative disorder (provisional)	6	100
Primary cutaneous acral CD8$^+$ T-cell lymphoma (provisional)	<1	100
Primary cutaneous peripheral T-cell lymphoma, NOS	2	15
CBCL		
PCMZL	9	99
PCFCL	12	95
PCDLBLC, LT	4	56
EBV$^+$ mucocutaneous ulcer (provisional)	<1	100
Intravascular large B-cell lymphoma	<1	72

MF/SS THERAPY AT A GLANCE: FIRST LINE

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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

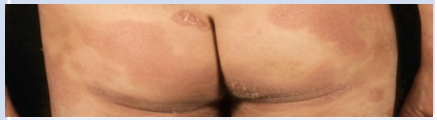
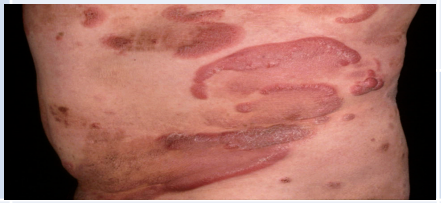
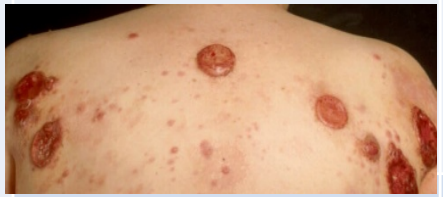
EORTC
European Organisation for Research and Treatment of Cancer

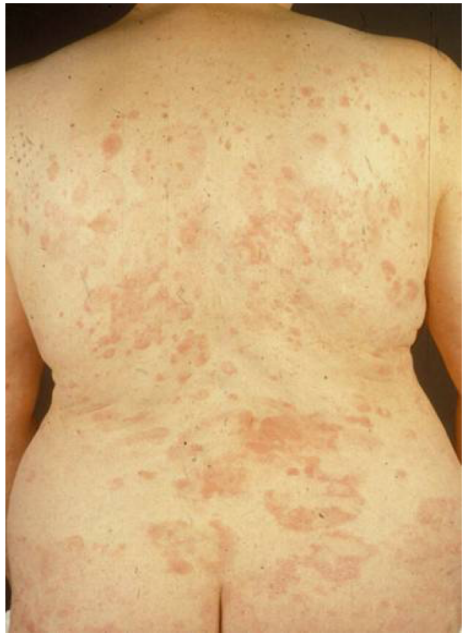
	Wait & see	Topical steroids	Photo therapy	Local RT	TSET	Interferon	Bexarotene	Mono-CT	MTX	PoliCT	ECP
IA											
IB											
IIA											
IIB											
III											
SS											
IVA - IVB											

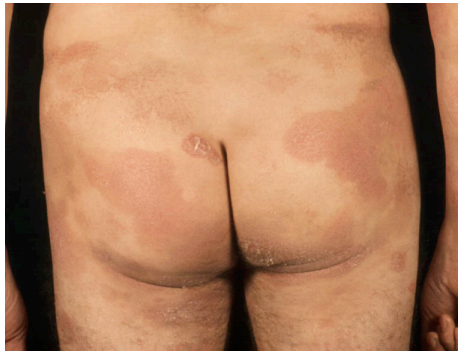
NO SPECIFIC ORDER: HETEROGENEITY OF APPROACHES

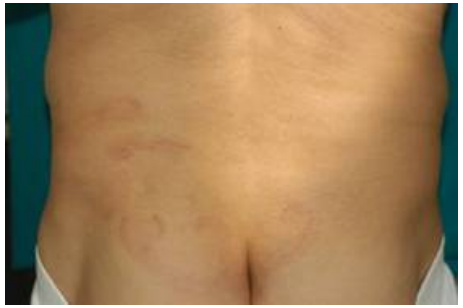
- Consensus and institutional preference
- Geographical regulatory status
- Availability of treatment modalities

- Age of the patient
- Comorbidities
- Patient compliance
- Clinical features

	Clinics	Stage	T	N	M	B	Definition	Median Sur (yrs)	10-year OS (%)
EARLY-STAGE		IA	T1	N0	M0	B0-1	Patches (T1a) or plaques (T1b) < 10% body surface area	35.5	80-100
		IB	T2	N0	M0	B0-1	Patches (T2a) or plaques (T2b) > 10% body surface area	21.5	58-75
		IIA	T1-T2	N1-N2	M0	B0-1	Nodal enlargement without histological involvement	15.8	45-52
ADVANCED-STAGE		IIB	T3	N0-2	M0	B0-1	Skin tumours	4.7	20-39
		IIIA	T4	N0-2	M0	B0	Erythroderma with no blood involvement	4.7	20-40
		IIIB	T4	N0-2	M0	B1	Erythroderma with low tumor burden in the blood	3.4	25
		IVA1	T1-4	N0-2	M0	B2	Blood involvement	3.8	18
	EXTRACUTANEOUS INVOLVEMENT	IVA2	T1-4	N3	M0	B0-2	Nodal involvement	2.1	15
		IVB	T1-4	N0-3	M1	B0-2	Visceral involvement	1.4	NR



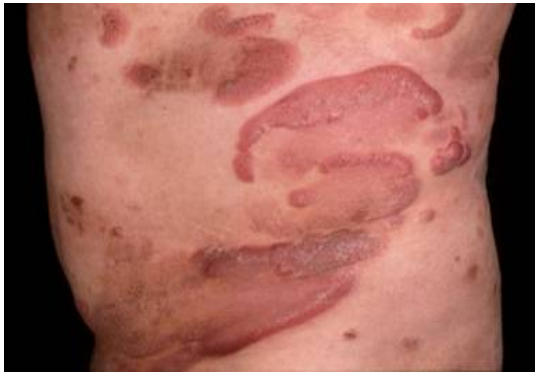


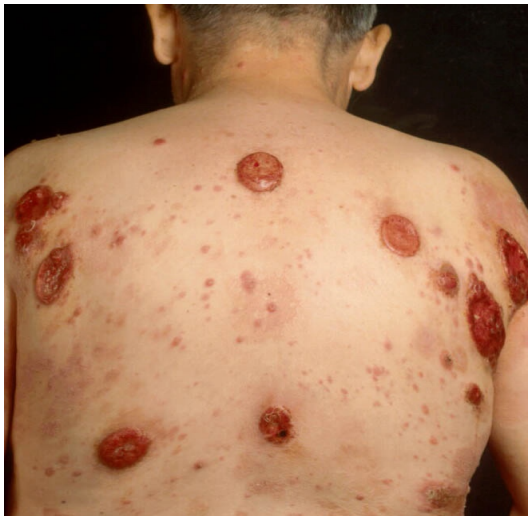


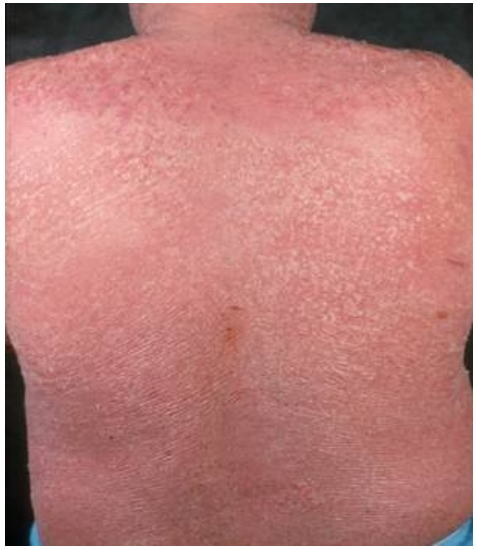
MYCOSIS FUNGOIDES

EARLY vs ADVANCED PHASE DISEASE

	EARLY	ADVANCED
% patients	70%	30%
Stage	IA – IB -IIA	IIB-III-IV
Lesion morphology	Patch plaque	Tumour erythroderma
Extracutaneous involvement	Extremely rare	Significant
Quality of life	Impaired	Severely impaired
Prognosis	Very good	Poor
Therapy	SDT	Systemic + SDT Chemo / HSCT







ISSUES FOR THE MANAGEMENT OF TREATMENT IN MF

EARLY	ADVANCED
Decision whether to treat or not the disease is related to the patient age, lesion site, associated symptoms and evolutivity	High clinical need of effective treatments
The objective of the therapy is not to induce the complete remission, but a significant improvement both from the clinical and quality of life point of view	Need of biomarkers to identify the best treatment and the most responsive patients
If SDT and immune modulators do not manage to induce a significant response but the patient still maintains only patches, there is no indication to use a therapy approach of advanced stage	Mantainance

MF/SS THERAPY AT A GLANCE: FIRST LINE

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III											
SS											
IVA - IVB											

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SECOND LINE

EORTC
European Organisation for Research and Treatment of Cancer

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IA											
IB											
IIA											
IIB											
III											
SS											
IVA - IVB											

MF/SS THERAPY AT A GLANCE: SECOND 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

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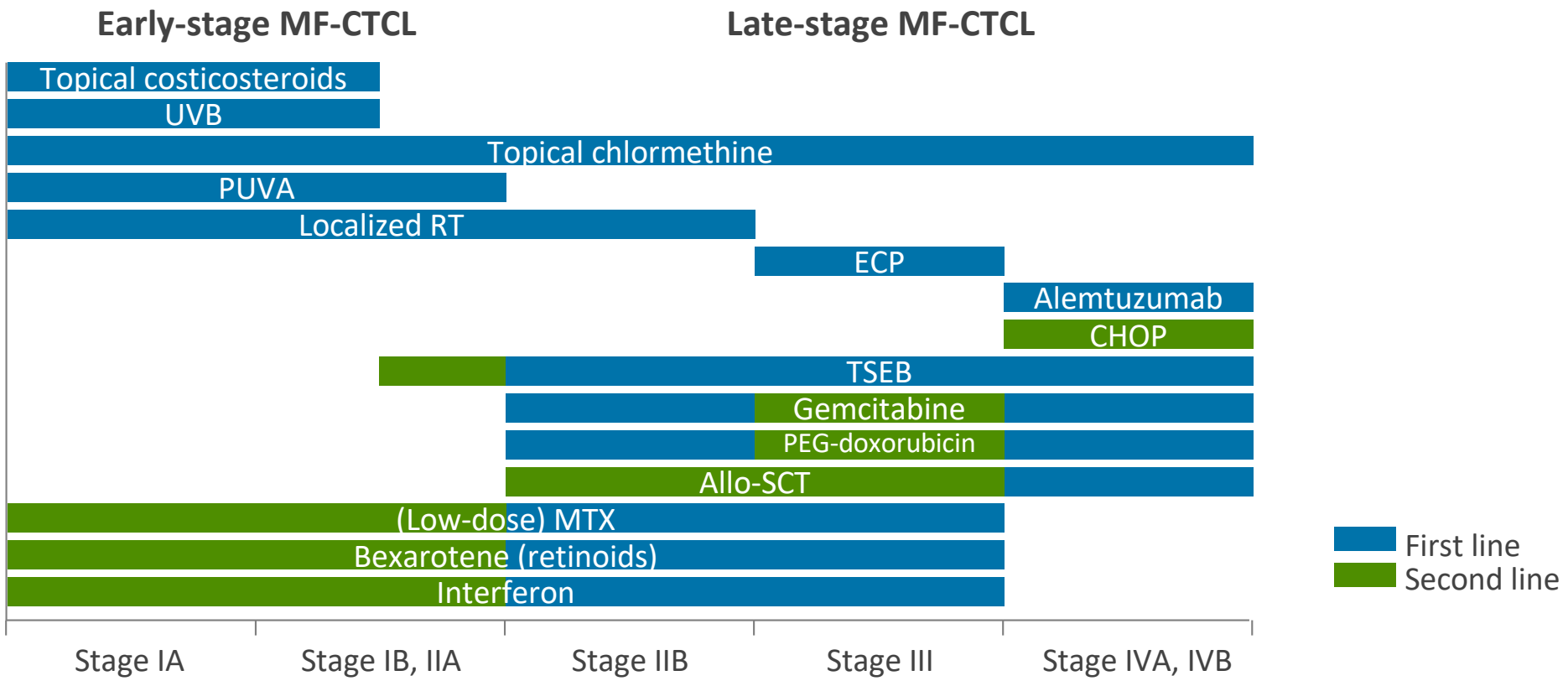
EORTC
European Organisation for Research and Treatment of Cancer

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

MF-CTCL stage-based treatment (EU overview)



Adapted from Trautinger F, et al. Eur J Cancer. 2017;77:57-74.

ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

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CLINICAL PRACTICE GUIDELINES

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

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[1]Department of Dermatology, Leiden University Medical Centre, Leiden, The Netherlands; [2]Department of Dermatology, Rabin Medical Centre, Beilinson Hospital, Petach Tikva, Israel; [3]Institute of Hematology and Medical Oncology, University of Bologna, Bologna, Italy; [4]Department of Oncology, Rigshospitalet, University of Copenhagen, Copenhagen, Denmark; [5]Divisione di Ematologia, Azienda Ospedaliera Santi Antonio e Biagio e Cesare Arrigo, Alessandria, Italy

*Correspondence to: ESMO Guidelines Committee, ESMO Head Office, Via Ginevra 4, 6900 Lugano, Switzerland. E-mail: clinicalguidelines@esmo.org

†Approved by the ESMO Guidelines Committee: December 2006, last update January 2018. This publication supersedes the previously published version—Ann Oncol 2013; 24 (Suppl. 6): vi149–vi154.

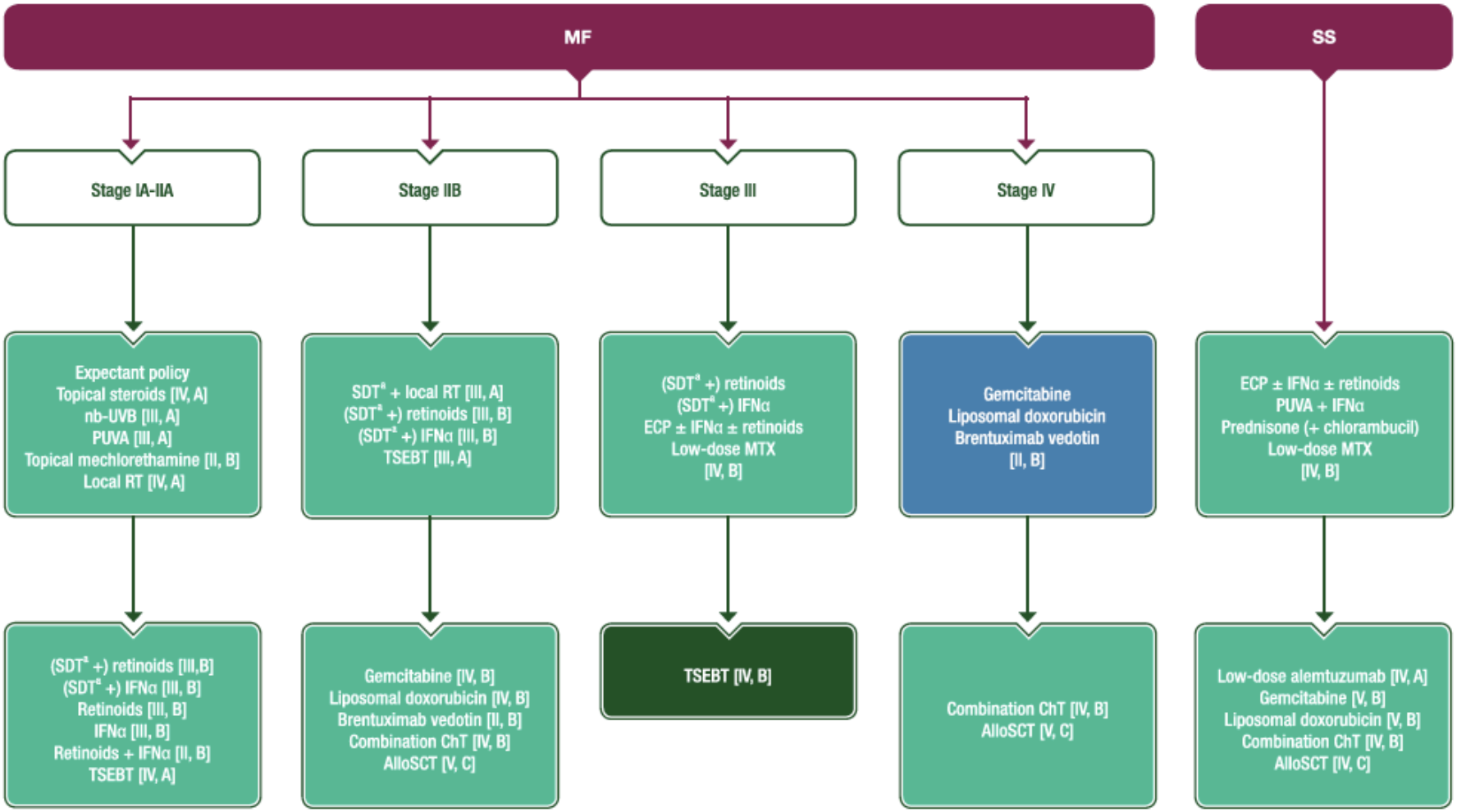
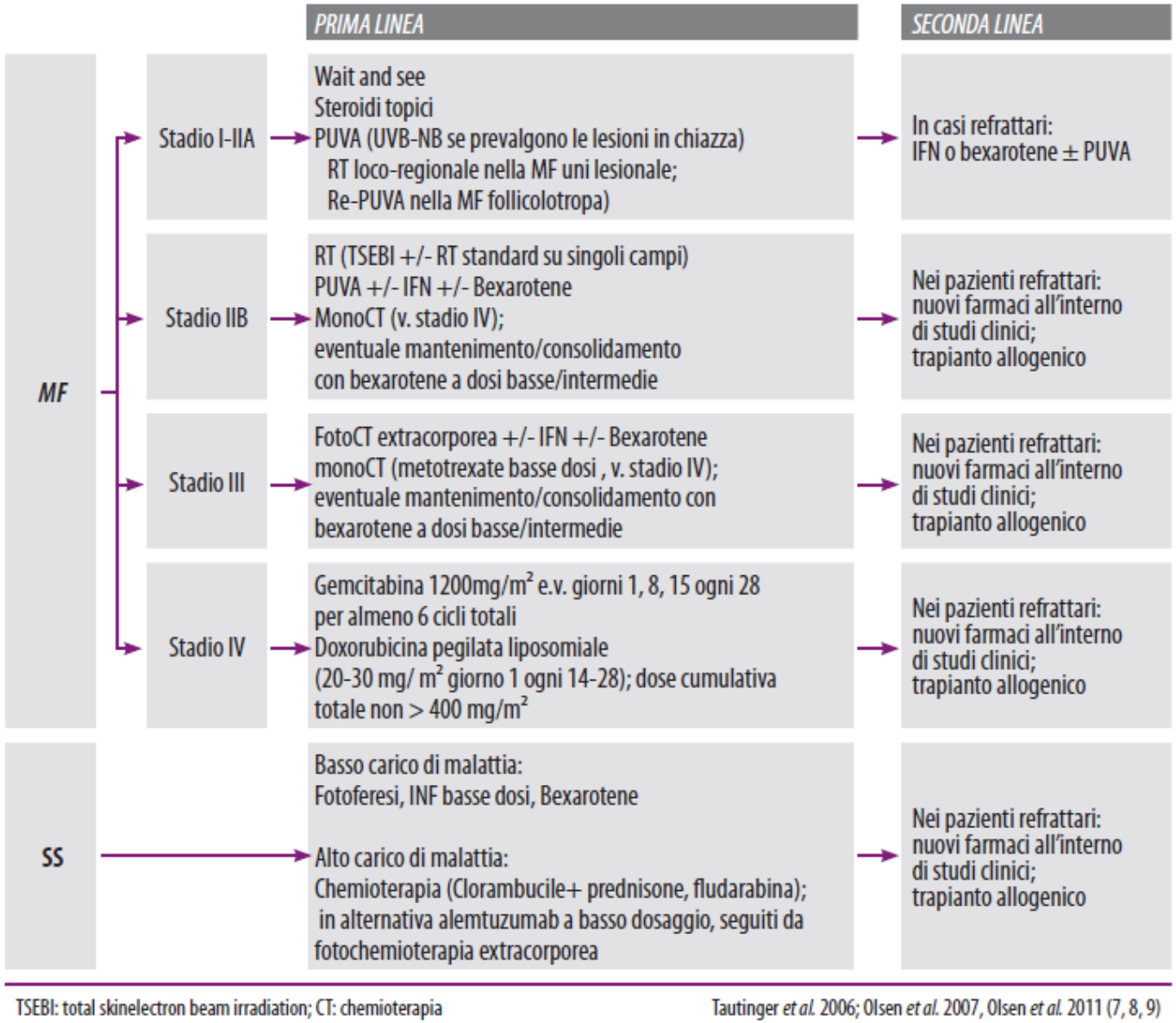


Figure 1. Recommendations for the treatment of MF/SS.
[a]Most commonly PUVA.
AlloSCT, allogeneic stem cell transplantation; ChT, chemotherapy; ECP, extracorporeal photopheresis; IFNα, interferon alpha; MF, mycosis fungoides; MTX, methotrexate; nb-UVB, narrow-band ultraviolet B; PUVA, psoralens plus ultraviolet A; RT, radiotherapy; SS, Sézary syndrome; SDT, skin-directed therapy; TSEBT, total skin electron beam therapy.

MF/SS linee guida di terapia Commissione Linfomi cutanei - FIL



Coordinate da Nicola Pimpinelli; Autori: Paolo Fava, Silvia Alberti Violetti, Chiara Delfino

LA TERAPIA DEI CTCL
Strategie di trattamento e ritrattamento

LINEE GUIDA DANNO INDICAZIONI..

