Prognostic Models in CTCL

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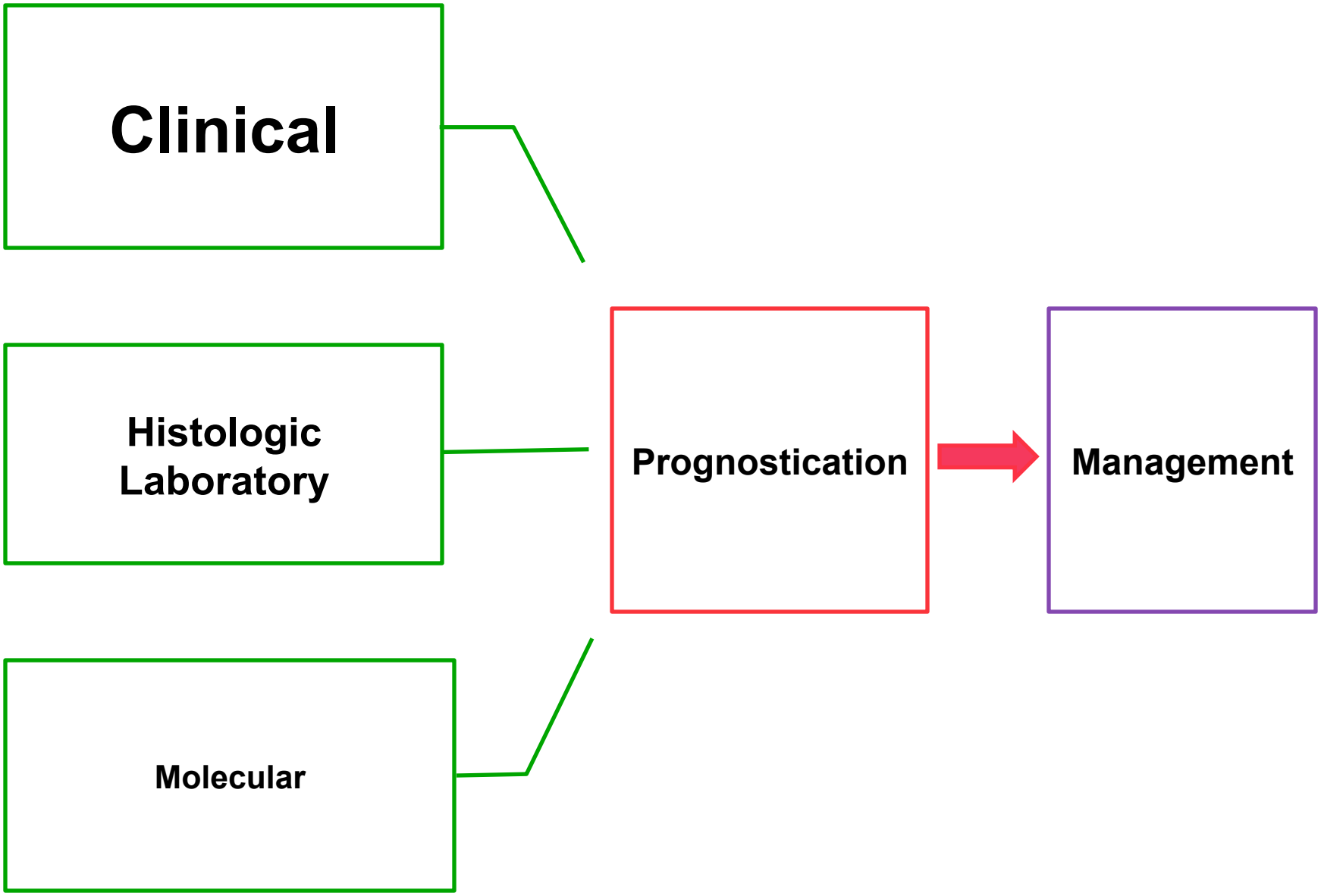
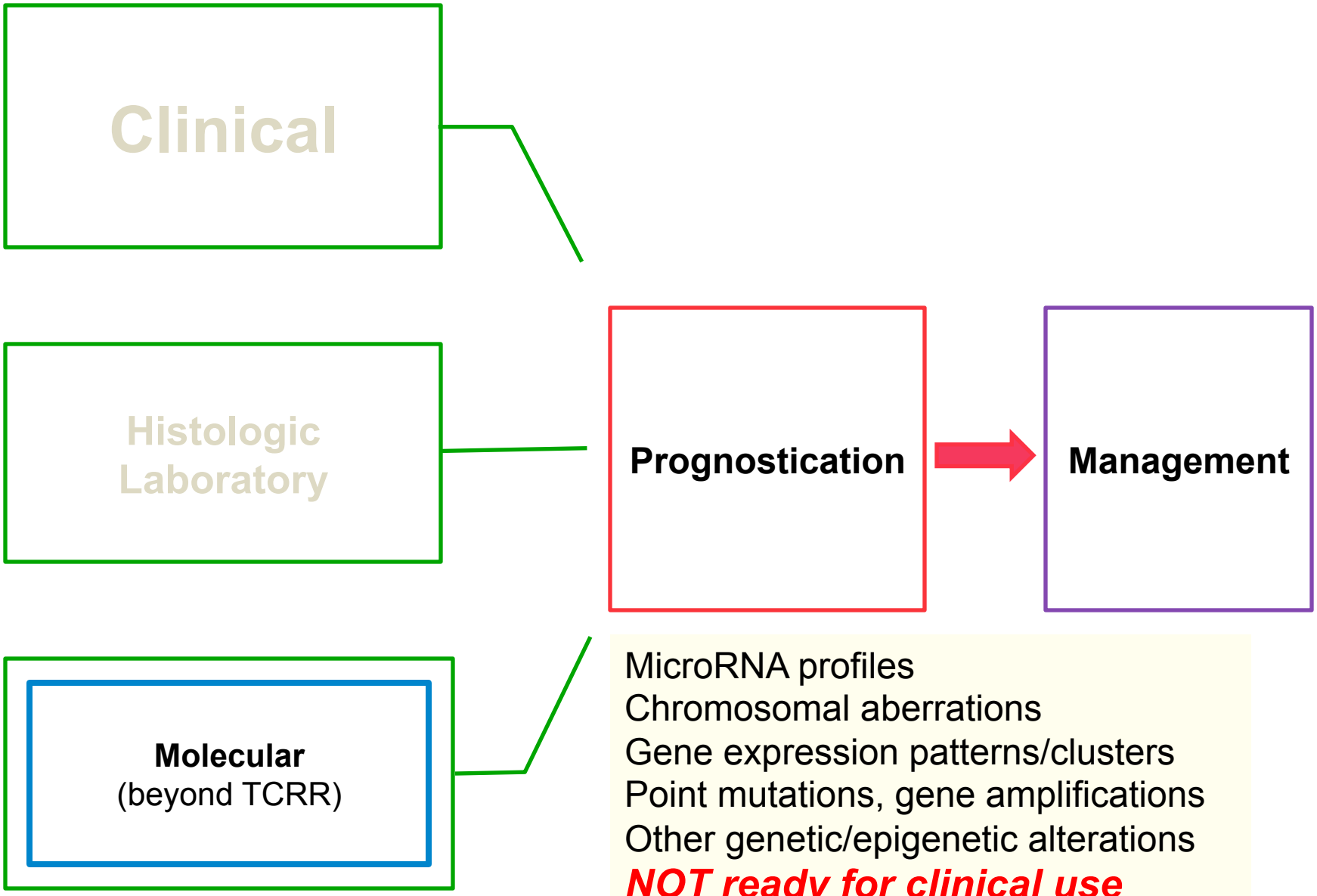
Prognostic Factors in CTCL



Prognostic Factors in CTCL



blood
2007 110: 3015-3027
Prepublished online July 16, 2007;
doi:10.1182/blood-2006-12-061507

Lesional gene expression profiling in cutaneous T-cell lymphoma reveals natural clusters associated with disease outcome

Jessica Shin, Stefano Monti, Daniel J. Aires, Madeleine Duvic, Todd Golub, David A. Jones and Thomas S. Kupper

miRNA expression profiling of mycosis fungoides

Marloes S. van Kester[a], Erica Ballabio[b], Marchina F. Benner[a], Xiao H. Chen[b], Nigel J. Saunders[c], Leslie van der Fits[a], Remco van Doorn[a], Maarten H. Vermeer[a], Rein Willemze[a], Cornelis P. Tensen[a,,1], Charles H. Lawrie[b,1]*

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[c]*Sir William Dunn School of Pathology, University of Oxford, Oxford, UK*

blood
2014 123: 2034-2043
doi:10.1182/blood-2013-05-504308 originally published online February 4, 2014

PLCG1 mutations in cutaneous T-cell lymphomas

José P. Vaqué, Gonzalo Gómez-López, Verónica Monsálvez, Ignacio Varela, Nerea Martínez, Cristina Pérez, Orlando Domínguez, Osvaldo Graña, José L. Rodríguez-Peralto, Socorro M. Rodríguez-Pinilla, Carmen González-Vela, Miriam Rubio-Camarillo, Esperanza Martín-Sánchez, David G. Pisano, Evangelia Papadavid, Theodora Papadaki, Luis Requena, José A. García-Marco, Miriam Méndez, Mariano Provencio, Mercedes Hospital, Dolores Suárez-Massa, Concepción Postigo, David San Segundo, Marcos López-Hoyos, Pablo L. Ortiz-Romero, Miguel A. Piris and Margarita Sánchez-Beato

Oligonucleotide Array-CGH Identifies Genomic Subgroups and Prognostic Markers for Tumor Stage Mycosis Fungoides

