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BIOLOGIC INSIGHTS

A-164

B cells are associated with aggressive Cases of Cutaneous T cell Lymphoma and a distinct spatio-temporal composition of the tumor microenviroenment

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Background
CTCL usually runs an indolent course, but patients in advanced stages (≥IIB) and presence of risk factors, i.e. increased LDH, large cell transformation and age >60 years, have a significantly worse prognosis. We and others have previously shown that aggressive or advanced CTCL cases have increased B cell infiltration in the tumor microenvironment. However, the biological relevance and underlying mechanisms need to be determined. Therefore, we performed an in-depth characterization of the spatio-temporal, cellular composition of the microenvironment of CTCL patients with a B-cell centered focus.

Methods
Clinically annotated fixed and formalin embedded CTCL tumor samples of 36 patients from two academic medical centers (Cologne, Munich) were analyzed, using multiplex immunohistochemistry (IHC, Vectra Polaris) as well as bulk (Nanostring) and spatial (10x Visium) mRNA expression analyses to characterize the cellular and transcriptional composition of these CTCL samples stratified by their B cell content and clinical course. To address the B cell – CTCL axis on a functional level, *in vitro* experiments were performed on four CTCL cell lines (SeAx, MyLa, HuT78 and HH) and human B cells from healthy donors.

Results
Multiplex IHC revealed that B cells were enriched in aggressive and advance stage CTCL subtypes and formed complex networks distinct from those in indolent CTCL cases. Gene expression analyses confirmed the B cell enrichment observed in IHC and uncovered distinct gene expression patterns including an M2 macrophage pattern in aggressive, B cell rich CTCL cases. Spatial gene expression analyses not only suggested a local M2 - B cell – CTCL interaction but also profound metabolic alterations of these tumors. At a functional level, factors derived from B cells and M2 macrophages were observed to modulate CTCL cell proliferation, migration, and metabolic profiles in a tumor-promoting manner. This modulation seem to effect the efficacy of treatments with drugs such as bexarotene, methotrexate, and ruxolitinib *in vitro.*

Conclusions
We demonstrate that tumor-infiltrating B cells and Tumor-associated immunosuppressive macrophages interact in the CTCL tumor microenvironment and shape a tumor promoting milieu. Detailed analyses of key molecular mechanisms are ongoing.

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CD30+ Primary Cutaneous Follicle Center Lymphoma: an atypical immunohistochemical profile

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Background
Primary cutaneous follicle center lymphoma (pcFCL) is a low-grade B-cell lymphoma with an excellent prognosis, characterized by slow-growing erythematous violaceous plaques, nodules, or tumors. Its histopathology displays irregular nodules mimicking follicles or sheets of medium-sized B cells expressing multiple germinal center markers, commonly BCL6, alongside varied immunohistochemical findings with a low Ki-67 expression.
We present a patient with a typical histopathology of a pcFCL, but an unusual expression of CD30 marker, which meant a challenging case both diagnostically and therapeutically.

Methods
A 49-year-old patient with history of Graves disease, hypertension since childhood and Jessner Lymphocytic Infiltration referred from another healthcare center with the diagnosis of a pcBCL. Physical examination revealed a slightly infiltrated erythematous linear scar secondary to surgical resection in the right scapular region. Regarding histopathology, a lymphoid proliferation with a nodular distribution pattern was evident at the superficial and deep dermal level, consisting of atypical B cells (CD20+), with large diameter nuclei with hyperchromatic chromatin and irregular nuclear contours with abundant cytoplasm. Immunohistochemistry showed an atypical B population with BCL2 expression (strong but irregular), BCL6, and CD30 highly positive, being negative for MUM1, CD10, CD3, CD5, CYCLIN D1, CD23. In addition, detection of Epstein-Barr virus turned out to be negative. The final diagnosis was a pcFCL, CD30+ with a diffuse pattern and Ki 67 of 70%. The results of the positron emission tomography did not show images of pathological concentrations, the bone marrow biopsy was normal and the laboratory studies had no alterations.

Results
The case was discussed with specialists in hematology and pathological anatomy, and it was decided to begin treatment with local radiotherapy associated with systemic treatment with rituximab.

Conclusions
In this case, an atypical presentation of what is assumed to be a cutaneous low-grade B cell lymphoma is presented. Due to the presence of CD30+ cells and the uncertainty of its meaning, an anti-CD20 treatment was added to local radiotherapy. There are few reports in the literature of low-grade lymphomas with CD30 expression, so interdisciplinary management and a careful follow up is essential to approach a proper diagnosis and treatment.

A-187

Circadian Rhythms in Hematological Malignancies

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Background
The circadian clock is a ubiquitous cellular mechanism regulating rhythmic functions across organs. At the molecular level, it involves interlinked transcription–translation feedback loops with key genes such as *CLOCK*, *BMAL1*, *NPAS2*, *PERs*, *CRYs*, *RORs* and *REV-ERBs*, which orchestrates the 24-hour expression of numerous genes and biological processes (1). Disruptions can lead to lymphomas such as cutaneous lymphomas, a subset of non-Hodgkin lymphomas (NHL) that primarily affect the skin (2). Therefore, the circadian clock can be a promising target for identifying novel prognostic markers and therapeutic interventions.

Methods
We evaluate the daily expression patterns of core-clock genes *BMAL1* and *PER2* in three human T-cell lymphoma cell lines—HH, Hut 78, and Jurkat—using lumiCycle luminometry and RT-PCR as models for hematological malignancies.

Results
The circadian oscillations dampen over time due to desynchronization in the absence of SCN signals. Additionally, lower BMAL1 expression correlates with higher PER2 mRNA levels.

Conclusions
our findings advance the current understanding of the potential role of the core-clock in the pathobiology of human T-cell lymphoma. Moving forward, our research aims to enhance cancer treatment through optimized chemotherapy timing aligned with circadian rhythms. This approach can maximize therapeutic efficacy and reduce systemic toxicities through both pharmacological and non-pharmacological agents.

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Clonal evolution, antigens, and triggers in Cutaneous T Cell Lymphoma pathogenesis

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Background
Among lymphomas, CTCL is uniquely characterized by the striking dermal tropism of transformed T cells—at the primary barrier between our bodies and the outside environment. Triggers of CTCL initiation and progression are poorly understood.

Methods
We utilized multimodal single-cell analysis to examine gene expression, surface phenotype, and clonality of circulating malignant cells and tumor microenvironment of skin tumors in advanced mycosis fungoides and Sezary disease.
We also leveraged our genetically engineered mouse model (GEMM) of CTCL to evaluate the role of microbial triggers and skin irritation in CTCL initiation and progression.

Results
Because little is known about the transcriptional and genomic relationship between skin- and blood-residing malignant T cells in CTCL we sought to examine malignant clones in matched skin and blood from patients with advanced CTCL. Our multimodal single-cell analysis (ECCITE-seq) revealed clonal evolution at a transcriptional and genetic level within the malignant populations of individual patients. Transcriptional analysis revealed that skin microenvironment in CTCL promoted a distinct signature within skin resident tumor cells that supported rapid proliferation and evolution of the malignant clone.
Next, we examined the role of skin pathobionts in CTCL disease progression using a novel animal model of this malignant disease. This GEMM is based on hyperactivation of one of the pathways identified as augmented in our analysis of genetic landscape of human malignant T cells – STAT3 signaling. Analysis of germ-free vs. conventional animals revealed that skin pathobionts promote disease progression in our pre-clinical model of CTCL. We also observed that other irritants can promote disease progression in the CTCL GEMM.

Conclusions
Taken together, our studies suggest that in addition to aberrant genetic events (mutations and translocations) critical to the malignant transformation of T lymphocytes, other triggers, including skin pathobionts, contribute to disease progression.

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Cytokines in CTCL: Current Insights and Therapeutic Targets

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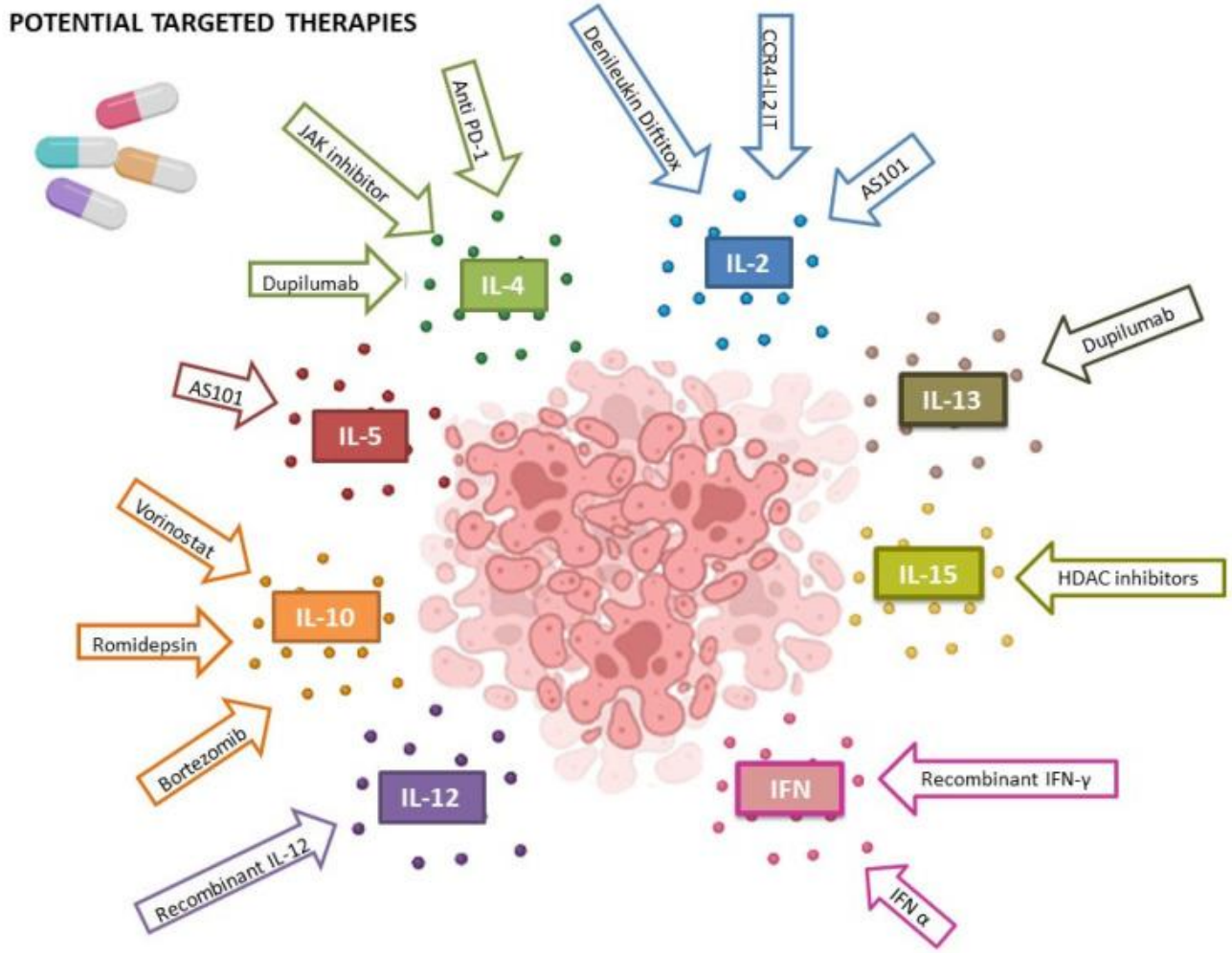
Background
Our work aimed to investigate the role of cytokines in cutaneous T-cell lymphomas (CTCLs), particularly focusing on mycosis fungoides (MF) and Sézary syndrome (SS). The goal was to understand the intricate interactions of cytokines and cellular responses in CTCL and to identify potential therapeutic targets influenced by cytokine alterations due to new emerging immunomodulatory drugs

Methods
We reviewed recent literature to summarize current scientific understanding of cytokines in CTCL. This includes other reviews and recent studies highlighting the roles of cytokines such as IFN-γ, TNF-α, interleukins (IL), growth factors, and other inflammatory mediators. Our discussion extends to genetic factors, cytokine profiles, and the role of the microenvironment in disease progression. We aimed to synthesize findings from various clinical and scientific reports to advocate for targeted therapies.

Results
Among the 40+ cytokines reviewed, Interleukin-1, -2, -5, -6, -10, IFN-γ, and TNF-α were notably significant



Potential and actual therapies to address CTCLs and their relative targets

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IL-2 enhances T cell and monocyte cytotoxicity, with therapies suggesting potential suppressive effects on CTCL, though effectiveness remains debated. IL-5 supports eosinophil activity, elevated in advanced CTCL stages, contributing to erythroderma and elevated IgE levels, potentially serving as a therapeutic biomarker.

IL-6, working with IL-1, drives inflammation and B cell differentiation; high levels in lesional skin suggest a significant role in CTCL pathogenesis and may indicate a worse prognosis in early-stage patients. IL-10, an anti-inflammatory cytokine, may facilitate tumor progression by dampening immune responses; elevated levels suggest involvement in disease progression, with drugs like Vorinostat and Romidepsin potentially downregulating it.

IFN-γ plays dual roles in cancer immunity, altering the cytokine environment and impacting tumor and immune cell dynamics. TNF-α promotes tumor growth via the NF-κB pathway; anti-TNF-α therapies have mixed results, indicating its role depends on the cytokine environment and patient response[1].

Conclusions

Understanding cytokine interactions in the cutaneous microenvironment[2] is crucial for effective CTCL treatments. Treating MF/SS requires a multi-faceted approach, balancing cytokines by reducing immunosuppressive and increasing antitumor ones, especially shifting from Th2 to Th1. Targeted therapies modulating specific cytokine pathways in CTCL pathogenesis show great promise for future research and clinical trials.

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Dissecting the role of CXCR4 in mycosis fungoides: from gene editing to therapeutic molecule

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Background

CXC chemokine receptor 4 (CXCR4) is a member of the GPCR family, overexpressed in several cancer types. Its ligand, CXCL12, is highly expressed in stromal cells, binds to CXCR4, thereby activating chemotaxis, gene transcription, survival, angiogenesis, metastasis, and proliferation. CXCR4 was identified as an essential gene for the leukemia-initiating cells in ALL. AMD3100 is the only FDA-approved CXCR4 antagonist authorized for the use in transplantation of NHL and MM patients to inhibit leukemic cell migration to the bone marrow. We previously found that primary mycosis fungoides fibroblasts (pMF-Fs) express high levels of CXCL12, the MF lymphoma cell line (MyLa) expresses high levels of CXCR4, the CXCL12/CXCR4 axis promotes MF cell survival, migration, and chemoresistance, and AMD3100 induces apoptotic death of MyLa cells. We aim to elucidate the role of CXCR4 in the cancerous phenotype of MF cells, and to develop a novel small molecule-based CXCR4 antagonist for MF.

Methods

Protein expression by immunohistochemistry, immunofluorescence, FACS, and western blot (WB). Protein phosphorylation by phospho-proteomics and WB. Viability assay by MTT, Apoptosis by FACS of annexin V and PI staining. Proliferation by FACS of CFSE staining. Gene editing by CRISPR/Cas9 technology. Gene expression by qRT-PCR. In vivo assay by MyLa xenograft mice. Drug discovery by computational structure-based drug design strategy.

Results

CXCR4 is overexpressed in MF biopsies vs inflammatory dermatoses, and in CTCL cell lines vs normal PBMCs (nPBMCs). AMD3100 exhibits selective toxicity towards MyLa cells co-cultured with pMF-Fs vs MyLa alone and nPBMCs. The CXCR4 gene was edited in MyLa cells, generating single clones with reduced CXCR4 expression (CXCR4+/-). CXCR4+/- cells exhibit slower growth rate until complete death, lower tumor volume in mice, decreased phosphorylation of prosurvival proteins, and reduced CXCR4 turnover to the cell membrane. Computational screening of small molecule libraries revealed several potential CXCR4 antagonists. One candidate, D36, demonstrated a promising anti-cancer effect in MyLa cells vs nPBMCs, pMF-Fs, and CXCR4+/- cells. D36 promotes apoptosis of MyLa cells, reduces proliferation, and exhibits a similar anti-cancer mechanism as seen in CXCR4 depleted cells.

Conclusions

CXCR4 is essential for the viability and tumor growth of MF. Our novel small molecule-based CXCR4 antagonist, D36, exhibits drug-like features and holds potential as a breakthrough in targeted therapy for MF.

A-165

Dissecting the role of macrophages in different spatial locations in Mycosis fungoides

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Background

While early-stage MF presents with patches and plaques up to one-third of MF patients progress to advanced diseases, which includes infiltrating tumors and a more unfavorable prognosis. There are few treatments available for advanced MF and better understanding of the mechanism of progression including the role of immune cells is needed. During progression of MF a shift towards an Th2 environment and an increase in myeloid cells and tumor promoting M2 macrophages was observed. The drivers of these alterations including the role of tissue localization and spatial distribution of cells are not well understood. Our aim is to uncover how different areas in the tumor alter the phenotype of macrophages either to a tumor promoting or suppressing one.

Methods

In currently ongoing experiments we are analyzing biopsies from three patches, three plaques and one tumor of seven MF patients. We are investigating macrophages through digital spatial profiling using an extensive immuno-oncological panel covering 570 proteins and protein phosphorylation. The panel includes information about signaling pathways commonly altered in cancer and multiple pro and anti-

inflammatory macrophage markers enabling us to extract valuable information.

Results
We will compare macrophages enriched areas to macrophage poor areas and dense tumor regions to sparse tumor regions, separately analyzing macrophages, identified through CD68 expression and suspected CD4-positive tumor cells and the total tumor areas. Furthermore, we aim to investigate the difference in protein expression between tumor center and periphery as preliminary data suggests that macrophages are more commonly found at the tumor margins.

Conclusions
If successful, we will identify properties of macrophages contributing to the development in MF and point towards targets for treatments.

A-243

Dissecting the Tumor Microenvironment in Mycosis Fungoides: Aberrant T Cell Subsets and Immune Profiling

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Background
In Mycosis Fungoides (MF), the heterogeneity of malignant T cells and their interaction with the tumor microenvironment (TME) are crucial for disease development and progression. This study aims to identify and quantify aberrant T cells and perform immune profiling of the TME in MF patients to uncover the cellular and molecular mechanisms driving the disease.

Methods
Skin biopsies from 26 MF patients (4 patches, 22 plaques, 7 tumors) and 4 psoriasis patients (controls) were collected. A panel of 36 antibodies targeting leukocyte surface markers, programmed death 1 protein (PD-1), programmed death-ligand 1 (PD-L1), and OX-40 was used on single-cell suspensions and analyzed by mass cytometry. scRNA-seq analysis of patch, plaque, and tumor lesions was performed using publicly available data. Group comparisons were made using the Kruskal-Wallis test, corrected by the two-stage linear step-up procedure of Benjamini, Krieger, and Yekutieli.

Results
Increased levels of two distinct aberrant T cell subsets were identified in tumors compared to plaques: $CD3^+CD4^+CD7^-CD26^-CCR4^{hi}$ (aberrant $CD4^+CCR4^{hi}$) and $CD8^+CD3^+CD7^-CD26^-CCR4^{hi}$ (aberrant $CD8^+CCR4^{hi}$). These subsets were absent in patches and controls. Conversely, aberrant $CD4^+CCR4^{low}$ T cells were elevated in patches. Tumors showed significantly increased PD-1, PD-L1, and OX-40-expressing aberrant $CD4^+CCR4^{hi}$ T cells, with $PD\text{-}L1^+$ cells exhibiting Central and Effector Memory phenotypes, and $PD\text{-}1^+$ cells displaying a Terminal Effector phenotype.
The TME of plaque and tumor lesions had a similar immune profile, except for lymphocytes. Patches lacked $CD4^+$ T cells (Central and Effector Memory), $CD8^+$ T cells (Naïve and Central Memory), and all B cell types and subtypes. Tumor-infiltrated immune cells exhibited elevated levels of PD-1-expressing T cells, indicating increased T cell exhaustion as MF progressed. Additionally, there was a significant increase in $PD\text{-}L1^+IgD^-$ Memory B cells, $PD\text{-}L1^+$ Regulatory T cells, and $PD\text{-}L1^+$M2 macrophages in tumors. scRNA-seq analysis supported these findings.

Conclusions
Aberrant $CD4^+CCR4^{hi}$ T cells may contribute to MF pathogenesis through the PD-1/PD-L1 axis, emphasizing their role in immune dysregulation within the TME.

A-136

Effects of Mogamulizumab on CD39, CD73 and CD38 ectonucleotidases expression in T-cells of Sézary syndrome patients.

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Background

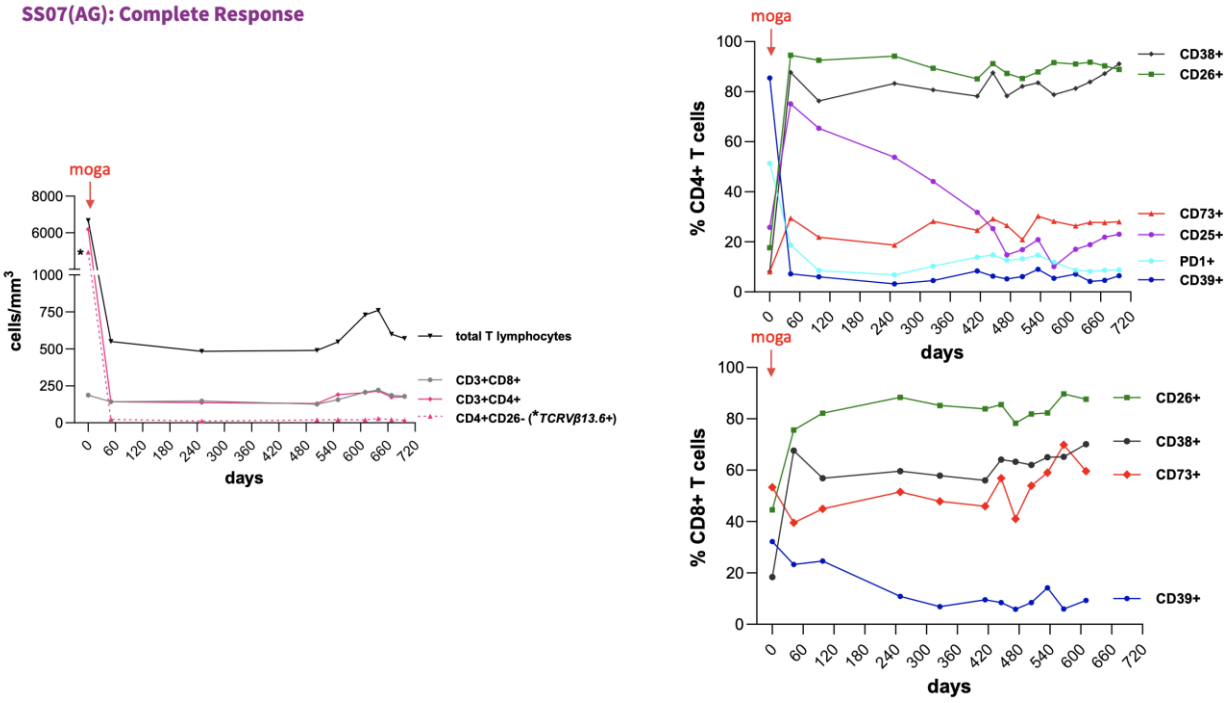
In patients with Sezary Syndrome (SS), a correlation between heightened CD39/CD73 expression and elevated extracellular adenosine concentrations has been described.[REFERENCE01] Adenosine contributes to the establishment of an immunosuppressive tumor microenvironment. Additionally, CD38 expression in SS cells has been reported to be lower than those of benign T cells from the same patients and CD4+ T cells from healthy donors. However, recent studies highlighted a significant association between high CD38 expression and reduced survival rates in aggressive forms of cutaneous lymphoma. Overall, the impact of systemic therapy on the modulation of these markers continues to be a subject of ongoing debate.

Methods

Building on preliminary data, we investigated the expression of CD39/CD73/CD38 ectoenzymes in a prospectively collected cohort of SS patients recently detailed in the literature. Whole blood multiparametric flow-cytometry was performed on CD4+ T cells, specifically the CD26– and CD26+ subsets, at initial encounter and subsequent follow-up visits. Analysis of CD39 and CD73 in the skin biopsy from each patient was performed at baseline.

Results

Over a follow-up period of 24 months, the evaluation of 8 patients treated with anti-CCR4 mogamulizumab yielded interesting outcomes. Among them, seven (87.5%) displayed early complete depletion of SS cells in the blood, partial skin response, and a significant upregulation of CD38 expression in residual circulating CD4+ T cells. Patients with GG or AG (high CD39) ENTPD1 SNP rs10748643 genotypes, showing high CD39 expression at baseline, experienced a concurrent reduction in CD39 expression. In one patient carrying the AA genotype, characterized by low CD39 and high CD73 expression at the baseline, response to treatment lead to reduction of CD73 expression.



Patient with AG genotype achieving CR

.

The only one patient unresponsive to mogamulizumab (AA genotype), showed no modulation of CD38 or CD39, while CD73 expression increased. In two out of seven responding patients, showing disease recurrence, CD39 and CD38 expression gradually increased.

Conclusions

These findings suggest mogamulizumab reduces malignant T cells in SS and affects CD39, CD73, and CD38 expression. It increases CD38 in responding patients and impacts CD39 in those with GG or GA genotypes, but not AA.This offers insights into CD38 as a potential response marker to mogamulizumab. Further research is needed to evaluate CD38 targeting in refractory SS patients.

References:

[REFERENCE01] Armand Bensussan, Baptiste Janela, Nicolas Thonnart, Martine Bagot, Philippe Musette, Florent Ginhoux, Anne Marie-Cardine, Identification of CD39 as a Marker for the Circulating Malignant T-Cell Clone of Sézary Syndrome Patients., J Invest Dermatol. 2019, doi:10.1016/j.jid.2018.09.026

A-264

Enhanced Phototherapeutic Efficacy Through Microbial Modulation in Cutaneous T-Cell Lymphoma delays tumour growth and increases survival in the murine EL4 model

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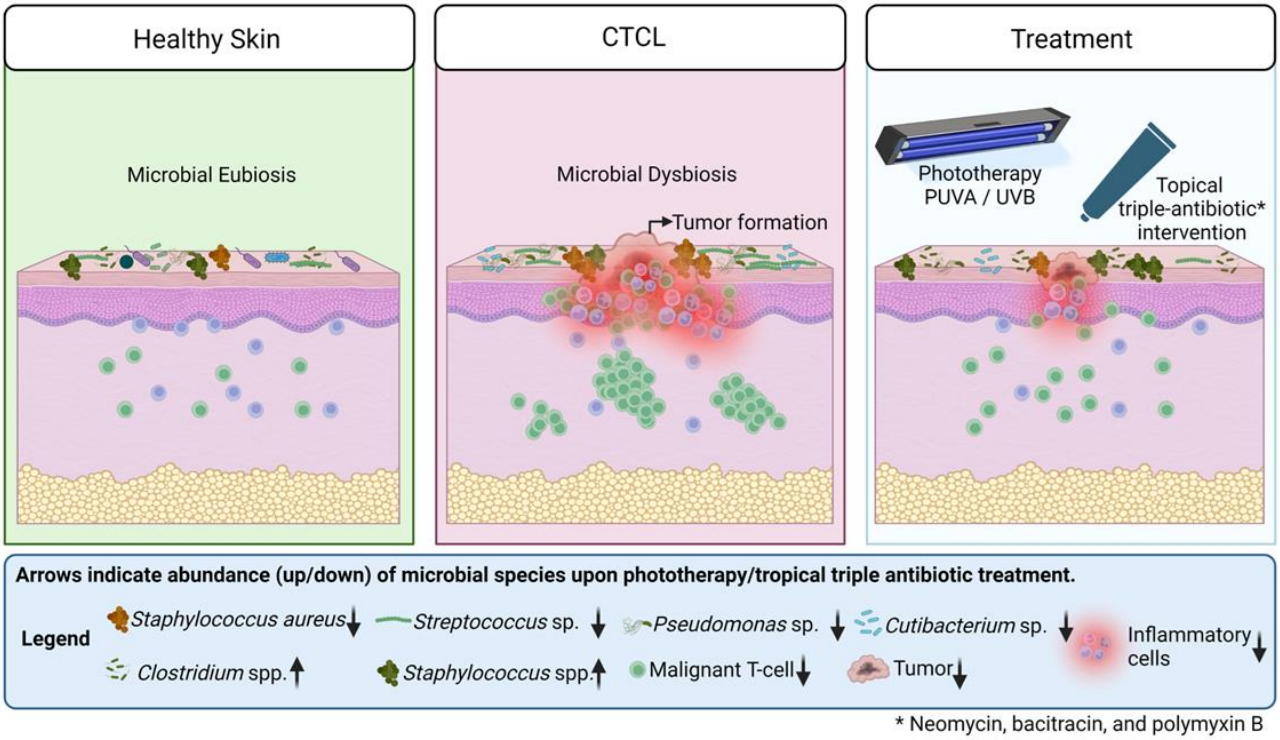
Background
Cutaneous T-cell lymphomas (CTCL), particularly in forms like mycosis fungoides and Sézary syndrome, present unique challenges due to their pathological interactions with microbial elements and resistance to conventional therapies. Our research explores the impact of phototherapeutic interventions combined with targeted microbial modulation on disease progression in CTCL.

Methods
EL4 T-cell lymphoma cells were intradermally grafted on the back of C57BL/6 mice. Animals were treated with conventional therapeutics such as psoralen + UVA (PUVA) or UVB in the presence or absence of topical antibiotic treatment (neomycin, bacitracin, and polymyxin B sulphate) as an adjuvant. Microbial colonization of the skin was assessed to correlate with disease severity and tumor growth.

Results
Triple antibiotic treatment significantly delayed tumour occurrence ($p = 0.026$), which prolonged the survival of the mice ($p = 0.033$). Allocation to phototherapeutic agents PUVA, UVB, or none of these, along with antibiotic intervention, reduced the tumour growth significantly ($p = 0.0327$, $p \leq 0.0001$, $p \leq 0.0001$ respectively). Upon modulating the skin microbiome by antibiotic treatment, we saw an increase in commensal Clostridium species, e.g., *Lachnospiraceae sp*. ($p = 0.0008$), *Ruminococcaceae sp.* ($p = 0.0001$)., Blautia sp. (p = 0.007) and a significant reduction in facultative pathogens Corynebacterium sp. ($p = 0.0009$), *Pelomonas sp.* ($p = 0.0306$), Streptococcus sp. ($p \geq 0.0001$), *Pseudomonas sp.* ($p = 0.0358$), and *Cutibacterium sp.* ($p = 0.0237$). Intriguingly, we observed a significant decrease in *Staphylococcus aureus* frequency ($p = 0.0001$) but an increase in the overall detection frequency of the *Staphylococcus* genus, indicating that antibiotic treatment helped regain the microbial balance and increased the number of non-pathogenic *Staphylococcus* populations.

Conclusions
Our findings suggest a synergistic strategy combining microbial modulation with phototherapy could support the management of CTCL, providing a dual front in the battle against this malignancy by both enhancing therapeutic outcomes and mitigating resistance pathways.



A graphical representation of the differences between healthy, CTCL lesional skin and CTCL lesional skin upon treatment. Arrows indicate abundance (up/down) of microbial species upon phototherapy along with topical antibiotic treatment as an adjuvant.

A-222

Flow cytometry of skin biopsies in CTCL patients during Mogamulizumab treatment

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Background

Cutaneous T-cell Lymphomas (CTCL) represent a group of mature T-cell-derived lymphomas, often associated with a poor prognosis in advanced cases. Mogamulizumab (Moga), a therapeutic monoclonal antibody against CCR4, is a novel treatment modality for CTCL patients with advanced (systemic) disease. Detection and characterization of skin resident tumor cells and correlation with circulating tumor cells during treatment of Moga not yet been described. Our goal was to develop a method enabling detection and immunophenotypic characterization of malignant T-cells from skin biopsies and correlate findings in skin resident tumor cells with circulating tumor cells during Moga treatment.

Methods

Of 8 patients a biopsy before treatment, followed by biopsies at 3-17 month intervals were analysed, in 3 patients samples were obtained during Moga treatment. Skin biopsies were dissociated with an optimized kit from Miltenyi and the single cell suspension was stained for flow cytometry with 14 cell surface markers and a viability stain. Stained samples were acquired with a BD Fortessa flow cytometer and manually analyzed using Infinicyt software. At the same time as a skin biopsy, blood was drawn from patients and the same 14 surface makers were assessed with flow cytometry.

Results

Skin biopsies before treatment showed tumor cells in 7/8 cases. Follow up biopsies showed tumor cells in 6 patients, while tumor cells had disappeared completely in 5 patients. The immunophenotype of tumor cells in skin with circulating tumor cells found that 93% of the samples (13/14) had a consistent immunophenotype (Fig1). The remaining case differed in expression of CD2. In all patients over time the phenotype of the tumor cells in skin did not change. In 5/11 cases the tumor cells were no longer detected in the skin under treatment of Moga; in 6/11 cases the tumor cells were no longer detected in the blood under treatment of Moga. 2/11 patients progressed during Moga treatment and succumbed to the disease.

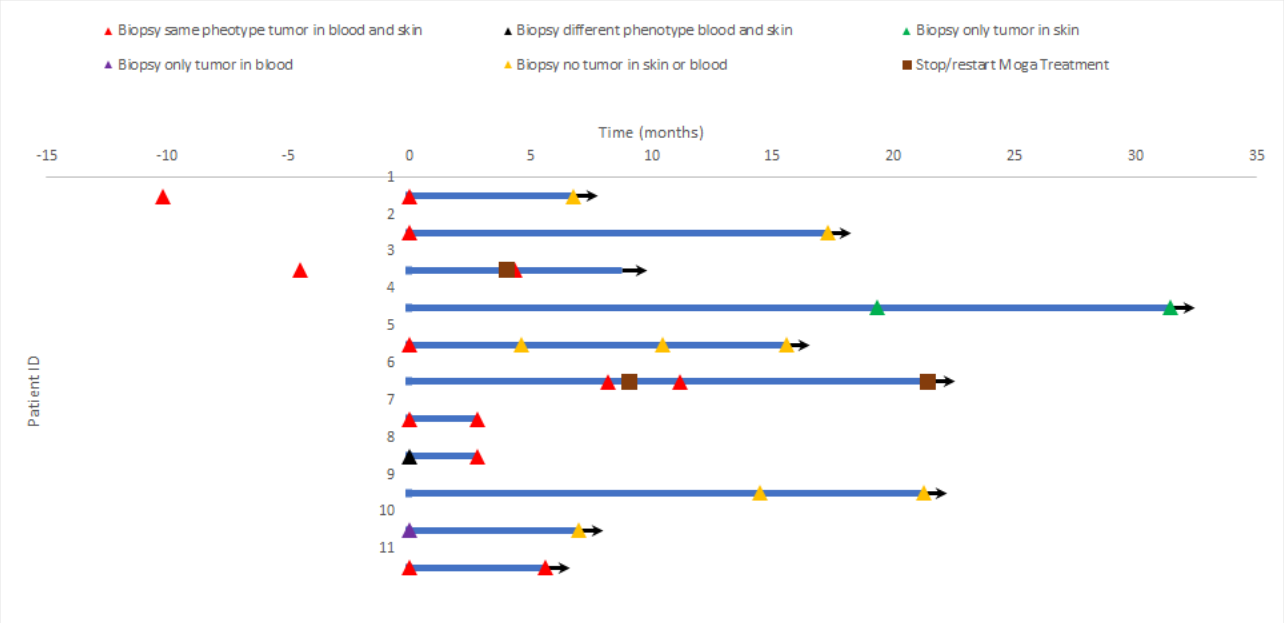

Fig 1: Overview of correlation of immunophenotype of tumor cells in skin and blood.

Conclusions

We conclude that our described method is able to characterize and monitor skin resident tumor cells in CTCL patients. Furthermore, we conclude that under the pressure of systemic Moga therapy the phenotype of skin resident tumor cells in CTCL patients does not change.

A-276

Immunogenic Cell Death (ICD) and ICD-dependent Dendritic Cell Activation triggered by Extracorporeal Photopheresis in CTCL

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Background

Immunogenic cell death (ICD) has emerged as a crucial mechanism in cancer immunotherapy, characterized by the release of damage-associated molecular patterns (DAMPs) that promote dendritic cell (DC) maturation and cytotoxic T lymphocyte (CTL) responses. Extracorporeal photopheresis (ECP) is a chemophototherapy used for cutaneous T-cell lymphoma (CTCL) treatment, involving leukapheresis, 8-methoxypsoralen (8-MOP) administration, and UVA irradiation of leukocytes. This study investigates whether ECP induces ICD in CTCL patients and healthy donors and its ability to induce DC activation.

Methods

We utilized an in vitro model to study ECP in detail. Furthermore, patients with CTCL were treated with ECP and blood samples were analyzed.

Results

In *in vitro* ECP treated healthy peripheral blood mononuclear cells (PBMCs) and ECP-treated white blood cells (WBCs) from CTCL patients we observed significant markers of ICD, including ATP release, HMGB1 secretion, and surface calreticulin (CALR) exposure. Our results demonstrated reduced cell viability and increased cell death in ECP-treated samples. Gene expression analysis showed significant upregulation of ICD-related genes, confirming ICD induction.

In CTCL patients, elevated CALR expression was notably higher in malignant T cells ($CD26^-$), suggesting greater susceptibility to ICD. We further demonstrated that ECP-treated $CD4^+$ T cells were phagocytosed by DCs, and this process was dependent on ICD signals, as blocking CALR and ATP halted phagocytosis.

Conclusions

Our findings reveal that ECP induces ICD in malignant T cells, and also - to a lower extent - in healthy T cells, facilitating DC activation and antigen presentation. These results underscore ECP's potential in enhancing targeted immune response to malignant T cells in CTCL, offering new insights into its therapeutic mechanisms and applications in cancer immunotherapy.

A-227

Improved detection of molecular disease using a personalized cell-free DNA assay in patients with cutaneous T-cell lymphoma

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Background

Biological and clinical heterogeneity poses challenges in the management of cutaneous T-cell lymphomas (CTCL). Disease assessment requires integrating evaluations of multiple disease compartments. Next-generation sequencing (NGS) assays using circulating cell-free DNA (cfDNA) show potential utility in assessing disease burden and detecting residual disease from multiple body compartments in patients with other lymphoma types. Here, we prospectively evaluated the performance of a personalized cfDNA-based NGS assay to monitor the disease status of 18 patients with advanced CTCL undergoing treatment.

Methods

Due to the genetic heterogeneity of CTCL, we identified patient-specific somatic variants and TCR clonotypes through whole exome sequencing. We then generated a customized hybrid-capture panel to track patient-specific lymphoma variants and TCR clonotypes. This personalized approach included 62 genes known to be recurrently altered in CTCL, as well as 25-389 mutations per patient, and 3-6 lymphoma TCR clonotypes per patient. Barcoded DNA libraries were prepared with cfDNA isolated from plasma and cellular DNA isolated from peripheral blood mononuclear cells (PBMCs). Libraries were enriched by hybrid capture and sequenced on an Illumina NovaSeqX.

Results

By analyzing the cellular (circulating PBMCs) and plasma (cfDNA) fractions of peripheral blood from the same timepoint, we found that detection of circulating tumor DNA by somatic variant tracking was significantly more sensitive in plasma than in cells (78% vs. 33%, Fisher’s exact test, p=0.0176), and levels of molecular disease were significantly more abundant in plasma as well (Wilcoxon test, p=0.0419). Detection of lymphoma-specific TCR clonotypes through hybrid capture was similar in cell-free and cellular fractions (67% vs. 56%, Fisher’s exact test, p=0.7). Detection of minimal residual disease (MRD) through integrated assessment of somatic variants and lymphoma TCR clonotypes suggested better detection of molecular disease by our cfDNA NGS approach as compared to commercial TCR high-throughput sequencing assays using cellular DNA (84% vs 63% sensitivity, p=0.27). Through the analysis of serial plasma samples during treatment, we observed that levels of molecular disease reflected response to therapy.

Conclusions

Overall, our findings suggest that detection of circulating tumor cfDNA may improve MRD detection and has potential clinical utility for disease surveillance in CTCL.