Review of the Treatment of Mycosis Fungoides and Sézary Syndrome: A Stage-Based Approach

Steven M. Horwitz, MD;[a] Elise A. Olsen, MD;[b] Madeleine Duvic, MD;[c] Pierliugi Porcu, MD;[d] and Youn H. Kim, MD,[e]
New York, New York; Durham, North Carolina; Houston, Texas; Columbus, Ohio; and Stanford, California

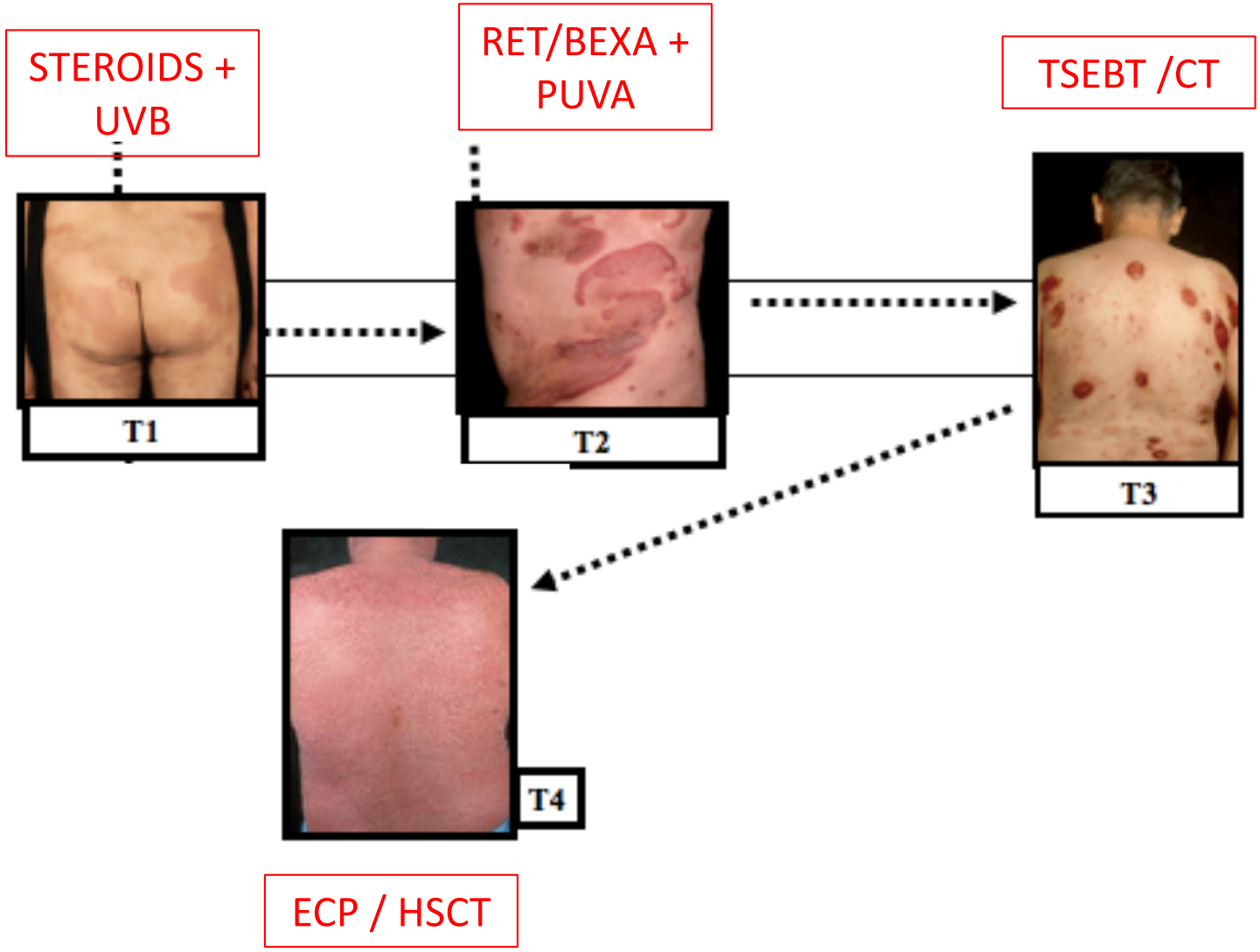
Key Words
Mycosis fungoides, Sézary syndrome, cutaneous T-cell lymphoma

Abstract
The NCCN Clinical Practice Guidelines in Oncology: Non-Hodgkin's Disease were recently revised to include recommendations for treating mycosis fungoides and Sézary syndrome. These uncommon lym-

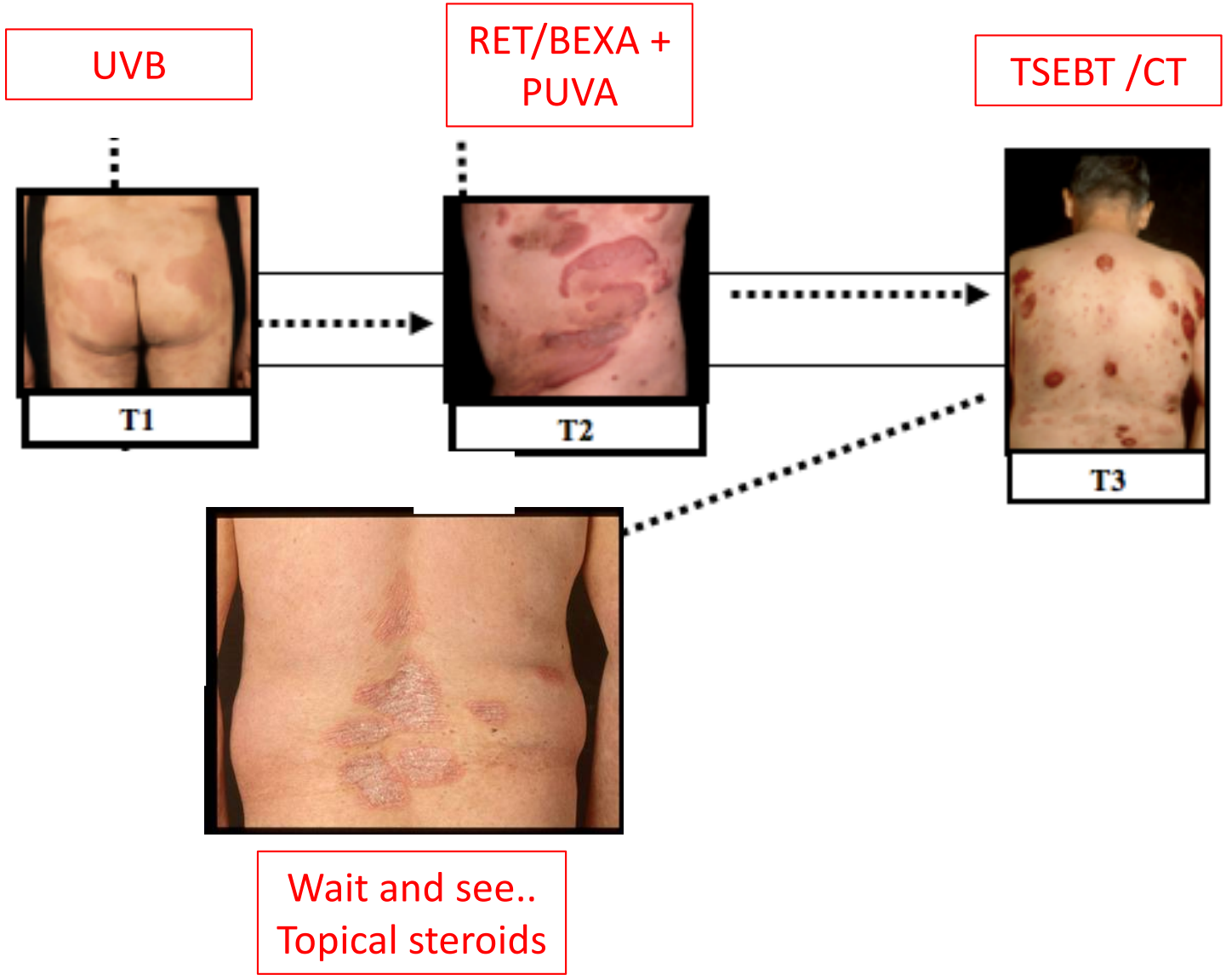
tients results in a much higher overall prevalence. In 2007, the NCCN created its first guidelines on MF/SS. There are not sufficient randomized studies to recommend a preferred treatment strategy for MF/SS, nor do universally accepted standard treatments exist. The chronicity of the disease results in many patients being

VEDI PERO' ULTIME SLIDES ….

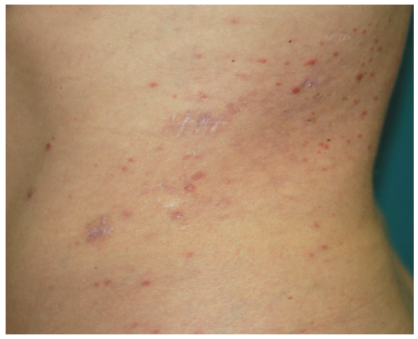
TREATMENT UP- GRADE



TREATMENT DOWN GRADE

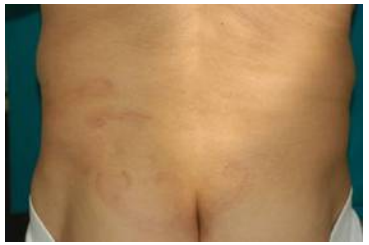


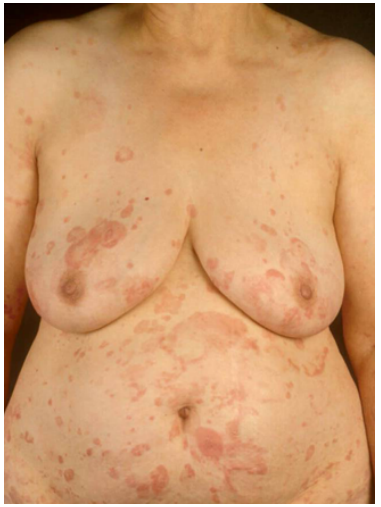
The re-challenge paradigm of CTCL therapy



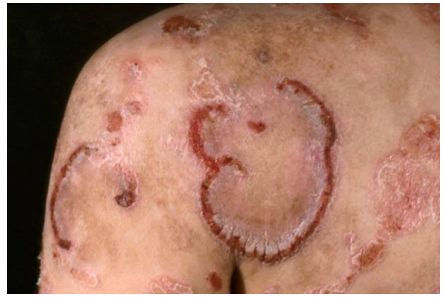
PUVA

Topical steroids



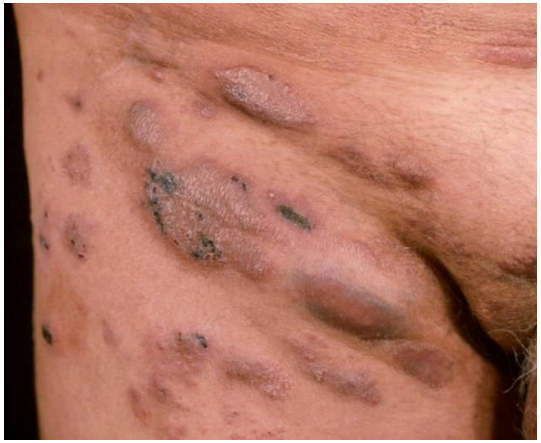


PUVA



TSET

gemcitabine



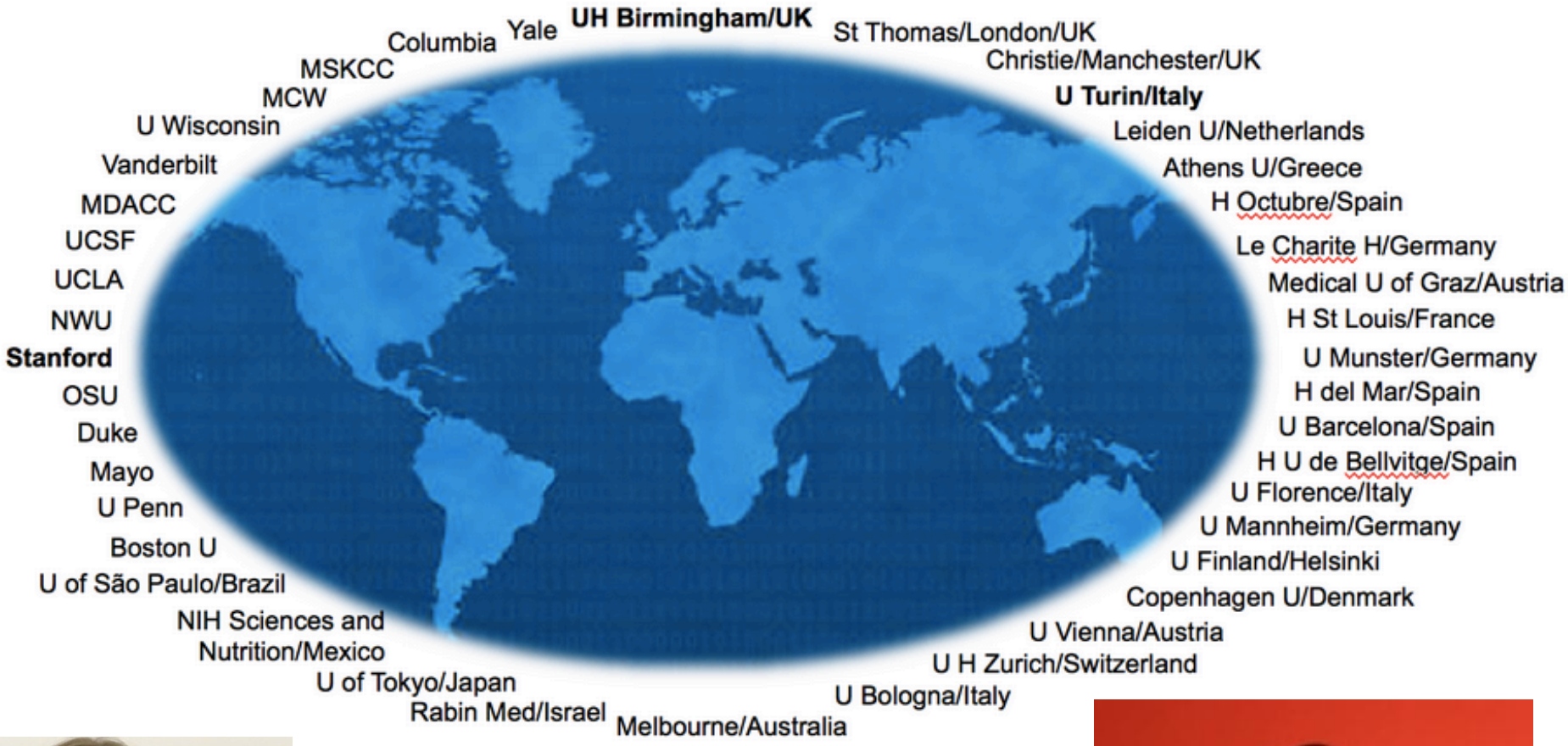
LA TERAPIA DEI CTCL
Strategie di trattamento e ritrattamento

LINEE GUIDA DANNO INDICAZIONI MA ….

UP – AND DOWN-GRADE DELLE TERAPIE, RE-CHALLENGE COME ELEMENTI CARATTERIZZANTI LA TERAPIA DEI CTCL

BASIC QUESTION..

- HOW MF/SS CTCLs ARE TREATED WORLDWIDE IN A REAL WORLD SETTING



JULIA SCARISBRICK, BIRMINGHAM

CLIC
CUTANEOUS LYMPHOMA INTERNATIONAL CONSORTIUM

YOUN KIM, STANFORD

ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

Annals of Oncology 00: 1–9, 2017
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ORIGINAL ARTICLE

Global patterns of care in advanced stage mycosis fungoides/Sezary syndrome: a multicenter retrospective follow-up study from the Cutaneous Lymphoma International Consortium

P. Quaglino[1*†], M. Maule[2†], H. M. Prince[3,4], P. Porcu[5], S. Horwitz[6], M. Duvic[7], R. Talpur[7], M. Vermeer[8], M. Bagot[9], J. Guitart[10], E. Papadavid[11], J. A. Sanches[12], E. Hodak[13,14], M. Sugaya[15], E. Berti[16], P. Ortiz-Romero[17], N. Pimpinelli[18], O. Servitje[19], A. Pileri[20], P. L. Zinzani[21], T. Estrach[22], R. Knobler[23], R. Stadler[24], M. T. Fierro[1], S. Alberti Violetti[16], I. Amitay-Laish[13,14], C. Antoniou[11], C. Astrua[1], S. Chaganti[25], F. Child[26], A. Combalia[22], S. Fabbro[5], P. Fava[1], V. Grandi[18], C. Jonak[23], E. Martinez-Escala[10], M. Kheterpal[6], E. J. Kim[27], C. McCormack[3,4], T. Miyagaki[15], D. Miyashiro[12], S. Morris[26], C. Muniesa[19], V. Nikolaou[11], G. Ognibene[28], F. Onida[16], S. Osella-Abate[1], S. Porkert[23], C. Postigo-Llorente[17], C. Ram-Wolff[9], S. Ribero[1], K. Rogers[28], M. Sanlorenzo[1], R. Stranzenbach[24], N. Spaccarelli[27], A. Stevens[25], D. Zugna[2], A. H. Rook[27], L. J. Geskin[28], R. Willemze[8], S. Whittaker[26], R. Hoppe[29], J. Scarisbrick[25‡] & Y. Kim[29‡]

CLIC
CUTANEOUS LYMPHOMA INTERNATIONAL CONSORTIUM

Materials & Methods:

853 patients stage IIB or higher diagnosed from January 2007 with treatment information retrospectively collected from 21 centres (14 European, 4 USA, 1 Australian, Brazilian and Japanese)

The objectives were:

- **to analyze treatment distribution according to geographical areas, stage and age of advanced-phase MF/SS patients;**
- **to ascertain the association between these parameters and survival.**

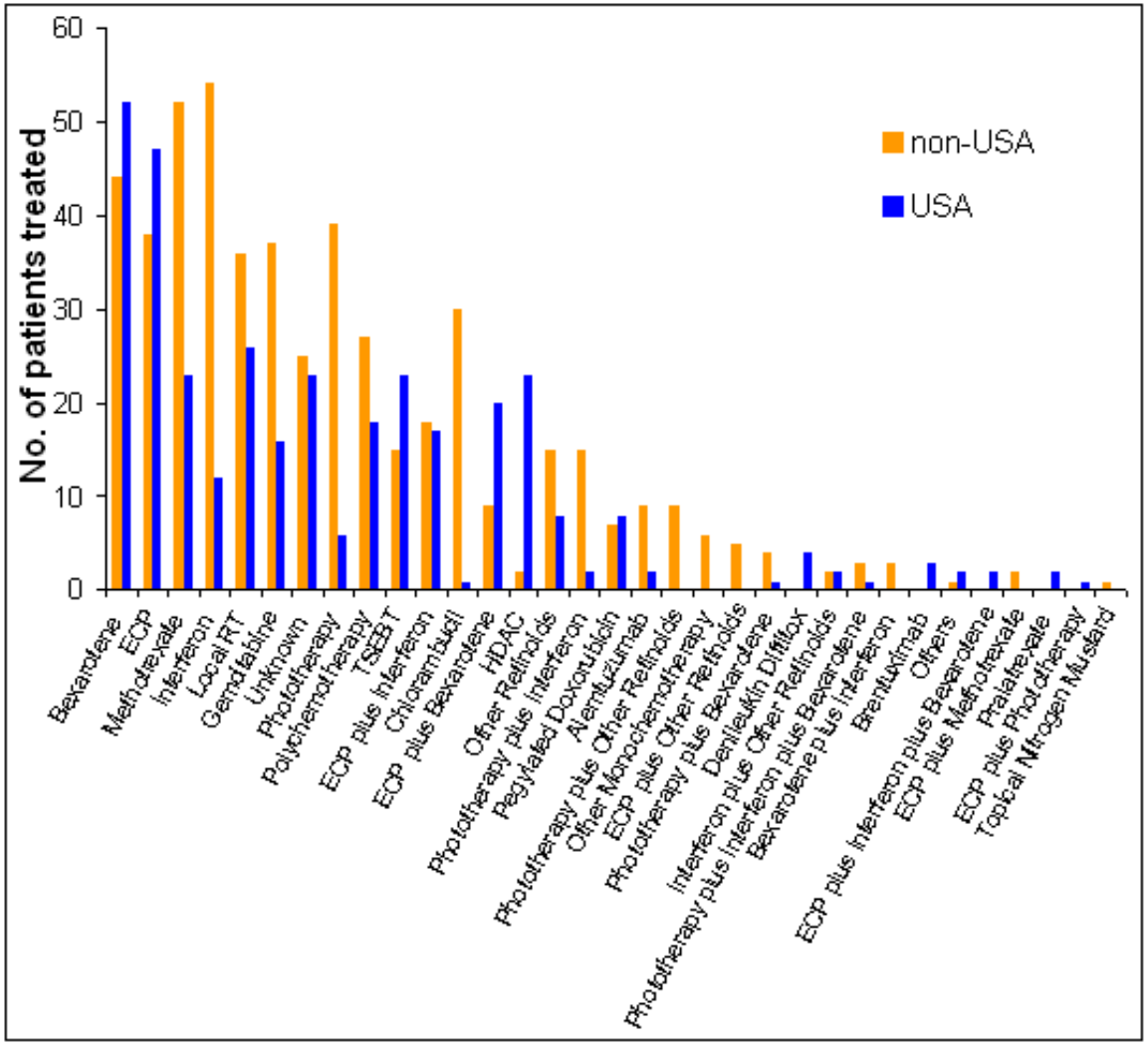
Distribution of treatments performed in time (percentage of patients treated with that therapy out of the total no. of patients treated in a given treatment line) in the first 10 treatment lines.