Rocío Salgado[1,2,3], Octavio Servitje[4], Fernando Gallardo[5], Maarten H. Vermeer[6], Pablo L. Ortiz-Romero[7], Maria B. Karpova[8], Marie C. Zipser[8], Cristina Muniesa[9], María P. García-Muret[10], Teresa Estrach[11], Marta Salido[1,3], Júlia Sánchez-Schmidt[5], Marta Herrera[7], Vicenç Romagosa[12], Javier Suela[13], Bibiana I. Ferreira[14], Juan C. Cigudosa[14], Carlos Barranco[1], Sergio Serrano[1], Reinhard Dummer[8], Cornelis P. Tensen[6], Francesc Solé[1,3], Ramon M. Pujol[5] and Blanca Espinet[1,3]

CLINICAL AND LABORATORY INVESTIGATIONS
BJD British Journal of Dermatology

A specific DNA methylation profile correlates with a high risk of disease progression in stage I classical (Alibert-Bazin type) mycosis fungoides

G. Ferrara,[1] M. Pancione,[3] C. Votino,[3] P. Quaglino,[4,5] C. Tomasini,[4,5] M. Santucci,[6] N. Pimpinelli,[6] F. Cusano,[2] L. Sabatino[3] and V. Colantuoni[3]

[1]Department of Oncology, Pathology Unit and [2]Dermatology Unit, "Gaetano Rummo" General Hospital, Benevento, Italy
[3]Department of Sciences and Technologies, University of Sannio, Benevento, Italy
[4]Dermatologic Clinic, Department of Medical Sciences, University of Turin, Turin, Italy
[5]Anatomic Pathology Unit, Hospital City of the Health and Science, Turin, Italy
[6]Department of Surgery and Translational Medicine, Divisions of Dermatology and Anatomic Pathology, University of Florence, Florence, Italy

blood
2010 116: 1105-1113
Prepublished online May 6, 2010;
doi:10.1182/blood-2009-12-256719

MicroRNA expression in Sézary syndrome: identification, function, and diagnostic potential

Erica Ballabio, Tracey Mitchell, Marloes S. van Kester, Stephen Taylor, Heather M. Dunlop, Jianxiang Chi, Isabella Tosi, Maarten H. Vermeer, Daniela Tramonti, Nigel J. Saunders, Jacqueline Boultwood, James S. Wainscoat, Francesco Pezzella, Sean J. Whittaker, Cornelius P. Tensen, Christian S. R. Hatton and Charles H. Lawrie

Molecular medical management

- Diagnostic
- Prognostic
- Actionable alteration/pathway (relevant + targetable)

Validation in larger sample size
Rigorous clinical annotation
Deliver precision management

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

blood

2007; 110:1713

JCO
2011:29:2598

2010;28:4730

JOURNAL OF CLINICAL ONCOLOGY

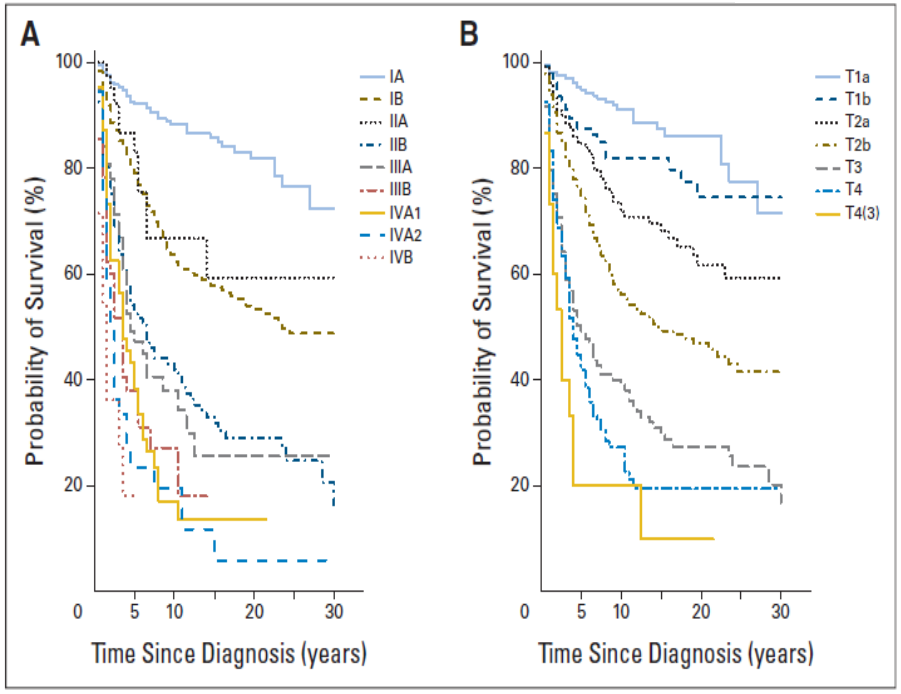
Table 1. Modified ISCL/EORTC Revisions to the TNMB Classification of MF/SS[1]

TNMB Stages	Description of TNMB
Skin*	
T_1	Limited patches, papules, and/or plaques covering < 10% of the skin surface; may further stratify into T_{1a} (patch only) *v* T_{1b} (plaque ± patch)
T_2	Patches, papules, or plaques covering ≥ 10% of the skin surface; may further stratify into T_{2a} (patch only) *v* 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 lymph nodes; biopsy not required
N_1	Clinically abnormal lymph nodes; histopathology Dutch grade 1 or NCI LN_{0-2}
N_{1a}	Clone negative
N_{1b}	Clone positive
N_2	Clinically abnormal lymph nodes; histopathology Dutch Grade 2 or NCI LN_3
N_{2a}	Clone negative
N_{2b}	Clone positive
N_3	Clinically abnormal lymph nodes; histopathology Dutch grade 3-4 or NCI LN_4; clone positive or negative
N_x	Clinically abnormal lymph nodes without histologic confirmation or inability to fully characterize the histologic subcategories
Visceral	
M_0	No visceral organ involvement
M_1	Visceral involvement (must have pathology confirmation and organ involved should be specified)
Blood	
B_0	Absence of significant blood involvement: ≤ 5% of peripheral blood lymphocytes are atypical (Sézary) cells
B_{0a}	Clone negative
B_{0b}	Clone positive
B_1	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
B_2	High blood tumor burden: ≥ 1,000/μL Sézary cells with positive clone‡; one of the following can be substituted for Sézary cells: CD4/CD8 ≥ 10, CD4+CD7- cells ≥ 40% or CD4+CD26- cells ≥ 30%

Table 2. Modified ISCL/EORTC Revisions to the Staging of MF/SS[1]

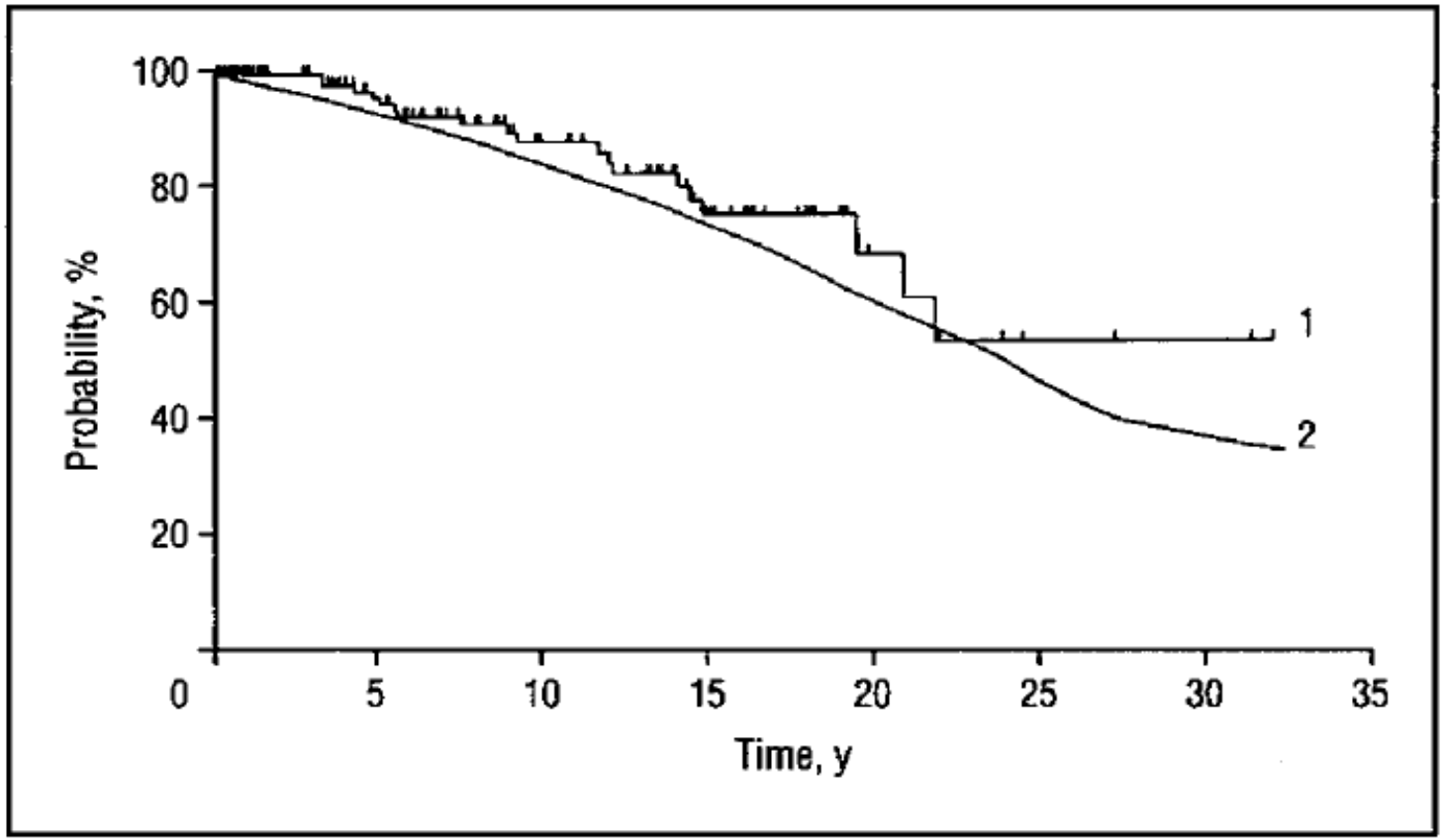
Stage	T	N	M	B
IA	1	0	0	0, 1
IB	2	0	0	0, 1
IIA	1-2	1, 2, X	0	0, 1
IIB	3	0-2, X	0	0, 1
IIIA	4	0-2, X	0	0
IIIB	4	0-2, X	0	1
IVA_1	1-4	0-2, X	0	2
IVA_2	1-4	3	0	0-2
IVB	1-4	0-3, X	1	0-2

