ALMA MATER STUDIORUM
UNIVERSITÀ DI BOLOGNA
DIPARTIMENTO DI
SCIENZE MEDICHE E CHIRURGICHE

POLICLINICO DI
SANT'ORSOLA

SERVIZIO SANITARIO REGIONALE
EMILIA-ROMAGNA
Azienda Ospedaliero - Universitaria di Bologna

# Aggressive Lymphoma Workshop

Bologna, Royal Hotel Carlton

**May 8-9, 2023**

# Cutaneous T-cell Lymphoma


## Maarten Vermeer

Leiden University Medical Center


President: **Pier Luigi Zinzani**

# Disclosures

## Disclosures of Name Surname

| Company name | Research support | Employee | Consultant | Stockholder | Speakers bureau | Advisory board | Other |
|---|---|---|---|---|---|---|---|
| Kyowa | X | | | | | X | |
| Takeda | X | | | | | | |
| Recordati | X | | | | | | |
| Innate | | | | | | X | |
| Galderma | | | | | | X | |
| | | | | | | | |
| | | | | | | | |

Leiden University
Medical Center

# Aggressive Cutaneous T-cell Lymphoma

## Aggressive Lymphoma Workshop
## Bologna 9th of May

Maarten Vermeer
Dermatology

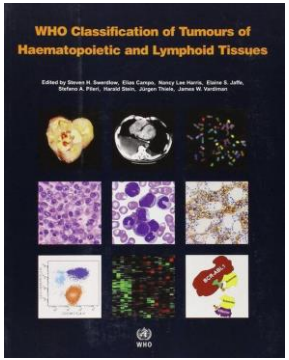
# 2022 WHO classification (revised 5th ed.)

## Cutaneous T-cell lymphomas

- **Mycosis fungoides** & variants of MF
  - Folliculotropic MF
  - Granulomatous slack skin
  - Pagetoid reticulosis
- **Sezary syndrome**
- Spectrum cutaneous CD30+ LPD
- Subcutaneous panniculitis-like T-cell lymphoma
- **Extranodal NK/T-cell lymphoma**
- **Hydroa vacciniforme-like LPD (CAEBVI)**
- Primary cutaneous peripheral T-cell lymphoma, NOS + rare subtypes
  - **- Primary cutaneous γ/δ T-cell lymphoma**
  - **- Aggressive cytotoxic epidermotropic CD8+ CTCL**
  - - Primary cutaneous CD4+ small/medium T-cell LPD
  - - Primary cutaneous acral CD8+ T-cell lymphoma

## Cutaneous B-cell lymphomas

- Primary cutaneous marginal zone lymphoma
- Primary cutaneous follicle center lymphoma
- Primary cutaneous DLBCL, leg type
- EBV-positive mucocutaneous ulcer
- Intravascular large B-cell lymphoma



**1. Skin homing memory CD4+ T-cells**

- Mycosis Fungoides
- Sezary syndrome

**2. EBV driving T-cell/NKT-cell lymphoma**

- NK/T-cell lymphoma
- Hydroa vacciniforme-like LPD

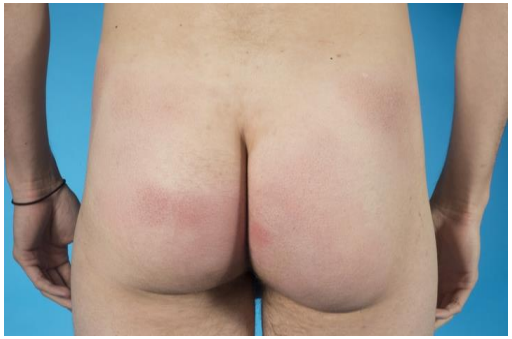
**3. Specific skin associated T-cell subsets**

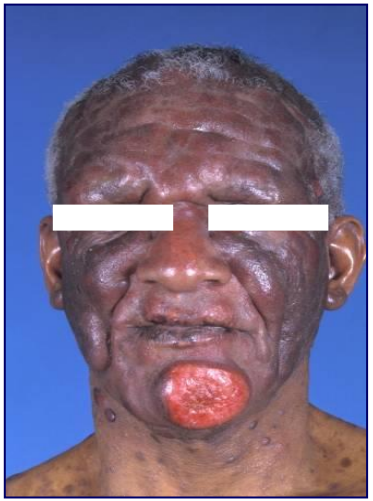
- Primary cutaneous γ/δ T-cell lymphoma
- Aggressive cytotoxic epidermotropic CD8+ CTCL

# Mycosis Fungoides

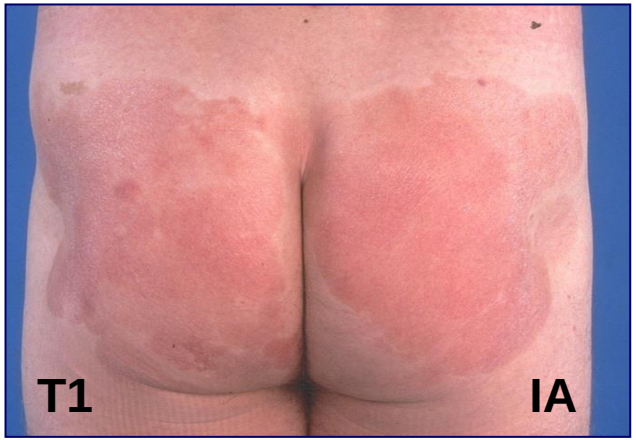
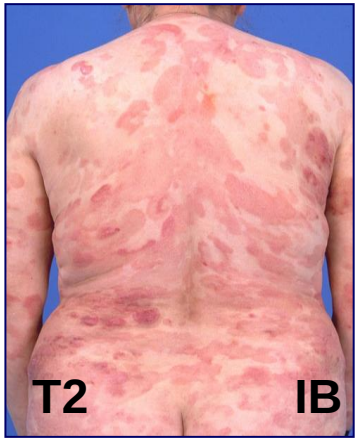
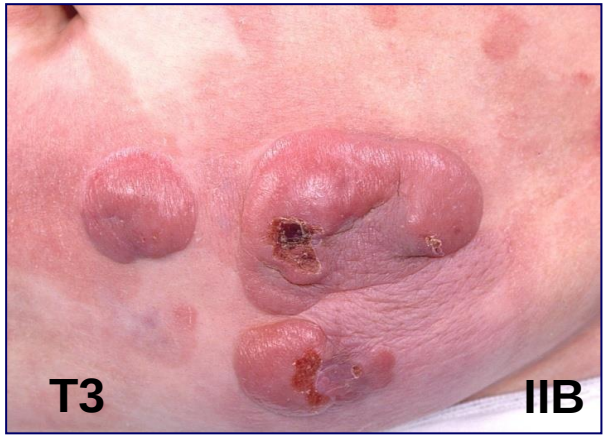
- Most common type of CTCL (ca. 50%).
- Presents later in life, 6th decade
- Indolent course (years to decades) with slow progression from patches to plaques to tumors.
- Development of nodal or visceral disease in a minority of patients.

- At present no prognostic biomarkers available

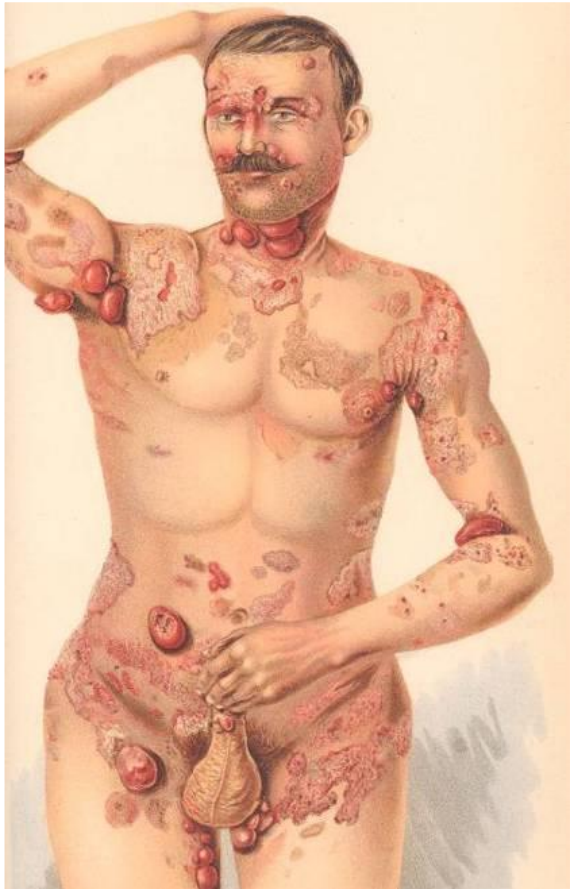


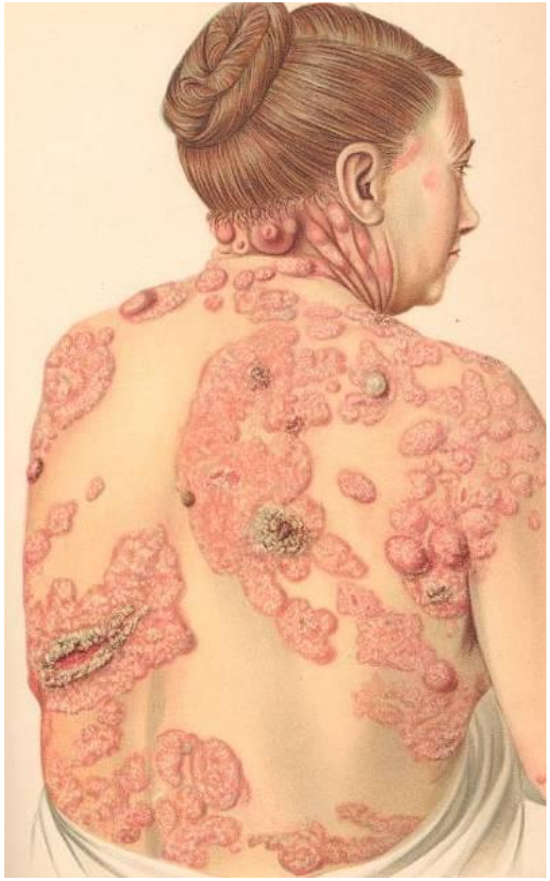


# Mycosis Fungoides

| Patches and plaques <10% of skin (T1 or IA) | Patches and plaques >10% of skin (T2 or IB) | Tumors (T3 or IIB) |
|---|---|---|
|   |   |   |
| Progression to systemic disease <5% | Progression to systemic disease 15% | Progression to systemic disease 40% |
| 10-year survival 97% | 10-year survival 83% | 10-year survival 42% |

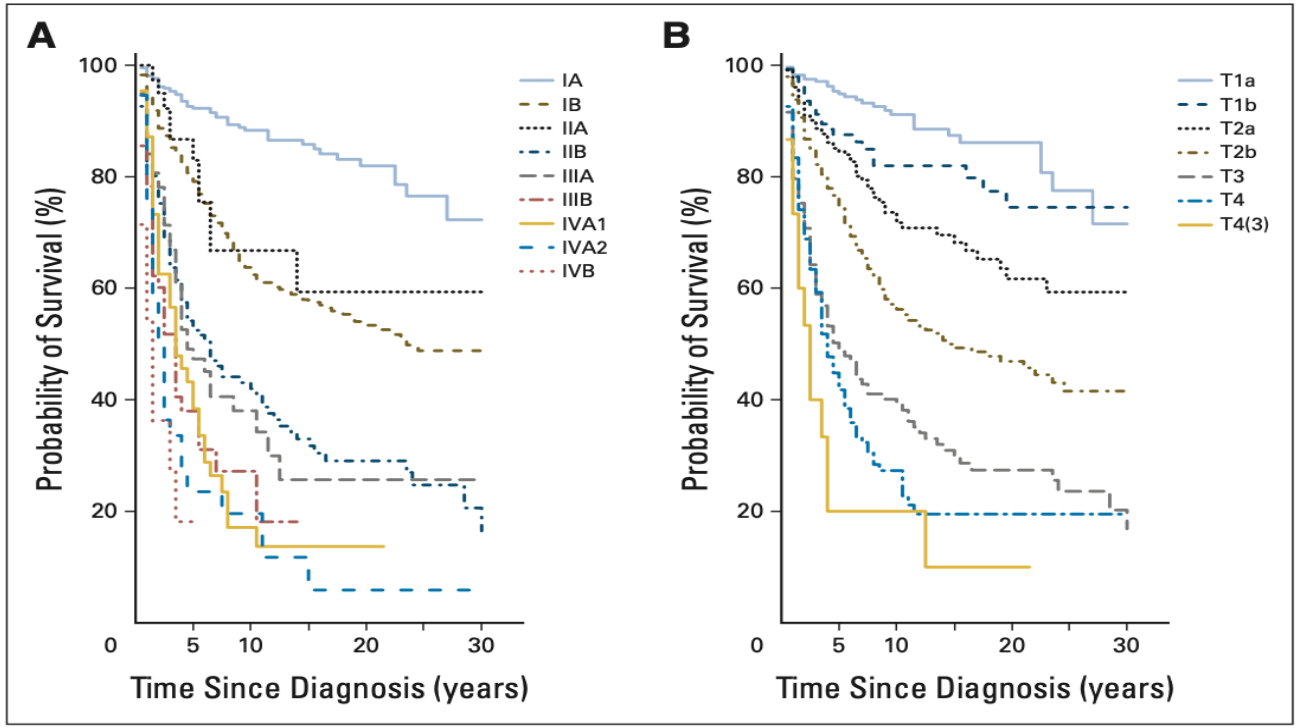
# Kaposi Handatlas der Hautkrankheiten 1899

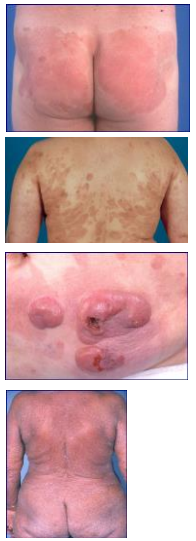




# Actuarial disease-specific survival

## Agar et al; J Clin Oncol, 2010; vDoorn Arch Dermatol 2001; Kim Arch Dermatol 2003



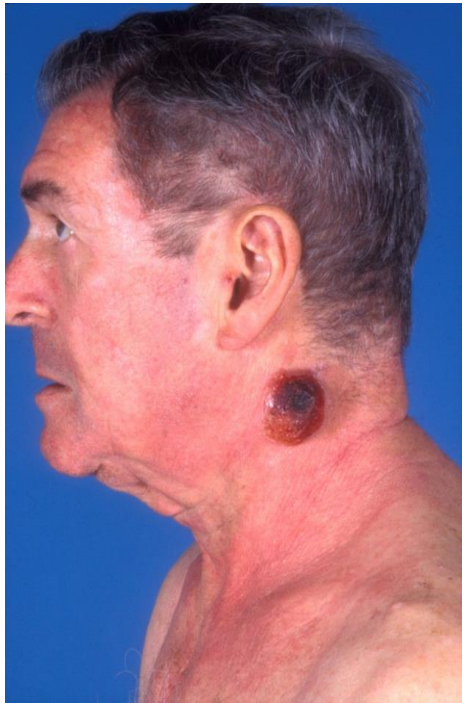
# MF IIb Tumors Radiotherapy

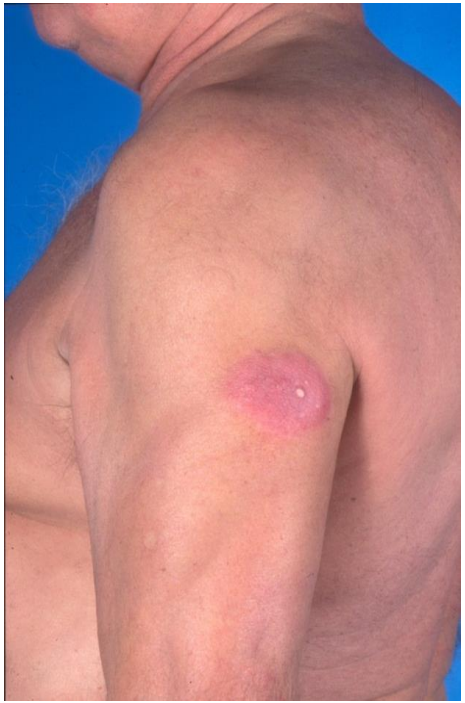
- Involved field : 8 Gy (2x4 Gy)
- Involved field relapse: 20 Gy (8x2,5 Gy)

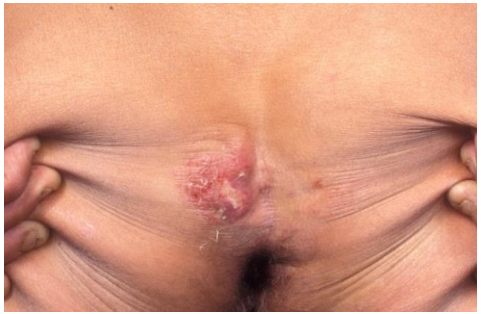
- Total Skin Electron Beam: 12 - 35 Gy (20x1,75 Gy)

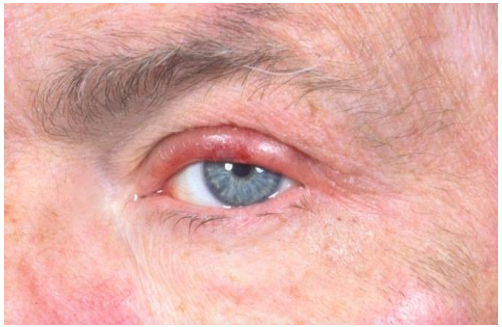
Cumulative dose of 60-80Gy is upper limit in skin because of cummulative radiotoxicity.