Therapy	1st	2nd	3rd	4th	5th	6th	7th	8th	9th	10th	P for trend
ECP (alone or in combination)	18.6	13.3	6.3	5.8	6.4	4.8	2.8	7.7	9.4	5.3	0.952
Bexarotene	11.3	12.8	10.3	7.4	7.4	5.6	4.2	1.9	6.3	10.5	0.001
Phototherapy (alone or in combination)	9.5	5.9	3.5	3.4	3.5	2.4	2.8	1.9		5.3	0.949
Methotrexate	8.8	5.9	7.0	6.8	4.5	9.6	6.9	9.6	6.3	10.5	0.232
Interferon	7.7	7.7	10.8	8.5	8.4	4.8	5.6	1.9	3.1	5.3	0.616
Local RT	7.3	5.7	7.0	5.1	5.0	8.0	6.9	7.7	6.3	5.3	0.442
Gemcitabine	6.2	5.6	6.8	6.1	4.0	8.8	1.4	1.9			0.378
Polychemotherapy	5.3	9.2	9.8	9.8	10.4	10.4	16.7	13.5	9.4	26.3	<0.0001
TSEBT	4.5	7.9	7.0	5.7	9.4	6.4	6.9	9.6	6.3	5.3	0.028
Chlorambucil	3.6	2.5	2.1	2.7	2.0	1.6		1.9			0.067
HDACi	2.9	5.6	5.4	12.5	5.5	8.8	11.1	1.9	9.4		<0.0001
Other Retinoids	2.7	2.7	1.9	1.0			1.4		3.1		0.029
Pegylated Doxorubicin	1.8	4.7	4.4	3.7	10.9	4.8	5.6	5.8	12.5	5.3	<0.0001
Alemtuzumab	1.3	2.9	3.5	3.4	2.0	2.4	5.6	1.9	3.1	15.8	0.006
Interferon plus Bexarotene or Other Retinoids	0.8	0.5	0.7	0.3							0.020
Other Monochemotherapy	0.7	1.7	2.1	2.0	3.0	3.2	5.6	5.8	6.3		<0.0001
Denileukin Diftitox	0.5	0.3	0.7	0.7	1.0		1.4	3.9	6.3		0.008
Brentuximab vedotin	0.4	0.7	4.0	2.4	3.0	5.6	5.6	1.9			<0.0001
Pralatrexate	0.2	0.8	1.4	2.0	1.0	1.6	1.4	5.8	3.1		<0.0001
Topical Nitrogen Mustard (Mechlorethamine)	0.1	0.2	0.5			1.6		1.9			0.001
Mogamulizumab		1.2	0.9	2.4	2.5	2.4	2.8	5.8	3.1		<0.0001
Transplantation		1.0	2.3	6.4	6.4	4.8	4.2	5.8	6.3	5.3	<0.0001
Zanolimumab		0.2	0.2	0.3				1.9			0.003

Most commonly used first approaches were extracorporeal photochemotherapy (ECP), bexarotene and phototherapy. As treatment numbers increased, they included poly-chemotherapy, total-skin-electron-beam therapy (TSEBT), histone-deacetylase inhibitors (HDACi), pegylated doxorubicin and allogeneic transplantation.

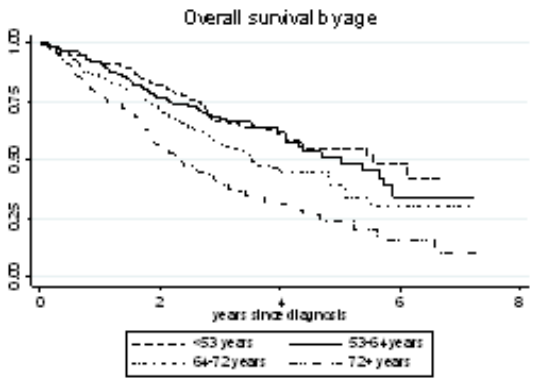
Therapy	1st	2nd	3rd	4th	5th	6th	7th	8th	9th	10th	
Bexarotene	17.2	13.8	6.3	9.1	2.7		4.3			14.3	
Local RT	17.2	13.3	14.6	12.7	12.3	25	13.0	13	11		
Phototherapy (alone or in combination)	11.7	7.8	7.0	6.4	8.2	5	8.7	6.7		14.3	IIB
TSEBT	10.4	15.1	10.8	7.3	5.5	13	8.7	13	22	14.3	
Gemcitabine	9.1	5.5	7.0	8.2	4.1	7.5	4.3	6.7			
Methotrexate	20.5	11.4	16.7	11.9		21.1	9.1				
ECP (alone or in combination)	15.4	20.3	7.4	9.5	7.7		9.1	12.5	33.3	50.0	IIIA
Phototherapy (alone or in combination)	15.4	8.9	3.7	2.4							
Bexarotene	9.4	15.2	7.4	11.9	11.5						
Interferon	7.7	5.1	14.8	11.9	19.2	5.3	9.1				
ECP (alone or in combination)	35.6	11.8	12.8	15.0	6.7	11.1					
Methotrexate	15.1	7.8	2.6	5.0	13.3	11.1					IIIB
Bexarotene	6.8	13.7	10.3	15.0	20.0	11.1	20.0		100		
Phototherapy (alone or in combination)	6.8	7.8		5.0							
Interferon	5.5	11.8	15.4	10.0	13.3	22.2	20.0			100.0	
ECP (alone or in combination)	36.6	29.7	9.9	3.8	11.5	2.5	4.3	11.1	9.1		
Interferon	9.8	9.0	9.9	7.6	3.3	5.0		5.6			IVA1
Chlorambucil	8.5	5.8	4.5	5.1	1.6						
Phototherapy (alone or in combination)	7.6	3.2	1.8	2.5	1.6						
Methotrexate	7.1	3.9	9.9	6.3	3.3	10.0	13.0	11.1	9.1	20.0	
Polychemotherapy	14.9	21.4	15.4	17.2	22.2		14.3		33.3	33.3	
ECP (alone or in combination)	12.2	8.9	12.8	13.8	11.1	20.0					IVA
Bexarotene	10.8	12.5	15.4	6.9	16.7	40.0	14.3				
Interferon	10.8	8.9	5.1	3.4	11.1						2-B
Metotrexato Sale Sodico	8.1	5.4	2.6	3.4				16.7			

Distribution of first treatment line between USA and non-USA centres

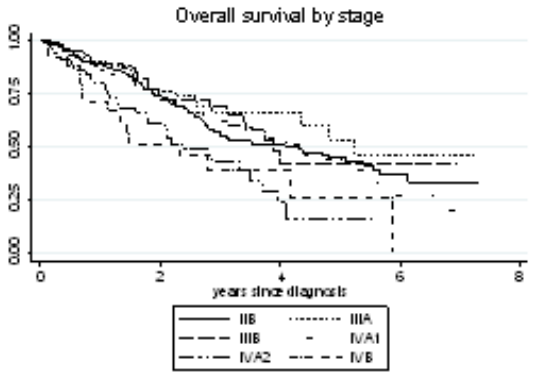


Differences in treatment modalities, partly due to difference in drug availability, were found between USA (bexarotene, ECP, HDACi most frequently prescribed independently from stage/age) and non-USA centers (phototherapy, IFN, chlorambucil and gemcitabine).

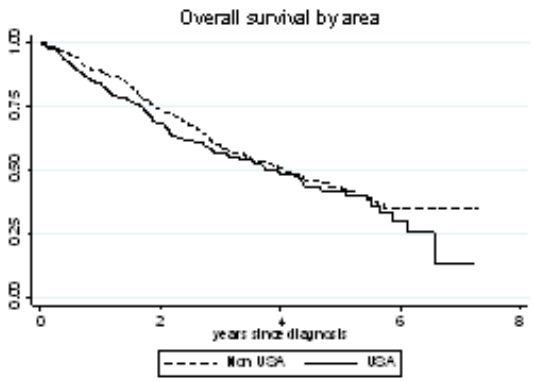
Overall survival estimated with Kaplan Meier curves by age, stage and geographical areas.



Log-rank test p<0.0001



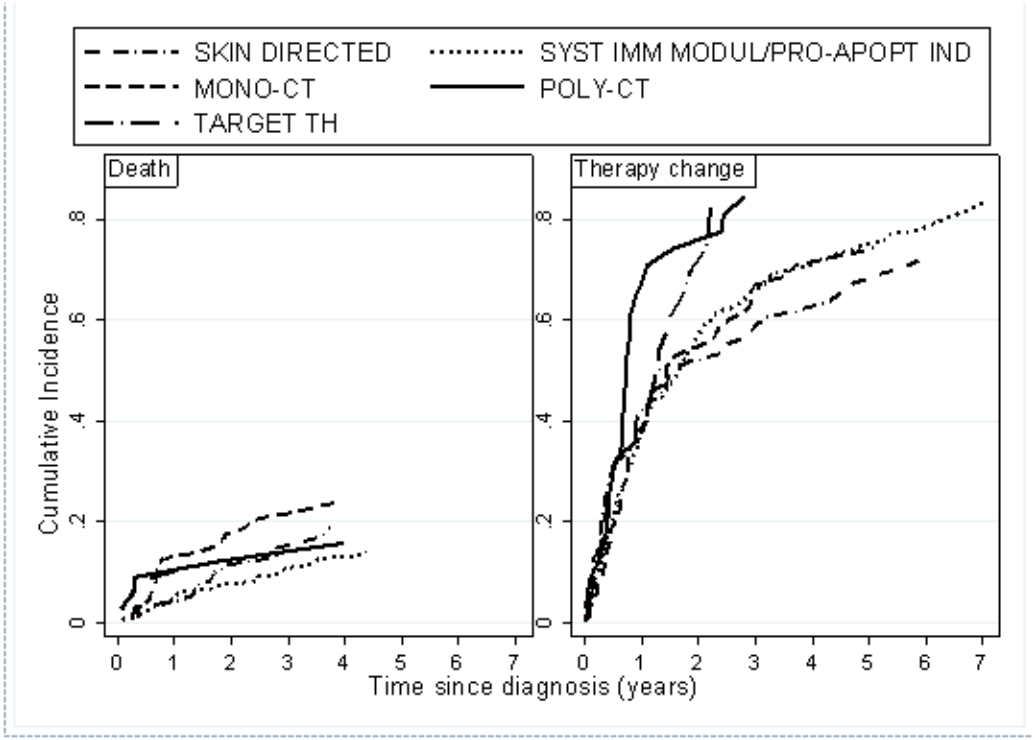
Log-rank test p=0.0011



Log-rank test p=0.1434

In the first multivariate analysis, end-point was death due to any cause and explanatory variables were age, stage and geographical site: age and stage exhibited prognostic significance whilst the geographical site was not associated with mortality.

Cumulative incidence curves for death and change of therapy considered as competing risk events by first treatment line



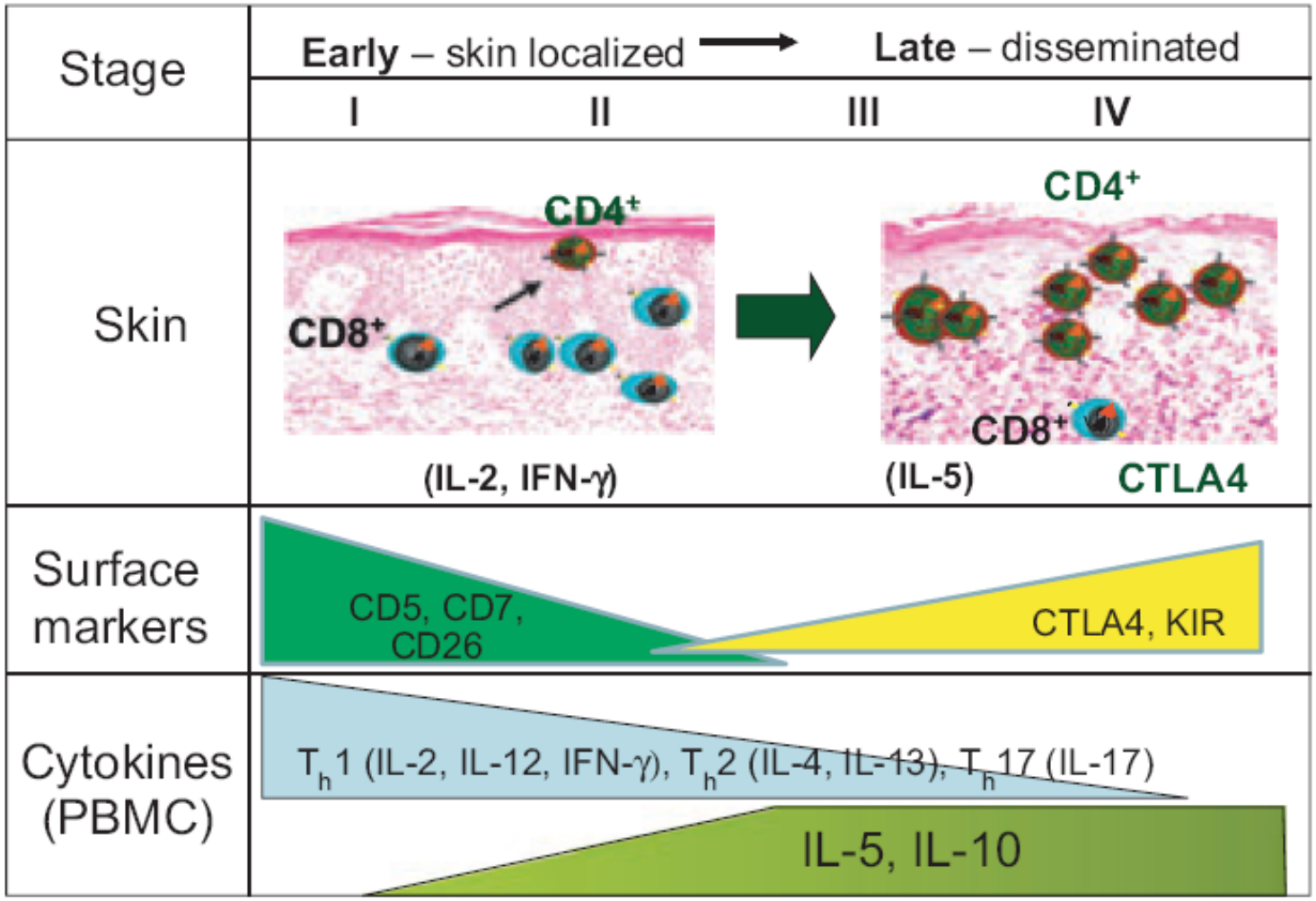
In the second multivariate analysis, death and change of therapy were considered as competing risk events and first-line treatment was included among predictors: first-line treatment was selected as independent prognostic variable (p=0.008), both mono- and poly-chemotherapy being associated with higher mortality.

Conclusions:

- **This unique large multi-centre retrospective study shows the heterogeneity of treatment approaches in advanced MF/SS and their high clinical treatment need.**

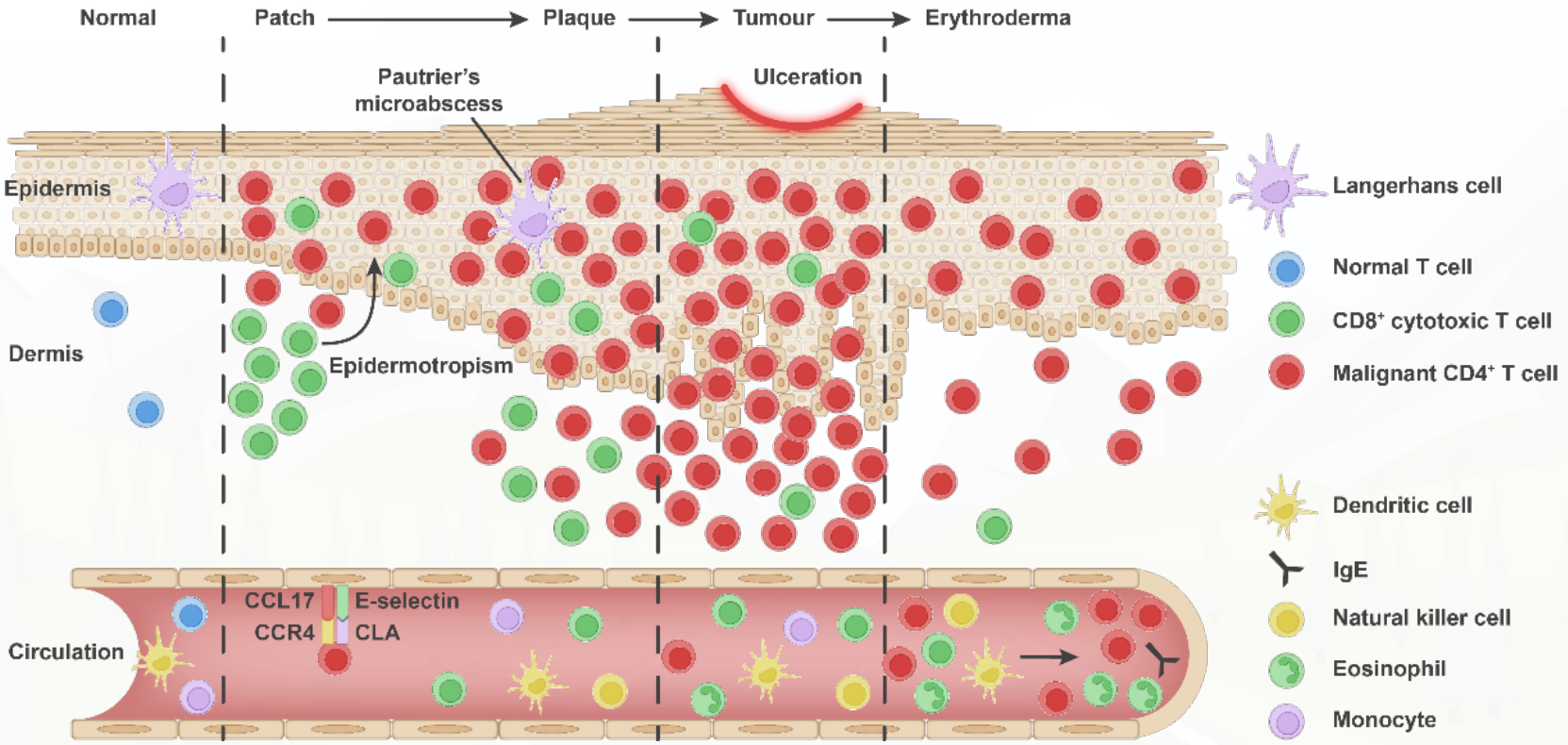
- **In spite of different availability and use of treatments in USA vs non-USA centres, these were not related to survival outcome**

- **These data reveal that taking stage into account, chemotherapy as first treatment is associated to a higher risk of death and thus other therapeutic options should be preferable as first treatment approach.**



Porcu PG, et al. BJH 2012

Immunopathogenesis



CCL, CC chemokine ligand;
CLA, cutaneous lymphocyte-associated antigen; IgE, immunoglobulin E.

Adapted from Kim EJ, et al. J Clin Invest. 2005;115:798-812.