Nita Sally Agar, Emma Wedgeworth, Siobhan Crichton, Tracey J. Mitchell, Michael Cox, Silvia Ferreira, Alistair Robson, Eduardo Calonje, Catherine M. Stefanato, Elizabeth Mary Wain, Bridget Wilkins, Paul A. Fields, Alan Dean, Katherine Webb, Julia Scarisbrick, Stephen Morris, and Sean J. Whittaker



Validation of revised MF/SS staging proposal

Actuarial survival of stage IA vs. control population: *Life-expectancy is not altered in treated patients with limited patch/plaque disease*



Kim et al, Arch Dermatol 1996;132:1309-13

VOLUME 28 · NUMBER 31 · NOVEMBER 1 2010

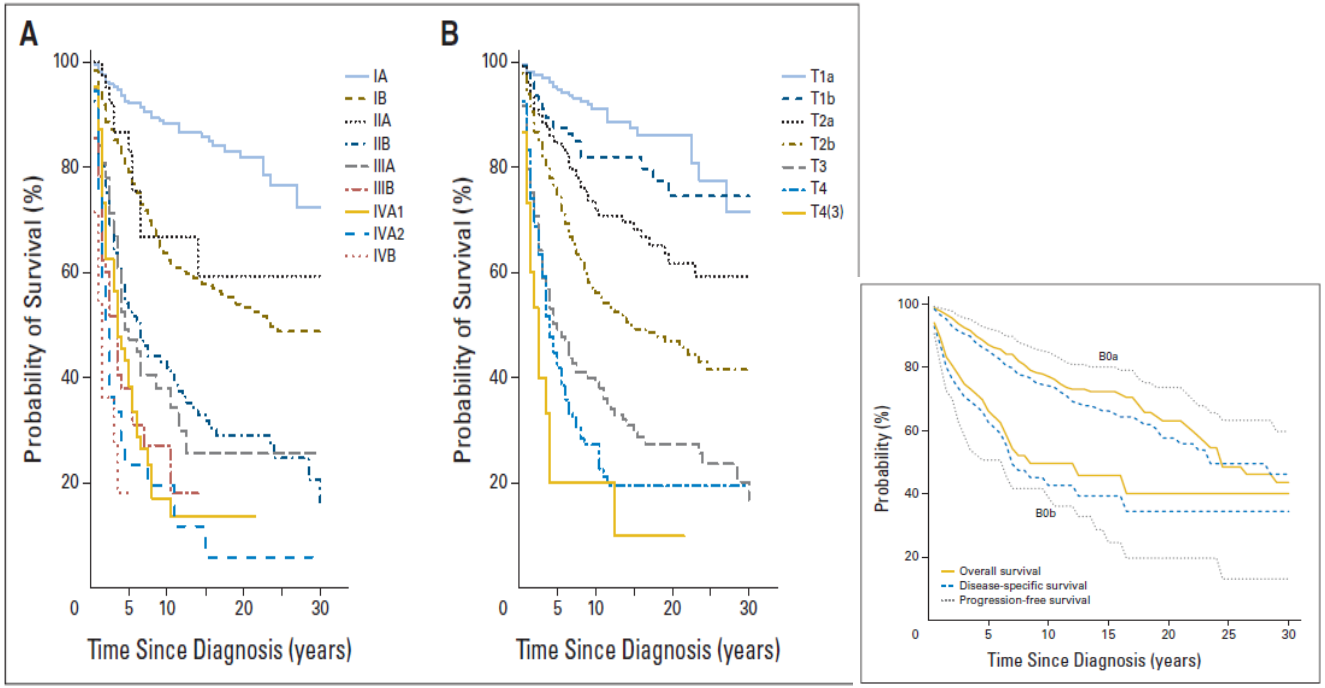
JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Survival Outcomes and Prognostic Factors in Mycosis Fungoides/Sézary Syndrome: Validation of the Revised International Society for Cutaneous Lymphomas/ European Organisation for Research and Treatment of Cancer Staging Proposal

Nita Sally Agar, Emma Wedgeworth, Siobhan Crichton, Tracey J. Mitchell, Michael Cox, Silvia Ferreira, Alistair Robson, Eduardo Calonje, Catherine M. Stefanato, Elizabeth Mary Wain, Bridget Wilkins, Paul A. Fields, Alan Dean, Katherine Webb, Julia Scarisbrick, Stephen Morris, and Sean J. Whittaker

Cohort N = 1,502
1980-2009
Median age, 54
MF 1,398; SS 104
M 62%
Median f/u, 5.9 yr



<u>Univariate factors:</u>

Age >60
Male
↑LDH
LCT
Plaque dz (esp T2)
B0b (vs B0a)

Poikiloderma
Hypopig
LyP

Folliculotropism (early vs late, RDP)

<u>Independent factors of OS/DSS in multivariate model:</u>
TNMB, gender, age, LDH, folliculotropism

2012; 18:5051

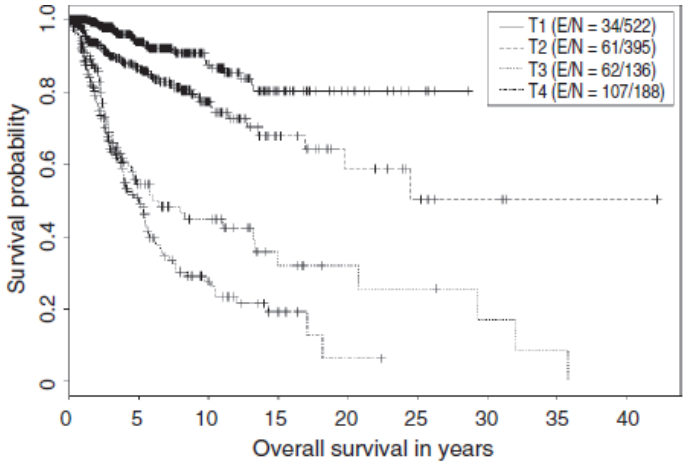
Clinical Cancer Research

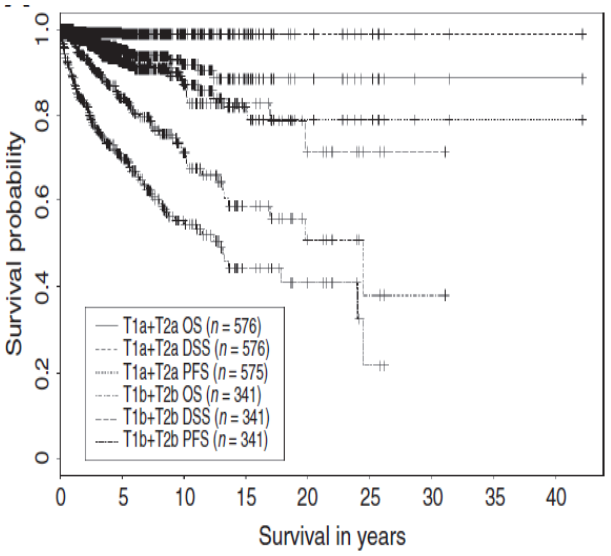
Cancer Therapy: Clinical

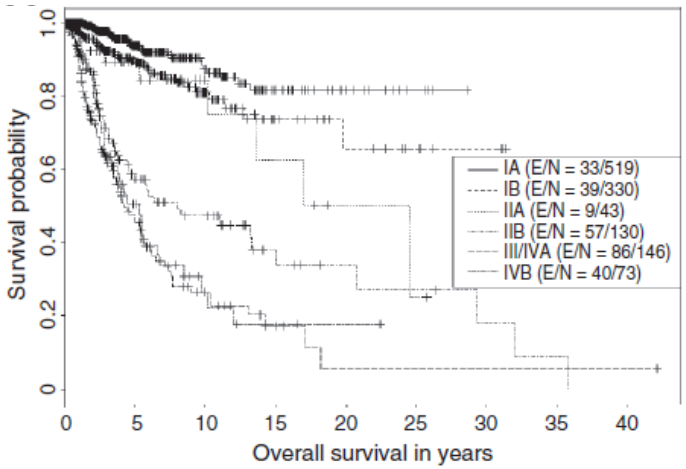
Cohort N = 1,263
Median age, 55
MF 1,062; SS 186
M 52%
Caucasian 73%; AA 13%

Long-term Outcomes of 1,263 Patients with Mycosis Fungoides and Sézary Syndrome from 1982 to 2009

Rakhshandra Talpur[1], Lotika Singh[1], Seema Daulat[1], Ping Liu[2], Sarah Seyfer[1], Tanya Trynosky[1], Wei Wei[2], and Madeleine Duvic[1]







Unfavorable:
↑Age
↑LDH
↑WBC
↑B2-microglobulin
LCT
Plaque dz
Extent of T3 lesions
Young African Am F

Favorable:
Poikiloderma
LyP

Not significant:
Gender
Folliculotropism
hypopig
CD25, CD30

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

Cancer 2012;118:5830

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)

Cohort N = 1,422
1975-2010
Classic MF only
No SS
Median age, 59
M/F = 1.72
median f/u, 15 yr