# MF, stage IIB



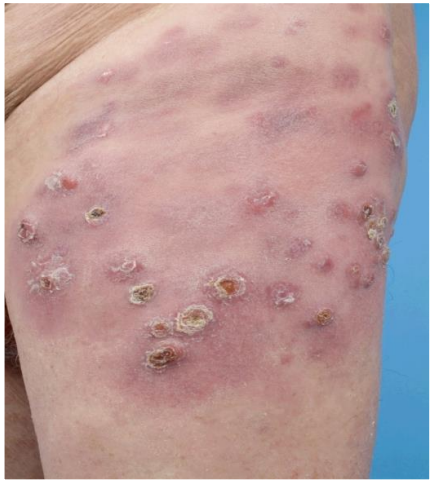


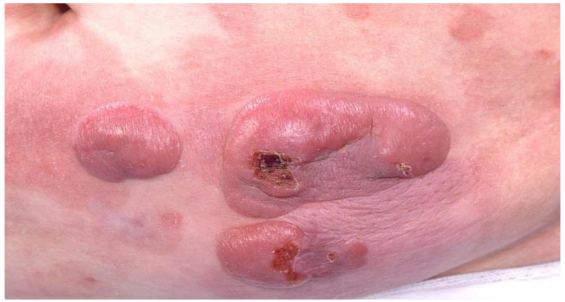


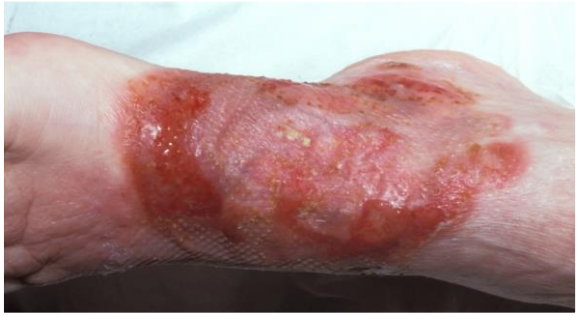


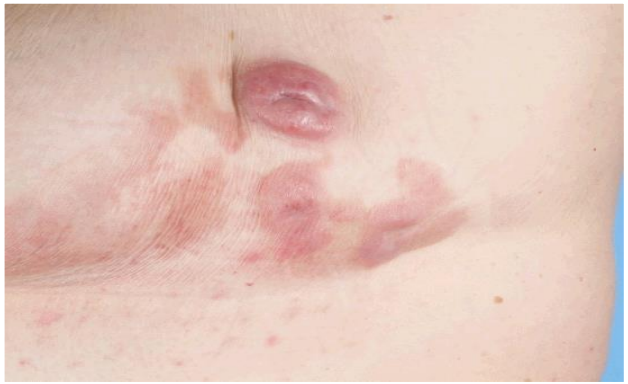
**Therapy: Low dose radiotherapy (2 x 4 Gy)**

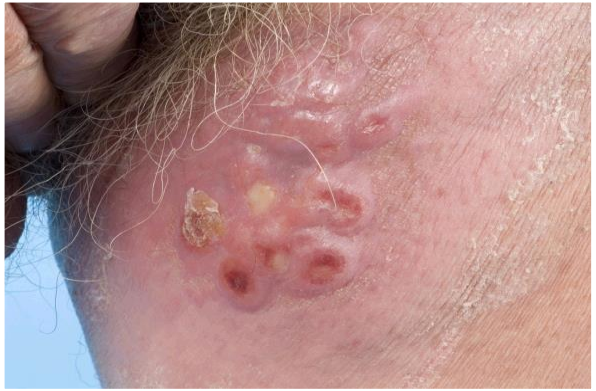
# MF tumors, stage IIB





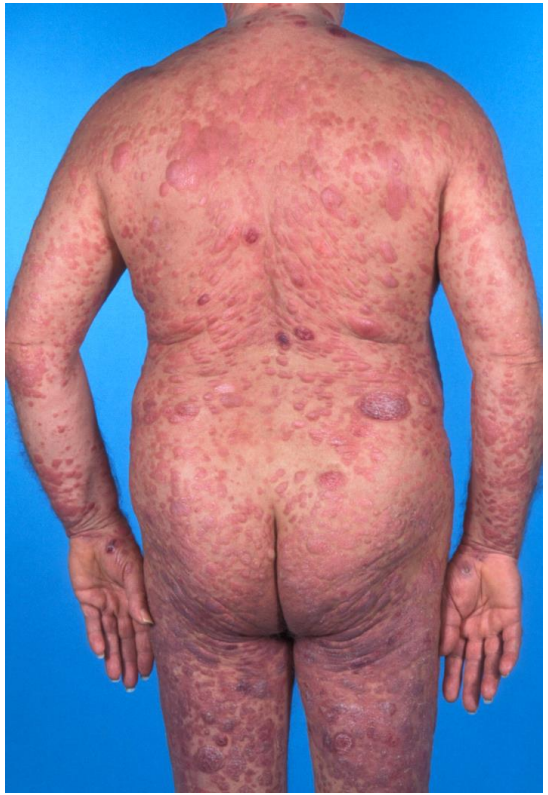


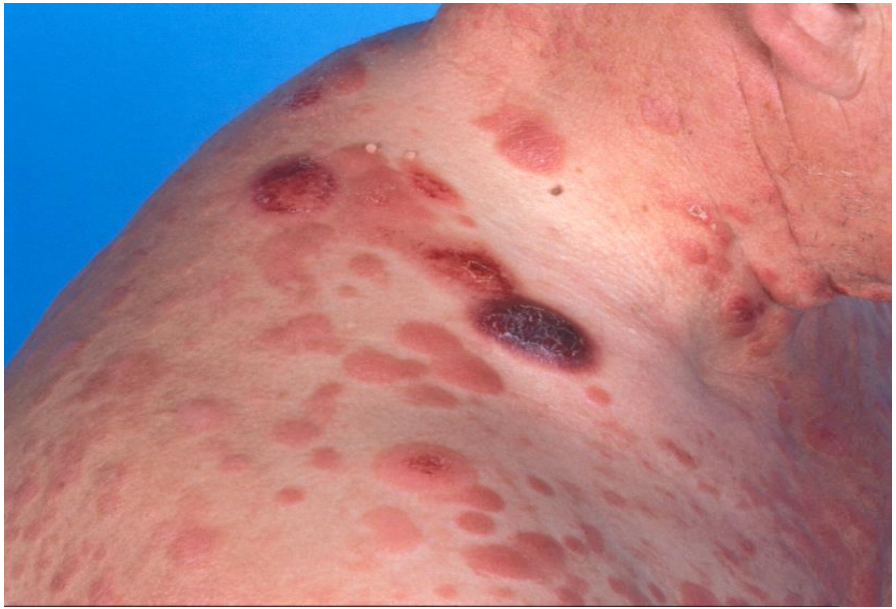




**Therapy: Low  dose radiotherapy (2 x 4 Gy)**

# MF, stage IIB





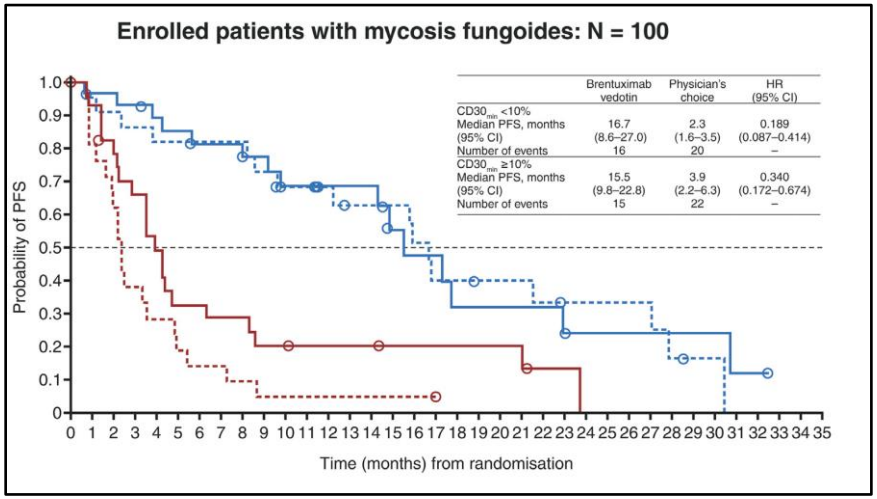
**Therapy: total skin electron beam irradiation**

# Brentuximab in MF and SS

**Cutaneous T-cell lymphoma**:

- Response in 85% of cutaneous ALCL and LyP patiënts
- Later also MF and SS

- Limitations:
  - Side effects: peripheral neuropathy
  - Number of CD30+ tumor cells needed for effective therapy is not known.
  - Variation in CD30 expression → <u>multipel samples</u>!




In MF PFS (16 months) and ORR4 (50%) greater than physician's choice.

# MF treatment ≥ stage IIB

- Around 15% of patients develop overt nodal or visceral disease
- Traditionally treated with CHOP but increasing reluctance to use because of short term effect and immunosuppression.

New therapeutic developments:

- Monochemotherapy
- Therapeutic antibodies
- New aSCT protocols.

# MF treatment ≥ stage IIB (extracutaneous disease)

- **CHOP or CHOP-like chemotherapy**
- **Mono chemotherapy**
  - Liposomal doxorubicin
  - Gemcitabin
  - Praletrexate
  - Pentostatin
- **Antibodies**
  - Mogamulizumab (anti-CCR4)
  - Brentuximab (anti-CD30)
  - Alemtuzumab (anti-CD52)
- **Stem cell transplantation (SCT)**
  - Allogeneic SCT

**HDACi**

- Vorinostat, Resminostat

**Novel treatment approaches**

- JAK/STAT inhibitor (Cerdulatinib)
- Anti miR155 (Cobomarsen)
- Anti CS158k (IPH4102)
- Checkpoint inhibitors:
  - PD1 (Pembrolizumab, Nivolumab)
  - PD-L1 (durvalumab, atezolizumab)

Optimal place and combinations are still to be defined.

# Sézary Syndrome (SS)

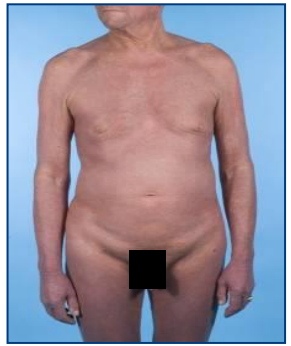
Rare and aggressive cutaneous T cell lymphoma (CTCL)

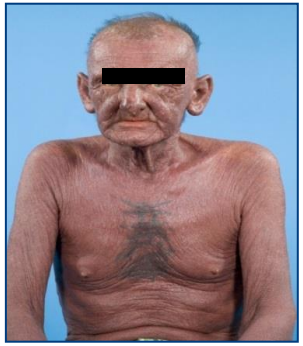
- CD4+, skin-homing, memory T cells

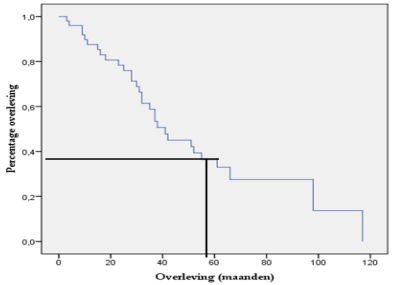
Clinical presentation:

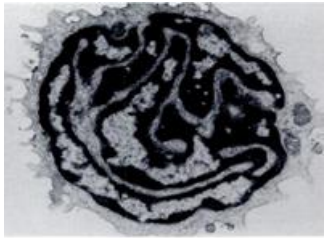
- Erythroderma, pruritus
- Alopecia, onychodystrophy
- Palmoplantar hyperkeratosis
- Lymphadenopathy
- Sézary cells in skin, lymph nodes and blood

5-year survival around 30%







Sézary cell
(Chu and Morris 1989)

# DD Erythroderma, a long list….

*Tabel 1 Oorzaken van Erythrodermie*

- Dermatitis
  - Atopische Dermatitis
  - Allergische/ irritant contact Dermatitis
  - Seborrhoische Dermatitis
  - Actinisch reticuloid
- Immunobulleuze ziekten
  - Bulleus pemfigoid
  - Pemphigus vulgaris
  - Pemphigus foliaceus
  - Paraneoplastische pemphigus
- Geneesmiddelenerupties
  - Toxische epidermale necrolyse
  - Drug reaction with eosinophilia and systemic symptoms and signs (DRESS)
  - Acute generalized exanthematous pustulosis (AGEP)
- Psoriasis
- Pityriasis rubra pilaris
- Lichen planus
- Cutane lymfomen
  - Mycosis fungoides
  - Sezary syndroom
  - Adult T-cel Leukemia Lymfoom (ATLL)
  - T-cel prolymphocytic leukemia (PTLL)
- Graft versus host ziekte
- Paraneoplastische erythrodermie
- Mastocytosis
- Hypereosinofiel syndroom
- Infecties/infestaties
  - Scabies
  - Staphylococcus scalded skin syndroom
  - Dermatophyte infectie
  - HIV
- Autoimmuun bindweefsel ziekten
  - Dermatomyositis
  - Lupus erythematodus
- Primaire immuundeficienties
  - Severe combined immunodeficiencies waaronder ook Omenn syndroom
  - Wiscott-Aldrich syndroom
- Congenitale ichthyosen
  - Netherton's syndroom
  - Bulleuze congenitale ichthyosiforme erythrodermie
  - Niet-bulleuze congenitale ichthyosiforme erythrodermie
  - X-gebonden dominante chondrodysplasia punctata

# Diagnostic criteria Sezary syndrome

**Clinic**

**T-cel clonality**

- Erythroderma en lymphadenopathy
- Identical T-cel clone (based on TCR-rearrangement) in blood and skin

**Abnormal T-cells based on:**

- Morphology
- Immuunphenotyping
- Number of CD4+ T-cellen

- Sézary cells >1000 cellen/microL
- Los of CD7 en/of CD26
- CD4:CD8 ratio >10

Ongoing EORTC-CLWG study to improve detection and quantification of tumor cells by flow cytometry

# Sezary Syndrome Genetics

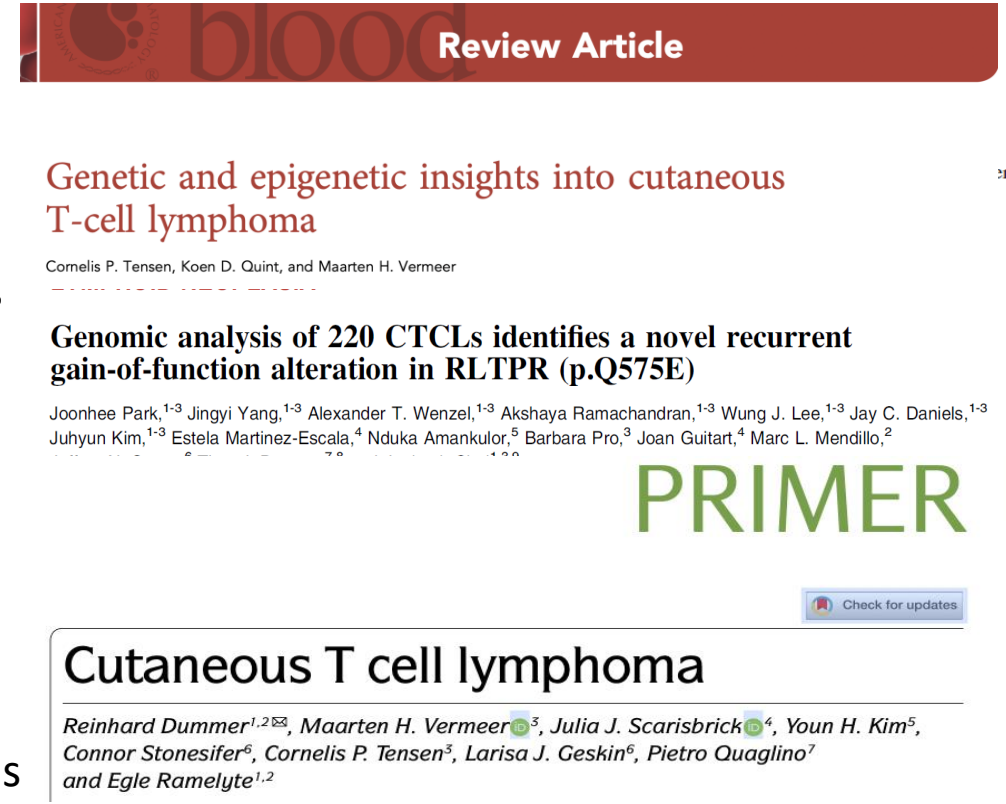
NGS studies (mainly WES)

High mutational burden

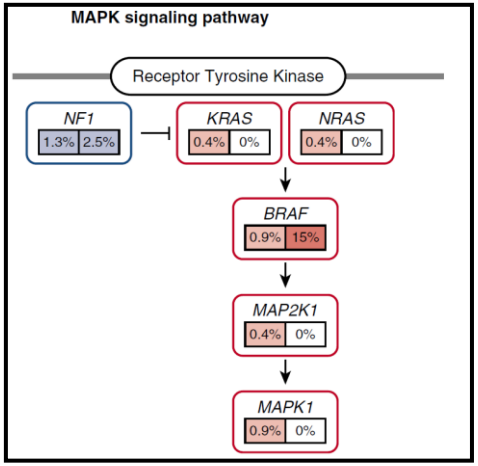
No recurrent translocations

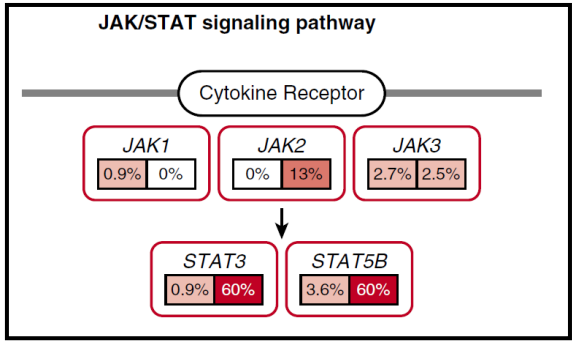
Affected genes:

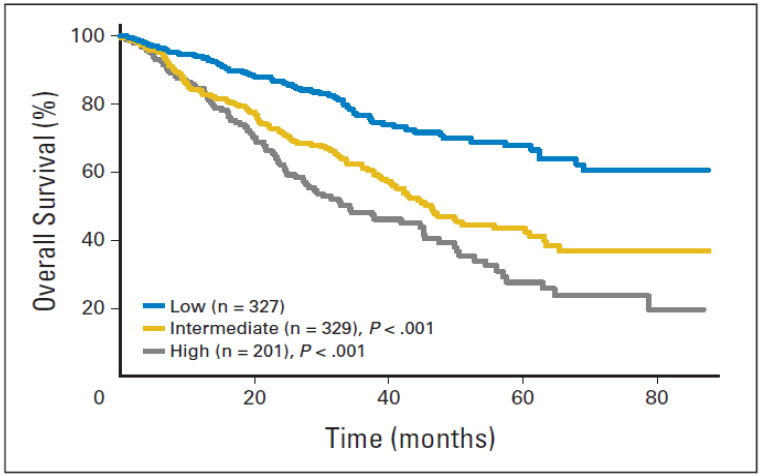
- DNA damage response
- TCR signaling
- JAK/STAT signaling
- Chromatin modifications

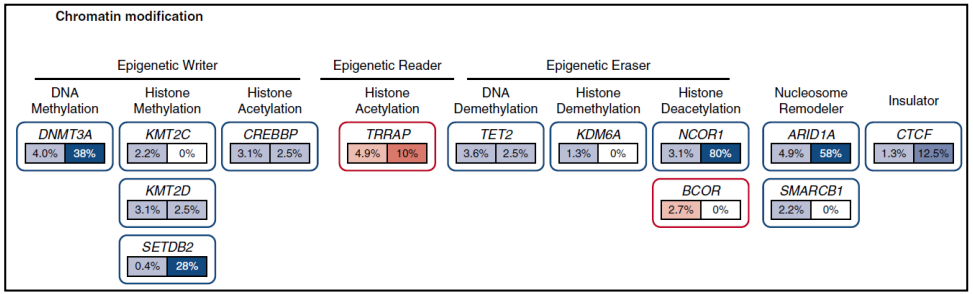


# Correlate CLIC Survival data with NGS results



# Treatment

**First line:**

- Topical therapies: Emolliens, topical steroids, PUVA
- Prednisone 10-20 mg dd
- MTX 10-20 mg/week, Neotigason 20-30 mg dd, pegIFNα
- Extracorporeal photopheresis

**Second line**

- Mogamulizumab (anti-CCR4)
- Alemtuzumab (anti-CD52)
- Brentuximab (anti-CD30)

Allogeneic Stem Cell Transplantation + Donor Lymphocyte Infusions

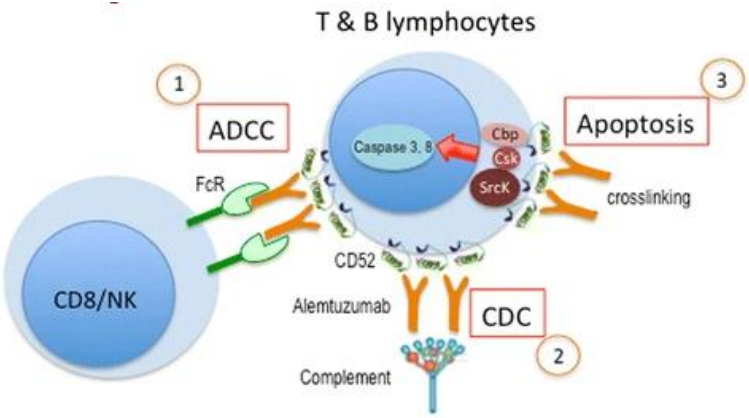
# Alemtuzumab (anti-CD52)

**CD52 expression**

- T and B cells, monocytes and dendritic cells.