J_ID: Z7B Customer A_ID: C11-2751 Cadmus Art: CNCR27627 Date: 21-April-12 Stage: Page: 1

Original Article

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

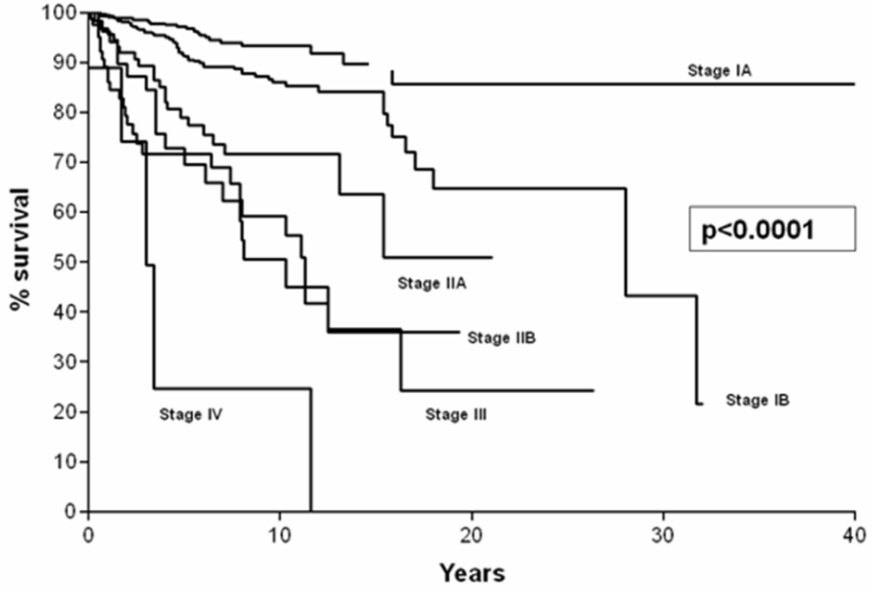
A Multicenter, Retrospective Follow-Up Study From the Italian Group of Cutaneous Lymphomas

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)

BACKGROUND: Mycosis fungoides (MF) is an indolent primary cutaneous T-cell lymphoma. To the authors' knowledge, no data currently are available regarding the evolution over time of the risk of developing specific pathways of disease progression. **METHODS:** This retrospective study analyzed 1422 patients with MF who were diagnosed and followed from 1975 through 2010 in 27 Italian Study Group for Cutaneous Lymphoma centers. The primary objectives were to ascertain the time course, pathways, and hazards risk trends of cutaneous/extracutaneous disease progression; to evaluate whether different tumor-lymph node-metastasis-blood (TNMB) stages have different pathways of disease progression; and to analyze differences between tumor-stage and erythrodermic MF with regard to clinical onset, disease evolution, and prognosis. The secondary objective was to provide a further validation for the revised International Society for Cutaneous Lymphomas and the Cutaneous Lymphoma Task Force of the European Organization of Research and Treatment of Cancer (ISCL/EORTC) classification. **RESULTS:** The median follow-up was 14.5 years; stage progression occurred in 29.7% of patients and blood involvement was the most frequent extracutaneous site of disease progression. Patients with stage IA to stage IB disease demonstrated a steady low annual incidence of disease progression to tumor-stage (1%-2%); patients with stage IIA disease had a higher risk within the first years (up to 9.4%). Erythroderma evolved with a significantly higher frequency from patches/plaques (13.9%/28.2%) than tumors ($P = .028$ and $P = .013$, respectively). Hazards rates of extracutaneous involvement were low (< 1%). T classification was found to

AQ7

Cancer 2012



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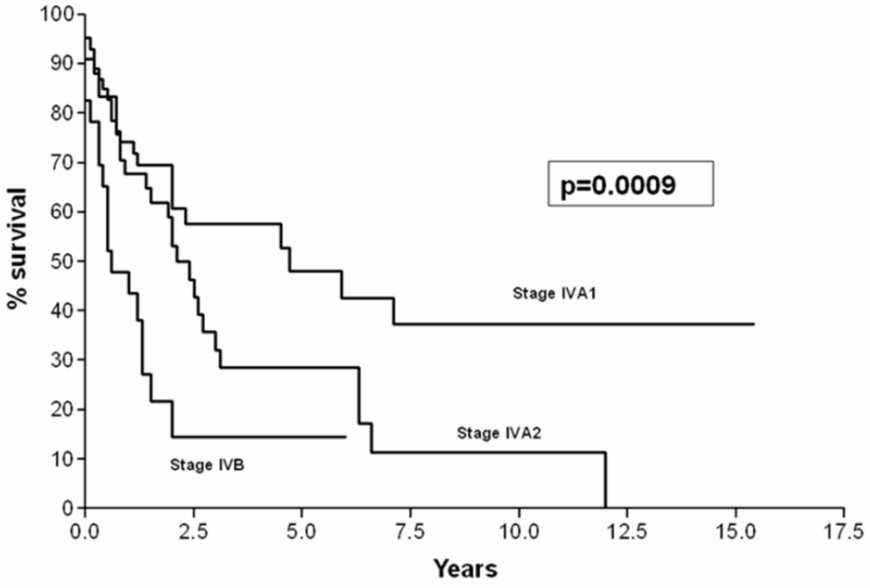


GILC: casistica MF retrospettiva (n=1422)

	Stage I	Stage II	Stage III	Stage IV
"Wait and see"	13.8%	-	-	-
Topical steroids	16.7%	3.3%	9.3%	-
Phototherapy alone	43.2%	24.2%	9.2%	2.6%
Phototherapy + IFN	9.7%	3.3%	2.1%	-
Phototherapy + retinoids	0.9%	3.3%	2.8%	3.1%
Acitretin	2.5%	2.6%	-	-
Bexarotene	0.2%	4.4%	9.2%	4.2%
IFN	8.9%	12.1%	23.4%	10%
Local RT	2.3%	16.5%	2.1%	6.7%
TSET	0.1%	1.8%	-	3.3%
Monochemotherapy[a]	1.7%	15.7%	22%	30%
ECP	-	7.7%	13.3%	16.7%
Polichemotherapy[b]	-	5.1%	6.4%	23.3%

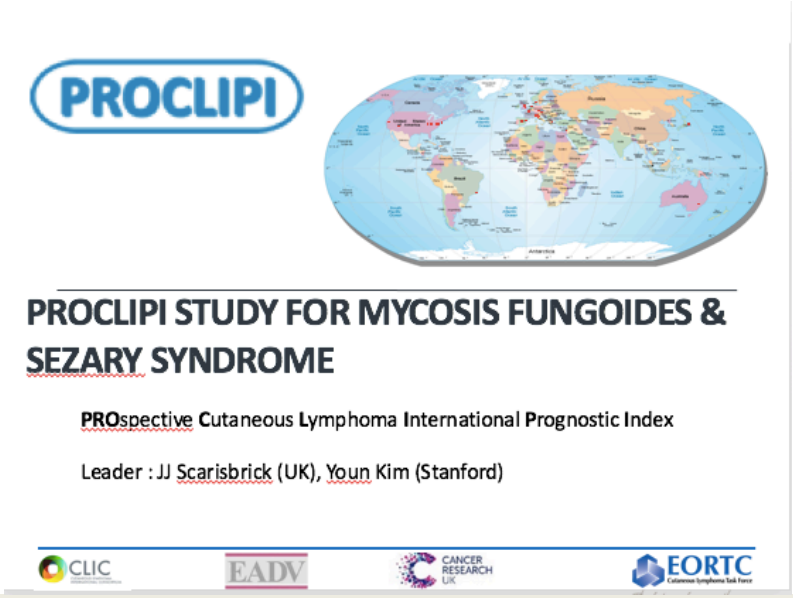
ECP: extracorporeal photochemotherapy; IFN: interferon; RT: radiotherapy; TSET: Total Skin Electron beam Therapy

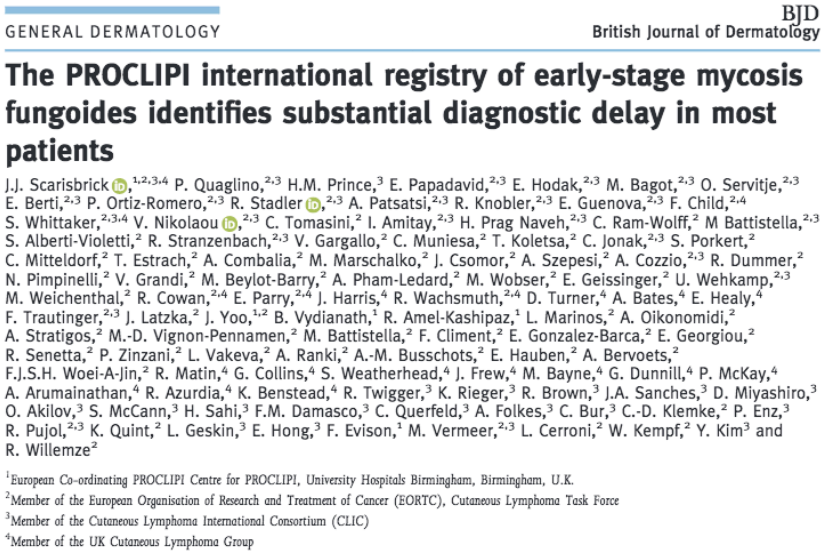
[a]: includes methotrexate, fludarabine, gemcitabine, liposomal pegylated doxorubicin

[b] : CHOP or CHOP-like regimens were performed in the majority of patients

Quaglino P, et al. Studio GILC, Cancer 2012

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

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[3]Member of the Cutaneous Lymphoma International Consortium (CLIC)
[4]Member of the UK Cutaneous Lymphoma Group

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.

PATIENT POPULATION

395

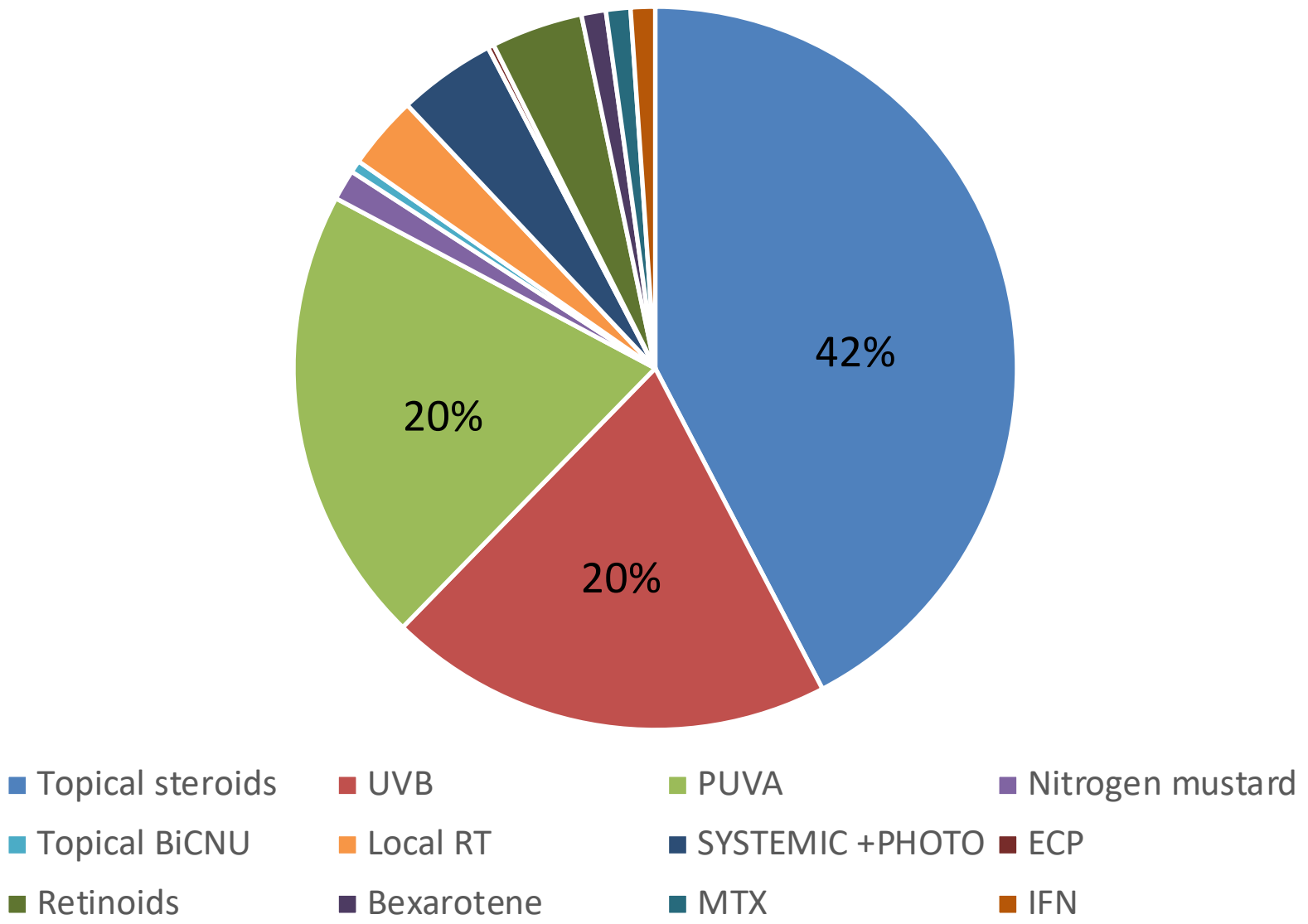
"early stage MF"

(stage IA, IB, IIA)

included in the database after passing central review process from january 2015 to december 2018

Parameter	Number	%
Male	243	62%
Female	152	38%
Age median (range)	56 (5-97)	
mSWAT median (range)	10 (0.3-120)	
Europe	349	88%
Outside Europe	46	12%
Stage IA	198	50%
Stage IB	164	42%
Stage IIA	33	8%
T1a	113	29%
T1b	96	24%
T2a	80	20%
T2b	106	27%
Patches only T1a+T2a	193	49%
Patches + plaques T1b + T2b	202	51%
FMF	71	18%

Summary of treatments registered at first visit (first-line therapies)

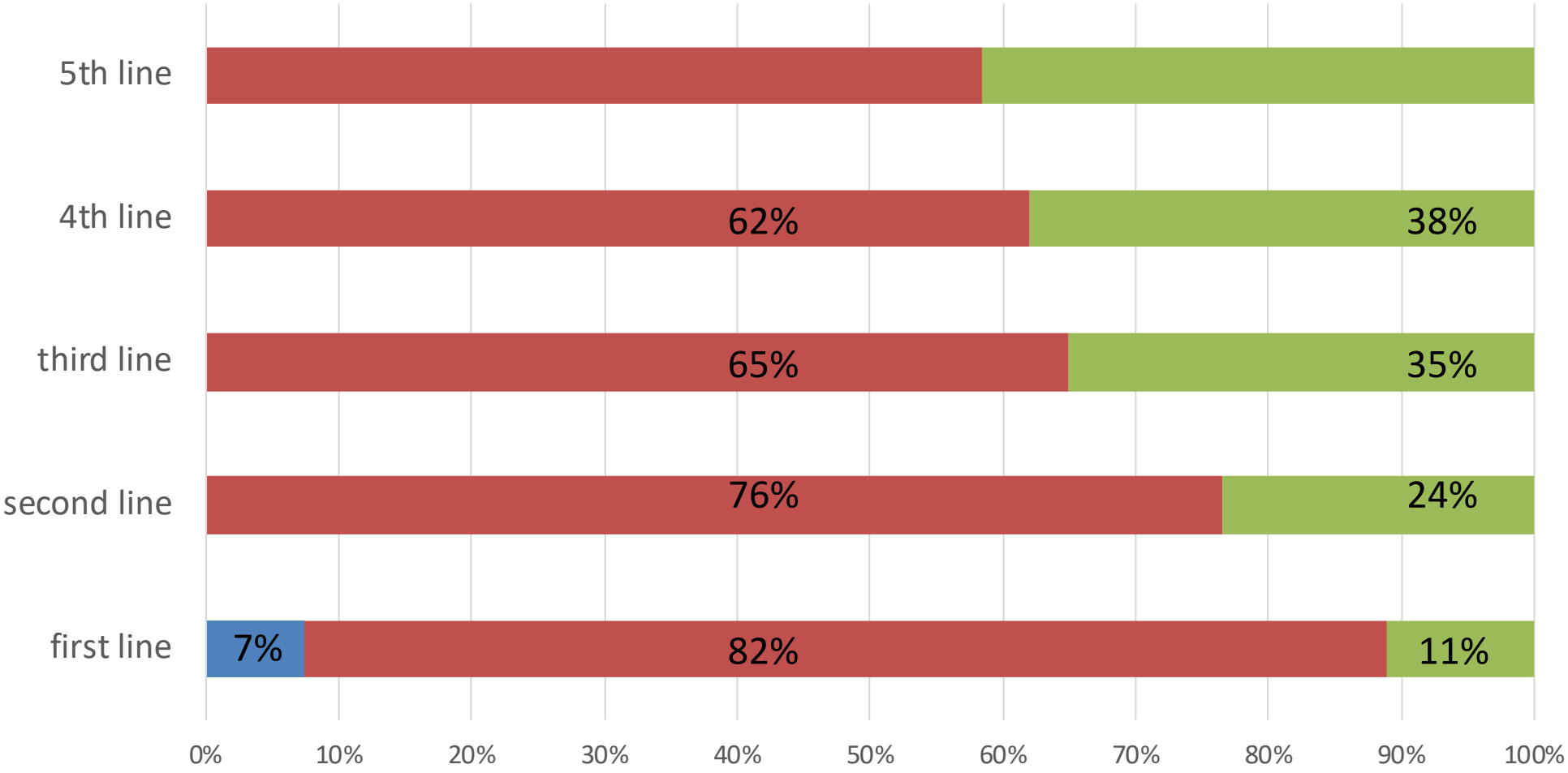


La terapia nel paziente ricaduto/refrattario con CTCL

Further treatment lines according to stage

	2nd line (n; %)	3rd line (n; %)	4th line (n; %)	>4 lines (n; %)
IA (n=207)	72; 35%	24; 12%	4; 2%	5; 2%
IB (n=188)	65; 35%	28; 15%	10; 5%	15; 8%
IIA (n=29)	28; 96%	5; 17%	3; 10%	5; 17%
ALL (n=424)	165; 39%	57; 13%	17; 4%	25; 6%
FMF (n=82)	32; 39%	10; 12%	6; 7%	9; 11%

Summary of treatments according to the therapy line



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

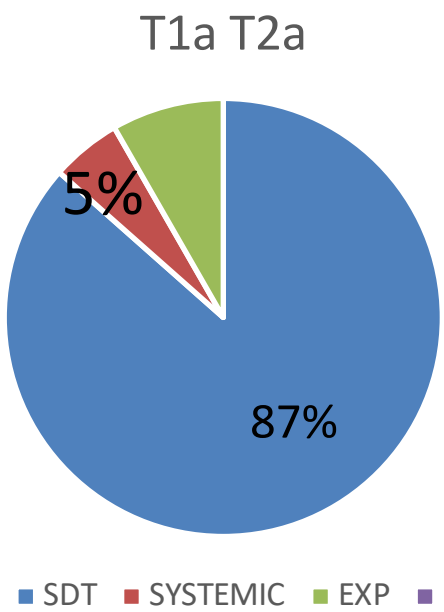
Summary of treatments registered at first visit (first-line therapies) and according to the stage

Treatment	All (n; %) N=395	IA (n; %) N=198	IB (n;%) N=164	IIA (n;%) N=33
Expectant	**29 (7%)**	**17 (9%)**	**9 (5%)**	**3 (10%)**
SKIN-DIRECTED	**322 (82%)**	**168 (85%)**	**131 (80%)**	**23 (70%)**
SYSTEMIC	**44 (11%)**	**14 (6%)**	**23 (14%)**	**7 (20%)**

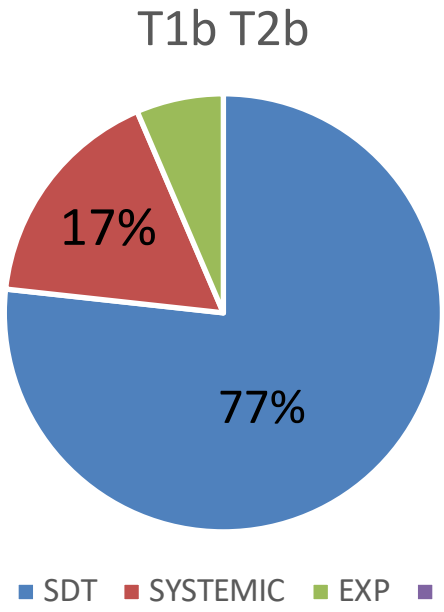
The percentage of patients undergoing a first-line systemic approach increased from stage IA to IB to IIA paralleling a decrease in skin-directed therapies (SDT)(particularly in stage IIA. The difference between stage IA-IB and IIA was statistically significant (chi square:15.398; $p<0.0001$).

