CLIC
CUTANEOUS LYMPHOMA INTERNATIONAL CONSORTIUM

PROCLIPI

PROGNOSTIC Modelling in CTCL: The PROCLIPI study

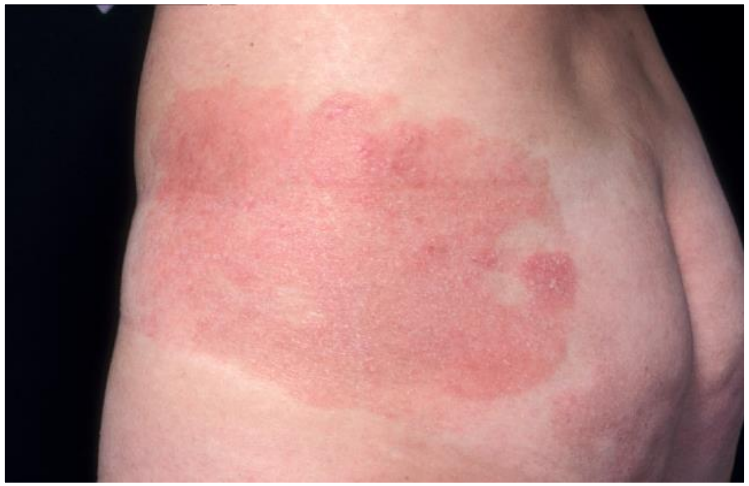
PROspective **C**utaneous **L**ymphoma **I**nternational **P**rognostic **I**ndex Study

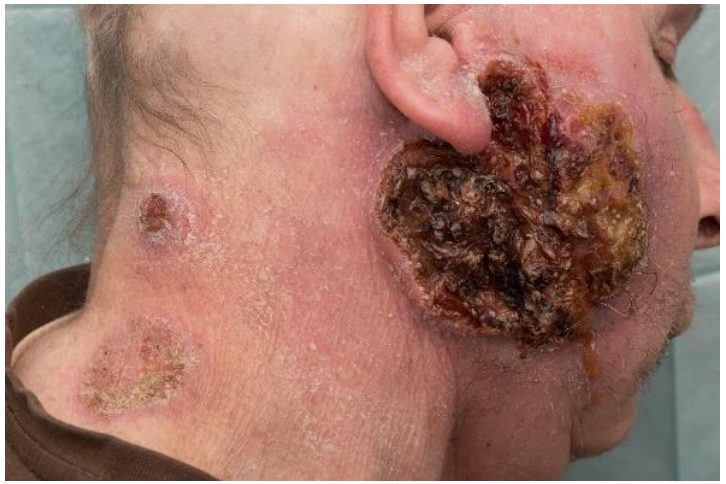
PI's – Julia Scarisbrick, U Birmingham, UK & Youn Kim – U Stanford, CA, USA

On Behalf of the EORTC Gp & Cutaneous Lymphoma International Consortium

PROspective **C**utaneous **L**ymphoma **I**nternational **P**rognostic **I**ndex Study

- The **PROCLIPI study opened 2015** collects well-defined parameters at first diagnosis, stage progression and annual follow up of MF/SS
  - Clinical
  - Pathological
  - Nodal
  - Haematological
  - Genotypic
  - Treatment
  - Biobank Material





- Prognostic variables are tested against overall & progression free survival (PFS)
- Treatments responses will be compared along side time to next treatment, PFS and quality of life
- We aim to recruit a minimum of 1500 patients with MF/SS over the 5 year study period, survival data for 10+ years
- 20% of patients will be used in the validation set