A-274

Indolent primary cutaneous B-cell lymphomas resemble persistent antigen reactions without signs of dedifferentiation

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Background

Primary cutaneous B-cell lymphomas comprise a heterogeneous group of extranodal non-Hodgkin lymphomas. While primary cutaneous diffuse large B-cell lymphoma - leg type (pcDLBCL-LT) is highly aggressive, the two other subtypes, primary cutaneous follicle centre lymphoma (pcFCL) and primary cutaneous marginal zone lymphoma (pcMZL), also termed primary cutaneous marginal zone lymphoproliferative disorder, usually follow an indolent course.

Methods
We here present an update of our single-cell RNA-sequencing study of pcFCL, pcMZL, and pcDLBCL-LT skin lesions in comparison to samples from benign reactive B-cell rich lymphoid proliferation (rB-LP) lesions, gastric MALT lymphoma, nodal FCL, and nodal DLBCL.

Results
Our data show that pcMZL and pcFCL, as well as rB-LP, showed a persistent germinal centre reaction, with all support cells and continuous somatic hypermutation within the expanded clone. By contrast, malignant clones of pcDLBCL-LT and gastric MALT lesions lacked these features. Further, pcMZL top expanded clones originated from naïve and not post-germinal centre B cells as currently presumed. Therefore, pcMZL may represent a non-malignant reaction against a yet to be determined antigen. Conversely, in pcFCL, B cells show a significantly larger clonal expansion, presumably through acquisition of a driver mutation. Nevertheless, these clones were still undergoing continuous somatic hypermutation. This may be linked to the lack of further differentiation of B cells in pcFCL, in contrast to nodal FCL, and may cause its indolent clinical course.

Conclusions
In contrast to pcDLCBL-LT, our data thus indicate that pcMZL and pcFCL, similar to rB-LP are characterised by a functional germinal centre reaction likely driven by antigen recognition which supports the classification of pcMZL as a lymphoproliferative disease.

A-258

JAK2 rearrangements in indolent CD8+ cytotoxic mycosis fungoides

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Background
Rearrangements in JAK2 have been occasionally documented in different groups of cutaneous T-cell lymphomas (CTCL), often presenting a cytotoxic profile (γδ T-cell lymphomas, CTCL-NOS, and CD8+ aggressive epidermotropic CTCL), leading to JAK/STAT pathway activation. Additionally, recurrent mutations in the JAK-STAT pathway have been identified in cases of primary cutaneous anaplastic large cell lymphoma and lymphomatoid papulosis.

Methods
The presence of JAK2 translocations/rearrangements was evaluated in a consecutive cohort of 55 patients with different subtypes of CTCL including classic mycosis fungoides (MF) (n: 14), folliculotropic MF (n: 11), CD8+ MF (n: 5), Sézary syndrome (n: 5), lymphomatoid papulosis (n: 10), aggressive cytotoxic CD8+ epidermotropic CTCL (n: 1), peripheral T cell lymphomas-NOS (n: 3) and primary CD30+ anaplastic large cell lymphoma (n: 6).
FISH technique was performed on formalin-fixed paraffin-embedded tissue sections from skin biopsies. JAK2 and MYC Break-Apart probes (Metasystems and Abbott Molecular, respectively) were applied in all cases. In JAK2 rearranged samples, t (8;9) PCM1/JAK2 dual fusion (Metasystems) was also evaluated. Deletion of CDKN2A loci (9p21) was analyzed in 8 cases using Vysis LSI CDKN2A SpectrumOrange/CEP 9 Spectrum Green Probes (Abbott Molecular).

Results
JAK2 rearrangements were detected in seven patients, including the three cases of indolent CD8+ cytotoxic MF (3 out of 5 patients), two cases of lymphomatoid papulosis (2/10), and two cases of folliculotropic MF (2/11) The fusion gene PCM1:JAK2 was detected in one patient with folliculotropic MF.
Conclusions
JAK2 rearrangements seem to be a non-exceptional feature in patients with CD8+ MF presenting clinically patches and/or plaques involving less than 10% of the skin surface (stage IA), showing a cytotoxic phenotype and an indolent evolution over years. None of those patients presented features of other more aggressive cytotoxic lymphomas such as primary cutaneous gd T-cell lymphoma or primary cutaneous CD8+ aggressive epidermotropic T-cell lymphoma. This observation expands the spectrum of CTCL presenting JAK2 rearrangements and illustrates that genetic activation of JAK/STAT pathway may be present in indolent forms of CTCL that could be candidates for more specific therapeutic interventions.

A-199

Keratinocytes Present Staphylococcus aureus Enterotoxins and Promote Malignant and Nonmalignant T Cell Proliferation in Cutaneous T-Cell Lymphoma

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Background

Cutaneous T-cell lymphoma is characterized by malignant T cells proliferating in a unique tumor microenvironment dominated by keratinocytes (KCs). Skin colonization and infection by Staphylococcus aureus are a common cause of morbidity and are suspected of fueling disease activity.

Methods

Single-cell seuqencing data from public dataset were analyzed. *In vitro* experiments on coculturing malignant-, non-malignant T cells and keratinocytes were designed. Flow cytometry, RT-qPCR, transient transfection, Cytokine secretion profile analysis were used to prove the hypothesis.

Results

In this study, we show that expression of HLA-DRs, high-affinity receptors for staphylococcal enterotoxins (SEs), by KCs correlates with IFN-γ expression in the tumor microenvironment. Importantly, IFN-γ induces HLA-DR, SE binding, and SE presentation by KCs to malignant T cells from patients with Sézary syndrome and malignant and nonmalignant T-cell lines derived from patients with Sézary syndrome and mycosis fungoides. Likewise, preincubation of KCs with supernatant from patient-derived SE-producing S aureus triggers proliferation in malignant T cells and cytokine release (including IL-2), when cultured with nonmalignant T cells. This is inhibited by pretreatment with engineered bacteriophage S aureus-specific endolysins. Furthermore, alteration in the HLA-DR-binding sites of SE type A and small interfering RNA-mediated knockdown of Jak3 and IL-2Rγ block induction of malignant T-cell proliferation. In conclusion, we show that upon exposure to patient-derived S aureus and SE, KCs stimulate IL-2Rγ/Jak3-dependent proliferation of malignant and nonmalignant T cells in an environment with nonmalignant T cells.

Conclusions

This study suggest that KCs in the tumor microenvironment play a key role in S aureus-mediated disease activity in cutaneous T-cell lymphoma. (Study has been published in *Journal of Investigative Dermatology*, DOI: 10.1016/j.jid.2024.04.018)

A-285

MHC-I Upregulation Safeguards Neoplastic T Cells in the Skin Against NK Cell-mediated Eradication in Mycosis Fungoides

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Background

Impairment of cellular immunity in cancer is a major hurdle to therapy. With the discovery of antibodies targeting tumor cell-surface antigens we witnessed remarkable advances in blood cancer. However, many tumors of hematopoietic origin in the skin remain resistant.

Methods

Here we use a clonality-supervised deep learning approach to identify cancer-predicting genes and the major histocompatibility complex (MHC)-I as a major T-cell lymphoma tumor intrinsic features of cancer immune evasion in the skin.

Results

In humans, MHC-I hindered natural killer (NK) cell function and antibody dependent cellular cytotoxicity and conferred skin tumor resistance to cell-surface antigen targeted therapeutic antibodies. In mice, blockade of the MHC-I interaction with NK cells' inhibitory Ly49 receptors restored anti-T-cell lymphoma activity *in vivo* and resulted in lymphoma elimination by tumor cell-surface antigens directed treatment.

Conclusions

These findings demonstrate how attenuation of MHC-I dependent tumor-driven immunosuppressive networks can revitalize NK cell antitumor activity to overcome resistance to therapy.

A-250

Modes of metastasis: scRNAseq profiling of cutaneous T-cell lymphoma highlights CXCL13, TUSC3, and ANK1 in malignant T cells

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Background

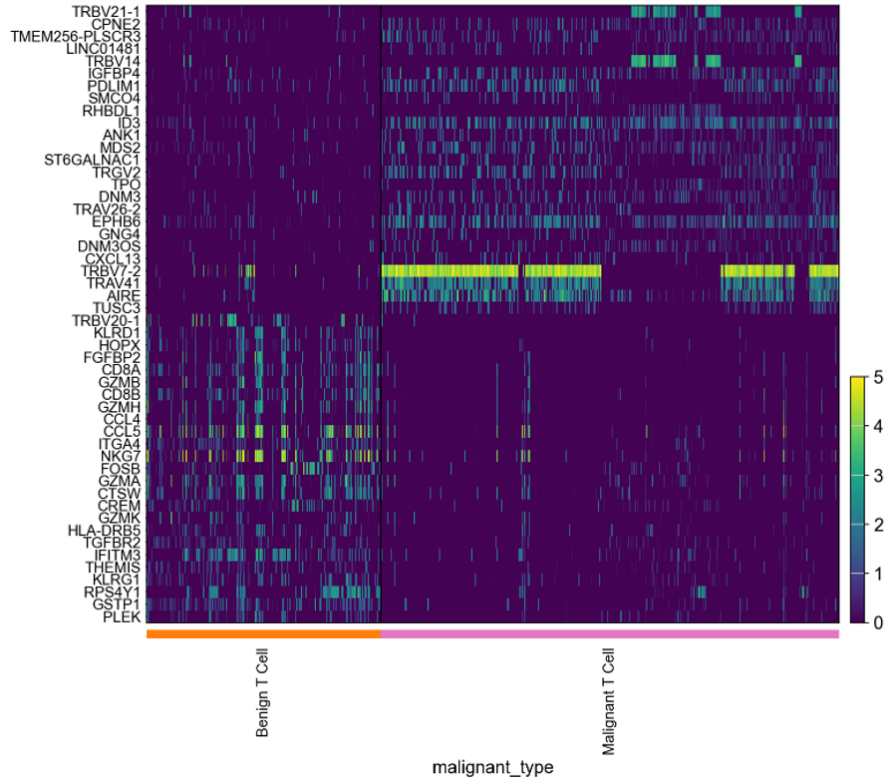
The transformative impact of single-cell RNA sequencing (scRNAseq) on our understanding of cellular heterogeneity has yet to be fully realized in cutaneous T-cell lymphoma (CTCL).

Methods

To characterize the full spectrum of cell diversity and function in CTCL, we utilized scRNAseq. We integrated 16,928 cells from UT Southwestern Dermatology patients alongside 83,610 cells from publicly available datasets, totaling 100,531 cells of patients with CTCL. After implementing rigorous quality control measures, we dissected the immune milieu and dynamic attributes of malignant T cells, aiming to understand the drivers of hematogenous spread.

Results

Our analysis identified twelve distinct clusters of malignant T cells, each with unique transcriptomic profiles. However, some genes were highly expressed consistently among all malignant clusters. Among these, genes such as *C-X-C chemokine ligand 13 (CXCL13)*, *tumor suppressor candidate 3 (TUSC3)*, and *ankyrin-1 (ANK1)* were significantly upregulated in malignant T cells compared to their benign counterparts (Log2FC: 2.69, 3.16, and 1.85, respectively, p<0.01). Additional differentially expressed genes included *AIRE, CPNE2*, *PDLIM1*, *EPHB6*, *GNG4*, and *DNM30S*, collectively contributing to the quest for a comprehensive genetic signature of CTCL.



This heatmap showcases the top 25 differentially expressed genes that distinguish malignant T cells from benign T cells. The upper section highlights genes significantly upregulated in malignant T cells, while the lower section features those that are significantly downregulated.

Conclusions

Our findings spotlight *CXCL13, TUSC3,* and *ANK1* as potential markers of metastasis in CTCL. *CXCL13* plays a crucial role in immune cell recruitment and activation, fostering metastasis. Upregulation has also been associated with treatment resistance in a variety of cancer types. Dysfunction of *TUSC3*, a gene involved in protein glycosylation, may promote tumor dissociation and subsequent metastasis. *ANK1*, encoding a cytoskeletal adaptor protein, is involved in the p53 pathway. It is induced following DNA damage and promotes cellular adhesion and motility, with higher expression correlating with poorer survival outcomes in cancer patients. Notably, these three genes have been found to harbor mutations in a number of cancer types, including CTCL.[1,2]

This study unveils specific genetic characteristics of CTCL at the single-cell level, offering insights for diagnostic algorithms and targeted therapies to impede tumor progression. Future research will incorporate immunohistochemical data to validate the alignment between protein and genetic expression.

1. [BorcherdingEtAl]
2. [Moermanetal]

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A-186

Molecular Insights into Primary Cutaneous CD30+ T-cell Lymphoproliferative Disorders: Wnt/Beta-Catenin Pathway Activation and Prognostic Role of TP53 mutations ?

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Background

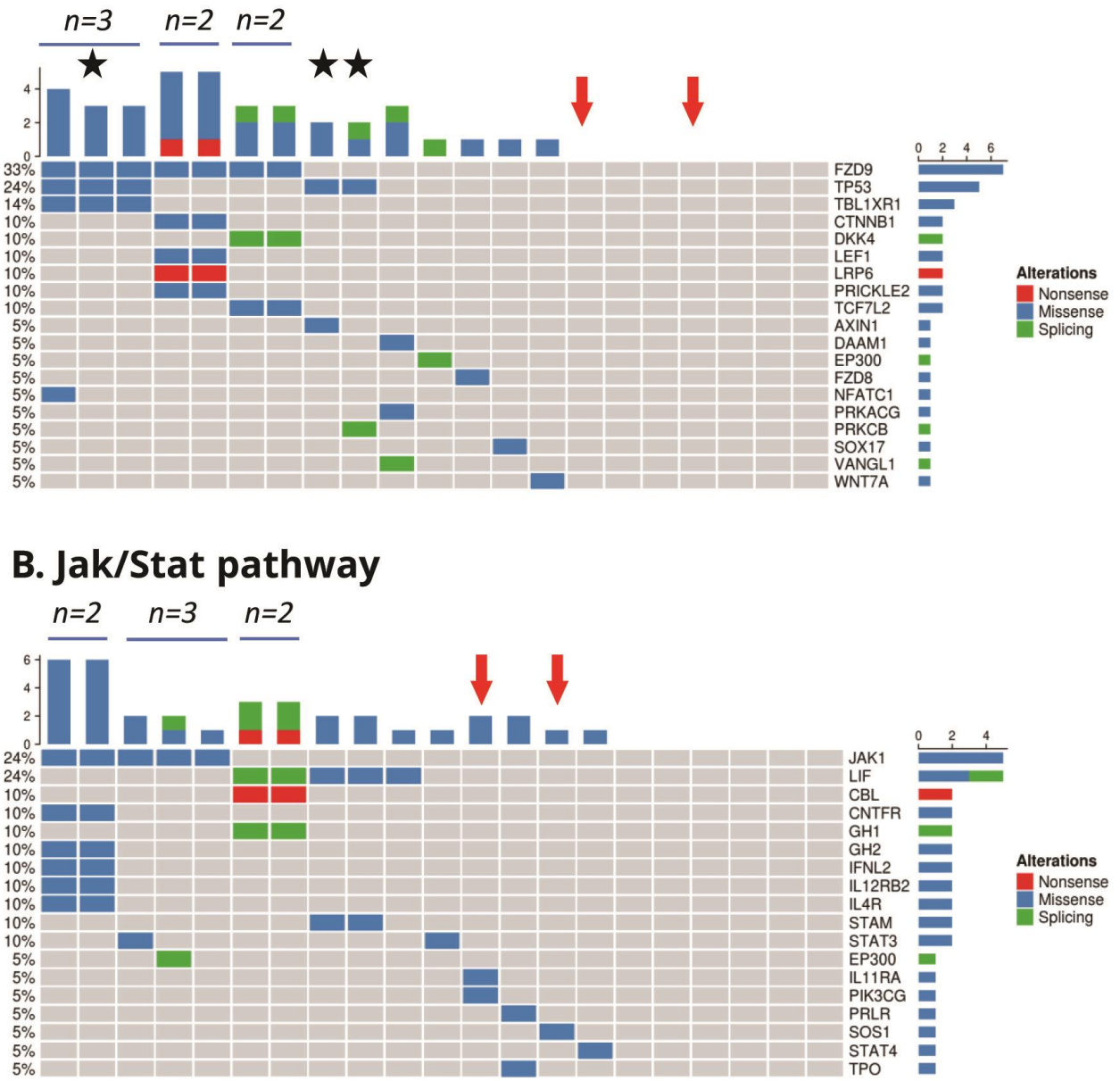
Primary CD30+ cutaneous T-cell lymphoproliferations (LPTCD30) are a diverse group of cutaneous lymphomas encompassing lymphomatoid papulosis (LyP) and primary cutaneous anaplastic large cell lymphomas (pcALCL). Their clinical presentations and molecular alterations are overlapping, making their diagnosis in some cases challenging. Previous molecular studies revealed the presence of several common rearrangements of DUSP22, TP63, and TYK2 and mutations in Jak/Stat pathway[30630983][34382383].

Methods

We have performed a histological and molecular characterisation of a cohort of 21 LPTCD30 samples from 17 patients (8 men and 9 women, average age of 59 years) including 7 LyP, 9 pcALCL, and one borderline lesion, using whole-exome sequencing (200x depth) on paired samples (tumor DNA and constitutional DNA), and in situ studies on paraffin-embedded tissue sections by semi-quantitative immunohistochemistry (IHC) (% x and intensity) of pSTAT3, p53, Beta-catenin, LEF1, and interphase FISH analysis of DUSP22-IRF4 locus.

Results

We identified G>A and C>T mutations (>50% of the mutations) in all cases, with the presence of an UV signature in 77% of cases, according to the Alexandrov et al. algorithm. The most frequently mutated genes were CADPS (24%), JAK1 (24%), FZD9 (18%), and TP53 (18%). Combinatorial pathway analysis showed frequent alterations in the Wnt/B-catenin pathway (47% of cases, 3/7 LyP and 5/9 pcALCL) and the Jak1/Stat pathway (53%, 3/7 LyP and 6/9 pcALCL), not mutually exclusive (associated in 7/11 mutated cases)



List of genes with molecular alterations affecting the Wnt/Beta-Catenin (A) and Jak/Stat (B) pathways, identified in the 21 samples. Cases with DUSP22 rearrangement are indicated with the red arrow. PcALCL with TP53 mutations who developed nodal/cutaneous relapses are indicated with a star.

. There was overexpression of pSTAT3 in 41.6% of cases, LEF1 in 25%, and nuclear expression of beta-catenin in 13.3%, without correlation with the mutational profile or DUSP22 rearrangement (11%). The 3 pcALCL cases with TP53 mutations (n=3) showed nuclear overexpression of P53 (score ≥30%) and were associated with aggressive behviour (cutaneous or nodal relapse).

Conclusions

LyP and pcALCL have a common mutational profile affecting the Jak1/Stat pathway and Wnt/B-catenin pathway in a non-mutually exclusive manner. We highlight the presence of a novel UV mutational signature in these cutaneous lymphomas. The Wnt/beta-catenin pathway may represent a new therapeutic target in LPTCD30. The presence of TP53 mutations with protein nuclear overexpression was present in pcALCL that had an aggressive clinical course, suggesting its possible role as a prognostic biomarker, which remains to be validated in a larger cohort that is currently under investigation.

References:

[30630983]
[34382383]

A-283

Multi-omics cytokine screening reveals immunosuppressive microenvironment in cutaneous T-cell lymphoma.

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Background
Immune dysregulation has been reported in several skin disorders, including neoplastic and inflammatory diseases. Accumulating evidence suggested the immune system of cutaneous T-cell lymphoma (CTCL) and atopic dermatitis (AD) is skewed toward immunosuppressive Type 2 responses, and therefore promotes the disease progression. A comprehensive study of key immune regulatory molecules will facilitate the understanding of disease microenvironment and may reveal novel therapeutic targets in Th2-biased skin disorders. In this study, we aim to screen cytokine molecules with comprehensive multi-omics approaches, and to identify dominant immunoregulatory factors in patients with Th2-biased skin disorders.

Methods
The study retrospectively enrolled 15 healthy individuals (HD) and 30 patients with Th2-biased skin disorders. We employed NanoString nCounter system and 10x Genomics single cell sequencing for accessing the transcriptional cytokine profile; and we performed multiplex antibody array and cytometric bead array to detect cytokines on protein level. Finally, we used functional enrichment analysis to study differential expressed immunoregulatory molecules in each group.

Results
Our result showed distinct cytokine profiles between CTCLs, ADs and HDs. In the skin lesions and sera collected from patients with type 2 inflammatory skin disorders we confrimed significant higher levels of Th2-related cytokines such as IL-9 and IL-13. We further detected several potent chemoattractant for Th2 cells, immunosuppressive IL-10 signaling pathway related molecules, and viral protein interaction related cytokines and receptors. These findings were comparable at both transcriptional and translational molecular level.

Conclusions
Our data point out towards targetable key factors in immunomodulation for patients with Th2-biased skin disorders assist the understanding of disease microenvironment and contribute to the identification of potential new therapeutic targets.

A-140

Mycosis fungoides: Searching for biomarkers associated with early-stage progression

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Background
Mycosis fungoides (MF) is the most common type of cutaneous T-cell lymphoma (CTCL), accounting for approximately 60% of them. The progression of MF can be classified into early and advanced stages, which are related to prognosis. Since there are currently no predictors of progression, the aim of this study is the identification of molecular markers which could predict patient outcome within the first 5 years of follow-up after early-stage disease diagnosis.

Methods
76 patients with early-stage MF were enrolled in this study, who were classified into those who progress (tumours, blood or extranodal involvement, erythroderma or metastasis) (24 cases) and those whose lesions remained as macules or plaques (non-progression) (52 cases), during the next 5 years after diagnosis.
76 formalin-fixed paraffin-embedded (FFPE) samples were used to perform gene expression analysis using NanoString's nCounter technology. Statistical analyses were performed with Graphpad Prism 9 and deconvolution of the expression data to analyse the cellular composition of the microenvironment using the CIBERSORTx, Morpheus and BigOmics Analytics platforms.

Results

Interestingly, progressing (P) and non-progressing (NP) patients had a different expression profile. NP-patients were characterized by an over-representation of the IL4 and IL13 cytokine pathways. In contrast, in P-patients there is an increase in co-stimulation by *CD28*. Differential gene expression analysis shows overexpression of 4 genes in P-patients: *CD30* with a p-value < 0.01, and CD16, *GZMA and CXCL13* with a p-value < 0.05.

Microenvironment analysis showed clear differences between groups. In the P microenvironment, elevated levels of Tfh lymphocytes were observed, and their association with the tumour was demonstrated by Pearson correlation analysis showing a relationship between T cell (*CD3*, *CD4* or *CCR7*) and Tfh (*CXCL13*, *PDCD1*) markers. A signature of activated NK cells was also observed, consistent with differential expression analysis (expression of *CD16* and *GZMA*).

A different series of 22 patients (9 P and and 13 NP) were used to validate the expression levels of both *CD30* and *CXCL13*. Those with progression showed a higher percentage of positive cells for *CD30* marker. *CXCL13* is in validation process.

Conclusions

This study identifies patients at early stages of MF which could progress to advanced stages in a period of 5 years after diagnosis. The use of *CD30* and *CXCL13* expression at diagnosis could help to identify these patients.

A-132

Navigating Modern Challenges in Early Mycosis Fungoides: A Case Report of a Peculiar Association and an Unusual Clinical Presentation

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Background

Mycosis fungoides (MF), a cutaneous T-cell lymphoma, has multiple presentations, including the poikilodermatous form (pMF) with parakeratosis variegata variant. In early stages, MF is often misdiagnosed as adult-onset atopic dermatitis (AD). We present a case of classic patch MF associated with parakeratosis variant of pMF that developed a disseminated thrombotic vasculopathy with uncertain cause, highlighting actual diagnostic, complication and management challenges.

Methods

A 52-year-old male presented to our clinic in 06/2023 with a disseminated, mainly acral, ulcero-necrotic eruption, developed after 5 months of Dupilumab and aggravated following 3 weeks of JAK inhibitor therapy. His medical history included treated chronic arsenic toxicity and recurrent eczematiform plaques on the trunk and extremities since 2016, diagnosed as late-onset atopic dermatitis. Comprehensive laboratory tests were normal. Biopsy revealed thrombotic vasculopathy. Under systemic corticosteroids (CS) and methotrexate (MTX), ulcerative lesions disappeared, but plaques escalated during CS dose reduction. In 12/2023, MF patch stage IB was confirmed by a new biopsy. By 05/2024, the patient had eczematiform, poikilodermatous plaques especially on the lateral aspects of the trunk and the diagnosis of pMF, parakeratosis variegata type was histopathologically confirmed. Concurrently, he presented disseminated round ulcero-necrotic lesions with a violin halo and violaceous macules. Histopathology of the latter showed thrombotic vasculopathy. The patient is undergoing hematological investigations for a possible coagulopathy.

Results

Early MF findings may mimic AD, leading to prescriptions of therapies like Dupilumab or JAK inhibitors. It remains unclear if Dupilumab unmasked or caused MF in this patient. Our case shows a rare association of MF with thrombotic vasculopathy. Vasculopathy with tumor infiltration of vessels manifesting as livedoid or ulcerated lesions is reported in syringotropic MF, but these histological features were absent in our case. Short-term JAK inhibitor treatment for skin conditions does not elevate the thromboembolism risk, but effects on microvasculature are unknown. Our patient responded only to high-dose CS, posing also a treatment dilemma.

Conclusions

This case unveils actual challenges with early MF, from potential misdiagnoses as adult-onset AD and the link to Dupilumab, to multifaceted manifestations and possible association with thrombotic vasculopathy raising treatment difficulties.

A-137

Oncogenic alterations in KIR3DL1 in cutaneous acral CD8+ lymphoproliferative disorder

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Background
Primary cutaneous acral CD8+ T-cell lymphoproliferative disorder (TLPD) is a rare and indolent lymphoma entity. Although known for years, the molecular pathogenesis is still unknown.
In order to better understand the molecular pathogenesis of cutaneous acral CD8+ TLPD and to identify further discriminatory markers to discern this lymphoma subtype from other CD8+ cutaneous lymphomas, we analysed five cases of cutaneous acral CD8+ TLPD for putative molecular alterations.

Methods
Somatic alterations were assessed by whole exome and targeted sequencing of paraffin-embedded tissue. Results were evaluated by immunohistochemical staining of respective relevant proteins. CD8+ cutaneous T-cell lymphomas (n=12) including cases of CD8+ mycosis fungoides served as control for KIR3DL1-staining.

Results
Copy number variations (CNV) analysis revealed a homozygous deletion of the *KIR3DL1* gene in two of the analysed cases. This resulted in loss of KIR3DL1 protein expression which was observed in all cases of cutaneous acral CD8+ TLPD. In contrast, KIR3DL1 expression was more variable in other CD8+ cutaneous T-cell lymphomas with about half of analysed cases being positive. In addition, one further case of cutaneous acral CD8+ TLPD harboured a loss of function mutation in the *PIK3R1* gene presumably activating the PI3K-AKT pathway.

Conclusions
For the first time, oncogenic aberrations are identified in cutaneous acral CD8+ TLPD. Alterations of *KIR3DL1* gene may be of pathogenetic relevance for this rare lymphoma subtype. Loss of KIR3DL1 protein expression may support the diagnosis of this indolent lymphoma entity, albeit not being a subtype-specific discriminative feature.

A-180

Pluripotency Factor DPPA4 in Cell lines of T-Cell Lymphoma

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Background
Transformation of healthy tissue into cancerous tissue is usually caused by the loss of a tight and complex regulatory genetic network that regulates the self-renewal capacity of stem cells. Stem cells of developing organisms are diverse and range from totipotent to unipotent. Each stem cell type is characterized by different self-renewal frequencies and pose by itself a threat of cancer development. It has been hypothesized that the founding cell of Cutaneous T-Cell Lymphoma (CTCL) is a multipotent stem cell or a cell that has acquired, at least temporarily, pluripotent properties, like the pluripotent stem cells of the early blastocyst that possess high self-renewal and differentiate into all tissues of the embryo. Developmental Pluripotency Associated 4 (DPPA4) is an essential pluripotency factor that is expressed only in the inner cell mass of the early human embryo (E5.5) before its expression is abolished in somatic tissues. However, DPPA4 is also known to be re-activated in certain cancers (1). This factor contains a SAP domain. SAP domain proteins are usually involved in chromosomal architecture, DNA repair and RNA metabolism. DPPA4 has also been shown to shuttle dynamically in form of cytosolic foci in and out of the nucleus and throughout the cytosol and to be associated with the cytoskeleton (2).

Methods
Here, we have examined the T-Cell Lymphoma cell lines HH, HUT78 and Jurkat for the expression of DPPA4.

Results
Indeed, we confirmed DPPA4 expression in Western Blots, RT-PCRs and immunofluorescence.To address our hypothesis further, we are currently examining the roles of DPPA4 in the proliferation of these cell lines as well as the involvement of other key pluripotency factors.

Conclusions
Key pluripotency factors are indeed expressed in T-Cell Lymphoma cell lines HH, HUT78 and Jurkat. The insights of this study will potentially highlight avenues for novel targets for the treatment of CTCL patients.

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A-265

Single cell sequencing delineates T-cell clonality and pathogenesis of the parapsoriasis disease group

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Background
Mycosis fungoides (MF) is often underdiagnosed in early stages due to similarities with benign dermatoses such as atopic dermatitis (AD). Furthermore, the delineation from so-called “parapsoriasis en plaque,” a disease that can appear either in a small- or large-plaque form, is still controversial.

Methods
To characterize the parapsoriasis disease spectrum, we performed single-cell RNA sequencing of skin biopsies from patients within the parapsoriasis-to-early-stage MF spectrum, stratified for small and large plaques, and compared them to AD and healthy control skin.

Results
6 out of 8 large-plaque lesions harbored either an expanded alpha/beta or gamma/delta T-cell clone with downregulation of *CD7* expression, consistent with a diagnosis of early-stage MF. By contrast, 6 out of 7 small-plaque lesions were polyclonal in nature thereby lacking a lymphomatous phenotype, and also revealed a less inflammatory microenvironment than early-stage MF or AD. Of note, polyclonal small- and large-plaque lesions characteristically harbored a population of *NPY*+ innate lymphoid cells and displayed a stromal signature of complement upregulation and antimicrobial hyperresponsiveness in fibroblasts and sweat gland cells, respectively. These conditions were clearly distinct from AD, which uniquely harbored CD3+CRTH2+ IL13-expressing “Th2A” cells.

Conclusions
These data position polyclonal small- and large-plaque dermatitis lesions as a separate disease entity, that characteristically harbors a so far undescribed ILC population within tissue microenvironment of misguided antimicrobial responses. We thus propose the new term “polyclonal parapsoriasis en plaque” to these kinds of lesions, as they can be clearly differentiated from MF and AD on several cellular and molecular levels.

A-269

Single-cell RNA sequencing of chronic idiopathic erythroderma compared to erythrodermic CTCL and atopic dermatitis defines disease-specific markers

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Background
Chronic erythroderma is a potentially life-threatening condition that can be caused by a variety of diseases, including erythrodermic MF and Sézary Syndrome. However, 30% of cases remain idiopathic, with an unclear relation to cutaneous lymphomas.

Objective
To comprehensively characterize the transcriptome of chronic forms of erythroderma.

Methods
We performed single-cell RNA sequencing combined with T-cell receptor sequencing of blood and skin from 5 chronic idiopathic erythroderma (CIE) patients, and compared results with 7 cases of erythrodermic CTCL (erythrodermic MF, Sézary Syndrome), as well as skin from 5 moderate-to-severe atopic dermatitis (AD) and 4 healthy control individuals.

Results
In erythrodermic CTCL, we found strong expansion of *CD4*+ malignant clones with a *CCR7*+*SELL*+ central memory phenotype. By contrast, CIE exhibited a pattern of low-level, but consistent expansion of *CD8A*+ T-cell clones, both in blood and skin samples. While CIE and CTCL patients lacked the strong type 2 immune skewing typically found in AD, they were characterized by upregulation of MHC II genes (*HLA-DRB1, HLA-DRA, CD74*) in keratinocytes and fibroblasts, most likely in an IFNG-dependent fashion. However, we found strongest upregulation of type 1 immune mediators in CIE samples, both in the expanded CD8 clones, as well as in the tissue microenvironment.

Conclusions
Despite the notion that CIE might be a mere bundle of various yet uncharacterized disease processes, we found disease-specific pathogenic signatures in these patients, that were different from other forms of erythroderma, particularly erythrodermic MF and Sézary Syndrome. These data suggest that CIE is a distinct entity and might help to improve our pathogenic understanding of the blood and skin compartments of CIE, aiding in discovery of future treatment targets.

A-287

Spatial atlas of noncommunicable inflammatory skin disease and cutaneous T cell lymphoma

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Background
Skin lymphomas are a heterogeneous group of rare T-cell disease with diagnostic challenges due to their varied clinical and histopathological manifestation, closely resembling benign inflammatory skin diseases.

Methods
To better understand the molecular underpinnings of these diseases and improve diagnostics, we performed highly multiplexed protein fluorescent imaging of 51 patients with malignant and benign non communicable skin disease (NCD).

Results
We leveraged image-based deep-learning algorithms to precisely phenotype cells showing an increased accuracy compared to classical methods. Using cell contact network, we define “immune pathological infiltrate—agglomerates of immune cells around blood vessels—and observe significant changes in infiltrate in malignant NCD. Using image analysis at the subcellular level, we assess protein functional interactions, revealing that T helper cells in malignant NCD manage to avoid antigen presentation to cytotoxic T cells. We investigate differences between responder and non-responder lymphoma patients and observe increased cytotoxic T cell frequencies, migration capabilities and proximity to T helper cells in responder. Finally, we classify malignant from benign disease using the defined spatial and functional features using random forest.

Conclusions
Collectively, these results provide a first of this kind spatial proteomic atlas of skin NCD, sheds light on the varying shades of immune dysregulations across disease or response to treatment and contribute to the development of effective precision medicine interventions in dermatology.

A-215

Spatial profiling of CD8⁺ T cells and lymphoma cells in mycosis fungoides patient skin

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Background
In mycosis fungoides (MF), skin-infiltrating benign $CD8^+$ T cells are decreased in advanced stages, and some patients have an altered expression of granzyme B and co-inhibitory receptors, indicating impaired $CD8^+$ T cell function. The exact role of $CD8^+$ T cells in MF is however not known. We aimed to determine the requirements for $CD8^+$ T cells to infiltrate lymphoma. To do this we investigated the protein expression of lymphoma cells and $CD8^+$ T cells in early vs. advanced MF lesions and compared regions that were $CD8^+$ T cell rich vs. poor, at the center vs. the periphery of an infiltrate, and regions located in the dermis, epidermis or perivascularly.

Methods
We performed multiplexed spatial proteomics on formalin fixed skin biopsies from four patch, four plaque and three tumor MF lesions, from eleven patients. Regions of interest (ROIs), including areas of illumination (AOIs) enriched with $CD8^+CD3^+$ T cells or $CD4^+CD3^+$ T cells including tumor cells, were selected and 77-plex GeoMx digital spatial profiling was applied.

Results
We found $CD8^+$ AOIs to have higher expression of the immune-check point protein Tim-3 in patches vs. plaques as well as in plaques vs. tumors. Furthermore, the $CD8^+$ AOIs of the $CD8^+$ T cell-poor infiltrates had increased phosphorylation of p38 MAPK and increased expression of immune-check point protein LAG3 compared to $CD8^+$ T cell rich infiltrates, indicating increased activation and exhaustion of $CD8^+$ T cells in regions with fewer $CD8^+$ T cells. Perivascular $CD8^+$ AOIs had increased phosphorylation of the protein kinase JNK1 compared to dermal $CD8^+$ AOIs, possibly indicating better anti-tumor activity by perivascular $CD8^+$ T cells. The expression of CD163 was increased in $CD8^+$ AOIs and $CD4^+$ AOIs of periphery vs. center of the infiltrates, indicating higher numbers of M2 macrophages at the periphery. Profiling of the $CD4^+$AOIs showed higher expression of CD66b and ARG1 in plaque compared to tumor lesions, possibly indicating higher infiltration of tumor associated neutrophils close to the $CD4^+$ lymphoma cells. $CD4^+$AOIs had furthermore increased expression of FOXP3 and CTLA4 in the epidermis compared to dermis, which could be attributed to regulatory T cell-like lymphoma cells or the presence of benign regulatory T cells in the proximity.

Conclusions
We found that the protein expression of benign $CD8^+$ T cells and lymphoma cells in MF skin differed depending on spatial localization and thereby found novel potential therapeutic targets in MF.

A-145

Spatial transcriptomic and proteomic profiling of a B-cell rich tumor microenvironment in Mycosis fungoides

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Background
Mycosis fungoides (MF) represents the predominant form of cutaneous T-cell lymphoma, characterized by clonal expansion of aberrant T-lymphocytes primarily affecting the skin. An intriguing aspect of MF is the localized proliferation of lymphocytes within the skin, suggesting a dependence of malignant cells on the cutaneous tumor microenvironment (TME). Recent research has focused on the significance of tumor-infiltrating B-lymphocytes in cancer immunity, revealing their complex role that can be either anti- or pro-tumorigenic. However, our understanding of the influence of tumor-infiltrating B-lymphocytes in MF, and how they may affect disease progression, is still limited.

Methods
We analyzed FFPE skin biopsies from 16 MF patients exhibiting a B-cell rich TME using NanoString's GeoMx® Digital Spatial Profiler (DSP). Morphological markers including CD3, CD20, and Cytokeratin as well as the GeoMx Human Whole Transcriptome Atlas were applied to all samples. A CD20+ region of interest (ROI) segmentation strategy was applied and 95 areas of illumination (AOIs) were analyzed. A deconvolution reference matrix was constructed to estimate the different cell types within the TME and enable advanced B-cell phenotyping. For further validation of the B-cell transcriptome, we performed Deep Visual Proteomics (DVP) on selected MF samples using the Orbitrap Astral mass spectrometer (Thermo Fisher Scientific) coupled with Evosep One LC system (EvoSep).

Results
Spatial profiling unveiled a highly patient-specific and heterogeneous tumor microenvironment, with a notable higher prevalence of regulatory T-cells in regions with fewer B-cells, and conversely, a lower prevalence of regulatory T-cells in B-cell rich regions.

Conclusions
Our study underscores the complex and interpatient heterogeneous TME, characterized by distinct B-cell profiles within each patient. This highlights the necessity for further investigations into the functional significance of these B-cell populations in MF pathogenesis and their potential implications for therapeutic intervention.

A-286

T cell receptor beta constant 1 as a potential marker for the assessment of T cell clonality in skin disease

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Background
Differentiating between benign inflammatory skin diseases and cutaneous T-cell lymphoma (CTCL) poses a significant diagnostic challenge, often resulting in delayed diagnosis and increased morbidity and mortality. Horna et al. demonstrated the potential of assessing T cell clonality as a marker for leukemic CTCL by exploiting the mutually exclusive expression of T cell receptor constant region 1 (TRBC1) and TRBC2. Under physiological conditions, TRBC1+ and TRBC2+ T cells are equally present, but the clonal expansion underlying CTCL results in an imbalanced TRBC expression in the T cell population. In this project, we aim to translate this approach into formalin-fixed, paraffin-embedded (FFPE) skin samples of early and late-stage CTCL patients to include skin T cell clonality in the diagnostic workflow.

Methods
We performed 6-plex multi-omics staining, combining FISH for the identification of the T cell receptor variable region and antibody staining with TRBC1 to demonstrate its reliability as a marker for T cell clonality. We added CD3, CD4 and CD8 to TRBC1 to create a comprehensive immunohistochemistry (IHC) panel to distinguish between skin samples from patients with CTCL and inflammatory skin diseases (ISD).

Results
Our multi-omics data demonstrate that TRBC1 is a reliable marker for T cell clonality. Our IHC-panel shows that the T cell population in CTCL is significantly more clonal than in ISD (p-value = 0.011) and that T cell clonality has a high positive predictive value (~90%). Additionally, we observed that in CTCL, high levels of T cell clonality can be detected irrespective of disease stage or clinical assessment of the skin lesion.