Summary of treatments registered at first visit (first-line therapies) and according to T score

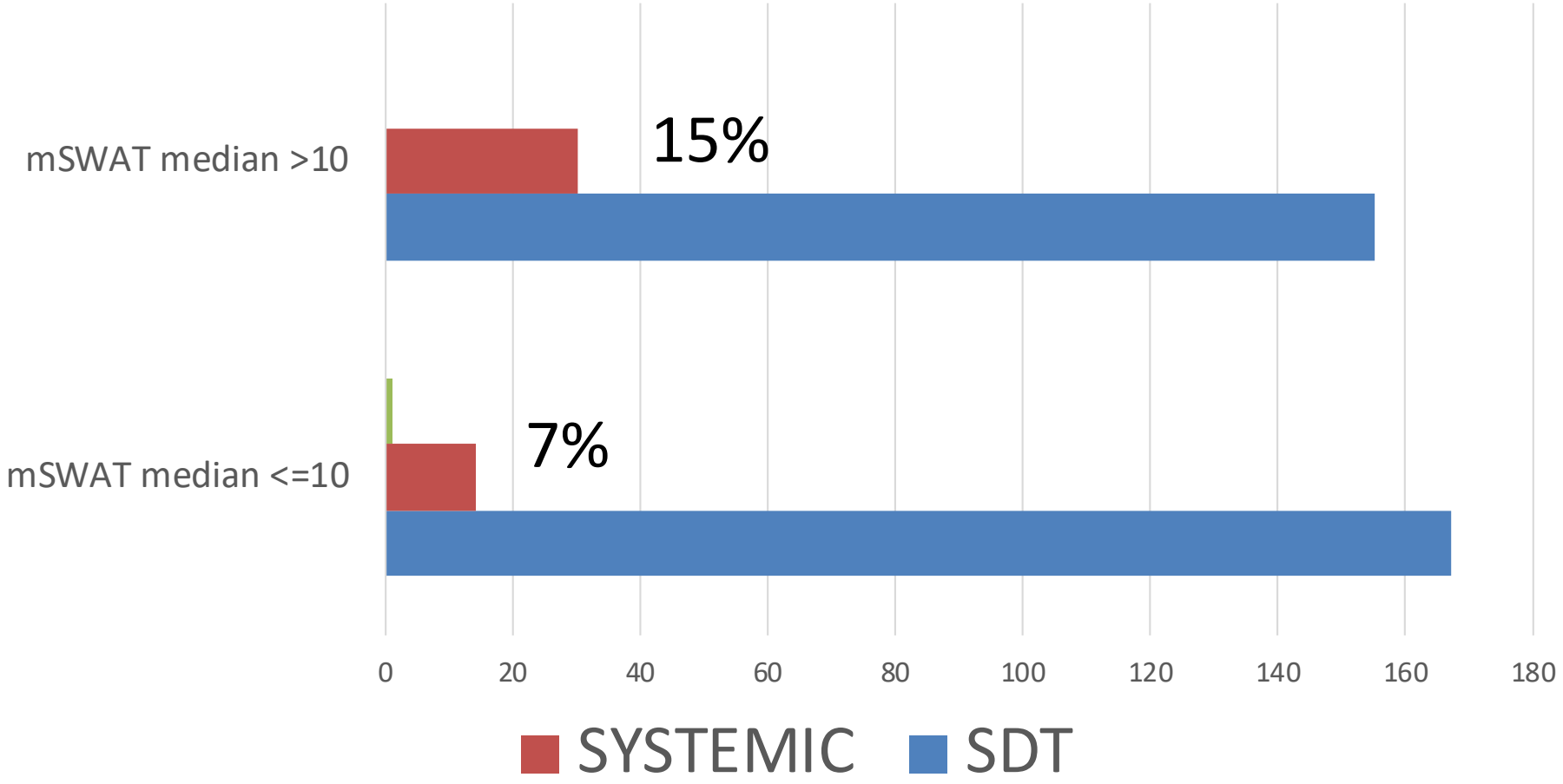
Treatment	T1a (n; %) N=113	T1b (n;%) N=96	T2a (n;%) N=80	T2b (n; %) N=106
Expectant	8 (7%)	9 (9%)	8 (10%)	4 (3%)
SKIN-DIRECTED	100 (89%)	76 (79%)	67 (84%)	79 (75%)
SYSTEMIC	5 (4%)	11 (12%)	5 (6%)	23 (22%)



Chi square: 13,159
P<0.001

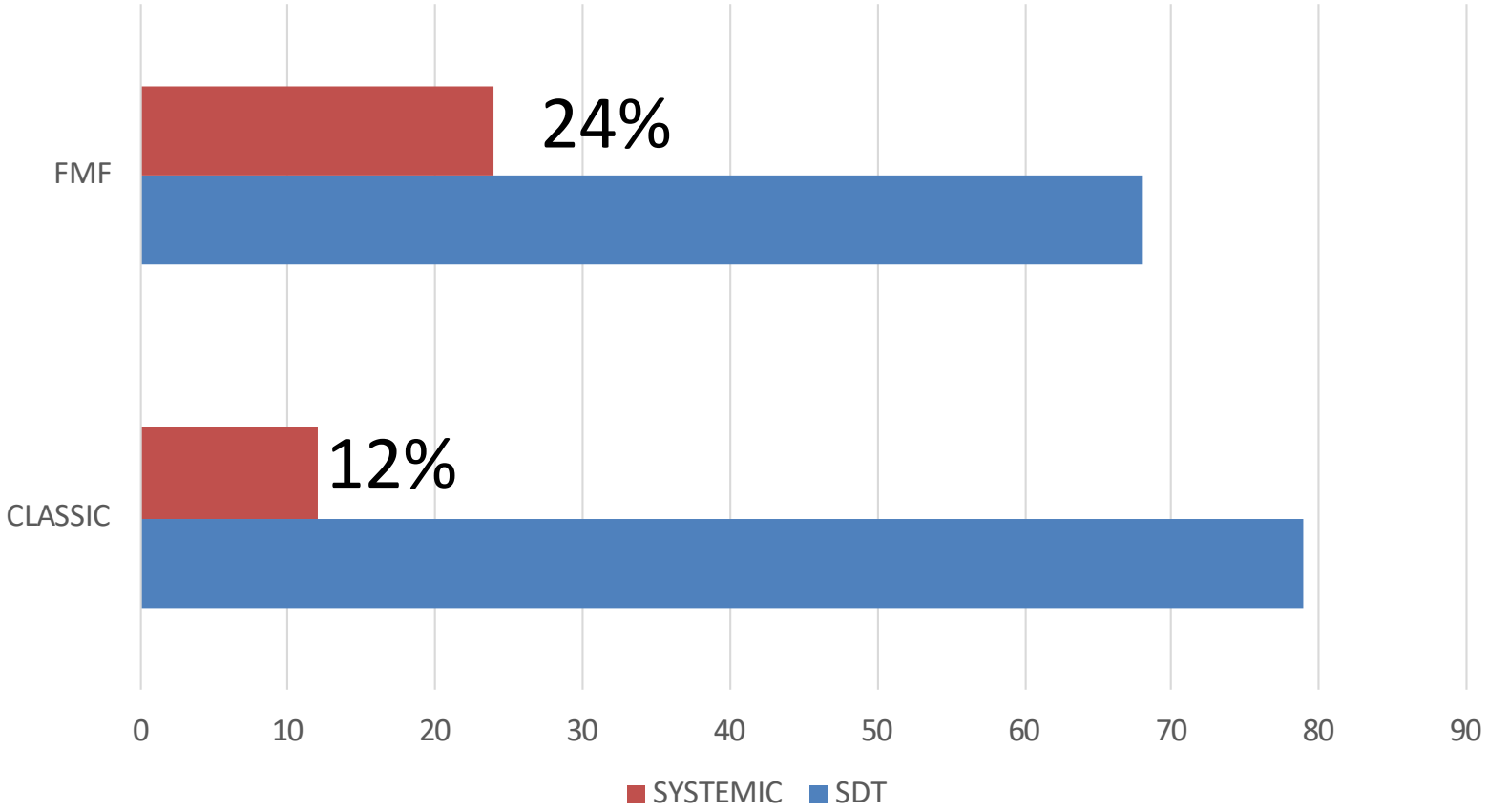


CLINICAL PARAMETERS RELATED WITH A MORE FREQUENT FIRST SYSTEMIC APPROACH



Chi square: 6.222; p=0.013

CLASSIC vs FMF MF



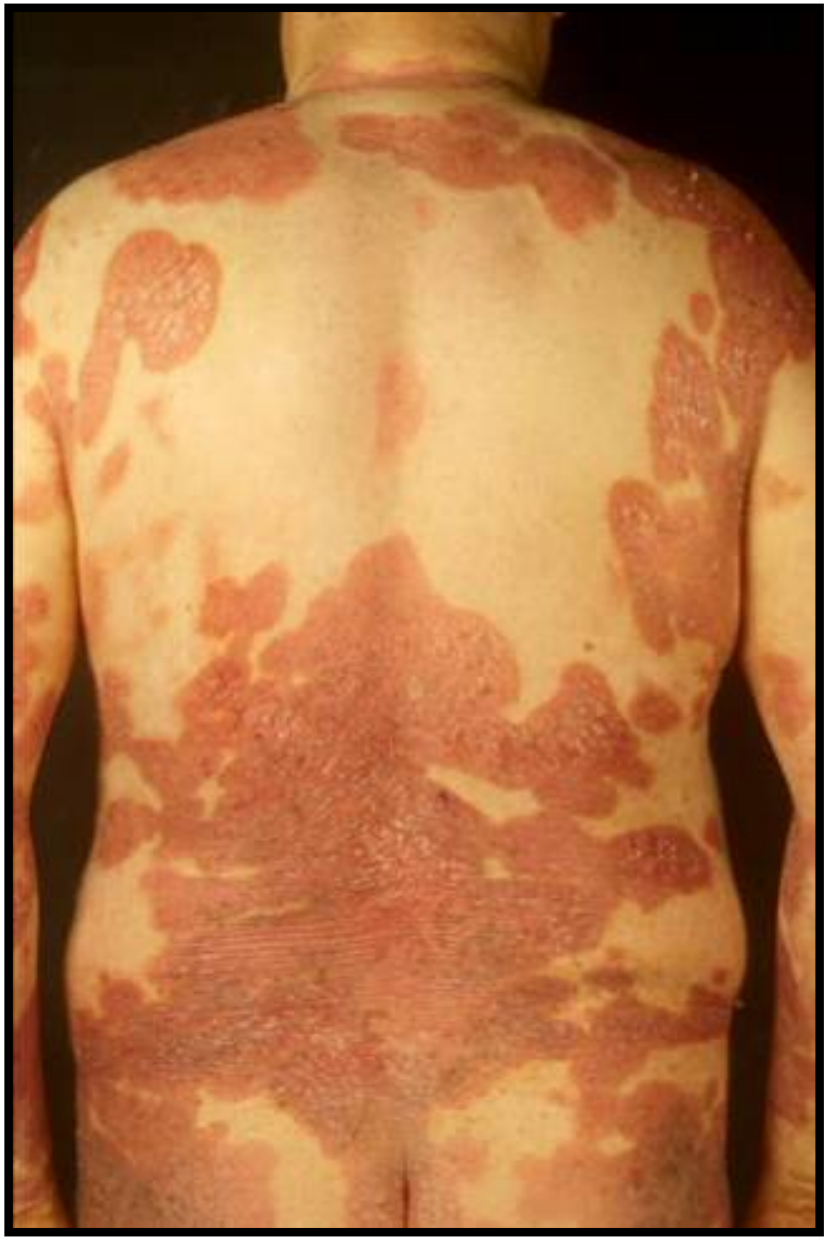
The percentage of patients treated as first line with a systemic approach (immune modifiers or retinoids) was significantly higher than in classic MF (24% vs 12%), whilst the percentage of patients treated by SDT was significantly lower (chi square: 10.779; p=0.0010).

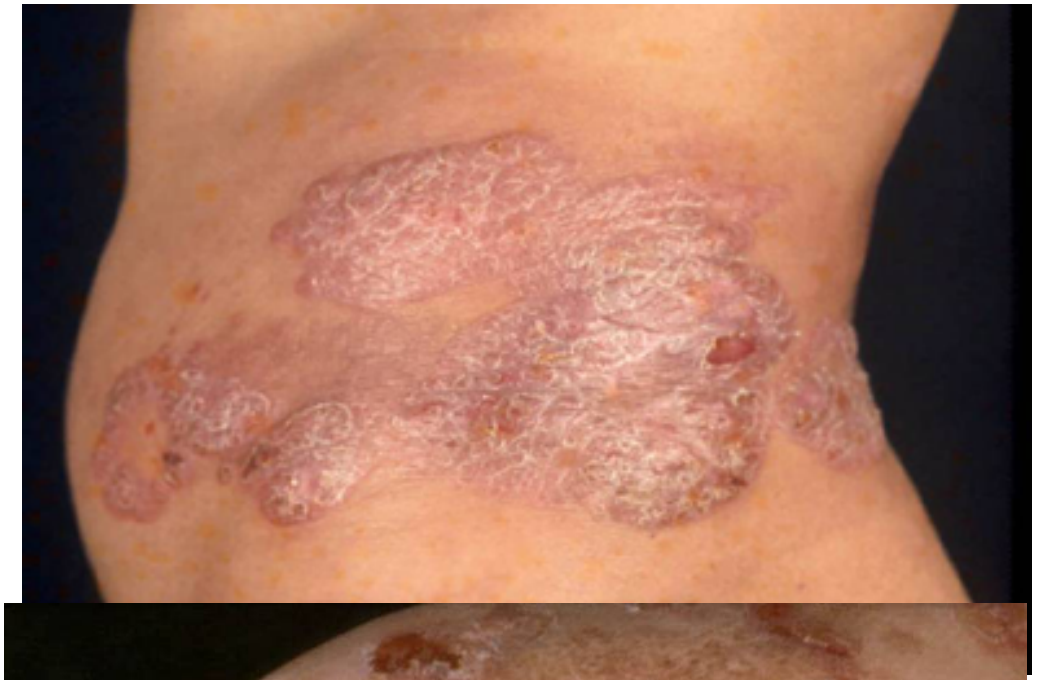
LA TERAPIA DEI CTCL
Strategie di trattamento e ritrattamento

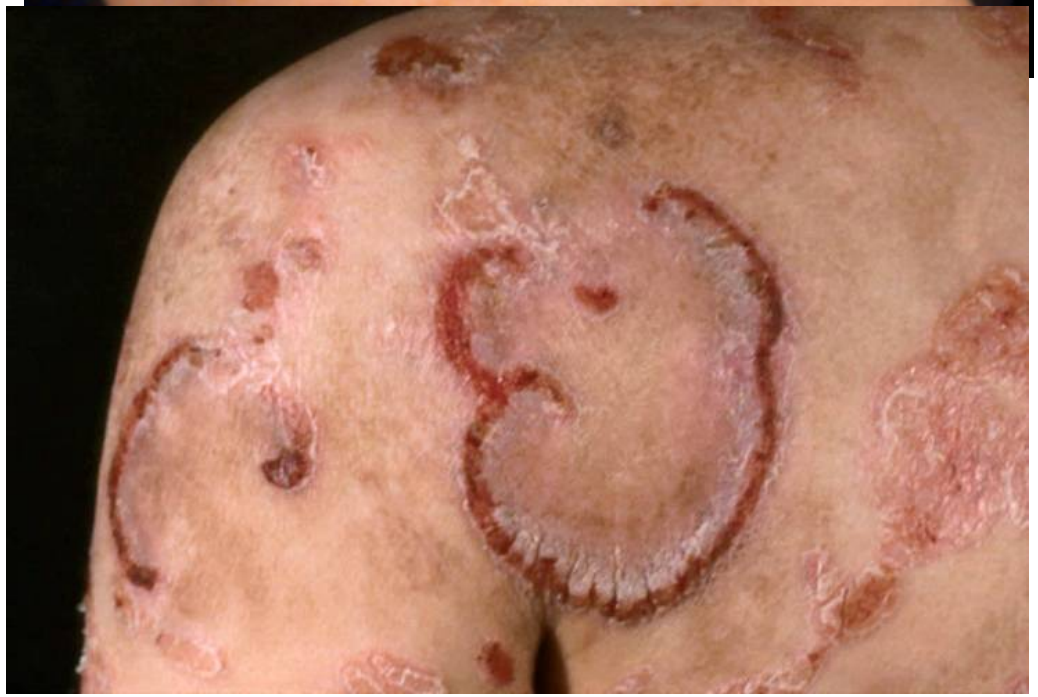
LINEE GUIDA DANNO INDICAZIONI MA ….

UP – AND DOWN-GRADE DELLE TERAPIE, RE-CHALLENGE COME ELEMENTI CARATTERIZZANTI LA TERAPIA DEI CTCL

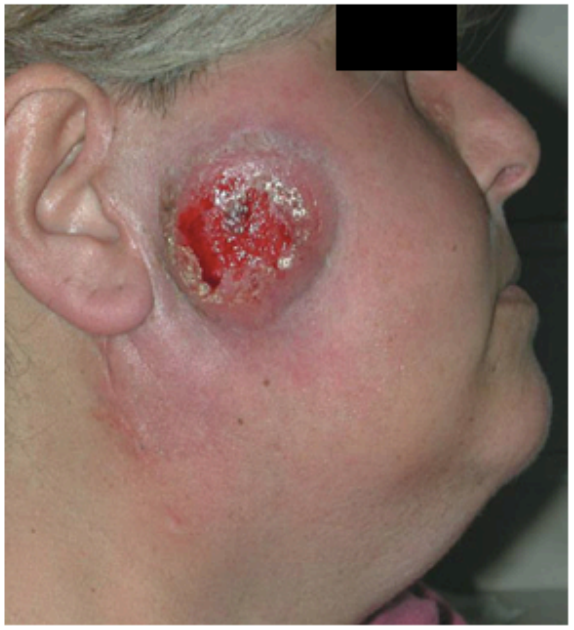
PARAMETRI CLINICO-BIOLOGICI NUOVI SONO NECESSARI PER STRATIFICAZIONE DI PAZIENTI..

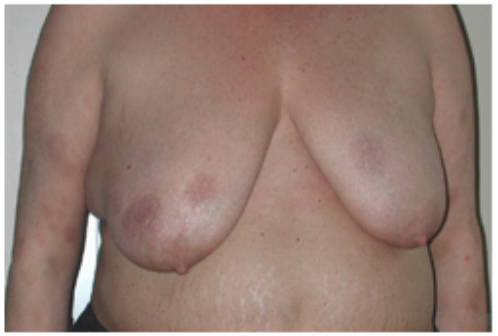


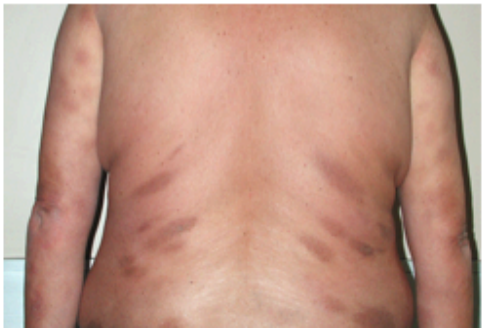


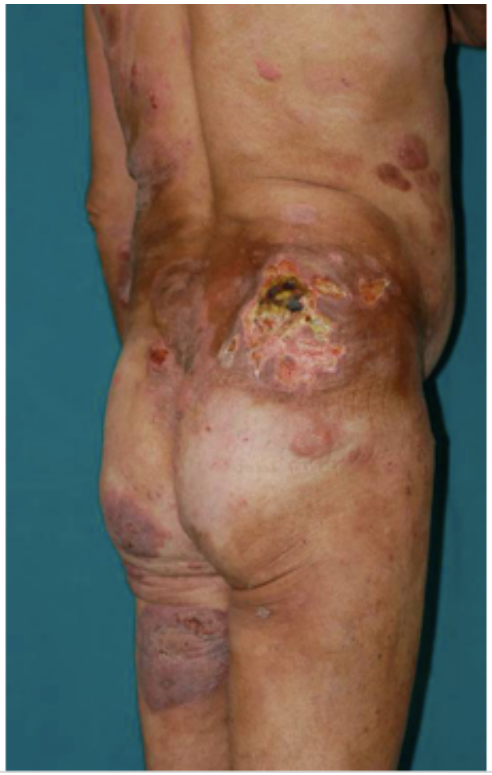


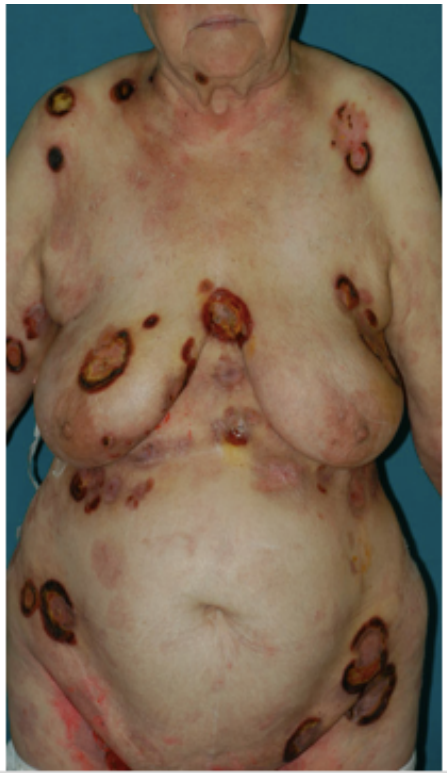
T2a TNMB stage IB or IIA T2b











Stadio IIB

VOLUME 33 · NUMBER 32 · NOVEMBER 10 2015

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Cutaneous Lymphoma International Consortium Study of Outcome in Advanced Stages of Mycosis Fungoides and Sézary Syndrome: Effect of Specific Prognostic Markers on Survival and Development of a Prognostic Model

Julia J. Scarisbrick, H. Miles Prince, Maarten H. Vermeer, Pietro Quaglino, Steven Horwitz, Pierluigi Porcu, Rudolf Stadler, Gary S. Wood, Marie Beylot-Barry, Anne Pham-Ledard, Francine Foss, Michael Girardi, Martine Bagot, Laurence Michel, Maxime Battistella, Joan Guitart, Timothy M. Kuzel, Maria Estela Martinez-Escala, Teresa Estrach, Evangelia Papadavid, Christina Antoniou, Dimitis Rigopoulos, Vassilki Nikolaou, Makoto Sugaya, Tomomitsu Miyagaki, Robert Gniadecki, José Antonio Sanches, Jade Cury-Martins, Denis Miyashiro, Octavio Servitje, Cristina Muniesa, Emilio Berti, Francesco Onida, Laura Corti, Emilia Hodak, Iris Amitay-Laish, Pablo L. Ortiz-Romero, Jose L. Rodríguez-Peralto, Robert Knobler, Stefanie Porkert, Wolfgang Bauer, Nicola Pimpinelli, Vieri Grandi, Richard C… Alain Rook, Ellen Kim, Alessandro Pileri, Annalisa Patrizi, Ramon M. Pujol, Henry Wong, Ke… Rene Stranzenbach, Christiane Querfeld, Paolo Fava, Milena Maule, Rein Willemze, Felicity E… Stephen Morris, Robert Twigger, Rakhshandra Talpur, Jinah Kim, Grant Ognibene, Shufeng L… Mahkam Tavallaee, Richard T. Hoppe, Madeleine Duvic, Sean J. Whittaker, and Youn H. Kim

Listen to the podcast by Dr Pinter-Brown at www.jco.org/podcasts

- stage IV
- age>60years
- large-cell transformation
- increased LDH

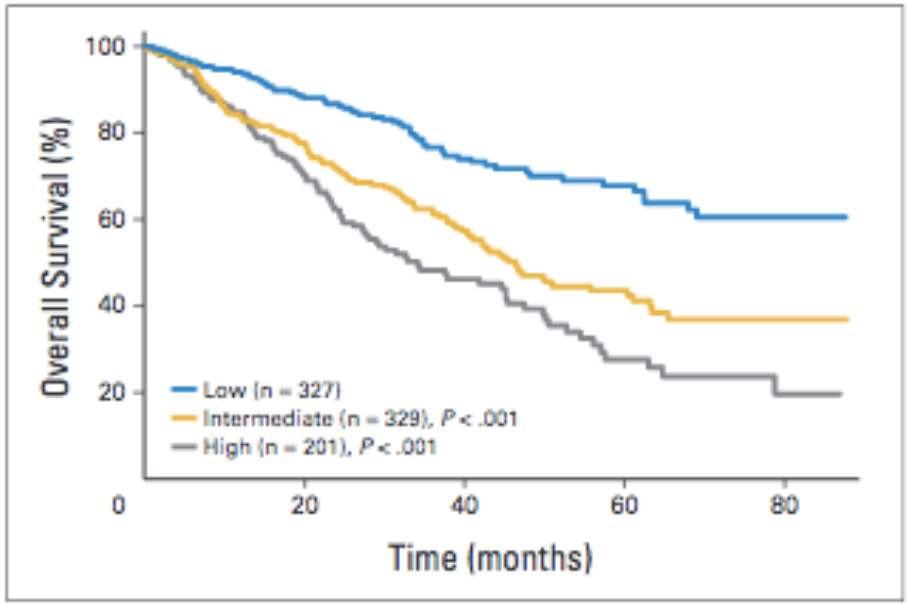


Fig 2. Kaplan-Meier plot showing prognostic index model for low-, intermediate-, and high-risk groups. Variables included in the prognostic index model were stage IV, elevated lactate dehydrogenase, age greater than 60 years, and large-cell transformation in skin (low risk = zero to one variable; intermediate risk = two variables; high risk = three to four variables).

