



Webinars Cutaneous Lymphoma

EuroBloodNet  Topic on Focus

Patients' Organizations

Introduction to Cutaneous Lymphomas, other subtypes, diagnosis and staging

Speaker: Prof Antonio Cozzio

ERN-EuroBloodNet member

Dept Dermatology KSSG, St. Gallen

ERN-EuroBloodNet subnetwork Lymphoid

St. Gallen - Switzerland

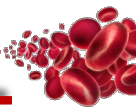
28 June, 2021

Speaker: Susan Thornton

CL Patient Representative

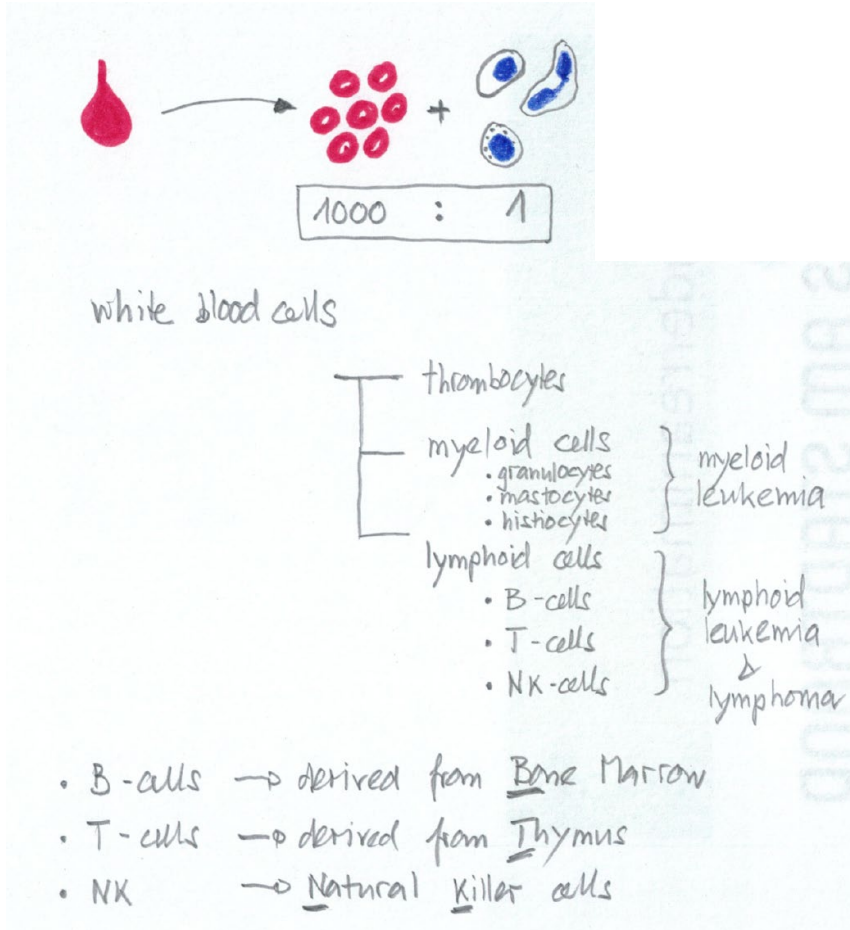
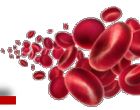
31st May 2021

What we will be discussing today



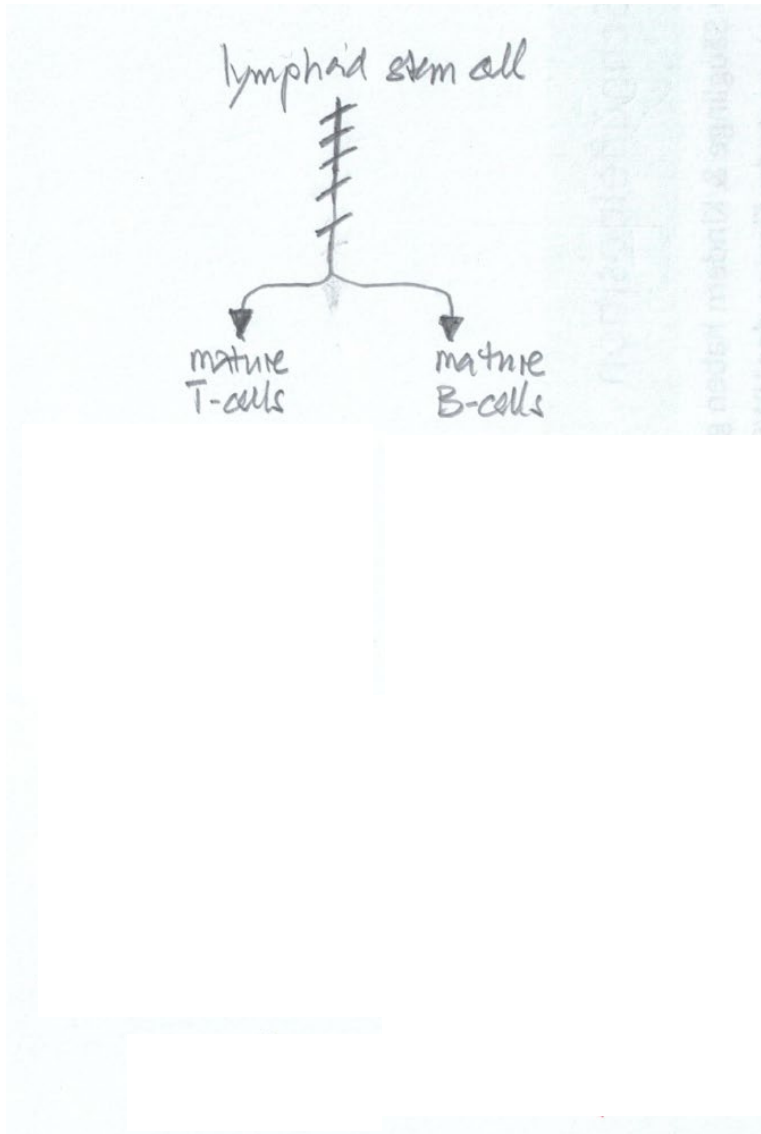
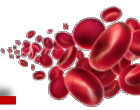
- Lymphoma introduction and overview
- Two types of skin T-cell lymphoma
 - Lymphomatoid papulosis (LyP)
 - CD30+ anaplastic large T-cell lymphoma (ALCL)
- Three types of skin B-cell lymphoma
 - Primary cutaneous marginal zone lymphoma (pcMZL)
 - Primary cutaneous follicle center lymphoma (pcFCL)
 - Primary cut. Diffuse large B-cell lymphoma (pcDLBCL)
- Open discussion

Lymphoma – leukemia - lymphocytes???