75 Registered PROCLIPI Centres

Principal Investigator	Centre Address
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Christiane Querfeld	City Of Hope National Medical Center, California, US
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Principal Investigator	Centre Address
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Deborah Turner	Torbay Hospital, Torbay, UK
Pier Luigi Zinzani	Università di Bologna, Bologna, Italy
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Ellen Kim	University of Pennsylvania, Pennsylvania, USA
Eugenia Piliotis	Sunnybrook Health Sciences Centre - Odette Cancer Center USCLC
Chalid Assaf	Le Charite Hospital , Berlin, Germany OR HELIOS Klinikum Krefeld, Germany
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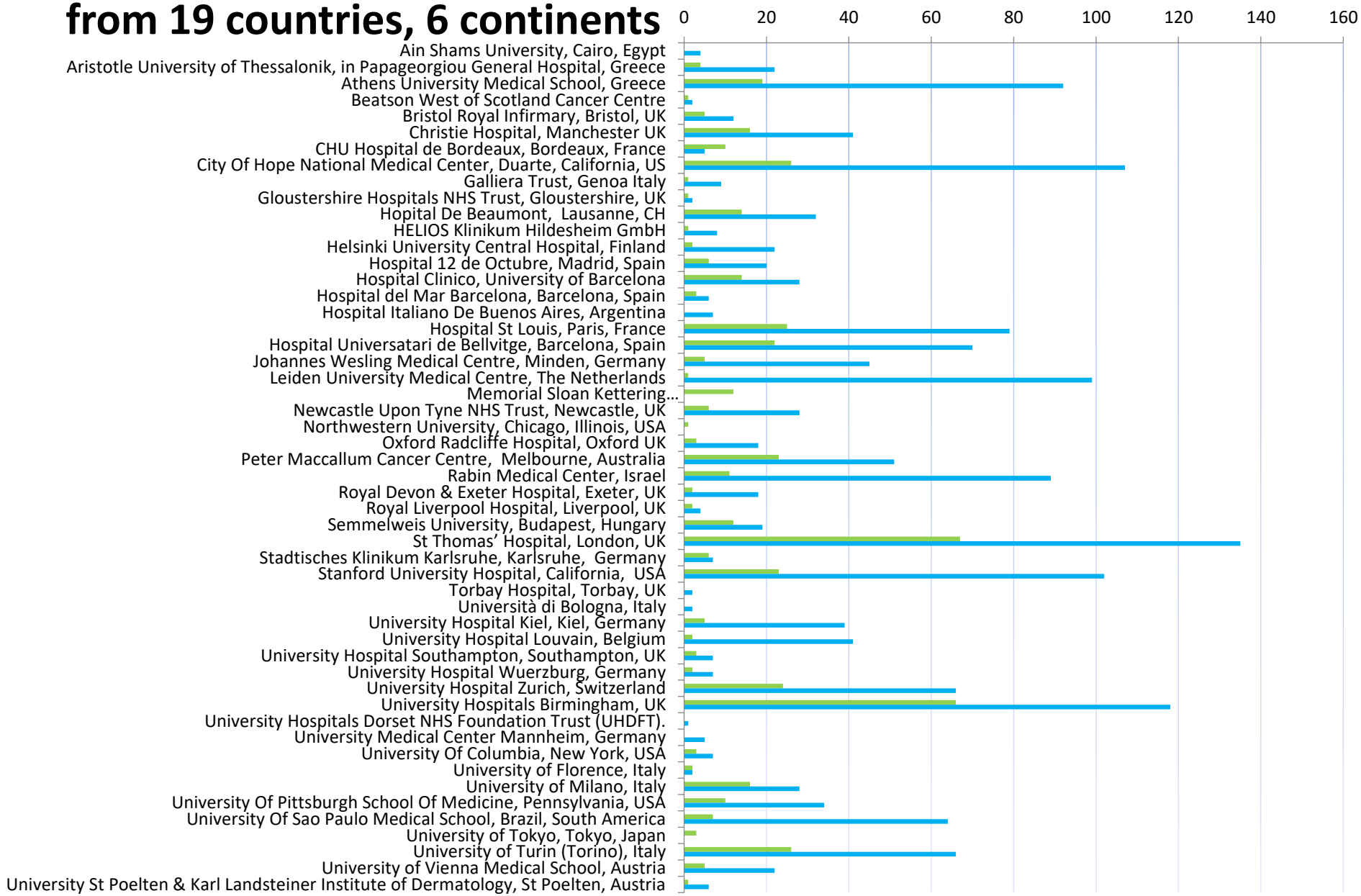
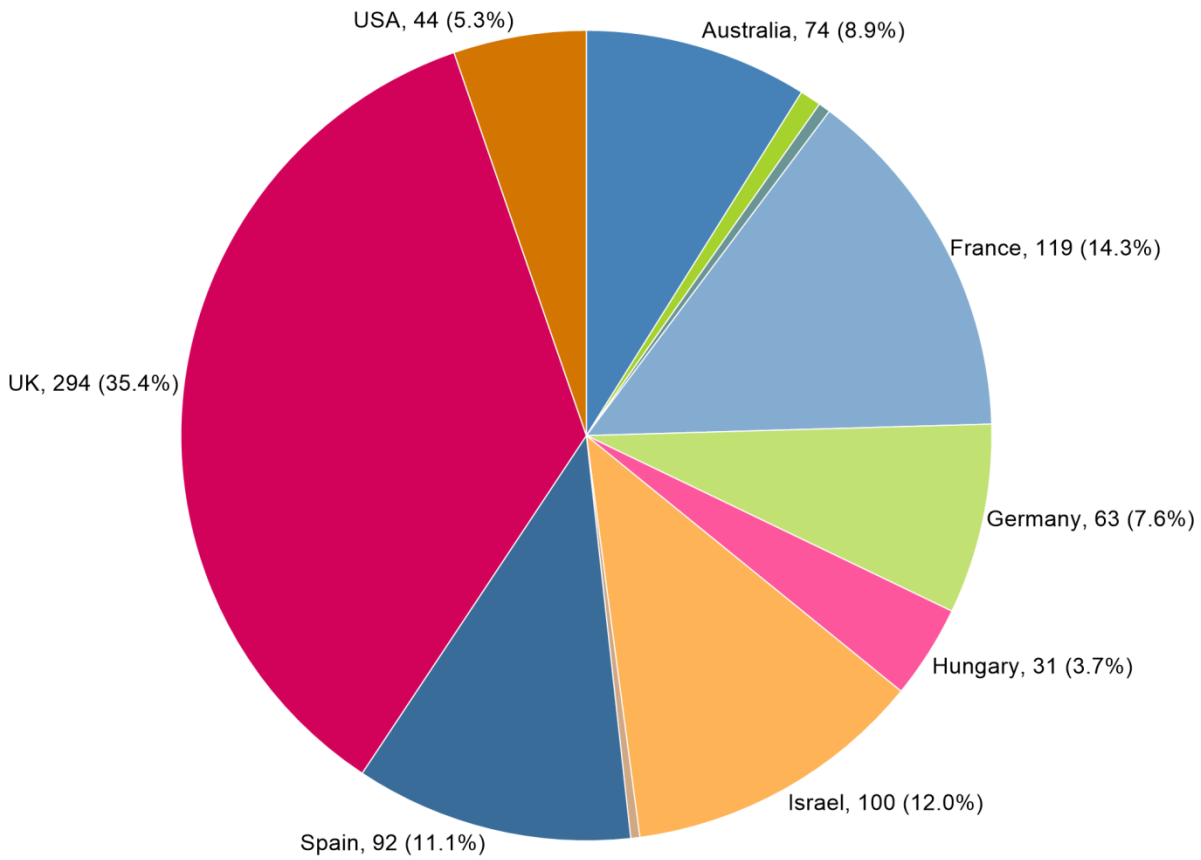
Eve Gallop-Evans	Velindre Hospital, Cardiff, Wales, UK
Adam Forbes	Royal Cornwall Hospitals NHS Trust, Truro, Cornwall, UK
Eleanor James	Nottingham University Hospitals, Nottingham, UK.
Antonio Cozzio	St Gallen Hospital, St Gallen, Switzerland
Lorenzo Cerroni	Department of Dermatology, University of Graz, Austria
Ricardo Fernández de Misa Cabrera	Medical University, Tennerife,
Rose Moritz	Universitätshautklinik Münster, Münster, Germany
Ilan Goldberg	Tel Aviv Sourasky Medical Center
Miguel A Piris	Hospital Universitario Marques de Valdecilla, Santander, Spain
Christina Mitteldorf	University Of Goettingen, Germany
Ale Gru	University Of Virginia, Virginia, USA
Yang Wang	Peking University First Hospital, Beijing, China
Joan Guitart	Northwestern University, Chicago, Illinois, USA
Larisa Geskin	University Of Columbia, New York, USA
Ellen Kim	Hospital Of The University Of Pennsylvania, Philadelphia, US
Salma Machan	Hospital Universitario Fundación Jiménez Díaz, Madrid, Spain
An Bervoets	Antwerp University Hospital, Belgium