RDP according to initial stage at diagnosis

Maximum stage / Stage at diagnosis	IA	IB	IIA	IIB	IIIA	IIIB	IVA1	IVA2	IVB	Disease Stage Progression
IA (n=552)	412 (74.6%)	40 (7.2%)	20 (3.6%)	37 (6.7%)	16 (2.9%)	1 (0.2%)	12 (2.2%)	5 (0.9%)	9 (1.6%)	140 (25.4%)
IB (n=556)		396 (71.2%)	24 (4.3%)	63 (11.3%)	29 (5.2%)	7 (1.3%)	14 (2.5%)	12 (2.2%)	11 (2.0%)	160 (28.8%)
IIA (n=122)			73 (59.8%)	12 (9.8%)	12 (9.8%)	2 (1.6%)	9 (7.4%)	11 (9.0%)	3 (2.5%)	49 (40.2%)
IIB (n=78)				44 (56.4%)	6 (7.7%)	0	10 (12.8%)	10 (12.8%)	8 (10.2%)	34 (43.6%)
IIIA (n=82)					50 (61.0%)	7 (8.5%)	15 (18.3%)	7 (8.5%)	3 (3.7%)	32 (39.0%)
IIIB (n=11)						5 (45.5%)	4 (36.4%)	2 (18.2%)	0	6 (54.5%)
IVA1 (n=1)							1	0	0	–
IVA2 (n=9)								8 (88.9%)	1 (11.1%)	1
IVB (n=1)									1	–

<u>Only "classic" MF included;</u> excluded folliculotropic, pagetoid reticulosis, granulomatous

- Cumulative %DP from early stage to advanced stage, 21.5% (14.5% IA – 40.1% IIA)
  - %DP to stage IVA1, 2.2% - 7.4%, to stage IVA2 0.9% - 9%, to stage IVB up to 2.5%

Clinical factors in CTCL

- **Age**
- **TNMB/clinical stage**
  - **T2 (plaque worse than patch),** T3 (extent of tumors), T4 (+/- T3)
  - N (clone neg vs pos), N1 v N2 v **N3,** number of LN sites
  - M (solid organ vs BM), **M0 vs M1**
  - B0 (clone neg vs pos) vs **B1, B2, +/- high SC load (B3)**
  - **Stage IA-IIA vs IIB-IV, +/- extracutaneous dz (stage IV)**
- MF clinical variants, more relevance in early vs advanced
  - Follicular (unfavorable; early vs advanced stage)
  - Poikilodermatous (favorable), hypopigmented (favorable)
  - +/- LyP (favorable)
- Change in pace, aggressive clinical behavior (+/- ↑large cells)
- *Gender, ethnicity (geographic variation)*

Arch Dermatol 2003;139:857, J Clin Oncol 2010;28:4730,
Clin Cancer Res 2012;18:5051, Eur J Cancer 2013;49:2859

Histologic and laboratory factors in CTCL

- **Large cell transformation**
  - Histologic criteria = “large cells form microscopic nodules or >25% of infiltrate”
  - +/- associated aggressive clinical behavior
    - If clinically aggressive **=> bad, triggers intensification of tx**
- Folliculotropism (**early** vs advanced stage dz)
- Tissue tumor cell features
  - Ki-67, CD30, CD25
- Tissue tumor microenvironment
  - CD8+ CTL, Tregs, macrophages, B cells
- ↑**LDH,** ↑**beta-2 microglobulin**, eosinophilia/IgE
- Soluble CD25, CD30, cytokine/cytokine receptor levels

J Clin Oncol 2010;28:4730, Blood 2012;119:1643, Clin Cancer Res 2012; 18:5051
J Am Acad Dermatol 1995;32:448, Leukemia 2007;21:2512, J Invest Dermatol 2012;132:703

American Journal of Pathology, Vol. 132, No. 2, August 1988

Transformation of Cutaneous T Cell Lymphoma to Large Cell Lymphoma

A Clinicopathologic and Immunologic Study

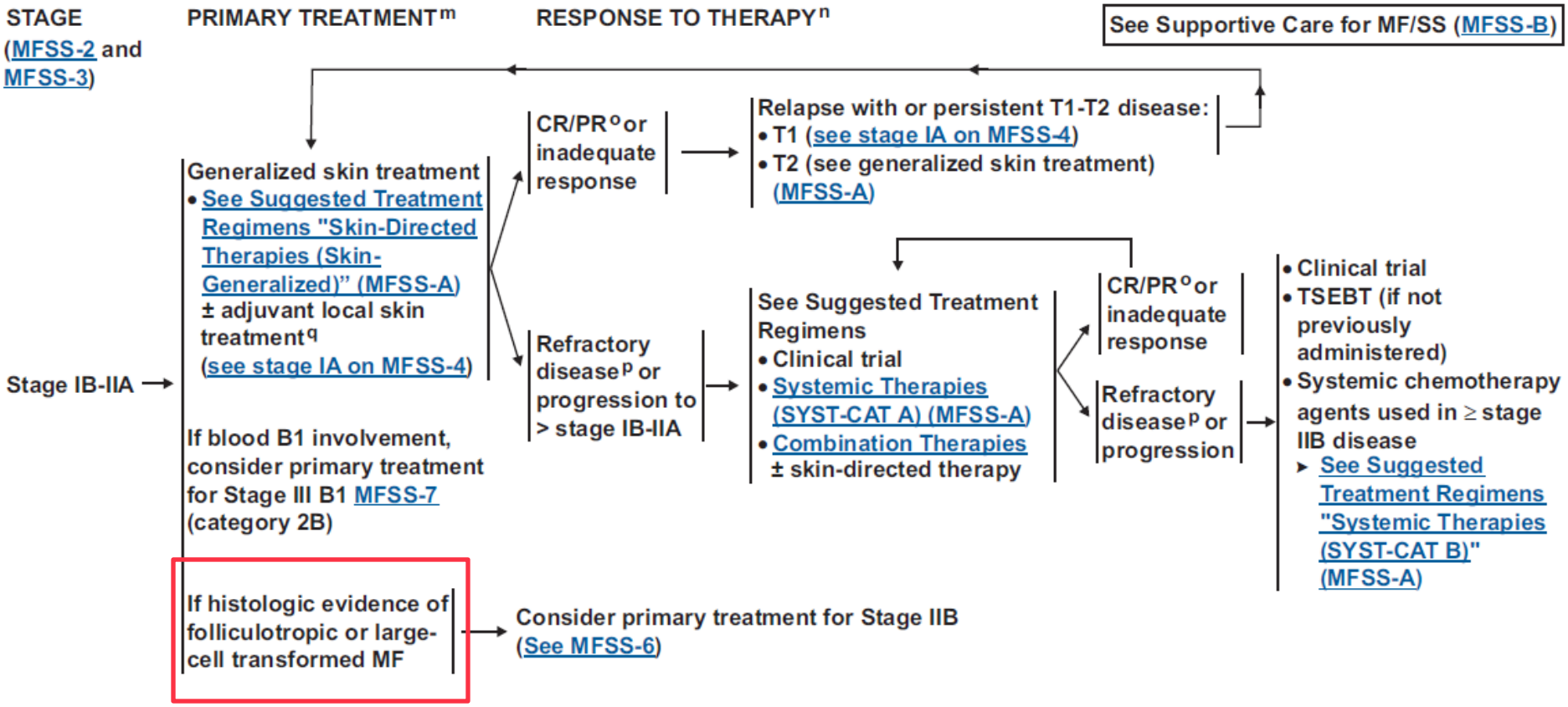
KEVIN E. SALHANY, MD,*
JOHN B. COUSAR, MD,*
JOHN P. GREER, MD,†
TERENCE T. CASEY, MD,*
JAMES P. FIELDS, MD,‡
and ROBERT D. COLLINS, MD,*

From the Divisions of Hematopathology, Hematology,† and Dermatology,‡ Department of Pathology and Department of Medicine, Vanderbilt University Medical Center, Nashville, Tennessee*

- **CTCL can transform morphologically into a large-cell variant a/w aggressive behavior and shortened survival**
- **Clinical-path process is similar to transformations of other hematopoietic or lymphoid neoplasms**
- **Histologic criteria = "large cells form microscopic nodules or >25% of infiltrate throughout"**

NCCN Guidelines Version 2.2015
Mycosis Fungoides/Sezary Syndrome

NCCN Guidelines Index
NHL Table of Contents
Discussion



Footnote that distinguishes indolent vs aggressive clinical behavior

Prognostic index models in CTCL

Integration of prognostic data to generate meaningful risk groups

National Comprehensive Cancer Network®

NCCN Guidelines Version 2.2015
Diffuse Large B-Cell Lymphoma

NCCN Guidelines Index
NHL Table of Contents
Discussion

INTERNATIONAL PROGNOSTIC INDEX[a]

ALL PATIENTS:
- Age >60 years
- Serum LDH > normal
- Performance status 2–4
- Stage III or IV
- Extranodal involvement >1 site

INTERNATIONAL INDEX, ALL PATIENTS:

• Low	0 or 1
• Low intermediate	2
• High intermediate	3
• High	4 or 5

AGE-ADJUSTED INTERNATIONAL PROGNOSTIC INDEX[a]

National Comprehensive Cancer Network®

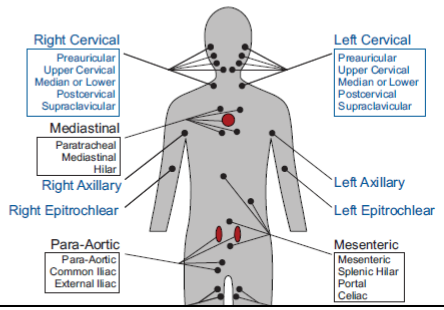
NCCN Guidelines Version 2.2015
Follicular Lymphoma (grade 1-2)

NCCN Guidelines Index
NHL Table of Contents
Discussion

GELF CRITERIA[a,b]