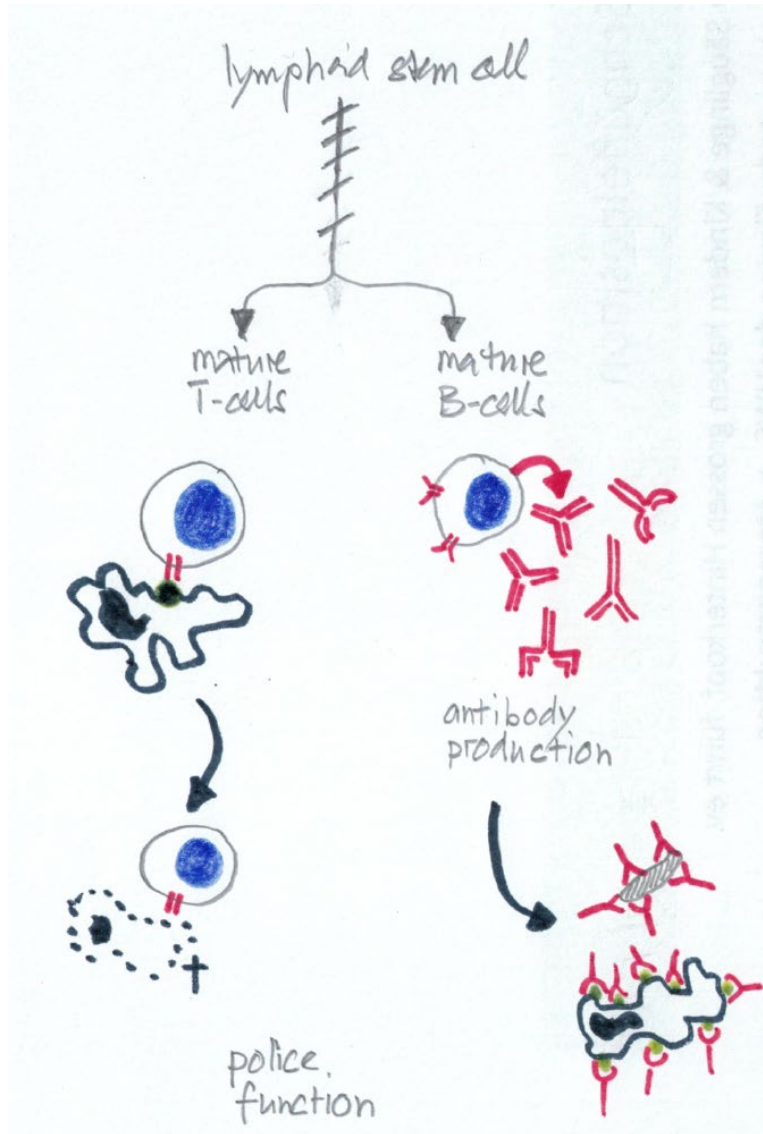
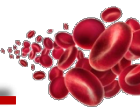
- Lymph-**oma**: cancer of lymphocytes in a solid, 3D form
- Leukemia: cancer of blood cells (lymphoid or myeloid), cells in the blood system
- CL: Lymphoma, originating in the skin
 - CTCL: cutaneous T-cell lymphoma
 - CBCL: cutaneous B-cell lymphoma

T- cells and B-cells



- Lymphoma is a cancer of the immune system cells
 - T- cell lymphoma
 - B- cell lymphoma
 - (NK cell lymphoma)
- Hence, advanced stages of CL can lead to a dysfunctional immune defense
 - Infections are a common problem in advanced CL
- On the other hand: infections may also trigger CL!

T- cells and B-cells



- Lymphoma is a cancer of the immune system cells
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- Hence, advanced stages of CL can lead to a dysfunctional immune defense
 - Infections are a common problem in advanced CL
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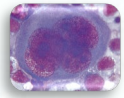
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What is nodal and extranodal lymphoma??

What is Hodgkin vs Non Hodgkin lymphoma??



"Nodal" lymphoma

Hodgkin lymphoma

+
Non-Hodgkin lymphoma



"Extranodal" lymphoma

- 1) GUT
- 2) SKIN
- 3) any organ!

Non-Hodgkin-lymphoma

- Since T-/B-cells are police cells, they can traffic in virtually any organs of the body
- Virtually any organ can start a lymphoma
- Skin lymphoma are the second most frequent



European
Reference
Network

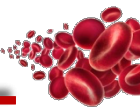
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**Table 1. 2016 WHO classification of mature lymphoid, histiocytic, and dendritic neoplasms**