PROCLIPI: 2219 patients recruited; 1700 early, 519 late stage, 52 sites, from 19 countries, 6 continents

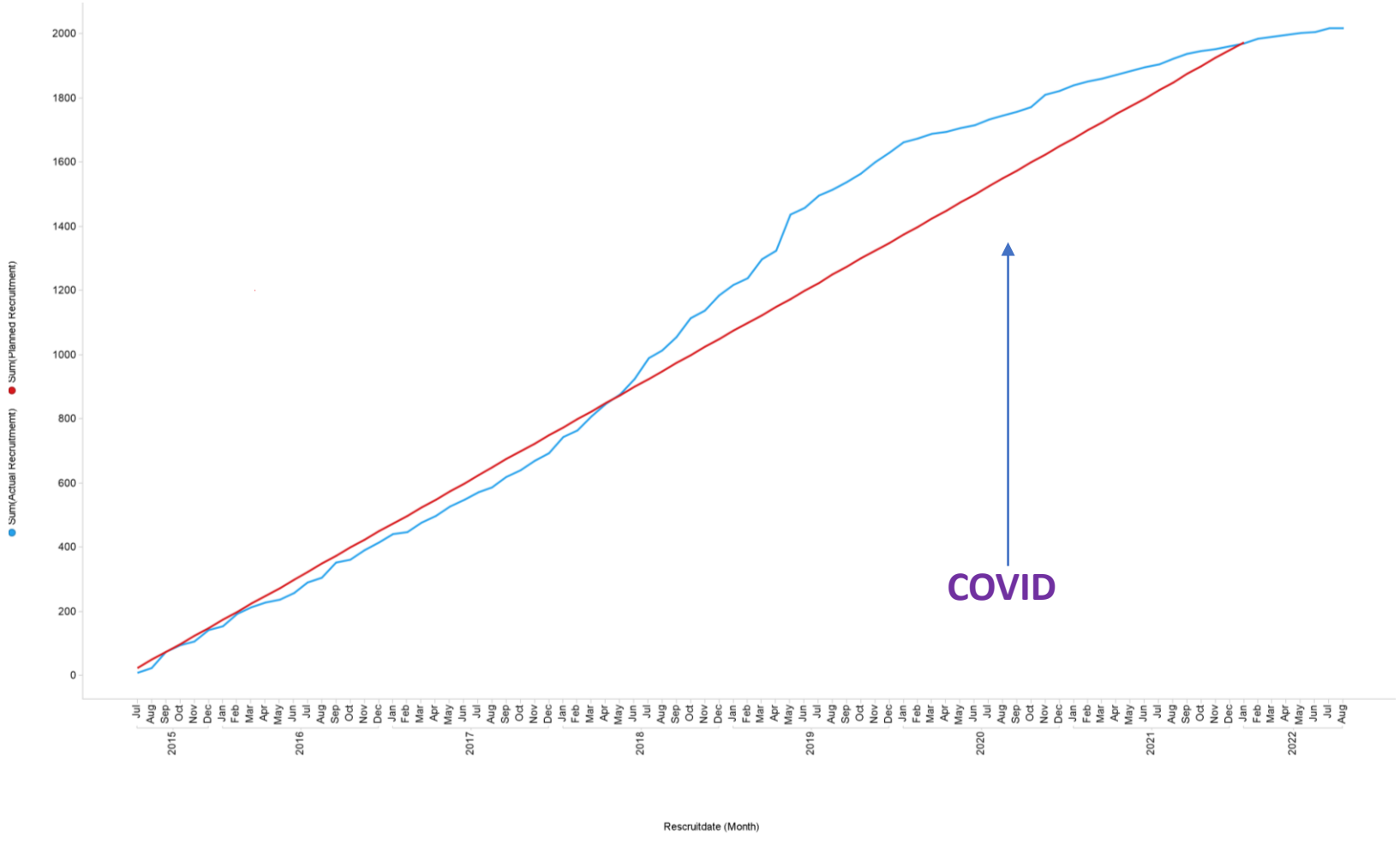


Recruitment number by 19 participating countries



Year 5: Planned PROCLIPI recruitment

Year 5: Actual PROCLIPI recruitment



Planned recruitment 1000 early stage patients over 5 years with data collected over 10 years, 500 advanced patients

Central Review Team : Clinical, histopathological & immunohistochemical

Virtual review of clinical and pathological photomicrographs followed by real-time review if required

Pass Rate 772/922 (83.7%)
150 failed 20 restaged advanced, 27 awaiting real time review, 16 incomplete data fro review, 114 non diagnsotic

Central Review Team Early Stage;

Rein Willemze

Werner Kempf

Lorenzo Cerroni

Central Review Team Late stage; ***Virtual review of scanned slides***

Ale Gru, Virginia, US

Maxime Battistella, Paris

Dermatopathology Panel

Melissa Pulitzer (MSKCC)

Joan Guitart (Northwestern)