- Involvement of ≥3 nodal sites, each with a diameter of ≥3 cm
- Any nodal or extranodal tumor mass with a diameter of ≥7 cm
- B symptoms
- Splenomegaly
- Pleural effusions or peritoneal ascites
- Cytopenias (leukocytes <1.0 x 10^9/L and/or platelets <100 x 10^9/L)
- Leukemia (>5.0 x 10^9/L malignant cells)

Nodal Areas



FLIPI - 1 CRITERIA[a,c,d]

Age	≥60 y
Ann Arbor stage	III–IV
Hemoglobin level	<12 g/dL
Serum LDH level	
Number of nodal site	

Risk group a

Low
Intermediate
High

National Comprehensive Cancer Network®

NCCN Guidelines Version 2.2015
Peripheral T-Cell Lymphomas

NCCN Guidelines Index
NHL Table of Contents
Discussion

INTERNATIONAL PROGNOSTIC INDEX[a]

ALL PATIENTS:
- Age >60 years
- Serum LDH > normal
- Performance status 2–4
- Stage III or IV
- Extranodal involvement >1 site

INTERNATIONAL INDEX, ALL PATIENTS:

• Low	0 or 1
• Low intermediate	2
• High intermediate	3
• High	4 or 5

PROGNOSTIC INDEX FOR PTCL-U (PIT)[b]

RISK FACTORS:	PROGNOSTIC RISK:	
• Age >60 years	• Group 1	0
• Serum LDH > normal	• Group 2	1
• Performance status 2–4	• Group 3	2
• Bone marrow involvement	• Group 4	3 or 4

AGE-ADJUSTED INTERNATIONAL PROGNOSTIC INDEX[a]

PATIENTS ≤60 YEARS:
- Stage III or IV
- Serum LDH > normal
- Performance status 2–4

INTERNATIONAL INDEX, PATIENTS ≤60 YEARS:

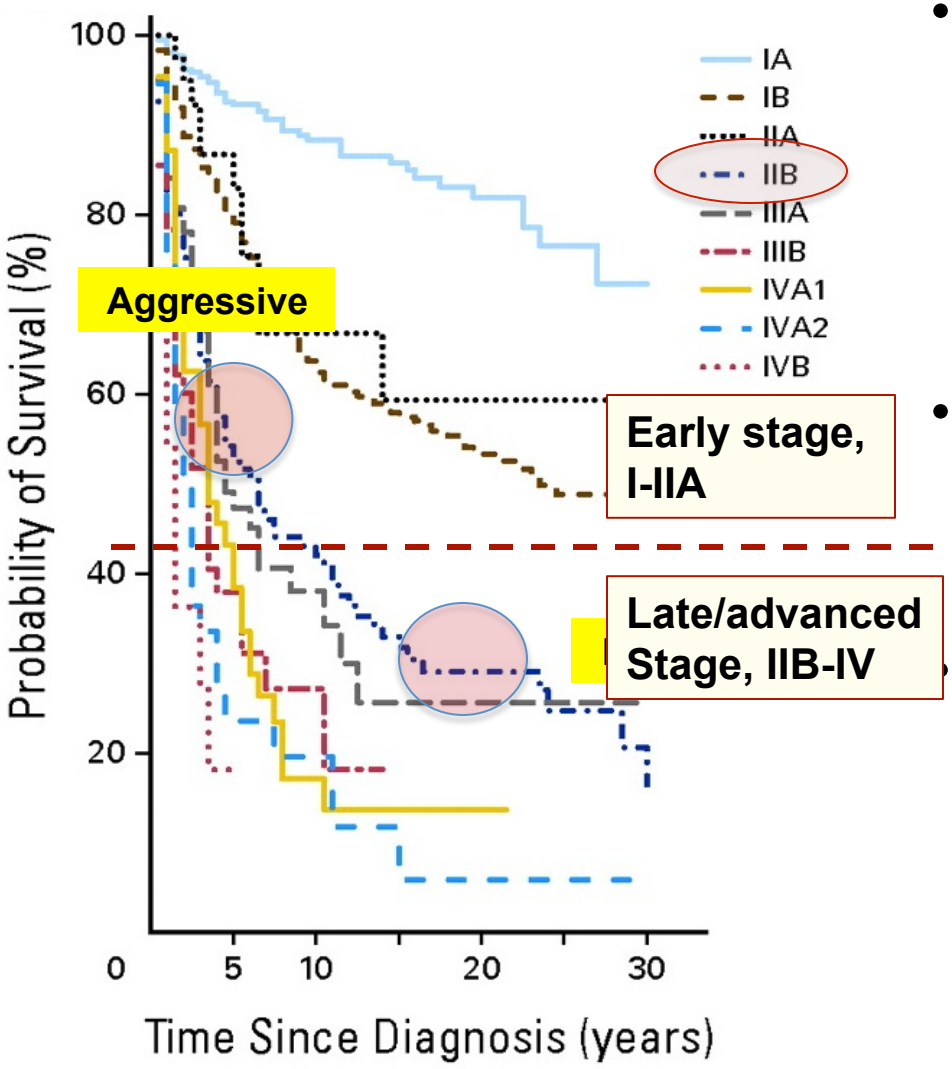
• Low	0
• Low/intermediate	1
• High/intermediate	2
• High	3

Prognostic index for CTCL

Do we need one?

- MF/SS TNMB/staging system is not adequate for prognostication
  - Wide range of clinical outcome within clinical stage
- Prognostic model that can augment current TNMB/ staging, enable precision, risk-stratified management would improve clinical outcome
- Allows clinical trials design by risk groups
  - More meaningful safety, efficacy, biomarker data
  - Better assessment of risk/benefit and unmet need

Beyond TNMB/stage: how can we predict the good from the bad within a stage/IIB?



- Are there additional clinical, path, lab factors, other biomarkers that distinguish between indolent and aggressive IIB?
- Can we identify which IIB pts will have worse outcome with distinguishing markers?

Are these adverse markers actionable targets or pathways that can be addressed and improve outcome?

Agar N S et al. JCO 2010;28:4730-4739

European Journal of Cancer (2013) 49, 2859–2868

A cutaneous lymphoma international prognostic index (CLIPi) for mycosis fungoides and Sezary syndrome

E.C. Benton [a], S. Crichton [b], R. Talpur [c], N.S. Agar [a], P.A. Fields [d], E. Wedgeworth [a], T.J. Mitchell [a], M. Cox [f], S. Ferreira [a], P. Liu [c], A. Robson [a], E. Calonje [a], C.M. Stefanato [a], B. Wilkins [g], J. Scarisbrick [a], E.M. Wain [a], F. Child [a], S. Morris [a], M. Duvic [c,h], S.J. Whittaker [a,e,*]

Risk stratification in early (I-IIA) and late/advanced (IIB-IV) stage MF/SS

Derivation set with St John/UK data (n=1502)
5 independent prognostic factors relevant in early and late stage disease

3 risk groups

- Low-risk, 0-1 factors
- Intermediate-risk, 2 factors
- High-risk, 3-5 factors

Exclusion of SS (n=104) from late stage model did not alter results

Validation set with MDACC/US data (n=1221)

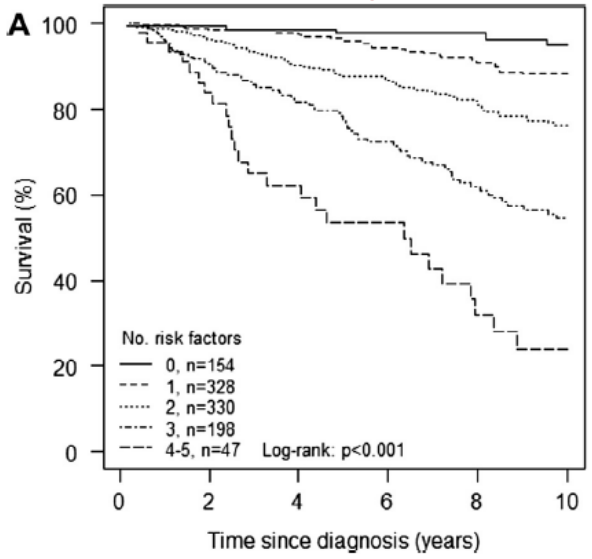
St John/UK n=1502

MDACC/US n=1221

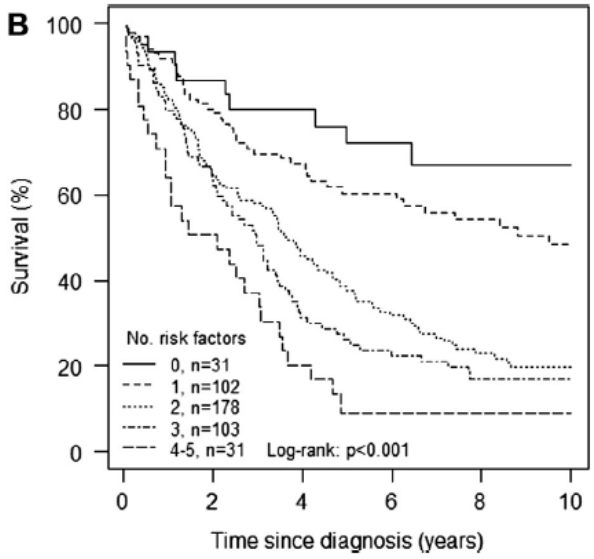
Table 1
Results of the Cox regression analysis for early and late stage disease in 1502 patients (derivation set) and for 1221 patients (validation set).