Published in final edited form as:
Sci Transl Med. 2018 May 09; 10(440): . doi:10.1126/scitranslmed.aar5894.

High-Throughput Sequencing of the T cell Receptor β gene identifies aggressive early-stage Mycosis Fungoides

Adele De Masson[1], **John T. O'Malley**[1], **Christopher P. Elco**[1], **Sarah S. Garcia**[1], **Sherrie J. Divito**[1], **Elizabeth L. Lowry**[1], **Marianne Tawa**[1], **David C. Fisher**[2], **Phillip M. Devlin**[3], **Jessica E. Teague**[1], **Nicole R. Leboeuf**[1], **Ilan R. Kirsch**[4], **Harlan Robins**[4], **Rachael A. Clark**[1], and **Thomas S. Kupper**[1,*]

[1]Department of Dermatology, Brigham and Women's Hospital, and the Center for Cutaneous Oncology, Dana-Farber / Brigham and Women's Cancer Center, Harvard Medical School, Boston MA 02115, USA

the advent of next-generation high-throughput DNA sequencing has revolutionized the diagnosis of MF. MF is nearly always a malignancy of CD4+ T cells with an αβ T cell receptor, encoded by the TCRA and TCRB genes (3). High-throughput sequencing of the TCRB gene can not only identify the unique T cell clone in MF, but can precisely determine the tumor clone frequency.

Langerin: cellule di Langerhans
CD303: PDc
Arginase-1: MDSc

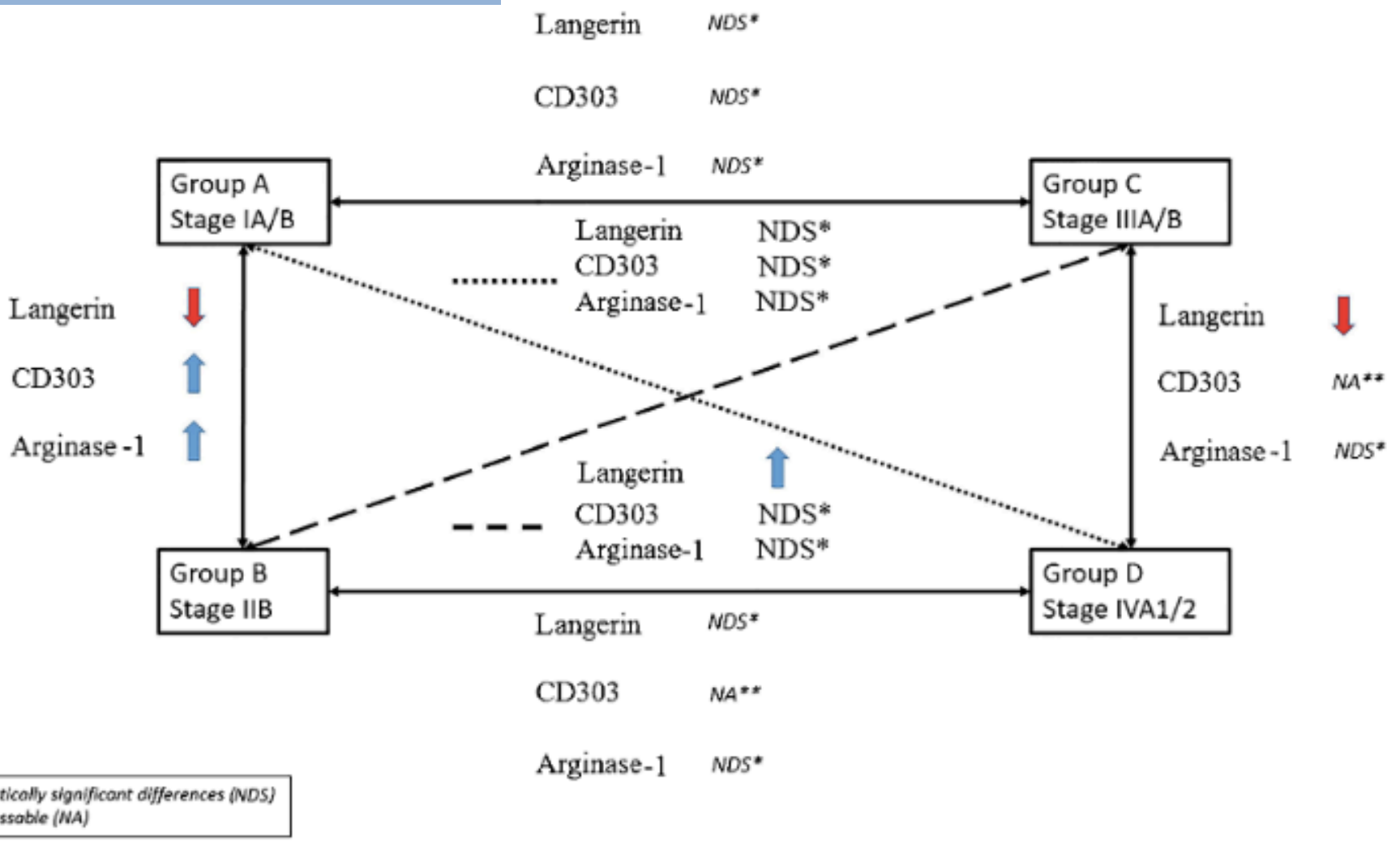
MODIFICAZIONI IN MICRO-ENVIRONMENT

Virchows Arch (2017) 470:575–582
DOI 10.1007/s00428-017-2107-1

ORIGINAL ARTICLE

Langerhans, plasmacytoid dendritic and myeloid-derived suppressor cell levels in mycosis fungoides vary according to the stage of the disease

Alessandro Pileri[1,2] · Claudio Agostinelli[3] · Maurizio Sessa[4] · Pietro Quaglino[5] · Marco Santucci[6] · Carlo Tomasini[7] · Vieri Grandi[2] · Paolo Fava[5] · Chiara Astrua[5] · Simona Righi[3] · Annalisa Patrizi[1] · Stefano A. Pileri[8,9] · Nicola Pimpinelli[2]



LA TERAPIA DEI CTCL
Strategie di trattamento e ritrattamento

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UP – AND DOWN-GRADE DELLE TERAPIE, RE-CHALLENGE COME ELEMENTI CARATTERIZZANTI LA TERAPIA DEI CTCL

PARAMETRI CLINICO-BIOLOGICI NUOVI SONO NECESSARI PER STRATIFICAZIONE DI PAZIENTI..

NUOVI TARGET, NUOVI FARMACI E NUOVI STUDI

Accepted: 28 May 2018

DOI: 10.1111/exd.13701

REVIEW

WILEY Experimental Dermatology

Molecular pathogenesis of cutaneous lymphomas

Rudolf Stadler | René Stranzenbach

TABLE 2 Molecular changes in CTCL

First author	Genes
Almeida et al[37]	TP53, RB1, PTEN, DNMT3a, CDKN1B, TET2, CREBBP, KMT2D, KMT2C, BRD9, SMARCA4, CHD3, MAPK1, BRAF, CARD11, PRKG1
Choi et al[36]	TP53, ZEB1, ARID1A, DNMT3A, NFKB2, CD28, RHOA, PLCG1, STAT5B, BRAF, ATM, CTCF, TNFAIP3, PRKCQ, IRF4
Kiel et al[40]	PLCG1, JAK1, JAK3, STAT3, STAT5B, ARID1A
McGirt et al[41]	JAK3, TP53
Prasad et al[42]	ITPR1, ITPR2, DSC1, RIPK2, IL6, RAG2
Ungewickell et al[43]	TNFRSF1B, TNFR2
Vaque et al[44]	PLCG1
Wang et al[30]	TP53, CARD11, CCR4, PLCG1, CDKN2A, ARID1A, RP56KA1, ZEB1
Woollard et al[45]	POT1, TP53, DNMT3A, BRCA2, PRKCQ, ATM

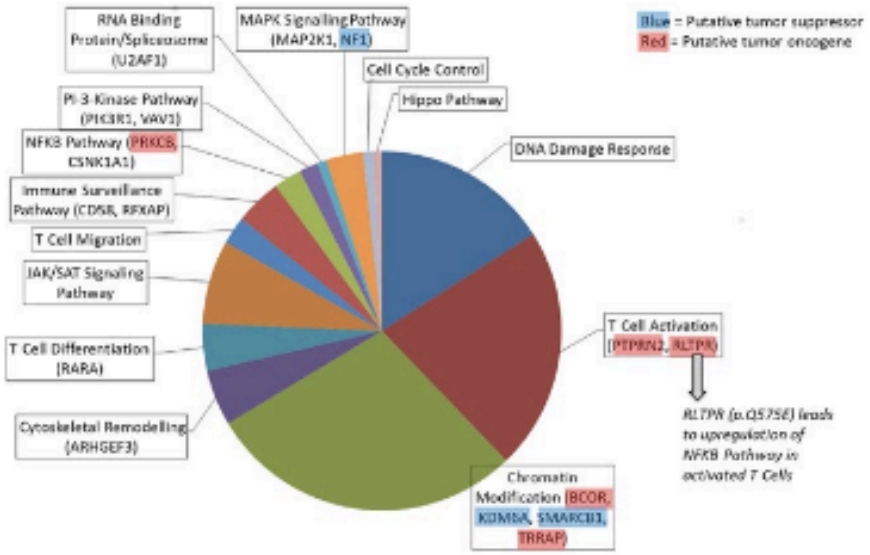
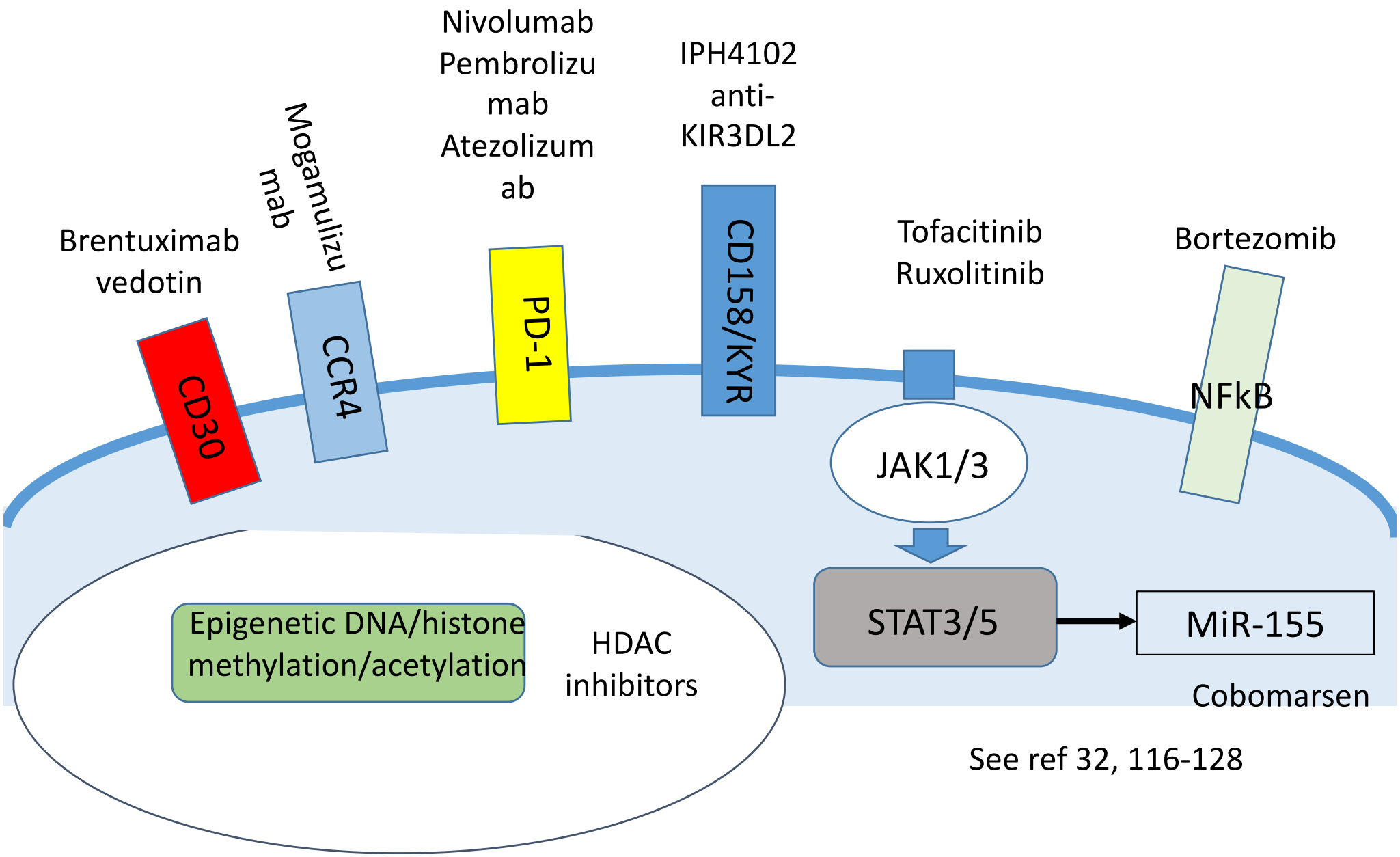


FIGURE 1 Affected pathways with driver genes in CTCL and 17 newly identified mutated genes by genomic analysis of 220 patients.[39] The size of each pie represents the number of mutations found in the corresponding pathway. Park et al further showed that RLTPR (p.Q575E) increases binding of RLTPR to downstream components of the NFkB signalling pathway and selectively upregulates the NFkB pathway in activated T cells



See ref 32, 116-128

New drugs and new studies in CTCL

Target	Drug	Phase	No of pts	Inclusion	ORR	Disease outcome	Drug approval
CD30	Brentuximab vedotin	III randomized vs best clinical choice (bexarotene or methotrexate) [118]	128	CD30-positive mycosis fungoides or primary cutaneous anaplastic large-cell lymphoma	56.3% vs 12.5% (ORR4); MF IIB: 63%;CD30+ anaplastic:75%	Median PFS: 16.7 vs 3.5 months	FDA/EMA
CCR4	Mogamulizumab	III randomized vs vorinostat [32]	372	MF/SS stage Ib to IV with at least one systemic therapy.	28% vs 5%; RR in SS 37%; 68% in the blood	PFS median 7.7 vs 3.1; p<0.0001	FDA/EMA
HDAC	Vorinostat	Open-label phase IIb trial [119]	74	IB-IVA MF/SS, at least two prior systemic therapies, at least one of which bexarotene	29.7% (32% pruritus relief)	Median DOR NR (>185 days). Median TTP 4.9 mo, 9.8 months stage IIB or higher responders.	FDA
HDAC	Vorinostat	II [120]	33	Refractory CTCL	24% RR; 14/31 patients had pruritus relief (45%)	Median DOR: 15.1 weeks; median TTP: 30.2 weeks	FDA
HDAC	Romidepsin	pivotal, single-arm, open-label, phase II [122]	96	stage IB-IVA CTCL at least 1 prior systemic therapy	RR=34%, 38% IIB-IV;pruritus relief 43%	Median DOR 15 months	FDA
HDAC	Romidepsin	II [121]	84	relapsed or refractory CTCL stage-IA to IVB and ECOG 0–2	RR 35% and 31% for patients with and without prior chemotherapy	Median DOR 23 months	FDA
HDAC	Resminostat	III maintenance randomized vs placebo	190	MF/SS stage IIB to IV in response or SD after a previous therapy.	-	-	-
PD-1	nivolumab	I open-label dose-escalation, cohort-expansion basket [123]	13	MF heavily pretreated	15%	DOR up to 81 weeks	-
PD-1	Pembrolizumab	II [124]	24	MF/SS patients (23 of 24 with stage IIB to IV) and heavily pretreated	38	8 durable responses (median DOR not reached > 58 weeks)	-
PD-1	Atezolizumab	II	25	stage IIb-IV MF/SS patients relapsed/refractory	-	-	Trail ongoing
CD158k	IPH4102	I open-label dose-escalation and cohort expansion [126]	44	dose-escalation: relapsed/ refractory CTCL stage>=IB, at least 5% skin-infiltrating or phenotypically abnormal circulating T-cells expressing KIR3DL2; cohort expansion: SS/MF patients with large cell transformation, independently from KIR3DL2	36.4%; in SS 42.9% global and 55.9% in the blood	Median DOR: 13.8 months	-
PI3K-δ,γ	duvelisib	I [127]	19	CTCL	31.6%	-	-
NfKb	Bortezomib	II [128]	12	CTCL	67%	DOR from 7 to > 14 months	-
miR-155	MRG-106, cobomarsen	II randomized versus vorinostat	126	CTCL and ATLL	-	-	Trial ongoing

Brentuximab vedotin or physician's choice in CD30-positive cutaneous T-cell lymphoma (ALCANZA): an international, open-label, randomised, phase 3, multicentre trial

H Miles Prince*, Youn H Kim*, Steven M Horwitz, Reinhard Dummer, Julia Scarisbrick, Pietro Quaglino, Pier Luigi Zinzani, Pascal Wolter, Jose A Sanches, Pablo L Ortiz-Romero, Oleg E Akilov, Larisa Geskin, Judith Trotman, Kerry Taylor, Stephane Dalle, Michael Weichenthal, Jan Walewski, David Fisher, Brigitte Dréno, Rudolf Stadler, Tatyana Feldman, Timothy M Kuzel, Yinghui Wang, Maria Corinna Palanca-Wessels, Erin Zagadailov, William L Trepicchio, Wenwen Zhang, Hui-Min Lin, Yi Liu, Dirk Huebner, Meredith Little, Sean Whittaker†, Madeleine Duvic†, on behalf of the

Summary

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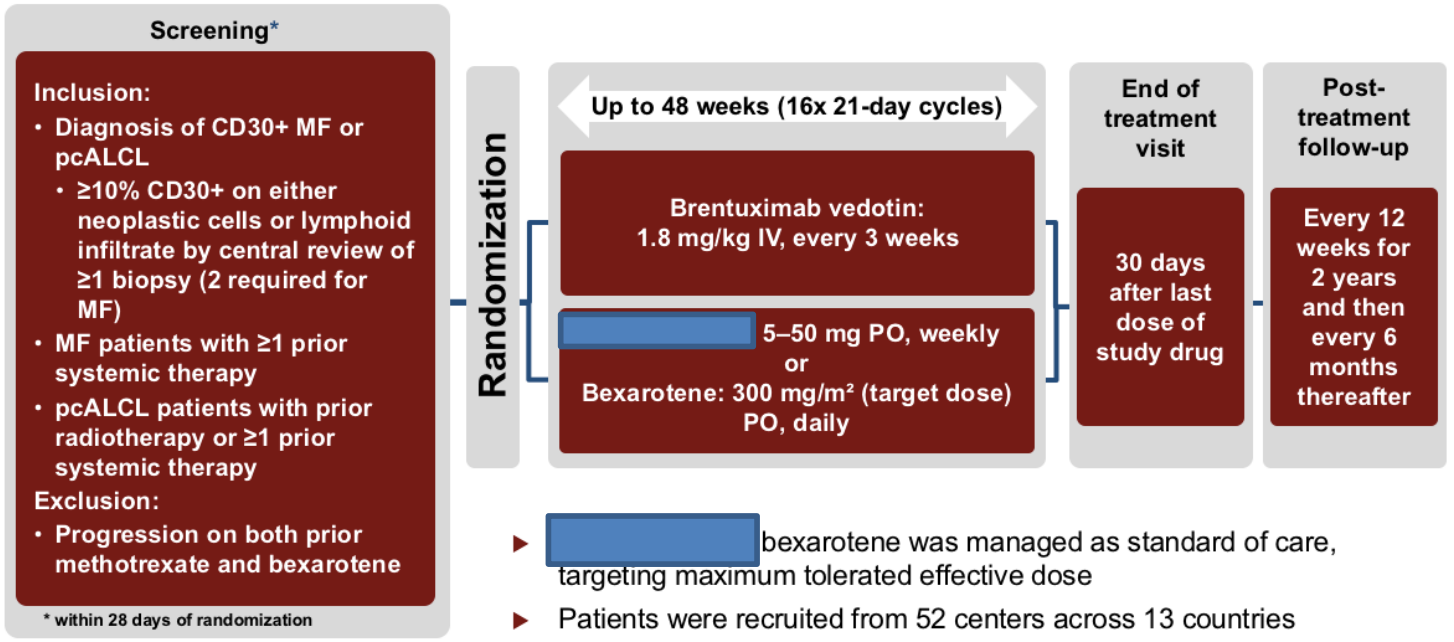
ALCANZA: a randomized, open-label, phase 3 trial of brentuximab vedotin vs physician's choice (methotrexate or bexarotene) in patients with CD30+ CTCL



- bexarotene was managed as standard of care, targeting maximum tolerated effective dose
- Patients were recruited from 52 centers across 13 countries

IV, intravenously; PO, orally

AIFA RIMBORSABILITA': CTCL CD30+ SOTTOPOSTI A 1 PREC TERAPIA SISTEMICA

Articles

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Background Cutaneous T-cell lymphomas are rare, generally incurable, and associated with reduced quality of life. Present systemic therapies rarely provide reliable and durable responses. We aimed to assess efficacy and safety of brentuximab vedotin versus conventional therapy for previously treated patients with CD30-positive cutaneous T-cell lymphomas.