Mature B-cell neoplasms
Chronic lymphocytic leukemia/small lymphocytic lymphoma
Monoclonal B-cell lymphocytosis*
B-cell prolymphocytic leukemia
Splenic marginal zone lymphoma
Hairy cell leukemia
Splenic B-cell lymphoma/leukemia, unclassifiable
Splenic diffuse red pulp small B-cell lymphoma
Hairy cell leukemia-variant
Lymphoplasmacytic lymphoma
Waldenström macroglobulinemia
Monoclonal gammopathy of undetermined significance (MGUS), IgM*
μ heavy-chain disease
γ heavy-chain disease
α heavy-chain disease
Monoclonal gammopathy of undetermined significance (MGUS), IgG/A*
Plasma cell myeloma
Solitary plasmacytoma of bone
Extraosseous plasmacytoma
Monoclonal immunoglobulin deposition diseases*
Extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue (MALT lymphoma)
Nodal marginal zone lymphoma
Pediatric nodal marginal zone lymphoma
Follicular lymphoma
In situ follicular neoplasia*
Duodenal-type follicular lymphoma*
Pediatric-type follicular lymphoma*
Large B-cell lymphoma with <i>IRF4</i> rearrangement
Primary cutaneous follicle center lymphoma
Mantle cell lymphoma
In situ mantle cell neoplasia*
Diffuse large B-cell lymphoma (DLBCL), NOS
Germinal center B-cell type*
Activated B-cell type*
T-cell/histiocyte-rich large B-cell lymphoma
Primary DLBCL of the central nervous system (CNS)
Primary cutaneous DLBCL, leg type
EBV* DLBCL, NOS*
EBV* mucocutaneous ulcer*
DLBCL associated with chronic inflammation
Lymphomatoid granulomatosis
Primary mediastinal (thymic) large B-cell lymphoma
Intravascular large B-cell lymphoma
ALK* large B-cell lymphoma
Plasmablastic lymphoma
Primary effusion lymphoma
<i>HHV8</i> * DLBCL, NOS*
Burkitt lymphoma
Burkitt-like lymphoma with <i>11q</i> aberration*
High-grade B-cell lymphoma, with <i>MYC</i> and <i>BCL2</i> and/or <i>BCL6</i> rearrangements*
High-grade B-cell lymphoma, NOS*
B-cell lymphoma, unclassifiable, with features intermediate between DLBCL and classical Hodgkin lymphoma
Mature T and NK neoplasms
T-cell prolymphocytic leukemia
T-cell large granular lymphocytic leukemia
Chronic lymphoproliferative disorder of NK cells
Aggressive NK-cell leukemia
Systemic EBV* T-cell lymphoma of childhood*
Hydroa vacciniforme-like lymphoproliferative disorder*
Adult T-cell leukemia/lymphoma
Extranodal NK-T-cell lymphoma, nasal type
Enteropathy-associated T-cell lymphoma

Table 1. (continued)

Monomorphic epitheliotropic intestinal T-cell lymphoma*
Indolent T-cell lymphoproliferative disorder of the GI tract*
Hepatosplenic T-cell lymphoma
Subcutaneous panniculitis-like T-cell lymphoma
Mycosis fungoides
Sézary syndrome
Primary cutaneous CD30* T-cell lymphoproliferative disorders
Lymphomatoid papulosis
Primary cutaneous anaplastic large cell lymphoma
Primary cutaneous γδ T-cell lymphoma
Primary cutaneous CD8* aggressive epidermotropic cytotoxic T-cell lymphoma
Primary cutaneous acral CD8* T-cell lymphoma*
Primary cutaneous CD4* small/medium T-cell lymphoproliferative disorder*
Peripheral T-cell lymphoma, NOS
Angioimmunoblastic T-cell lymphoma
Follicular T-cell lymphoma*
Nodal peripheral T-cell lymphoma with <i>TFH</i> phenotype*
Anaplastic large-cell lymphoma, ALK*
Anaplastic large-cell lymphoma, ALK**
Breast implant-associated anaplastic large-cell lymphoma*
Hodgkin lymphoma
Nodular lymphocyte predominant Hodgkin lymphoma
Classical Hodgkin lymphoma
Nodular sclerosis classical Hodgkin lymphoma
Lymphocyte-rich classical Hodgkin lymphoma
Mixed cellularity classical Hodgkin lymphoma
Lymphocyte-depleted classical Hodgkin lymphoma
Posttransplant lymphoproliferative disorders (PTLD)
Plasmacytic hyperplasia PTLD
Infectious mononucleosis PTLD
Floral follicular hyperplasia PTLD*
Polyomorphic PTLD
Monomorphic PTLD (B- and T-/NK-cell types)
Classical Hodgkin lymphoma PTLD
Histiocytic and dendritic cell neoplasms
Histiocytic sarcoma
Langerhans cell histiocytosis
Langerhans cell sarcoma
Indeterminate dendritic cell tumor
Interdigitating dendritic cell sarcoma
Follicular dendritic cell sarcoma
Fibroblastic reticular cell tumor
Disseminated juvenile xanthogranuloma
Erdheim-Chester disease*

Provisional entities are listed in italics.
*Changes from the 2008 classification.

small population, but in others associated with a lymphocytosis.⁴ Whereas in 2008 it was unknown whether MBL was a precursor of CLL, we now know that MBL precedes virtually all cases of CLL/small lymphocytic lymphoma (SLL).⁵ The updated WHO will retain the current criteria for MBL, but will emphasize that “low-count” MBL, defined as a PB CLL count of $<0.5 \times 10^9/L$, must be distinguished from “high-count” MBL because low count MBL has significant differences from CLL, an extremely limited, if any, chance of progression, and, until new evidence is provided, does not require routine follow-up outside of standard medical care.^{6,7} In contrast, high-count MBL requires routine/regular follow-up, and has very similar phenotypic and genetic/molecular features as Rai stage 0 CLL, although immunoglobulin heavy chain variable region (IGHV)-mutated cases are more frequent in MBL.⁸ Also impacting our diagnostic criteria, the revision will eliminate the option to diagnose CLL with $<5 \times 10^9/L$ PB CLL cells in the absence of extramedullary

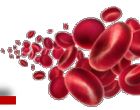
- The classification of lymphoma is a science for itself!
- Confusing also for doctors not active in the field
- Even lymphoma with similar names, but arising in different organs may behave totally different
- Existence of many subtypes of T-/B-cells may explain, why there is such a wealth of different lymphoma types!

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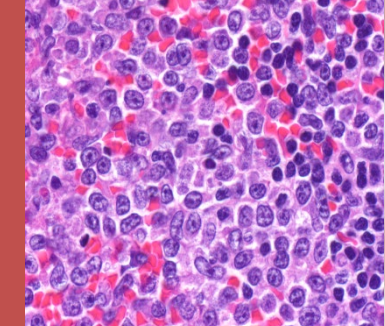
Cutaneous lymphoma current classification

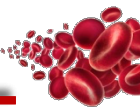


WHO-EORTC Classification 2018	Frequency, %*	5-y DSS, %*
CTCL		
MF	39	88
MF variants		
Folliculotropic MF	5	75
Pagetoid reticulosis	<1	100
Granulomatous slack skin	<1	100
SS	2	36
Adult T-cell leukemia/lymphoma	<1	NDA
Primary cutaneous CD30 ⁺ LPDs		
C-ALCL	8	95
LyP	12	99
Subcutaneous panniculitis-like 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
PCDLBCL, LT	4	56
EBV ⁺ mucocutaneous ulcer (provisional)	<1	100
Intravascular large B-cell lymphoma	<1	72



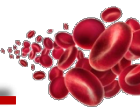
Within the group of CTCL, the clinical appearance is often suggestive for the diagnosis. The clinical picture is extremely important to allow for a concise diagnosis and thus correct treatment.