Carlos Torres Cabala MD Anderson

Werner Kempf, Zurich

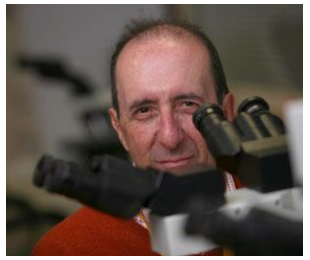
Helmut Beltraminelli, Zurich

Joya Pawade, Bristol UK

Haematopathology Panel

Andrew Feldman, Mayo

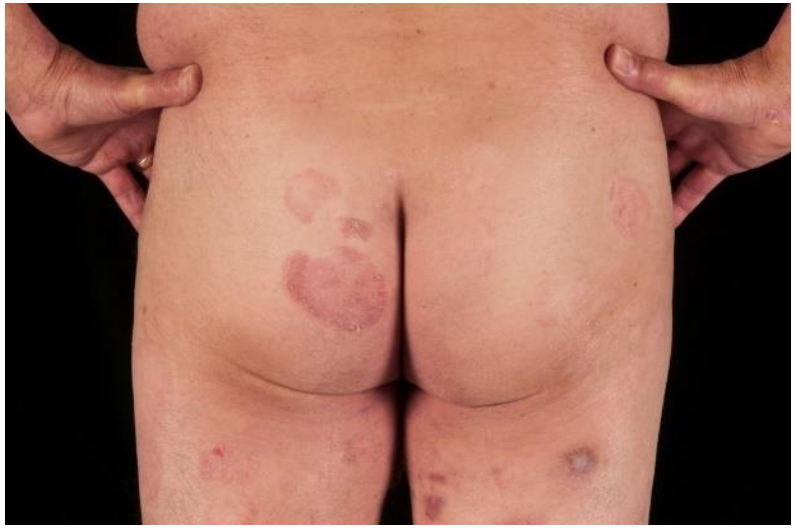
Nancy L Harris, MGH



Miguel Angel Piris, Madrid

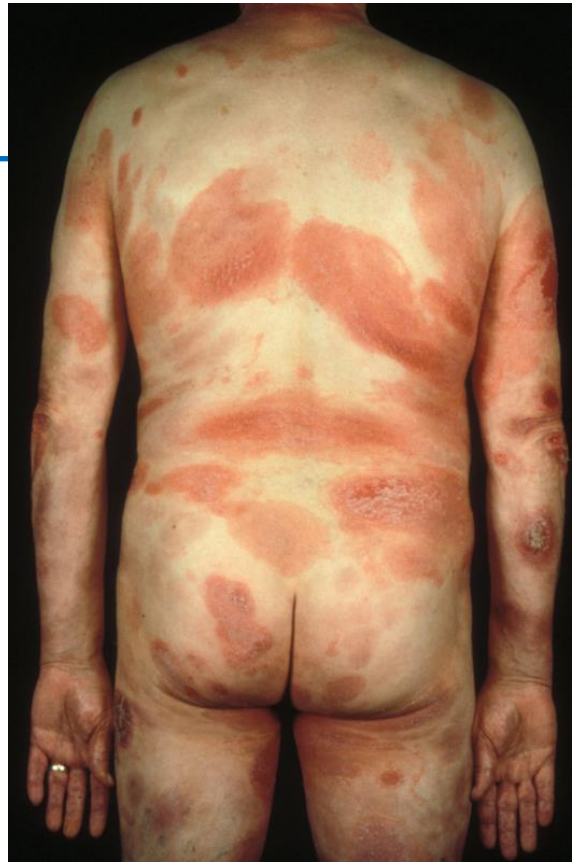
Maxime Battistella, Paris

Early stage data: 1700 patients (77%)

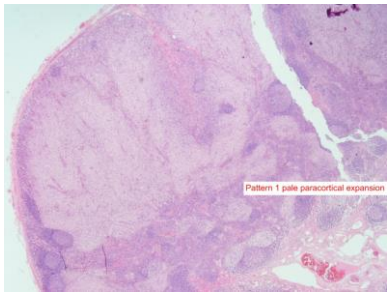


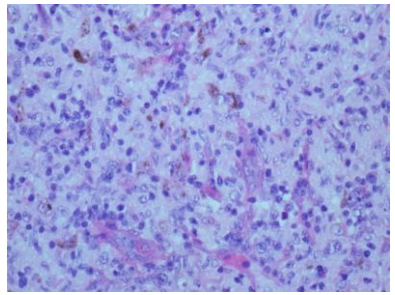
Stage IA; <10% patches & plaques
n=847 patients (50%)

Stage IB; >10% patches & plaques
n=711 patients (42%)

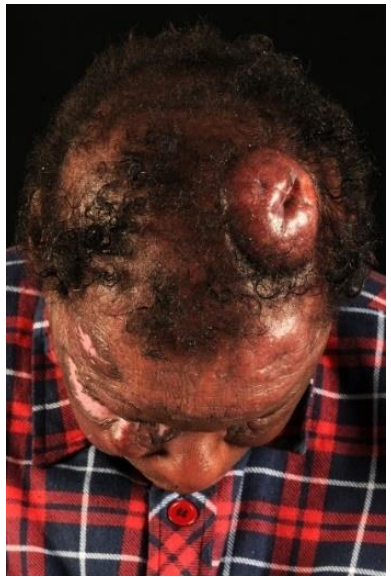


Stage IIA; Patches & plaques with enlarged lymph nodes showing dermatopathic changes or early involvement with MF (not effaced)
n=142 patients (8%)





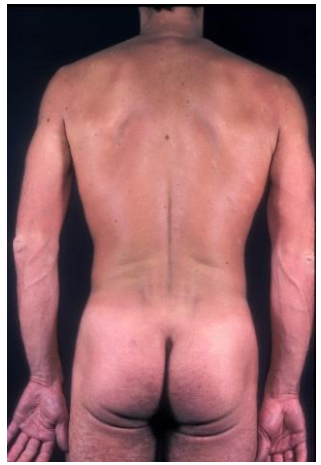
Late stage data: 460 patients (23%)