Conclusions
The inclusion of TRBC1 in combination with routine T cell markers has the potential to recognise T cell clonality in FFPE skin samples. Utilizing T cell clonality as an additional parameter may help overcome current diagnostic challenges, leading to earlier detection and appropriate management of CTCL.

A-247

Targeting metabolic requirements of malignant lymphocyte migration and disease dissemination

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Background
Spread of malignant lymphocytes in the skin and other tissues critically determines prognosis and treatment decisions in cutaneous lymphoma. While metabolic flexibility is a central feature of normal lymphocyte physiology, fuel preferences and metabolic activities of malignant lymphocytes are poorly understood. We define fuel choice, metabolic flux, and downstream signaling pathways as critical regulators of the invasive phenotype of malignant lymphocytes and identify novel drug targets in the metabolic network selective for malignant lymphocytes.

Methods
Malignant lymphocytes lines and isolated normal and leukemic lymphocytes incl Sézary cells were used in vitro and in mouse xenografts to determine metabolic factors influencing invasive and disseminative properties through multiomics, metabolic tracing, genetic, and pharmacologic studies.

Results
Lymphoid cancer cell migration and organ infiltration in xenograft models is controlled by variations in mitochondrial reactive oxygen species (mROS) allowing us to dissect fuel preferences and metabolic requirements of malignant lymphocyte migration and spread. Cells with enhanced migratory potential show broad metabolic reprogramming. Glucose is an essential fuel driving migration through activation of mROS/HIF-1a signaling. Using [U-^{13}C]-glucose tracing, we demonstrate reduced glucose-carbon contribution to the Krebs cycle and increased conversion into lactate promote an enhanced migratory phenotype. Highly invasive cells show reduced expression and activity of several Krebs cycle enzymes including citrate synthase providing the basis for the altered metabolic phenotype. The functional relevance of reductive pyruvate metabolism and Krebs cycle reprogramming for lymphocyte invasiveness and spread is demonstrated through pharmacologic and genetic manipulation in cell lines, isolated leukemic cells, and xenograft models. We identify the pyruvate branching point as a critical metabolic decision point for migration and spread and identify a novel pharmacological target in malignant lymphocyte neoplasms.

Conclusions
Our findings highlight the critical role of pyruvate flux and Krebs cycle activity in regulating invasive properties of malignant lymphocytes through mROS/HIF-1a. Importantly, we show that regulation of lymphocyte migration and spread through metabolic flux and mitochondrial activity is a selective drug target in malignant lymphocytes sparing their healthy counterparts.

A-262

Targeting the hyperactive STAT3/5 Pathway in Cutaneous T-Cell Lymphoma: superior efficacy of multi-kinase inhibitor IQDMA over conventional PUVA therapy

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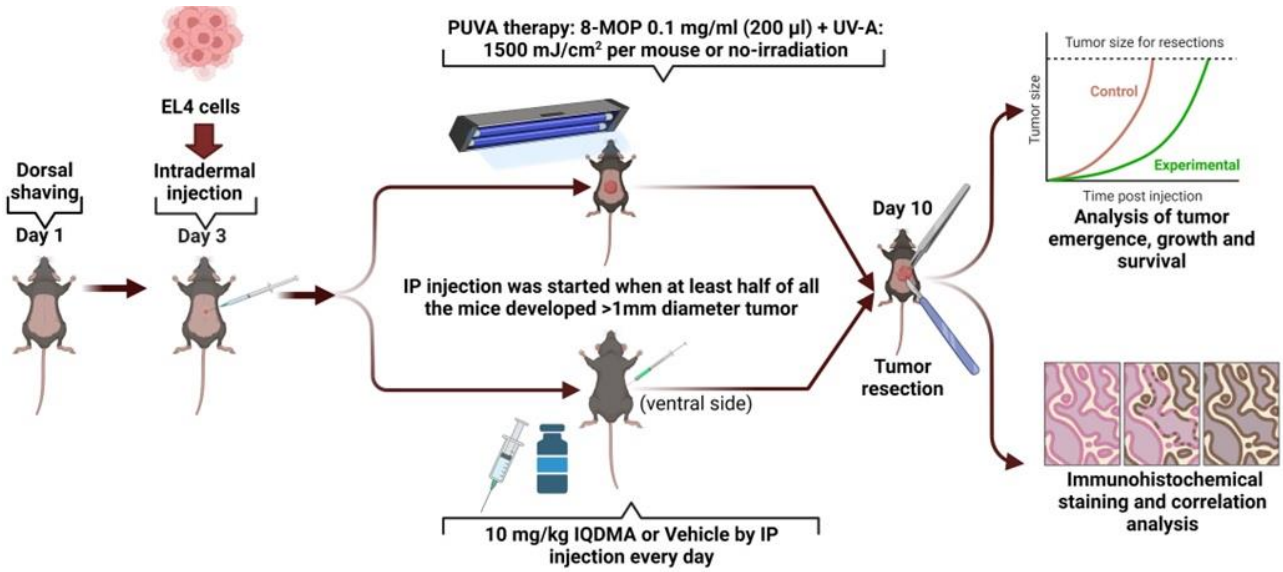
Background
Cutaneous T-cell lymphoma (CTCL), particularly its tumor stage mycosis fungoides (MF) subtype, presents a considerable therapeutic challenge, with current treatment modalities showing limited efficacy. This study aims to address the acute unmet need for novel targeted therapies by focusing on the inhibition of the STAT3/5 pathway, which is found to be hyperactive in CTCL.

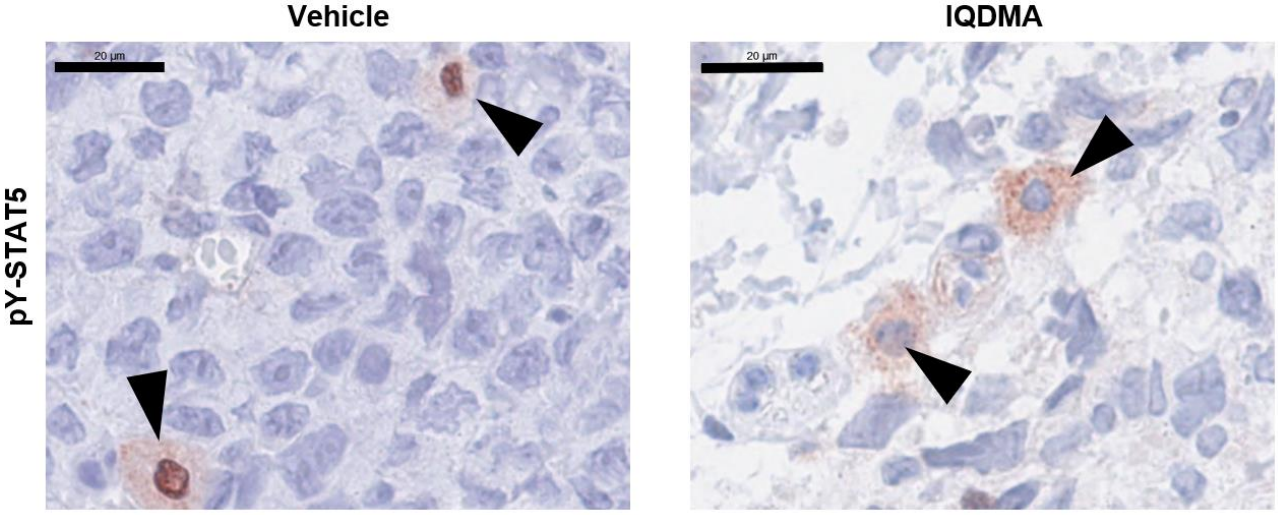
Methods
Utilizing a murine model with intradermally grafted malignant T-cell lymphoma cells, we compared the efficacy of IQDMA, a multi-kinase inhibitor, with the conventional, topical psoralen (PUVA) phototherapeutic regimen.



Experimental setup starting with EL4 cell inoculation, followed by either PUVA therapy or IQDMA treatment, and subsequent tumor resection and analysis

Results

Our data show that IQDMA reduced tumor volume (p=0.0001) and was significantly more effective than PUVA (p=0.0074). Immunobiological analysis revealed that IQDMA treatment resulted in decreased $CD3^+$ tumor cell infiltration (p=0.03) and induced apoptosis, evidenced by elevated cleaved caspase-3 levels. Furthermore, IQDMA treatment led to a significant decrease in $KI67^+$ cells (p=0.03), indicating a reduced rate of tumor cell proliferation. A remarkable reduction was observed in both total STAT5 (p=0.05) and STAT3 (p=0.01) levels of the infiltrated tumor cells. A positive correlation was identified between total STAT5 levels and $CD3^+$ tumor cell infiltration, confirming the role of the STAT3/5 pathway in the disease's pathogenesis. Intriguingly, while the vehicle-treated group showed a positive correlation between phospho-STAT5 and total STAT5 levels, this correlation turned negative in the IQDMA-treated group. As IQDMA targets PAK kinase, a nuclear transporter for phospho-STAT5, we observed a compartmental shift of phospho-STAT5 from the nucleus to the cytoplasm, corroborating our initial hypothesis.



Subcellular localization shifts in pY-STAT5 signaling effects of IQDMA treatment.

Conclusions

In summary, this study addresses the critical gap in targeted therapies for CTCL, particularly the tumor-stage MF subtype. This study bridges a critical gap in CTCL therapy, particularly for the tumor-stage MF subtype, by demonstrating the superior efficacy of IQDMA over conventional PUVA therapy in reducing tumor volume, inducing apoptosis, and attenuating the hyperactive STAT3/5 pathway. These key findings establish the properties of IQDMA as a potent targeted therapy for CTCL and offer compelling evidence for its clinical evaluation.

A-143

The role of OX-40 in tumor microenvironment of a Cutaneous T-cell Lymphoma (CTCL) in vivo chick embryo model

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Background
In CutaneousT-cell Lymphoma (CTCL), T cells are activated either by malignant T-cell–derived cytokines or via immunologic synapses with dendritic cells such as OX40-OX40L interactions (Vieyra-Garcia P et al, 2019).This study focuses on the immune checkpoint modulator OX-40. OX40/OX40L co-expressed on tumor cells in MF/SS and correlated with disease severity markers (Kawana et al, 2021). This research aimed to investigate the role of OX-40 in tumor microenvironment of MF/SS using the chick embryo metastasis model and to evaluate the potential of OX-40 as a therapeutic target for MF/SS.

Methods
We investigated the role of OX-40 in MyLa and SeAx cells engrafted in the chick embryo model by performing **CRISPR OX-40 knockout** in vivo and studying the role in tumor microenvironment by i) the **spontaneous metastasis model in the presence/absence of macrophages ii) transendothelial cell migration** of CRISPR OX-40 and OX-40 overexpressed CTCL cells using a transwell-based transendothelial migration assay, and **iii) co-culture of CTCL cells in the presence/absence of macrophages**.

Results
We developed a CAM assay to monitor CTCL cell metastasis and study new therapeutic targets in vivo. Our results showed that CRISPR OX-40 plays a significant role in CAM intravasation (72% in MyLa, $p < 0.05$, 49% in SeAx embryos, $p < 0.05$) and CTCL cell dissemination to the lung (67% in MyLa, $p < 0.05$, 78% in SeAx embryos, $p < 0.05$) and liver (58% in MyLa, $p < 0.05$, 83% in SeAx embryos, $p < 0.05$). Overexpression of OX-40 restored transendothelial migration and dissemination. The Th2 cytokine profile in CTCL co-cultures and xenografts correlated with M2-like TAMs. OX-40 overexpression promoted CTCL cell intravasation, metastasis, IL secretion, and increased M2-like TAMs. Although no angiogenesis differences were previously observed between CRISPR Control and OX-40 CTCL cells in chick embryos, real-time PCR showed that OX-40 regulates lymphangiogenesis via VEGF-C in tumors in vivo.

Conclusions
Using the chick embryo CTCL spontaneous metastasis model, we demonstrated that **OX-40 regulates tumor microenvironment to promote M2-like TAMs increase, lymphangiogenesis, CAM intravasation**, **as well as liver and lung metastasis**. We, therefore, suggest that the *in vivo* **chick embryo metastasis model** could be **a good pre-clinical model to discover new anti-tumoral targets for CTCL.**

A-175

Toward patient-tailored immunotherapy: targeting the TCR idiotype of clonal Sézary lymphomas

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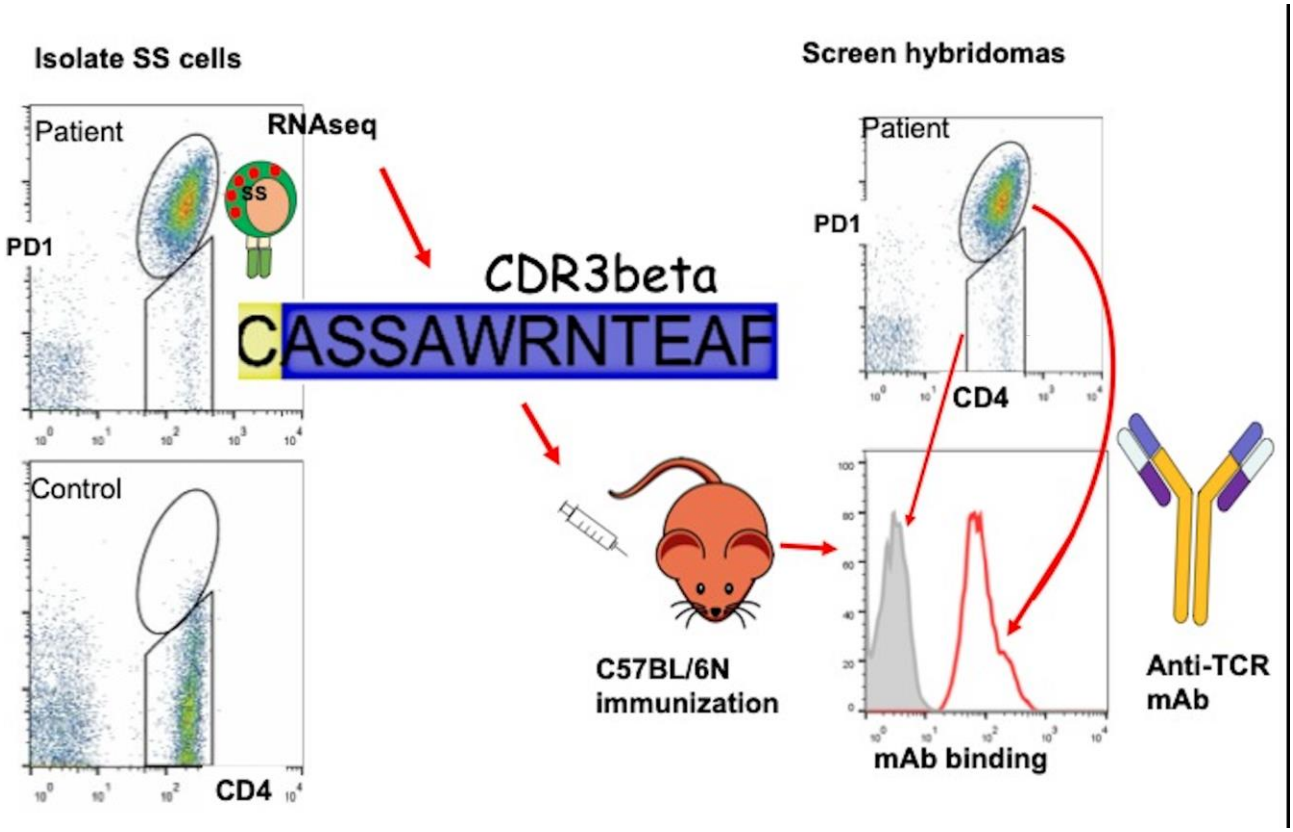
Background

Sézary Syndrome (SS) is an aggressive ultra-rare leukemic form of cutaneous T-cell lymphoma characterized by circulating malignant CD4+ T lymphocytes (SS cells). Patients with SS have poor prognosis and current treatments show high rates of relapse and target also non-malignant T cells, causing immunodeficiency. Thus, there is an unmet need for an efficient treatment. SS cells have potentially targetable epitopes, including their clonal TCR

Methods

We aimed to generate SS TCR-specific monoclonal antibodies (mAb) by immunizing mice with the unique CDR3βpeptide of the TCR expressed by the malignant T cell clone of each patient



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Results

Out of 144 hybridomas tested in one case under study (SS1), one showed binding to SS1 malignant T cells (defined as CD4+PD1+) but not to autologous non-malignant T cells (CD4+ PD1Ø). The mAb was an IgM kappa, and**:** 1- it did not bind to malignant T cells from different SS patients; 2- it did not bind to T cells from different healthy donors; and 3- it bound to Jurkat cells expressing the SS1 TCR cloned from malignant T cells. These results indicate that it is a patient specific **anti-SS1 TCR CDR3β mAb.** Its lymphoma-killing capacity is currently being tested, and a single-chain variable fragment (scFv) for future chimeric antigen receptor (CAR) production is under construction.

Conclusions

This scheme of patient-tailored immunotherapy is thus feasible, offering lymphoma-specific reagents with promising prospects in the treatment of clonal cutaneous T cell lymphomas

A-183

Utility of optical genome mapping in the study of Sézary syndrome

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Background
Sézary syndrome (SS) is an aggressive leukemic variant of cutaneous T-cell lymphoma. Cytogenetic studies have identified alterations in 1p, 2p, 6q, 8q, 9, 10q, 13q, 17p, and 21. Exome sequencing studies show high genomic complexity with copy number variants (CNVs), deletions and/or duplications, fusion genes, and point mutations contributing to its pathogenesis. Optical genome mapping (OGM) is a technology based on imaging long DNA molecules (>250Kb) to detect numerical and structural chromosomal anomalies with high resolution and sensitivity. This study aims to establish the utility and diagnostic performance of OGM in SS.

Methods
Six SS patients were included, five men and one woman. Peripheral blood samples were collected for karyotyping (72-hour culture with phytohemagglutinin) and OGM (Bionano Genomics) at diagnosis. FISH validation was performed using TP53 and CDKN2AB probes (Abbott Molecular). OGM results were compared with those from karyotyping in five patients with cytogenetic information.

Results
Overall, more alterations were identified by OGM compared to karyotyping (median: 13 [range: 12-15] vs 10 [range: 6-10], respectively). OGM detected all the alterations identified by karyotyping and uncovered cryptic alterations or allowed redefinition in all patients. Additionally, it detected rearrangements generating fusion genes [i.e., ASXL2::TET3] or CNVs smaller than 10Mb (karyotype resolution): in 2 cases, a 9p21 deletion including the CDNKN2AB-MTAP genes was detected and validated by FISH, and in 2 other cases, a 1p36p35 deletion was identified. OGM identified catastrophic events on chromosome 10 (chromoplexy) in one patient and chromosome 11 (chromothripsis) in another. Recurrent alterations detected included +4, +8q, +17q, 8p-, 17p- (TP53), 1p36p35-, and 9p21 deletion (CDKN2AB-MTAP).

Conclusions
OGM is a diagnostic tool that reveals the genomic complexity characteristic of SS, identifying alterations with higher resolution than karyotyping and characterizing fusion genes associated with chromosomal rearrangements. These preliminary results suggest the utility of OGM in studying the genetic bases involved in SS development.

A-209

Utility of TCR-β and TCR- γ gene rearrangement to distinguish between tumour-stage mycosis fungoides and early-stage mycosis fungoides associated with CD30+ lymphoproliferative disorders.

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Background
Cutaneous T-cell lymphomas (CTCLs) comprise a heterogeneous group of non-Hodgkin lymphomas that primarily involve the skin. The most common type of CTCLs is mycosis fungoides (MF), which accounts for almost 50% of all CTCLs. Primary cutaneous CD30 lymphoproliferative disorders (CD30+ LPDs) are the second most frequent group of CTCLs, and include lymphomatoid papulosis (LyP) and primary cutaneous anaplastic large cell lymphoma (PC-ALCL). MF and CD30+ LPDs may be present in the same patient, and their coexistence does not worsen the prognosis of either of them. The histopathologic hallmark of CD30+ LPDs is the presence of large, anaplastic and pleomorphic lymphocytes that express CD30. However, CD30 expression is not restricted to CD30+ LPDs, and it is a common finding in other CTCL, particularly tumour-stage MF. Thus, it can be challenging to histopathologically differentiate between the coexistence of early-stage MF and CD30+ LPD, which has a good prognosis; or a tumour-stage MF, which is associated with an increase in mortality rates.
Each T-cell lineage has a unique TCR rearrangement. Although around 95% of T-cells are phenotypically αβ, γ region is rearranged in almost all T-cells during thymus maturation. Thus, TCR- γ rearrangement is identifiable (but not expressed) in T αβ cells, which can serve as an additional parameter in the molecular study of a T-cell population.

Methods
Five patients with tumour-stage MF and six patients with coexistence of MF and CD30+ LPD were identified from our medical database. TCR- γ and TCR-β rearrangements were studied in samples from all cases.

Results
The presence of one or two clones in the TCR- γ gene was demonstrated in all included patients. Tumour-stage MF patients showed one or two clones that usually exceeded 50% of the sample readings, and the total count of readings increased as the disease worsened. On the other hand, patients with the coexistence of early-stage MF and CD30+ LPD showed a poorer defined clonality pattern. Despite TCR- γ clonality, patients with the coexistence of MF and LyP showed a lower number of total readings in LyP lesions than in MF lesions.

Conclusions
The determination of TCR-β and TCR- γ genes rearrangement may be useful to distinguish between tumour-stage MF and early-stage MF associated with CD30+ LPD.

CLINICAL STUDIES

A-206

4 cases of pediatrics mycosis fungoides revealed by recalcitrant psoriatic palmoplantar keratoderma

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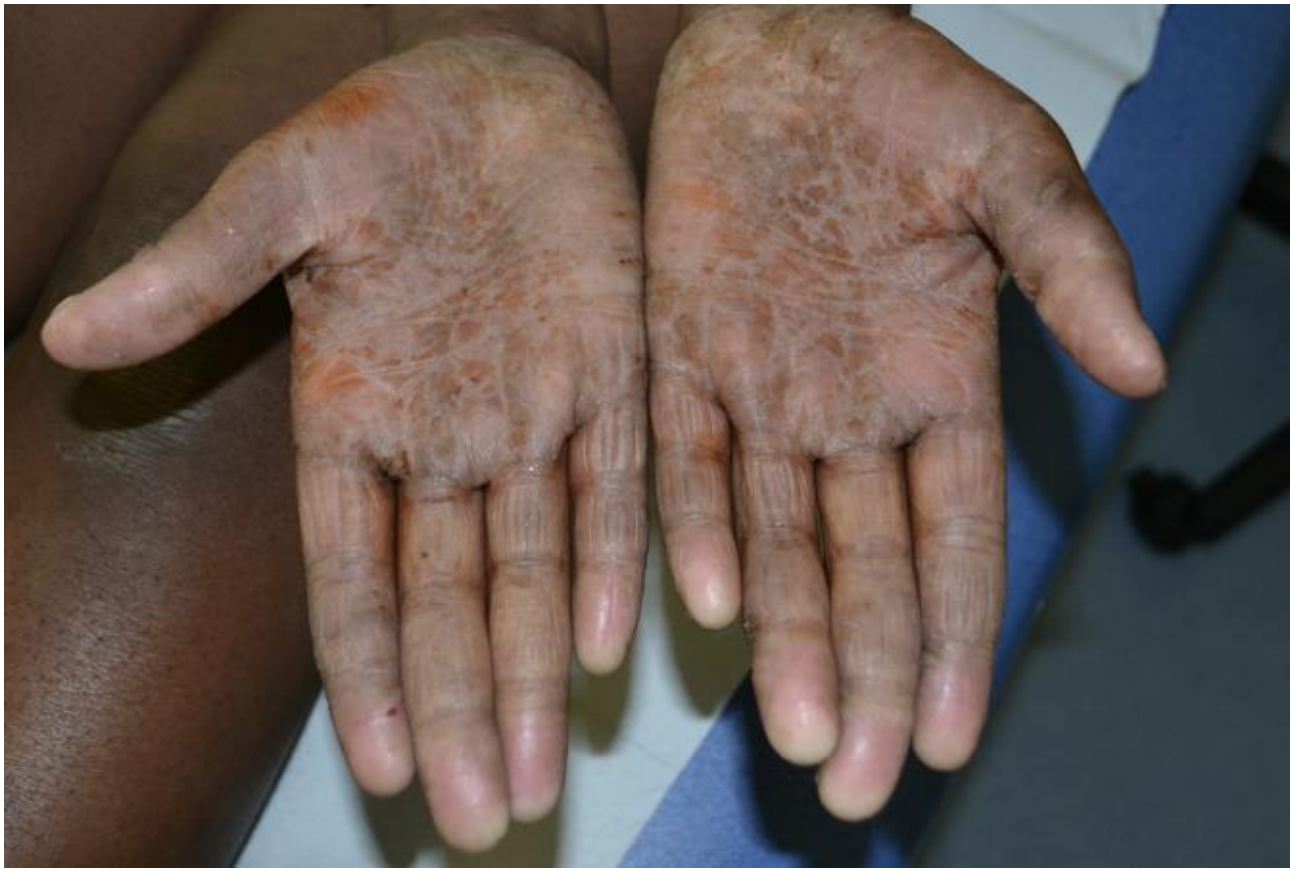
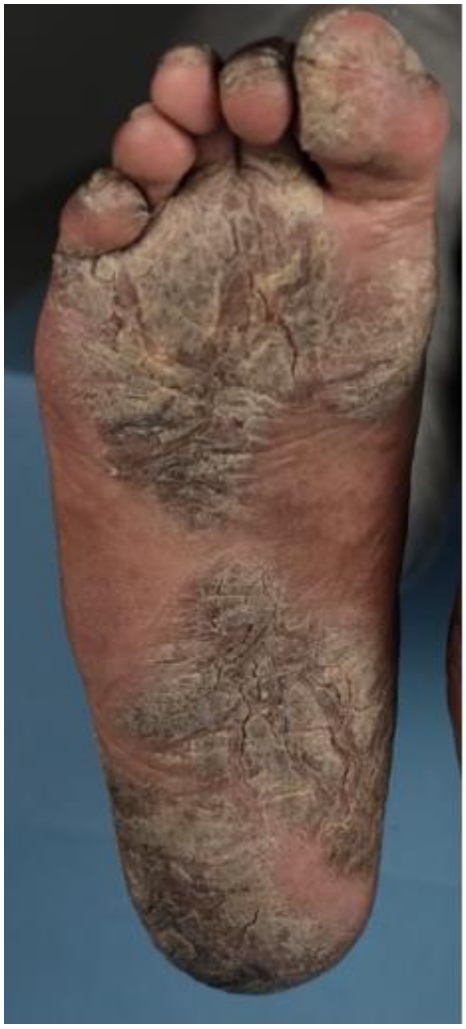
Background
Psoriasis is a common cause of inflammatory acquired palmoplantar keratoderma (PPK) across all age groups. Conversely, PPK is rarely a manifestation of epidermotropic T-cell lymphoma. In adults, PPK occurs in 0.6% of cases as a manifestation of cutaneous T-cell lymphoma, mainly found in erythrodermic mycosis fungoid (MF) or Sezary syndrome.

Methods
We report 4 pediatric cases of inflammatory PPK initially treated as psoriatic PPK but then diagnosed as mycosis fungoides (MF) after resistance to psoriasis treatment.

Results
The average age of the four children (2 boys and 2 girls) at diagnosis was 11 years (range, 6 to 15 years). 3 patients were phototype VI and 1 was phototype II. Psoriasiform PPK was the primary manifestation.



Diffuse palmoplantar keratoderma in a 11 years old patient



Thick and cracked palmoplantar keratoderma in a 15 years old patient

All patients received several lines of systemic treatments: acitretin (1 patient), methotrexate (2 patients), adalimumab (2 patients), IL-12/23 inhibitors (1 patient), and IL-17 inhibitors (1 patient). None of these treatments achieved adequate remission, prompting a reconsideration of the psoriasis diagnosis, especially since other lesions appeared elsewhere : the trunk and scalp in 3 cases, nails in 2 cases, and periungual area in all four cases. Histological examination of biopsies (palmoplantar and/or distant lesions) suggested MF : epidermotropism, basal alignment of lymphocytes, and lymphocytic atypia. Immunohistochemistry revealed a CD4+ and CD8+ infiltrate in 3 patients and CD4+ and CD8- in 1 patient. A dominant T-cell clone in the skin was detected in 2 patients. All patients were at stage Ia of MF. The average time between the onset of PPK and the diagnosis of MF was 2.3 years (range 1 to 4 years). Treatments proposed for MF included UVB then UVA phototherapy in 1 patient, currently under peginterferon after failure, acitretin in 1 patient, and methotrexate in 2 patients. No patient has yet achieved complete remission. The median follow-up was 2 years (range 1 to 3 years).

Conclusions

Diagnosis of MF in children is challenging and may be easily misdiagnosed as a common benign dermatosis (e.g., follicular eczema, achromic eczema), with the most common presentation being the hypopigmented form. We emphasize that psoriasiform PPK can be the initial manifestation of MF in children. Resistance to multiple lines of psoriasis treatment should raise suspicion of MF in pediatric inflammatory PPK cases, warranting a biopsy since the semiological appearance of PPK seems identical in both etiologies

A-278

Assessing Inter-Rater Reliability in Mycosis Fungoides: Impact of Clinician Experience on Skin Involvement Assessments

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Background

Mycosis fungoides (MF) is the most common form of cutaneous T-cell lymphoma (CTCL). Body surface area (BSA) involvement over

10% is a critical factor in early-stage prognosis. The impact of BSA over 10% on prognosis is a topic of current research. Variability in clinician evaluations can affect patient outcomes.
This pilot study assessed agreement among clinicians with different experience levels in evaluating skin involvement and examined the influence of clinical experience.

Methods
A survey was conducted at Leiden University Medical Center, a national lymphoma referral center. Seventeen clinicians evaluated six MF cases, estimating skin involvement in 10% increments up to 100%. Fleiss' kappa was used to measure inter-rater reliability among all 17 clinicians, a subgroup of seven more experienced clinicians (with a history of full-time or recently full-time engagement), and a subgroup of three clinicians with continuous exposure. Cases were also categorized based on skin involvement (<10%, 10-39%, >40%), and Fleiss' kappa was recalculated.

Results
Overall, inter-rater agreement was modest among all 17 clinicians, with a Fleiss' kappa 0.242, indicating slight agreement. The agreement improved among the seven more experienced clinicians with a Fleiss' kappa 0.308 and was highest among the three continuously exposed clinicians (Fleiss' kappa 0.597), showing moderate agreement. When cases were categorized by skin involvement, Fleiss' kappa values increased to 0.301 for all clinicians, 0.320 for the more experienced, and 0.810 for the continuously exposed clinicians, indicating substantial agreement.

Conclusions
This study shows that clinician experience, particularly continuous exposure to similar cases, leads to higher agreement in assessing skin involvement in MF. The findings highlight the importance of specialized experience for consistent and accurate MF assessments. To confirm these findings and explore the influence of clinician experience on the assessment of mycosis fungoides, we encourage experts to contribute to our ongoing research by scanning the QR code on this poster and completing the survey.

A-139

B2 involvement as a surrogate marker for a rapid and sustained response to treatment with mogamulizumab in mycosis fungoides and Sézary syndrome

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Background
Since 2020 the CCR4 antibody mogamulizumab is approved in Germany as a second-line therapy for mycosis fungoides (MF) and Sézary syndrome (SS). Currently, an induction phase with four weekly infusions and a two-week treatment interval from the 5th infusion onwards is recommended. A recommendation on the duration of therapy or an optional extension of the interval during the course of therapy and long-term data are not yet available. We therefore, investigated the effect of mogamulizumab on CD3+/CD4+ lymphocytes and on the aberrant T- cell population (CD4+/CD7- and CD4+/CD26-) during the course of therapy. Blood involvement is defined as >=1000/ µl neoplastic cells CD4+/CD26-) or CD4+/CD7-> 500 µl (B2), <1000/µl or <500 µl (B1), and <500 µl /250/µl (B0).

Methods
In this prospective analysis, we included 19 patients, 15 patients with SS (IVA1) and 4 patients with MF (IIB to IVA1) with B2 blood involvement. We analyzed the levels of the neoplastic cell populations by flow cytometry before the start of therapy (baseline) and before infusions 2, 3, 4, 5, 6 and then after every second infusion.

Results
In the overall cohort, there was a significant decrease in the CD4+/CD7- and CD4+/CD26- T-cell populations (73% and 75%, respectively) already after the first infusion of mogamulizumab. After the induction phase, there was a mean reduction of 66% in CD3+ lymphocytes, 77% (median 86%) in CD4+/CD7- lymphocytes and 81% (median 93%) in CD4+/CD26- lymphocytes compared to the individual baseline. On average, 79% of patients achieved B0 status after three infusions. This B0 status was maintained even when therapy was interrupted or the intervals had to be extended due to adverse events or patient condition. In terms of overall response, 84% of patients had a CR, 5% had a PR and 11% had progressive disease. Mogamulizumab rash was seen in 26% of patients but we did not see any evidence of tachyphylaxis.

Conclusions
In CTCL patients with B2, mogamulizumab leads to a rapid conversion to B0 in 79% of patients. Our data suggest that this conversion to B0 is maintained during treatment interruptions. Therefore, a prolongation of the maintenance treatment interval based on the development of the aberrant T-cell population should be discussed.

A-148

Chlormethine Gel Effectiveness as second-line Treatment in Mycosis fungoides: a single-centre Retrospective Study

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Background
Our study evaluated the effectiveness of chlormethine gel as a second-line treatment for Mycosis fungoides (MF)[1] in patients unresponsive to prior skin-directed therapies (SDTs) alone or combined with systemic treatments[2]. We wanted to prove in a real-world setting how chlormethine gel can provide significant therapeutic benefits even as a second line treatment with manageable adverse reactions for patients with MF[1].

Methods
A retrospective observational study was conducted in our dermatological unit from April 2021 to December 2022. The study included adult patients with histologically confirmed MF who had not responded to at least one prior SDT. Patients received daily applications of chlormethine gel, and their responses were evaluated at 3, 6, and 12 months using the Modified Severity-Weighted Assessment Tool (mSWAT). Statistical analyses, including one-way ANOVA and univariate regression, were performed using SPSS ver 26 (IBM).

Results
The study reported 21 patients (12 males, 9 females) with a mean age of 61 years. Among them, 81% had early-stage MF (13 stage IA, 4 stage IB), while 19% had advanced-stage disease (IIB). Chlormethine gel showed a 90% response rate, with 33.3% achieving complete response (CR) and 57.1% partial response (PR). Adverse reactions were primarily contact or irritative dermatitis, which were manageable and did not significantly affect treatment outcomes. The median mSWAT scores showed significant reductions from baseline at 3, 6, and 12 months (P=0.002).

Conclusions
The findings support the effectiveness and safety of chlormethine gel as a second-line treatment for MF, even in patients with advanced-stage disease. Limitations include the small sample size and the retrospective study design, which may introduce biases. Future research should aim to confirm these results in larger, prospective studies. The study highlights the potential of chlormethine gel for integration into combination therapies and underscores the importance of continued treatment to achieve optimal therapeutic outcomes.

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A-163

Chlormethine Gel Shows Efficacy as Monotherapy in Stages IA-IIB Mycosis Fungoides

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Background
Chlormethine 0.016% topical gel has been approved for use as a first line treatment option in Europe for early stage Mycosis Fungoides (MF) (stage IA-IIA), however its use may be limited by adverse cutaneous reactions[1]. We reviewed data from all patients prescribed chlormethine at our centre to assess efficacy and safety, quantity of treatment required, as well as any pharmacy issues in obtaining the treatment.

Methods
All patients prescribed topical chlormethine gel as monotherapy were included and notes reviewed retrospectively to investigate the time taken from prescription to issue of treatment, and how many tubes were required. Length of treatment, side effects and response were also noted, and documented as either partial response (PR), complete response (CR), stable disease (SD) or progressive disease (PD).

Results
34 patients were identified; 26 with classical MF, 5 folliculotropic, 2 poikilodermatous and 1 hyperpigmented, with a median age of 60 years (range 21-90). Stage ranged from IA to IIB. Median time from diagnosis to start of Chlormethine treatment was 5 years (range 0-22), and baseline BSA ranged from 1.5-60%. Median time from prescription of the gel to issue was 17 days (range 7-68) and patients required on average 2 tubes every 2 months (range 1-5).

Median length of treatment was 6 months (range 1-26). Out of the intention to treat population, at 3 months 19/24 (79%) had PR, 3/24 had PD, and 2/24 had discontinued treatment. At 6 months 15/21 (71%) responded (13/21 PR, 2/21 CR), 1/21 SD and 1/21 PD. Four had stopped treatment. At 12 months, 7/13 (54%) had PR, 1/13 PD after previous CR, 5/13 stopped treatment.

Side effects were reported in 15/34 (44%), most commonly itching, soreness, dryness and blistering. Eight patients discontinued treatment due to side effects, 5 stopped due to inefficacy and 2 because it was no longer required due to CR.

Response to treatment was observed across all stages from IA to IIB. There did not appear to be any correlation between severity of the disease and response to treatment or likelihood of side effects.

Conclusions
Chlormethine gel shows efficacy as monotherapy in stages IA-IIB MF. Skin reactions were common, which resulted in discontinuation of treatment in a quarter of our cohort, however 79% of patients had rapid response to treatment which was sustained in over half, therefore we feel that Chlormethine gel remains a useful option for skin directed treatment, both for early and later stage disease.

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A-294

Clinical diversity and treatment approaches to blastic plasmacytoid dendritic cell neoplasm: a retrospective multicentre study [PUBLISHED ARTICLE]

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Background
Blastic plasmacytoid dendritic cell neoplasm (BPDCN) is a rare, aggressive type of hematologic precursor malignancy primarily often manifesting in the skin. We sought to provide a thorough clinical characterisation and report our experience on therapeutic approaches to BPDCN

Methods
In the present multicentric retrospective study, we collected all BPDCN cases occurring between 05/1999 and 03/2018 in 10 secondary care centres of the German-Swiss-Austrian cutaneous lymphoma working group

Results
A total of 37 BPDCN cases were identified and included. Almost 90% of the patients had systemic manifestations (bone marrow, lymph nodes, peripheral blood) in addition to skin involvement. The latter presented with various types of cutaneous lesions: nodular (in more than 2/3) and bruise-like (in 1/3) skin lesions, but also maculopapular exanthema (in circa 1/6). Therapeutically, 22 patients received diverse combinations of chemotherapeutic regimens and/or radiotherapy. Despite initial responses, all of them ultimately relapsed and died from progressive disease. Eleven patients underwent hematopoietic stem cell transplantation (HSCT; autologous HSCT n=3, alloHSCT n=8). The mortality rate among HSCT patients was only 33.33% with a median survival time of 60.5 months

Conclusions

Our study demonstrates the clinical diversity of cutaneous BPDCN manifestations and the positive development observed after the introduction of HSCT

A-161

CTPS1 is a novel therapeutic target in cutaneous T cell lymphoma

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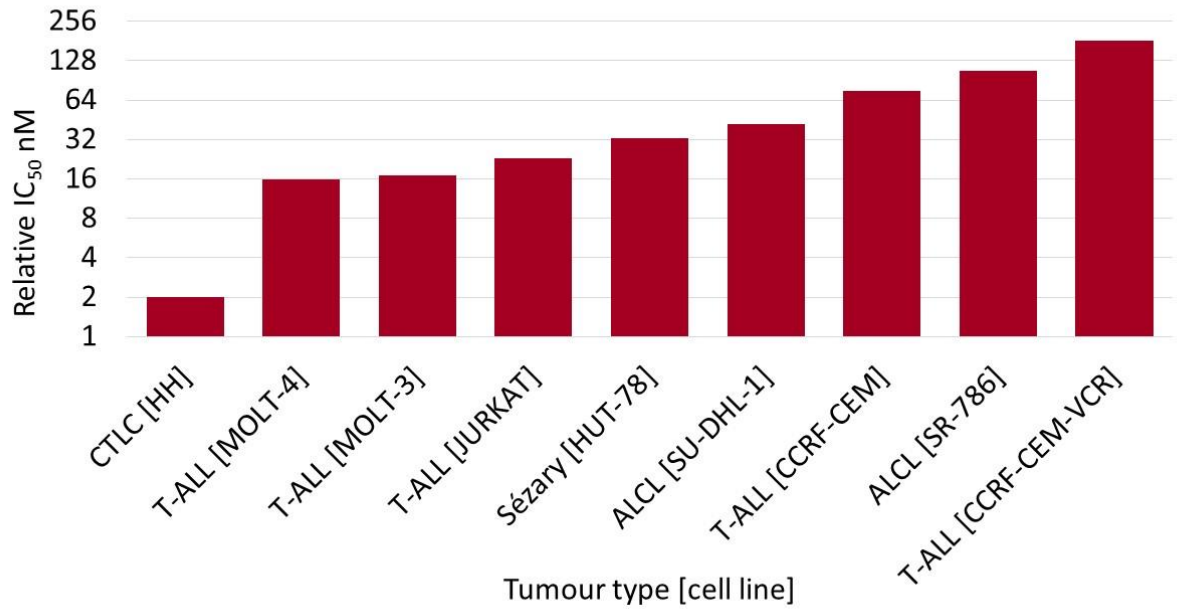
Background

Figure 1



Sensitivity of different neoplastic T cell lines to the CTPS1 inhibitor dencatistat.