Q&A

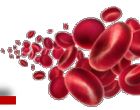
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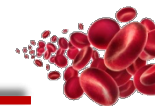
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8 ~20%
12

Lymphomatoid papulosis – small papules



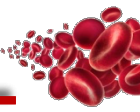
Lymphomatoid papulosis – solitary or multiple lesions



- No itch, no pain
- Waxing and waning of lesions
- Pigmented or white small scars
- Chronic disease

- Long term prognosis excellent, but risk for other lymphoma is increased

Lymphomatoid papulosis – 5 YRS >98%



Careful → increased risk for other lymphoma types



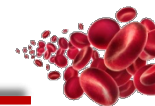
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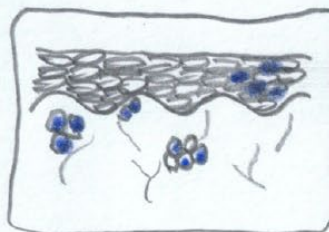
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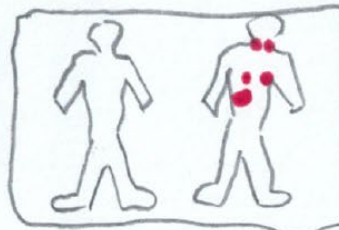
Diagnostic steps for LyP/ALCL



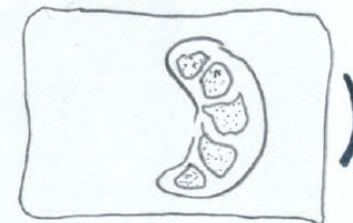
Skin → Biopsy



Organs & lymph nodes → Imaging

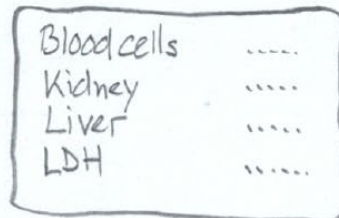


lymph node excision / organ biopsy

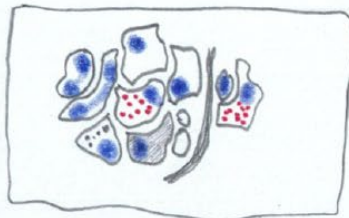


Rarely necessary!

Blood → Test



Bone marrow → Puncture



not necessary!



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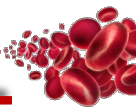
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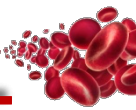
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Anaplastic large cell lymphoma (pcALCL)



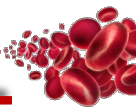
- If originating in skin → very good prognosis
- 5 YRS 95%
- Check for dissemination!

Anaplastic large cell lymphoma (pcALCL)

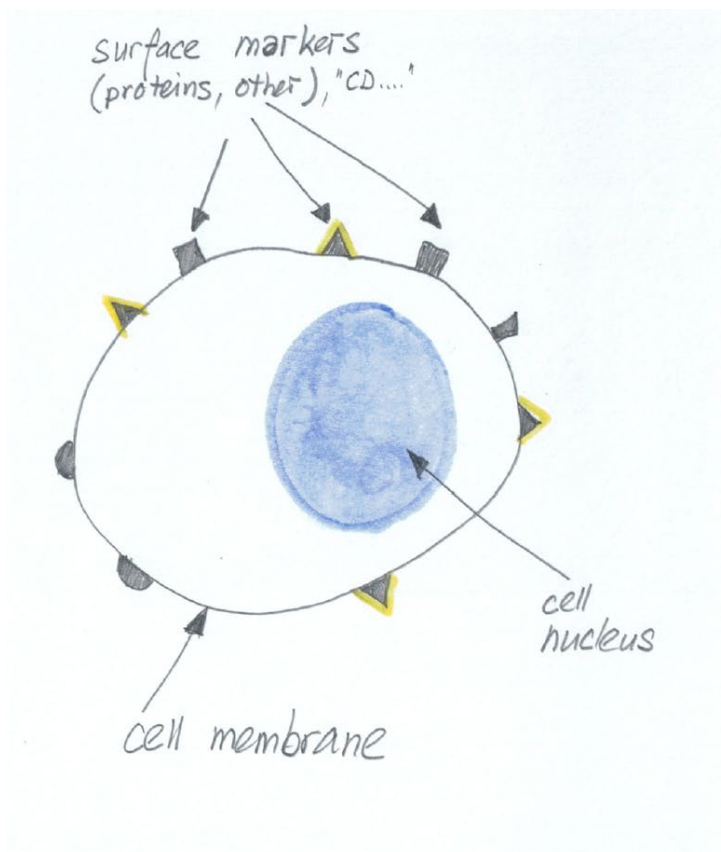


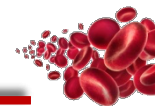
- 30 yr old,
- CD30+ ALCL
- Staging negative
- Excision/Radiotherapy

Skin analysis - Immunohistology

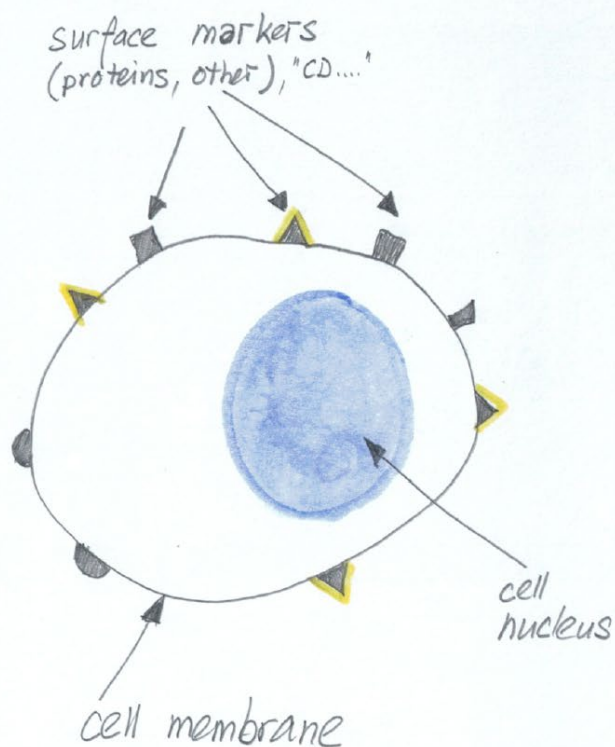


- CD30 is a useful marker for LyP and ALCL





- CD30 is a useful marker for LyP and ALCL



Important question:
Is there a marker
unique for the
specific lymphoma type?