**Cutaneous T-cell lymphoma**:

- Response in 85% of CTCL patiënts, in particular effective in SS
- Side effects: <u>infections</u> (CMV, aspergillosis)
- Disease free interval 6-12 months.
- With 10 mg 1x/wk less infectious complications




Lundin *et al* Blood 2003, Querfeld C, *et al* Leuk Lymphoma. 2009, Bernengo MG, *et al*. Haematologica. 2007, Clark *et al* Sci Transl Med 2012, De Masson et al Br J Dermatol 2014

# Mogamulizumab (anti-CDR4)

**CCR4 expression**

- Type II helper  T cells, regulatory T cells  (FoxP3+), skin homing T-cells6
- ATL, PTCL, en CTCL[4,7]

**Cutaneous T-cell lymphoma**:

- Response in 85% of CTCL patiënts (MF and SS)
- In particular effective in SS, <u>blood compartment</u>
- Side effects: moga rash
- Progression free survival 13 months (SS).

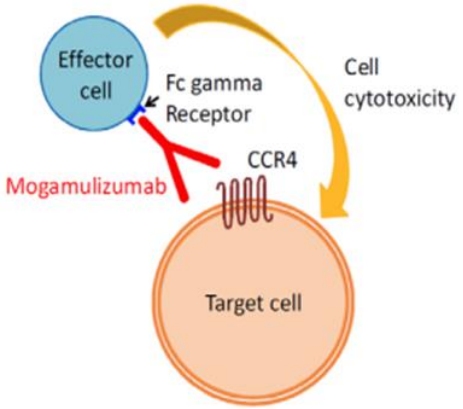
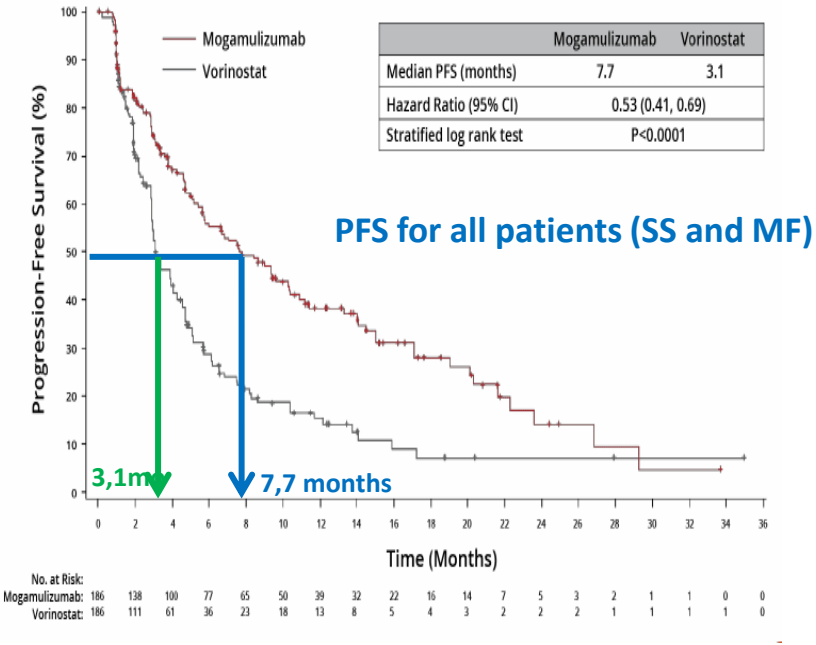



**Figure 1: Mogamulizumab MoA**

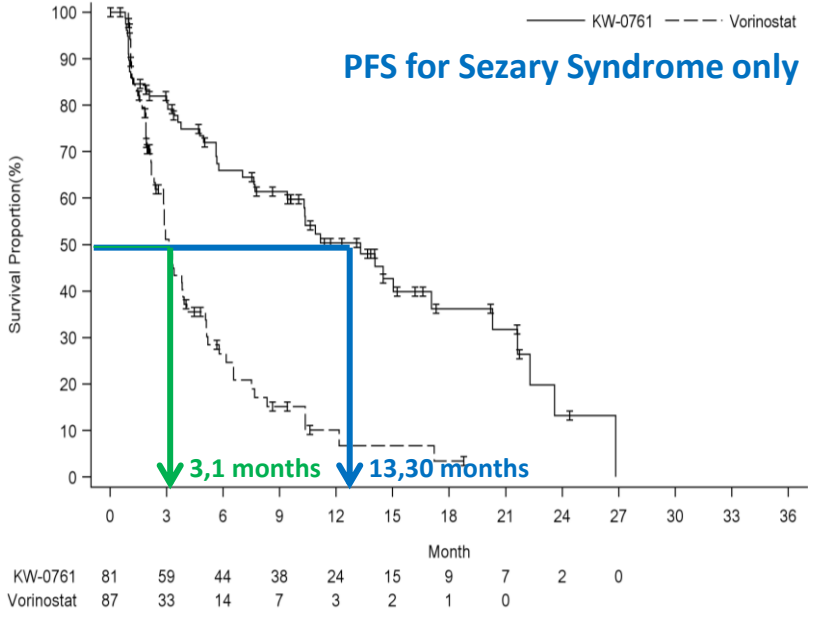
Lundin *et al* Blood 2003, Querfeld C, *et al* Leuk Lymphoma. 2009, Bernengo MG, *et al*. Haematologica. 2007, Clark *et al* Sci Transl Med 2012, De Masson et al Br J Dermatol 2014

# MAVORIC: Progression Free Survival as primary endpoint




| | Mogamulizumab | Vorinostat |
|---|---|---|
| Median PFS (months) | 7.7 | 3.1 |
| Hazard Ratio (95% CI) | 0.53 (0.41, 0.69) | |
| Stratified log rank test | P<0.0001 | |

**PFS for all patients (SS and MF)**




**PFS for Sezary Syndrome only**



Kim YH, Bagot M, Pinter-Brown L, et al. *Lancet Oncol.* 2018;19(9):1192-1204.

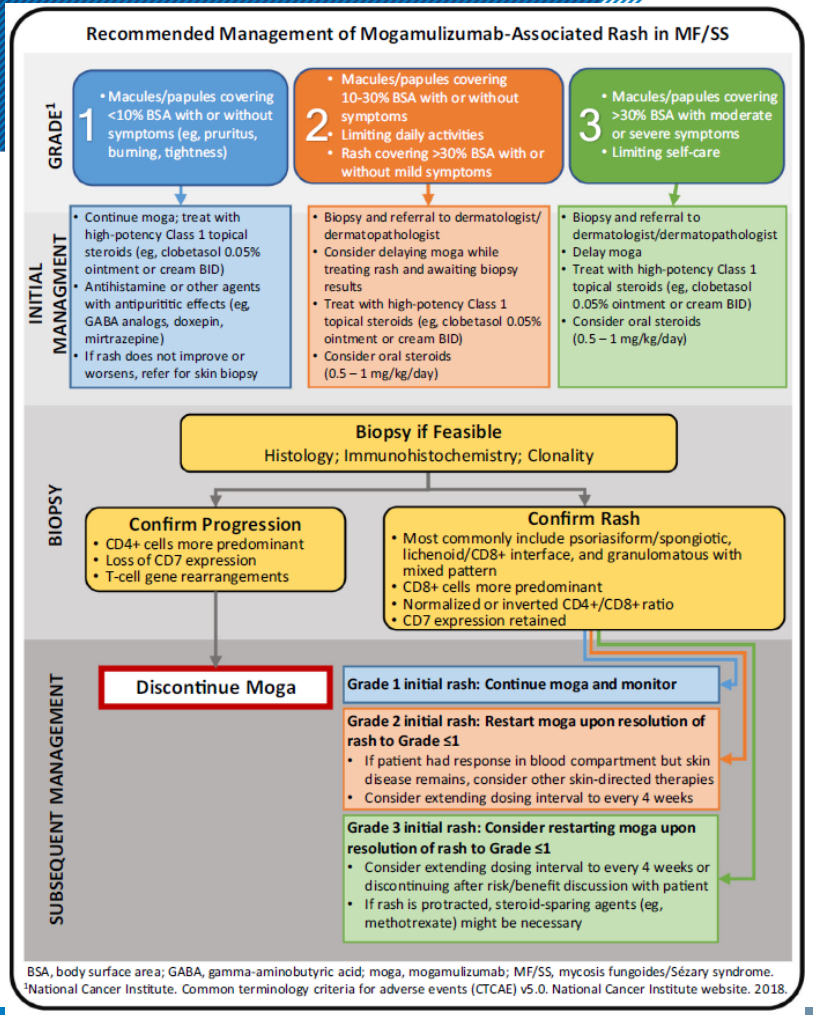
# Mogamulizumab side effects

## Dermatologic Events Associated with the Anti-CCR4 Antibody Mogamulizumab: Characterization and Management

Amy C. M. Musiek · Kerri E. Rieger · Martine Bagot · Jennifer N. Choi · David C. Fisher · Joan Guitart · Paul L. Haun · Steven M. Horwitz · Auris Onn-Lay Huen · Bernice Y. Kwong · Mario E. Lacouture · Sarah J. Noor · Alain H. Rook · Lucia Seminario-Vidal · Maarten H. Vermeer · Youn H. Kim

- "Moga-rash" is described in 12% patients.
- Treatment with topical steroids.
- Rash is associated with better prognosis

- Biopsy in grade 2 and 3 reactions to exclude localization of disease.



# Resistance to Mogamulizumab or Alemtuzumab

Resistance to Mogamulizumab

- Mutations or copy number loss of CCR4 leading to loss of CCR4 expression

Resistance to Alemtuzumab

- Epigenetic silencing of PIG gene leading to loss of anchor protein and loss of CD52 expression

Illustrating ongoing evolution of tumor cells

Beygi Blood 2022; Halkes J Invest Dermatol 2008

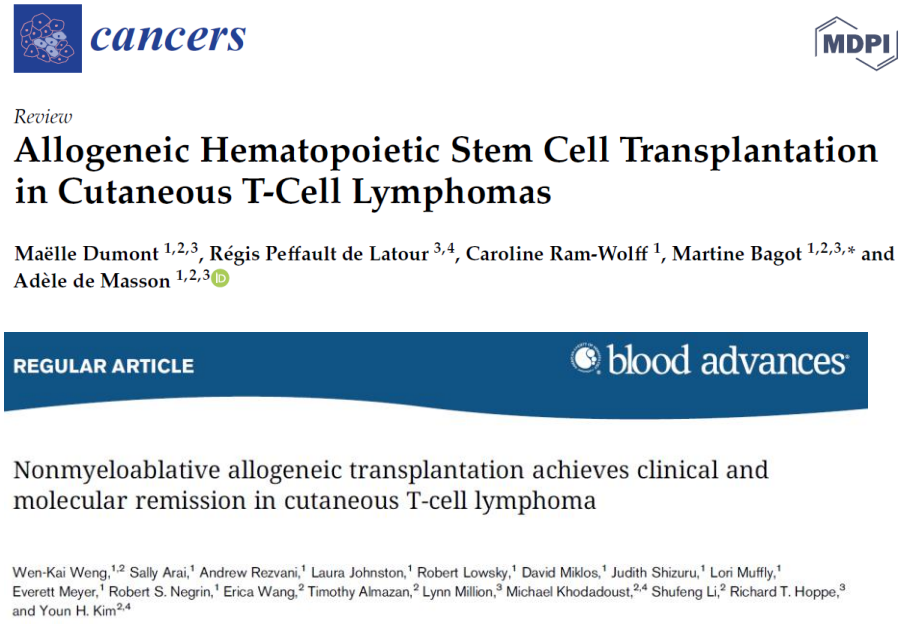
# Allogeneic Stem Cell Transplantation

Nonmyeloablative allogeneic SCT

New conditioning regimes:
2-, 5-, and 7-year survival of 68%, 56% and 32%.

Complicated by mortality, infections, and GVHD (30%)

Selected cases



cancers

MDPI

*Review*

**Allogeneic Hematopoietic Stem Cell Transplantation in Cutaneous T-Cell Lymphomas**

Maëlle Dumont [1,2,3], Régis Peffault de Latour [3,4], Caroline Ram-Wolff [1], Martine Bagot [1,2,3,*] and Adèle de Masson [1,2,3]

REGULAR ARTICLE

blood advances

Nonmyeloablative allogeneic transplantation achieves clinical and molecular remission in cutaneous T-cell lymphoma

Wen-Kai Weng,[1,2] Sally Arai,[1] Andrew Rezvani,[1] Laura Johnston,[1] Robert Lowsky,[1] David Miklos,[1] Judith Shizuru,[1] Lori Muffly,[1] Everett Meyer,[1] Robert S. Negrin,[1] Erica Wang,[2] Timothy Almazan,[2] Lynn Million,[3] Michael Khodadoust,[2,4] Shufeng Li,[2] Richard T. Hoppe,[3] and Youn H. Kim[2,4]

# aSCT Prospective trial de Masson Lancet Oncol 2023

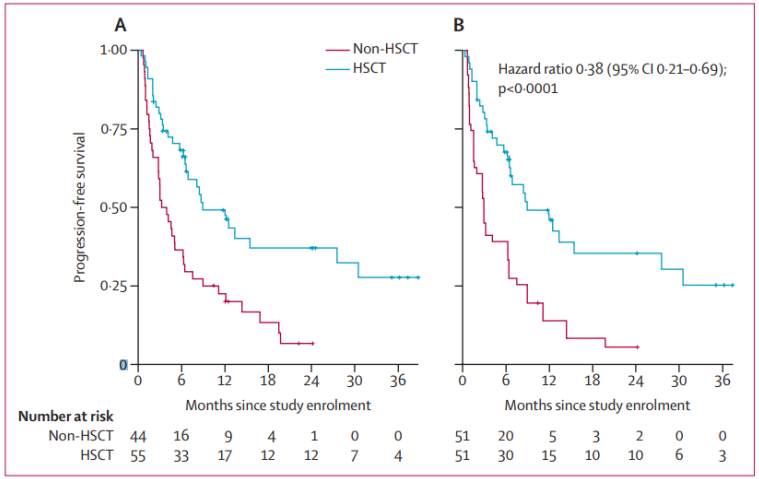



*Figure 2:* **Progression-free survival after study enrolment in the intention-to-treat analysis, according to study group**

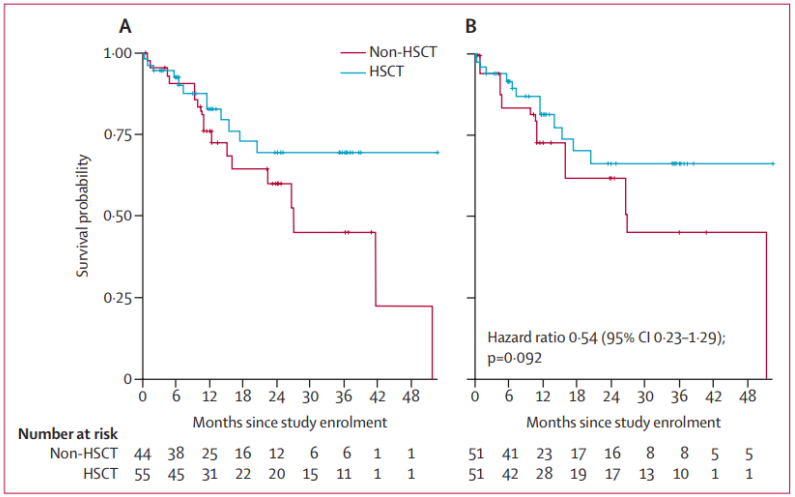



*Figure 3:* **Overall survival after study enrolment in the intention-to-treat analysis, according to study group**

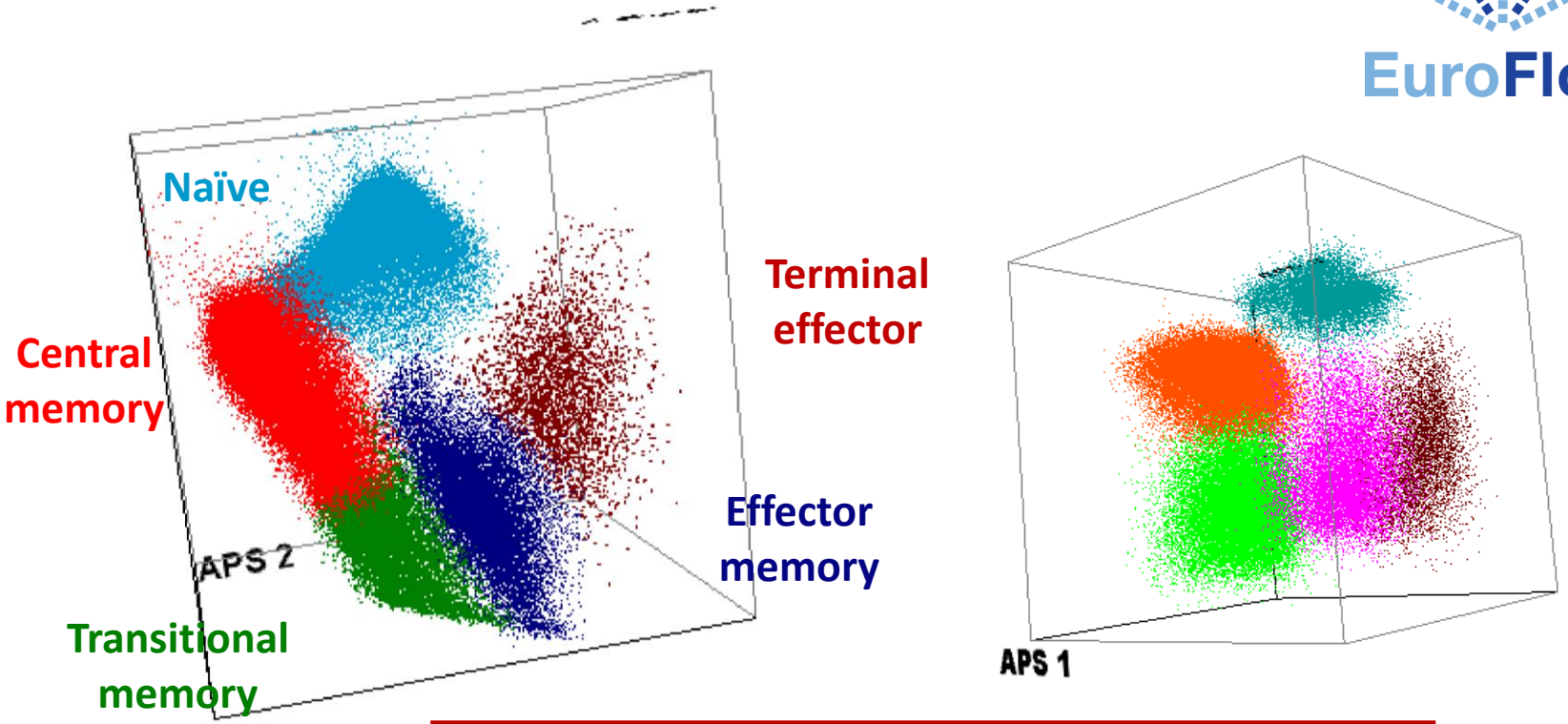
| | HSCT | Non-HSCT |
|---|---|---|
| Progression Free Survival | 9 months (6.6 – 30.5) | 3 months (2.0 - 6.3) |
| Median Overall Survival | Not reached | 26.9 months (16.1- not reached) |

# Remaining questions

- Optimal conditioning regime?
- Optimal patient selection?
- Optimal timing of aSCT in disease course?