Methods In this international, open-label, randomised, phase 3, multicentre trial, we enrolled adult patients with CD30-positive mycosis fungoides or primary cutaneous anaplastic large-cell lymphoma who had been previously treated. Patients were enrolled across 52 centres in 13 countries. Patients were randomly assigned (1:1) centrally by an

Lancet 2017; 390: 555-66
Published Online June 6, 2017
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See Comment page 533

*Both authors contributed equally to this Article
†Both authors contributed

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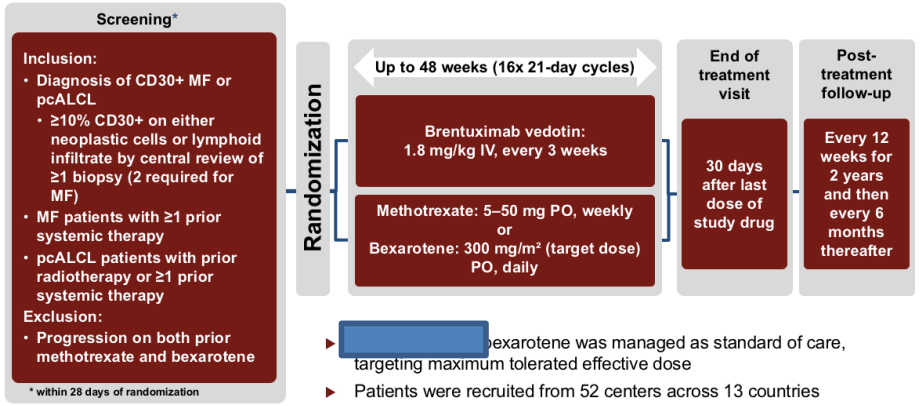

Endpoint	Brentuximab vedotin N=64	Physician's Choice N=64	Difference Between Arms (95% CI)	Statistical Significance
Primary endpoint				
ORR4, n (%)	36 (56.3%)	8 (12.5%)	43.8% (29.1, 58.4)	p<0.0001
Key secondary endpoints				
CR, n (%)	10 (15.6%)	1 (1.6%)	14.1% (-4.0, 31.5)	p=0.0046 adj
Median PFS, months	16.7	3.5		p<0.0001 adj HR=0.270 (95% CI: 0.169, 0.430)
Mean maximum reduction in Skindex-29 symptom domain, points	-27.96	-8.62	-18.9 (-26.6, -11.2)	p<0.0001 adj

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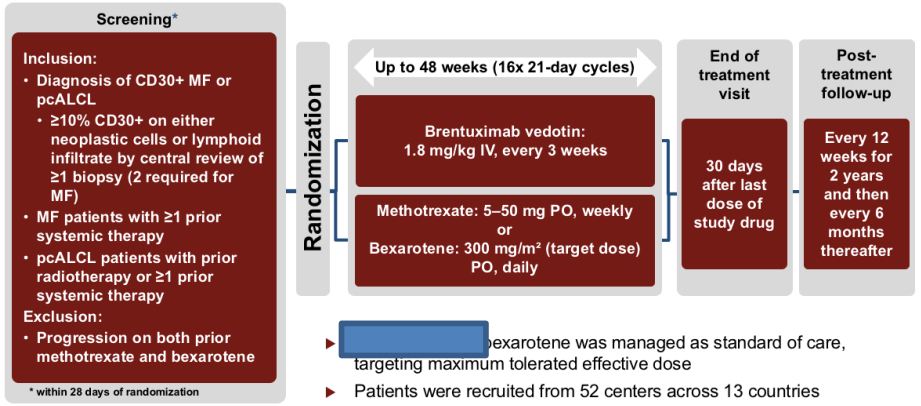

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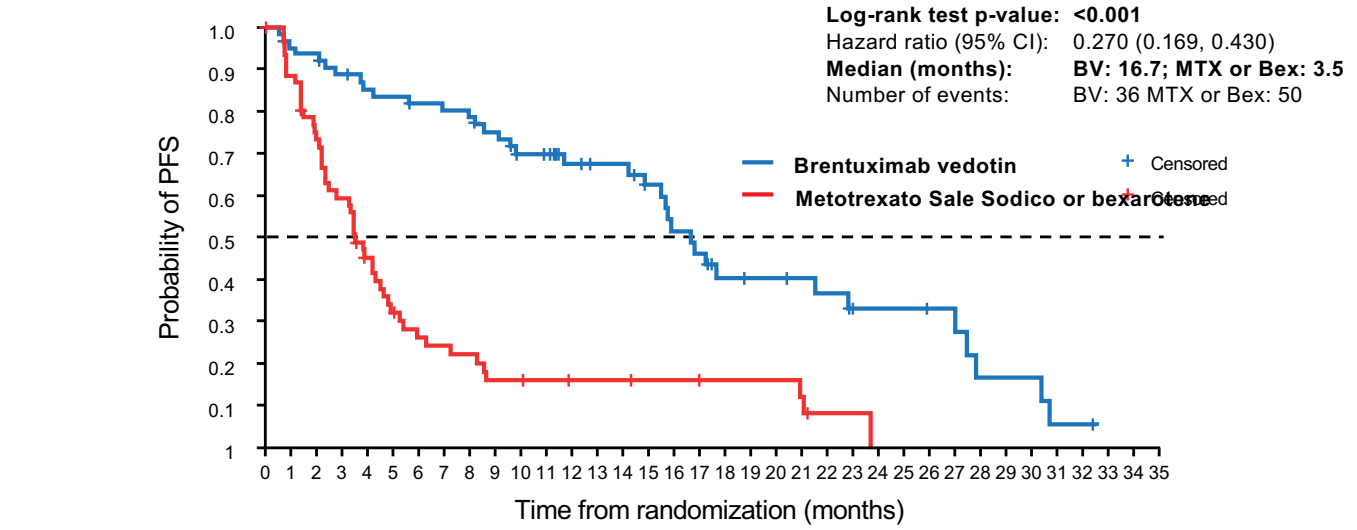
AIFA RIMBORSABILITA': CTCL CD30+ SOTTOPOSTI A 1 PREC TERAPIA SISTEMICA

ORR4 and response rates by disease type and extent

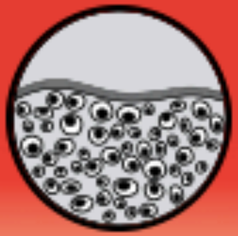
	Brentuximab Vedotin				Bexarotene or Metotrexato Sale Sodico			
	Total N = 64 n (%)	**ORR4 (%)**	ORR (%)	CR (%)	Total N = 64 n (%)	**ORR4 (%)**	ORR (%)	CR (%)
ITT population	64 (100)	56	67	16	64 (100)	13	20	2
MF	48 (75)	**50**	65	10	49 (77)	**10**	16	0
Stage								
IA-IIA	15 (31)	40	53	7	18 (37)	22	28	0
IIB	19 (40)	63	68	16	19 (39)	5	16	0
IIIA-IIIB	4 (8)	50	75	0	2 (4)	0	0	0
IVA	2 (4)	100	100	50	9 (18)	0	0	0
IVB	7 (15)	29	57	0	0	NA	NA	NA
pcALCL	16 (25)	**75**	75	31	15 (23)	**20**	33	7
Disease involvement								
Skin-only	9 (56)	89	89	44	11 (73)	27	45	9
Extracutaneous disease	7 (44)	57	57	14	4 (27)	0	0	0

NA, not applicable

Progression-free survival (ITT population)



Assessed by independent review
Bex, bexarotene; MTX, methotrexate



Final data from the phase 3 ALCANZA study: Brentuximab vedotin versus physician's choice in patients with CD30-positive cutaneous T-cell lymphoma

Poster 232

Steven M. Horwitz,[1*] Julia Scarisbrick,[2] H. Miles Prince,[3] Sean Whittaker,[4] Madeleine Duvic,[5] Youn H. Kim,[6] Pietro Quaglino,[7] Pier Luigi Zinzani,[8] Oliver Bechter,[9] Herbert Eradat,[10] Lauren Pinter-Brown,[11] Oleg Akilov,[12] Larisa Geskin,[13] Jose Sanches,[14] Pablo Ortiz-Romero,[15] Julie Lisano,[16] Lisa Brown,[16] Maria Corinna Palanca-Wessels,[16] Ashish Gautam,[17] Veronica Bunn,[17] Meredith Little,[17] Reinhard Dummer[18]

[1]Department of Medicine, Memorial Sloan Kettering Cancer Center, New York, NY, USA; [2]Department of Dermatology, University Hospital Birmingham, Birmingham, UK; [3]Division of Cancer Medicine, Peter MacCallum Cancer Centre and Sir Peter MacCallum Department of Oncology, The University of Melbourne, Victoria, Australia; [4]St John's Institute of Dermatology, Guys and St Thomas NHS Foundation Trust, London, UK; [5]The University of Texas MD Anderson Cancer Center, Houston, TX, USA; [6]Department of Dermatology, Stanford University School of Medicine and Stanford Cancer Institute, Stanford, CA, USA; [7]Department of Medical Sciences, Dermatologic Clinic, University of Turin, Turin, Italy; [8]Institute of Haematology, University of Bologna, Bologna, Italy; [9]Department of General Medical Oncology, University Hospitals Leuven, KU Leuven, Belgium; [10]Division of Hematology-Oncology, David Geffen School of Medicine at UCLA, Los Angeles, CA, USA; [11]Chao Family Comprehensive Cancer Center, University of California, Irvine, CA, USA; [12]Department of Dermatology, University of Pittsburgh, Pittsburgh, PA, USA; [13]Department of Dermatology, Columbia University, New York, NY, USA; [14]Department of Dermatology, University of São Paulo Medical School, São Paulo, Brazil; [15]Department of Dermatology, University Hospital 12 de Octubre, Institute i+12 Medical School, University Complutense, Madrid, Spain; [16]Seattle Genetics, Inc., Bothell, WA, USA; [17]Millennium Pharmaceuticals, Inc., Cambridge, MA, USA, a wholly owned subsidiary of Takeda Pharmaceutical Company Limited; [18]Department of Dermatology, University Hospital Zürich, Zürich, Switzerland

Background

- CTCL represents a heterogeneous group of T-cell lymphomas, primarily involving the skin, that includes MF (the most common type of CTCL) and pcALCL.[1]
- CTCLs can have a chronic course, as well as considerable symptom burden and impact on patients' QoL.[2,3]
- Early-stage CTCLs are treated using skin-directed therapies. Systemic therapies can be used to treat advanced CTCL, but no regimen has been shown to prolong survival in advanced stages and treatment is focused on reducing disease burden, delaying progression and improving QoL.[1,4]
- In pcALCL, by definition, CD30 is expressed by the majority of tumour cells,[5] whereas in MF the proportion of CD30-expressing cells is variable.[6,7]
- Brentuximab vedotin is approved in the US for patients with pcALCL or CD30-expressing MF who have received prior systemic therapy[8] and in the EU for adults with CD30+ CTCL after at least 1 prior systemic therapy.[9] The approval was based on the results of the randomised ALCANZA study.[10]
- ALCANZA is an international, open-label, randomised phase 3 trial of brentuximab vedotin vs physician's choice (PC) of methotrexate or bexarotene in patients with previously treated MF or pcALCL.[10]
  - With median follow-up of 22.9 months, the original analysis showed that brentuximab vedotin was superior to physician's choice,[10] demonstrating:
  - Significantly improved ORR4 (56% vs 13%; p<0.0001)
  - Significantly higher CR rate (16% vs 2%; adjusted p=0.0046)
  - Significantly longer PFS (median 16.7 vs 3.5 months; HR=0.270, 95% CI: 0.169–0.430; adjusted p<0.0001)
  - Significant reduction in patient-reported symptoms per Skindex-29 symptom domain (–27.96 vs –8.62; adjusted p<0.0001).
- The primary analysis was performed 10 months after the last patient's end of treatment visit (data cut-off May 31, 2016).
- Here we report final results from the ALCANZA study (data cut-off September 28, 2018).

Objectives of the current analysis

- To report long-term efficacy and safety data from the ALCANZA study in terms of:
  - Primary study endpoint: ORR4 (median follow-up TBC)
  - Other select endpoints: PFS, OS, TTNT, response by disease subtype (MF or pcALCL), and resolution and improvement of PN.

Table 1. Patient baseline characteristics (ITT population)

	Treatment group	
	Brentuximab vedotin (N=64)	Physician's choice (N=64)
Median age, years (range)	62 (22–83)	59 (22–83)
Male gender, n (%)	33 (52)	37 (58)
ECOG PS 0–1, n (%)	61 (95)	62 (97)
Median CD30 expression, % (range)*	32.5 (3–100)	31.3 (5–100)
MF,† n (%)	48 (75)	49 (77)
Early stage (IA–IIA)	15 (31)	18 (37)
Advanced stage (IIB–IVB)	32 (67)	30 (61)
pcALCL, n (%)	16 (25)	15 (23)
Skin only	9 (56)	11 (73)
Extracutaneous disease	7 (44)	4 (27)
Total number of prior therapies, median (range)	4.0 (0–13)	3.5 (1–15)
Number of prior systemic therapies, median (range)	2.0 (0–11)	2.0 (1–8)

[illegible]

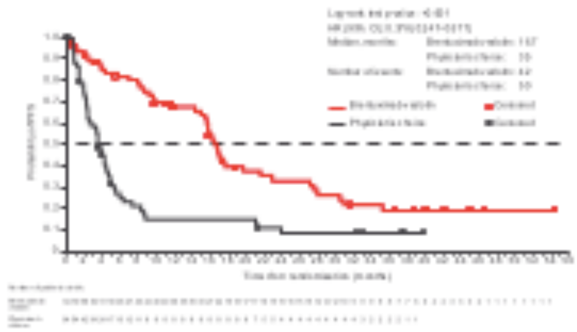
Patient responses, PFS and OS

- Final results demonstrate significantly improved efficacy with brentuximab vedotin vs PC (**Table 2**):
  - ORR4 per IRF: 54.7% vs 12.5% (p<0.001)
  - CR rate per IRF: 17.2% vs 1.6% (p=0.002)
  - 6/11 patients treated with brentuximab vedotin who achieved CR had pcALCL.
- With a median follow-up 36.8 months, median PFS per IRF was 16.7 months in the brentuximab vedotin arm vs 3.5 months with PC (p<0.001; **Figure 2** and **Table 2**).
- There were 23 deaths in the brentuximab vedotin arm and 25 in the PC arm (HR=0.745; 95% CI: 0.421–1.318; p=0.310; **Table 2**).

Table 2. ORR4, best response to treatment, PFS and OS (ITT population)

	Brentuximab vedotin (N=64)	Physician's choice (N=64)	p-value
ORR4 per IRF, n (%)	35 (54.7)	8 (12.5)	<0.001
Best response to treatment per IRF, n (%)			
Overall response (CR + PR)	42 (65.6)	13 (20.3)	<0.001
CR	11 (17.2)	1 (1.6)	0.002
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*	16.7	3.5	<0.001
3-year OS estimates, % (95% CI)	66.4 (50.7–78.2)†	61.8 (47.3–73.4)†	

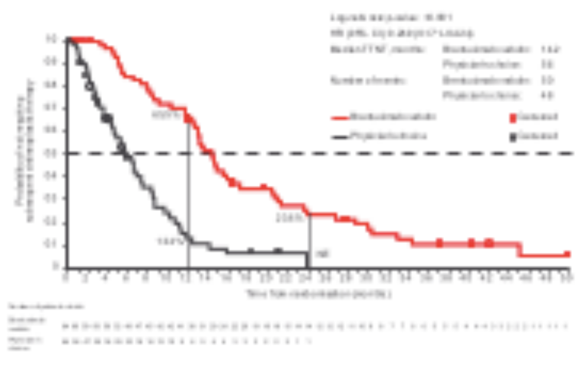
Figure 2. PFS per IRF (ITT population)



TTNT

- With median follow-up for TTNT of 37.3 months, in the brentuximab vedotin and PC arms, 50 (78%) and 48 (75%) of patients had received subsequent antineoplastic therapy, respectively (**Figure 3**).
  - Median TTNT was significantly longer with brentuximab vedotin vs PC (14.2 [95% CI: 12.2–16.4] vs 5.6 months [95% CI: 4.3–7.3]; HR=0.269; 95% CI: 0.171–0.424; p<0.001).
  - In the brentuximab vedotin vs PC arms, the probability of patients not requiring subsequent antineoplastic therapy was greater at 1 year (65.5% [95% CI: 51.8–76.2] vs 13.4% [95% CI: 5.5–24.9]) and 2 years (23.6% [95% CI: 13.3–35.4] vs NE) post-randomisation.

Figure 3. TTNT (ITT population)



Poster presented at the International Co

Mogamulizumab versus vorinostat in previously treated cutaneous T-cell lymphoma (MAVORIC): an international, open-label, randomised, controlled phase 3 trial

Youn H Kim, Martine Bagot, Lauren Pinter-Brown, Alain H Rook, Pierluigi Porcu, Steven M Horwitz, Sean Whittaker, Yoshiki Tokura, Maarten Vermeer, Pier Luigi Zinzani, Lubomir Sokol, Stephen Morris, Ellen J Kim, Pablo L Ortiz-Romero, Herbert Eradat, Julia Scarisbrick, Athanasios Tsianakas, Craig Elmets, Stephane Dalle, David C Fisher, Ahmad Halwani, Brian Poligone, John Greer, Maria Teresa Fierro, Amit Khot, Alison J Moskowitz, Amy Musiek, Andrei Shustov, Barbara Pro, Larisa J Geskin, Karen Dwyer, Junji Moriya, Mollie Leoni, Jeffrey S Humphrey, Stacie Hudgens, Dmitri O Grebennik, Kensei Tobinai, Madeleine Duvic, for the MAVORIC Investigators*

Lancet Oncol 2018; 19: 1192-204
Published Online August 9, 2018
http://dx.doi.org/10.1016/

Summary

Background Cutaneous T-cell lymphomas are rare non-Hodgkin lymphomas with substantial morbidity and mortality in advanced disease stages. We compared the efficacy of mogamulizumab, a novel monoclonal antibody directed against C-C chemokine receptor 4, with vorinostat in patients with previously treated cutaneous T-cell lymphoma.

Methods In this open-label, international, phase 3, randomised controlled trial, we recruited patients with relapsed or

MAVORIC - R/R CTCL

Phase 3, N= 372
Worldwide (~70 sites - US, EU, Japan, Australia)

PATIENT POPULATION:
- Stage IB, II-A, II-B, III and IV
- ECOG status – 0 or 1
- Subjects who have failed at least 1 prior course of systemic therapy.
- Histologically confirmed diagnosis of mycosis fungoides (MF) or Sezary Syndrome (SS)

Endpoints

1. PFS (investigator assessed using GRS)
2. ORR, QofL, Pruritis evaluation

R

- mogamulizumab 1.0 mg/kg weekly x 4 in cycle 1 then every other week until progression
- vorinostat 400 mg once daily (upon progression or intolerable toxicity, can crossover to moga)

Stratified by disease type (MF or SS) and Stage (IB/II or III/IV)

Primary Completion Date: March 2017

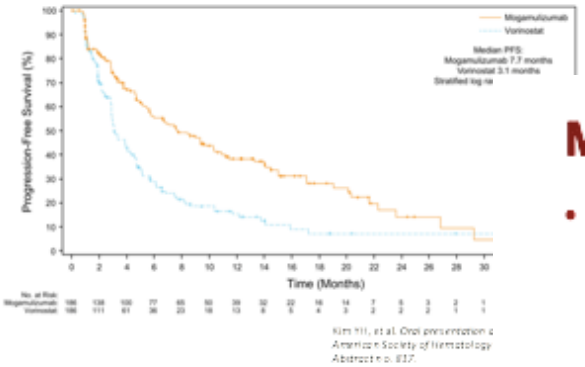
Notable Events
- April 7, 2017 – Study was positive, *"Top-line results demonstrated a statistically significant improvement in progression free survival in the mogamulizumab arm compared to the control (vorinostat) arm, and tolerable safety profile of mogamulizumab."*
- Data was presented at ASH 2017 on Monday, Dec 11, 2017

PFS results

ASH 2017 Abstract Summary

	Mogamulizumab	Vorinostat	
PFS per INV	7.7 months (95% CI: 5.7, 10.3)	3.1 months (95% CI: 2.9, 4.1)	HR 0.53 [95% CI: 0.41, 0.69], *P*<0.0001
PFS per IRF	6.7 months	3.8 months	HR 0.64 [95% CI: 0.49, 0.84], *P*=0.0007

Plot of Kaplan-Meier Curve of Progression-Free Survival by Investigator's Assessment (Intent-to-Treat Population)



Kim YH, et al. Oral presentation at American Society of Hematology Abstract no. 837.