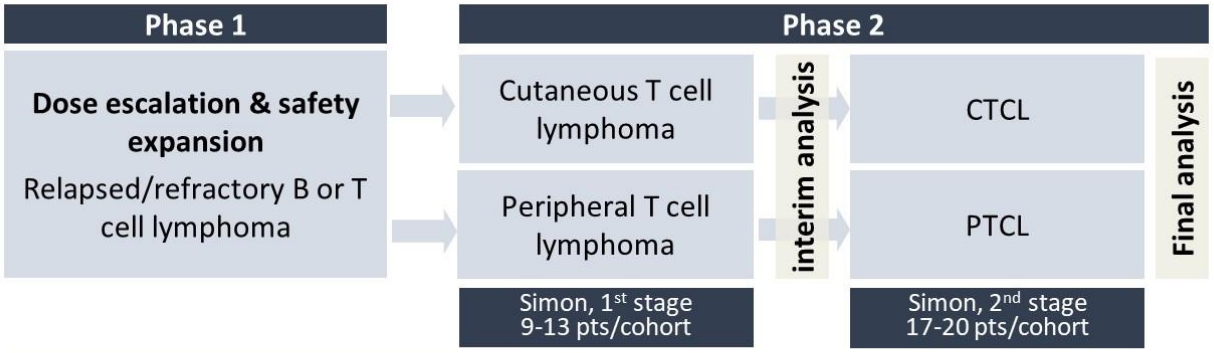
Pyrimidine synthesis is a potential target for cancer therapy. The rate limiting step in *de novo* pyrimidine synthesis is catalysed by two homologous enzymes, CTPS1 and CTPS2. CTPS1 is essential for lymphocyte proliferation, whereas CTPS2 is sufficient for the growth of non-haemopoietic cells. Selective CTPS1 inhibition has the potential to deliver anti-cancer activity without associated toxicity. Dencatistat (STP938) is a first in class oral CTPS1 inhibitor showing >1,300-fold selectivity over CTPS2. In preclinical studies, dencatistat induced apoptosis of malignant T cells at nanomolar concentrations (Figure 1) and inhibited the growth of lymphoid tumours *in vivo*.

Methods

Dencatistat entered clinical development late 2022 in a first in human dose escalation study (Figure 2) for patients with relapsed/refractory lymphoma with a focus on peripheral and cutaneous T cell lymphoma (which comprise 52% and 17%, respectively, of patients recruited to date). Dose escalation is on-going. Early pharmacokinetic data are consistent with twice daily oral dosing. Key phase 1 endpoints are safety and tolerability.

Results

Figure 2



Objectives	Phase 1	Phase 2
Primary	Safety & tolerability Define RP2D	Objective response rate Duration of response
Secondary	PK, food effect Clinical activity	Safety & tolerability CR, TTR, PFS
Exploratory	Target engagement Biomarkers of response Drug metabolites	PK Target engagement Biomarkers of response

Design and objectives of a phase 1/2 trial of the first in class CTPS1 inhibitor dencatistat.

The phase 2 study will comprise efficacy cohorts exploring peripheral and cutaneous T cell lymphoma. The study will follow a Simon two-stage design with an interim futility analysis based on predefined response rates. Should dencatistat show promising efficacy, cohorts may be expanded using an adaptive approach based on early efficacy signals (Mehta and Pocock, 2011). Standard exclusion criteria apply; patients with ECOG performance score >2 or known CNS involvement by lymphoma are not eligible. Key phase 2 endpoints are objective response rate and duration of response. Exploratory studies include analysis of tumour biopsies, circulating tumour DNA and plasma cytokines for biomarkers of response. The phase 2 study will recruit patients in France, the UK and the US.

Conclusions

Differential targeting of CTPS1, sparing the paralog CTPS2 enzyme, is a potential novel therapeutic strategy in cutaneous T cell lymphoma. Dencatistat is an orally administered selective CTPS1 inhibitor currently in clinical development in a phase 1/2 clinical trial (NCT05463263); the phase 2 study will include a dedicated cohort for individuals living with cutaneous T cell lymphoma, and is expected to commence late 2024.

A-116

Cytokine-pathway blockers worsen mycosis fungoides masquerading as psoriasis.

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Background

Mycosis fungoides (MF) is the most common form of cutaneous T-cell lymphoma (CTCL) with diverse clinicopathological manifestations.

Methods

A 77-year-old female presented with erythematous psoriasiform plaques and disseminated eczematoid lesions.

Results

Despite an atypical presentation, two separate biopsies confirmed a histological diagnosis of psoriasis. Skin cytokine profile revealed a Th17-skewing, further strengthening this assumption. Treatment with anti-IL23 guselkumab worsened the disease. Ixekizumab, anti-IL17A, was administered for seven months, during which her skin continued to deteriorate, and she developed alopecia areata-like patchy hair loss. Treatment with JAK-inhibitor tofacitinib led to further clinical worsening. The disease history coupled with the development of erythroderma and palmoplantar keratoderma following multiple cytokine-pathway blockers raised suspicion for CTCL. A follow-up skin biopsy revealed atypical lymphocytic infiltrate and clonal TCR rearrangement. Retrospective clonality analysis confirmed

the same clone in all previous skin biopsies. Clinical-pathological correlation led to a diagnosis of psoriasis-mimicking MF in advanced disease stage IIIA, five years after initial symptoms. She achieved complete remission with UVB phototherapy and acitretin.

Conclusions

A multicenter study of 19 MF patients treated with biologics found that IL-17A, -12/23 and -23 blockers were associated with CTCL progression. Undiagnosed MF under anti-IL17 may shift the Treg/Th17 balance towards Tregs leading to further immunosuppression. Consistently, our patient worsened significantly with IL-23 and IL-17A blocker. In a phase 2 study of JAK inhibitor ruxolitinib, in T-cell lymphomas, only 1 out of 7 MF patients responded. Our patient's condition significantly worsened after JAK-inhibition. Data on the use of JAK-inhibitors in large CTCL cohorts is missing and their indication should be considered on a case-by-case basis in the absence of alternatives. For atypical dermatosis, conventional therapies such as phototherapy and acitretin may be preferable first-line choice compared to biologics. It is of particular interest for a CTCL with a Th17 phenotype to worsen on anti-IL-17A therapy. This phenomenon is consistently observed in CTCL, particularly in its more classical manifestation: Th2-biased CTCL not responding or worsening under dupilumab. The delineation of CTCL from inflammatory skin diseases becomes a crucial question in the modern era of biological treatments.

A-158

Dermatoscopy in CTCL: Evaluating Diagnostic Potential and Patterns

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Background

Cutaneous T-cell lymphomas (CTCL), including Mycosis Fungoides (MF) and Sézary Syndrome (SS), are challenging due to their varied clinical presentations. Traditional diagnostic methods, though effective, may sometimes lead to delays in accurate detection and treatment[1]. This study investigates the use of dermatoscopy, a non-invasive diagnostic tool, in identifying MF and SS. It also examines whether specific dermatoscopic patterns can reliably distinguish these diseases from other inflammatory skin disorders, highlighting the potential of this technique.

Methods

This observational, single-center, retrospective study involved patients with histologically confirmed MF or SS at a specialized cutaneous lymphoma clinic. Data were collected from clinical and dermatoscopic images taken in 2019. Dermatoscopic features analyzed included pigment presence, vessel patterns, and scaling. Data were processed using standardized dermatoscopic terminology and analyzed through regression to correlate dermatoscopic findings with disease stages according to the TNMB classification.

Results

The study included 30 patients with a balanced representation of early-stage and advanced CTCL. Dermatoscopy revealed vascular patterns such as dotted and clod vessels across different CTCL stages. However, dermatoscopic features did not significantly correlate with the TNMB stage or other clinical indicators. Specific patterns, like clustered dots and certain background colors, were frequently observed but did not significantly correlate with disease progression.

Conclusions

While dermatoscopy provides valuable visual clues that may aid in suspecting CTCL, our sample did not show specific characteristics or patterns useful for diagnosing MF or SS without histological confirmation. The technique's utility lies in supporting clinical assessments and guiding biopsies rather than replacing traditional diagnostic methods. The data reported in the literature remain very heterogeneous[2], especially compared to ours.

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A-249

Effectiveness and safety of chlormethine gel in the treatment of mycosis fungoides affecting "sensitive" areas: A real-world experience from two tertiary referral centres

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Background

Chlormethine (CL) gel is the first skin-directed therapy developed for the treatment of mycosis fungoides (MF). Although clinical trials and real-world evidence support its efficacy in both early and advanced stages of MF, the occurrence of local adverse events (AEs) such as irritant contact dermatitis (ICD) can limit its use. This study aims to address the knowledge gap by assessing the effectiveness and safety of CL gel in managing MF lesions in highly sensitive areas.

Methods

Retrospective case series on individuals affected by MF with involvement of sensitive areas treated with chlormethine gel in monotherapy or associated with other therapies receiving care at two Italian referral centers.

Results

The study included eight patients (five males and three females), with a median age of 56.5 years (IQR 17.75), at various stages of MF, with 75% in the early stage. The diagnosis of MF was histologically confirmed at a median age of 43.5 years (IQR 10.5). Most patients had classical MF (n=5, 62.5%). CL gel was initiated either as monotherapy (n=5, 62.5%) or in combination with systemic treatments (n=3, 27.5%). The CL gel application regimen varied between daily or alternate-day applications. CL gel was co-administered with topical high-potency corticosteroids in four patients. Treatment sites included the eyelid in three patients, with individual patients treating the groin, cheek, perineum, pubis, and scrotum respectively. The median treatment duration was 3 months, with a range from 5 days to 9 months. Response to therapy was evaluated using a modified CAILS (mCAILS), excluding considerations of hyperpigmentation. At T3 (three months post-CL introduction), there was a notable reduction in mCAILS. The improvement continued at T6 and T12. At a median follow-up of 24 months (IQR 31), six patients had a mCAILS score of 0, while others maintained low mCAILS scores, reflecting the long-term benefits of the treatment. AEs were reported in six patients (72.5%). Most AEs were mild ICD; (n=3, 37.5%) followed by moderate ICD (n=2, 25%) and severe ICD (n=1, 12.5%). Except for one patient, none of the AEs led to treatment discontinuation, although temporary stops or reduced dosing frequencies were necessary for five patients to manage ICD. The treatment left transient hyperpigmentation in the treated area in six patients.

	1	2	3	4	5	6	7	8
Age/sex	46/M	57/M	42/M	81/M	59/F	54/F	56/F	58/M
Age at MF Diagnosis (years)	38	42	19	68	46	48	50	43
Fitzpatrick Skin Type	II	III	III	III	III	III	III	II
Clinical Variants	Classical MF	Poikilodermatous MF	Classical MF	Classical MF	Folliculotropic MF	Classical MF	Folliculotropic MF	Classical MF
Prior MF Therapy	TCS, nb-UVB, acit	TCS, pUVA, nb-UVB,	TCS, acit,	TCS, nb-UVB, RT	TCS, pUVA, acit, bexa, ifn, RT	TCS, pUVA, aci, RT	TCS, nb-UVB, acit, pUVA	TCS, nb-UVB, acit
Age at CL Introduction	44	40	41	80	55	50	54	57
Stage at CL Introduction	Ia	Ia	Ib	Ib	IIb	Ib	IIb	IIa
Affected Sensitive Areas	Groin	Perineum	Eyelid	Pubis	Eyelid	Eyelid	Cheek	Scrotum
Type of Lesion Treated	Patch	Plaque	Patch	Plaque	Plaque	Plaque	Plaque	Plaque
Frequency of CL Application	Every other day	Every other day	Every day	Every other day	Every other day	Every day	Every other day	Every other day
Duration of CL Treatment	3 months	4 months	5 days	2 months	3 months	9 months	3 months	2 months
Use of Combination Topical Therapies	TCS	TCS	None	TCS	None	None	None	TCS
Use of Combination Systemic Therapies	None	None	None	None	Bexa	none	pUVA	Acit
mCAILS at CL introduction (T0)	16	20	11	22	12	13	15	11
mCAILS at T3	9	9	0	0	0	8	2	6
mCAILS at T6	0	0	0	0	0	5	0	3
mCAILS at T12	0	0	0	0	0	3	0	3
Months to Last Follow-Up	36	14	14	24	48	48	24	12
mCAILS at the last follow-up	0	0	0	0	0	3	0	3
Hyperpigmentation	Yes	Yes	Yes	Yes	Yes	No	Yes	No
Adverse Events	ICD (mild)	ICD (moderate)	ICD (severe)	ICD (moderate)	ICD (mild)	None	None	ICD (mild)
Management of Adverse Events	Use of TCS	Temporary stop	Stop, use of TCS	Temporary stop, reduced dosing frequency, use of TCS	Temporary stop	/	/	Reduced dosing frequency

Abbreviations: TCS, topical corticosteroids; nb-UVB, narrow-band ultraviolet B; pUVA, psoralen and ultraviolet A; RT, radiotherapy; acit, acitretin; bexa, bexarotene; ifn, interferon; mCAILS, modified Composite Assessment of Index Lesion Severity; ICD, irritant contact dermatitis; MF, Mycosis Fungoides; CL, chlormethine.

Summary of patient characteristics

Conclusions

Our study supports the safe and effective use of CL gel for the treatment of MF in sensitive areas.

A-296

Efficacy and safety of pembrolizumab and radiotherapy in relapsed/refractory cutaneous T cell lymphoma: results of the PORT trial

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Background

Background: The outlook for patients with advanced cutaneous T-cell lymphomas (CTCL; mycosis fungoides (MF) and Sézary syndrome (SS) remains poor and an unmet clinical need, with most systemic agents providing short-lived remissions. Immunotherapies may offer a solution, with radiotherapy (RT) an attractive partner due to the acute radiosensitivity of CTCL and its ability to induce an immune response that may augment the effect of immunotherapy.

Methods

Methods: PORT was a single-arm, multicentre phase II trial for patients with relapsed/refractory CTCL. Patients received 3-weekly 200mg intravenous pembrolizumab for ≤2 years in combination with radiotherapy (RT) at a total dose of 12Gy between 3 fractions over 3 days. RT was given at the earliest of disease progression or 5th pembrolizumab infusion (inf). An area involved by measurable CTCL was left untreated by RT for assessment of abscopal effect. Primary endpoint was overall response rate (ORR) at inf9; 16/46 responses required. Secondary endpoints included duration of response (DOR), abscopal response, progression-free survival (PFS), overall survival (OS), treatment compliance and safety.

Results

Results: 46 patients (41 MF, 5 SS) were registered between 04/2019 and 12/2022 from 9 UK sites. In this heavily pretreated population, median age 63 (24-83), 63% male, 63% WHO PS 0, 24% stage IV. Median follow-up was 21.4 months (1.6-44.0). 24% of patients remained on treatment for >1 year whilst 57% received <9 infusions, including all those with stage IV disease or SS. Disease progression was the leading cause for stopping treatment (39%). 76% of patients proceeded to RT, 6 (13%) receiving it before inf5. The primary endpoint was not met as only 9 patients (20%) achieved response at inf9. Though best ORR was 26% (95% CI 14-41), DOR rates at 1 and 2-years were 74% (95% CI 39-91) and 65% (95% CI 31-85) leading to an encouraging median PFS of 12.6 months. Abscopal mSWAT scores were significantly lower at inf9 compared to RT (p=0.006), suggesting a RT induced “abscopal” or systemic immune effect. 54% of patients experienced a grade 3+ adverse event, with infections most common (17%). 19 deaths were reported (10 CTCL, 3 Covid-19, 1 Sepsis, 5 Other). 2-year OS was 64% (47-77).

Conclusions

Conclusion: Pembrolizumab in combination with RT did not show efficacy for patients with SS or stage IV relapsed/refractory CTCL however a subset of patients benefited with enduring clinical responses and encouraging evidence of a RT induced abscopal effect.

A-246

Extranodal natural killer/T-cell lymphoma, nasal-type, with extranasal cutaneous presentation – report of 3 cases

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Background

Extranodal NK/T-cell lymphoma (ENKTL) is a rare and aggressive subtype of T-cell lymphoma. It is more common in Asians and mainly presents on the nose, but a primary cutaneous involvement is seen in 15-20% of cases.

Methods

We present the cases of three Caucasian patients with ENKTL with a primary presentation in the skin.

Results

Clinical picture - We present the cases of three Caucasian patients:

- *Case 1*: An 82-year-old male with a 1-month history of asthenia and ulcerated lesions with an undermined border on the left leg and forearms.
- *Case 2:* A 65-year-old woman, with end stage chronic kidney disease, with a 5-month history of a malar ulcer with infiltrated borders, that expanded to over 5cm in diameter. She later developed similar lesions on the upper and lower limbs.
- *Case 3:* A 77-year-old female with a 6-month history of two erythematous cutaneous nodules on the left leg, one of them with superficial ulceration.

Diagnostic procedures: In all patients, a cutaneous biopsy revealed an atypical lymphoid infiltrate throughout the dermis and subcutis, predominantly composed of medium to large-sized cells, which were positive for T-cell markers, cytotoxic markers (TIA-1 and granzyme

B) and CD56. *In situ* hybridization showed diffuse positivity for Epstein-Barr-encoded RNA. EBV viral load was high. Nasopharyngeal and bone marrow involvement was excluded, and a PET-CT showed no suspicious lesions apart from adenopathies in the second patient. Blood counts were normal, except for mild lymphopenia in the first patient. The diagnosis of primary cutaneous *extranasal* ENKTL was then established.

Treatment and evolution: The *SMILE* protocol, standard treatment for advanced ENKTL, was considered unsuitable in all cases given advanced age and/or comorbidities. Combination chemotherapy (*mini*-CHOP) was started in the first two cases. While the first patient is in complete remission after 14 months, the second showed rapid disease progression, with paraneoplastic pleural effusion and severe pancytopenia, dying 2 weeks after the first cycle. The third case will be discussed in our tumour board, with radiotherapy and mini-CHOP being the main options.

Conclusions

ENKTL is very rare in Caucasian populations and an extranasal location is also exceedingly uncommon. These three cases underline its polymorphic cutaneous presentation and the therapeutic challenges that arise in patients with advanced age or important comorbidities.

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Identification of clones by TCR Vβ repertoire analysis supports diagnosis of leukemic cutaneous T-cell lymphoma

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Background

Erythrodermic leukemic cutaneous T-cell lymphoma (L-CTCL) comprises progressive erythrodermic mycosis fungoides (MF) with infiltration of blood and Sézary syndrome (SS). Clinically established diagnostic procedures do not always allow sufficient distinction of L-CTCL and erythrodermic conditions of other origin. Diagnosis of L-CTCL might be supported by identification of clones via TCR Vβ repertoire analysis.

Methods

In the time span between March 2017 and April 2024 blood samples were collected from 63 patients with erythroderma (female/male: 22%/78%; mean age: 64±14 years). Patients included had a diagnosis of L-CTCL in 17 cases (7 patients with SS, 10 patients with erythrodermic leukemic MF), whereas 46 patients presented with erythroderma due to another origin (23 patients with non-leukemic MF, 13 patients with atopic dermatitis, 10 patients with other conditions). Whole peripheral blood mononuclear cells (PBMCs) were isolated from blood samples and examined for T-cell clones by applying a multiparametric analysis tool designed for quantitative determination of the TCR Vβ repertoire of T-lymphocytes via flow cytometry (Beckman Coulter #PN IM3497, USA).

Results

As significant T-cell clones were detected in blood samples of all 17 patients with diagnosed L-CTCL, TCR Vβ repertoire analysis showed a 100% sensitivity in identification of L-CTCL and thereby presented superior to FACS with conventional T-cell panels (sensitivity of 70.6% [12 of 17 patients]). Intriguingly, T-cell clones were also found in 5 of 23 patients (21.7%) with non-leukemic MF and 5 of 23 patients (21.7%) with benign erythrodermic conditions such as atopic dermatitis (n=3), GvHD (n=1) and psoriasis (n=1), indicating a 78.3% L-CTCL specificity of the method ($p<0.0001$). A further significant difference between L-CTCL and no-L-CTCL group could be revealed, when comparing percentages of clonal TCR Vβ repertoire (median±IQR in patients with L-CTCL (n=17): 68.4%±25.9%; median±IQR in patients with other conditions (n=10): 43.3%±23.6%; [$p<0.0001$]).

Conclusions

In summary, TCR Vβ repertoire analysis represents a highly sensitive method regarding detection of malignant clones in the blood of patients with L-CTCL. Moreover, the methodology might support therapeutic decisions, as it allows screening for molecules such as CCR4, CD30, CTLA-4 and CD52.

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Identifying Patients With Poor Outcomes in Mycosis Fungoides & Sezary syndrome For Improved Management Choices

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Background
Introduction: Advanced mycosis fungoides (MF) and Sezary syndrome typically have a poor prognosis of <5 years. In addition over 25% with early stage MF progress to advanced disease. Developing a prognostic index in MF/SS will identify patients with poor outcomes and allow better treatment choices and improve survival.

Methods
The Cutaneous Lymphoma International Consortium (CLIC) launched the PROCLIPI (**Pro**spective **C**utaneous **L**ymphoma **I**nternational **P**rognostic **I**ndex) Study in 2015 at >50 international expert MF/SS Centres, prospectively collecting pre-defined datasets to determine a prognostic index.

Results
2172 patients have been recruited at 52 international sites, 1622 (74.6%) early-stage patients and 550 (25.3%) advanced. Early-stage patients (IA-IIA) present with median age=58years(IQR=44-69yrs). Factors associated with progression to advanced disease included presence of cutaneous plaques; p<0.001, nodal involvement (Nx-N2); p<0.001, age>60yrs;p=0.016 and large cell transformation(LCT) in skin; p<0.001. The 5-year overall survival (OS) rates are: IA=94.3% IB=84.3% IIA=74.3% with a significant worsening of survival with increasing stage p<0.001. The median age at diagnosis of advanced patients (IIB-IVB) is 69-years (IQR=56-75years) and significantly older than early-stage cohort at 58yrs p<0.001. The 5-year OS is IIB=49.7%, IIIA=64.2%, IIIB=43.5%, IVA1=48.9%, IVA2=25.4%, IVB=39.4%. Factors at diagnosis associated with a significantly worse survival in advanced stages were N3 status; p<0.001, age>60yrs; p=0.01, raised serum LDH above normal; p=0.004 and LCT in skin; p=0.001. Modelling these 4 independent risk factors into a prognostic index with low, intermediate and high risk-groups found there was a statistically significant worse OS in high- versus low-risk p<0.001 and high- versus intermediate-risk p=0.004 as well as intermediate versus low-risk p=0.0242.

Conclusions
Early-stage MF is typically reported as a low-grade lymphoma however data from PROCLIPI have found 5-year survival rates of 84.3% in IB and 74.3% in IIA coupled with a median age of diagnosis of 58 years there is a marked reduction in life expectancy for many early-stage MF patients. In advanced stages there is a worse 5-year survival than early stages between 25.4%-64.2% but excluding IVA2 increasing stage doesn't correlate with worse survival. However using the prognostic index stratifies advanced patients into low, intermediate and high-risk group for worse survival which may lead to improved treatment choices.

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Immunologic changes following chlormethine gel treatment in Cutaneous T-cell Lymphoma patients

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Background
Mycosis fungoides (MF) is the most common form of cutaneous T-cell lymphoma (CTCL). In treating MF, topical chlormethine gel directly targets malignant T cells within skin lesions and modulates the tumor microenvironment (TME). This therapy modulates local immune responses, potentially enhancing immune surveillance. This study aims to elucidate the role of chlormethine gel in immune cell profiling and TME shift in MF patients.

Methods
Skin biopsies (n=12) were collected from plaques and tumors of four MF patients: 2 stage IB using as monotherapy and 2 stage IIB in combination with interferon, before and after treatment of the same lesion with chlormethine gel. Single-cell suspensions were stained

with a panel of 36 antibodies targeting leukocyte surface markers, programmed death 1 protein (PD-1), programmed death-ligand 1 (PD-L1) and OX-40 and analyzed using mass cytometry (Helios, CyTOF). Comparisons across groups were conducted using the Wilcoxon matched-paired rank test.

Results

Treatment with chlormethine gel led to a statistically significant reduction in aberrant $CD4^+CD7^-CD26^-CCR4^{hi}$ T cells expressing $PD\text{-}L1^+$ compared to baseline lesions. Clinical response was seen in plaques in contrast to tumors whereas in histology there was loss of epidermotropism and presence of lymphocytes around the follicles. There was no significant change in PD-1 expression post-treatment, indicating that chlormethine gel reduces PD-L1 levels while leaving PD-1 on T cells relatively unchanged. Additionally, there was a significant reduction in $PD\text{-}L1^+$ plasmacytoid dendritic cells (pDCs), $PD\text{-}L1^+$ Central Memory $CD4^+$ T cells, $PD\text{-}L1^+$ Regulatory T cells (Treg), and $OX\text{-}40^+IgD^-$ Memory B cells. No significant differences were observed in the immune profile of plaques between pre-treatment and post-treatment samples.

Conclusions

Topical chlormethine gel significantly impacts the local immune profile by reducing malignant T cells and modulating the TME in the skin lesions. These changes are crucial for its therapeutic efficacy in treating CTCL, with effects largely localized and minimal systemic impact. Monitoring and managing local skin reactions are essential to ensure continued therapeutic benefit. A larger study to validate these findings is currently ongoing.

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International study of Sezary Syndrome reveals improved disease-specific survival from modern systemic therapies

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Background

Traditionally, Sezary syndrome (SS) has been associated with few therapeutic options and poor prognosis, with 5-year disease-specific survival (DSS) less than one-third in historical cohorts. Newer therapies and combinations are associated with impressive time-to-next-treatment (TTNT), particularly allogeneic stem-cell transplantation (AlloSCT) and combination therapies including extracorporeal photopheresis.[1] In this multicentre, international study, we explored the prognostic outcomes of patients managed for SS in the modern therapeutic era.

Methods

Three international quaternary centers participated in this retrospective study: University Hospitals Birmingham, United Kingdom, Peter MacCallum Cancer Centre, Australia, and Hôpital Saint-Louis, France. Eligibility required clinicopathological diagnoses of mycosis fungoides (MF)/SS with B2 blood involvement, diagnosed between 1/1/2012-31/12/2020.[1]

Results

178 patients were eligible. 58 different therapies were delivered, 13.5% of patients received AlloSCT. Long-term survival exceeded historical reports with 5-year DSS and overall survival (OS) of 56.4% and 53.4%, respectively. In patients receiving AlloSCT, prognosis was excellent: 5-year DSS and OS were 90.5% and 78.0%, respectively. For patients ineligible for AlloSCT, prognosis remained poor. Confirming the results from the Cutaneous Lymphoma International Consortium (CLIC)[2], LDH and large cell transformation had significant prognostic impact. Unlike earlier studies, stage did not have prognostic impact.

Conclusions

Outcomes for patients with SS have improved. Patients with nodal effacement (N3, stage IVA2) may be deriving greatest relative benefit from modern therapeutic strategies. AlloSCT provides the only potentially curative therapy with impressive survival gains for eligible patients. For patients ineligible for AlloSCT, the overall poor prognosis demonstrates an ongoing unmet need for improved therapeutics and combinations for patients with SS.

References:

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Investigating Brentuximab Vedotin (BV) as a radiosensitizer in combination with low-dose TSEBT for Advanced CTCL: Clinical observations and experimental findings

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Background
Patients with advanced-stage mycosis fungoides (MF) or Sézary syndrome (SS) have a poor prognosis. Current single-agent treatments for cutaneous T-cell lymphoma (CTCL) often result in low remission rates & short-lasting responses. Combination therapies can enhance therapeutic effects through synergistic or additive mechanisms. A small pilot study showed a rapid & substantial clinical response using simultaneous Brentuximab Vedotin (BV) & ultrahypofractionated low-dose total skin electron beam therapy (TSEBT) with a total dose of 8 Gy in 2 fractions. Hypothesis: BV acts as a radiosensitizer, enhancing the effects of radiation therapy.

Methods
14 patients with tumor stage MF (IIb) were treated and observed under simultaneous BV and TSEBT therapy according to the “Krefeld scheme”. Patients received 6-8 cycles of BV at the standard dose combined with 2x4 Gy TSEBT. Treated patients exhibited CD30 expression ranging from less than 5% to 30%. All patients had previously undergone more than one systemic therapy, including two who had received BV monotherapy. Patients achieving a complete response (CR) or partial response (PR) under the combination therapy received maintenance therapy with methotrexate 10-15 mg per week. Experimental analyses investigated the effect of radiation on CD30-expression in CTCL cell lines and apoptosis with/without BV.

Results
14 patients were included (2 females, 12 males; mean age 58.9 years). Patients treated with simultaneous BV & TSEBT showed a rapid response, with a median time to response of 12 days. The overall response rate (ORR) was 100% (14/14), with 64% (9/14) achieving CR and 36% (5/14) achieving PR. The BV/TSEBT combination therapy was well-tolerated, with all patients completing treatment. Side effects included maculopapular rash in 21% (3/14) and peripheral neuropathies in 36% (5/14) of patients. No hematological side effects were observed. All side effects were grade 1-2. Initial translational research suggests a synergistic effect of the combination and enhanced efficacy, to be detailed at the conference.

Conclusions
The simultaneous combination of BV & low-dose TSEBT is a highly effective and safe treatment strategy for MF stage IIB. The ORR was higher with BV/TSEBT compared to BV monotherapy, indicating an additive/synergistic effect. BV as a radiosensitizer appears to enhance radiotherapy efficacy, potentially leading to better clinical outcomes. Maintenance treatment is crucial for advanced-stage CTCL patients. Clinical trials are needed.

Keywords: Mycosis Fungoides, Brentuximab Vedotin, Total Skin Electron Beam Therapy, Cutaneous T-cell Lymphoma, Radiosensitizer, Combination Therapy

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Lacutamab in Patients with Relapsed and Refractory Sézary Syndrome: Results from the TELLOMAK Phase 2 Trial

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Background

Sézary syndrome (SS) is a rare and aggressive cutaneous T-cell lymphoma, which commonly expresses KIR3DL2, a killer immunoglobulin-like receptor, reported in ≥ 85% of patients (pts). SS is characterized by erythroderma, significant blood involvement and lymphadenopathy. and poor prognosis (median survival ~5 years). Lacutamab is a first-in-class monoclonal antibody designed to specifically deplete KIR3DL2-expressing cells via antibody-dependent cell-cytotoxicity and phagocytosis.

Methods

TELLOMAK is an international, Phase 2 trial with multiple cohorts (NCT03902184). We report here results from Cohort 1, evaluating lacutamab in pts with relapsed/refractory (R/R) SS after at least 2 prior systemic therapies including mogamulizumab. Lacutamab 750 mg is administered until progression or unacceptable toxicity. Primary endpoint was Objective Response Rate (ORR) by global response score according to Olsen 2011. Secondary endpoints included but not limited to additional efficacy endpoints, safety, QoL assessments.

Results

As of May 1, 2023, 56 SS pts were enrolled . Median age was 69 years (range: 42-86), the median prior lines of systemic therapies was 6.0 (range: 2-15), 60.7 % had stage IVA1, 32.1 % had stage IVA2 and 7.1% had stage IVB disease at baseline, all pts had blood involvement (B2), 67.9% had confluence of erythema covering ≥ 80% body surface area (T4), 35.7% had lymph node lymphoma involvement (N3). Median follow-up was 14.4 months (95% CI 9.0-18.4). Global confirmed ORR was 37.5% (95% CI 26.0-50.6) including 2 CRs, with a median time to response of 2.8 months (range 1-9). ORR in skin was 46.4% (95% CI 34.0-59.3) including 5 CRs. ORR in blood was 48.2% (95% CI 35.7-61.0) including 15 CRs.

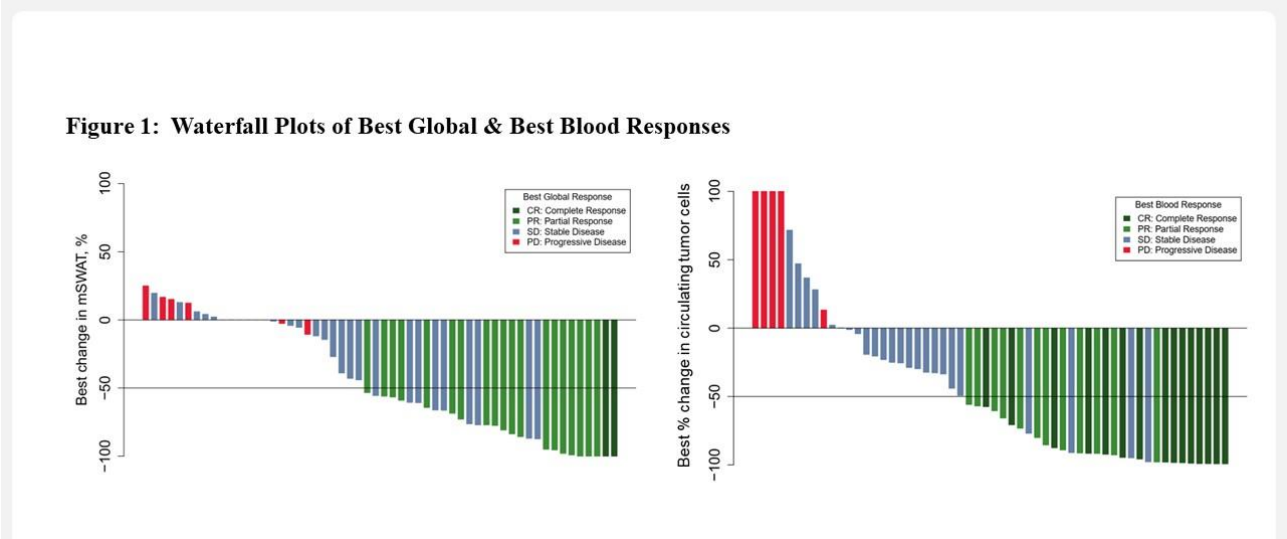

Figure 1: Waterfall Plots of Best Global & Best Blood Responses

Clinical Benefit Rate (CBR, defined as CR+PR+SD) was 87.5 % (95% CI 76.4-93.8). Median PFS was 8.0 months (95% CI 4.7-21.2). Grade ≥ 3 Treatment-related (TR) Treatment-Emergent Adverse events (TEAEs) were observed in 17.9% pts. Serious TR TEAEs were observed in 7.1% and 5.4% pts discontinued study drug due to TR TEAE. Data from additional key endpoints will be presented.

Conclusions
In this SS cohort from the TELLOMAK study, our data confirm that lacutamab shows promising clinical activity in a R/R SS population previously treated with 2 or more prior systemic therapies including mogamulizumab, and an overall favourable safety profile. Continued evaluation of this new targeted treatment option for pts with SS is warranted.

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Lacutamab in patients with relapsed and/or refractory mycosis fungoides: results from the TELLOMAK phase 2 trial

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Background
The most common type of cutaneous T-cell lymphoma is Mycosis Fungoides (MF) accounting for 50-60% of cases. Extracutaneous involvement occurs mainly in lymph nodes or blood; 25% of patients (pts) are diagnosed at advanced stage with a 5-year survival of 15-25%. KIR3DL2 is a killer immunoglobulin-like receptor, expressed in 50% of MF pts. Lacutamab is a first-in-class monoclonal antibody designed to specifically deplete KIR3DL2-expressing cells via antibody-dependent cell-cytotoxicity and phagocytosis.

Methods
TELLOMAK is an international, multi-cohort phase 2 trial (NCT03902184). MF pts who had received at least 2 prior systemic therapies were treated with lacutamab until disease progression or unacceptable toxicity. Primary endpoint was Objective Response Rate (ORR) by global response score based on the evaluation of 4 compartments: skin, blood, lymph nodes and viscera according to International Consensus criteria Olsen 2011. Secondary endpoints included other efficacy endpoints, safety, and quality of life. Here we report data of all MF patients, and according to KIR3DL2 status.

Results
As of October 13, 2023, recruitment was completed, with 107 pts enrolled. Median age was 62 years. Median number of previous systemic lines was 4 (range: 1-14). Median follow-up was 11.8 months (m) (95% CI 9.9-13.8). ORR was 16.8% (CI 10.9, 25.0; Olsen 2011), and 22.4% (CI 15.6, 31.2; Olsen 2022), response in skin was 29.0% (CI 21.2, 38.2). Median time to response was 1.0m and median PFS 10.2m (CI 6.5, 16.8).

Among the KIR3DL2 ≥1% pts (N=48), ORR was 20.8% (CI 11.7,34.3; Olsen 2011), and 29.2% (CI 18.2, 43.2; Olsen 2022), response in skin was 33.3% (CI 21.7, 47.5). Median time to response was 1.0 m and median PFS 12.0 m (CI 5.6, 20.0). Median duration of response was not reached.

Grade ≥ 3 Treatment-related (TR) Treatment-Emergent Adverse events (TEAEs) were observed in 4/107 (3.7%) pts, serious TR TEAEs in 4/107 (3.7%) pts and 3/107 (2.8%) pts discontinued study drug due to TR TEAEs. The most common (>10%) TR TEAEs were fatigue (11.2%), nausea (11.2%), asthenia (10.3%), and arthralgia (10.3%).

Conclusions
The data from the heavily pre-treated MF population enrolled to the TELLOMAK study confirms promising clinical activity of lacutamab regardless of KIR3DL2 expression, with a favorable safety and tolerability profile. These data support the further development of lacutamab in an effort to bring improved treatments to patients with CTCL.

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Mogamulizumab in patients with mycosis fungoides or Sézary syndrome: Update on the German non-interventional MINT study

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Background

Mogamulizumab (moga), approved for use in ≥40 countries globally, is indicated in Europe for the treatment of adult patients (pts) with mycosis fungoides/Sézary syndrome (MF/SS) who have received at least one prior systemic therapy. MINT, a real-world, retrospective/prospective, non-interventional study, assesses the effectiveness and tolerability of moga in German clinical practice.

Methods

We present interim analyses, conducted for pts with ≥3 months (mos) data (n=76), following the statistical analysis plan. The primary endpoint was time to next treatment (TTNT; defined as start of moga to start of new therapy [not including topical steroids/focal radiation] after moga discontinuation); secondary endpoints included overall response rate (ORR; defined as global complete/partial response [CR/PR]), concomitant CTCL treatments and tolerability. Follow-up was defined as date from first moga dose to database extraction date or pt death.

Results

Pt characteristics are in Table 1. Median follow-up was 20.5 mos.

Antineoplastic concomitant treatments were received by 32.9% (n=25) pts, **Table 1**. Most commonly (>5%) extracorporeal photopheresis (17.1%), total skin electron beam (TSEB) (including low dose TSEB; 7.9%), radiotherapy (not TSEB; 6.6%) and brentuximab vedotin (5.3%).