- Diagnosis
- Therapy



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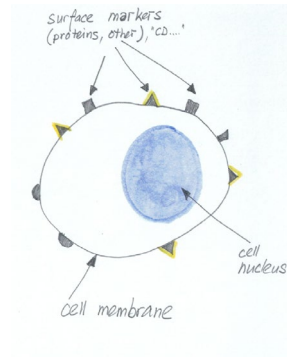
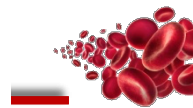
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Targeting a tumor cell surface molecule

Anti-CD30-antibody: Brentuximab



Antibody

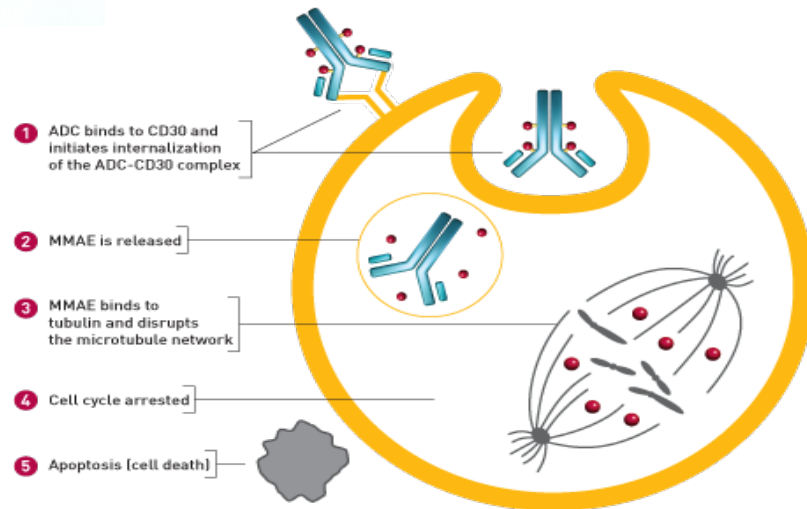
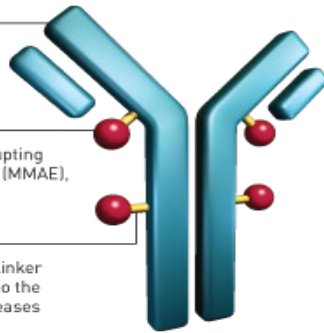
The antibody, brentuximab, specific for CD30¹

Cytotoxic agent

The synthetic microtubule-disrupting agent, monomethyl auristatin E (MMAE), that induces target cell death¹

Linker

A synthetic protease-cleavable linker that covalently attaches MMAE to the CD30-directed antibody and releases the agent within the target cell¹



<http://www.adcetris.com/hcp/>



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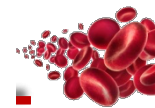
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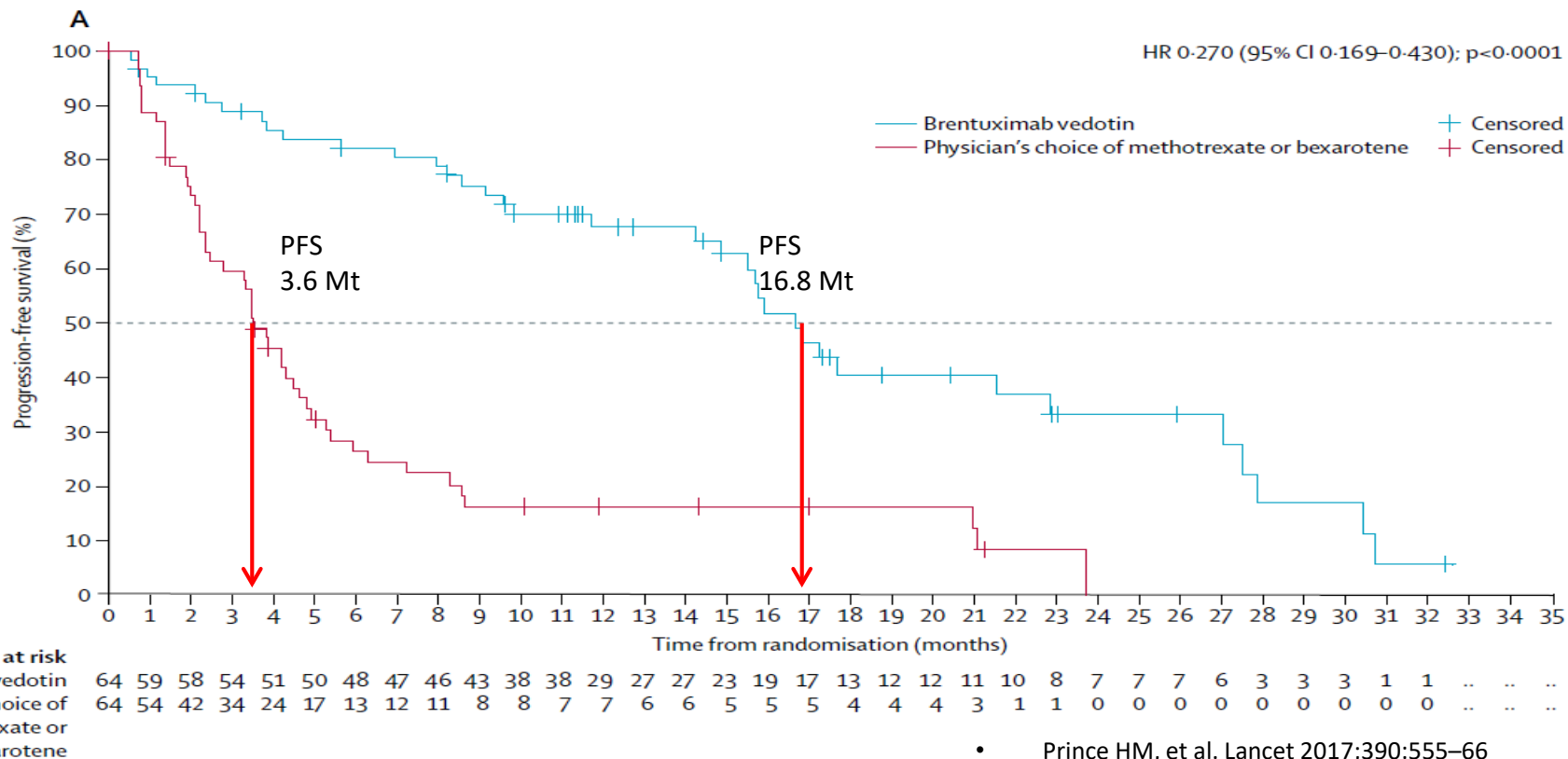
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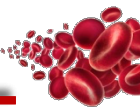
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Brentuximab significantly better than the former gold standard (MTX/Bexarotene)