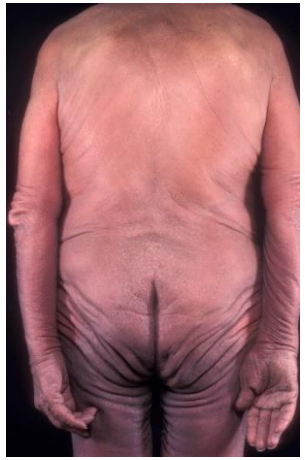
Stage IIB; tumour stage n=157 patients (34%)

Erythroderma IIIA-IVA1 n= 252 patients (55%)

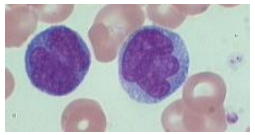
Stage IIIA; low blood tumour burden (B0) n=50 patients (11%)



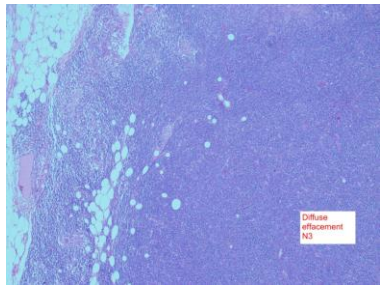
Stage IIIB; Moderate blood tumour burden (B1) n=50 patients (11%)

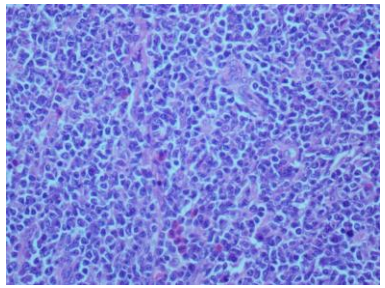


Stage IVA1; high tumour burden (B2) n=152 patients (36%)



Stage IVA2; Lymph nodes showing effaced lymph nodes n=36 patients (8%)





Stage IVB; Visceral disease n=15 patients (3%)

Clinical Data Set on 1818 patients – median FU 29mnths [23-31]

- Median age early stage (IA-IIA) is 58 years which is significantly younger than late stages IIB-IVB at 66 years (p<0.0001)
- Patients presented in advanced disease had a shorter duration of disease prior to diagnosis at 12 months compared to 24 months in early stages (p=0.0001)
- Median QOL significant different in Early vs Late stage (Global p<0.0001, Symptoms p<0.0001, Emotions p=0.0016, Functioning P<0.0001)

	Early	IIB	IIIA	IIIB	IVA(1)	IVA(2)	IVB	Late
Number of Patients	1409	157 (34%)	50(11%)	50 (11%)	152 (33%)	36 (8%)	15 (3%)	460
Classical Mycosis Fungoides	1132 (80.3%)	105 (66.9%)	27 (54.0%)	13 (26.0%)	6 (10.5%)	8 (22.2%)	6 (40.0%)	175 (38.0%)
Folliculotropic Mycosis Fungoides	200 (14.2%)	29 (18.5%)	6 (12.0%)	5 (10.0%)	4 (2.6%)	4 (11.1%)	2 (13.3%)	50 (10.9%)
Median age years (IQR)	58 (44-69)	65	64	67.5	68	65	56	66 (55-74)
m:f ratio	1.7:1	2.2:1	2.8:1	1.9:1	1.6:1	1.1:1	2.0:1	1.9:1
Median duration MF-like lesions, months	24 (2-74)	17	24	17	6	22.5	15	12 (0-48)
Median MSWAT score	15 (6-35)	39	100	100	90	90	65	84 (44.5-104.5)
No. with stage progression (to advanced stage)	157 (90)	8	8	10	5	1	0	32
Number of deaths	73 (5.2%)	41 (26.1%)	13 (26.0%)	13 (26.0%)	38 (25.0%)	17 (47.2%)	7 (46.7%)	129 (28.0%)
Number of lymphoma related deaths	25 (1.8%)	26 (16.6%)	4 (8.0%)	7 (14.0%)	19 (12.5%)	14 (38.9%)	4 (26.7%)	74 (16.1%)
QOL Global (Median (IQR))	25.3 (137-41.3)	34.9 (21.2-61.5)	36.0 (15.9-57.5)	46.2 (40.9-62.3)	46.4 (28.7-66.9)	46.8 (34.9-68.0)	55.9 (34.6-66.1)	43.9 (27-62.8)

Associations with progression to advanced stage in early stage disease has been reported in 90 (6%)

Ethnicity isn't recorded very well – 40% missing no significance

	Numbers early stage patients progressed to advanced stages	Total	P-Value
B0	39 (7.3%)	532	B0 v B1 p=0.424
B1	10 (9.6%)	104	
Bx	41 (5.4%)	764	
N0	71 (5.5%)	1284	N0 vs Not N0 p<0.0001
N1	4 (21.1%)	19	N0 vs Not (restricted to N1/N2) P=0.029
N2	0	2	
NX	15 (15.8%)	95	
Age > 60 yrs	56 (8.9%)	630	p=0.001
Male Sex	61(7.0%)	873	P=0.273
Low ALC	13 (10.6%)	123	p=0.151
Raised Serum LDH	18 (11.4%)	157	P=0.034
Identical Clone on Blood	6 (9.4%)	64	p=0.998
Plaque (T1b or T2b)	69 (10.9%)	634	P<0.001
Folliculotropism	27 (10.8%)	250	P=0.002
LCT	10 (34.5%)	29	P<0.001

Associated with progression to advanced stage:

- Nx-N2
- Raised LDH
- Presence plaques
- Folliculotropism
- LCT in skin

Key:
Significant
Not Significant

Multivariable analysis for stage progression of patients presenting in early stage using Cox regression

N0	1 (reference Value)	
N1	4.19 (1.62-10.84)	p = 0.003
N2	2.28 (0.31-16.64)	p = 0.417
Nx	2.09 (1.19-3.67)	p = 0.010
Over 60	1.97 (1.30-2.97)	p = 0.001
LCT	3.99 (2.14-7.44)	p<0.001
Folliculotropic MF	1.52 (0.97-2.39)	p = 0.066
Lyp like Lesions	0.86 (0.31-2.40)	p = 0.773
Hypopigmentation	0.96 (0.43-2.13)	p = 0.921
Plaques	2.81 (1.72-4.56)	p <0.001