Table 1. Patient characteristics

	N=76
Mean age, years (SD)	67.4 (12.4)
Gender, n (%)	
Female	33 (43.4)
Male	43 (56.6)
Median Follow-up, mos	20.5
Initial Diagnosis, n (%)	
SS	38 (50.0)
MF	38 (50.0)
MF subtype, n (%)	
Classical	28 (36.8)
Folliculotropic	5 (6.6)
Pagetoid reticulosis	1 (1.3)
Other	4 (5.3)
Disease stage at moga start, n (%)	
IB	9 (11.8)
IIA	1 (1.3)
IIB	13 (17.1)
IIIA	2 (2.6)
IIIB	8 (10.5)
IVA (NOS)	3 (3.9)
IVA1	23 (30.3)
IVA2	12 (15.8)
IVB	4 (5.3)
Missing	1 (1.3)
Blood tumour burden at moga start, n (%)	
B0	16 (21.1)
B1	14 (18.4)
B2	17 (22.4)
Missing	29 (38.2)
Concomitant[a] MF/SS treatment received, n (%)	
Antihistamines	20 (26.3)
Topical corticosteroids	17 (22.4)
Systemic corticosteroids	8 (10.5)
TSEB (inc. low-dose TSEB)	6 (7.9)
Radiotherapy (not TSEB)	5 (6.6)
ECP	13 (17.1)
Bexarotene	2 (2.6)
Etoposide	2 (2.6)
(PEG) IFN alfa-2a	1 (1.3)
UV-B/nbUV-B	1 (1.3)
Chlormethine	1 (1.3)
PUVA	1 (1.3)

Abbreviations: ECP, extracorporeal photopheresis; IFN, interferon; MF, mycosis fungoides; PEG, pegylated; SD, standard deviation; SS, Sézary syndrome; TSEB, total skin electron beam; PUVA, psoralen + ultraviolet A; nbUV-B, narrowband ultraviolet B.

[a] Defined as therapies started for indication of 'MF/SS' prior to mogamulizumab start and continued thereafter, or with a start date on/after mogamulizumab start. Multiple concomitant treatments possible.

Table 1. Patient characteristics

Median overall TTNT (95% confidence interval [CI]) was 20.2 mos (11.0–34.8). ORR was 60.5% (46/76): 73.7% (28/38) for SS and 47.4% (18/38) for MF, **Table 2**. Moga-associated rash (MAR) occurred in 27 pts: 19 (50.0%) SS and 8 (21.1%) MF pts and ORR was higher for pts with MAR (74.1%, 95% CI 53.7–88.9) vs pts without MAR (53.1%, 95% CI 38.3–67.5).

	Overall Response Rate (CR + PR)
Overall population	
n/N (%)	46/76 (60.5)
95% CI	48.6 – 71.6
SS	
n/N (%)	28/38 (73.7)
95% CI	56.9 – 86.6
MF	
n/N (%)	18/38 (47.4)
95% CI	31.0 – 64.2
MAR+	
n/N (%)	20/27 (74.1)
95% CI	53.7 – 88.9
MAR-	
n/N (%)	26/49 (53.1)
95% CI	38.3 – 67.5

Abbreviations: CI, confidence interval; CR, complete response; MAR, mogamulizumab-associated rash; MF, mycosis fungoides; PR, partial response; SS, Sézary syndrome.

Table 2. Patient outcomes

Grade ≥3 treatment-related treatment-emergent adverse events (TEAEs) were reported in 34.2% (26/76) pts; most commonly lymphopenia or 'lymphocyte count decreased' (15.8% [12/76]) and drug eruption or rash (13.2% [10/76]). Serious Grade ≥3 treatment-related TEAEs were seen in 14.5% (11/76) pts; most commonly lymphopenia or 'lymphocyte count decreased' (2.6% [2/76]) and drug eruption or rash (3.9% [3/76]). The most common TEAE leading to discontinuation was drug eruption or rash (15.8% [12/76]).

Conclusions

Clinical responses were seen in pts with MF and SS. No new safety signals were seen; drug eruption was the most common cause of discontinuation in the Phase 3 MAVORIC trial, and lymphopenia is an expected pharmacological effect of moga. Real world evidence shows that combination therapies are frequently used. However, further investigation is warranted.

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Mogamulizumab in Patients with Sézary Syndrome and Mycosis Fungoides Over 75 Years of Age: Real-World Data from 7 Italian Centers.

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Background
Mogamulizumab is a monoclonal antibody that is approved for treating adult patients with mycosis fungoides (MF) and Sézary syndrome (SS) who have undergone at least one prior systemic therapy. Its efficacy was demonstrated in the open-label, phase 3 MAVORIC clinical trial, which compared mogamulizumab to vorinostat and included patients with a median age of 64 years. Unfortunately, in clinical practice, we often treat older patients than those in the registration study.

Methods
This retrospective observational study, conducted in seven centers across Italy, aims to further evaluate the efficacy and safety of mogamulizumab in elderly patients (over 75 years).

Results
The 23 analyzed patients (17 with SS, 6 with MF) were aged 81 years (range, 75-91) at the initiation of mogamulizumab. Prior to treatment, they received a median of three systemic CTCL therapies (range, 2-8). Ten patients had previously undergone therapy with ECP. Overall, 96.2% of patients suffered from advanced disease (Stage IIB–IVB), with frequent B2 blood involvement (60%). Over the treatment period (median: 11 months, range, 1.2–54.3), 92.3% of patients received all the planned mogamulizumab infusions. The median number of infusions was eight cycles (range, 1-38). Four patients received combination therapy: two with skin-directed therapy and two with systemic therapy. The ORR was 61.5% (CR 26.9%, PR 34.6%), and 64.7% in SS. The median duration of response was 16 months (range, 9-32). A compartmental response in the blood was observed in 93.3% of SS patients, and skin responses were observed in 82.3% of patients overall. The median reduction in modified mSWAT scores among responding patients was 95.5 points (range, 0 to -248). Side effects related to treatment were recorded in just 49.9% of the patients. The most common serious adverse drug reactions were rash (30.7% of patients), and was treated with topical steroids in 6 out of 8 cases, and infusion-related reactions (7.7%) that did not lead to treatment discontinuation. Other serious adverse drug reactions that led to treatment discontinuation were anemia and Grade 3 thrombocytopenia in 3.8% and 7.7% of patients, respectively. After discontinuation, three patients started maintenance therapy.

Conclusions
This real-life- study has demonstrated the efficacy and good safety profile of mogamulizumab in elderly patients over 75 years old, without a significant increase in serious adverse events leading to drug discontinuation.

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NanoString analysis of mycosis fungoides samples from patients included in EORTC 1652 clinical trial and treated with Atezolizumab.

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Background
Atezolizumab targets human PD-L1 and inhibits its interaction with its receptors, programmed cell death−1 (PD-1) and B7.1 (CD80, B7-1). Both of these interactions are reported to provide inhibitory signals to T cells and other immune cells.
PARCT clinical trial (EORTC 1652) was organized to treat patients diagnosed of mycosis fungoides or Sézary syndrome stages IIB to IVB with atezolizumab. The main objective was to determine the antitumor activity of atezolizumab for patients with refractory or relapsed advanced stages of mycosis fungoides and Sézary syndrome, assessed in terms of the overall response rate (ORR) according to EORTC-ISCL-USCLC criteria. We believe that gene expression profile measured with a robust NanoString platform can provide information to predict response/resistance to Atezolizumab and could be hypothesis generating to overcome that resistance. Patients signed informed consent to perform additional molecular studies not included in the clinical trial on biopsies taken at different time points

Methods
We analyzed a series of seven patients to study gene expression on lesional MF skin, using a customized panel of 95 genes on NanoString nCounter® platform pre-treatment with Atezolizumab within EORTC clinical trial. Three patients were responders (R) and four patients were non-responders (NR). A customized CTCL-directed gene panel of around 95 genes was constructed, based on the PanCancer Pathway panel (780 genes) and the T-cell lymphoma panel (216 genes) (NanoString Technologies, nCounter®, USA). The data analysis was performed with nSolver advanced analysis software 4.0.

Results
The study has made it possible to analyze routine paraffin-embedded MF samples using a personalized gene expression panel, in which the technique was informative in all cases analyzed. Interestingly, the supervised analysis revealed significant differential expression (Benjamini–Hochberg-adjusted $p < 0.05$) in 28 genes between the R and NR groups. We indicate the top 20 genes most differentially expressed between these groups. *LYN*, *VCAM1*, *IL-15*, *CXCR3*, *IL-10*, *CD38*, *CXCL12* and *CD16* were strongly overexpressed in the R group, while *CXCR4*, *FGFR3*, *CXCL13*, *CD5*, *CCR7* and *TRBC1* were highly overexpressed in the NR group.

Conclusions
Gene-expression profiling using a customized gene set in the NanoString platform can be applied to routine paraffin embedded MF samples and provides a detailed molecular signature for non-responders and responders patients to Atezolizumab.

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Pagetoid reticulosis of the Ketron-Goodman type: a rare variant of Mycosis Fungoides

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Background
Pagetoid reticulosis is a low-grade rare malignant variant of mycosis fungoides. Two variants of the disease are described: the localized type Woringer-Kolopp disease (WKD) and the disseminated type Ketron-Goodman disease (KGD)[InternationlaJournlaofDermatology2023Volume62Issue3312321]. Herein we report the case of a-36 year-old man in whom the diagnosis of KGD was made.

Methods
We report a rare case of disseminated pagetoid reticulosis (PR)

Results
A 36-year-old man presented with a one year history of erythematous plaque on the left flank, gradually the lesions increased in number on both buttocks and appeared in lower extremities in the past 2 months. He was first diagnosed with systemic eczema and fixed drug eruption and was treated with topical betamethasone for several months without improvement. Physical examination revealed scattered plaque-like lesions on the left flank, and buttocks. The Lesions were flat, well defined and slightly infiltrated. There were no other signs or symptoms. Histopathologic examination revealed psoriasiform hyperplasia of the epidermis and a dense, diffuse, lymphocytic infiltrate, mainly in the papillary dermis, with massive infiltration of the epidermis. Immunohistochemistry revealed a predominance of CD8+ cells over CD4+ cells in the infiltrate without staining for CD20, CD30, consistent with the diagnosis of WKD. Chest X-ray, PET/Scan and peripheral blood immunophenotyping revealed no systemic involvement. The Patient was referred to the lymphoma outpatient department for systemic treatment.

Conclusions
This *case* highlights a rare and challenging *presentation* of *Ketron-Goodman disease*. Although this form of lymphoma is notorious for its indolent, therefore, long-term observation is necessary.

References:

[InternationlaJournlaofDermatology2023Volume62Issue3312321] Muhammad Osto BS, Omar Afify BA, Arif Musa MS, Uddin Ahmed BS, Rafey Rehman BS, Darius Mehregan MD, (2023), Woringer-Kolopp disease (localized pagetoid reticulosis): a systematic review, Wiley online library, international journal of dermatology , Page 312-321, Volume62, Issue3, https://onlinelibrary.wiley.com/doi/epdf/10.1111/ijd.16224

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Phase 2a Study of Topical 0.25% Hypericin in Mycosis Fungoides: Results and Review of the FLASH Study.

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Background

Objective: Hypericin, a naturally occurring pigment found in plants such as St. John's Wort, has garnered interest for its potential therapeutic applications. Rook et al. (1998) first described the anti-proliferative effect of photoactivated synthetic hypericin in malignant T cells. Unlike psoralen, another photoactivated plant compound, hypericin is activated by visible light. Additionally, hypericin's mechanism of action involves inducing reactive oxygen species, apoptosis, and necrosis induced through the mitochondrial pathway, presenting a potentially safer alternative to the mutagenic effects associated with psoralen.
In the Phase 3 Fluorescent Light Activated Synthetic Hypericin (FLASH) study, we conducted the first randomized, controlled clinical trial utilizing topical hypericin for treating mycosis fungoides (2022). Building on these findings, our ongoing research aims to further understand this promising therapeutic option. In this presentation, we will discuss our latest findings on synthetic hypericin.

Methods

Methods: A prospective, open-label interventional study in stage IB and IIA mycosis fungoides with more than 10% body surface area of involvement

Results

Results: Our recent study cohorts continue to demonstrate that synthetic hypericin is effective in treating early-stage mycosis fungoides, consistent with results from the FLASH study. Furthermore, we observed that hypericin levels remain minimally detectable in the blood even after application to large body surface areas (e.g., >10% BSA). Cardiac evaluations of patients subjected to extensive synthetic hypericin application revealed no abnormalities. Moreover, increasing the dose of visible light administered, compared to the FLASH study, resulted in no change in the safety profile as reported in FLASH and blood laboratory evaluations showed no clinically significant abnormalities.

Conclusions

Conclusion: Given the solid safety profile of topical synthetic hypericin observed to date, we are investigating whether its therapeutic benefits can be enhanced by increasing the visible light energy delivered to the skin. Ongoing studies will further elucidate the role of this promising topical therapy for patients with mycosis fungoides.

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Positron emission tomography/computed tomography guided choice of lymph node core biopsy. A useful tool.

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Background

The prognosis and treatment of mycosis fungoides (MF) and Sézary syndrome (SS) depends on lymph node (LN) involvement. According to ISCL/EORTC guidelines, clinically abnormal or enlarged LN (>1.5cm in the long axis or 1.0cm in the short axis) should be biopsied. The role of positron emission tomography/computed tomography (PET/CT) on screening and selecting the pathological LN biopsy is not well established. We aimed to correlate PET/CT data with histopathologic findings of LNs from MF/SS patients performed with core-needle biopsy (CNB).

Methods

We conducted a single-center retrospective study of consecutive patients with MF/SS evaluated previously with PET/CT that underwent core-needle biopsy (CNB) between January 2010 and June 2024. PET/CT was used to select the LN with maximum standardized uptake value (SUVmax) to perform the CNB. LN biopsies were staged according to ISCL/EORTC guidelines.

Results

Thirty LN from 27 patients were included, 74% (20/27) were male, mean age (SD) was 66.7 (12.7) years, 10% (3) had stage I-IIA, 27% (8) had stage IIB, 3% (1) had stage IIIA-IIIB, 43% (13) had stage IVA1 and 7% (2) had stage IVA2 . LN biopsied locations were axillar (57%, 17), inguinal (37%, 11) and cervical (7%, 2). N0-N1 were diagnosed in 14% (4), N2 in 20% (6) and N3 in 57% (17). PET/TC followed by CNB changed the stage of 50% of patients to IVA2. LN classified as N3 presented a median SUVmax of 6.8 compared to 4.98 of N0, N1 and N2 ($p = 0.11$).

Conclusions

PET-CT offers significant additional information about physiologic and metabolic activity and can guide selecting LNs of MF/SS patients for biopsy. In our study, N3 stage presented median SUVmax of 6.8 versus 4.98 of non-N3 stage.

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Potential mogamulizumab-associated inflammatory bowel disease in cutaneous T-cell lymphoma management.

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Background
Mogamulizumab, a monoclonal antibody targeting C-C chemokines receptor 4 (CCR4), has gained a rapidly growing importance in the management of cutaneous T-cell lymphomas (CTCL). Mogamulizumab has a favorable side effect profile. However, some rare adverse events may not have been observed yet due to its relatively recent introduction.

Methods
An 87-year-old female with stage IVA1 Sézary syndrome achieved complete remission after only three cycles of mogamulizumab. After 3 months of treatment, she developed severe chronic diarrhea. The chronology of events raised the suspicion of an immune-related etiology associated with mogamulizumab treatment. Endoscopy revealed drug-induced ulcerative pancolitis. Systemic corticotherapy was initiated, followed by selective immunosuppressive therapy with vedolizumab with limited response. Treatment with the anti-tumor necrosis factor alpha blocker infliximab led to a favorable intestinal response. Initially, the patient maintained complete response one year after stopping mogamulizumab. Following infliximab, a worsening of skin and blood tumor burden was observed. Extracorporeal photopheresis was initiated and the patient has since remained in complete remission. Similarly, a 64-year-old female with heavily pretreated folliculotropic mycosis fungoides showed a good clinical response to mogamulizumab. A few weeks after treatment initiation, she developed symptoms of IBD, confirmed by endoscopy. Systemic corticotherapy was initiated, followed by a recent introduction of vedolizumab.

Results
We present two CTCL patients who developed mogamulizumab-induced inflammatory bowel disease within three months of mogamulizumab initiation. Since the implementation of mogamulizumab into clinical practice, several autoimmune complications, including hepatitis, vitiligo or alopecia areata, have been reported. Such patients frequently experience an ongoing CTCL skin and blood response, attributed to the activation of cytotoxic antitumor T-cells via the depletion of CCR4-positive regulatory T-cells. This mechanism might also explain the prolonged remission observed in our first patient, further supporting the proposition that mogamulizumab-induced autoimmune manifestations might indicate a favorable prognosis.

Conclusions
Further research is needed to fully comprehend the long-term safety profile of mogamulizumab and better understand the association between autoimmunity and long-term remission following mogamulizumab treatment.

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Preliminary Results from an Ongoing Phase 2, Open-Label, Multicenter, Single-Arm Study Assessing an Every-4-Week Dosing Schedule of Mogamulizumab in Patients with Cutaneous T-Cell Lymphoma

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Background

Mogamulizumab (moga) is approved for treatment of relapsed/refractory mycosis fungoides/Sézary syndrome (MF/SS) after ≥1 prior systemic therapy. In the phase 3 MAVORIC study (N=372), moga was given 1mg/kg weekly in cycle (C) 1 and then every 2 weeks (Q2W) and showed superior efficacy vs vorinostat in MF/SS with a manageable safety profile. We present preliminary results from an ongoing phase 2 study of moga using an alternative 2mg/kg Q4W dosing schedule (NCT04745234) (Fig 1).

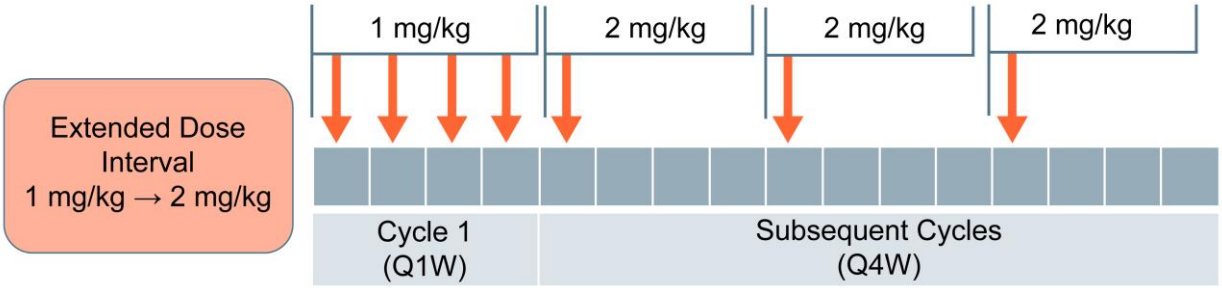

Figure 1: Mogamulizumab every 4 weeks (Q4W) dosing schedule. The dosing schedule consisted of a first 28-day cycle (Cycle 1) of moga administered at 1mg/kg on Days 1, 8, 15, and 22 (Q1W), followed by administration at 2mg/kg on Day 1 of each subsequent 28-day dosing cycle (Q4W). Moga, mogamulizumab; Q1W, weekly; Q4W, every 4 weeks.

Methods

The study planned to enroll 33 patients (pts) with stage IB–IV MF/SS after ≥1 systemic therapy. The primary objective of this preliminary analysis (data cut Nov 2023) was to assess the safety and tolerability of a 2mg/kg Q4W dosing regimen. Secondary objectives included pharmacokinetic/pharmacodynamic (PK/PD) characterization and investigator-assessed anti-tumor activity: overall response rate (ORR, defined as complete/partial response [CR/PR] lasting ≥4 weeks), time to response (TTR), duration of response (DOR), compartmental response, progression-free survival (PFS). Descriptive statistics for continuous variables, frequency distributions and percentages for discrete variables were used.

Results

34 pts were enrolled (median age: 64.0 years; 64.7% male). At baseline, 17.6% pts had SS, 82.4% MF; 23.5% presented at stage IB–IIA, 58.8% IIB–IIIB, 17.6% IVA–IVB. Median follow-up was 8.61 months (mo). Treatment-emergent adverse events (TEAEs) occurred in 97.1% (33/34) of pts; 26.5% had serious adverse events (SAEs). Treatment-related TEAEs occurred in 73.5%: most frequent were drug eruption (32.4%), infusion-related reaction (23.5%), diarrhea (14.7%), fatigue (14.7%); 17.6% had drug-related SAEs.

The efficacy evaluable set (n=32) included pts who completed C1 and received ≥1 dose at 2mg/kg. ORR was 37.5% (12/32; 1 CR): 30.8% (8/26; 0 CR) in MF, 66.7% (4/6; 1 CR) in SS (Fig 2). Compartmental response was 40.6% (13/32; 1 CR) in skin; 20.0% (2/10; 0 CR) in lymph nodes; 100% (9/9; 8 CR) in blood; no response in viscera (0/1). Median TTR was 1.82 mo (range 1.0–3.8). DOR and PFS were not estimable at data cut. PK/PD results showed an increase in moga concentrations with repeated doses reaching steady state by C3 (range on C3–7 day 1: 17,972.8–21,046.0 ng/mL) and significant depletion of circulating $CD7^-$ and $CD26^-$ malignant T–cells.

Conclusions

Preliminary results showed a promising safety profile and response rate of 2mg/kg Q4W moga in pts with relapsed/refractory MF/SS after ≥1 systemic therapy.

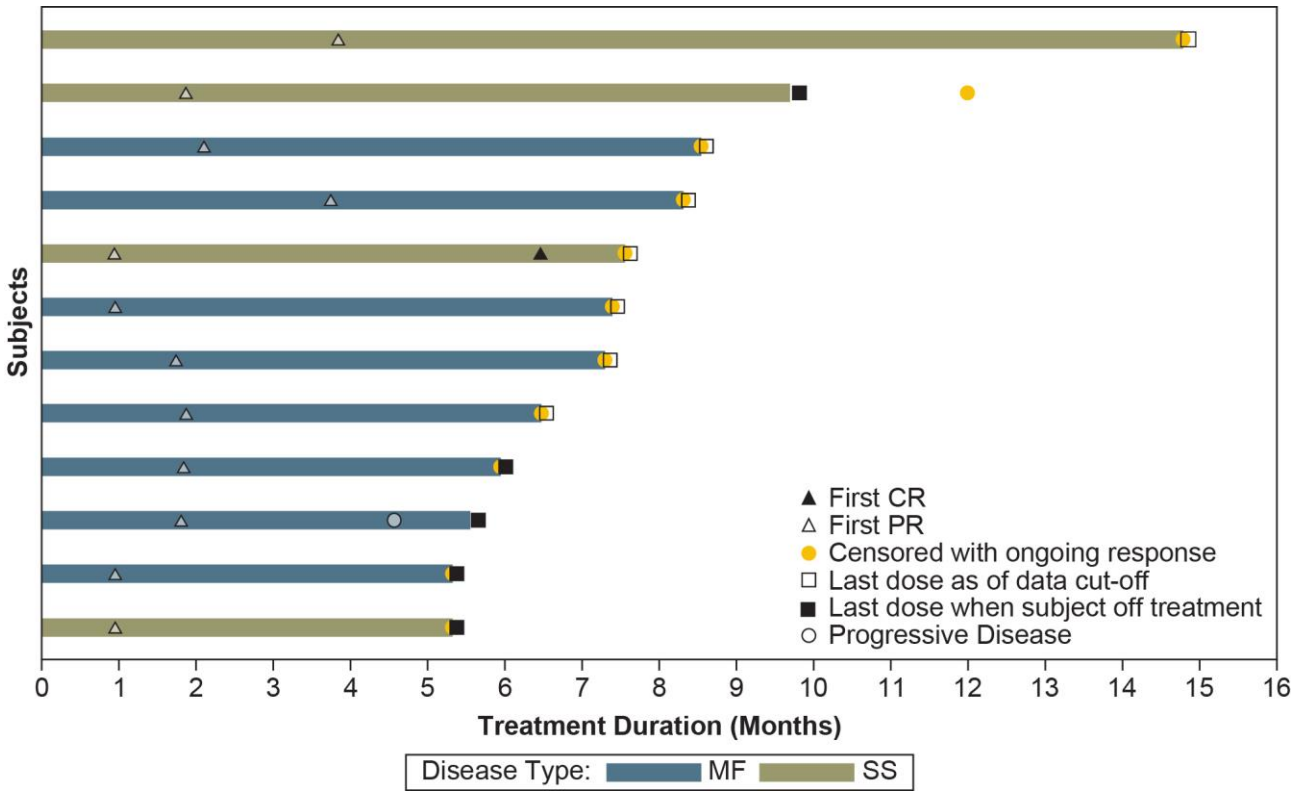

Figure 2: Swimmer plot of patients who reached an overall response. Swimmer plot depicting treatment duration, treatment cessation and outcomes for pts with MF or SS treated with moga and that achieved an overall response (n=12). CR, complete response; MF, mycosis fungoides; moga, mogamulizumab; PR, partial response; SS, Sézary syndrome.

A-153

Primary cutaneous T-cell lymphoma not otherwise specified (NOS) uncovering a novel RAB27A variant in Griscelli syndrome type 2

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Background

A 47-year-old female was referred to our dermatology clinic for a 15-year history of diffuse erythematous plaques and nodules treated previously as systemic lupus erythematosus and sarcoidosis without success. Correlation between clinical, histological and radiological findings established the diagnosis of a Primary cutaneous T-cell lymphoma not otherwise specified (NOS) (Fig. 1) with an atypical, chronic disease course.

Methods

Due to a personal history of recurrent infections, parental consanguinity and an atypical lymphoproliferative disorder, the patient was investigated for an underlying primary immunodeficiency.

Results

Targeted exome sequencing revealed two previously unreported compound heterozygous variants in *RAB27A*: a pathogenic deletion c.514-518delCAAGC; p.Gln172AsnfsTer in exon 7, and a variant of unknown significance c.227C>T; p.Ala78Val in exon 4, suggesting the diagnosis of Griscelli syndrome type 2 (GS2, ORPHA:79477, OMIM #607624).

Conclusions

GS2 is a rare autosomal recessive disorder typically appearing in childhood. It manifests with partial albinism, silvery hair, immunodeficiency, hemophagocytic lymphohistiocytosis predisposition (HLH) and frequent neurological abnormalities. Further examination of our patient's personal history revealed the presence of silvery-gray hair since infancy. Hair shaft analysis showed large melanin granules in the medullary zone, further indicating GS2 (Fig. 2). Despite multiple episodes of recurrent fever and pancytopenia,

our patient has never met the criteria for HLH.
In summary, skin lymphoproliferative disorders may be part of the dermatological spectrum of GS2. The variant c.227C>T in *RAB27A* should be considered as probably pathogenic and linked to GS2. It might lead to a residual RAB27A protein activity, possibly explaining the delayed disease onset as well as the absence of HLH in our patient.

A-120

Radiotherapy of Cutaneous Lymphomas: Real-world Pattern-of-Care Analysis Among EORTC Members

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Background
We aim to ascertain the current pattern of care and recommendations among physicians treating cutaneous lymphomas and to identify skin lymphoma types for which current radiation regimens warrant improvement.

Methods
A European Organisation for Research and Treatment of Cancer (EORTC) questionnaire was sent to all Cutaneous Lymphoma Tumour Group and radiation oncology members. The online questionnaire comprised 13 questions on treating practices for cutaneous lymphoma patients. The survey was conducted between August 21 and December 18, 2023. Frequency distributions and subgroup comparisons were calculated and described.

Results
We collected 51 completed questionnaires from investigators from 19 countries specializing in cutaneous lymphoma treatment. Radiation doses varied significantly (range, 4-60 Gy). Based on the histologic entity, up to one-third of the investigators delivered hypofractionated regimens (range, 14% - 35%). Reduced-dose radiotherapy was considered by 27% to 63% of investigators. Meanwhile, 18 (35%) investigators considered adapting the radiation dose to the response to immunochemotherapy when treating primary cutaneous diffuse large B-cell lymphomal-leg type. Regarding total skin electron beam therapy, 91% of centres delivered reduced-dose regimens, and 18% of investigators applied ultra-hypofractionated protocols.

Conclusions
Radiotherapy of cutaneous lymphoma patients is highly heterogeneous among EORTC centres. Development of evidence-based recommendations for radiotherapy dose, fractionation, and technique for cutaneous lymphomas is required for optimization and standardization of treatment.

Keywords: cutaneous B cell lymphoma, cutaneous T cell lymphoma, marginal zone lymphoma, follicular lymphoma, diffuse large B cell lymphoma, anaplastic large cell lymphoma, mycosis fungoides, Sézary syndrome, hypofractionation, low dose, overtreatment

A-198

Real-world effectiveness of mogamulizumab in Spain and Portugal: Second interim analysis of the MIBERIC study

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Background

Mogamulizumab (moga) is a monoclonal antibody targeting CC chemokine receptor 4 (CCR4), which is overexpressed in cutaneous T-cell lymphoma (CTCL). Moga depletes tumour cells in CTCL by antibody-dependent cellular cytotoxicity and is licensed in Europe for treatment of adult patients with mycosis fungoides (MF) and Sézary syndrome (SS) who have received at least one prior systemic therapy.

Methods

MIBERIC is a real-world retrospective chart review study involving patients (pts) with MF and SS treated with ≥1 dose of moga assessing the effectiveness and tolerability of moga in Spain and Portugal. All evaluable pts that had baseline disease assessment and data from at least one follow-up assessment between Jan-2019 and Mar-2024 were included. We present the results of the second interim analysis. The primary endpoint is best overall response rate (bORR), defined as percentage of patients achieving best global response (complete [CR] or partial [PR])[1] from the start of treatment until disease progression. Secondary endpoints include compartmental response, duration of treatment, reason for discontinuation, progression-free survival (PFS; time from first dose of moga to disease progression or death from any cause) and tolerability.

Results

Seventy-three pts were included (see **Table 1**) across 18 Spanish and 2 Portuguese sites, for whom the median (IQR) duration of follow-up was 12 (6-24) months (mos); 71.2% were diagnosed with SS and 28.8% with MF.

	N=73
Mean age (SD), years	66.9 (10.22)
Gender, n/N (%)	
Female	25/73 (34.3)
Male	48/73 (65.8)
Initial Diagnosis, n/N (%)	
SS	52/73 (71.2)
MF	21/73 (28.8)
Disease stage at baseline, n/N (%)	
IA	1/73 (1.4)
IB	4/73 (5.6)
IIA	1/73 (1.4)
IIB	6/73 (8.3)
IIIA	1/73 (1.4)
IIIB	4/73 (5.6)
IVA1	37/73 (51.4)
IVA2	13/73 (18.1)
IVB	5/73 (6.9)
Missing	1/73 (1.4)
Blood tumour burden at baseline, n (%)	
B0	11/73 (15.1)
B1	11/73 (15.1)
B2	46/73 (63.0)
Missing	5/73 (6.8)
Lines of previous systemic MF/SS treatment received, median (range)	3 (1–10)
Patients receiving concomitant[a] MF/SS treatment, n/N (%)	
Yes	25/73 (34.2)
No	45/73 (61.6)
Unknown	3/73 (4.1)

Abbreviations: MF, mycosis fungoides; SD, standard deviation; SS, Sèzary syndrome.

[a] Defined as therapies started for indication of 'MF/SS' prior to mogamulizumab start and continued thereafter, or with a start date on/after mogamulizumab start.

Table 1. Patient characteristics

A global bORR was achieved by 75.3% of pts (35.6% CR and 39.7% PR) with 82.2%, 78.2%, 57.8%, and 50.0% of pts with baseline compartmental involvement achieving skin, blood, nodal, and visceral responses, respectively (see **Table 2**). In SS global bORR was 80.8% and in MF was 61.9%. Median time to bORR was 6 mos in SS and 7 mos in MF.

	GLOBAL	Skin	Blood[a]	Lymph Node[b]	Viscera
Responses Observed in Overall Population, n/N (%)					
bORR (CR + PR)	55/73 (75.3)	60/73 (82.2)	43/55 (78.2)	26/45 (57.8)	2/4 (50.0)
CR	26/73 (35.6)	28/73 (38.4)	37/55 (67.3)	20/45 (44.4)	2/4 (50.0)
PR	29/73 (39.7)	32/73 (43.8)	6/55 (10.9)	6/45 (13.3)	0/4 (0.0)
SD	11/73 (15.1)	9/73 (12.3)	6/55 (10.9)	12/45 (26.7)	2/4 (50.0)
PD	5/73 (6.9)	4/73 (5.5)	4/55 (7.3)	7/45 (15.6)	0/4 (0.0)
NE	2/73 (2.7)	0/73 (0.0)	2/55 (3.6)	0/45 (0.0)	0/4 (0.0)
bORR by Disease Subtype, n/N (%)					
SS	42/52 (80.8)	45/52 (86.5)	36/44 (81.8)	19/29 (65.5)	2/3 (66.7)
MF	13/21 (61.9)	15/21 (71.4)	7/11 (63.6)	7/16 (43.8)	0/1 (0.0)
bORR by Disease Stage at baseline, n/N (%)					
Early-stage (IA-IIA)	5/6 (83.3)	6/6 (100.0)	2/3 (66.7)	2/4 (50.0)	NA
Advanced-stage (IIB+)	49/66 (74.2)	53/66 (80.3)	41/52 (78.8)	23/40 (57.5)	2/4 (50.0)
bORR by No. previous systemic treatments, n/N (%)					
1	5/6 (83.3)	5/6 (83.3)	5/6 (83.3)	NA	NA
2	9/11 (81.8)	9/11 (81.8)	9/11 (81.8)	4/5 (80.0)	NA
3	18/22 (81.8)	20/22 (90.9)	12/14 (85.7)	10/14 (71.4)	1/1 (100.0)
>3	21/32 (65.6)	24/32 (75.0)	15/22 (68.2)	11/25 (44.0)	1/3 (33.3)
Time to bORR, by Disease Subtype, median months (95% CI)					
SS	6 (4-9)	6 (4-8)	4 (3-6)	13 (9-24)	11 (0-NE)
MF	7 (4-8)	7 (4-13)	7 (3-8)	10 (6-NR)	7 (NE-NE)

Abbreviations: bORR, best overall response rate; CR, complete response; MF, mycosis fungoides; NE, not evaluable; PD, progressive disease; PR, partial response; SD, stable disease; SS, Sèzary syndrome.

[a] 2/57 pts with baseline blood involvement were censored due to missing data on compartmental (blood) response.

[b] 20/65 pts with baseline lymph node involvement were censored due to missing data on compartmental (lymph node) response.

Table 2. Patient outcomes

Twenty of the 73 pts had PFS events (progression or death) and median PFS was 33 mos (72% pts censored), with a median time to discontinuation of moga of 13 mos.

Any-Grade adverse events (AEs) were reported in 52.8% of pts; of the 85 AEs reported, the most frequent (21.2%) were skin conditions, and 36.5% of all AEs were considered either ‘probably’ or ‘possibly’ related to moga.

Conclusions

Moga demonstrated effectiveness and tolerability in the real-world clinical setting in Spain and Portugal.

References:

[1] Olsen EA, Whittaker S, Kim YH, et al., (2011), Journal of Clinical Oncology, 2598-607, 29 (18), https://doi.org/10.1200/JCO.2010.32.0630

A-298

RESMAIN: Results of a multicenter, randomized, double blind, placebo-controlled trial to evaluate RESminostat for MAINtenance treatment in advanced stage Mycosis fungoides or Sézary syndrome

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Background
In advanced-stage CTCL, the current therapy rarely provide long-lasting responses

Methods
The primary objective of the RESMAIN trial (NCT02953301) was to determine if maintenance treatment with the HDAC-inhibitor resminostat increases PFS compared to placebo in patients with advanced stage MF or SS who have achieved disease control with previous systemic therapy or total skin electron beam radiation (TSEB).
From January 2017 to May 2022, 201 patients with histologically confirmed MF (Stage IIB-IVB; N=164) or SS (N=37) in an ongoing complete remission (CR), partial remission (PR) or stable disease (SD) after prior systemic therapy or TSEB were stratified according to disease stage and remission status and randomized to resminostat (N=100) or placebo (N=101). Trial treatment was administered orally once daily on days 1-5 followed by a 9 day treatment-free period, in 14 day cycles. Patients who discontinued treatment due to PD were unblinded and those randomized to placebo were offered to rollover to open label resminostat. All patients were followed for survival every 3 months.

Results
Resminostat significantly improved PFS versus placebo (median 8.3 vs 4.2 months, p=0.015) with a 38% reduction in risk of disease progression (HR=0.62, 95%CI: 0.42-0.92) in the ITT population. Median TTNT was 8.8 vs 4.2 months (HR=0.59, 95%CI: 0.43-0.83, p=0.002). There was no difference in time to symptom worsening of pruritus or overall survival. Resminostat did not improve HrQoL compared to placebo based on the pre-defined measures.
Posthoc analyses revealed a benefit of resminostat with regards to skin involvement. Changes from baseline in mSWAT scores were analyzed based on the ITT population using a mixed model for repeated measures. The observed changes from baseline over time for resminostat versus placebo were statistically significant in favor of resminostat (p=0.0199). Further, the time to development or worsening of skin tumors was analyzed as time to tumor event (TTTE) based on mSWAT assessments for the ITT population. A median TTTE of 44.2 months was observed for resminostat compared to 6.5 months for placebo (HR=0.333; p=0.0001).
The RESMAIN trial confirmed the known safety profile of resminostat, with gastrointestinal disorders, such as nausea (68%), diarrhoea (44%) and vomiting (32%) as the most frequent treatment-related AEs, followed by fatigue (29%), dysgeusia (24%) and decreased appetite (21%). The side effects were mainly mild to moderate and usually improved or resolved during the 9-day treatment-free interval.

Conclusions
The RESMAIN trial is the first to prove the benefit of a maintenance treatment strategy in advanced CTCL. Resminostat significantly prolonged PFS compared with placebo and demonstrated clinically meaningful benefit in a broad population of advanced stage MF/SS patients.

A-151

Secondary Malignancy and Visceral Involvement in Cutaneous T-Cell Lymphoma: Diagnostic Differentiation

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Background
Visceral involvement in Cutaneous T-cell Lymphoma (CTCL) is rare but presents diagnostic and therapeutic challenges. This study aims to characterize CTCL patients with visceral involvement and compare them to those with secondary solid tumors to enhance understanding of the disease course and improve diagnostic strategies.

Methods
We reviewed 824 Mycosis Fungoides (MF) and Sézary Syndrome (SS) patients at Johns Hopkins from January 2011 to June 2024. Fifteen patients had visceral involvement, confirmed pathologically or via imaging and clinical judgment, with one also having a secondary malignancy. Additionally, 31 CTCL patients without visceral involvement had secondary solid tumors.

Results
The median age at CTCL diagnosis was 63 years for patients with secondary malignancies and 55 years for those with CTCL visceral involvement. Visceral involvement, which is more common in males (4:1) and equally distributed by race (53.3% Black), primarily affected the lungs and CNS/CSF. The median time to diagnosis was 1 year and 10 months (range: 0 days to 19 years). Mycosis fungoides (MF) was the predominant diagnosis (60%), followed by Sézary syndrome (SS) (26.67%) The incidence rate of visceral involvement was 18.2 per 1000. For CTCL patients without visceral involvement, the incidence rate of secondary malignancies was 37.8

per 1000, with an equal sex distribution (51.6% male) and white patients (61.3%). MF was the most common diagnosis (90.3%), followed by SS (6.5%). The most common secondary malignancies were breast and prostate cancer, with a median diagnosis time of 4 years and 2 months (range: 0 days to 18.5 years), occurring mostly in stages IA and IB (70%).

Conclusions
CTCL patients tend to be younger at diagnosis of their visceral involvement and predominantly male, with a median time to diagnosis significantly shorter than that for secondary malignancies. The incidence rate of visceral involvement is significantly lower than that of secondary malignancies, which occur more frequently in older patients. Notably, secondary malignancies often occur in earlier-stage CTCL (stages IA and IB) compared to visceral involvement, which mostly arises in stage IV. These findings highlight the need for better diagnostic strategies to distinguish between visceral CTCL involvement and secondary malignancies, thereby improving patient management. Our ongoing analysis aims to identify clinical and laboratory markers to aid in this differentiation.

A-203

Sezary syndrome revealed by PD-L1 blockade for tumor stage mycosis fungoides.