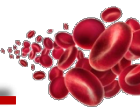


- Prince HM, et al. Lancet 2017;390:555–66



Q&A

Cutaneous lymphoma current classification



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CTCL		
MF	39	88
MF variants		
Folliculotropic		
Pagetoid reticuloid		
Granulomatous		
SS		
Adult T-cell leukemia/lymphoma		
Primary cutaneous T-cell lymphomas		
C-ALCL		
LyP		
Subcutaneous panniculitis-like lymphomas		
Extranodal marginal zone B-cell lymphoma of the skin		pcMZL
Follicle center lymphoma of the skin		pcFCL
Diffuse large B cell lymphoma of the skin		pcDLBCL
All very rare tumours, approx. 1:200'000/year		
Primary cutaneous CD8+ peripheral T-cell lymphoma (provisional)	<1	100
Primary cutaneous peripheral T-cell lymphoma, NOS	2	15
CBCL		
PCMZL	9	99
PCFCL	12	95
PCDLBCL, LT	4	56
EBV+ mucocutaneous ulcer (provisional)	<1	100
Intravascular large B-cell lymphoma	<1	72

Marginal zone lymphoma of the skin

pcMZL

Follicle center lymphoma of the skin

pcFCL

Diffuse large B cell lymphoma of the skin

pcDLBCL

All very rare tumours, approx. 1:200'000/year

9

99

12

~25%

95

4

56

<1

100

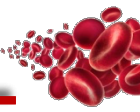
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72



Within the group of CBCL, the diseases often have similar clinical appearances despite significant differences in prognosis.



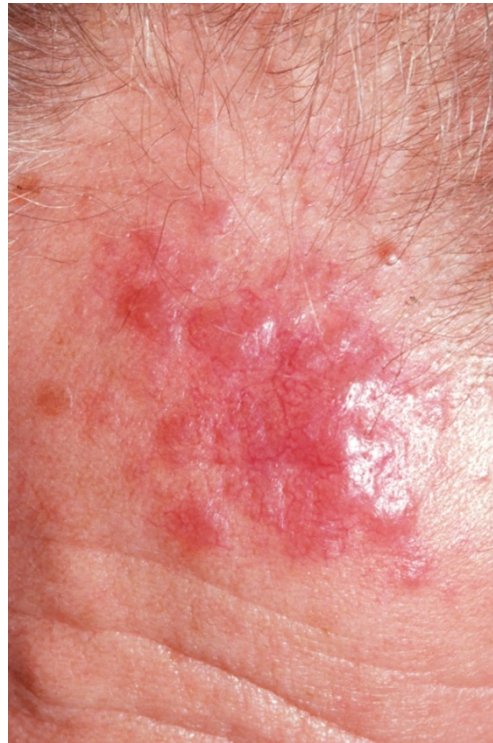


Marginal zone lymphoma



39 yrs

Follicle center lymphoma



59 yrs

Diffuse large B-cell lymphoma



78 yrs



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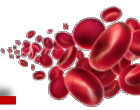
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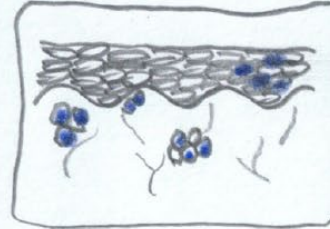
Golling et al., Leuk&Lymphoma, 2008;49:1094

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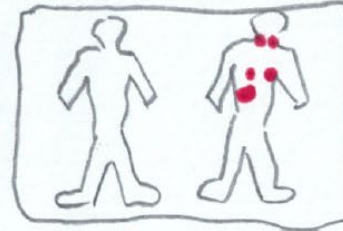
Diagnostic steps for cutaneous B-cell lymphoma



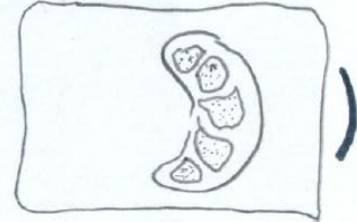
Skin → Biopsy



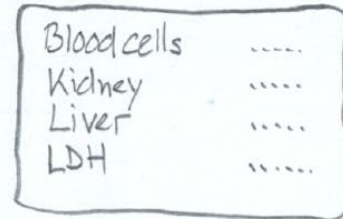
Organs & lymph nodes → Imaging



lymph node excision / organ biopsy



Blood → Test

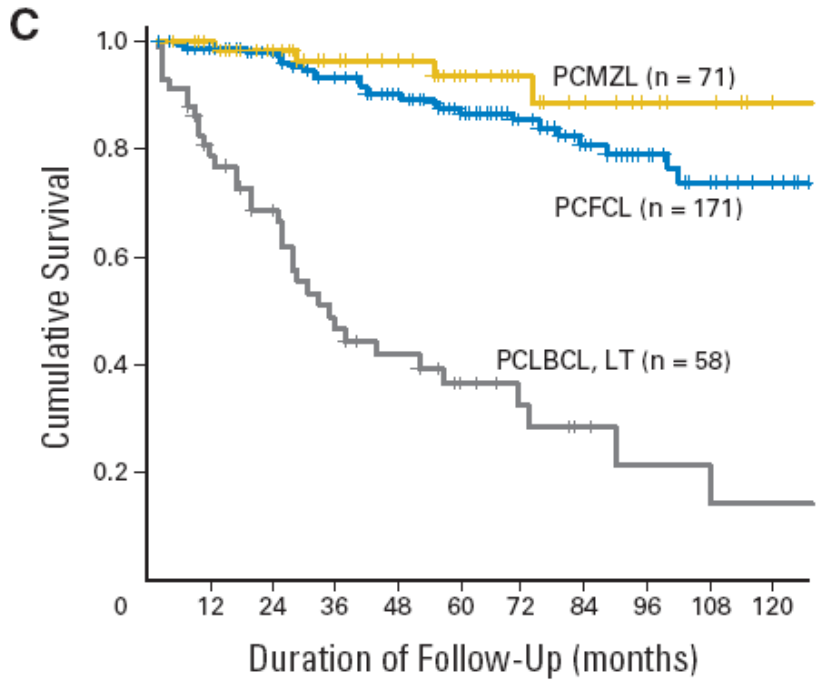
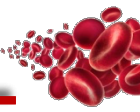