# CD4+ T-cell Maturation Pathway in Healthy Adults

EuroFlow

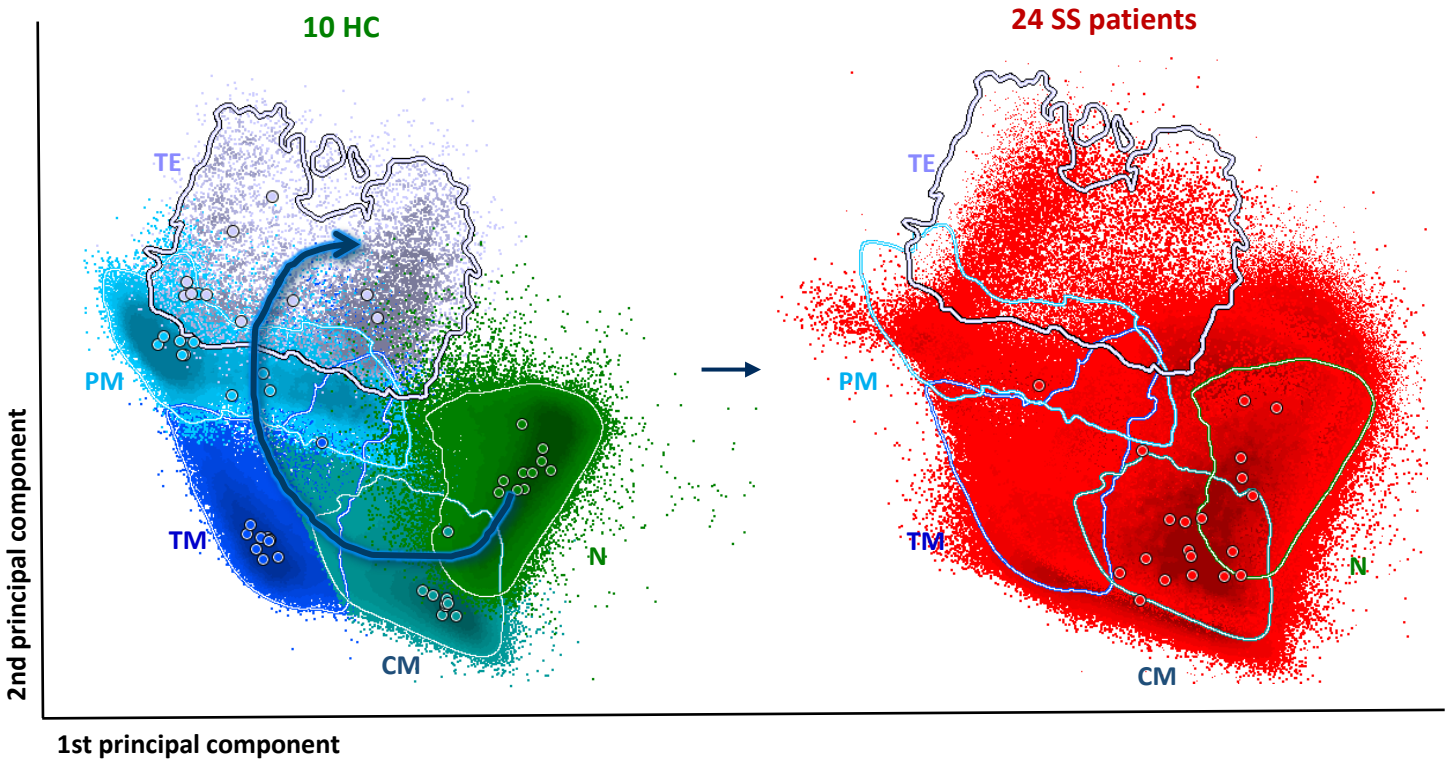



14-color combination: ~85 CD4+ T-cell subsets in blood

Botafogo V et al. *Frontiers Immunol*. 2020;11:166.

# Sézary cells show different maturation profiles

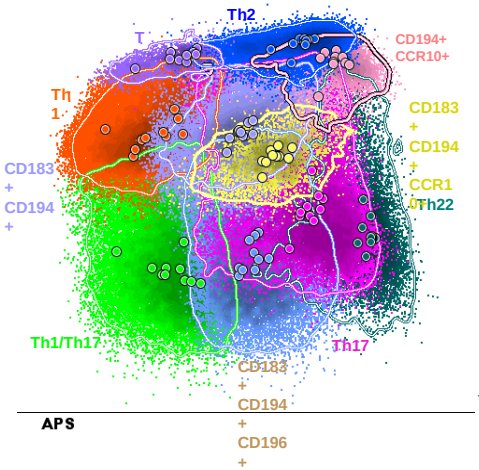
Naïve (N) → Central Memory (CM) → Transitional Memory (TM) → Peripheral memory (PM) → Terminal effector (TE)



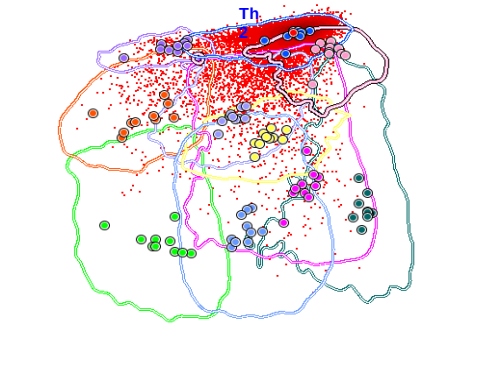

*Najidh Blood 2022*

# Sézary cells; not always the typical Th2-phenotype

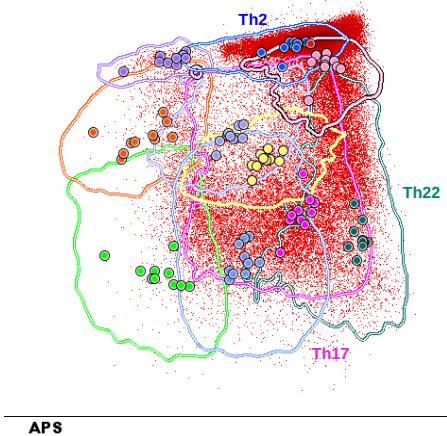
**Normal CD4⁺ T cells HCs**



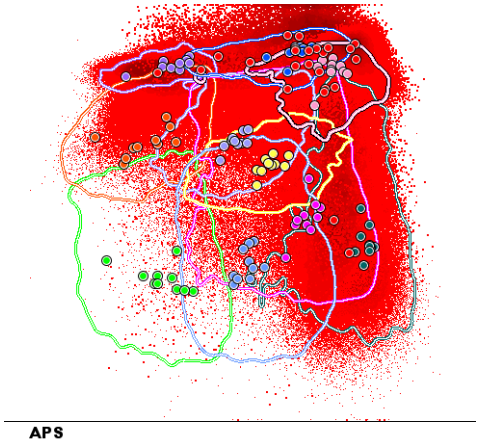

**Individual SS case**




**Individual SS case**




**24 SS patients**




- Sézary cells exhibit a wide range of classical and non-classical T helper subsets

  **Inter-patient heterogeneity**

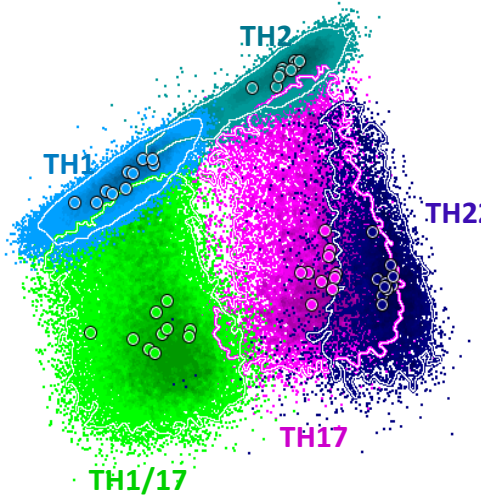
- Sézary cells from same patient show distinct T helper subsets

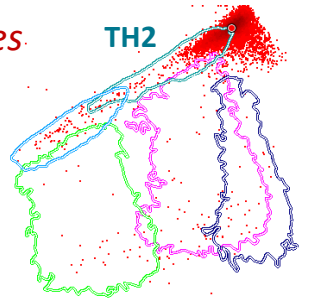
  **Intra-patient heterogeneity**

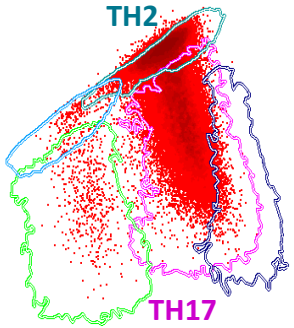
*Najidh Blood 2022*

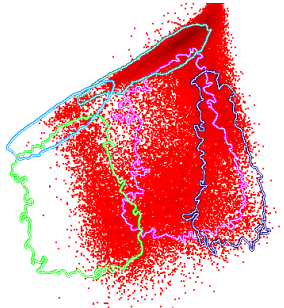
# EuroFlow-Sézary Study – Results

*Examples of SS samples*



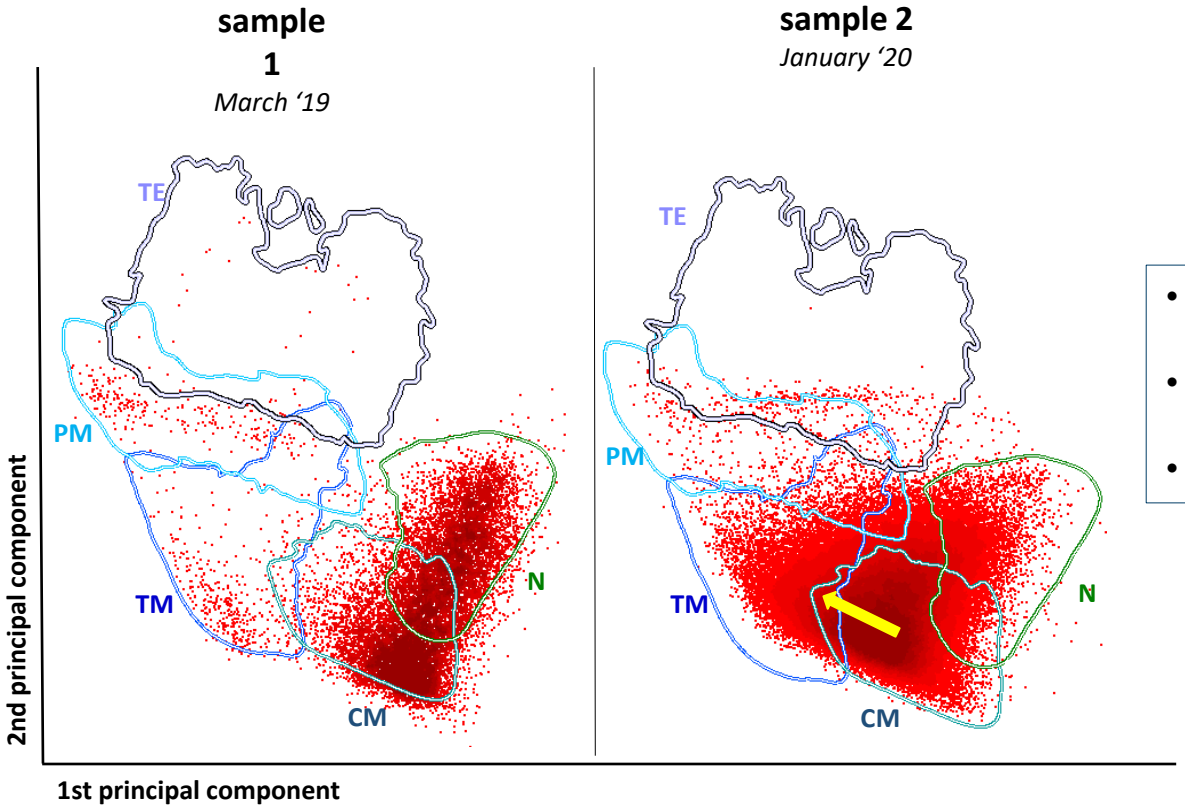
**Predominantly one subset (3/20; 15%)**

**Predominantly two subsets (8/20; 40%)**

**SCs at least three subsets (9/20; 45%)**

EuroFlow

# Sézary Syndrome: Phenotypic Shift During Follow-up




- Tumour population 30% → 90%
- All tumour cells remain mainly TH2
- **Clinical deterioration**

*Najidh Blood 2022*

EuroFlow

# Conclusions EuroFlow-Sézary pilot study

**Sézary syndrome patients are highly heterogeneous**

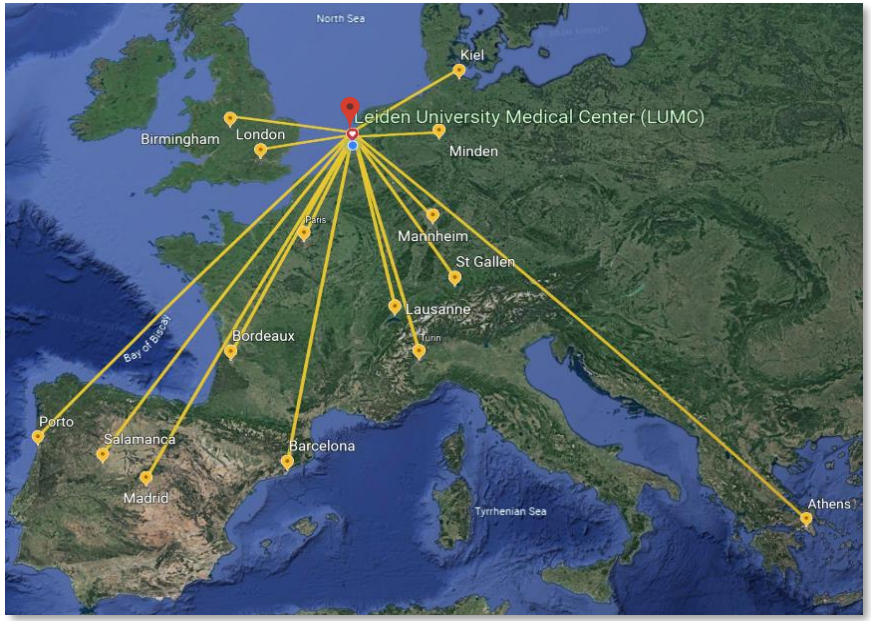
- Inter-patient heterogeneity
- Intra-patient heterogeneity
- Phenotypic shifts

**Questions**:

- Are different tumor cell subpopulations functionally different?
- Do different subpopulations correlate with disease course and prognosis?
- Does blood involvement correlate with disease course?
- Can we detect circulating tumour cells in early stages of MF?