Associations with death (disease specific) in late stage disease has been reported in 74 of 460 patients (16.1%)

	Numbers late stage patients died	Total	P-Value
T1	2(14.3%)	14	
T2	6 (8.6%)	70	
T3	32 (18.8%)	170	P=0.221 (t3 vs Not T3)
T4	34 (16.5%)	206	P=0.826 (T4 vs Not T4)
B0	23 (20.4%)	113	B0, B1 v B2 p=0.396
B1	10(17.5%)	57	
B2	23 (15.8%)	146	
Bx	18 (12.5%)	144	
N0	24 (9.9%)	243	N0 vs Not N0 p<0.001 N0 vs Not (restricted to N1/N2/N3) P=0.003 N3 vs not N3 p<0.001
N1	3 (8.3%)	36	
N2	2 (13.3%)	15	
N3	15 (39.5%)	38	
NX	30 (23.4%)	128	
Age > 60 yrs	55(18.6%)	296	p=0.050
Male sex	50 (16.7%)	300	P=0.643
Low ALC	14 (26.9%)	52	p=0.148
Raised Serum LDH	38 (20.0%)	190	P=0.187
Identical Clone on Blood	25(26.9%)	93	P=0.428
LCT in skin	15 (23.8%)	63	P=0.136
Folliculotropism	17 (27.0%)	63	P=0.087

Associated with disease specific deaths:

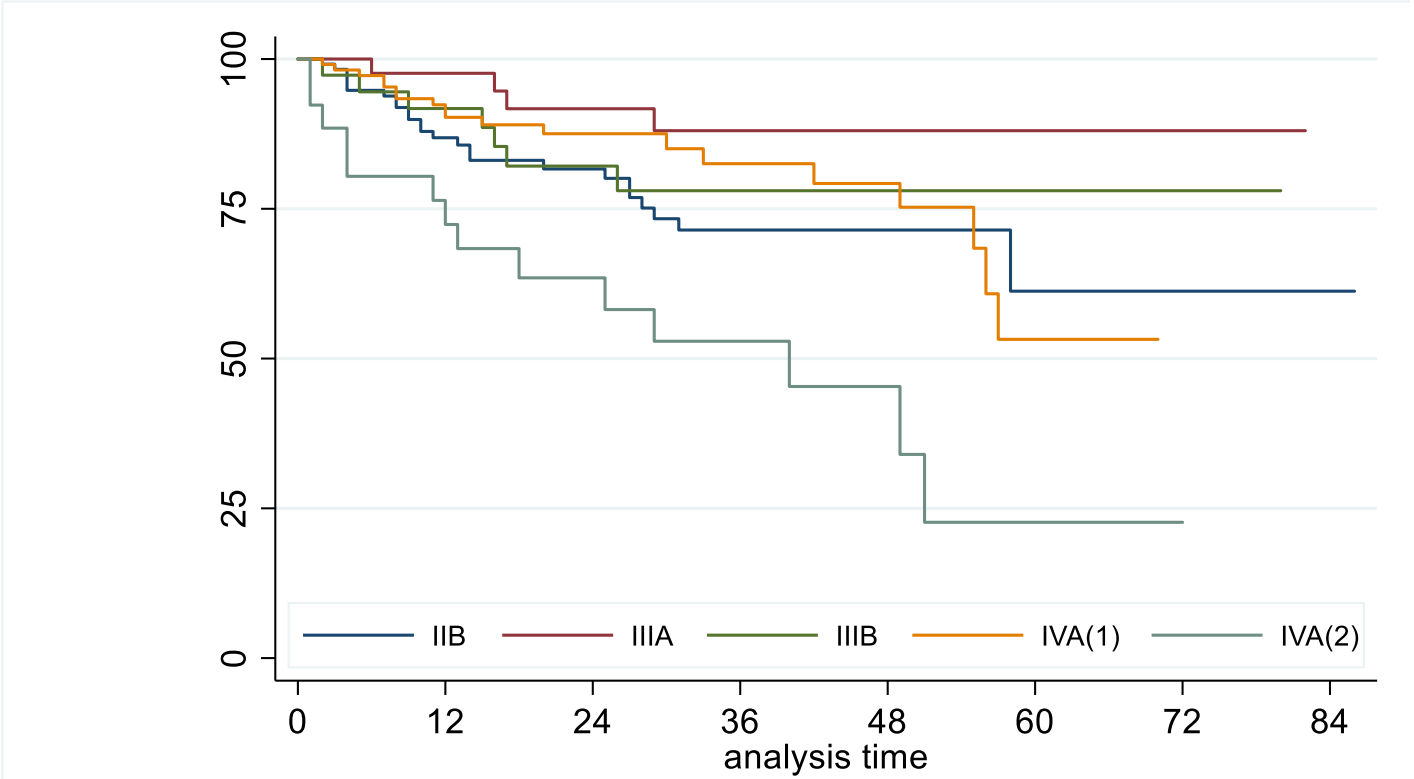
- Nx-N3
- N3
- Age >60years

Key:

Significant

Not Significant

Overall (Disease Specific survival) – Advanced Stage



Number at risk

IIB	157	78	53	31	21	10
IIIA	50	37	26	18	13	8
IIIB	50	33	21	14	6	3
IVA(1)	152	88	50	31	20	7
IVA(2)	36	19	12	10	4	1

IVA2 vs not IVA2
(Excluding IVB) p=0.002

JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

J Clin Oncology. 2015;33(32):3766-73

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

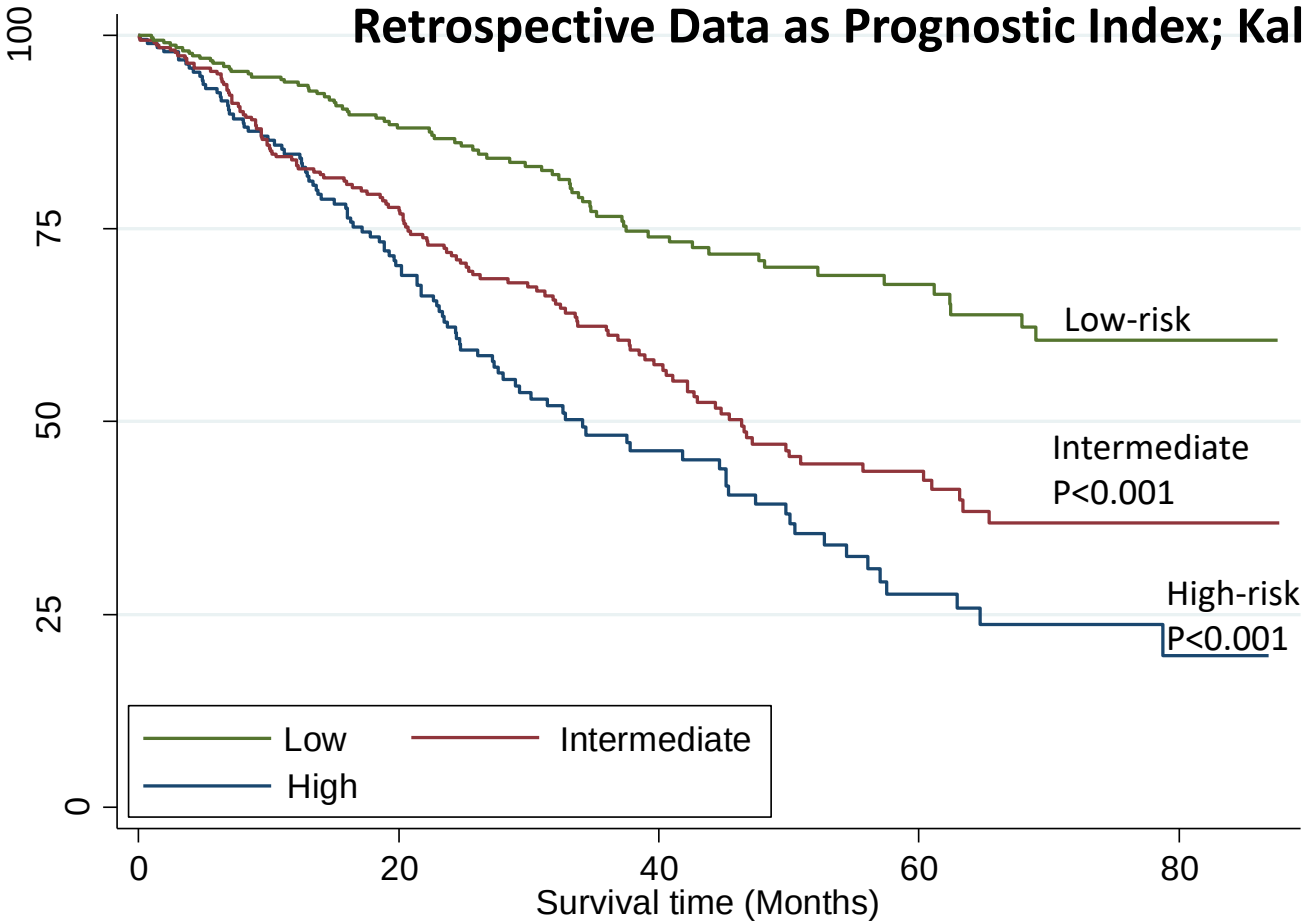
Julia J. Scarisbrick, H. Miles Prince, Maarten H. Vermeer, Pietro Quaglino, Steven Horwitz, Pierluigi Porcu, Rudolf Stadler, Gary S. Wood, Marie Beylot-Barry, Anne Pham-Ledard, Francine Foss, Michael Girardi, Martine Bagot, Laurence Michel, Maxime Battistella, Joan Guitart, Timothy M. Kuzel, Maria Estela 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 Cowan, Alain Rook, Ellen Kim, Alessandro Pileri, Annalisa Patrizi, Ramon M. Pujol, Henry Wong, Kelly Tyler, Rene Stranzenbach, Christiane Querfeld, Paolo Fava, Milena Maule, Rein Willemze, Felicity Evison, Stephen Morris, Robert Twigger, Rakhshandra Talpur, Jinah Kim, Grant Ognibene, Shufeng Li, 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

Retrospective Data as Prognostic Index

- Prognostic modelling combined these 4 factors into a prognostic index
  - Stage IV
  - Age >60 years
  - Raised LDH
  - LCT in skin
- Divides patients into risk groups for disease progression
  - Low-risk = 0-1 factors
  - Intermediate-risk = 2 factors
  - High-risk = 3-4 factors
- Separated advanced cohort into
  - **Low-risk: n = 327** (IIB n=166, III n=134, IV n=27)
  - **Intermediate-risk: n= 329** (IIB n=91, III n=82, IV n=156)
  - **High-risk: n = 201** (IIB n=20, III n=4, IV n=177)

Retrospective Data as Prognostic Index; Kalpein Meier



Excluded patients with missing age, stage, LDH and LCT from these analyses n=857 (IIB=277, III=220, IV=360)