	Adverse factor	Derivation				Validation			
		N (%)	HR	95% CI	*p*-Value	*N* (%)	HR	95% CI	*p*-Value
Early	Male	636(60.2)	1.90	1.37–2.63	<0.001	449(50.7)	1.41	0.87–2.28	0.162
	>60 years	356(33.7)	3.88	2.87–5.27	<0.001	339(38.4)	3.89	2.31–6.55	<0.001
	Plaques	534(50.5)	1.64	1.20–2.25	0.002	319(36.0)	2.83	1.70–4.72	<0.001
	Folliculotropic	161(15.2)	1.65	1.14–2.37	0.007	31(3.5)	1.61	0.50–5.24	0.425
	N1/Nx	85(8.0)	1.90	1.37–2.63	<0.001	46(5.2)	1.26	0.54–2.96	0.591
Late	Male	297(66.7)	1.35	1.03–1.96	0.030	211(59.8)	0.86	0.63–1.19	0.367
	>60 years	274(61.6)	1.54	1.19–1.99	0.001	191(54.4)	1.84	1.33–2.53	<0.001
	B1/B2	175(39.3)	1.50	1.17–1.91	0.001	188(53.3)	1.29	0.93–1.77	0.133
	N2/N3	134(30.1)	1.65	1.28–2.12	<0.001	80(22.7)	1.26	0.88–1.79	0.205
	Visceral (M1)	13(2.9)	2.28	1.23–4.26	0.009	4(1.13)	1.10	0.27–4.51	0.899

Early



Late



Derivation (UK)

Early/IA-IIA, n= 1057

Late/IIB-IV, n= 445

5 independent factors in each

3 risk groups

- **Low-risk, 0-1 factors**
- **Intermediate-risk, 2 factors**
- **High-risk, 3-5 factors**

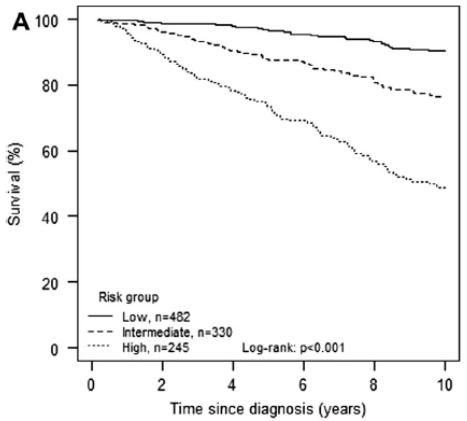
Eur J Cancer 2013;49:2859

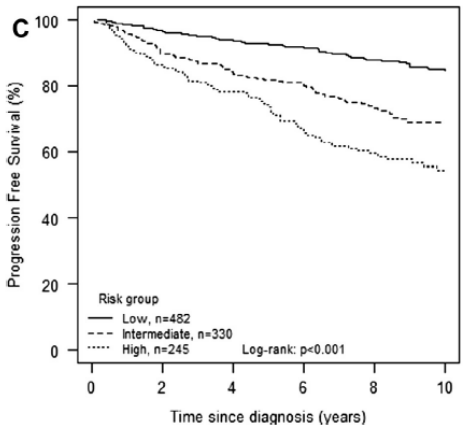
Early stage (I-IIA) risk groups

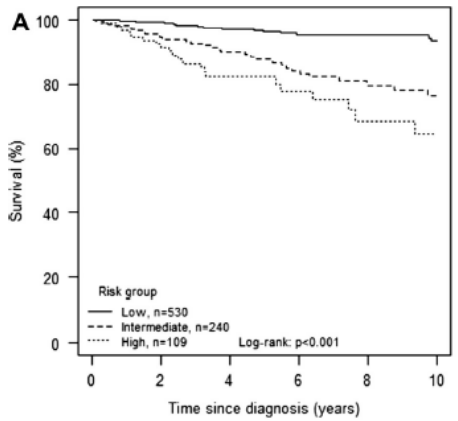
		Risk group	Derivation						Validation					
			N (%)	5 years, (%)	10 years, (%)	HR	95% (CI)	*p*-Value	*N* (%)	5 years, (%)	10 years, (%)	HR	95% CI	*p*-Value
Overall survival	Early	Low	485	96.0	90.3	1		<0.001	530	96.5	93.4	1		<0.001
		Intermediate	330	87.6	76.2	2.8	1.9–4.3		240	87.7	76.4	4.2	2.3–7.7	
		High	245	73.5	48.9	7.5	5.0–11.2		109	82.3	64.5	6.9	3.6–13.3	
Progression free survival	Early	Low	485	92.7	84.5	1		<0.001	530	95.3	92.3	1		<0.001
		Intermediate	330	81.7	68.8	2.4	1.7–3.3		240	85.7	72.3	3.4	2.1–5.7	
		High	245	73.5	54.5	3.9	2.8–5.5		109	71.5	49.1	7.3	4.3–12.4	

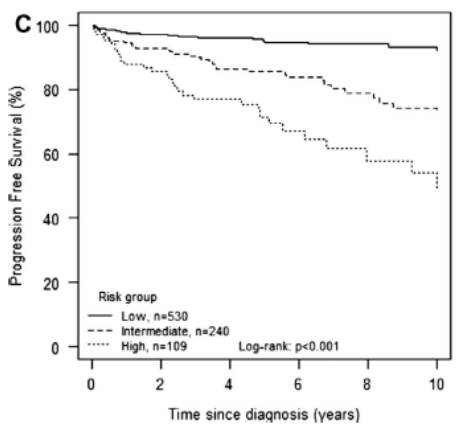
Derivation (UK)
Early/IA-IIA,
n= 1057

3 risk groups
- **Low-risk, 0-1 factors**
- **Intermediate-risk, 2 factors**
- **High-risk, 3-5 factors**









Validation (US)
Early/IA-IIA,
n= 879

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Late/advanced stage (IIB-IV) risk groups

		Risk group	Derivation						Validation					
			N (%)	5 years, (%)	10 years, (%)	HR	95% (CI)	*p*-Value	*N* (%)	5 years, (%)	10 years, (%)	HR	95% CI	*p*-Value
Overall survival	Late	Low	133	63.2	53.2	1		<0.001	114	61.4	46.4	1		0.002
		Intermediate	178	37.8	19.8	2.3	1.7–3.2		132	49.4	31.9	1.5	1.0–2.2	
		High	134	22.1	15.0	3.1	2.2–4.3		96	42.3	19.5	2.0	1.4–3.0	
Progression free survival	Late	Low	133	58.3	48.6	1		<0.001	114	78.4	59.1	1		0.2417
		Intermediate	178	42.9	25.3	1.6	1.2–2.2		132	70.2	46.8	1.5	0.9–2.6	
		High	134	26.6	21.2	2.2	1.6–3.1		96	734	46.8	1.5	0.8–2.7	

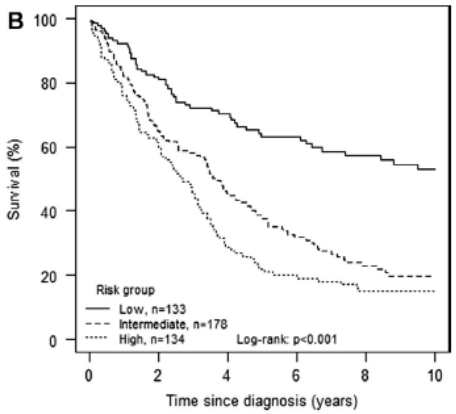
Derivation (UK)

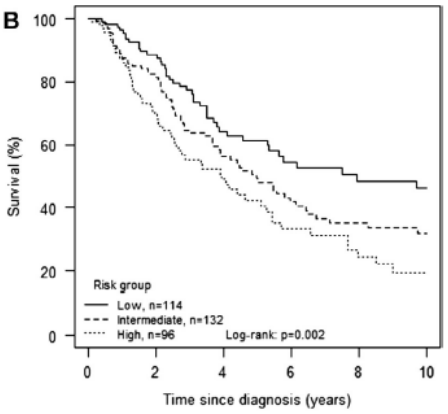
Late/IIB-IV,

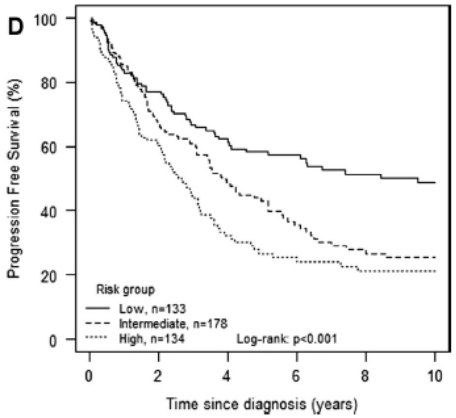
n= 445

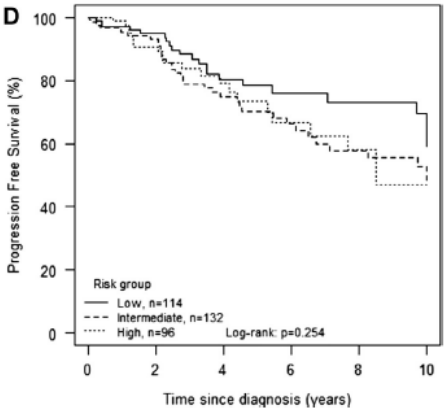
3 risk groups

- **Low-risk, 0-1 factors**
- **Intermediate-risk, 2 factors**
- **High-risk, 3-5 factors**









Validation (US)