# Initiation of European multicenter study

Start **European multicenter collaboration** between **17 EORTC-Cutaneous Lymphoma Working Groups and EuroFlow centers**




Athens – Barcelona – Berlin – Birmingham – Bordeaux – Kiel – Lausanne – Leiden – London - Madrid – Mannheim – Minden – Paris – Porto – Salamanca – St. Gallen - Turin

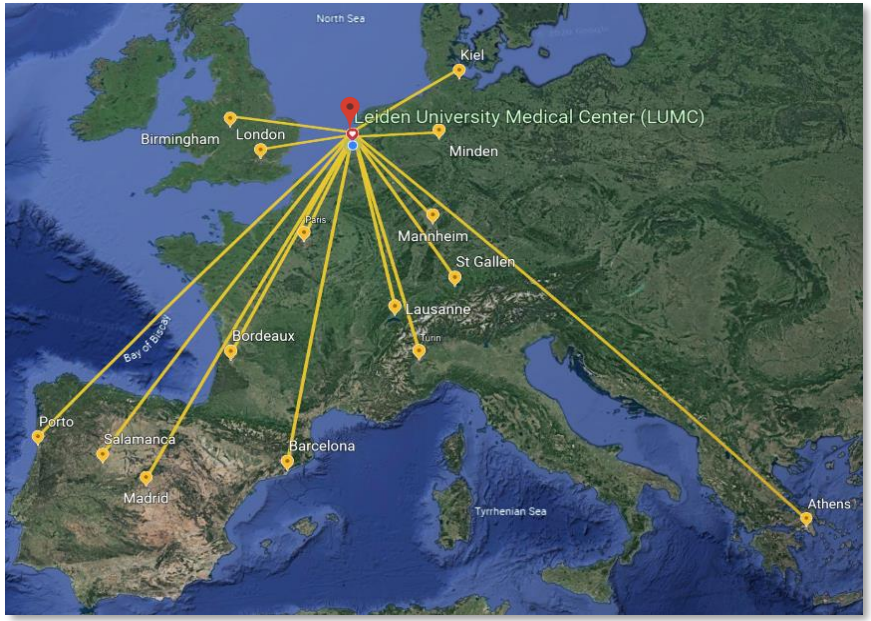
# Initiation of European multicenter study

Start **European multicenter collaboration** between **17 EORTC-Cutaneous Lymphoma Working Groups and EuroFlow centers**

EORTC
European Organisation for Research and Treatment of Cancer
50 years of Progress Against Cancer

EuroFlow

Athens – Barcelona – Berlin – Birmingham – Bordeaux – Kiel – Lausanne – Leiden – London - Madrid – Mannheim – Minden – Paris – Porto – Salamanca – St. Gallen - Turin




objectives

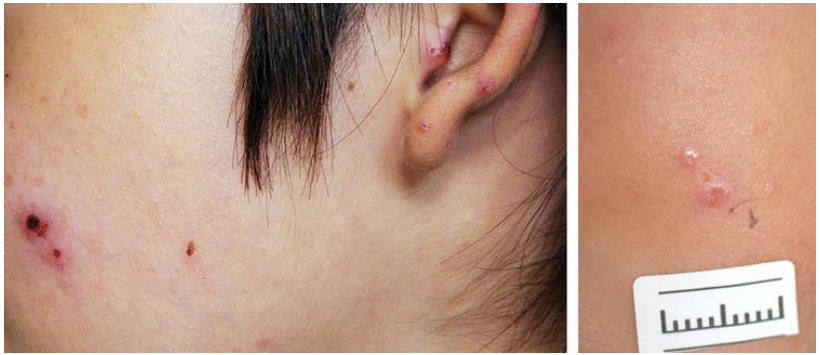
→ **Building European collaborative network**
→ **Achieving high levels of FC standardization across centers**
→ **Testing and validation of CTCL-specific classical and novel markers in three 8-color FC panels**

# Hydroa-vacciniforme-like lymphoproliferative disorder

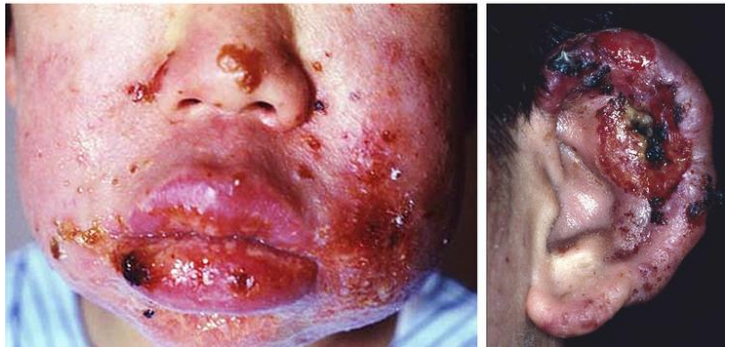
- Uncommon mainly seen in children and adolescents from Asia, South- and Central-America.
- Cutaneous manifestations of chronic active EBV infection
- Clonal TCR with EBV in clonal form:
  - CD8+ cytotoxic T-cells (CD8+, GrB+, TIA-1+ Perf+)
  - NK cells (CD56+, CD5-, TCRs-)
- Both condition may either run an indolent clinical course or progress to frank lymphoma.

# Clinical presentationand progression of disease

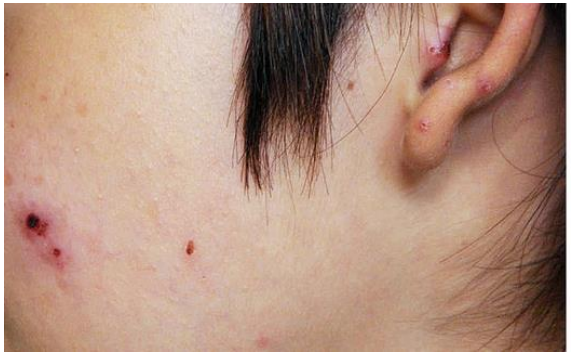
- Skin
  - Papulovesicular eruption on sun-exposed skin, blisters and ulceration

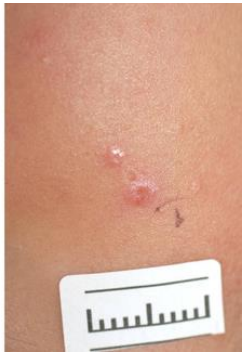


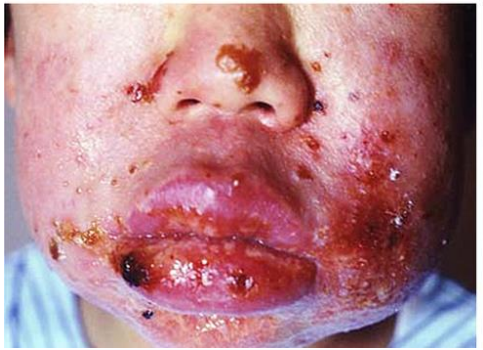
- Progression
  - Fever
  - Lymphadenopathy, hepatosplenomegaly,
  - Periorbital and lip edema

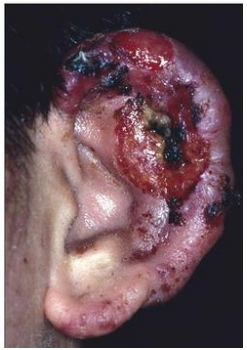


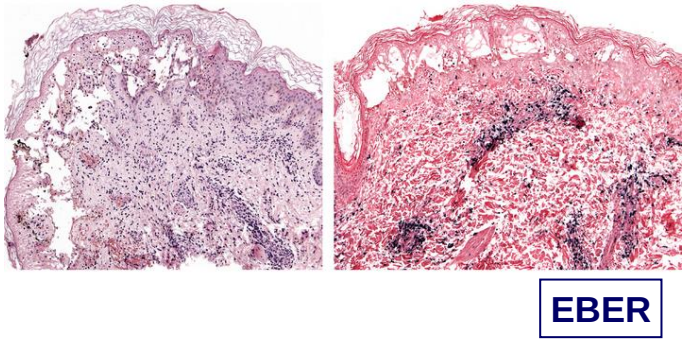
# Hydroa-vacciniforme-like lymphoproliferative disorder

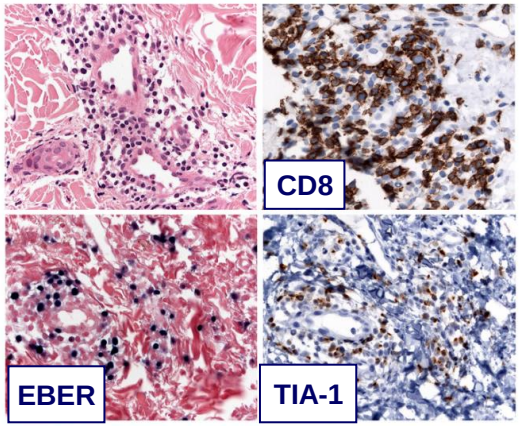






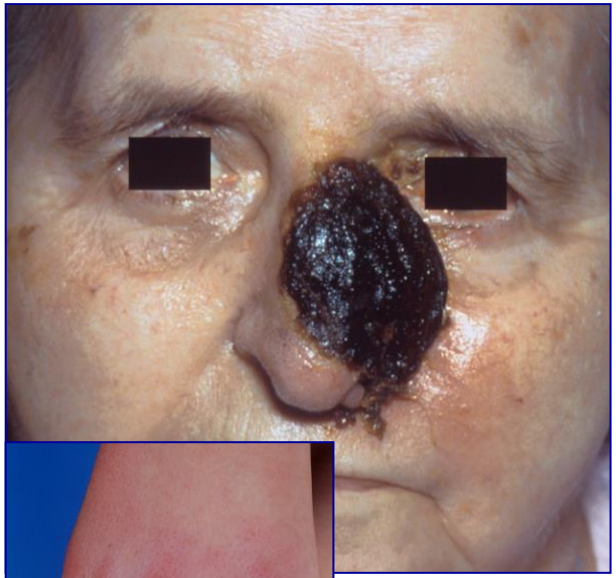


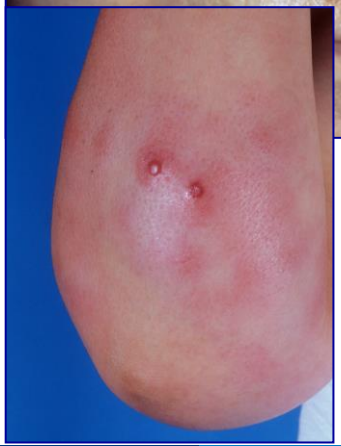



EBV infection driving T-cell lymphomagenesis

# Extranodal NK/T-Cell lymphoma, nasal type (lethal midline granuloma)

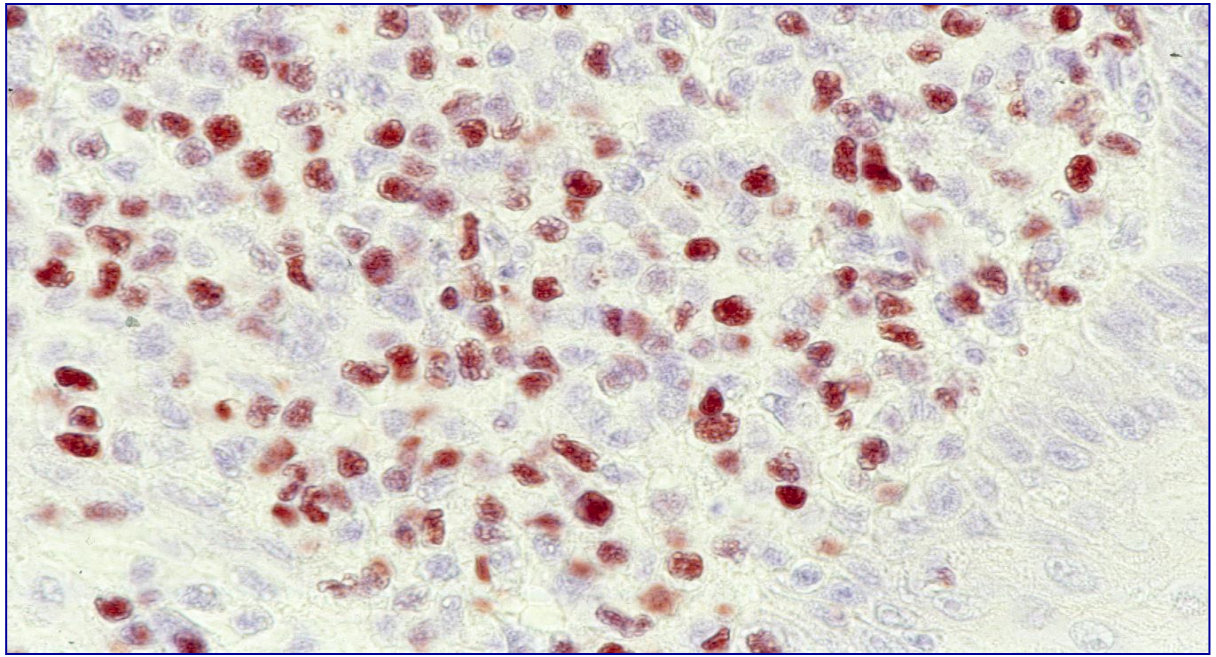




- Rare; median age 35-58
- More common in Asia and central and south America, (HLA associated)
- Nasopharynx/nasal cavity 80%; less commonly at other sites
- EBV-associated (nearly 100%)
- Usually NK-cell phenotype; more rarely a cytotoxic T-cell phenotype

- L-asparaginase containing chemotherapy.
- SCT in selected cases.
- PD1 blocking has shown promising results

# Extranodal NK/T-cell lymphoma, nasal type

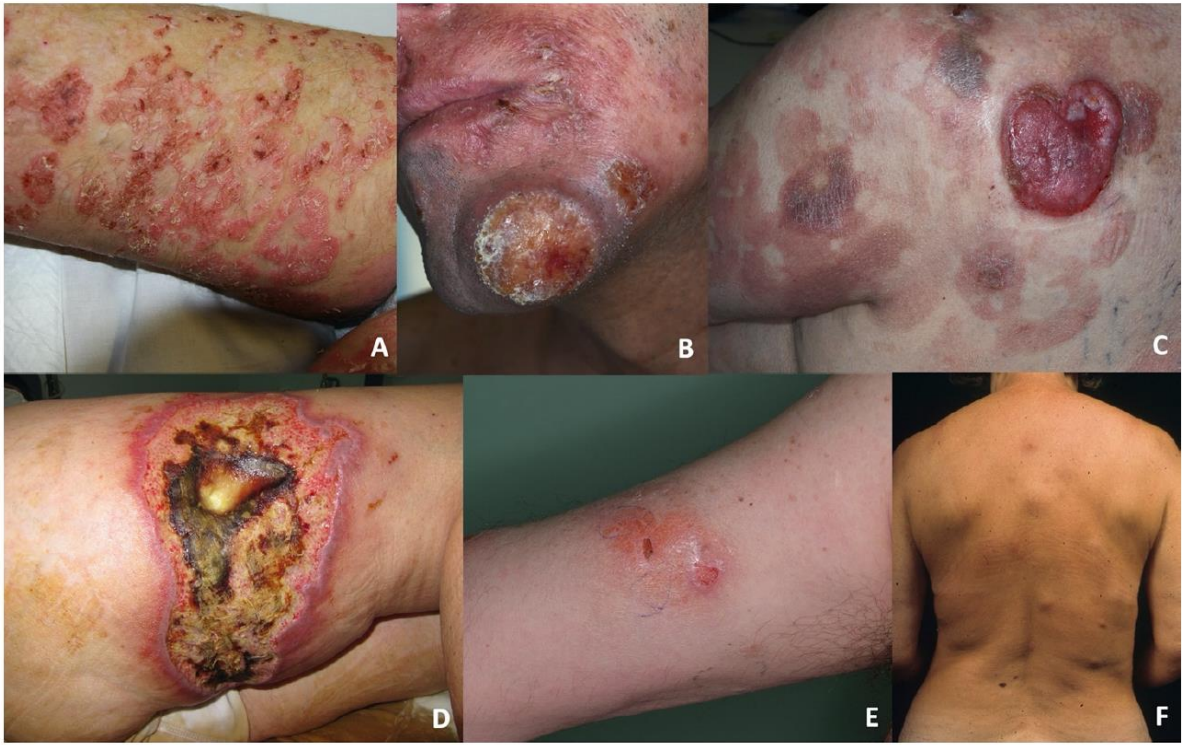


EBER1/2

# PC Gamma-Delta TCL

- Rare and aggressive CTCL derived from activated mature ˙γδ T-cells
- Infiltration of activated mature ˙γδ T-cells in epidermis-dermis-panniculus
- CD3+, CD2+, CD7+/-, CD5-, cytotoxic proteins, CD4-, CD8-/+ occ. CD56+ (50%)
- Variation in clinical presentation
- Variation in histology

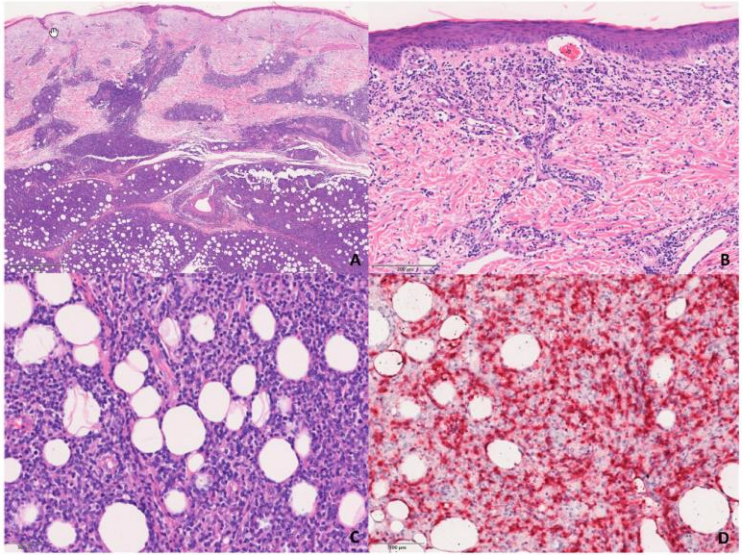
# Gamma Delta TCL Clinical Presentation

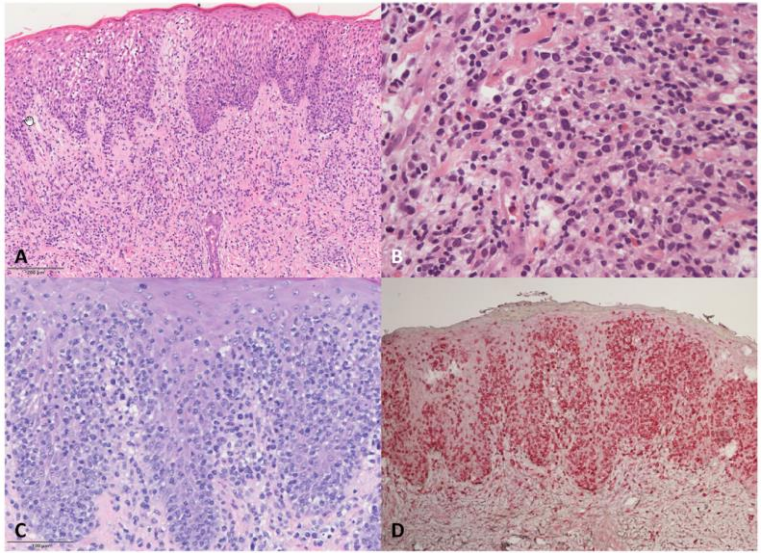



**Plaques – Nodules - Tumors**

Violetti Dermatopathology 2021

# PC Gamma-Delta TCL: Histology



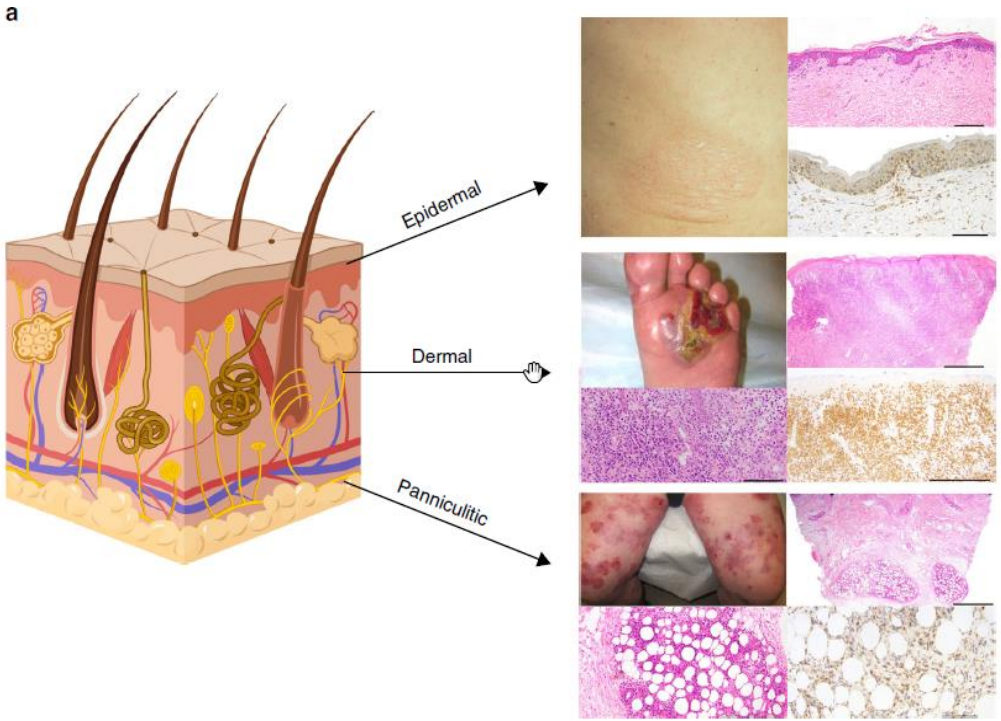




**Dermal/Panniculus Infiltration**

**Epidermal Infiltration**

Violetti Dermatopathology 2021

# TCR Delta V1 or V2 correlates with skin compartment




TRDV1

TRDV1

TRDV2

Mutations:

- JAK/STAT
- MAPK
- MYC

Daniels Nature Comm 2020

# PC Gamma-Delta TCL, Italian study

*dermatopathology*

MDPI

*Article*

## Primary Cutaneous Gamma-Delta T Cell Lymphomas: A Case Series and Overview of the Literature

Silvia Alberti-Violetti [1,2,*], Carlo Alberto Maronese [1,2], Luigia Venegoni [2], Valentina Merlo [1] and Emilio Berti [1,2]

| | Epidermal/Dermal | Subcutaneous |
|---|---|---|
| V 1 (n=4) | 3 | 1 |
| V 2 (n=7) | 1 | 6 |

No correlation of Vδ1 Vδ2 subtype and prognosis

# Prognosis

- Complicated by hemophagocytic syndrome and spread to mucosa and extranodal sites with sparing of lymphnodes and bone marrow.