4 Variables: age>60, LCT skin, raised LDH, stage IV

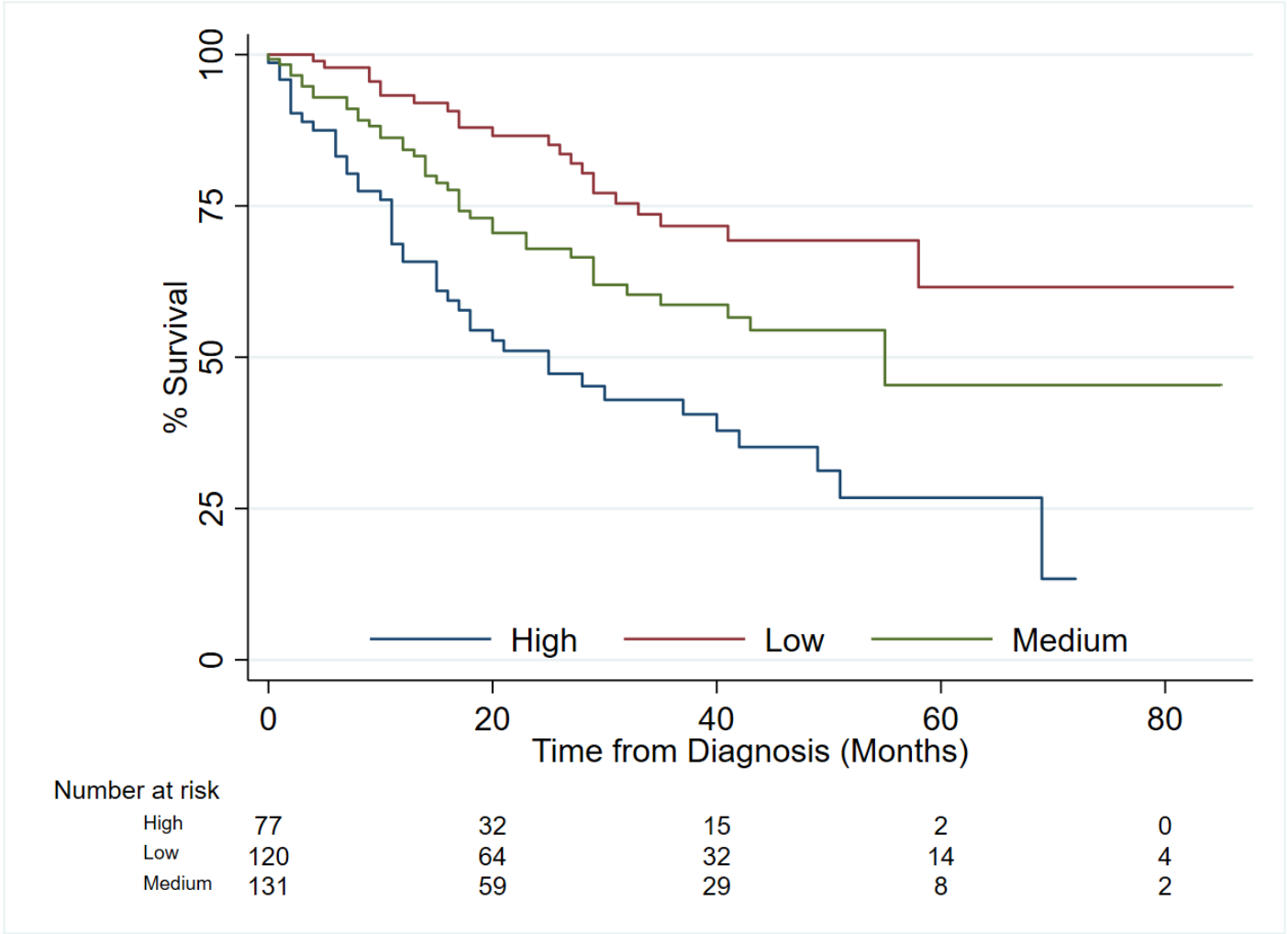
Low risk – 0-1 variable
Intermediate risk – 2 variables
High risk - 3-4 variables

Risk of poor survival (No risk factor)	N (deaths)	N IIB	N III	N IV	1-year survival	2-year survival	5-year survival	Median OS months	Hazard ratio (95% CI, p-value)
Low (0-1)	327(100)	166 (60%)	134 (61%)	27 (8%)	94%	87%	68%	NR	1
Intermediate (2)	329 (123)	91 (33%)	82 (37%)	156 (43%)	84%	72%	44%	46	2.09 (1.56, 2.80; p<0.001)
High (3-4)	201(100)	20 (7%)	4 (2%)	177 (49%)	85%	62%	27%	34	2.91 (2.15, 3.96; p<0.001)

Stratifying PROCLIPI advanced stage patients using the prognostic index developed by retro CLIC

	Number of Advanced Stage Patients	IIB	IIIA	IIIB	IVA1	IVA2	IVB
Low	120	68	20	17	11	4	0
Intermediate	131	36	16	17	46	9	7
High	77	14	1	1	39	19	3
TOTAL	328	118	37	35	96	32	10

Kaplan Meier of Survival According to CLIC Prognostic Index at Diagnosis in MF/SS from the PROCLIPI Study



Low vs high risk p<0.001

Low vs medium p=0.0157

Medium vs high risk p=0.0024

4 risk factors for survival:

1. Stage IV
2. Age >60 years
3. Raised serum LDH
4. LCT in skin










Clinical | Blood | Skin Biopsy | Lymph Nodes | Bone Marrow | Other Visceral | Clonality | Treatments | Fed Biobank | Death | Exploratory | QOL Skindex 29

Treatment

+

		Visit	Date Of Visit	Type	Reason for Stopping Therapy	Best Response	Date Started	MSWAT at Start of Treatment	Date Ended	MSWAT at End of Treatment	Other
✎	✕	1	03/10/2016	Methotrexate Low Dose < 35mg per week	Stage Progression	PD	21/10/2016	60	12/12/2016	150	
✎	✕	1	03/10/2016	Interferon alfa	Toxicity	PR	28/12/2016	150	01/11/2017	35	low lymphocytes
✎	✕	1	03/10/2016	ECP	Ongoing	SD	03/01/2017				last seen 22/6/18 - ECP ongoingTLI/ATG unrelated donor stem cell transplant with HLA-DQ mismatch, 13
✎	✕	2	24/12/2016	Oral Bexarotene	Toxicity	SD	29/05/2017	40	19/06/2017	40	
✎	✕	4	06/11/2017	Allogeneic Transplant	Treatment Course Complete	CR	07/02/2018	0	17/02/2018	0	relapse at oct 2018 skin DLI



New datasets for LCAL, CBCL

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PROCLIPI

'Working together for improved research'

"It always seems impossible until it's done" *Mandela*

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