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Background
Cutaneous T-cell lymphomas (CTCLs) are unique non-Hodgkin lymphomas due to the proliferation of skin-homing T cells. Sezary syndrome (SS), a subtype of CTCL, typically presents as erythroderma with specific blood involvement and seldomly evolves from tumor-stage mycosis fungoides (MF)

Methods
We present a case of a 62-year-old female diagnosed with tumor-stage mycosis fungoides, transformed from an earlier plaque-stage mycosis fungoides, which was initially managed with standard therapies including topical corticosteroids and phototherapy. Achieving a complete response initially, the disease relapsed and progressed over three years despite subsequent interventions with oral drugs, radiation therapy, and a series of other therapeutic agents.

Results
Subsequently, atezolizumab therapy, an antibody targeting programmed death ligand 1 (PD-L1) was initiated. While initial treatment phases indicated a promising disappearance of skin tumors, continued atezolizumab administration resulted in the development of symptoms consistent with stage IVA1 SS (Figure 1). Notably, there was an evident shift in the dominance of malignant T-cell clones. She was rechallenged with mogamulizumab without efficacy, followed by chemotherapy and died 2 years later with progressive disease.

Conclusions
Atezolizumab, a humanized monoclonal antibody, impedes the interaction of PD-L1 with its receptor PD1, which is notably overexpressed in malignant T-cells of SS. However, this case illustrates that the immune modulation associated with PD-L1 inhibition may also facilitate the expansion of malignant T-cell clones, culminating in the emergence of SS, underlining the potential risks and complexities in using PD-L1 inhibitors for treating CTCL. This paradoxical response highlights the complexity of immune checkpoint inhibition in CTCL and underscores the necessity for ongoing monitoring and evaluation of T-cell phenotypes during treatment.

A-255

Spontaneously regressive primary cutaneous diffuse large B-cell lymphoma, leg-type: a single-center retrospective study

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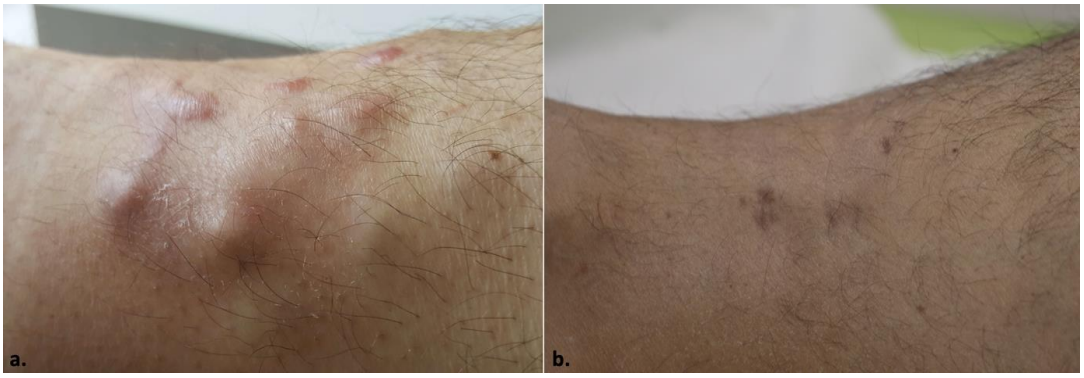
Background
Primary cutaneous diffuse large B cell lymphoma, leg-type (PCDLBCL-LT) are rare lymphomas with a poor prognosis, requiring first-line rituximab-polychemotherapy (R-PCT). However, very rare spontaneously regressive cases have been reported but with limited follow-up data.

Methods

All cases of PCDLBCL-LT seen between 2008 and 2023 in our center were included to identify cases with spontaneous regression without any therapeutic intervention and analyze their characteristics and outcome.

Results



62 year old men with nodules of the leg confirmed PCDLBCL, leg type by biopsy (a) and spontaneous regression 4 months after (b)

Among 73 patients diagnosed with PCDLBCL-LT in this period, 5 experienced initial spontaneous regression, representing 6.8% of the whole cohort (Images 1 and 2). The median age at diagnosis was 78 years [62-90], versus 81 [39-106] in the cohort. Skin involvement primarily affected the lower limb (n = 4), presenting as nodules (n = 3), plaque (n = 1), or subcutaneous tumor (n = 1). Stages were T1a (n = 3), T1b (n = 1), and T2a (n = 1) versus T2 stage in half of the other patients (31/61). All patients had undergone skin biopsy before regression. The phenotype was that of typical for PCDLBCL-LT (Bcl2+, MUM1+, and CD10-). *MYD88* mutation was identified in 4/5 cases, including 2 outside the L265P hot spot. The 5th case was *MYD88*^{WT} , but harbored *CD79A and CARD11* mutations suggestive of PCDLBCL-LT. Extra-cutaneous staging (CT and/or PET) was negative, and due to complete regression, none receive any treatment. Two experienced localized cutaneous recurrences, at the initial site after 1 month and 3 years respectively, treated with R-PCT. Both had the *MYD88*^{L265P} hot spot mutation. The other 3 cases remain in complete remission without treatment with follow-up from 22 months to 7 years.

Conclusions

Sex and Age at Diagnosis	Patient 1 Female, 90 y	Patient 2 Female, 68 y	Patient 3 Male, 62 y	Patient 4 Male, 85 y	Patient 5 Female, 78 y
Location	Right temple	Left leg	Right leg	Left leg	Right leg
TNM Stage	T1b	T1a	T2a	T1a	T1a
Type of Lesion	Subcutaneous tumor	Single nodule	7 Nodules + Local edema	Single nodule	Erythematous reticulated plaque 33x18 mm
Associated Symptoms	None	None	None	None	None
LDH Level at Diagnosis	Normal	Normal	Normal	Normal	Normal
Regression Time	1 month	1 month	3 months	1 month	1.5 months
CD20	+	+	+	+	+
CD10	-	-	-	-	-
Bcl2	+	+	+	Partial +	Partial +
Bcl6	-	+	+	+	+
MUM1	+	+	+	+	+
Ki-67	86%	80%	95-100%	90%	ND
Molecular Biology	MYD88 Mutation c.794T>C (p.L265P)	MYD88 Mutation c.826C>T (p.Gln2762Ter) Mutation CCND3 Mutation NOTCH 2 Mutation TNFRSF14	MYD88 Mutation c.695T>C (p.Met232Thr) Mutation CCND3 Mutation CD79B Mutation TNFRSF14	MYD88 Mutation c.794T>C (p.L265P)	CARD11 Mutation CD79A MYC NOTCH 1 TP53 No MYD88 Mutation
EBV	Negative	Negative	Negative	ND	Negative
Biopsy After Regression	Light perivascular lymphocytic infiltrate non-immunophenotyped	ND	ND	ND	ND
Recurrence / Delay	After 1 month: 2 subcutaneous nodules of the right temple T2aN0M0	No	No	After 3 years: 1 nodule of the left leg T1aN0M0	No
Recurrence Treatment	R-CHOP	None	None	R-CHOP	None
Long-Term Outcome	R-mini-COP followed by closure radiotherapy Recurrence T3bN0M0 at 6 months (masseter, right and left leg): Current treatment with Rituximab and Lenalidomide	CR + 22 months	CR + 36 months	Initial CR after R-CHOP but recurrence 1 year later. Palliative care, death from digestive hemorrhage	CR + 7 years

Abbreviations: ND : Not Determined, CR : Complete Remission

Characteristics of the 5 patients from the cohort who experienced spontaneous regression without specific therapy
This study is the first focusing on spontaneous regression within a large cohort of PCDLBCL-LT. This phenomenon, found in 6.8% of patients, does not seem exceptional, while only 6 cases have been previously reported. In these cases as ours, clinico-pathological presentation was similar to other PCDLBCL-LT. The rapid regression after biopsy may suggest an immune mechanism induced by the procedure. Moreover, the fact that the 3 cases without recurrence either did not have the *MYD88* hot spot mutation or no *MYD88* mutation may not be fortuitous, and remains to be elucidated. The absence of recurrence in 3 of our patients and a late recurrence in one, suggests to favor wait-and-see despite the aggressive nature of this lymphoma, in case of spontaneous regression.

A-220

Standardized flow cytometry for the detection and characterization of circulating CTCL cells: Update on a multicenter study

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Background
Cutaneous T-cell Lymphomas (CTCL) represent a group of mature T-cell-derived lymphomas, often associated with a poor prognosis in advanced cases. Accurate detection of circulating neoplastic cells in CTCL primarily relies on flow cytometric (FC) assessment, which is pivotal for diagnosis, hematologic staging, and monitoring of immunophenotypic changes. Nevertheless, current FC procedures lack standardization, prompting a multicentric initiative to address this issue. The objective of this multicenter study is to develop a standardized FC tool to enable the detection and characterization of circulating neoplastic cells in CTCL patients.

Methods
Fifteen participating laboratories processed over 100 peripheral blood samples from patients with CTCL, erythrodermic inflammatory diseases (EID), and healthy controls (HCs) across multiple sample-inclusion rounds using newly developed 3-tube, 8-color FC panels and standardized EuroFlow protocols for instrument setup and sample preparation. Centralized analysis of all data files included the evaluation of the number of acquired events, scatter characteristics, median fluorescence intensity (MedFI) values for individual markers, and the ability to distinguish between immunophenotypically normal and aberrant cells. Tumor cell counts were assessed using both conventional FC methods (CD4+ CD7- and/or CD26-) and according to novel FC based on 17 cell-surface markers.

Results
Previously, the analysis of the HC data demonstrated that standardized and reproducible FC is feasible across multiple centers using the current FC panel. This was shown by the low variability in MedFI values for individual markers expressed by T-cell subsets, consistent scatter characteristics, and a homogenous number of acquired events. In CTCL cases, neoplastic T cells were accurately detected in all samples. Using unsupervised clustering, the separation of neoplastic cells from non-malignant CD4+ T cells was significantly increased using the complete novel standardized FC panels with 17 cell-surface markers compared to the conventional assessment of tumor load based on the loss of CD7 and/or CD26 expression on CD4+ T cells.

Conclusions
The implementation of the novel standardized FC panels enhances the accurate detection of circulating CTCL cells. EuroFlow-based FC protocols significantly improved data reproducibility, demonstrating the feasibility of achieving robust inter-and intra-laboratory FC standardization across different sites and instruments.

A-118

Targeting TGF-beta activation in cutaneous T-cell lymphomas.

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Background
T-cell lymphomas are a heterogeneous group of malignancies involving T lymphocytes and generally characterized by a poor prognosis. Among them, cutaneous T-cell lymphomas (CTCL) involve primarily the skin. The most frequent CTCL are mycosis fungoides and Sézary syndrome (SS) (Dobos G, et al. Cancers. 2020). There is no cure for advanced-stage CTCL, the remissions are generally rare and short, and the overall survival is around 5 years with an impaired quality of life. Thus, the development of new treatments inducing longstanding responses in CTCL is a major unmet need (Scarisbrick JJ, et al. Br J Haematol.2021).
Because Sézary cells express several Treg markers as PD-1, ICOS, CD39 or CCR8 (Giustiniani J, et al. Blood Adv, 2022), we analyzed the expression of CD51, the αV integrin, which is expressed with the β8 integrin on Treg cells (Stockis J, et al. Proc Natl Acad Sci, 2021). CD51 is involved in the production of active form of TGF-β, a cytokine with immunosuppressive properties that promotes tumor escape. Thus, targeting the αVβ8 integrin with a specific antibody has been shown to inhibit TGF-β activation while not inhibiting cell adhesion (Tsui P, et al. mAbs, 2017). With CD51, the major process in the release of active TGF-β involves two other proteins named GARP and LRRC33 which are docking receptors for Latent-TGF-β (Batlle E.et al. Immunity,2017).

Methods
This study was conducted using several CTCL cell lines and a study cohort including 19 patients with Sézary syndrome (13 males and 6 females, mean age 71 years old, range 41-88; stage T4N3M0B2, n=7, T4N0M0B2, n=3, T1N0M0B2, n=1, T3N0M0B2, n=1, T4N2M0B1, n=1, T4N2M0B2, n=1, T4N3M1B2, n=1, T4NxM0B2n=1, unavailable in 3 patients).
Flow cytometry, Western blot, PCR and mRNA expression analysis were performed for this work.

Results
Our results revealed that CD51 as well as GARP and/or LRRC33 are significantly overexpressed in circulating lymphocytes from SS patients as compared to healthy individuals. Interestingly, CD51 is not associated with the β8 integrin but with CD29 (β1 integrin). MyLa and Seax CTCL cell lines were found able to activate recombinant latent TGF-β1 at various degrees *in vitro.*

Conclusions
CD51/CD29 appear as potential therapeutic targets in T-cell lymphoma, which can be associated with the activation of TGF-β produced by tumor cells themselves.Targeting these heterodimers with specific antibodies to prevent the release of active TGF-β could improve patient's antitumor immune response and immunotherapy efficacy.

A-261

The impact of atopic dermatitis preceding cutaneous T-cell lymphoma and its effect on clinical outcomes: a retrospective review at a single tertiary referral center

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Background
Cutaneous T-cell lymphoma (CTCL), a malignancy characterized by cutaneous infiltration of monoclonal T-lymphocytes, may mimic benign dermatoses such as atopic dermatitis (AD). Beyond phenotypic similarities, reports have associated the severity of AD with an increased risk of lymphomas. However, the clinical significance of AD preceding CTCL remains unclear.

Methods
We retrospectively reviewed 518 patients who presented to the Johns Hopkins Hospital system with a confirmed diagnosis of mycosis fungoides (MF) or Sézary syndrome (SS). Of these patients, 139 had a history of AD that preceded their CTCL diagnosis. Demographics and clinical outcomes of these patient populations were compared, and t-tests and ANOVA statistical tests were used for continuous and categorical variables, respectively.

Results
Our study population consisted of 49.4% male and 50.6% female patients, with a median age of 68 years at the time of CTCL diagnosis. 56.6% of the population identified as white and 41.5% as black. MF (90.9%) was the predominant diagnosis, followed by SS (5.60%). 26.8% (n=139) of patients were diagnosed with AD prior to their CTCL diagnosis, and 73.2% had no history of AD (n=379). Patients with AD had a median of 4 years (range=37.92 years) to CTCL diagnosis, while those without a history of AD had a median of 2 years (range=26.92 years) from initial cutaneous symptoms to diagnosis ($p<0.001$). Folliculotropism of MF was observed at a higher rate in patients with a history of AD compared to those without (17.39% vs. 10.67%, $p=0.05$). In addition, eosinophil counts at the time of CTCL diagnosis were higher in patients with a previous history of AD ($p<0.001$).

Conclusions
Our study demonstrates that CTCL patients with a history of AD have distinct clinical features of CTCL that may affect patient outcomes. Currently, we are analyzing the prevalence of comorbidities including cardiovascular disease, psychological disorders, and infection

between the two cohorts and their potential impact on prognosis. This approach aims to comprehensively explore these variables, enhancing our understanding of disease progression and refining patient management strategies.

A-270

Tinea in Cutaneous Lymphoma Patients

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Background
The differential diagnosis of annular lesions often poses a challenge for dermatologists. This is particularly true for patients with cutaneous lymphoma, where the underlying disease itself can present with annular symptoms.

Methods
We present the cases of three patients under treatment for cutaneous lymphoma, where newly appearing skin symptoms were found to be due to superficial fungal infections rather than progression of the underlying disease. The cases include a man with mycosis fungoides, a woman treated for folliculotropic mycosis fungoides, and a woman managed for Sézary syndrome.

Results
Clinical suspicion was raised due to the emergence of symptoms that differed from those previously observed. In all three cases, the superficial fungal infections manifested with increased speed and extent compared to those seen in patients with a competent immune system. Diagnosis was confirmed in all cases through skin scraping and fungal culture.The appropriate antifungal therapy led to an improvement in symptoms without modifying the original lymphoma treatment.

Conclusions
For patients with cutaneous lymphoma, regular physical examinations are crucial. It is important to keep in mind that trivial infections can mimic the skin symptoms of the underlying disease and may follow a different course than in patients with a healthy immune system.

A-146

Topical hypericin ointment photodynamic therapy for early stage mycosis fungoides/CTCL – a Phase 2 real world investigator-initiated study.

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Background
Given the chronicity of mycosis fungoides/cutaneous T-cell lymphoma (MF/CTCL), additional therapies with minimal short- and long-term side effects are urgently needed. Topical synthetic hypericin ointment 0.25% (SGX301) activated with external cool-white visible light is a novel, non-mutagenic photodynamic therapy that demonstrated efficacy and safety over three 6-week treatment cycles in a multicenter randomized placebo-controlled Phase 3 trial (FLASH study) conducted. The FLASH study had limitations including 2 week treatment breaks between treatment cycles, requirement to repeat dose escalation each cycle and a maximum of 12 J/cm^2 administered per cycle. Our study investigates the effects of continuous treatment (without treatment breaks) over a longer time period on clinical response and safety.

Methods
We are conducting an Investigator Initiated, open-label multicenter Phase 2 trial enrolling 50 early stage (IA-IIA) MF/CTCL patients ³ 18y.o. SGX301 is applied to any active lesions 18-30 hours prior to light therapy, twice weekly (starting dose 5 J/cm^2 escalated as tolerated without dose limit) for up to 1 year. Three to five index lesions were prospectively identified and used to assess the primary endpoint, index lesion response rate (ILRR, based on the Composite Assessment Index for Lesion Severity, CAILS, score) every 6 weeks. Secondary endpoints include mSWAT, physician global assessment and HR-QoL measures (Skindex-29, VASitch, Patient Benefit Index). Optional correlative studies on tissue and blood for immunophenotyping, apoptosis and molecular analysis are being performed.

Results
Six patients have enrolled at the lead site (3M/3F, median age 62.5 yr, MF subtypes include classic [1], hyperpigmented [2], folliculotropic [3]), 4 of whom have been on treatment at least 6 weeks (range W17-W45) with 3 partial responders and 1 with stable disease. Aside from mild expected post therapy local skin effects, no drug-related nor serious adverse events have been observed.

Conclusions
Continuous treatment with higher dose light escalation with SGX301 PDT appears to be well tolerated with an excellent safety profile i and clinical efficacy is consistent with that reported from the previous Phase 3 trial in enrolled patients thus far.

A-235

Ultrasound patterns of cutaneous lymphomas

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Background
Primary cutaneous lymphomas represent a heterogeneous group of non-Hodgkin's lymphomas that do not present with extracutaneous disease at diagnosis. Their clinical manifestations, biological behaviour and prognosis vary depending on the entity. TNM is used for staging (TNMB in the case of mycosis fungoides and Sezary syndrome), and clinical indices such as BSA or mSWAT are used to assess the degree of cutaneous involvement or response to treatment. However, these indices are subjective and there may be interobserver variability and other perception biases at successive visits.
Clinical ultrasound has proven to be a useful test for the diagnostic suspicion and follow-up of patients with cutaneous lymphomas. It allows diagnostic approach by recognition of ultrasound patterns, identification of cost-effective areas for skin biopsy, patient follow-up and ultrasound-guided infiltration. However, no clear ultrasound patterns have been described in the literature to enable diagnostic classification.
The main objective of this study was to describe the existing ultrasound patterns in the different types of cutaneous lymphoproliferative disorders.

Methods
We conducted a descriptive study including a series of 34 patients with cutaneous lymphoproliferative disorders (excluding mycosis fungoides in patch or plaque stage and lymphomatoid papulosis) confirmed histopathologically. A descriptive statistical analysis was performed looking for associations between histological diagnosis and certain ultrasound variables.

Results
A statistically significant association was found between the histological diagnoses of the different subtypes of cutaneous lymphomas and the five ultrasound patterns described in our study. Furthermore, we found that cutaneous lymphomas with more indolent behaviour usually present ultrasonographically with well-defined edges and hypoechogenicity with respect to adjacent tissue, whereas in aggressive cutaneous lymphomas we generally find ill-defined and heteroechogenic structures.

Conclusions
We describe the five ultrasound patterns that cutaneous lymphomas may present and how they relate to each entity. This positions cutaneous ultrasound as a useful tool in the diagnosis and management of cutaneous lymphomas.

A-106

Use of pegylated interferon-α2a in cutaneous T-cell lymphoma - a multicentre retrospective data analysis with 70 patients

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Background
Interferon-alpha is an important therapeutic option for the treatment of the cutaneous T-cell lymphomas (CTCL) mycosis fungoides (MF) and Sézary-syndrome (SS). Since recombinant interferon-α-2a (IFN-α2a) has no longer been produced since January 2020, pegylated interferon-α2a (pegIFNα-2a) can be used as an alternative treatment, even though it is not approved for the treatment of CTCL and only limited data is available to date. The aim of this multicentre study was to generate comprehensive data on the efficacy and tolerability of pegIFNα-2a for the treatment of CTCL.

Methods
A multicentre, retrospective study was conducted with 70 patients with CTCL (MF and SS) from twelve German centres belonging to the lymphoma network of the Dermatological Oncology Association (*Arbeitsgemeinschaft Dermatologische Onkologie*, ADO).

Results
In total, 70 patients were included in the study, with 57.2% being male and the mean age being 58.8 ± 14.9 years. MF was present in 71.4% of cases and SS in 28.6%. An overall response rate of 55.2% was observed with pegIFNα-2a therapy. Adverse events occurred in 68.6% of patients and were classified as severe in 29.2%. The most frequently reported side effects were blood count changes (26/48, 54.2%), fatigue (13/48, 27.1%) and an increase in liver enzymes (12/48, 25%). Treatment was discontinued in 50% of all cases, the most common reason being side effects. The mean time to next treatment (TTNT) was 40.2 ± 36.9 weeks (range 4.0 to 165.3).

Conclusions
Our analysis provides comprehensive data on the efficacy and tolerability of pegIFNα-2a therapy in patients with CTCL. In terms of response rates and side effect profile, pegIFNα-2a appears to be comparable to IFN-α2a therapy.

A-284

VEXAS: a new clonal disease with specific diagnostic clues

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Background
The diagnostic process in dermatology can be challenging, especially for rare auto-inflammatory diseases.
A 63-year-old man presents with widespread asymptomatic sweetoid erythematous plaques and pustules, which appeared 3 days prior, accompanied by recurrent nocturnal fever and arthralgia. He had been diagnosed with urticarial vasculitis 2 years prior and was under investigation for unclear dyspnoea. Upon questioning, there were also episodes of chondritis of the left ear lobe.

Methods
Investigations: Laboratory findings showed a slight anaemia, and the microbiological analysis was negative. The histopathological analysis identified intra-epidermal pustules as well as dense band-like peri-vascular and peri-adnexal lympho-histiocytic infiltrates with signs of vasculopathy. A CT scan revealed bilateral segmental pulmonary embolisms. A bone marrow biopsy showed vacuoles in the myeloid and erythroid lineages, which led us to conduct a genetic analysis confirming a UBA1 mutation. To further characterize the inflammatory pattern, we performed a Nanostring analysis on skin samples. This showed a unique inflammatory gene expression signature consistent with neutrophil and type I interferon-driven inflammation. Moreover, immunohistochemistry shows predominant expression of type I interferon by neutrophils in lesional skin.

Results
We diagnosed a VEXAS syndrome (Vacuoles, E1 enzyme, X-linked, Autoinflammatory, Somatic), a newly described systemic syndrome associated with a poor prognosis, therefore requiring prompt diagnosis.
This syndrome is caused by a somatic mutation occurring at the haematopoetic stem cell level but affecting only the myeloid lineage in the blood. Different clonal patterns, including typical clonal haematopoesis mutations, have been described, contributing to the heterogeneity in presentation and severity of the disease. Moreover, overall clonal growth is also influenced by the concurrent inflammation and activity of circulating immune cells.
In addition to the classical diagnostic clues (including sweetoid lesions, arthritis, thromboembolic events, polychondritis and cytopenia), we describe specific neutrophilic and type I interferon molecular signatures within the skin.

Conclusions
Our study opens the way to new diagnostic possibilities and further research objectives in view of better understanding the disease and developing new therapeutic options based upon the pathophysiology.

EPIDEMIOLOGY

A-113

Eleven years Real World Data: Epidemiology and care reality of patients with CTCL in Germany - Retrospective statuory health insurance (SHI) claims data analyses

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Background
Cutaneous T-cell lymphomas (CTCL) are rare heterogeneous non-Hodgkin's lymphomas. Mycosis fungoides (MF) and Sézary syndrome (SS) together account for more than 50% cases. Due to the rarity, population-based studies of care reality and epidemiology are limited. Therefore, analyses with representative and robust claims data from German statutory health insurances (SHI) were conducted. The aim of this study was to evaluate epidemiological data for >10 years and generate insights about the care reality for patients with CTCL.

Methods
Two Real world data studies were conducted retrospectively using an anonymized, age- & sex-adjusted SHI claims data set with approximately five million insured persons; representing 6% of the German population. The analyses were performed following the Good Practice Guidelines for Secondary Data Analysis and covered the observation period from 2012 to 2022 with an cross-sectional and longitudinal approach. Patients were identified and assigned by means of confirmed ICD-10-GM-coding of mature T/NK cell lymphoma, CTCL and solely MF/SS patientl.

Results
CTCL increased from 14.5 in 2017 to 16.4/100,000 in 2022. MF increased from 7.93 in 2012 to 9.18 in 2022. An increase of 20% of the prevalent SS patients was also observed (2012: 0.45, 2022: 0.54/100,000).
The prevalence <18-year-old CTCL patients was between 1 and 4 per 1 million individuals. The five years OS of the CTCL patients was 84.1%, while the MF patients had the highest rate (85.1%), SS patients the lowest (72.2%). During the follow-up period, utilisation of dermatological contacts decreased and for every fifth patient. Within total follow-up-period 12% of the MF/SS patients suffered from infections, Actinic keratosis (11%), Pruritus (11%) and 15% were diagnosed with Covid-19. Compared to 2015, the use of flow cytometry (FACS) increased from 10% to 15% (2020). For newly diagnosed patients with MF/SS 84% received skin directed medication with corticosteroids and 38% skin directed intervention (phototherapy 36%).

Conclusions
Prevalences in children, patient characteristics and mortality rates (except SS) seem comparable to published data. As a result of the new therapy opportunities patients live longer, which can also explain an increase in prevalence and OS rates. Nevertheless, due to small patient counts this should be further investigated and validated. Overall this data provides the first representative long-term insights for CTCL patients and should help to raise awareness.

A-144

Exploring the association of CD30+ Lymphoproliferative Disorders and Inflammatory Conditions in a Dutch Cohort

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Background
Primary cutaneous CD30+ lymphoproliferative disorders (CD30+ LPD) may be associated with inflammatory conditions.
The aim of this study is to investigate the frequency of inflammatory conditions in CD30+ LPD patients compared to the Dutch population.

Methods
In this multicenter cohort study, the entire Dutch population of CD30+ LPD patients, as recorded in the Dutch Cutaneous Lymphoma Registry (DCLR) between 2000 and 2020, was included. The study population was divided into three subgroups: lymphomatoid papulosis (LyP), cutaneous anaplastic large cell lymphoma (C-ALCL), and borderline CD30+ LPD (borderline). Histopathological and clinical information was collected from each patient.

Results
Preliminary results indicate a possible association between CD30+ LPD and inflammatory conditions. In the cohort of 581 CD30+ LPD patients, a small percentage was observed to have an associated inflammatory condition. The proportion of patients with associated inflammatory conditions varied statistically among the CD30+ LPD subgroups.

Conclusions
Although the results are preliminary, they suggest an increased prevalence of inflammatory conditions in CD30+ LPD patients compared to the Dutch population. Statistical analysis will be performed to quantify the potential increased risk. Further studies are needed to confirm the nature and strength of this association. This research contributes to a better understanding of lymphoproliferative disorders and their possible connection to inflammatory conditions, which may have important implications for the diagnosis and treatment of patients with these conditions.

A-205

Incidence patterns of primary cutaneous lymphoma in Greece: A 15-year study

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Background
Primary cutaneous lymphomas (PCLs) are a heterogenous group of non-Hodgkin lymphomas arising in the skin from T- or B-lymphocytes, with limited epidemiological data available.

Methods
We conducted a retrospective study of all PCL diagnoses in the hemopathology referral center for PCL in Attica, Greece from 2009 to 2023. The statistical analysis was performed with Stata SE, version 13.0 (StataCorp) and for the estimation of annual percentage changes (APC), the US National Cancer Institute Joinpoint Regression Program was used.

Results
Between 2009 and 2023 a total of 1434 (872 males, 562 females) patients were diagnosed with PCL. Those included 1161 (743 males, 418 females) primary cutaneous T-cell lymphomas (PCTCL) and 273 (129 males, 144 females) primary cutaneous B-cell lymphomas (PCBCL). In the 2009-2011 period, the crude IR of PCL per 100,000 was 1.2, while in the 2022-2023 period it was 3.2. The crude IR for PCTCL and mycosis fungoides (MF) increased significantly by approximately 15% per year from 2009 to 2018, which was followed by a decrease in crude IRs until the year 2023 (from 2018 to 2023: APC:-4.8, 95%CI: -39.2 to 5.2 and APC: -4.4, 95% CI: -23.1 to 4.2, respectively). This downward trend, however, did not reach the statistical significance level. In contrast, the PCBCL IR steadily increased throughout the study period. The IR of lympomatoid papulosis (LyP) was increased from 0.11/100,000 person-years during the years 2019 and 2020 to 0.21/100,000 person-years in 2021 followed by a decrease to the previous level during 2022 and 2023.

Conclusions
The incidence of CTCL in Greece has stabilized since 2018. This stabilization could be multifactorial. A possible reason is the progress in diagnostic tools of CTCL and the efficiency of physician detection that have stabilized since 2018 after an increasing trend from 2009. Despite the PCL IRs have not been affected by the COVID-19 pandemic, an increase of LyP cases was observed during 2021, the year of massive vaccination against Sars-CoV-2. Whether the robust immune response to vaccines' components during COVID-19 immunization acted as a new trigger leading to the appearance of LyP or this increase was a random event remains to be further

elucidated. This study provides an update on the epidemiology of PCL in Greece citing a change trend of the IRs. The exact etiologies behind those epidemiological trends remain unknown and further studies are warranted to uncover the possible reasons that drive this phenomenon.

A-238

Increased mortality due to lymphoma and infections in patients with mycosis fungoides and Sézary syndrome: A Swedish nationwide, population-based cohort study

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Background
Early-stage mycosis fungoides (MF) patients show a good prognosis, contrasting with poorer survival in advanced stages of MF and Sezary syndrome (SS). Data from large population-based cohorts on the survival and cause-specific mortality in MF/SS are scarce. This study aimed to investigate mortality and causes of death among MF/SS patients in a large population-based cohort using Swedish national health registers.

Methods
The study population consisted of 643 patients with MF/SS diagnosed 2000-2019 and 6420 age- and sex-matched controls from the general population. In a sub-analysis, patients were classified as having advanced disease if they had records of systemic drugs and/or had been hospitalized with MF/SS as the main diagnosis during the first 6 months following diagnosis. Patients were followed from the date of diagnosis until death or December 31, 2019, whichever came first. Cox regression models with hazard ratios (HR) and 95% confidence intervals (CI) were used to measure the association between MF/SS vs. controls and cause-specific death (lymphoma, other malignancy, cardiovascular disease, infection, or other). In addition, the real-world probabilities of cause-specific death were estimated non-parametrically, accounting for competing risks.

Results
MF/SS patients had a median OS of 14.2 years (95% CI 11.1-18.9) and higher all-cause mortality compared to controls, adjusted for education and Carlson comorbidity index, aHR 1.6 (95% CI 1.3-1.9). Mortality due to lymphoma (including MF/SS), aHR 179.8 (95% CI 63.0-513.1), and infections, aHR 2.8 (95% CI 1.1-7.3), was significantly increased, but not for other causes. Fourteen percent of MF/SS patients were classified as having advanced disease. Their median OS was 4.5 years (95% CI 3.1-6.8), and their lymphoma mortality was markedly increased compared to those with mild disease, aHR 5.7 (95% CI 3.2-10.1). Lymphoma was the primary cause of death, with a 5-year probability of 13.4% (95% CI 10-16.3) in the overall MF/SS cohort. In severe MF/SS patients, the 5-year probability of death due to lymphoma was 29.2% (95% CI 18.8-40.5), compared to 6.3% (95% CI 4.2-8.9) in mild patients.

Conclusions
In this population-based cohort study, we saw increased mortality rates due to lymphoma and infections in MF/SS patients but not due to causes like other malignancies or cardiovascular disease. Lymphoma was the major cause of death, particularly pronounced in severe MF/SS patients highlighting the heterogeneity in the disease spectrum.

A-150

Paediatric onset lymphomatoid papulosis: results of a multicentre retrospective cohort study, on behalf of the EORTC Cutaneous Lymphoma Tumours Group (CLTG)

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Background
Lymphomatoid Papulosis (LyP) is a rare cutaneous T-cell lymphoproliferative disorder. Comprehensive data on LyP in the paediatric population is scarce. The objectives were to characterize epidemiological, clinical, histopathological, and prognostic features of paediatric LyP.

Methods
This was a retrospective, multicentre international cohort study including 87 cases of children and adolescents with LyP diagnosed between 1998 and 2022. Patients aged ≤ 18 years old at disease onset were included. Diagnosis was made in each centre based on clinical-pathological correlation.

Results
Eighty-seven patients from 12 centres were included. The mean age at onset was 6.98 years (range 3 months-18 years) with a male to female ratio of 2:1. The mean time between onset of first cutaneous lesions and diagnosis was 1.27 years (range 0-14 years). Initial misdiagnosis concerned 26.4% of patients. Initially, LyP was most often misdiagnosed as Pityriasis lichenoides et varioliformis acuta (PLEVA), insect bites, or mollusca contagiosa. Erythematous papules or papulonodules were the most frequent clinical presentation. Pruritus was specifically mentioned for 20.7% of patients. The main histological subtype was type A in 55.1% of the cases. If analysed, monoclonal TCR rearrangement was found in 76.5% of the skin biopsies. The overall survival rate was 100% with follow up at 5 years available for 33 patients and at 15 years for 8 patients. A development of associated haematological malignancy (HM) occurred in 9.6% of the cases (7/73), including four mycosis fungoides (MF) cases, one primary cutaneous anaplastic large cell lymphoma (pc-ALCL), one systemic ALCL and one case of acute myeloid leukaemia. If we compare incidence rates of cancer with the world 0-19 years old population from 2001-2010, we estimate a significantly higher risk of associated malignancy in general, occurring before the age of 19 years old with incidence rate ratio of 87.49 (CI 86.01-88.99).

Conclusions
We report epidemiological data from a large international cohort of children and adolescents with LyP. Overall the prognosis of the disease is good, with excellent survival rates for all patients. Due to increased risk of associated HM, a long-term follow-up should be recommended for LyP patients.

A-117

Prognosis and management of Large Cell Transformation (LCT) in Mycosis Fungoides and Sézary Syndrome: LCT has poor outcome independent of clinical stage

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Background
Large cell transformation (LCT) in mycosis fungoides (MF) is defined as the histological presence of >25% large cells (>4x the size of small lymphocytes) within a specimen or clusters of atypical large cells[1]. LCT generally indicates a poor prognosis, though there is some heterogeneity in survival time and disease course. Previous work has identified factors alongside LCT that indicate poorer prognosis, including age >60 years, higher clinical stage at time of LCT, and elevated serum LDH[1].

Methods
A retrospective study of all patients diagnosed after January 2012 at a single tertiary centre with primary cutaneous T-cell lymphoma (MF or Sézary syndrome [SS]) with LCT. Patients identified through review of histology reports for presence of >25% large cells in specimens. Case notes, histology reports, and other relevant investigations were reviewed.

Results
63 patients (27 female) were diagnosed with LCT between June 2012 - October 2023. 57 had MF, 6 had SS. Median age at time of LCT was 68 (34-91). 32 cases had LCT at the time of diagnosis of MF/SS (29 MF, 3 SS). Median time to LCT from diagnosis was otherwise 28 months (range 2-358). 52 cases had skin only LCT, 9 had skin and lymph node (LN) LCT, and 2 had LN only LCT. 35 cases had a serum lactate dehydrogenase (LDH) above the upper limit of normal at time of LCT (normal range 125-220 U/L), with a median serum LDH value of 230.5U/L (140-653). 43 cases had LCT with cells that were CD30+.
20 patients had early-stage disease at time of diagnosis (8 Stage IA, 12 IB, 0 IIA). 6 patients had folliculotropic MF (FMF). 8 patients had early-stage MF at time of LCT (3 stage IA, 5 IB, 0 IIA), with 4 having FMF.
43 patients (64%) had advanced disease (32 Stage IIB, 3 III, 8 IV) at the time of diagnosis of MF/SS, with 55 patients (86%) having advanced disease at time of LCT.
44 patients received radiotherapy for LCT (first line in 31 cases). 46 patients received systemic treatment following LCT, with 14 receiving Brentuximab.
3-year overall survival (OS) following LCT was 50%. 5-year OS was 32.5%. Of 38 patients known to have died, 17 died of MF/SS, with another 3 attributed to treatment for MF/SS.

Conclusions
LCT may occur at the time of diagnosis of MF/SS, or at any time up to several years post-diagnosis. LCT occurs more commonly in advanced MF but can occur in early-stage plaque MF and FMF, where it was associated with a 50% mortality rate. Radiotherapy is most frequently used for local tumour LCT, though systemic therapies are often required.
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A-212

Retrospective Review of Mycosis Fungoides and Sézary Syndrome in Chinese Patients at a Hong Kong Tertiary Center

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Background
This study aimed to investigate Mycosis Fungoides (MF) and Sézary Syndrome (SS) in the Asian population, with a particular focus on Hong Kong. Previous research has primarily focused on Western populations, leaving limited information about Chinese patients.

Methods
We conducted a retrospective analysis of MF and SS cases diagnosed at Tuen Mun Hospital, a tertiary hematology center between 2000 and 2024. Patient demographics, staging, treatment, survival outcomes, and histology were collected and analyzed.

Results
Fourteen Chinese patients diagnosed with MF and SS were included in the study. Among them, 10 patients were male (71.4%) and 4 were female (28.6%). The age range was 23 to 78 years, with a median age of 57 years. Mycosis fungoides was diagnosed in all patients, while 2 patients had Sézary syndrome (14.3%). The average time from symptom onset to diagnosis was 2.4 years. Disease staging revealed 6 patients with Stage IB (42.9%), 3 with Stage IIB (21.4%), 1 with Stage IIA (7.1%), 2 with Stage III (14.3%), and 2 with Stage IVA (14.3%).

6 patients received skin-directed therapy alone (42.9%), 4 received systemic therapy alone (28.6%), and 4 underwent a combination of both (28.6%). Skin-directed therapies included psoralen plus ultraviolet A (PUVA) for 10 patients (71.4%), local radiotherapy (RT) for 4 patients (28.6%), and total skin electron beam therapy (TSEBT) for 3 patients (21.4%).

Among patients receiving systemic therapy alone or in combination, 6 out of 7 patients (85.7%) received methotrexate (MTX) as the first-line treatment, with dosages ranging from 5 mg to 20 mg per week. One patient with Stage IVA disease received CHOP

chemotherapy for 6 cycles as the initial treatment. One developed large cell transformation with Hemophagocytic lymphohistiocytosis and was given etoposide with dexamethasone.

Second-line treatments included brentuximab vedotin for one patient, who later received gemcitabine as a third-line treatment. Two patients received chlorambucil as the second-line treatment, and one patient received gemcitabine as the second-line treatment.

The overall response rate (ORR) was 63%, with a complete remission rate of 21%. The median duration of response was 15 months (range: 6 to 72 months). Median overall survival was 72 months (range: 8 months to 216 months), with infection being the most common cause of death.

Conclusions
This study provides insights on MF and SS in Chinese patients, highlighting treatment approaches and the importance of early detection.

HISTOPATHOLOGY

A-172

Atypical Epidermotropic Infiltrate with NK cell immunophenotype Following Systemic Therapy for Atopic Dermatitis - A Case Report

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Background
Mycosis fungoides (MF) may present with atypical immunophenotypes, including loss of CD4 and/or CD8 and other T-cell markers, without known effects on the disease prognosis.

Methods
We present a case of atypical epidermotropic lymphoid infiltrates with a natural killer (NK) cell immunophenotype under the clinical picture of mycosis fungoides.