- Poor prognosis with median survival <2 years and 5-year survival around 20%.
- Agressive therapy indicated: aSCT

- Indolent disease course in exceptional cases.

# Indolent course of disease

CASE REPORT

## Radiation therapy for primary cutaneous γδ T-cell lymphoma: Case report and literature review

Chris R. Kelsey, MD,[a] Endi Wang, MD, PhD,[b] Alexandra Stefanovic, MD,[c] and Meenal Kheterpal, MD[d]
*Durham, North Carolina*

***Key words:*** cutaneous T-cell lymphoma; primary cutaneous γδ T-cell lymphoma; radiation therapy.



*J Cutan Pathol 2013: 40: 896–902*
*doi: 10.1111/cup.12091*
*John Wiley & Sons. Printed in Singapore*



Journal of
Cutaneous Pathology

## Indolent course of cutaneous gamma-delta T-cell lymphoma

Cutaneous gamma-delta T-cell lymphoma (γδTCL) is a rare malignancy that typically displays an aggressive clinical course. We present an unusual case of a 57-year-old woman with a 3-year history of lower extremity nodules. Histopathologic, immunophenotypic and molecular genetic studies revealed a clonal, predominantly pannicular

**Dawnielle C. Endly[1], Roger H. Weenig[2], Margot S. Peters[3,4], David S. Viswanatha[4] and Nneka I. Comfere[3,4]**

*J Cutan Pathol 2008: 35: 1063–1067*
*doi: 10.1111/j.1600-0560.2007.00931.x*
*Blackwell Munksgaard. Printed in Singapore*



Journal of
Cutaneous Pathology

## Indolent Primary Cutaneous γ/δ T-Cell Lymphoma Localized to the Subcutaneous Panniculus and Its Association With Atypical Lymphocytic Lobular Panniculitis

*Cynthia M. Magro, MD, and Xuan Wang, MD, PhD*

**Key Words:** Primary cutaneous γ/δ T-cell lymphoma; Subcutaneous panniculitis-like T-cell lymphoma; Indolent

DOI: 10.1309/AJCPQGVLTZQ77VFF

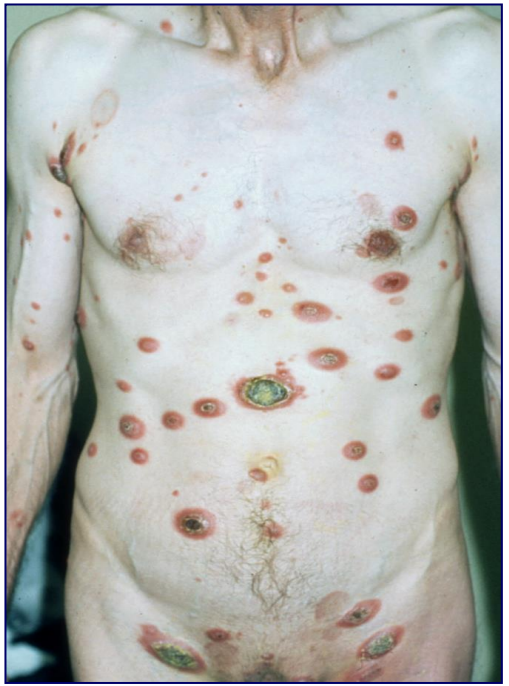
## Transformation of cutaneous gamma/delta T-cell lymphoma following 15 years of indolent behavior

Subcutaneous gamma/delta (γ/δ) T-cell lymphoma is a rare lymphoma, characterized by its unique immunophenotype and clinical course. It has been shown to behave more aggressively than its

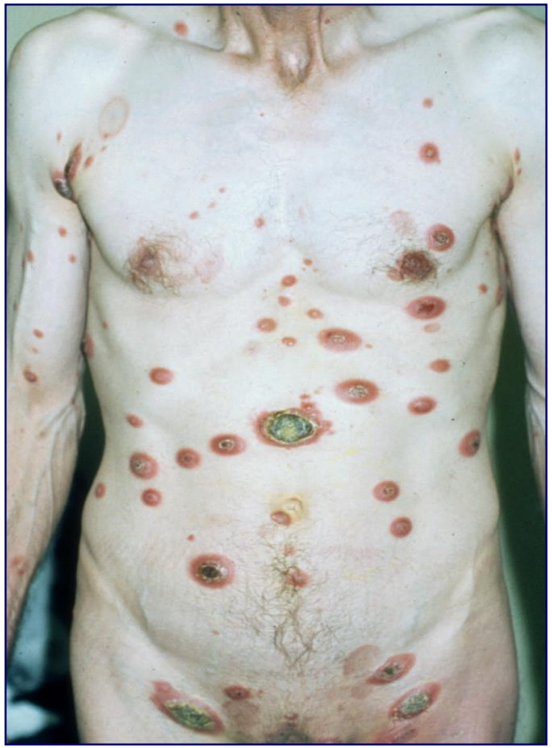
**Gregory A. Hosler[1,2,3], Nanette Liégeois[1], Grant J. Anhalt[1] and J. Margaret Moresi[1]**

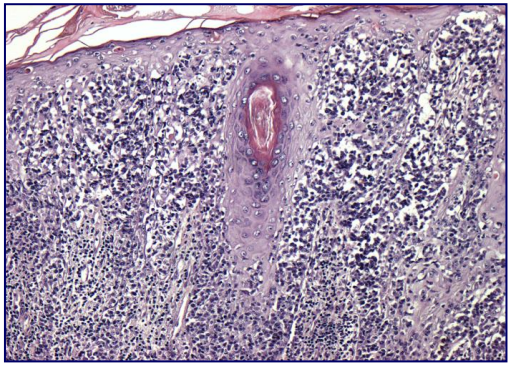
# Primary cutaneous aggressive epidermotropic cytotoxic T-cell lymphoma (PCAECTL)

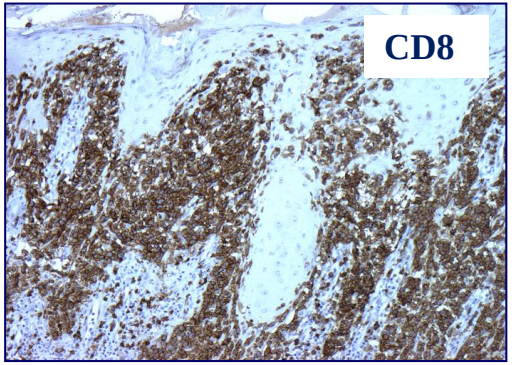
- Adults more often in males
- Generalized papules, ulcerating nodules, tumors and plaques with erosion and central necrosis.
- Dissemination to visceral sites (lumg, testes, CNS)
- Lymphnodes are usually spared
- Pagetoid epithelial involvement of atypical CD8+ T-cells with cytotoxic proteins

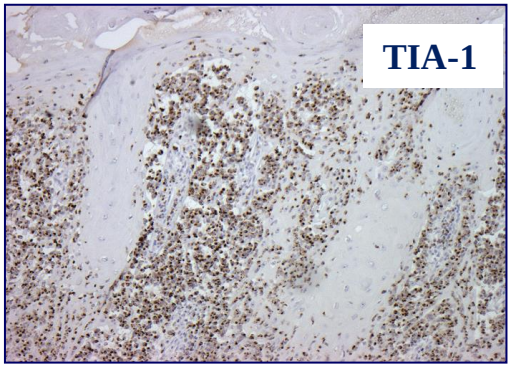


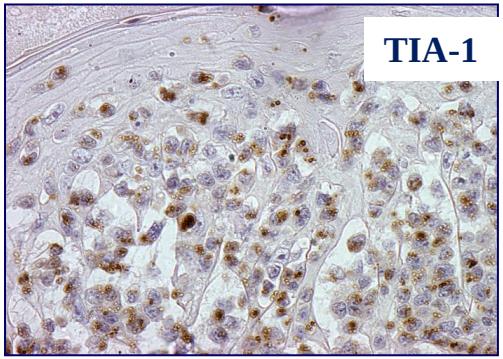
# Aggressive epidermotropic CD8+ CTCL








Berti E. et al; Am J Pathol 1999;155: 483-492

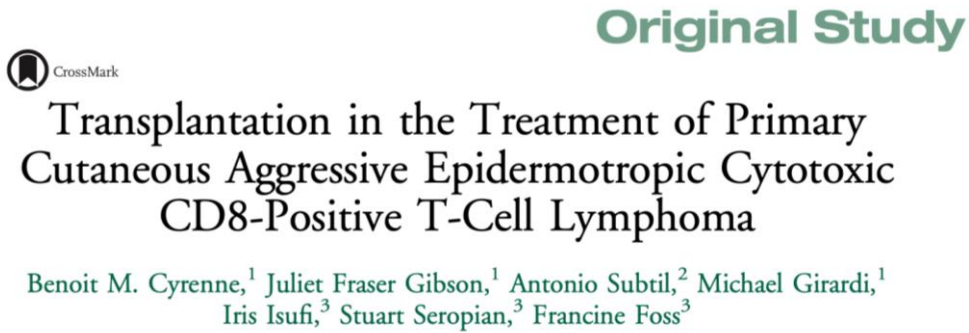
# Prognosis and Treatment

Prognosis: median survival of 12 months

Incidental succes with polychemotherapy and aSCT

New developments:

- Brentuximab
- Pralatrexate


Original Study

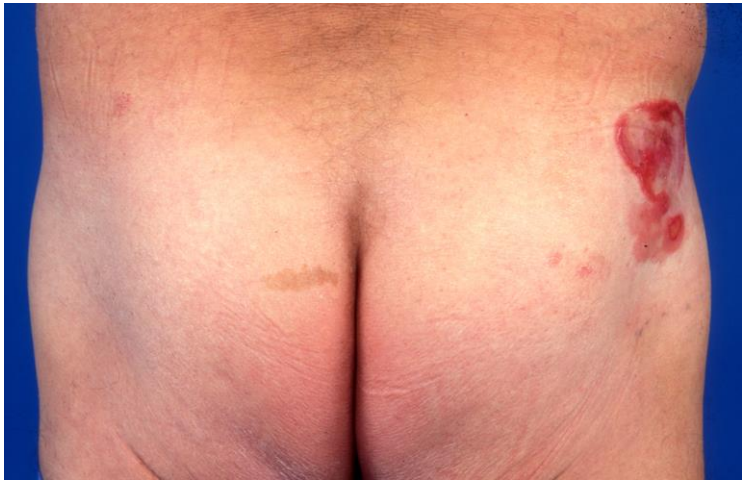
CrossMark

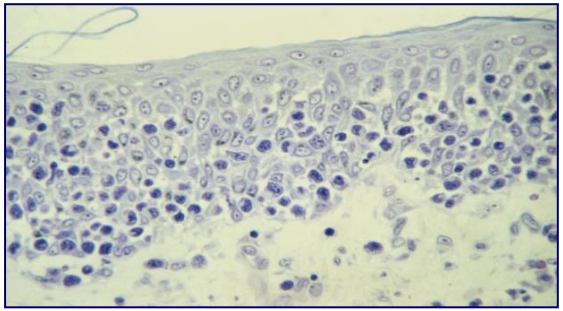
Transplantation in the Treatment of Primary Cutaneous Aggressive Epidermotropic Cytotoxic CD8-Positive T-Cell Lymphoma

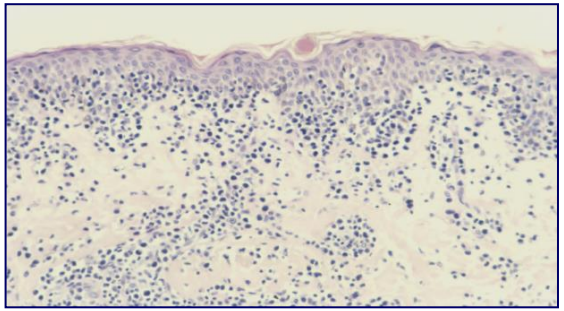
Benoit M. Cyrenne,[1] Juliet Fraser Gibson,[1] Antonio Subtil,[2] Michael Girardi,[1] Iris Isufi,[3] Stuart Seropian,[3] Francine Foss[3]

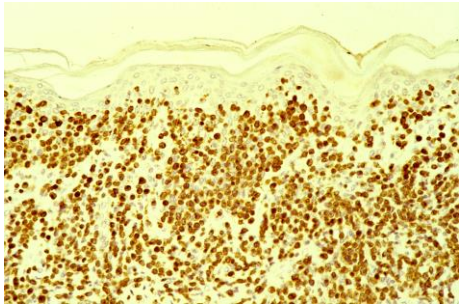
# Case October 1994, solitary plaque

- Male, 59 years
- Since 6 months red plaques on the trunk.
- Histology: epidermotropic CD8+ CTCL: atypical MF; DD: AETCL, PTCL, NOS
- No lymphadenopathy.
- Therapy: topical nitrogen mustard