Immunoglobulin

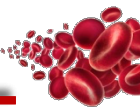
Bone marrow → Puncture



For some pcFCL and mainly pcDLBCL

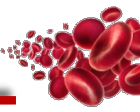


- pc Marginal zone lymphoma and pc Follicle center lymphoma both have an excellent prognosis
- It is very important to differentiate these two from pc diffuse large B-cell lymphoma (worse prognosis, more intense therapy)



Indolent or aggressive B-cell lymphoma type?

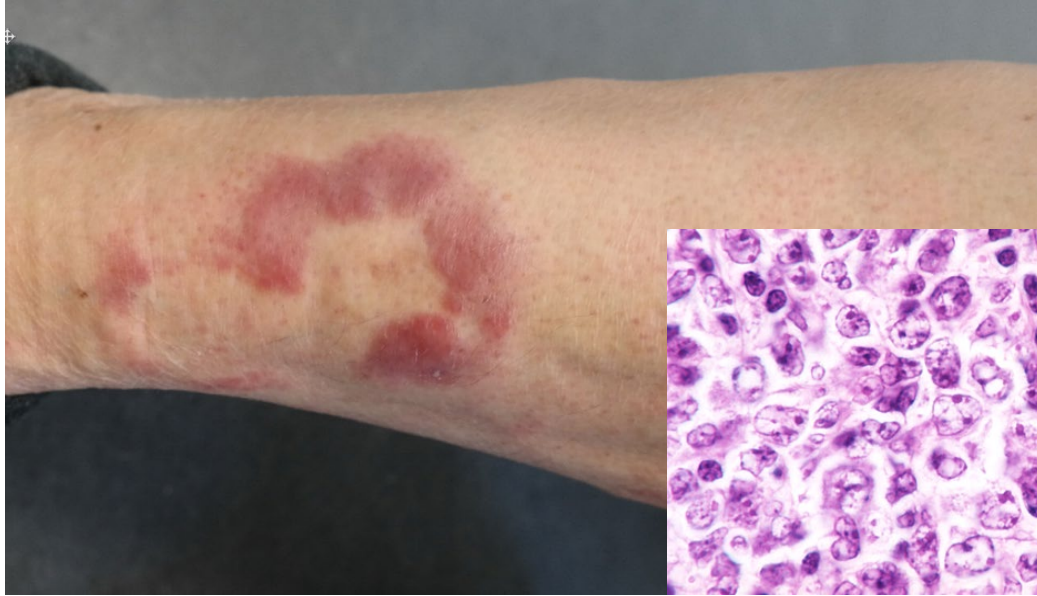
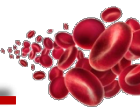




shark



Dolphin



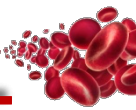
Diffuse large B cell lymphoma

+	Bcl-2	-
(+)	Bcl-6	+
+	MUM-1	-
+	CD20/79	+



Follicle center lymphoma

Treatment & Follow-up



- For discussed CTCL: **LyP and ALCL**
 - Skin-directed therapies:
 - UV-light, topical steroids, surgery, radiotherapy
 - Ev. MTX, Brentuximab in rare occasions
 - Clinical follow-up according to activity
 - No imaging if no skin symptoms, no B-symptoms

- For discussed CBCL: **pcMZL and pcFZL**
 - Skin-directed therapies:
 - Surgery, wait&watch, corticosteroids, radiotherapy
 - Clinical follow-up according to activity
 - No imaging if no skin symptoms, no B-symptoms

- For discussed CBCL: **pcDLBCL**
 - Chemo-/immunotherapy
 - Clinical trials





Thank you for your attention!



Webinars Cutaneous Lymphoma

EuroBloodNet  Topic on Focus

Patients' Organizations

Introduction to Cutaneous Lymphomas, other subtypes, diagnosis and staging

Speaker: Prof Antonio Cozzio

**Chairman, Department of Dermatology, Venerology
and Allergology
Kantonsspital
St. Gallen, Switzerland
28th June 2021**

Speaker: Susan Thornton

**CL Patient Representative
Cutaneous Lymphoma Foundation
Birmingham, Michigan, USA
28th June 2021**



Co-funded by
the Health Programme
of the European Union


**LYMPHOMA
COALITION** 

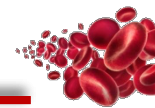
 **CUTANEOUS
LYMPHOMA
FOUNDATION**



 **EURORDIS**
RARE DISEASES EUROPE



**European
Reference
Network**
for rare or low prevalence
complex diseases
 **Network**
Hematological
Diseases (ERN EuroBloodNet)



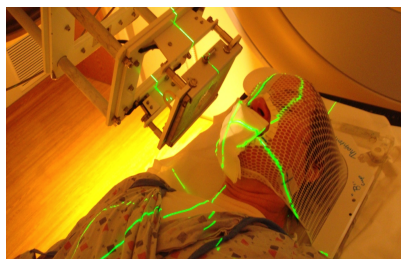
Stages of My Journey (so far...)