Results
A 56-year-old male patient with a 25-year history of atopic dermatitis presented to our department with pruritus and disseminated erythematous plaques with a fine scale. He had discontinued treatment with dupilumab three months previously, which had partially improved his skin condition. He was then treated with baricitinib and tralokinumab without marked improvement. Six months after stopping tralokinumab, a dramatic worsening of his skin condition was observed with increased infiltration of the plaques and erythrodermia.
Skin biopsy showed atypical epidermotropic lymphoid cells combined with a bandlike infiltrate of small monomorphic lymphoid cells in the upper dermis. The epidermotropic cells were positive for CD2 and CD56 and cytotoxic proteins, negative for T-cell markers (CD3, CD4, CD8, CD7), and showed no expression of beta F1 or T-cell receptor beta or gamma/delta chains. EBER in situ hybridization was negative. T-cell receptor rearrangement showed a polyclonal infiltrate. Further staging examinations showed no evidence of blood or organ involvement.
We initiated a treatment with topical corticosteroids, PUVA-therapy and extracorporeal photopheresis which led to a marked improvement of the skin lesion within 5 months with some residual patches and plaques on the trunk and lower extremities.

Conclusions
IL4-antibody therapy has been associated with newly diagnosed cutaneous T-cell lymphoma, but it remains unclear whether this is due to the unmasking of a previously undiagnosed disease or a pro-oncogenic effect. The effects of kinase-inhibitor therapy and IL 13-inhibition on cutaneous lymphoma are still poorly understood and we can only speculate on their effect in the presented case. Mycosis fungoides may exhibit a loss of various T-cell markers, yet a complete switch to a NK cell immune phenotype has not been reported. NK/T-cell-proliferations are often associated with EBV and usually show a very aggressive behavior, which is in contrast with a clinical picture of MF with patches and plaques and lack of blood or organ involvement. The patient is currently undergoing close monitoring for disease progression.

A-196

Can histopathology contribute to a better definition of patches and plaques in early stage mycosis fungoides?

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Background
In early stage mycosis fungoides (MF) patients with plaques have a significantly worse prognosis than patients with only patches. Distinction between patches and plaques is therefore important, but can be extremely difficult, if only based on clinical examination. Whether histological criteria can contribute to a better distinction between patches and plaques is a matter of debate. The aim of this study was to assess differences in the extent and depth of the infiltrate between patches and plaques and to find out if histopathological criteria can serve as an adjunct to differentiate between both lesions.

Methods
In this retrospective cohort study, 100 early MF lesions were included and scored in a blinded fashion for clinical and histopathological features by three individual clinicians and five individual (dermato)pathologists. Clinical images were scored as either patch or plaque and histopathologically four categories were distinguished: 1. minimal or mild infiltrate in the papillary dermis; 2. Moderate infiltrate in the papillary dermis; 3. thick band-like infiltrate in papillary dermis; 4. infiltrate extending into reticular dermis/subcutis.

Results
Clinical laesions were classified as either patch or plaque by consensus resulting in 65 patches and 36 plaques. Histopathologically, lesions were classified by consensus as category 1, 2, 3 or 4 in 21%, 39%, 16% and 24% of cases. Most patch-type lesions (41/65; 63%) were classified as category 1 (n=17) or 2 (n=24), but a significant minority (24/65; 37%) as category 3 (n=9) or even 4 (n=15). Plaque-like lesions were classified as category 1 in 4 cases (11%), category 2 in 15 cases (42%) and category 3 in 7 cases (20%). However, infiltration in the reticular dermis was observed in only 9 of 35 cases (26%).

Conclusions
Our results show considerable overlap in the extent and depth of the cutaneous infiltrates between patches and plaques and thus do not support the suggestion that these histopathological criteria contribute to a better distinction between these lesions.

A-135

Challenges in differentiating among the primary cutaneous lymphoproliferative diseases with gamma-delta phenotype - a case report

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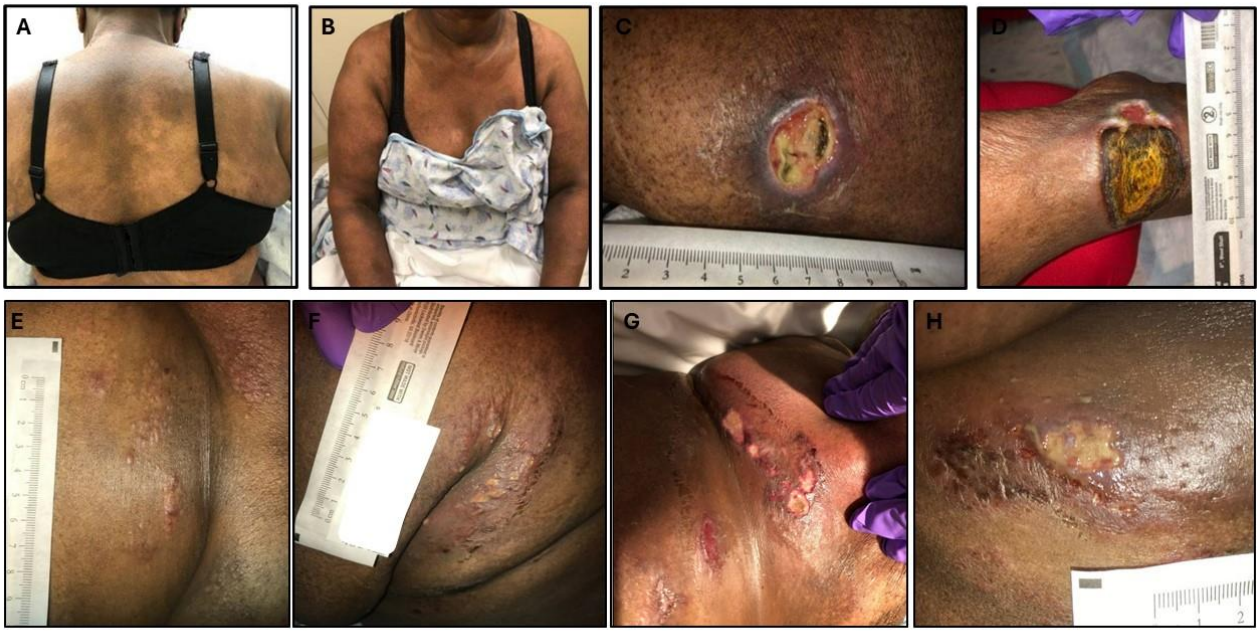
Background
Lymphomatoid papulosis (LyP) is a low-grade CD30+ lymphoproliferative disorder that manifests as recurrent, self-remitting papulonodular lesions and exhibits a range of histopathologic findings. Gamma-delta positive LyP is a rare subtype of LyP that may demonstrate immunophenotypic overlap with other more aggressive gamma-delta positive cutaneous lymphomas [1].

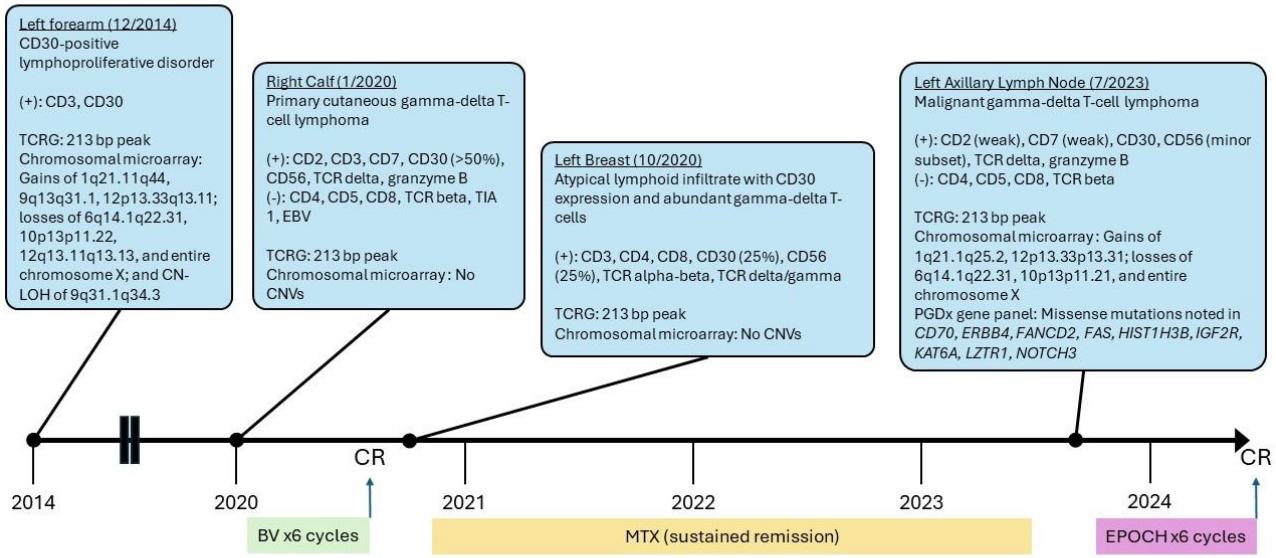
Methods
We present a case report of LyP with gamma-delta phenotype in a patient who later developed a clonally-related aggressive gamma-delta positive peripheral T-cell lymphoma.

Results
A 55-year-old female presented for evaluation in 2019 for a 1-month history of ulcerating skin lesions (Figure 1, C-D). Biopsy of a calf lesion showed a dense, angiotrophic, atypical CD30+ lymphoid infiltrate involving the dermis and subcutis. TCRG clonality was positive and chromosomal microarray was negative for copy number abnormalities. PET/CT did not show any systemic disease, and a diagnosis of primary cutaneous gamma-delta T-cell lymphoma (PCGDTCL) was made. She was treated with brentuximab vedotin for 6 cycles and achieved complete response (CR). One month after completing Bv, she developed new ulcers on the trunk and breast (Figure 1, E-H), and biopsy showed an atypical CD30+ lymphoid infiltrate with abundant gamma-delta T-cells. She was treated with romidepsin and achieved complete resolution of all lesions with only one dose. Based on the clinical behavior, the prior diagnosis of PCGDTCL was

reconsidered and LyP with gamma-delta phenotype was favored instead. In the absence of any active skin lesions, she was initiated on oral weekly methotrexate (MTX) which she remained on for 3 years without recurrence. She then developed multi-station lymphadenopathy without skin lesions, and lymph node biopsy was consistent with malignant gamma-delta T-cell lymphoma. Genomic profiling revealed multiple variants of potential or unknown clinical significance and chromosomal microarray showed multiple copy number abnormalities involving chromosomes 1, 6, 9, 10, 12, and X (Figure 2). MTX was discontinued, and she was treated with EPOCH chemotherapy for 6 cycles and achieved CR. She refused consolidation with allogeneic stem cell transplant but remains in CR 4 months after completing EPOCH.



Hypo- and hyperpigmented macules involving 80-90% BSA (A-B) along with shallow ulcers of right thigh (C) and right leg (D) prior to treatment with brentuximab vedotin. New-onset erythematous and ulcerated papules on the right chest (E), axilla (F), breast (G), and abdomen (H) noted 1 month after completion of Bv and clearance of prior lesions.



Treatment history and biopsy results from first diagnosis of CD30-positive cutaneous lymphoproliferative disorder in 2014 to diagnosis of malignant gamma-delta peripheral T-cell lymphoma in 2023. CNV; copy number variant, LOH; loss of heterozygosity, PGDx; personal genome diagnostics multi-gene panel, TCRG; T-cell receptor gene rearrangement PCR

Conclusions

This case highlights the challenges in distinguishing LyP from malignant T-cell lymphomas and highlights the wide spectrum of clinical behavior of disease among the gamma-delta subtype T-cell lymphoproliferative disorders of the skin.

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A-114

Deep learning-based classification of early-stage mycosis fungoides and benign inflammatory dermatoses on hematoxylin and eosin-stained whole-slide images: a retrospective, proof-of-concept study

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Background

The diagnosis of early-stage mycosis fungoides (MF) is challenging due to shared clinical and histopathological features with benign inflammatory dermatoses (BIDs). Recent evidence has shown that deep learning (DL) can assist pathologists in cancer classification, but its application to cutaneous lymphomas remains largely unexplored. This study significantly advances our pilot research presented at the EORTC Cutaneous Lymphoma Tumour Group Annual Meeting in 2022 [abstract Hist-O-01].

Methods

In this single-center proof-of-concept study, we trained DL-based models using CLAM to distinguish early-stage MF from BIDs using a unique dataset of 924 hematoxylin and eosin-stained whole-slide images (WSIs) from skin biopsies, including 233 patients with early-stage MF, 96 patients with BIDs with clinical/histological suspicion of MF but without MF diagnosis after clinicopathological correlation, and 260 patients with BIDs without clinical/histological suspicion of MF. The dataset was divided into two cohorts: a development set used for model development, consisting of patients diagnosed from January 2015 to August 2021 (n=724 WSI, 78.4% of total sample), and a temporal test set encompassing the data for further, independent validation, consisting of patients diagnosed from September 2021 to December 2023 (n=200 WSI, 21.6% of total sample). The classification accuracy of the weakly-supervised DL models was benchmarked against three expert pathologists.

Results

With 10-fold cross-validation at 200x magnification and a 256x256 pixel patch size using the UNI feature extractor, our models achieved mean WSI-level AUCs of 0.955 and 0.827, and mean WSI-level balanced accuracies of 90.6% resp. 76.2% on the internal test set and the temporal test set. The final balanced accuracy of 76.2% was similar to that of three CL-expert pathologists, who achieved a mean balanced accuracy of 77.7% on the temporal test set. Additionally, most attention heatmaps corresponded well to moderately with the pathologists' region-of-interest (94.5%).

Conclusions

Considering the difficulty of the MF versus BID classification task, the results of this study
show promise for future applications of weakly-supervised DL in diagnosing early-stage MF. Achieving clinical-grade performance will require usage of large, multi-institutional datasets, such as the CLIDIPA Registry initiative, and improved methodologies, such as multimodal DL with incorporation of clinical data.

A-149

For something completely different: granuloma annulare-like histiocytosis as skin specific manifestation of ETV6::SYK rearranged myeloid neoplasm with eosinophilia.

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Background

Leading from the diagnosis of a novel case, we aim at discussing the clinic-pathologic picture and published literature on a very rare instance of myeloid/lymphoid neoplasm with eosinophilia (MLNE), featuring *ETV6::SYK* rearrangement and an histiocytic proliferation akin to sarcoidosis or granuloma annulare (GA)

Methods

A novel case is discussed. PubMed database was queried for “SYK ETV6 myeloid” and “SYK ETV6 rearrangement”

Results

Case description

67 y.o. F, developing monocular diplopia and paresis (eye examination suspicious for choroidal granulomas), followed by cutaneous plaques arising from the scalp and progressing to the face, back and limbs over a course of 3 years, initially regarded as consistent with ocular and cutaneous sarcoidosis. For worsening of the ocular signs and progression of the skin lesions, she came to our Institution, where a hematological workup revealed isolated eosinophilia (Eo 5650/mmc, 37%) and PET hypercaptation involving cutaneous-subcutaneous lesions, hepatic venous branches, superior mesenteric artery and endometrial cavity.

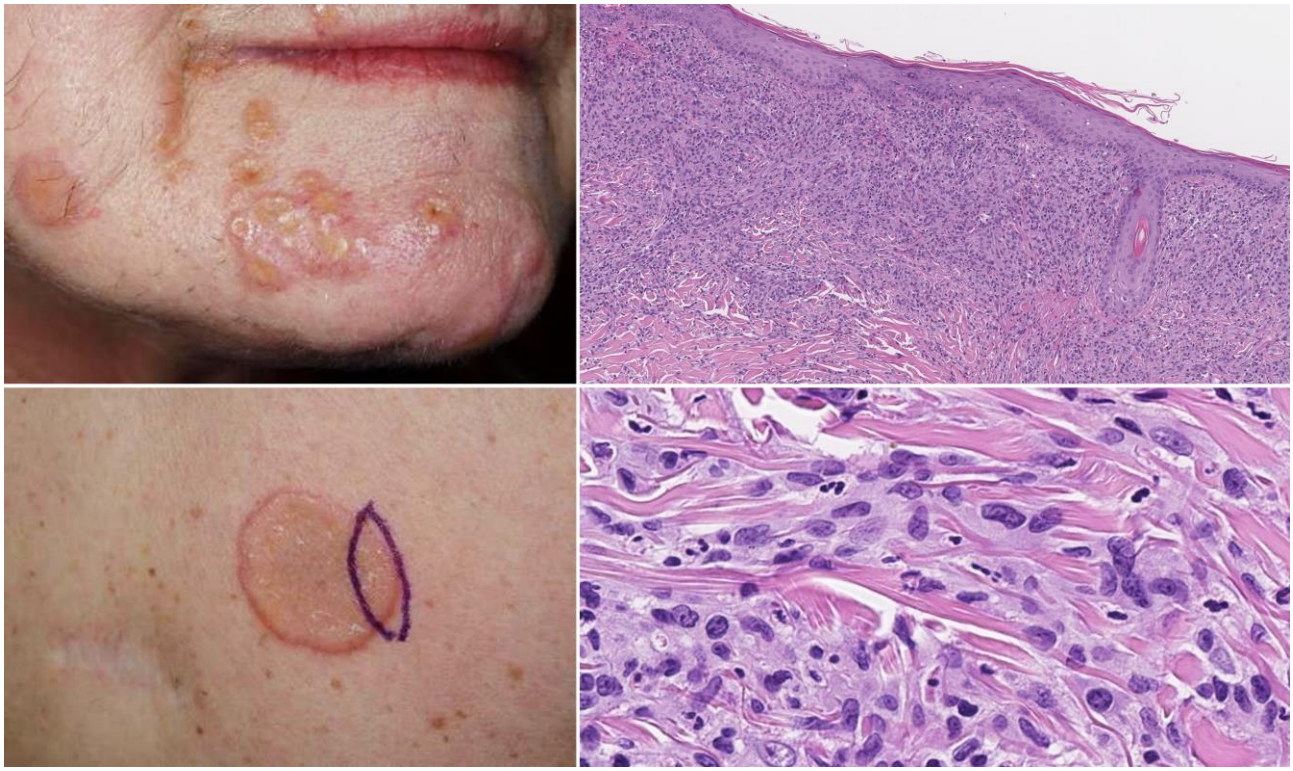
A skin biopsy revealed an interstitial accumulation of histiocytoid histiocytes with a nondescript phenotype, reminiscent of interstitial GA, while bone marrow (BM) aspirate and biopsy supported a clonal eosinophilia.

BM karyotype revealed t(9;12)(q22;p13), further confirmed as *ETV6::SYK* by RT-PCR in the peripheral blood, where *ASXL1* mutation was also found by targeted NGS, the latter lacking in the skin.

A final diagnosis of histiocytic proliferation of undetermined significance / unclassifiable histiocytosis as skin manifestation of MLNE and other tyrosine kinase (TK) gene fusions (WHO 2022) was rendered.

Literature review

A total of 4 cases of myeloid neoplasm, featuring eosinophilia and skin lesions and rearrangement of *ETV6* locus at 12p13 was retrieved and summarized in the table.



Clinic-pathologic picture of presented case

Clinical picture (n=5) *Current case* • steadily developing cutaneous plaques, ocular signs (monocular diplopia and paresis) • isolated eosinophilia. *Published cases* (n = 4) • skin lesions involving the head in all cases + trunk and limbs in 3 cases • ocular signs and arthralgia reported in 1 case • absolute eosinophilia (range 1590-9500/mmc); variable leukocytosis and anaemia.
Histology (n = 4) *Current case + published case* • skin biopsy showing interstitial to diffuse dermal infiltration of spindle/histiocytoid histiocytes; very few granulocytes; non-Langerhans / non-descript histiocytic phenotype (CD68+, CD1a-, S100-, langerin-, MPO-) • bone marrow featuring megakaryocyte dysplasia, myeloid hyperplasia and eosinophilia
Molecular features (n=5) • *ETV6* locus involvement in all cases; 4 cases demonstrating *ETV6::SYK* fusion • in our cases, *ASXL1* mutation found in peripheral blood, not detected in the skin • in 1 case, presence of a minor clone with complex karyotpe
Therapy and follow up (n=5) *Current case* • imatinib with clinical response of the ocular and cutaneous lesions; switch to dasatinib due to steady increase of eosinophilia; • died of infectious complications 1.5 years after the diagnosis *Published cases* • 1 patient, remission of skin lesions after HSCT; 2 cases, partial response to thalidomide or cobimetinib

Clinic-pathologic experience on ETV6::SYK rearranged myeloid neoplasm

Conclusions

The collected experience points towards a stereotyped pattern of *ETV6::SYK* rearranged hematopoietic neoplasm, comprising progressive eosinophilia and an unclassifiable histiocytic proliferation, recapitulating the clinical features of disseminated sarcoidosis or, alternatively, the cutaneous clinic-pathologic picture of GA. *ETV6::SYK* related neoplasms are exceedingly rare, but easily overlooked or disregarded as inflammatory processes: their recognition should prompt proper management, which may benefit from TK inhibition and, ultimately, allogeneic stem cell transplantation

A-218

New histopathologic patterns of Mogamulizumab-associated rash and a revision of already described histopathologic findings

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Background

Mogamulizumab is monoclonal anti-CCR4-antibody, which is approved for second-line treatment of adult patients with mycosis fungoides or Sezary syndrome. A Mogamulizumab-associated rash (MAR) is a common side effect, which occurred in MOVORIC trial in about 25% of the treated patients. Current data has shown that MAR is more common than initially expected. The correct diagnosis of MAR and its differentiation from tumour progression is critical for the further treatment and outcome. The skin biopsy plays a key role in making the correct diagnosis. Three major histopathologic patterns of MAR (spongiotic/psoriasiform, interface, granulomatous) were already identified. A shift of CD4 expression towards CD8 is a helpful additional diagnostic criterion.

Methods

The evaluation of our database revealed new histopathologic patterns of MAR.

Results
The newly described pattern encompasses (a) epidermotropic (pagetoid) CD8+ infiltrate, perfectly simulation a primary cutaneous CD8+ aggressive epidermotropic cytotoxic T-cell lymphoma; (b) a perivascular deep lymphocytic infiltrate, with mucine deposits and a mild interface dermatitis, simulating lupus erythematodes (LE) and (c) a mixed infiltrates with (residual) parts of the tumour in combination with MAR.
Additionally, the main patterns initially described were not leading in all biopsies, esp. a folliculotropic infiltrate was often predominant.

Conclusions
Next to the already described three major histologic reaction patterns other histopathologic patterns should be considered. On the one hand the newly described patterns: epidermotropic-pagetoid, LE-like and mixed, but also the already described finding: epidermotropic – MF-like and folliculotropic. It should be also considered that the MAR-infiltrate is usually rich of histiocytes, even if they are not forming classical granulomas. It is important to know that the histological spectrum can be extremely broad and that a clinical correlation and comparison with the initial diagnostic biopsy is essential. It is also important to have in mind that one single biopsy does not necessary predict the reaction in all skin lesion and that a therapy decision should not be based on a histological result alone.

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A-194

Primary cutaneous anaplastic large cell lymphoma with locorregional lymph node involvement in a pregnant woman

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Background
Primary cutaneous anaplastic large cell lymphoma (PC-ALCL) belongs, together with lymphomatoid papulosis (LyP), to the group of primary cutaneous CD30+ lymphoproliferative disorders (PC CD30+ LPD). Its diagnosis requires a multidisciplinary approach, considering clinical, histological, immunohistochemical, and molecular criteria, including CD30 expression in at least 75% of tumor cells. The disease is usually limited to the skin, and extracutaneous dissemination is very rare. In some cases, it is considered a poor prognostic factor, along with recurrences and age over 60 years.

Methods
In this study, we conducted an exhaustive and systematic literature review focused on PC-ALCL with nodal dissemination, based on the description of a clinical case diagnosed at the HCU Lozano Blesa in Zaragoza.

Results
We present a case of a 32-year-old pregnant female with a lesión on her left arm diagnosed as PC CD30+ LPD. During the pregnancy, the lesión grew considerably. After delivery, the patient was reevaluated and given a final diagnosis of ALK negative PC-ALCL with regional dissemination to an ipsilateral axillary lymphadenopathy. She was treated with CHP combined with BV, achieving a complete response with no recurrences to date.

Conclusions
The development of PLP during pregnancy is rare. These cases usually present as clinically advanced systemic lymphomas, determining the clinical management of the patients. Presentation as PC-ALCL is exceptional, as is nodal dissemination. This represents a diagnostic challenge. Accurate differential diagnosis, especially with systemic ALCL, is crucial for understanding prognosis and managing patients appropriately. The recent approval of Brentuximab Vedotin (BV), an anti-CD30 monoclonal antibody, has transformedthe management of these patients, particularly in cases of advanced locoregional disease. Further studies are needed to establish the optimal treatment with a low relapse rate and minimal secondary toxicity.

A-300

Skin microRNA profile of 12 cases of granulomatous slack skin - an extremely rare variant of mycosis fungoides

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Background

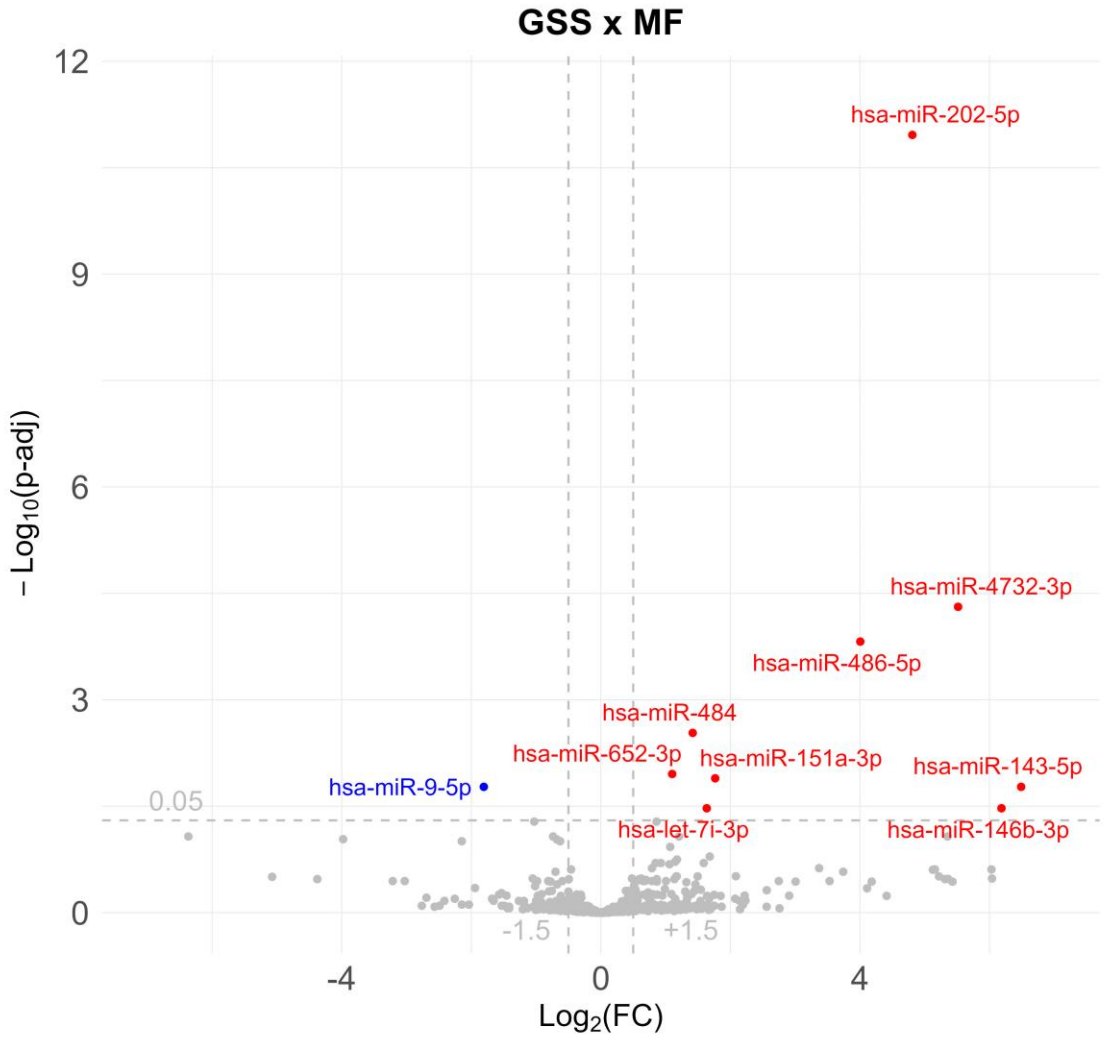
Granulomatous slack skin (GSS) represents the rarest variant of mycosis fungoides (MF), with approximately 50 cases documented worldwide. The hallmark features of GSS are granulomatous, histiocytic infiltrates with clinical and histologic elastolysis. MicroRNAs (miRNAs) are post-transcriptional regulators of gene expression that play critical roles in regulatory mechanisms of biological processes. The profile of microRNAs in GSS has yet to be evaluated.

Methods

Total RNA samples were obtained from Paraffin-embedded tissue of lesional skin of 12 GSS patients and 6 classical MF cases via miRNeasy FFPE Kit. The small library preparation and sequencing was carried out by BGI using the platformDNBseqTM. Differential expression analysis and target gene prediction were performed (padj < 0.05 and Fold Change ≥ 1.5).

Results

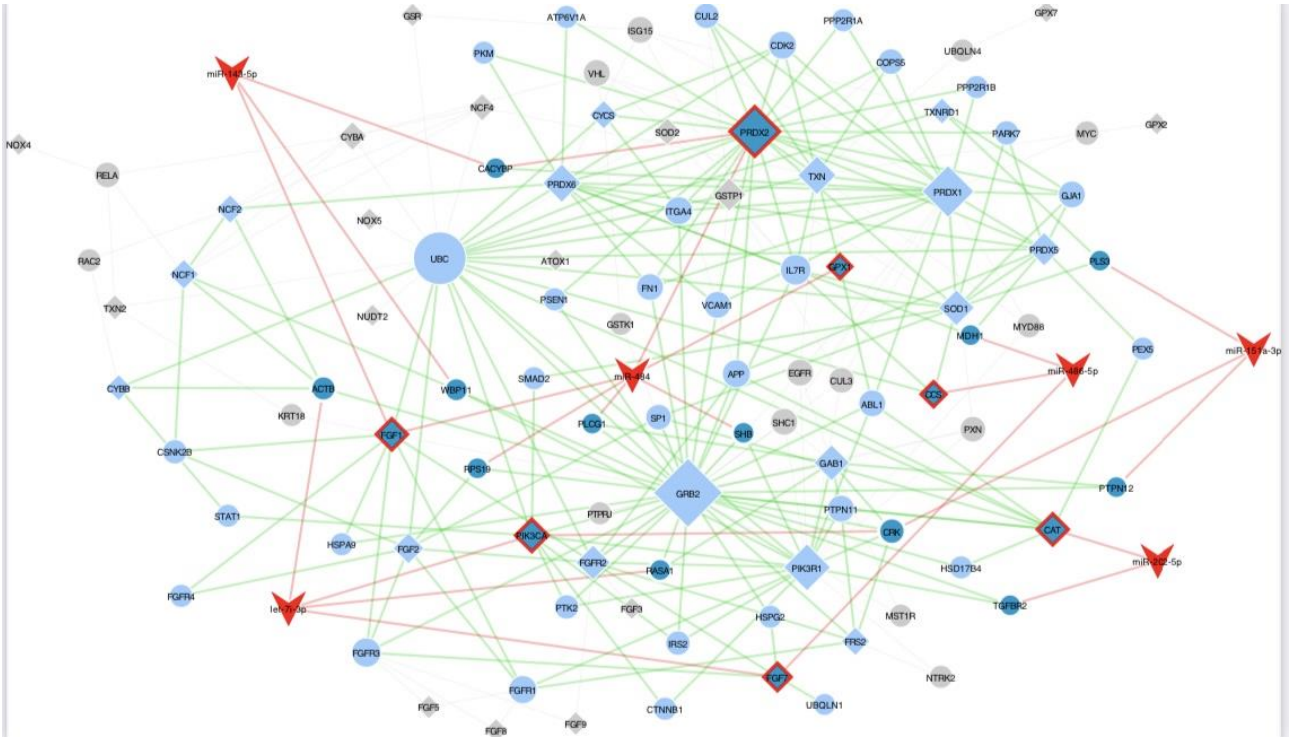
We identified ten differentially expressed microRNAs (DEMs) in the GSS cases when compared to classical MF cases, with nine being upregulated and one downregulated, as shown in Figure 1



Volcano plot of differential expressed miRs. Note: red (up); blue (down); gray (not significant. |log2FC|>1.5 and p<0.05

. As microRNAs exert their function by binding to the complementary sequence of the target mRNA, a target gene prediction was performed in order to evaluate the effects of the upregulated DEMs detected. The target prediction analysis resulted in 976 predicted

targets. An over-representation-based enrichment analysis with the predicted target genes list was carried out to understand the biological implication of upregulated DEMs. The KEGG pathway enrichment analyses identified 23 groups while reactome pathway enrichment analyses resulted in 37 groups, the most relevant were selected. The PP2A-mediated dephosphorylation, AKT phosphorylation and Detoxification of Reactive Oxygen Species are among the enriched pathways and the relationship between oxidative stress and skin damage has been reported. Therefore, we performed a prediction of interaction of the 9 upregulated DEMs with genes of the detoxification of reactive oxygen species, Figure 2



Network interaction between DEMs and predicted target genes of the Detoxification of Reactive Oxygen Species (Reactome) pathway . Gene interaction network showed that upregulated DEMs are predicted to interact directly with genes of the pathway of interest, which suggests a negative regulation of detoxification of reactive oxygen species in these patients.

Conclusions

Our findings indicate that the ROS detoxification pathway is impaired in GSS patients, which may be a contributing factor to the dermatological manifestations observed in GSS. Nevertheless, the present study is preliminary and further validation experiments, such as evaluation at the protein level, are required. This represents a preliminary step towards the identification of the mechanisms that might explain the distinctive clinical and histological characteristics of this rare MF variant. In the near future, this may also facilitate the development of more effective therapeutic strategies.

A-179

The Cutaneous Lymphoma International DIgital PAthology (CLIDIPA) Registry – a multi-center, collaborative initiative to facilitate Artificial Intelligence-driven research within Cutaneous Lymphomas.

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Background

Cutaneous lymphomas (CLs) are a rare group of hematological skin cancers with a wide variety in clinical presentation, histopathology, and disease course. Due to the rarity of CLs, experience is mostly limited to expert centers. In order to improve clinical care and outcome of this rare patient population, adjunct diagnostic and prognostic tools are welcomed, especially by clinicians/pathologists without expertise in this field or with limited access to a specialized center.

Artificial Intelligence (AI)-based deep-learning techniques have demonstrated to be capable of identifying biomarkers that are both affordable and easy to translate into digital pathology worldwide. Deep learning can be used to extract subtle patterns from whole-slide pathology images (WSIs) that can aid in detecting specific subclasses and can be applied for complex diagnostic or prognostic tasks. Especially rare diseases, like CLs, may benefit from these adjunct techniques. Currently, AI-based research within CLs is still in its infancy, partly due to the rarity of the diseases. In order to go along with these innovations in clinical care of CL patients, only large international datasets would be sufficient to perform and validate meaningful AI-based research within this rare patient population.

Methods
For this purpose, we founded the Cutaneous Lymphoma International Digital Pathology (CLIDIPA) Registry. The CLIDIPA Registry is a joined effort of Cutaneous Lymphoma expert centers across Europe with the shared goal of facilitating international Research Projects with large sample-datasets of digital pathology and clinical data of patients who have been diagnosed with a Cutaneous Lymphoma or a mimicker thereof, in order to execute AI-based research.

Results
At the time of abstract submission, ten centers have stated their collaboration in the Registry and are either completing the legal documents (n=3) or are in the process of uploading their data (n=7). The first set of data will be used to serve as an international, multi-center validation cohort for the single-institution study performed by Doeleman, et al. (abstract A-114).

Conclusions
During the EORTC-CLTG annual meeting 2024, we will provide an update on the progress of inclusion in the CLIDIPA Registry, as well as to bring the Registry to attention for future research collaborations in the field of AI.

A-202

Validation Of Next Generation Sequencing Using EuroClonality-NDC Panel In Primary Cutaneous Lymphomas and comparison with Traditional PCR Techniques

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Background
Primary cutaneous Lymphomas (PCLs) are challenging to diagnose partly due to their clinical and histological similarities with benign inflammatory dermatosis (BID). Clonality and particularly identical clones in separate samples aids diagnosis in PCL. Testing is typically performed using PCR techniques with Biomed 2 primers but sensitivity and specificity are low. Next generation sequencing (NGS) has many advantages over PCR testing including higher specificity and more accurate comparison of clones between individual specimens. NGS also has the ability to detect sequence and structural variants if it has been programmed. EuroClonality-NDC is a recently available NGS, validated on FFPE samples of lymph nodes but has not yet been validated on skin samples.

Methods
We analysed skin biopsies from 70 patients with PCL and 13 BID using EuroClonality-NDC on FFPE samples. 57 of these patient samples were also analysed using our standard BIOMED-2 PCR protocols performed on fresh skin samples for comparison.

Results
98 skin biopsies were obtained from 60 patients with PCL. PCL histological subtypes included 29 mycosis fungoides, 10 marginal zone lymphoma, 5 large cell anaplastic lymphoma, 2 Sezary Syndrome, 3 follicle centre lymphoma, 5 CD4+ lymphoproliferative disorder, 6 other. Additionally, 13 control cases (17 samples) were analysed with BID.
Euroclonality analysis on 98 samples failed in 24 (24.5%) including 16 PCL samples. Of the 74 samples successfully analysed by Euroclonality 65 were PCL samples and 49 (75.4%) were reported as clonal with no false positives. 16 samples were reported as polyclonal, including 11 false negatives. All 9 BID were polyclonal. Providing a sensitivity of 63/74 (85.1%) and specificity of 100%.
Biomed2 analysis was performed on 65 samples and 8 failed (12.3%). Of those 57 successfully analysed 45 were from PCL patients and 12 from BID. 46 (80.7%) were identified as clonal with 11 false positives. 12 samples (21.1%) were polyclonal, including 7 false negatives. Providing a sensitivity of 40/57 (70.2%) and specificity 5/16 (31.3%).

Conclusions
NGS Euro-clonality testing on FFPE samples is highly specific (100%) compared to BIOMED2 (31.3%) and offers better sensitivity (85.1%) to Biomed2 (70.2%) on fresh samples. However the failure rate was twice as high using Euroclonality (24.4%) and may be improved using fresh samples. Euroclonality offers an exciting new test for aiding diagnosis of PCL & differentiating from BID.

PRECLINICAL STUDIES

A-289

Allogeneic stem cell transplantation in advanced cutaneous T cell lymphoma offers the potential for cure

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Background
The lack of curative therapies and poor survival (<50% 5 year) in patients with advanced stage cutaneous T cell lymphoma (CTCL) has led us to evaluate AlloSCT in advanced CTCL with the aim of modifying the disease course and as a potential for cure.

Methods
Patients in remission with advanced CTCL who are eligible for AlloSCT are treated with a chemo-free conditioning regime of total skin electron beam, total nodal irradiation, anti-thymocyte globulin and extracorporeal photopheresis according to the Stanford Protocol.

Results
22 patients received AlloSCT with a median age at transplant of 46.7 years (range 31-67yrs). Subtypes included Mycosis Fungoides (MF) n=15, Sézary Syndrome (SS) n=4 and Large Cell Anaplastic Lymphoma (LCAL) n=3.
MF stage at transplantation (mean age 49.8) included IIB n=5, IIIA n=1, IIIB n=3, IVA2 n=5, IVB n=1. SS stages included IVA1 n=1, IVA2 n=3 and LCAL included IV n=2, IVB n=1.
Each patient had an average of 4.5 systemic therapies prior to AlloSCT. The most common bridging therapies included brentuximab (n=7) or gemcitabine (n=7). Median time from diagnosis to Allo-SCT was 60 months (range 8 months-21yrs). The most common forms of BMT administered were Matched Unrelated Donor (n=12) and Sibling-Allogenic transplantations (n=8). Following BMT, 54.5% of the cohort suffered from graft versus host disease (GvHD) and 22.7% received an additional donor lymphocyte infusion (DLI). To date, across the cohort of 22 patients, 21/22 (95.5%) had a response. 11 (50.0%) patients relapsed typically with low grade disease. This was managed with DLIs and/or skin directed therapy. The overall survival rate was 60.0% at 3 yrs and 55.6% at 5 yrs. Current patient status includes 1 PR and 10 CR (11 patients). 4 patients died from CTCL including the non responder. Other deaths included GvHD n=3, PE n=1, sepsis n=1, sarcoma n=1 and 1 cardiovascular event.