Late/IIB-IV,

n= 342

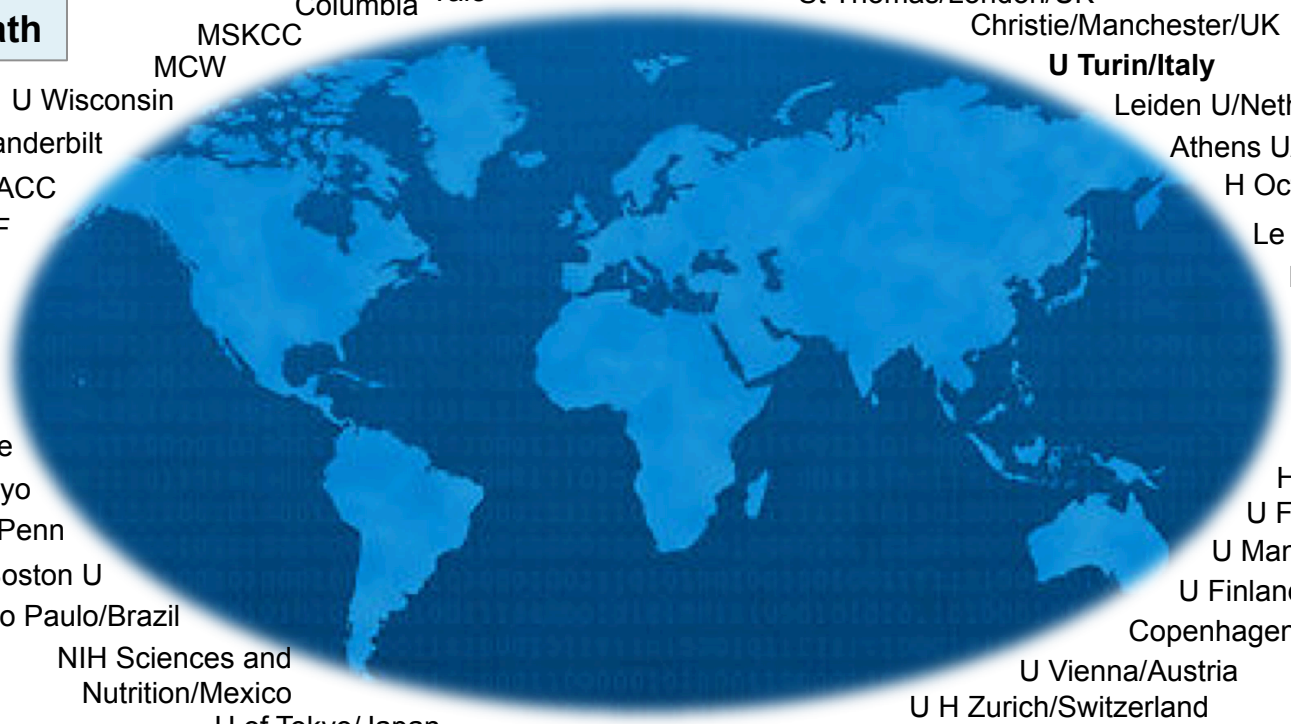
Eur J Cancer 2013;49:2859

Limitations of published studies

- Retrospective and/or single-center
- Changes in CL classification
- Lack of consistency in definition/criteria
  - Criteria for folliculotropic disease, clonality method, LN scoring, etc. may vary
- Bias in pt inclusion or ordering tests
  - Referral center bias
  - Lab test (flow, molecular studies) or imaging may be ordered in those with more severe disease or concern of progression
- Problems with missing data, inconsistent data completion
  - False interpretation of no data as negative data

Cutaneous Lymphoma International Consortium (CLIC): an International Alliance for Large-Scale Collaborative Investigations in Cutaneous Lymphoma

45+ centers
Derm, Onc, Path



CLIC Background & Goals

- CLIC is project-based, research collaborative alliance of CL expert centers worldwide to generate large-scale clinical and translational data for greater impact
- Initiated as ISCL-based interest in late 2012, officially supported by EORTC, USCLC, and other regional CL organizations
- Although inclusive in concept, the participants/sites are primarily determined by proposed projects, funding, and commitment

Multicenter Prospective Study for Development of a CL International Prognostic Index in Mycosis Fungoides and Sézary syndrome (PROCLIPI)

Cutaneous Lymphoma International Consortium 'CLIC'
Initial Collaborative Project

PROCLIPI Study

- This project aims to collect well-defined parameters at initial diagnosis, progression events, and annual update
  - Clinical/Lab
  - Pathological/molecular
    - Dermpath, Hemepath
- These prognostic variables will be tested against overall & progression free survival
- *CLIC federated Biobank establishment (Led by Maarten Vermeer)*

PROCLIPI study as initial collaborative project

Steps

- **Retrospective feasibility studies** that shows CLIC can be productive, *led by Julia Scarisbrick and Pietro Quaglino*
  - Retrospective study of key prognostic parameters
  - Retrospective treatment-focused analysis
  - Highlight issues with retrospective study
- Set ground work for **prospective study**
  - PROCLIPI work groups to identify candidate parameters and establish well-defined criteria for consistency
  - Investigator meetings (Paris/EORTC, Stanford/ASH)
  - Bridge funding towards securing larger awards

Cutaneous Lymphoma International Consortium (CLIC) Study of Outcome in Advanced Stages of Mycosis Fungoides & Sézary Syndrome: Effect of specific prognostic markers on survival and development of a prognostic model

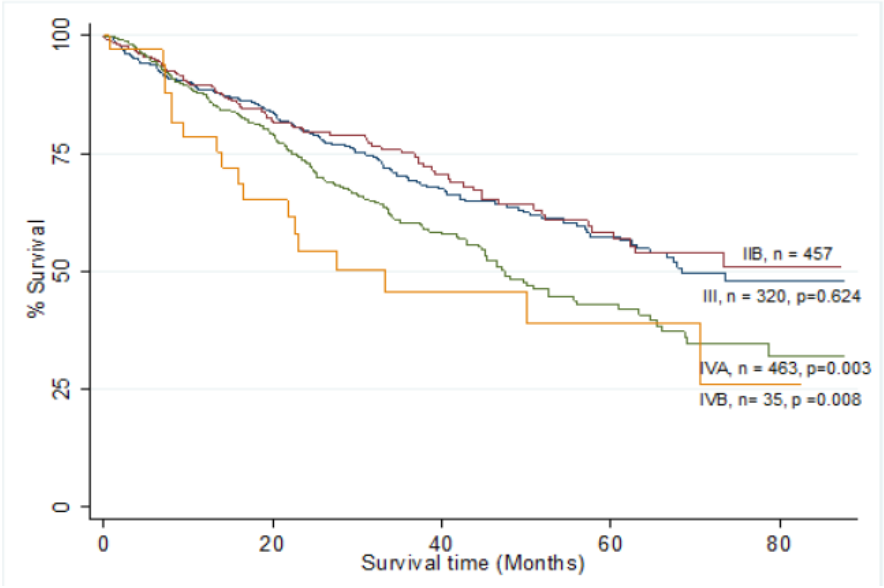
Retrospective study

Julia J Scarisbrick[1], H.Miles Prince[2], Maarten H Vermeer[3], Pietro Quaglino[4], Steven Horwitz[5], Pierluigi Porcu[6], Rudolf Stadler[7], Gary S. Wood[8], Marie Beylot-Barry[9], Anne Pham-Ledard[9], Francine Foss[10], Michael Girardi[10], Martine Bagot[11], Laurence Michel[11], Maxime Battistella[11], Joan Guitart[12], Timothy M Kuzel[12], Maria Estela Martinez-Escala[12], Teresa Estrach[13], Evangelia Papadavid[14], Christina Antoniou[14], Dimitis Rigopoulos[14], Vassilki Nikolaou[14], Makoto Sugaya[15], Tomomitsu Miyagaki[15], Robert Gniadecki[16], José Antonio Sanches[17], Jade Cury-Martins[17], Denis Miyashiro[17], Octavio Servitje[18], Cristina Muniesa[18], Emilio Berti[19], Francesco Onida[19], Laura Corti[19], Emilia Hodak[20], Iris Amitay-Laish[20], Pablo L Ortiz-Romero[21], Jose L Rodríguez-Peralto[21], Robert Knobler[22], Stefanie Porkert[22], Wolfgang Bauer[22], Nicola Pimpinelli[23], Vieri Grandi[23], Richard Cowan[24], Alain Rook[25], Ellen Kim[25], Alessandro Pileri[26], Annalisa Patrizi[26], Ramon M Pujol[27], Henry Wong[6], Kelly Tyler[6], Rene Stranzenbach[7], Christiane Querfeld[5,28], Paolo Fava[4], Milena Maule[4], Rein Willemze[3], Felicity Evison[1], Stephen Morris[29], Robert Twigger[2], Rakhshandra Talpur[30], Jinah Kim[31], Grant Ognibene[31], Shufeng Li[31], Mahkam Tavallaee[31], Richard T Hoppe[31], Madeleine Duvic[30], Sean J Whittaker[29] and Youn H Kim[31]

1. U Hosp Birmingham, UK; 2. Peter MacCallum CC East Melbourne, Victoria, Australia; 3. Leiden U, The Netherlands; 4. U of Turin, Italy; 5. Memorial Sloan Kettering CC, New York, US; 6. Ohio State Univ, Ohio, USA; 7. Unit U Munster, Minden, Germany; 8. U of Wisconsin, USA; 9. CHU Hosp de Bordeaux, Bordeaux, France; 10. Yale U, New Haven, Conneticut, USA; 11. Hosp St Louis, Paris, France; 12. Northwestern U, Chicago, USA; 13. Hosp Clínico, U of Barcelona, Villarroel, Barcelona, Spain; 14. Athens U Med Sch, Greece; 15. U of Tokyo, Tokyo, Japan; 16. Bispebjerg Hosp, Copenhagen U, Denmark; 17. U of Sao Paulo Med Sch, Brazil; 18. Hosp U de Bellvitge, Idibell, Barcelona, Spain; 19. Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico - U of Milano-Bicocca, Italy; 20. Rabin Medical , Beilinson Hosp, Tel Aviv U, Israel; 21. Hosp 12 de Octubre. Institute i+12. Med Sch. U Complutense, Madrid, Spain; 22. Med U of Vienna, Austria; 23. U of Florence, Florence, Italy; 24. The Christie Hosp, Manchester, UK; 25. U of Pennsylvania, Pennsylvania, USA; 26. U of Bologna, Bologna, Italy; 27. Hosp del Mar. U Autònoma Barcelona, Barcelona, Spain; 28. City of Hope Hosp, Duarte, CA, US; 29. St Thomas' Hosp, London, UK; 30. MD Anderson CC, Houston, USA; 31. Stanford U, California, USA