MAVORIC study endpoints

- **Primary endpoint**
  - **PFS** (based on investigator assessment)
    - Used global composite response score (based on skin, blood, lymph nodes, and viscera) according to consensus guidelines[1]
    - Sample size calculation: 90% power to detect a 50% improvement in PFS

ASH 2017 Abstract Summary

Measures of Response by Investigator's Assessment for Mogamulizumab vs Vorinostat

	Mogamulizumab N=186	Vorinostat N=186
ORR[a,b], n (%)	52 (28.0)	9 (4.8)
ORR in MF[c], n/N (%)	22/105 (21.0)	7/99 (7.1)
ORR in SS[b], n/N (%)	30/81 (37.0)	2/87 (2.3)
ORR in stage IB/II[d], n/N (%)	12/68 (17.6)	6/72 (8.3)
ORR in stage III/IV, n/N (%)	40/118 (33.9)	3/114 (2.6)
Duration of response, median, mo	14.1	9.1
Duration of response in MF, median, mo	13.1	9.1
Duration of response in SS, median, mo	17.3	6.9
Compartment response		
Skin response rate[a], n/N (%)	78/186 (41.9)	29/186 (15.6)
Blood response rate[a], n/N (%)	83/124 (66.9)	23/125 (18.4)
Lymph nodes response rate[a], n/N (%)	21/136 (15.4)	5/133 (3.8)
Viscera response rate[a], n/N (%)	0/6 (0)	0/4 (0)

Note: Overall response rate (ORR) is based on Global Composite Response score.
[a]ORR and response rate are the percentage of patients with confirmed CR or confirmed PR.
[b]$p<0.0001$
[c]$p=0.0042$
[d]In stage IIB (tumor-type skin presentation), ORR was 15.6% for Moga and 4.3% for Vor.

Kim YH, et al. *Oral presentation at the 59th Annual Meeting & Exposition of the American Society of Hematology 2017, Atlanta, USA. Abstract no. 817.*

Maggiore attività su cellule circolanti B2

IPH4102, THE FIRST-IN-CLASS ANTI-KIR3DL2 MAB, IS SAFE AND CLINICALLY ACTIVE IN ADVANCED CUTANEOUS T-CELL LYMPHOMA (CTCL) PATIENTS: RESULTS FROM THE DOSE-ESCALATION PART OF THE IPH4102-101 PHASE I STUDY

M. BAGOT[1,8], P. PORCU[3], C. RAM-WOLFF[1,8], M. KHODADOUST[2], B. WILLIAM[4], M. BATTISTELLA[1], A. MARIE-CARDINE[1,8], S. MATHIEU[1], M. VERMEER[5], S. WHITTAKER[6], M. DUVIC[7], A. BENSUSSAN[1,8], C. PATUREL[9], C. BONNAFOUS[9], C. BONIN[9], F. MORIETTE[9], L. LAGACHE[9], H. SICARD[9], C. PAIVA[9], K. PILZ[9] AND Y. H. KIM[2]

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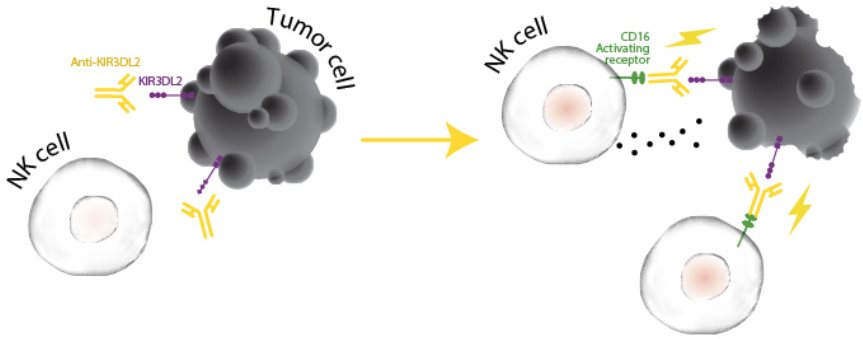
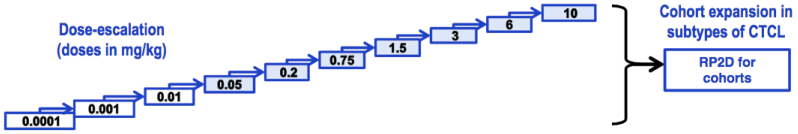
IPH4102-101



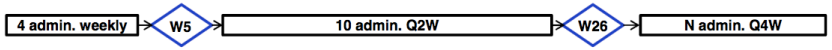
IPH4102 binds to KIR3DL2 on tumor cells

Recruitment of NK cells and depletion of tumor cells

IPH4102-101 PHASE 1 STUDY DESIGN AND OBJECTIVES



- Dose-escalation (10 dose levels – accelerated 3+3 design) followed by cohort expansion
- **Primary objective**: determination of MTD and RP2D, overall safety
- **Secondary objectives**: clinical activity, PK/immunogenicity
- **Exploratory objectives**: changes in KIR3DL2+ cells in involved compartments, NK cell function pre-dose
- **Key inclusion criteria**:
  - Any CTCL subtype, ≥ 2 prior lines of systemic therapy, if MF/SS stage ≥ IB
  - > 5% aberrant cells KIR3DL2pos in skin or blood
  - Treatment until progression or unacceptable toxicity
- Intra-patient dose-escalation allowed after W5



PRELIMINARY CLINICAL RESPONSE RESULTS

	Best Response in all patients	Best Response in Sézary Syndrome patients		
	Global N=25	Global n=20	Skin n=20	Blood n=20
Best Response (n)				
CR	1	1	2	5
PR	10	9	10	8
SD	12	8	8	6
PD	2	2	0	1
ORR	44 %	50 %	60 %	65 %
ORR4, n (%)	9 (36%)	8 (40%)		
DOR (days) - median (min – max)	251 (8.2 months) (64 – 519+)	302 (9.9 months) (64 – 519+)		
PFS (days) - median (min – max)	299 (9.8 months) (28 – 610+)	329 (10.8 months) (28 – 610+)		

ORR: Overall Response Rate
ORR4: Rate of responses lasting ≥4 mo
PFS: Progression-Free Survival
DOR: Duration of Response

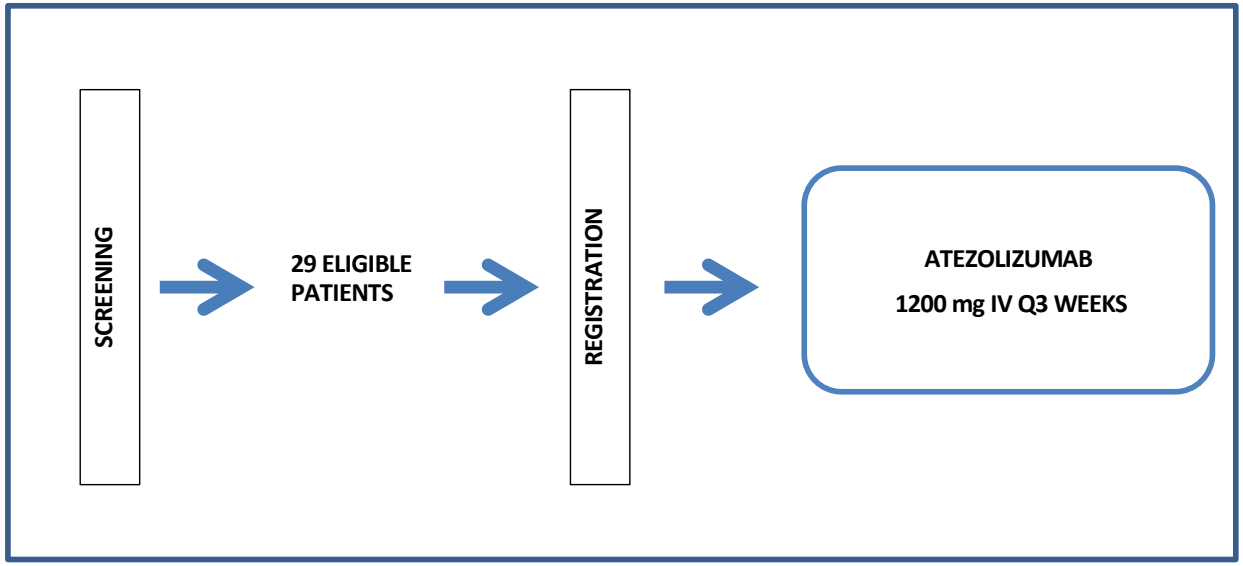
- Results for 25 patients (20 SS) treated with doses ranging from 0.0001 to 10 mg/kg
- All clinical responses are confirmed; 4 responses ongoing (DOR range 104 – 519 days)
- 2 patients reached "near CR" skin response, ie >90% reduction in mSWAT

Lancet Oncol. 2019 Aug;20(8):1160-1170. doi: 10.1016/S1470-2045(19)30320-1. Epub 2019 Jun 25.

EORTC – CLTF Study 1652:

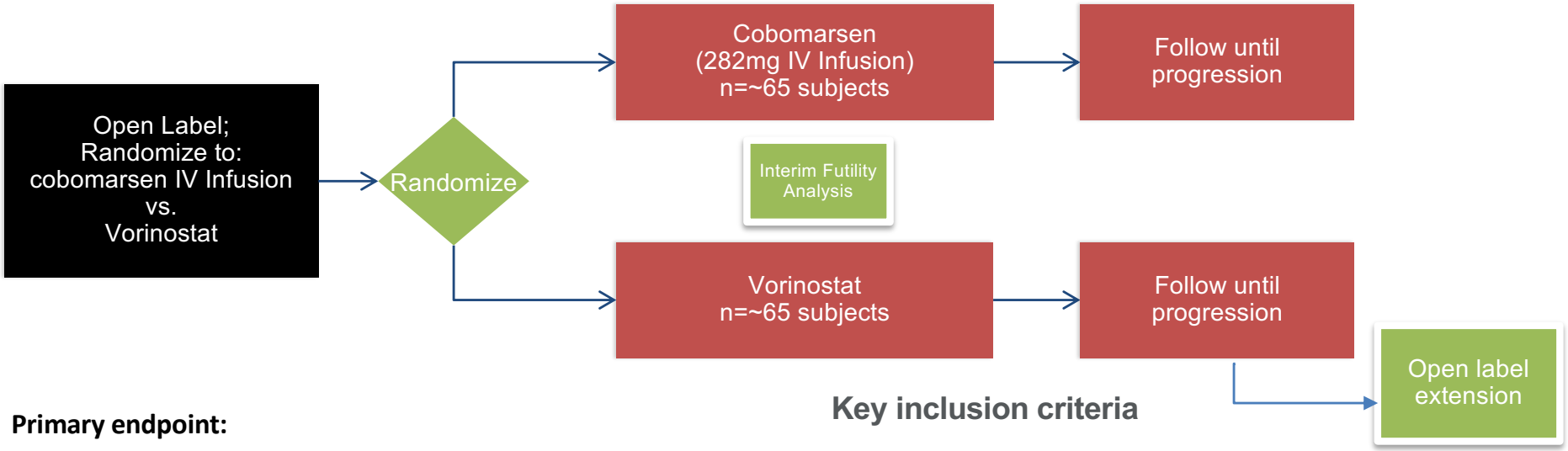
Phase II trial of atezolizumab (anti-PD-L1) in the treatment of stage IIb-IV mycosis fungoides/sezary syndrome patients relapsed/refractory after a previous systemic treatment

SC: Rudolf Stadler (University Hospital Johannes Wesling Klinikum, Minden, Germany)
SC: Robert Knobler (Medical University of Vienna, Vienna, Austria)



SOLAR Phase 2 Clinical Trial Anticipated to Initiate in 2H18

A Randomized, Open-Label, Parallel-group, Active Comparator, Global Trial in Patients with Stage Ib-III Mycosis Fungoides



Primary endpoint:

– Overall Response Rate of four months (ORR4) using Global Response Criteria

Key Secondary endpoints:

- Progression-free survival
- Patient reported outcomes
  - Pain, itching

Key inclusion criteria

- Stage Ib-III
- Must have received at least one prior therapy for CTCL (per NCCN guidelines for generalized skin involvement)
- mSWAT score ≥ 10
- No concurrent systemic therapy

A multicentre, double blind, randomized, placebo controlled, Phase II trial to evaluate resminostat for maintenance treatment of patients with advanced stage (Stage IIB-IVB) mycosis fungoides (MF) or Sézary syndrome (SS) that have achieved disease control with systemic therapy – the RESMAIN Study

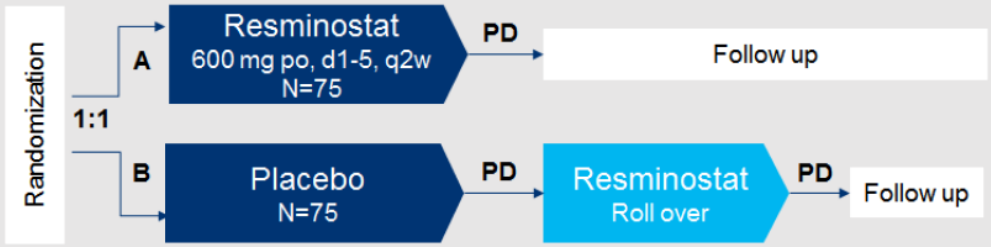
RESMAIN - Study Design

Patients

- Mycosis fungoides (advanced stages IIB – IV) or Sézary Syndrome
- CR, PR or SD 2-12 weeks after prior systemic therapy

Design

- Maintenance treatment
  - Primary endpoint: Progression free survival (PFS)
  - Secondary endpoints: TTSW (pruritus), ORR, PFS2, Safety, HrQoL, etc.

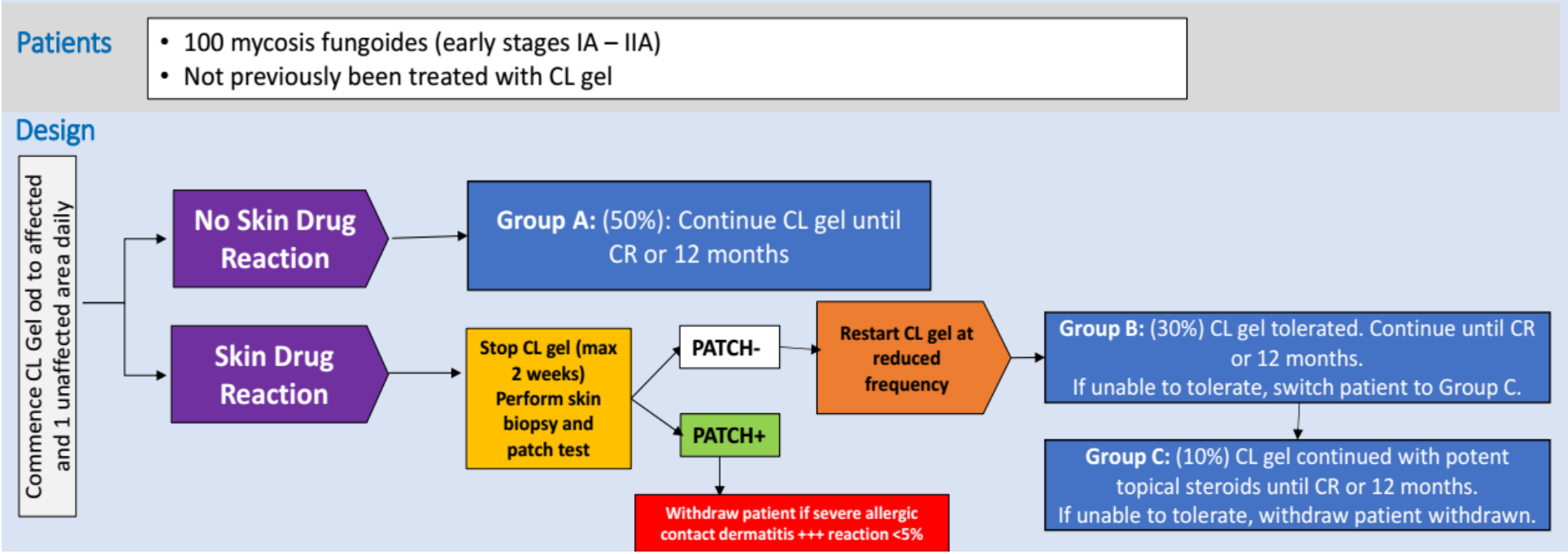


PD: progressive disease; po: per os; q2w: every 2 weeks
PFS: progression free survival; TTSW: time to symtom worsening
ORR: overall response rate; HrQoL; health related quality of life

EORTC – CLTF Study 1754:

STUDY TO DETERMINE THE AETIOLOGY OF SKIN DRUG REACTIONS WITH CHLORMETHINE GEL IN EARLY STAGE MYCOSIS FUNGOIDES

REACH Study (**R**ash **E**tiology **A**fter **CH**lormethine gel)



MF: from the pathogenesis to the treatment strategy

- MF is believed to originate from the mature, memory, tissue-resident T cells expressing skin homing markers cutaneous leucocyte-associated antigen and CCR4.
- This straightforward hypothesis explains the affinity of MF to the skin and its low capacity to disseminate to extracutaneous sites.

MF: from the pathogenesis to the treatment strategy

Some clinical and molecular features of MF are incompatible with the model of the skin-resident memory T cell.

- Why the disease usually starts multifocally indifferent areas of the skin rather than at a single site representing the location of the founding, transformed T cell.
- Even profound depletion of lymphocytes in the skin (eg, by electronbeam radiation therapy or psoralen UV A therapy) almost never results in a cure and only provides short-term responses.
- Cells sharing molecular characteristics of malignant T cells in MF have been found in the bone marrow of the patients years before the emergence of skin lesions of the disease and CTCL can be transmitted via bone marrow transplant from asymptomatic donors.

blood® Regular Article

LYMPHOID NEOPLASIA

Skin colonization by circulating neoplastic clones in cutaneous T-cell lymphoma

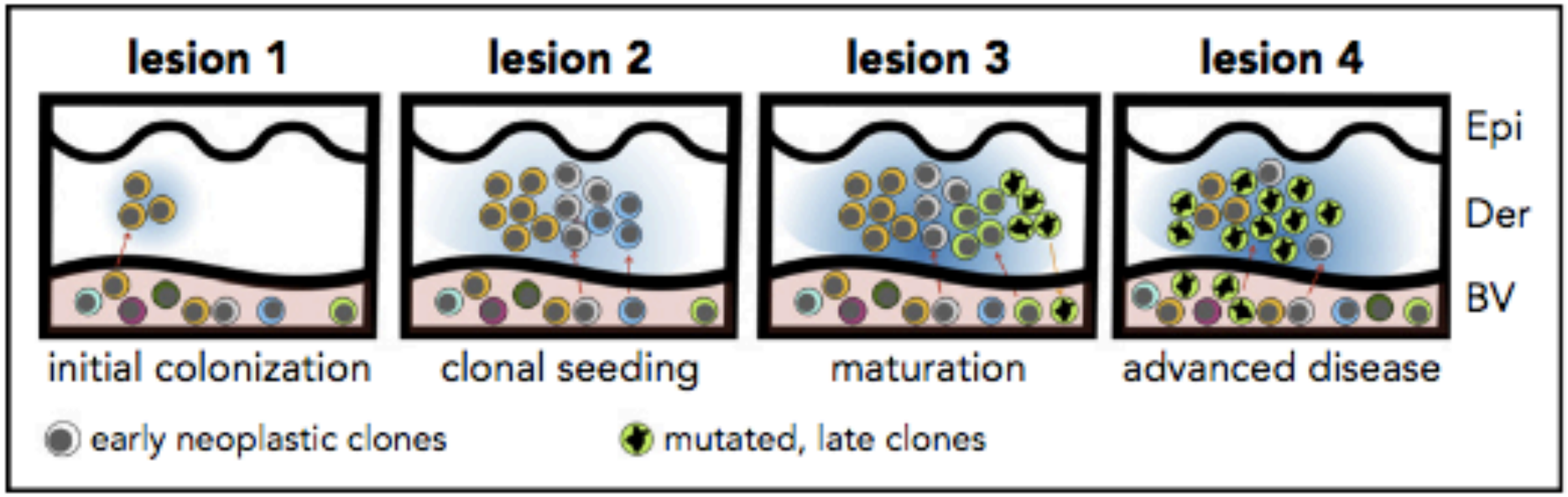
Aishwarya Iyer,[1] Dylan Hennessey,[1] Sandra O'Keefe,[1] Jordan Patterson,[2] Weiwei Wang,[2,3] Gane Ka-Shu Wong,[2,4] and Robert Gniadecki[1,5]

[1]Division of Dermatology, Department of Medicine, University of Alberta, Edmonton, AB, Canada; [2]Department of Medicine, University of Alberta, Edmonton, AB, Canada; [3]Genesis, Beijing, China; [4]Department of Biological Sciences, University of Alberta, Edmonton, AB, Canada; and [5]Department of Dermatology, Bispebjerg Hospital, University of Copenhagen, Copenhagen, Denmark

Whole-exome sequencing approach to detect and quantify TCR-alfa, bet and gamma clonotypes in tumour cell clusters microdissected from MF lesions.

- Analysis of TCR sequences from 29 patients with MF stage I to IV proved the existence of multiple T-cell clones within the tumor cell fraction
- Multiple neoplastic clones in the peripheral blood in all examined patients.

(Blood. 2019;134(18):1517-1527)



- Circulating neoplastic T-cell clones continuously replenish the lesions of MF
- Heterogeneity through a “consecutive tumor seeding” mechanism
- Circulating neoplastic promising target for therapy and potential biomarker in MF.

Blood. 2019;134(18):1517-1527


CITTA DI TORINO


Caffarel
Gianduia 1865


Chi non sopportava il rumore
della città andava nel bosco