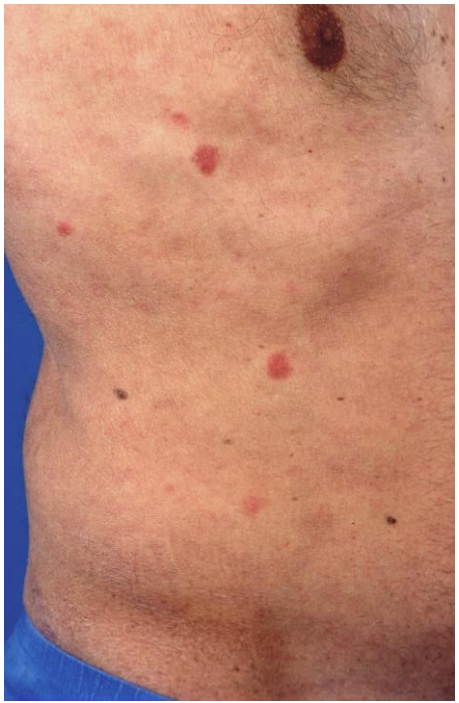


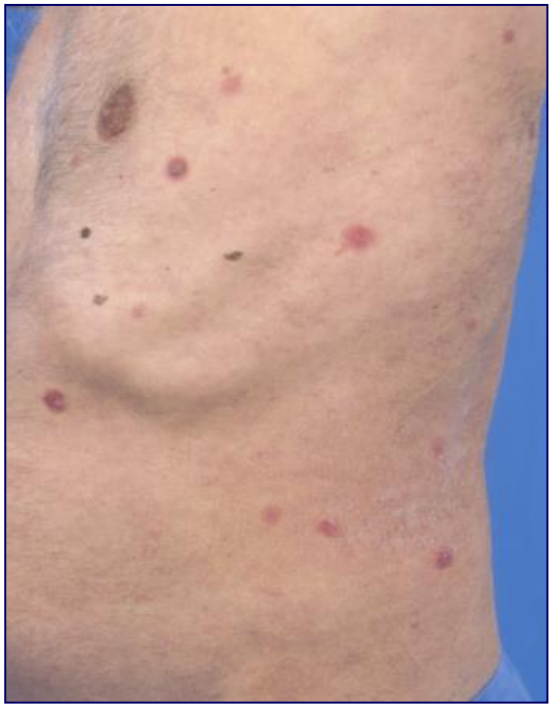


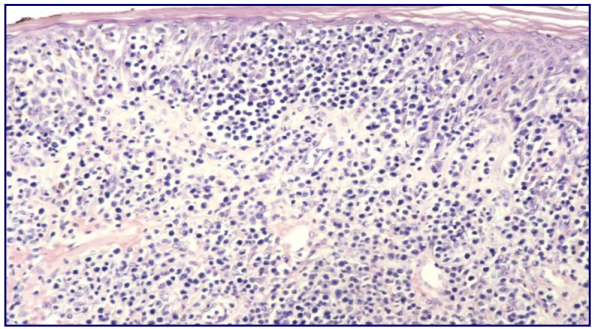


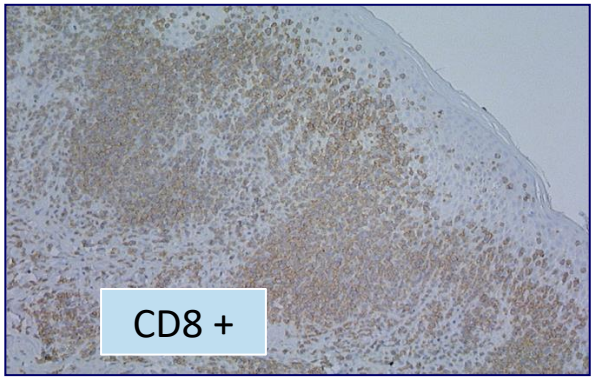
WCL 883

# Case 14: December 1994, multiple plaques



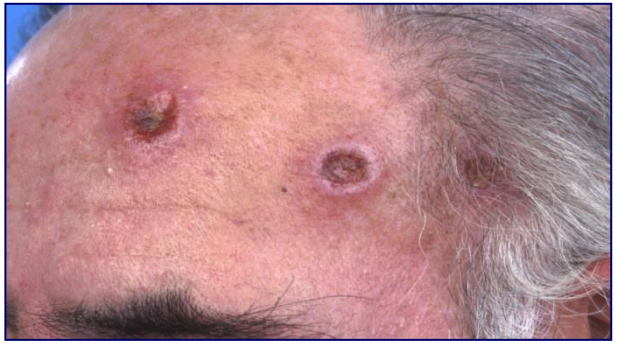




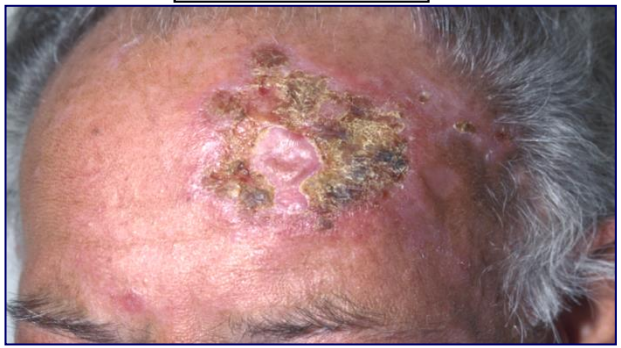



WCL 883

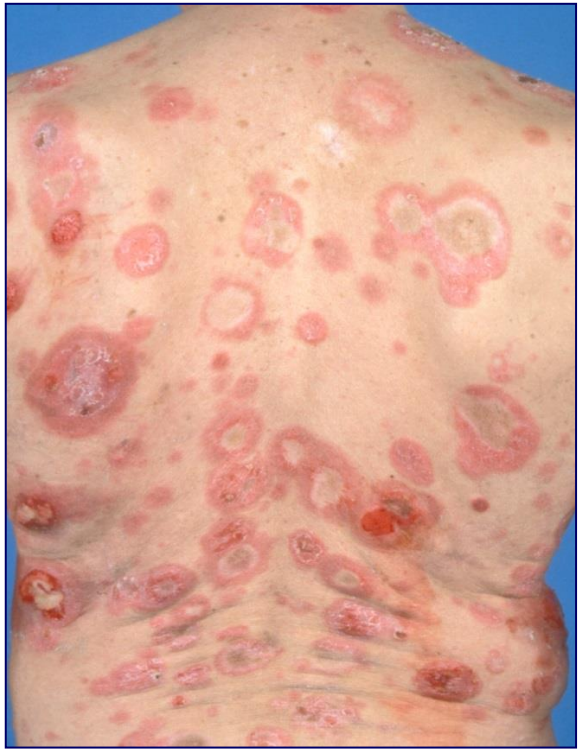
# Case 14, development of ulceronecrotic lesions

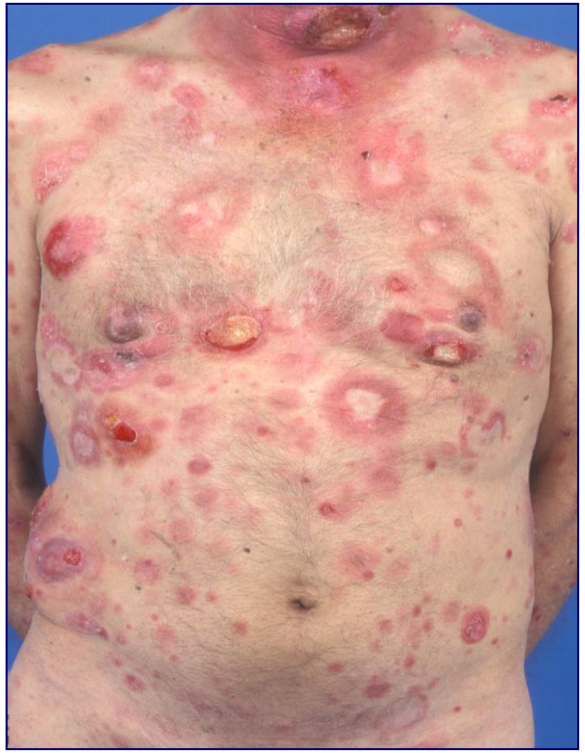


February 1995



April 1995

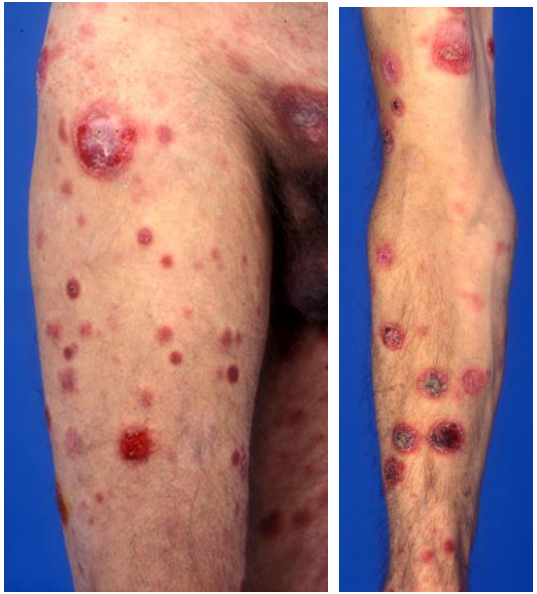




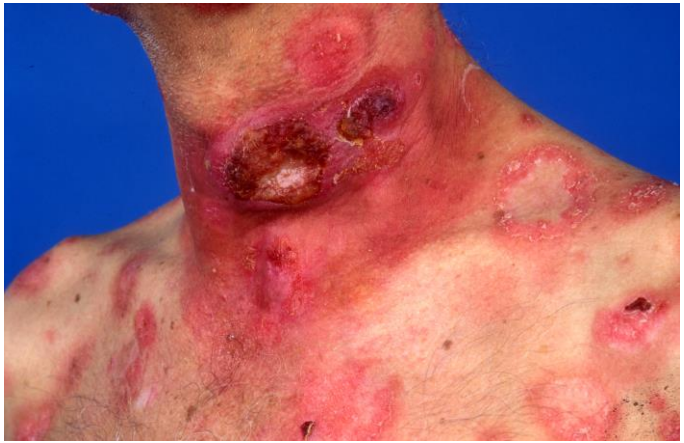
February 1996

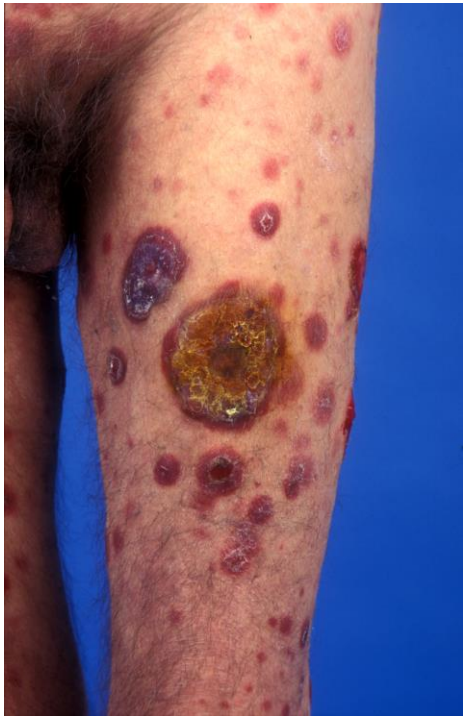
# Case Treatment and Follow up

| | |
|---|---|
| 10-1994 | Diagnosis epidermotropic CD8+ CTCL (atypical MF, IB)<br>Clinical examination: plaques; Therapy: HN2 |
| 12-1994 | Development of nodular lesions → ulceronecrotic. |
| 04-1995 | Widespread ulcerating nodules and tumors.<br>Staging: no extracutaneous disease<br>Therapy: CHOP → complete remission (09-1995)! |
| 03-1996 | Progressive skin disease. Therapy: TSEB followed by HN2 |
| 12-1996 | Progressive skin disease. Therapy: Etoposide, PECC, etc. |
| 01-1997 | Died of lymphoma (27 months after diagnosis) |

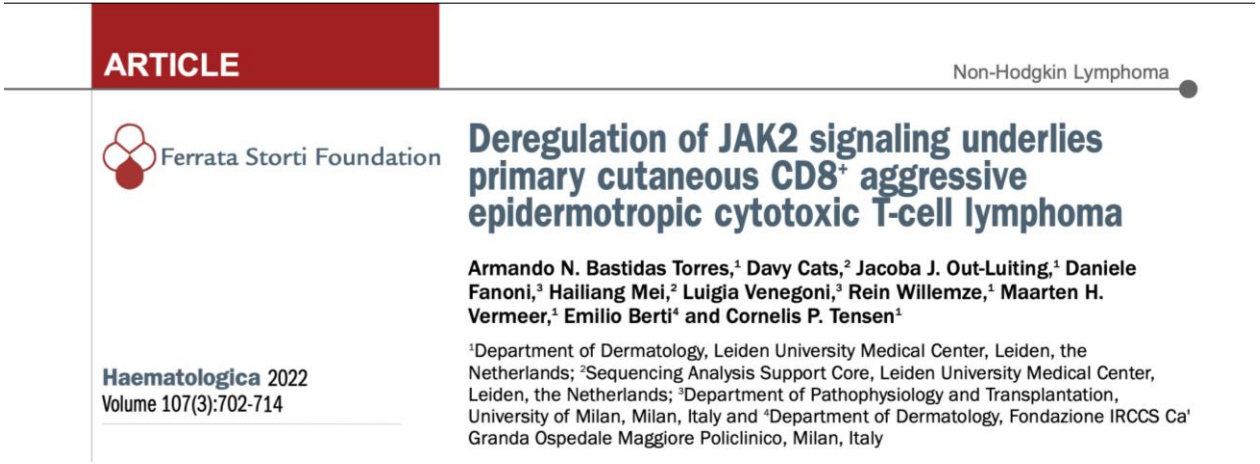


# Case 14





# Molecular alterations and Therapeutic targets



ARTICLE

Non-Hodgkin Lymphoma

Ferrata Storti Foundation

## Deregulation of JAK2 signaling underlies primary cutaneous CD8+ aggressive epidermotropic cytotoxic T-cell lymphoma

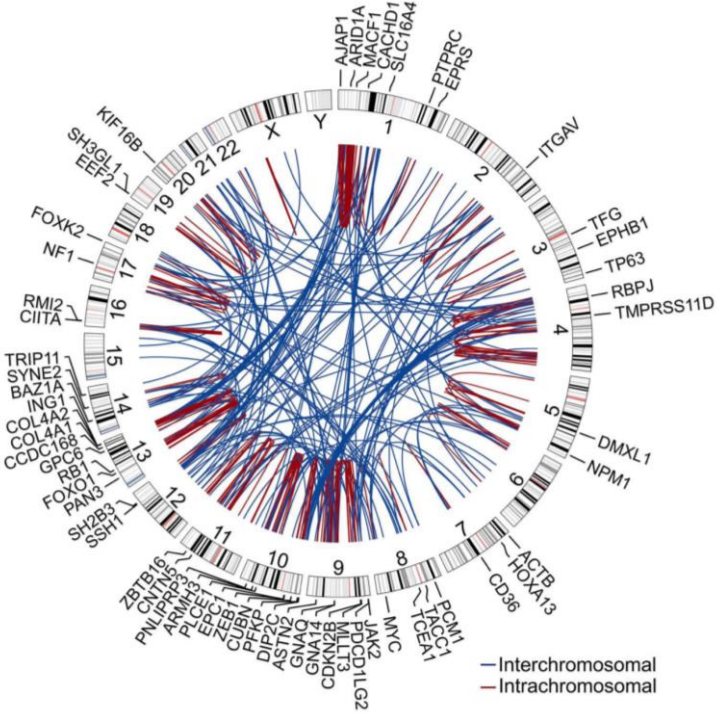
Armando N. Bastidas Torres,[1] Davy Cats,[2] Jacoba J. Out-Luiting,[1] Daniele Fanoni,[3] Hailiang Mei,[2] Luigia Venegoni,[3] Rein Willemze,[1] Maarten H. Vermeer,[1] Emilio Berti[4] and Cornelis P. Tensen[1]

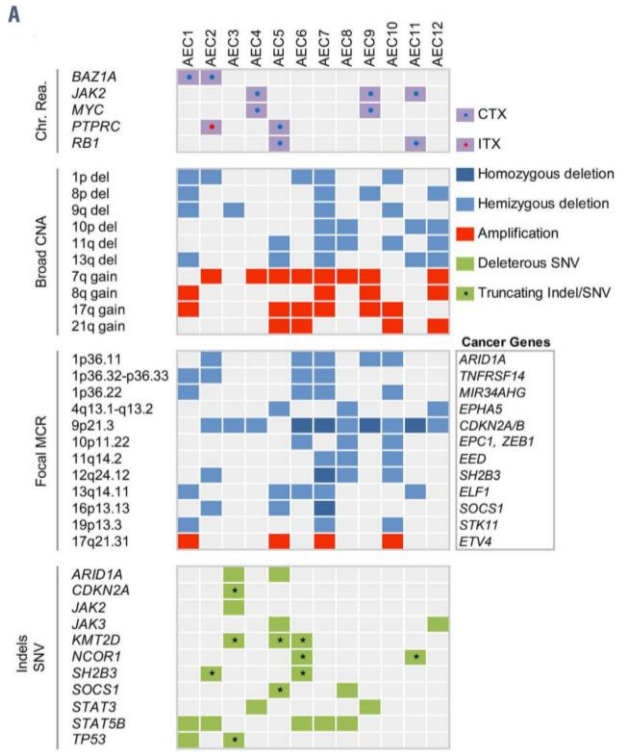
[1]Department of Dermatology, Leiden University Medical Center, Leiden, the Netherlands; [2]Sequencing Analysis Support Core, Leiden University Medical Center, Leiden, the Netherlands; [3]Department of Pathophysiology and Transplantation, University of Milan, Milan, Italy and [4]Department of Dermatology, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy

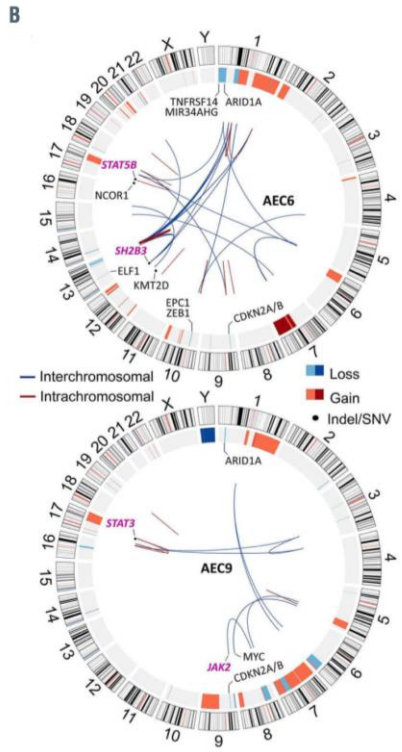
Haematologica 2022
Volume 107(3):702-714

Whole genome Sequencing (n=12) and RNA seq (n=6)

# Translocations, cna and mutations



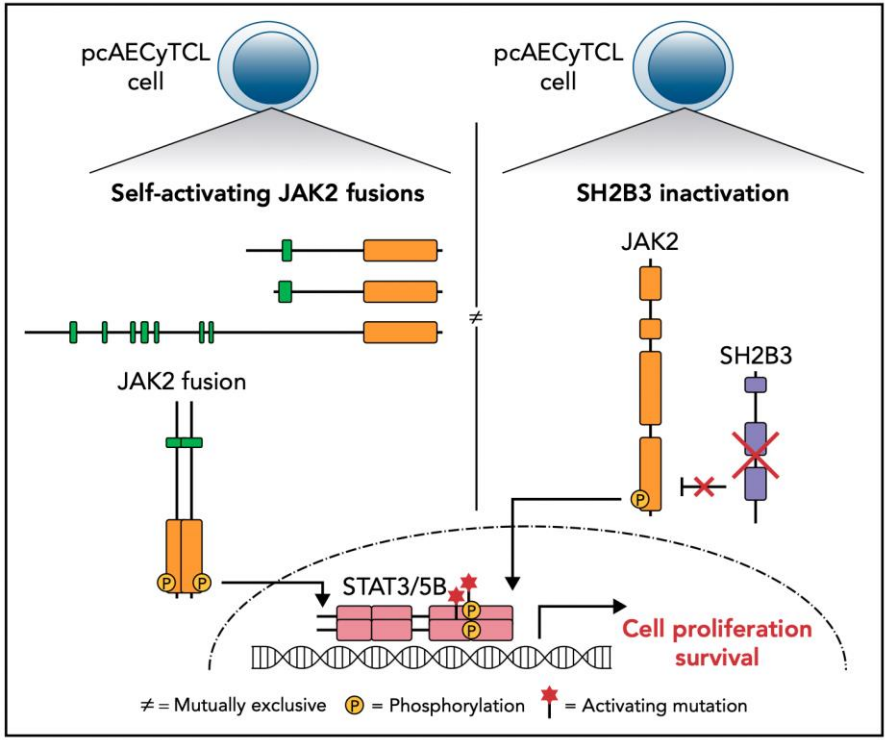



# JAK2 overactivation in AECTCL

- Overactivation of JAK2 in virtually all cases (not detected in other cytotoxic CTCLs).