	No. of patients	Median OS mnths	IQR OS mnths	RM Survival mnths	1- year OS	2-year OS	5-year OS
IIB	457	68.37	31.0 – NR	59.5	88.50%	80.10%	57.40%
III (all*)	320	NR	36.8 – NR	60.9	89.50%	79.50%	58.20%
IIIA	187	NR	35.2 – NR	61.7	89.60%	79.80%	60.20%
IIIB	119	62.4	32.8 – NR	58.2	88.50%	77.80%	55.70%
IVA (all)	463	47.5	22.3 – NR	50.9	87.60%	73.20%	42.90%
IVA1	290	52.7	31.5 – NR	55.7	90.40%	79.40%	48.30%
IVA2	127	29	13.6 – 68.7	40.4	81.00%	59.60%	32.90%
IVB	35	33.3	14.0 – NR	42.5	78.50%	54.30%	39.00%
Stages (all)	1275	63	25.4 – NR	56.3	88.10%	76.60%	51.90%

Fig 1 Kaplan Meier Showing Survival by Stage

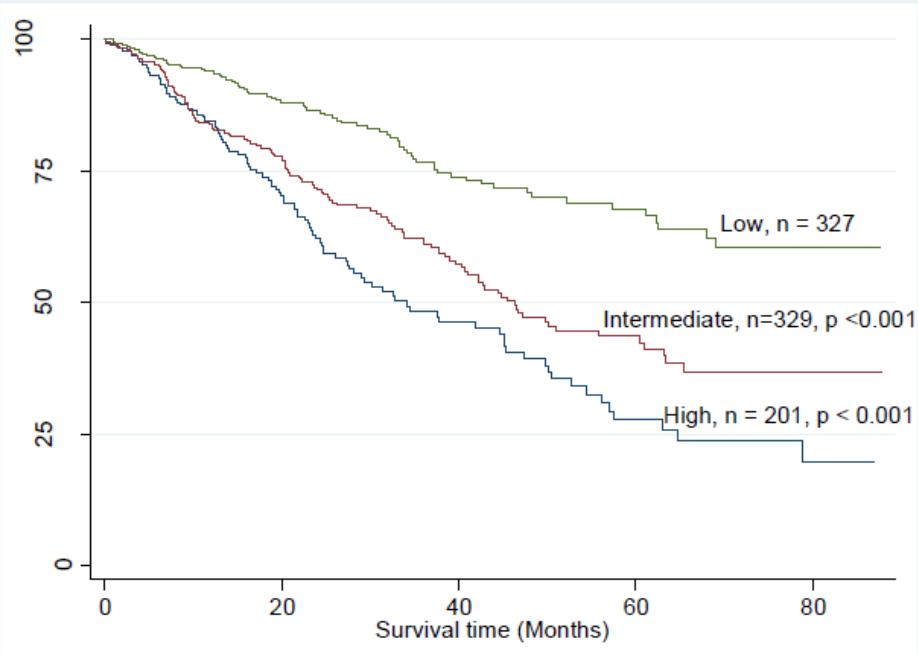


IIB, III

IV

Data completeness n=patient number (%)	Parameter	No. of patients	Median OS	IQR Survival months	RM Survival	Probability of survival to at least 1 year	to at least 2 years	to at least 5 years	P value
Sex: n =1262 (99.0%)	Male	789	63.0	25.0 – NR	56.2	87.3%	76.0%	52.1%	P=0.937
	Female	473	60.3	26.1 – NR	55.8	89.3%	77.3%	50.4%	
Age n =1265 (99.2%)	≤60 years	452	NR	34.2 – NR	63.6	92.8%	84.7%	62.5%	P<0.001
	>60 years	813	51.0	21.7– NR	51.7	85.4%	71.9%	45.6%	
FT n =1062 (83.3%)	FT - absent	879	57.5	24.4 – NR	54.6	87.9%	75.2%	49.3%	P<0.001
	FT - Yes	183	NR	44.8 – NR	65.9	91.4%	86.6%	66.5%	
WCC n =716 (56.2%)	Raised WCC	252	37.7	17.8-78.8	44.3	85.8%	67.5%	35.3%	P=0.006
	Non raised WCC	436	54.4	24.8 – NR	53.8	87.9%	75.8%	46.1%	
Absolute lymphocyte count n =847 (66.4%)	Low WCC	28	57.5	34.4 – NR	60.0	95.5%	84.9%	48.8%	
	Raised ALC	248	52.7	24.5– NR	53.5	88.8%	76.8%	49.5%	P=0.358
	Non Raised ALC	485	57.3	23.4 –NR	54.7	87.8%	74.1%	48.4%	
	Low ALC	114	42.2	18.6 – NR	47.4	82.0%	72.0%	37.8%	
LDH n =894 (70.1%)	Raised LDH	457	44.7	19.2– NR	48.6	84.6%	68.6%	39.0%	P<0.001
	Non Raised LDH	437	78.8	33.2– NR	60.5	90.9%	81.9%	58.4%	
TCR Clone n =727 (57.0%)	Identical Clone Blood to skin Y	357	49.8	24.4– NR	53.8	88.4%	76.2%	45.6%	P=0.086
	No identical Clone blood to skin N	370	73.4	30.2– NR	59.3	87.1%	78.5%	58.7%	
LCT n =1098 (86.1%)	LCT - Yes	215	49.8	20.1– NR	48.9	84.8%	68.6%	38.5%	p=0.003
	LCT - No	883	66.2	27.7– NR	57.8	89.3%	78.4%	54.9%	
CD30 n =639 (50.1%)	CD30 +ve >10%	149	55.7	22.3– NR	54.9	88.6%	74.6%	44.9%	p=0.331
	CD30 +ve ≤10%	490	68.7	28.0– NR	58.7	87.8%	78.2%	56.7%	
Ki 67 n =471 (36.9%)	Ki 67 +ve >20%	182	50.1	25.2– NR	55.9	89.3%	76.9%	46.8%	p=0.552
	Ki 67 +ve ≤20%	289	NR	30.8– NR	58.7	86.7%	78.6%	55.6%	

Risk of Poor Survival (No. of risk factor)	N (deaths)	N IIB	N III	N IV	1-year survival months	2-year survival months	5-year survival months	Median OS months	Hazard ratio (95% CI, p-value)
Low (0-1)	327(100)	166	134	27	94.0	86.6	67.8	NR	1
Intermediate (2)	329 (123)	91	82	156	83.9	71.9	43.5	46.4	2.09 (1.56, 2.80; p<0.001)
High (3-4)	201(100)	20	4	177	84.7	62.2	27.6	34.2	2.91 (2.15, 3.96; p<0.001)



Prognostic model

Independent variables:
age >60, stage IV, ↑LDH, LCT+

Low risk = 0-1

Intermediate risk = 2

High risk = 3-4

PROCLIPI: Prospective Study to Determine Prognostic Parameters, CL Prognostic Index, and Impact of Major Therapies in Advanced MF and SS

- **Aim 1. Determination of prognostic factors in advanced MF and SS in a prospective design**
- **Aim 2. Development of Cutaneous Lymphoma International Prognostic Index (CLIPI) towards improved prognostication and stratification for management in advanced MF and SS**
- **Aim 3. Characterization of geographic pattern of treatment utilization and CLIPI-based differential clinical outcome of major systemic treatments in advanced MF and SS**

- ***Establishment of SOP for federated Biobank for future CLIC translational projects***

CLIC Steering Committee

Youn Kim (US), US Director, Stanford Cancer Institute
Julia Scarisbrick (UK), Non-US Director, U Hospital Birmingham
Pietro Quaglino (Italy), PROCLIPI Project Director, U of Turino
Maarten Vermeer (The Netherlands), Co-Leader PROCLIPI, U of Leiden
Sean Whittaker (UK), Co-Leader PROCLIPI, Guys and St Thomas
Gary Wood (US), Co-Leader PROCLIPI, Path/Molecular, U of Wisconsin
Richard Hoppe (US), Co-Leader PROCLIPI, Radiation Oncology, SCI
Madeleine Duvic (US), Dermatology, MD Anderson CC
Miles Prince (Australia), Haematology/Oncology, Peter MacCallum CC
Steve Horwitz (US), Medical Oncology, Memorial Sloan Kettering CC
Pierluigi Porcu (US), Medical Oncology, OSU, representative of USCLC
Rudolf Stadler (Germany), Dermatology, representative of EORTC CLTF
Joan Guitart (US), Dermatology, Pathology, NWU
Alistair Robson (UK), Pathology, Guys and St Thomas

PROCLIPI Work Groups

Clinical/lab

- Julia Scarisbrick
- Madeleine Duvic
- Steve Horwitz
- Pierluigi Porcu
- Rudi Stadler

Treatment

- Pietro Quaglino
- Steve Horwitz
- Youn Kim
- Miles Prince
- Pierluigi Porcu

Biobank

- Maarten Vermeer
- Sean Whittaker
- Wen-Kai Weng
- Gary Wood

Pathology/Molecular

- Gary Wood
- Joan Guitart
- Jinah Kim
- Werner Kempf
- Dennis Weisenburger
- Alejandro Gru

Regulatory & Data Management

- Rich Hoppe
- John Allen
- Antonio Cozzio
- Sean Whittaker
- Data manager, statistician reps

Future Projects, Grant Applications, Publications Committees

Prognostic Models in CTCL
Work-in-progress summary, *2015*

- In MF/SS, clinical factors (TNMB, stage, age) as consistent basic prognostic factors, additional variables to consider
  - E**arly stage MF**, plaque+ and folliculotropism+
  - A**dvanced stage MF & SS**, stage IV, ↑LDH, and LCT+ as independent adverse factors of importance
- Integrated prognostic models are needed to augment prognosticating power for improved risk-stratification
- Establishment of CLIC, an unprecedented scale of international collaborative alliance, allows an opportunity for prospective validation and translation, ***PROCLIPI***
- **Importance of molecular/biomarker discoveries** with prognostic value, validated before utilized in the clinics
- Taking steps towards personalized, precision medicine