Wake-up Call

Diagnosis
MF Stage IA

1991



Aggressive
Tumor Stage
MF

1997-98

Life/Death Disease

Gratitude & Challenge

Remedial
Treatment

2001-2010

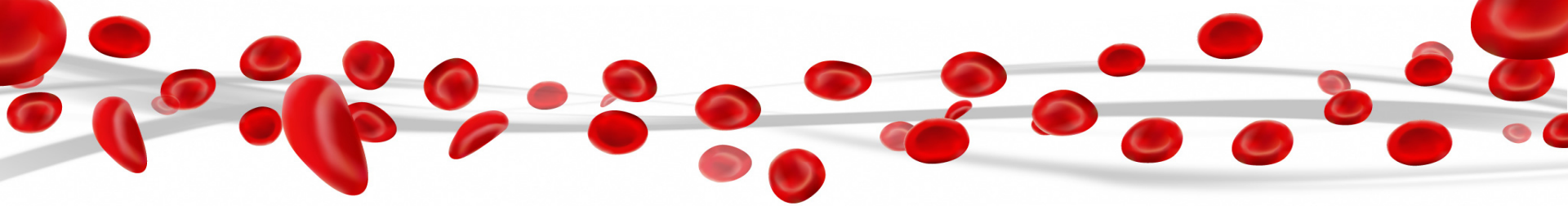


Maintenance
MF Stage IIB

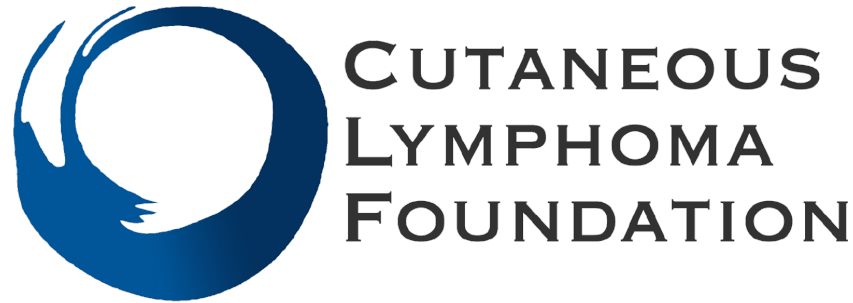
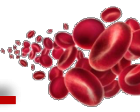
2011...

Share, Serve & Give
Back





Discussion



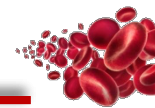
Making sure each person with cutaneous lymphoma gets the best care possible.



Webinars
Cutaneous Lymphoma

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Patients' Organizations



Cutaneous Lymphoma Foundation Overview

Founded In 1998 by Three Passionate People : A Patient, Physician and Caregiver

We do this globally through:

- Live patient/caregiver education programs
- One-on-one support and personal assistance
- Online and in-print educational materials, videos and publications
- Clinical treatment center referral network
- Research support
- Awareness and advocacy initiatives

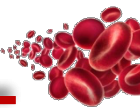


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Cutaneous Lymphoma

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The Cutaneous Lymphoma Foundation is committed to supporting promising cutaneous lymphoma research

RESEARCH



"The CLARIONS award provided a significant boost for my research at a time when I was becoming established in the CTCL field." Patrizia Fushiotti

"The CLF Catalyst Grant has given me the opportunity to accelerate my research into how our bacterial world interacts with and shapes skin lymphoma. It has helped me establish a niche in CTCL. I'm very grateful to the foundation for this award." Dr. Alan Zhou



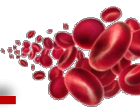
Supporting Young Investigators for over 20 years



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Cutaneous Lymphoma

EuroBloodNet Topic on Focus

Patients' Organizations



Expanding Our Research Agenda

RESEARCH AREAS OF INTEREST

Focusing on answering three critical questions posed by patients and to fund the best research projects, our team of top scientists and physicians identified 3 *pillars of research*, filling critical gaps in knowledge.

Why Did I Get Cutaneous Lymphoma?

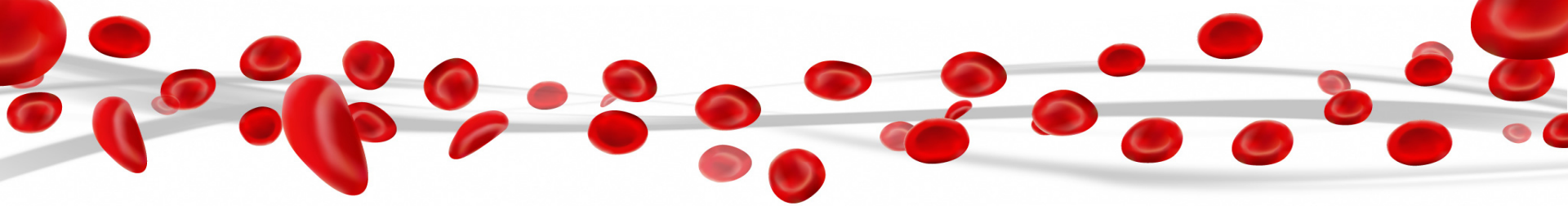
- Lymphoma cell biology
- Skin immunology
- Lymphocyte-skin interactions
- Genetic/cellular alterations
- Tumor microenvironment

What Cutaneous Lymphoma Do I Have?

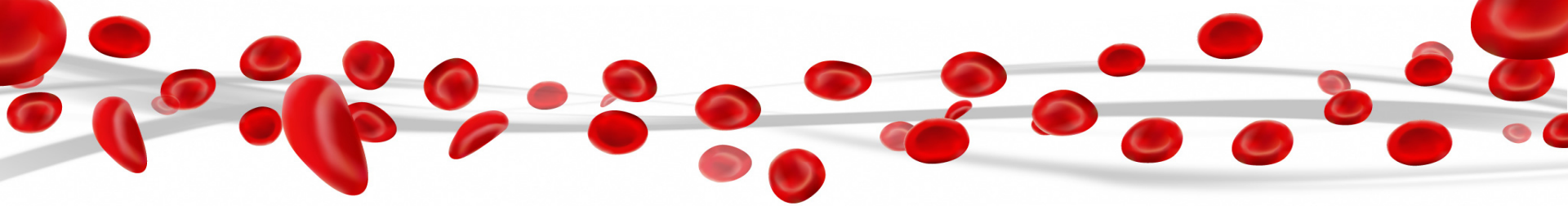
- Diagnosis & staging
- Diagnostic/prognostic biomarkers
- Risk stratification models
- Disease burden & response measures

How Do I Treat My Cutaneous Lymphoma?

- Immunotherapies/targeted drugs
- Personalized therapies
- Improve use of existing therapies
- Quality of life/quality of care
- Biology of itch
- Therapy resistance/relapse
- Population science



Discussion



Open Audience Q&A