- Self-activating JAK2 fusion
- Gain of function mutations:
  - *JAK2, STAT3, STAT5B*
- Loss of negative regulators:
  - *SH2B3*

- Deletion 9p21.3 (CDKN2A) in 10/12 cases (83%)




Fanoni D, et al. Genes Chromosomes Cancer. 2018;57:622-629; Bastidas Torres AN, et al. Haematologica. 2021; Lee K, et al. Blood 2021

# Conclusions

Rare and aggressive T-cel lymphoma

Often have a dismal prognosis

New and promising drugs but optimal use to be established

Progress in molecular characterization, has given insight in biology but has not changed therapeutic approach, yet

# Future: Skin as Window in Tumor Micro Environment

**Combined therapeutic approach**

- Cytotoxic drugs
  - Classic cytotoxic drugs
  - Cell surface directed
- Inhibition of cell signaling
- Immune checkpoint
- Cellular therapies

**Translational research**

- Bioavailability of drugs (MALDI-TOF)
- Tumor infiltrate (CyTOF)
- Spatial transcriptomics
- Single cell NGS

Monitor changes in Tumor cells and Tumor Immune Response

# EORTC Cutaneous Lymphoma
# Leiden The Netherlands 21-23 September

## LEIDEN
## The Netherlands

### HISTORIC CENTER

- 28 kilometers of canals
- More than 3000 registered monuments
- 35 almshouse courtyards
- 88 bridges connecting the streets

### CULTURAL HERITAGE

- 13 Museums in walking distance
- Birthplace of the Dutch painter Rembrandt
- European city of Science 2022

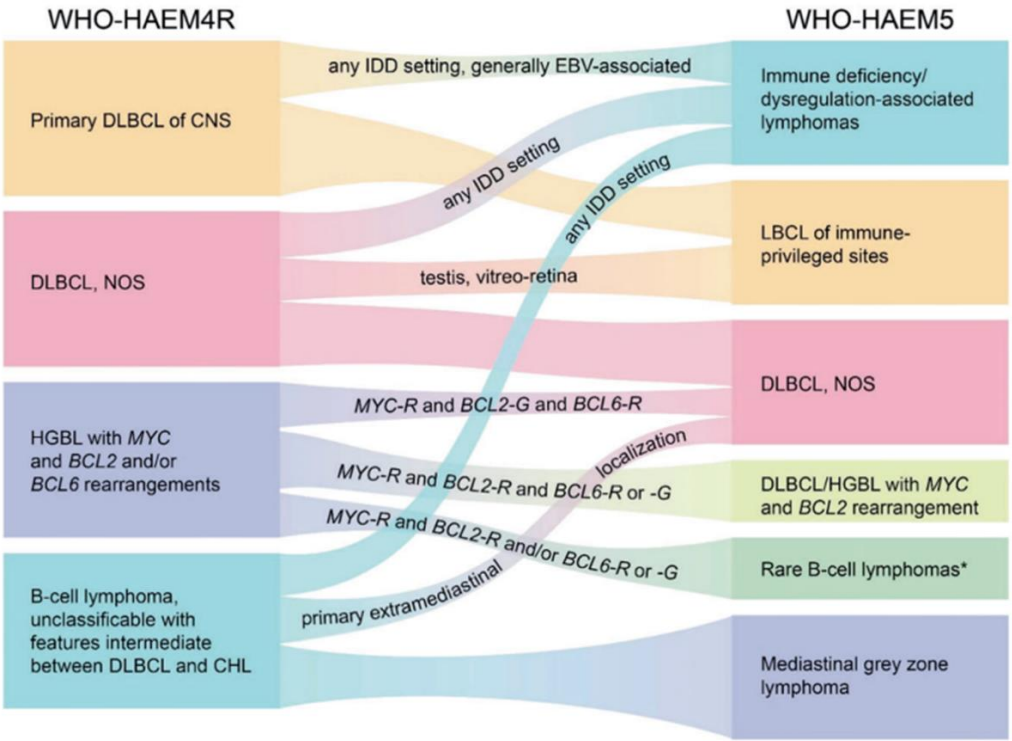
### BIOSCIENCE PARK

- Largest Life Science & Health cluster in the Netherlands with 150 LSH companies
- 6 Education institutions

Leiden University
Medical Center

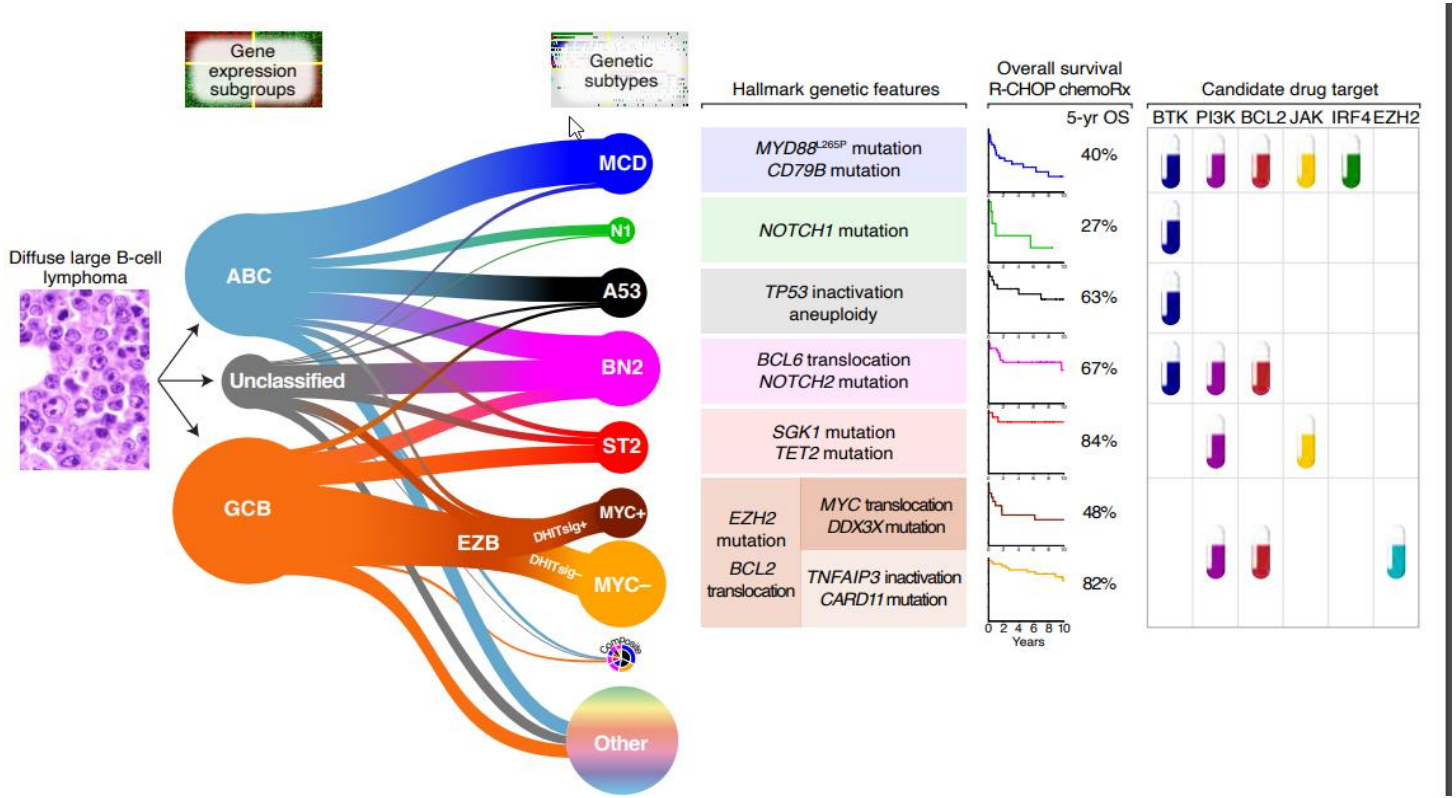
# Future developments…

Incorporation of genetic alterations in classification



# Future developments….

Incorporation of genetic alterations in classification and treatment



# PC Gamma-Delta TCL: Conclusions

Cell of origin (Vδ1 or Vδ2) correlates with clinical presentation and histology and prognosis is unclear.

| Cell of Origin | Vδ1 | Vδ2 |
|---|---|---|
| Clinic | Plaques | Nodules |
| Histology | Epidermal | Dermal |
| Survival (median) | 30 | 12 |

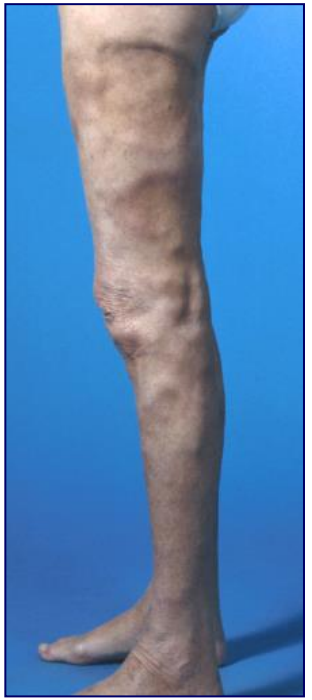
# New Developments

1. Subcutaneous Panniculitis T-Cell Lymphoma
- Germline mutation predisposes for SPTL
- Biological insight in relation with lupus

2. Primary Cutaneous Gamma-Delta T-cell lymphoma
- Cell of origin corelates with clinical presentation

# Subcutaneous Panniculitis-like T-cell Lymphoma (SPTL)

- Rare type of CTCL (<1% of CTCL)
- Young (median age 36 years), female > male
- Subcutaneous nodules and tumors resulting in lipodystrophy.
- Systemic B-symptoms (fever, malaise)



- CD8+, cytotoxic T-cells infiltrating subcutaneous adipose tissue with rimming of individual fat cells.
- By definition TCRάβ

# Subcutaneous panniculitis-like T-cell lymphoma (WHO-EORTC: only alpha/beta positive cases!)

Staging: complete

First choice of treatment:

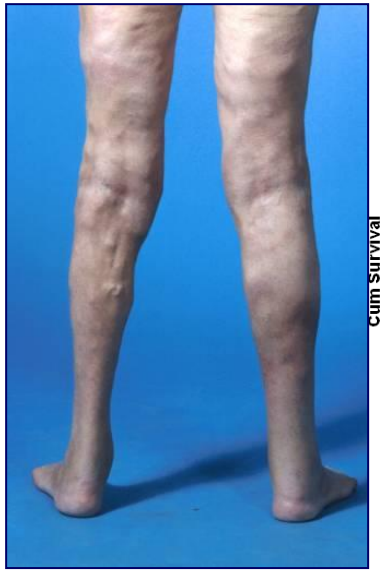
- prednison, methotrexate
- ciclosporin
- radiotherapy

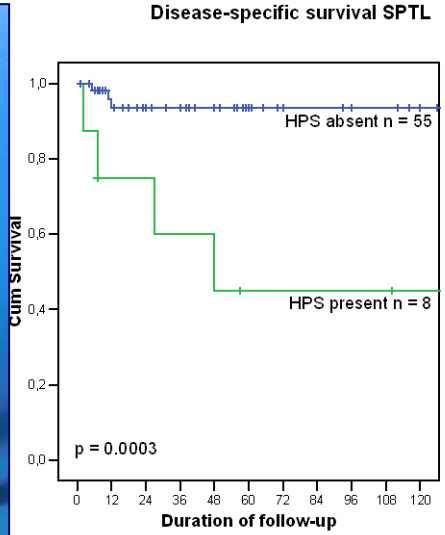
If not responsive:

- systemic chemotherapy

Prognosis

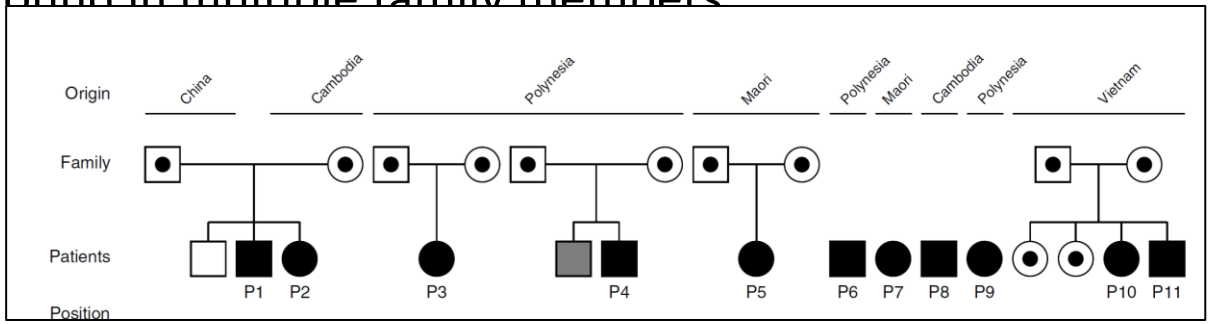
- Five-year survival >80%
- Around 20% hemophagocytic





# SPTL: clinical observations

SPTL found in multiple family members




LETTERS
https://doi.org/10.1038/s41588-018-0251-4
nature genetics
Corrected: Author Correction

**Germline *HAVCR2* mutations altering TIM-3 characterize subcutaneous panniculitis-like T cell lymphomas with hemophagocytic lymphohistiocytic syndrome**

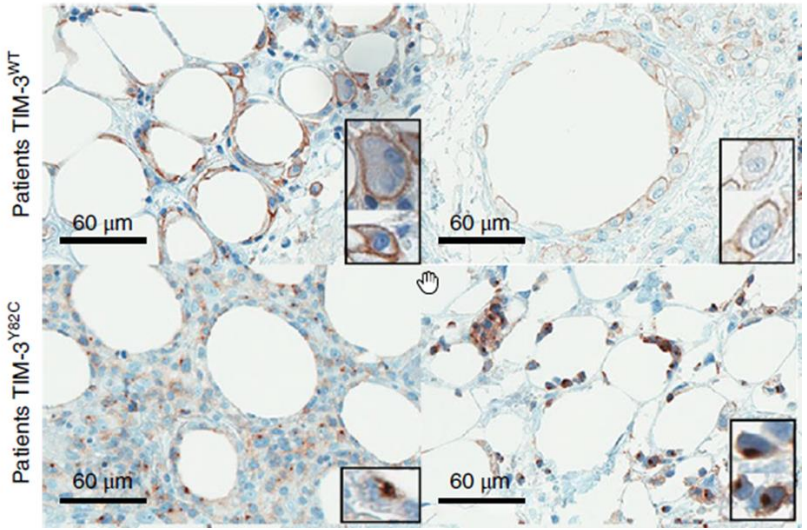
# HAVCR2 mt is associated with SPTL

- HAVCR2 encodes TIM3 a checkpoint molecule regulating immune response

- HAVCR2mt → impaired folding, decreased expression and loss of function of TIM3 protein → loss of immune checkpoint → ongoing cytokine production and inflammation

Mutations include:

- Y82C Asian, polynesia
- I97M Europe
- T101I Asian




Gayden Nature Gen 2018

# Other case series confirm *HAVCR2*mt in SPTL

REGULAR ARTICLE

blood advances

Frequent germline mutations of *HAVCR2* in sporadic subcutaneous panniculitis-like T-cell lymphoma

REGULAR ARTICLE

blood advances

Genetic profiles of subcutaneous panniculitis-like T-cell lymphoma and clinicopathological impact of *HAVCR2* mutations


TO THE EDITOR:

HAVCR2 mutations are associated with severe hemophagocytic syndrome in subcutaneous panniculitis-like T-cell lymphoma

# SPTL Case series

| | Sonigo (France) | | Koh (Korea) | | Polprasert (Thailand and Japan) | |
|---|---|---|---|---|---|---|
| SPTL | SPTL mt | SPTL wt | SPTL mt | SPTL wt | SPTL mt | SPTL wt |
| N = | 5 I97M<br>8 Y82C | 40 | 25 y82C | 24 | 11 Y82C | 2 |
| Age (med.) | 34 | 44 | 26 | 40 | 32 | 30 |
| F:M | 10:3 | 31:9 | 16:9 | 18:6 | 7:4 | 2F |
| Severe HLS | 3/13 | 0/40 | 13/24 | 1/23 | 3/11 | 1/2 |
| RFS (mo) | na | na | 57 | 11 | na | na |

Sonigo Blood 2019, Blood Adv, Koh Blood Adv 2021

# SPTL: Conclusions

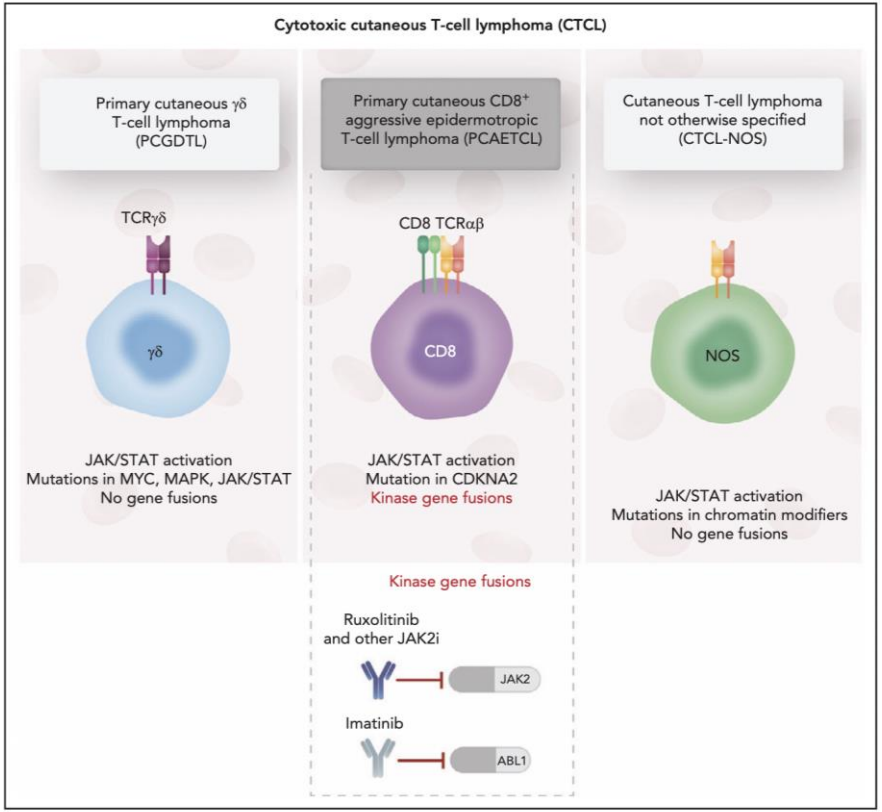
SPTL are associated with germline HAVCR2 mutations

Patients from different geographical regions have different HAVCR2 mutations

But all HAVCR2 mutations lead to loss of TIM3 expression

SPTL patients with HAVCR2 mutations:

- Are younger
- More often complicated by HLS
- Shorter RFS


Cytotoxic cutaneous T-cell lymphoma (CTCL)
Primary cutaneous γδ T-cell lymphoma (PCGDTL)
Primary cutaneous CD8+ aggressive epidermotropic T-cell lymphoma (PCAETCL)
Cutaneous T-cell lymphoma not otherwise specified (CTCL-NOS)
TCRγδ
γδ
CD8 TCRαβ
CD8
NOS
JAK/STAT activation
Mutations in MYC, MAPK, JAK/STAT
No gene fusions
JAK/STAT activation
Mutation in CDKNA2
Kinase gene fusions
JAK/STAT activation
Mutations in chromatin modifiers
No gene fusions
Kinase gene fusions
Ruxolitinib and other JAK2i
JAK2
Imatinib
ABL1