Conclusions
AlloSCT offers advanced stage CTCL patients a better survival, achieving responses in 95.5%. 45.5% remain in CR at median follow up of 8.3 yrs suggesting this may be curative. The treatment carries significant risks, such as GvHD, which affected 54.5% of patients and resulted in 3 transplant-related mortalities. This highlights the need for careful patient selection and management to reduce complications. AlloSCT doesn't offer all patients a cure but may modify the disease and those relapsing typically have low grade CTCL. AlloSCT is a viable treatment option for improving outcomes in advanced CTCL.

A-119

CD30 expression on mast cells in cutaneous mastocytosis as a potential therapeutic target

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Background
The spectrum of mastocytosis includes the purely cutaneous form with an excellent prognosis, systemic forms and a mast cell sarcoma. CD30, which is not expressed by normal mast cells, can used as an additional diagnostic criterion. This aberrant expression was first described in systemic forms of mastocytosis, particularly using bone marrow biopsies[2] and has been recently reported in cutaneous forms.
CD30 belongs to the TNF-R (tumor necrosis factor receptor) superfamily and can activate various signalling pathways, including the NF-kB pathway. Its activation via CD30 on Hodgkin-Reed-Sternberg cells is important for the growth and survival of Hodgkin's lymphoma cells. CD30 has become an important therapeutic target for cutaneous and systemic lymphomas. Specific anti-CD30 antibodies (e.g. Brentuximab Vedotin (BV)) can bind to tumour cells and induce cell death by liberation of a cytotoxic drug. Initial studies on systemic mastocytosis suggest that the effect of BV is related to the subcellular localization of CD30. A therapeutic effect was achieved particularly in cases with superficial / membranous localization of CD30.

Methods
We performed a retrospective multicentre study using 147 formalin-fixed paraffin-embedded and (immune-) histochemical stained skin biopsies from 143 patients with cutaneous mast cell infiltrates. The density, distribution and frequency as well as the subcellular CD30 expression and the presence of eosinophils were examined. Existing clinical information was correlated.

Results
All biopsies showed CD30 expression (cut-off: >/=1%), with cytoplasmic staining noted in 99%. Membrane staining was detected in 62% of cases and was mostly combined with cytoplasmic staining. Membranous CD30 expression was seen more frequently in cases with a higher mast cell density and higher overall CD30 expression rate. Eosinophils were detected in 58% of the samples.

Conclusions
The results suggest that therapy with BV could be effective due to the high and often membranous CD30 expression on mast cells in cutaneous mastocytosis.

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A-273

Clinician Practice Patterns and Recommendations for Bone Marrow Biopsy in Cutaneous T-Cell Lymphoma

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Background
Consensus on the standard use of bone marrow (BM) biopsies cutaneous T-cell lymphoma (CTCL) is lacking.[1][2] Information on frequency of BM involvement at different disease stages is also limited. This study evaluates experts' opinions on BM biopsies for diagnosing, staging, and managing CTCL and explores the implications of histologic findings.

Methods
In 2024, dermatologists, hematologists, oncologists, dermatopathologists, and hematopathologists from the U.S. and Europe participated in a survey on their CTCL practices, focusing on the role of BM biopsies in diagnosis, staging, and prognosis. Hematopathologists answered tailored questions on histopathologic findings. Descriptive statistics were calculated for demographics, flow cytometry, and IHC marker significance. Secondary analysis assessed differences based on respondents' years in practice, specialty, location, and practice setting.

Results
Sixty-six specialists completed the general survey, while 37 hematopathologists completed a tailored survey. Respondents were 44% male and 56% female, with the 38% having 10-19 years of practice and 84% working in academic hospitals. Among general survey respondents, 64% rarely recommended bone marrow biopsies, though 87.5% did so for suspected MF/SS patients with potential hematologic malignancies. Conversely, 37.5% of hematopathologists recommended BM biopsies in select cases, often for differential diagnosis of other T-cell lymphomas.
Dermatologists most often recommend BM biopsy in instances of B2 blood involvement (21.6%), while hematopathologists favored them in cases of large cell transformation (16.7%). When performed, 82% reported no patient upstaging in over 75% of cases and 65% of general respondents stated management rarely changed based on biopsy results. Additionally, 29% never recommended repeat biopsies, whereas 36% recommended them in preparation for bone marrow transplants or clinical trial enrollment.

Conclusions
Most physicians treating suspected MF/SS patients do not recommend BM biopsies for CTCL diagnosis but find them valuable for assessing other hematologic malignancies. The use of various markers on flow cytometry and IHC was assessed, addressing their significance in diagnosis and prognosis. Without RCTs for guidance, this survey reflects expert practices, differences between specialties and practice settings, and highlights gaps in the literature, paving the way for consensus guidelines.
References:

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A-253

Functional characterization of SAMDH1 in Cutaneous T-cell lymphoma

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Background
Currently, only a limited number of patients with Cutaneous T-cell Lymphoma (CTCL) receive curative treatment, highlighting an urgent need to identify new therapeutic targets and develop novel strategies. SAMHD1, a protein crucial in nucleotide metabolism and innate immune responses, significantly impacts the tumor immune microenvironment, influencing inflammatory reactions such as macrophage polarization and NK cell infiltration. Studies have demonstrated that SAMHD1 expression levels often are low in CTCL patients and vary across different clinical stages. indicating the potential importance of SAMHD1 in the development and progression of CTCL. However, the exact functional roles of SAMHD1 in CTCL are not yet fully understood. This study aims to assess the impact of SAMHD1 in CTCL and within the immune tumor microenvironment, to identify mechanisms with potential therapeutic implications for CTCL.

Methods
For this purpose, to probe the functional roles of SAMHD1 in MF/SS, we knocked out SAMHD1 in HUT78 (SS) and Myla CD8+ (MF) cell s using CRISPR technology; To assess the activation of the cGAS-STING pathway which can be negatively regulated by SAMHD1, we quantified pSTING levels using immunoblotting, and examined a group of SAMHD1/STING-regulated genes through qPCR. Furthermore, the impact of SAMHD1 on macrophage polarization was studied using flow cytometry.

Results
The results demonstrated that the cGAS-STING pathway could be activated by cGAMP (a STING agonist) in CTCL cells. This activation led to the upregulation of gene expression associated with cGAS-STING. Additionally, we observed that supernatant from CTCL cells stimulated with cGAMP can induce monocyte differentiation into M1 and M2 macrophages, indicating the involvement of the cGAS-STING pathway in polarizing macrophages in the CTCL microenvironment. In comparing the conditioned medium from SAMHD1 WT and KO CTCL cells, we observed that the deletion of SAMHD1 led to M1\M2 macrophages radio changes in PMA-activated THP1 cells.

Conclusions
These findings highlight the importance of the cGAS-STING pathway and SAMHD1 in controlling macrophage differentiation within the CTCL microenvironment. Further research into the interaction between the cGAS-STING pathway and SAMHD1 in the regulation of macrophages may lead to innovative therapeutic strategies to benefit CTCL patients.

A-216

Identification of subgroups of early-stage mycosis fungoides patients with increased itch and impaired quality of life

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Background
Mycosis fungoides (MF), Sézary syndrome (SS) and other cutaneous T-cell lymphomas (CTCLs) can have a severe impact on quality of life (QoL) and itch, but early MF is insufficiently investigated despite representing most patients. This study investigated associations between QoL/itch/depressive symptoms and clinical phenotypes, lifestyle factors as well as education in CTCL with particular focus on early MF-stages.

Methods
Patients were included from a single center during routine dermatological care. The primary outcomes included Dermatology Life Quality Index (DLQI), EuroQoL 5D (EQ-5D) index, Montgomery-Åsberg Depression Rating Scale – Self report (MADRS-S), and itch measured with a visual analogue scale (VAS-itch).

Results
In the total CTCL cohort (n=76), median EQ-5D index was impaired in female vs male patients (0.73 vs 0.85, p = 0.040). Among early MF patients (n=58), increased disease activity correlated with impaired DLQI (r = 0.413, p = 0.0014) and EQ-5D index (r = -0.317, p = 0.0161). Early MF patients with plaques vs only patches reported impaired EQ-5D index (median 0.725 vs 0.848, p = 0.0032) and increased itch (median VAS 3.27 vs 0.43, p = 0.0006). MF patients with stage IB vs IA reported impaired DLQI (median 5.00 vs 1.00, p = 0.0006), impaired EQ-5D (median 0.725 vs 0.848, p = 0.0440) and increased itch (median VAS 3.37 vs 0.54, p = 0.0487). In MF/SS patients, the median mSWAT score was lower in patients with higher education (> 12 vs ≤ 12 years, p = 0.0066). In the total CTCL cohort, greater BMI correlated with higher EQ-5D index scores in males (r = 0.46, p = 0.0065), but not in females or with other primary outcomes.

Conclusions
Although early MF patients reported generally a mild impact on QoL, this study highlights the need for disease management optimization for subgroups of early MF patients, including those with plaques, stage IB and higher disease activity.

A-240

Mogamulizumab-Associated Rash in Patients with Mycosis Fungoides or Sezary Syndrome: A Real-World Analysis

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Background
Mogamulizumab (Moga), a monoclonal antibody against the CCR4 chemokine receptor, has been approved for treatment of mycosis fungoides (MF) and Sezary syndrome (SS). Mogamulizumab-associated rash (MAR) is a well-known adverse event associated with Moga. However, MAR has been tied to better disease outcomes in MF/SS patients. This study aims to summarize our real-world experience with MF/SS patients on Moga who developed MAR versus those that did not.

Methods
We identified 20 patients with MF/SS on Moga at our institution and compared the differences in clinical characteristics and outcomes between patients with and without MAR.

Results
The median age prior to Moga initiation was 70.5 years and the male to female sex ratio was 1.9:1. All patients except two had advanced-stage disease prior to Moga initiation. Out of 20 patients, 10 patients had MAR confirmed on biopsy. There was no difference in overall survival between patients with and without MAR (p=0.634). Patients with MAR had a significant reduction in their CD4+CD26- Sezary cell count from time of Moga initiation to time of best response assessment when compared to those without MAR (MAR p-value=0.03; No MAR p- value: 0.34). In addition, a complete or partial global response was more commonly observed in patients with MAR (MAR: 70% vs No MAR: 30%). Overall, the median duration of response was longer in patients with MAR when compared to those without MAR (8 months vs 4 months; p-value: 0.012).

Conclusions
Based on our preliminary results, MAR seems to be a positive prognostic indicator in patients with MF/SS. Additionally, analysis of variables including pathology will be presented at the meeting.

A-230

Overlap: mycosis fungoides / Sezary syndrome and inflammatory dermatosis, a case series.

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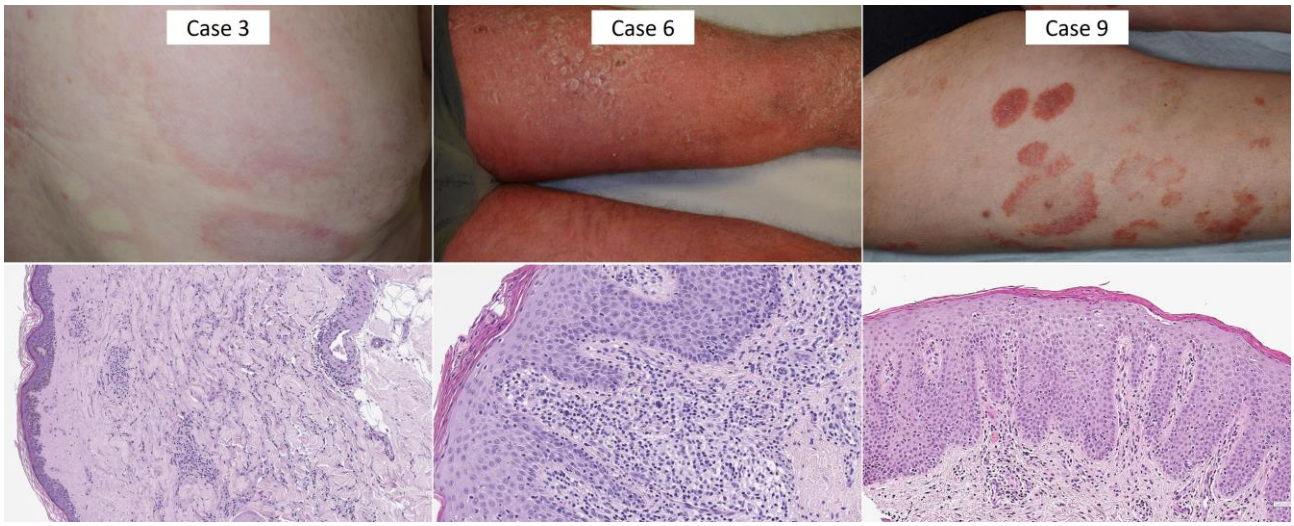
Background
To some extent, mycosis fungoides (MF), Sezary syndrome (SS) and inflammatory skin diseases (ISD) share their biology, as being mostly driven by skin homing T-cells, which reflects on overlapping clinic-pathologic features.

Methods
Series of patients with ambiguous/overlap features between ISD and MF/SS, routinely diagnosed at a single Institution. *TCRG* clonality assessed according to BIOMED-2 guidelines. Nosologic ambiguity was challenged at clinic-pathologic correlation. Definition of the ISD profile was based on the dominant ISD-like picture, comprising pattern of acanthosis, spongiosis and inflammatory background, exceeding the common histologic traits of MF/SS.

Results
Major presenting features of 11 patients (M/F, 7/4; median age 64y): erythematous/keratotic plaques (6/11), mostly as multiple lesions in the trunk and limbs, and erythroderma (5/11), over a variable clinical course (0.5-31 yrs). Histology showed an eczematous/spongiotic profile in 7 cases, psoriasis or localized scleroderma (LS) in 2 cases each. Mayor clues to lymphoma diagnosis, mostly MF (10/11), with a single psoriasis/SS, included cytologic atypia (10/11), phenotypic aberration (9/11), epidermotropism (10/11), eccrinotropism (2/11) and density of the dermal infiltrate.
TCRG proved monoclonal in all cases, with evidence of clonal identity at different sites and/or different timepoints in 10/11 cases.
Three cases (2 eczema/MF, 1 LS/MF overlap) experienced MF progression, 1 eczema/MF case after cyclosporine administration, but followed by very good response to brentuximab; 1 eczema/MF patient died of septic complications.



Prototypic clinic-pathologic profiles

	Initial suspicion	Final diagnosis	Lesion type and distribution	Major clues to MF/SS diagnosis	Follow up (yrs), status
1	PSO	SS/PSO	Erythroderma, PPK, alopecia	Dense dermal infiltrate, SS-type cells; sequential *TCRG* assessment	0.5, lost
2	MF	MF/SD	Patches	Epidermotropism, antigen loss	32, AWD
3	LS	MF/LS	Erythematous patches Ulcerated plaques at transformation	Dermal lymphocyte density, pleomorphism at transformation; sequential *TCRG* assessment	11, tMF, AWD
4	PSO	MF/E	Erythroderma	Lymphocyte atypia, antigen loss; sequential *TCRG* assessment	0.5, AWD
5	LS	MF/LS	Erythematous plaques	Epidermotropism, CD7-/CD8+ phenotype	0.5, AWD
6	PSO	MF/SD	Erythroderma, keratotic plaques Nodules at transformation	Dermal lymphocyte density and atypia; sequential *TCRG* assessment	29, tMF, AWD
7	PSO	MF/E	Erythroderma, keratotic plaques	Lymphocyte atypia, epidermotropism and eccrine involvement; sequential *TCRG* assessment	31, tMF, DUC
8	AD/E	MF/SD	Erythroderma, keratotic plaques	Lymphocyte atypia, epidermotropism and eccrine involvement, antigen loss; sequential *TCRG* assessment	4, AWD
9	PSO	MF/PSO	Erythematous plaques	Epidermotropism, antigen loss; sequential *TCRG* assessment	8, AWD
10	AD/E	MF/SD	Erythematous plaques	Lymphocyte atypia, epidermotropism and adnexal involvement; sequential *TCRG* assessment	5, AWD
11	MF	MF/E	Erythematous plaques	Lymphocyte atypia, epidermotropism	25, AWD

Legend: AD, atopic dermatitis; AWD, alive with disease; DUC, died of unrelated cause; E, eczema; LS, localized scleroderma; MF, mycosis fungoides; PPK, palmo-plantar keratosis; PSO, psoriasis; SD, spongiotic dermatitis; SS, Sezary syndrome; tMF, transformed mycosis fungoides

Clinic-pathologic features of the patients

Conclusions

Whether the ISD-like manifestations depend on the immunologic function of the neoplastic cells, predispose to neoplasm or act as independent bystanders, possibly favoring the homing of the MF/SS clones, is a matter of debate.

The diagnostic conundrum requires close monitoring of the patient, multidisciplinary discussion and careful assessment of histologic pattern and morphology and phenotype of the lymphocytes, in the puzzling setting of inflammation. *TRCG* clonality does not prove neoplasm, but clonal persistence at spaced sites and/or timepoints may support the diagnosis.

Therapies for MF/SS mostly aim at targeting the malignant cells, but do not address the ISD-like symptoms, which may benefit from a composite approach. On the contrary, with the notable exception of TNF-inhibitors, biologic therapies for ISD are acknowledged as carrying safe profiles.

A-185

Primary cutaneous follicule center lymphoma- differential diagnostic and prognostic aspects

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Background
Primary cutaneous follicule center lymphoma (PCFCL) is an indolent, localized disease of the neoplastic follicule centrum B-cells. Local relaps are common however, distant cutaneous spread and systemic progression are rare and these cases are difficult to differentiate from secundary cutaneous manifestation of nodal follicular lymphoma (nFL). Unlike the systemic disease, the genetic background of PCFCL is little explored.

Methods
39 cutaneous specimens from 30 patients with PCFCL diagnosed and followed up at Semmelweis University were studied. Collection of clinical datalinical data, histopathological revision, cytogenetic studies by fluorescent in situ hybridization and shallow genom sequencing (lcWGS) was done and was compared to 64 cases of nodal follicular lymphoma (nFL) samples.

Results
97% of the PCFCL patients (21 female, 9 male) are alive, 70% are in complete remission after 52 months median follow up time. Progression was detected in 11 patients: distant cutaneous spread was found in 7, systemic involvement in 4 cases. 60% of the lesions occured at the head and neck area and these cases more often remained localized (p=0,023). Although the copy number profile of PCFCL was similar to that of nFL, PCFCL lacked amplifications of 18q (p=0.018). Development of distant cutaneous spread was significantly associated with higher genomic instability, as well as the enrichment of 2p22.2-p15 amplification involving *REL* and *XPO1* (p=0.005), 3q23-q24 amplification (p=0.004), 6q16.1-q23.3 deletion (p=0.018), and 9p21.3 deletion covering *CDKN2A* and *CDKN2B* loci (p=0.014) in PCFCL. Analysis of sequential tumor samples in a case developing distant cutaneous spread, and a case showing nodal progression pointed to the acquisition of 2p amplification in the earliest common progenitor underlining its pivotal role in malignant transformation.

Conclusions
Based on our results, the copy number profile of PCFCL is only slightly different from that of nFL, with the notable exception of the scarcity of 18q amplifications including 18q21.33 which covers the *BCL2* locus. This further highlights its potential utility in differential diagnosis of PCFCL and secondary cutaneous infiltration of nFL. Our results point to higher genomic instability in patients developing distant disease spread. We further deciphered the role of 2p amplifications in the disease course of PCFCL, which could be an early prognostic marker in the future for the prediction of distant disease spread.

A-184

Primary cutaneous marginal zone Lymphoma or Lymphoproliferative disorder?Comparison of initial tumor, recurrence and outcome in 61 patients

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Background

Primary cutaneous marginal zone lymphoma (PCMZL) is classified either as a lymphoproliferative disorder (according to the International Consensus Classification, ICC[35653592]) or as an overt lymphoma (according to the WHO Classification of Hematopoietic and Lymphoid Tissues, WHO-HAEM5[35732829]). To explore arguments in favor of PCMZL being characterized as an "exaggerated" immune response versus a true lymphoma, we analyzed data from recurrent PCMZL patients in the French Study Group of Cutaneous Lymphoma (GFELC) database.

Methods

We included patients with at least one skin recurrence during follow-up to compare histology, phenotype (light chain restriction, Ig and IRTA1 expression), and clonality status at diagnosis and recurrence. Comparisons were made according to the location of recurrence (local, locoregional, or distal) and patient outcomes.

Results

We included 61 patients (average age 52 years). Initial lesions were mostly on the trunk (48%) and classified as T1 (70%). The time to first recurrence was 20 months for distant, 29.5 months for locoregional, and 37 months for local recurrences. Light chain restriction did not significantly differ between local/locoregional and distant recurrences (p=0.064). A similar B-cell clone was identified in most local and locoregional recurrences (23/26), but different profiles were observed for all distant recurrences (5/5) (p=0.0003)

Recurrence location	Nb of patients	Initial T stage (TNM) /nb of cases	Median age (y) at diagnosis	Sex (M/F)	Initial location*	Recurrence free survival (months)	comparison of light chain restriction**	comparison of B-cell clonality **	Mean follow-up (months)
Local	21	T1/17	52 (20-90)	8M/9F	T(6), UE (8), HN(2), LE(1)	20	8S, 4P, 5PC	8S,4P,3PC,1NC,1D	59
		T2/3	48(32-63)	3M	T(3)	42	1S,2PC	2S,1NC	77
		T3/1	50	1M	T(1)	48	1S	1NC	141
Locoregional	21	T1/14	52(21-71)	9M/5F	T(6), HN(4), UE (3), LE(1)	20	7S,4P,3PC	8S,1P, 4PC,1D	75
		T2/4	62(32-84)	2M/2F	T(2), HN(2)	39	1P,1PC, 1NC,1D	4S	100
		T3/3	41 (29-50)	2M/1F	T(1), HN(1), UE (1)	28	1S, 1P, 1PC	1S, 1PC, 1D	69
Distant	19	T1/12	53(38-64)	7M/5F	T(6), UE (3), HN(2), LE(1)	16	2S,5P,3PC,2D	1P,8PC, 3D	88
		T2/5	46(28-76)	1M/4F	UE(3), T(1), HN(1),	15	2S,3PC	1P,2PC, 1NC,1D	88
		T3/2	35(28-42)	2M	LE(1), UE+T (1)	29	2S (1D**)	1S(D**), 1P	77

Patients clinical features and comparison of light chain and clonality between initial tumor and recurrence.

. No case expressed immune receptor translocation-associated protein 1 (IRTA1). Fifty-eight patients had heavy chain (IgG/IgG4) class-switched PCMZL, while three had IgM+/IgD- PCMZL.

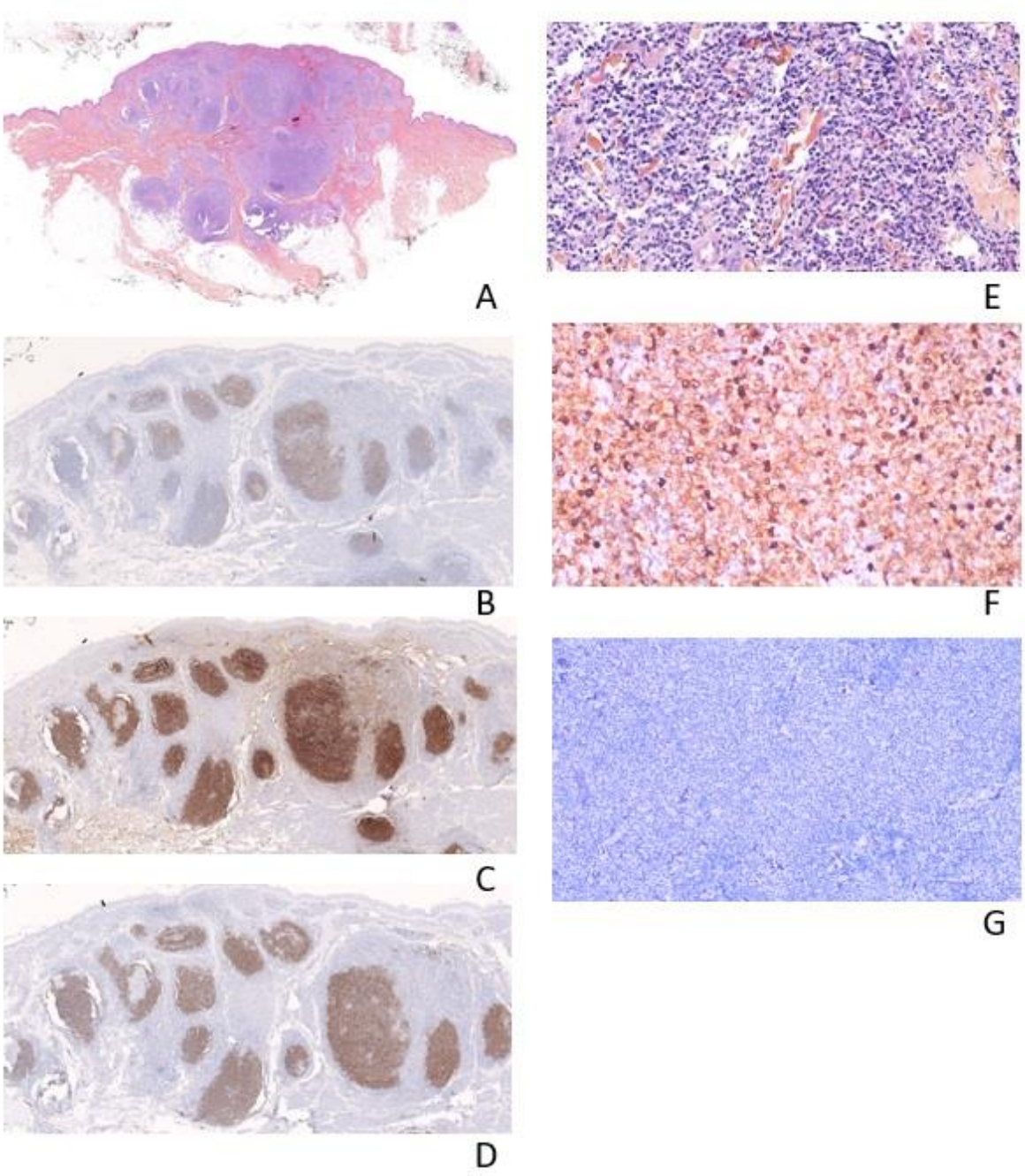

IMAGE01: A to D : IgG class switched PCMZL (A nodular and diffuse lymphoproliferation, HES staining ; B CD21 ; C IgM ; D IgD). E to F : IgM+ PCMZL (E diffuse lymphoproliferation, HES staining ; F IgM ; G IgD)
All IgM+ cases transformed into diffuse large B-cell lymphoma (DLBCL) with extracutaneous spread.

Conclusions

The statistically significant difference in B-cell rearrangement between distant class-switched recurrent PCMZL and locoregional recurrences suggests different antigen stimulation processes rather than a lymphoma originating from a single transformed lymphoid cell. Assessing the Ig phenotype (IgM in parallel with IgD/CD21) at the initial PCMZL diagnosis seems useful for identifying an IgM+(IgD-) PCMZL, which may be more aggressive, from class-switched PCMZL, as proposed by the ICC classification.
References:

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A-252

Prognosis about survival in primary cutaneous B cell lymphoma: a monocentric study of clinical characteristics of 98 patients

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Background
CBCL are chronic diseases associated with multiple relapses. Currently, evidence about prognostic factors about overall and relapse-free survival (OS; RFS) is lacking.

Methods
In this monocentric study, clinical data were retrospectively extracted. After descriptive statistics, univariate and multivariate analyses of clinical characteristics and RFS were performed. One endpoint was time to next treatment (TTNT), which reflects clinical benefit and patient-centered perspectives of treatments.

Results
In total, 98 patients with CBCL were identified: 46 follicle center lymphomas (FCL), 41 marginal zone lymphoproliferative disorders (MZLPD) and 11 diffuse large B-cell lymphomas, leg type (DLBCL-LT).

Elevated LDH levels were found in 8 of 32 (25 %), 1 of 19 (5 %) and 5 of 6 (83 %) patients with FCL, MZLPD and DLBCL-LT, respectively ($p < .001$).
The 5-year OS was 100 %, 100 % and 55 % in FCL, MZLPD and DLBCL-LT, respectively. The 5-year RFS was 71 %, 87 % and 23 % in FCL, MZLPD and DLBCL-LT, respectively.
4 DLBCL-LT patients received radiotherapy with a mean TTNT of 13 months (SD: 10 months).

In the entire cohort, univariate analysis showed that the 5-year RFS was 81 % and 64 % in patients with upper body involvement (above the umbilical level) and without upper body involvement at initial diagnosis, respectively. After 10 years, RFS was 56 % and 24 % ($p = .076$).
In patients with FCL and MZLPD, univariate analysis illustrated that the 5-year RFS was 86 % and 54 % in patients without leg involvement and with leg involvement at initial diagnosis, respectively ($p = .052$).

In multivariate analysis, leg involvement at initial diagnosis, diagnosis of a FCL and comorbidities were statistically significant of the dependent variable TTNT of the first-line treatment.
Topical steroids as first-line treatment, trunk and lower body involvement (below the umbilical level) at initial diagnosis and secondary malignancies had a statistically significant impact on the number of relapses.

Conclusions
This study analyzed patient survival in a cohort with a large sample size identifying potential prognostic factors which might be indicative of patients' disease course. To our knowledge, this study is the first to have ever applied the endpoint TTNT in a multivariate analysis in CBCL. Future studies should focus on other, e.g. histological, prognostic factors in multicentric cohorts.

A-288

Retrospective Clinicopathological Comparative Study between Hypopigmented Mycosis Fungoides and Pityriasis Lichenoides Chronica

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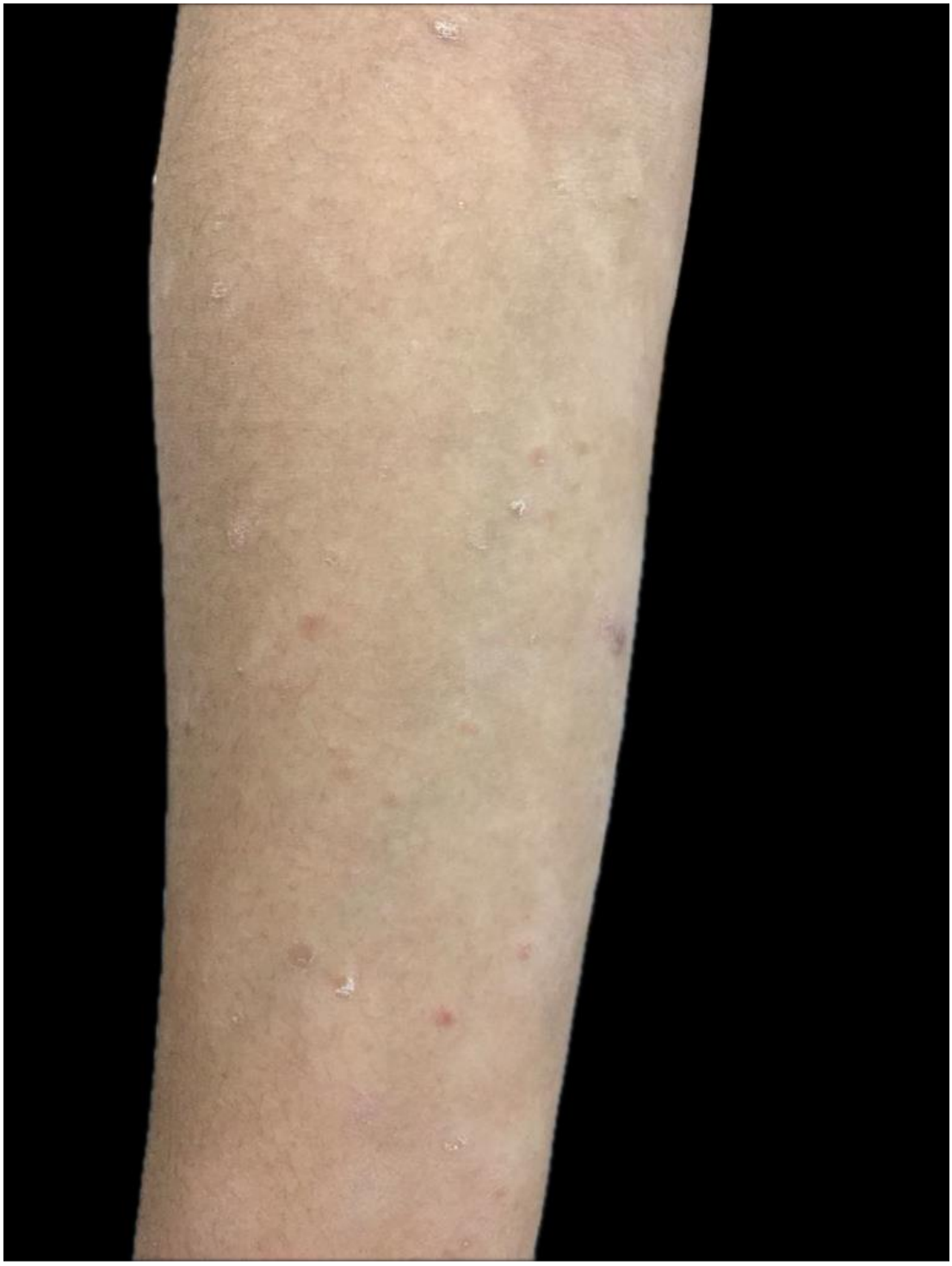
Background
Pityriasis lichenoides chronica (PLC) is a reactive inflammatory dermatosis that often manifests with hypopigmentation in individuals with darker skin tones. This clinical presentation can be challenging to diagnose, as cases of hypopigmented mycosis fungoides (HMF) can have similar clinical and histopathological features.[1] A relatively recent term, atypical pityriasis lichenoides, describes cases that exhibit overlapping features of PLC, MF, and lymphomatoid papulosis.[2] This overlapping and unclear relationship between MF and PLC requires additional investigation, particularly for cases that exhibit hypopigmentation.

Methods
A retrospective clinico-histopathological analysis was conducted on archived cases of HMF and PLC seen at the dermatology clinic of Ain Shams University between 2018 - 2022. The clinical data were obtained from the medical records, including age, sex, duration, age

of onset, type of lesions, and anatomical distribution of lesions. Two independent dermatopathologists examined the H&E-stained slides. The dermatopathologists recorded the following findings: the degree/pattern of epidermotropism, lymphocyte tagging, folliculotropism, changes in the stratum corneum, spongiosis, acanthosis, the size, site, and degree of atypia in lymphocytes, haloed lymphocytes, Pautrier's microabscess, RBC extravasation, vacuolar degeneration, necrotic keratinocytes, and papillary wiry fibroplasia.

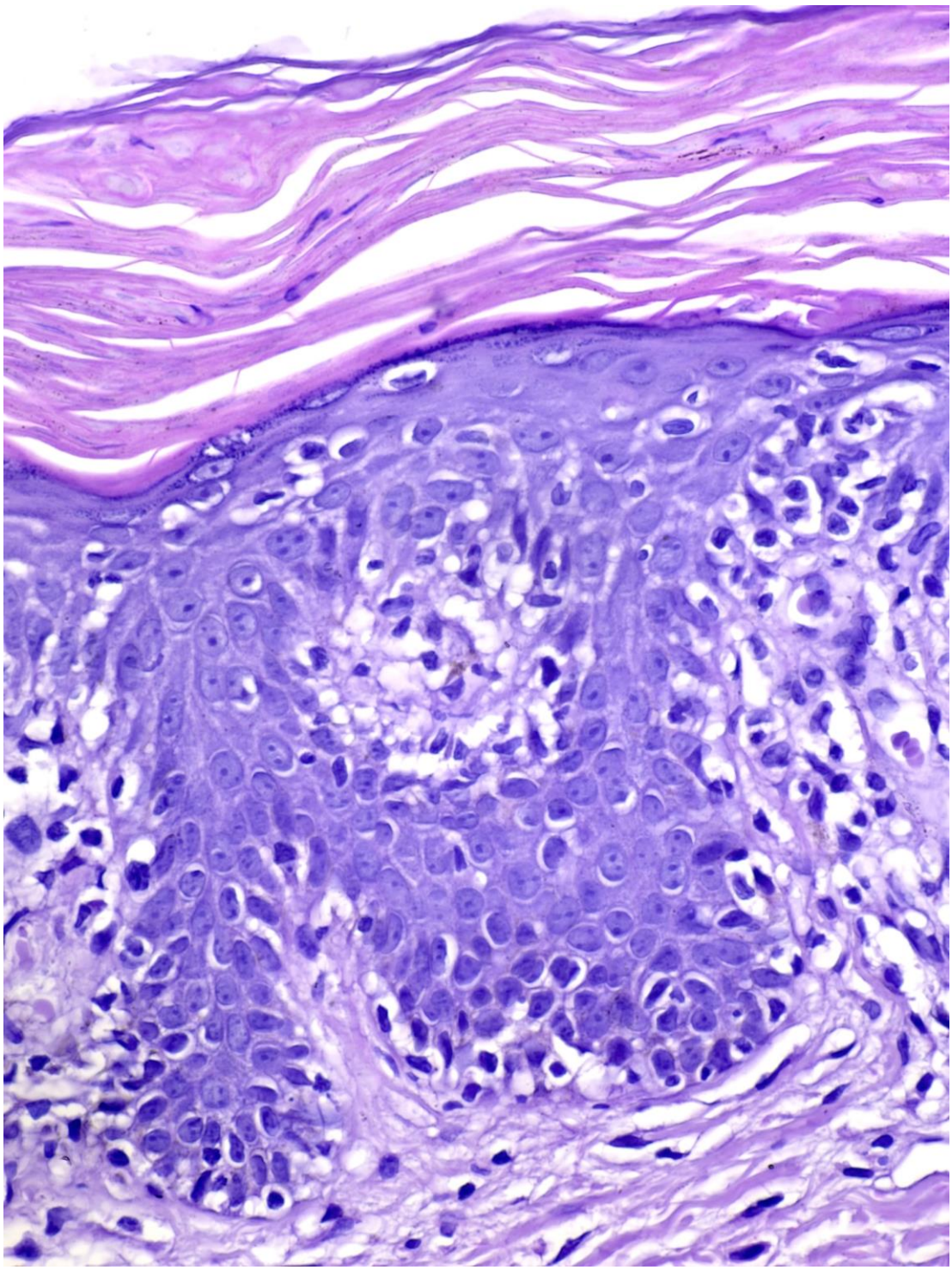
Results

The study involved 25 patients with HMF and 17 patients with PLC. A group of 12 patients with atypical PLC displayed features that overlapped between HMF and PLC. Patients with atypical PLC often exhibit papules and hypopigmented patches.



A case of atypical PLC in a 12 Y female patient presented with generalized papules and hypopigmented patches of 1 year duration.

The presence of diffuse/ moderate epidermotropism, with both basilar and pagetoid epidermotropism patterns, was observed in cases of HMF and atypical PLC. Significant presence of lymphocyte tagging, haloed lymphocytes, and atypia of the epidermal lymphocytes were observed in patients with HMF and atypical PLC. There was a significant presence of hyper/parakeratosis in both PLC and atypical PLC. RBC extravasation was observed in patients with atypical PLC.



Pathology shows hyper/parakeratosis, diffuse/moderate epidermotropism with basilar tagging of mildly atypical lymphocytes and mild erythrocyte extravasation.
In patients with HMF, there was a noticeable presence of fibroplasia.

Conclusions

Atypical PLC patients exhibit papules and hypopigmented patches and histopathologic overlap between PLC and HMF, indicating that this distinctive clinical presentation is a precursor to HMF. Further research is required to more accurately characterize and identify the prognosis of these patients.

References:

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A-127

Sézary Syndrome in West Sweden: A Comprehensive Registry- Based Retrospective Analysis on Epidemiology, Clinical Features, and Treatment Patterns

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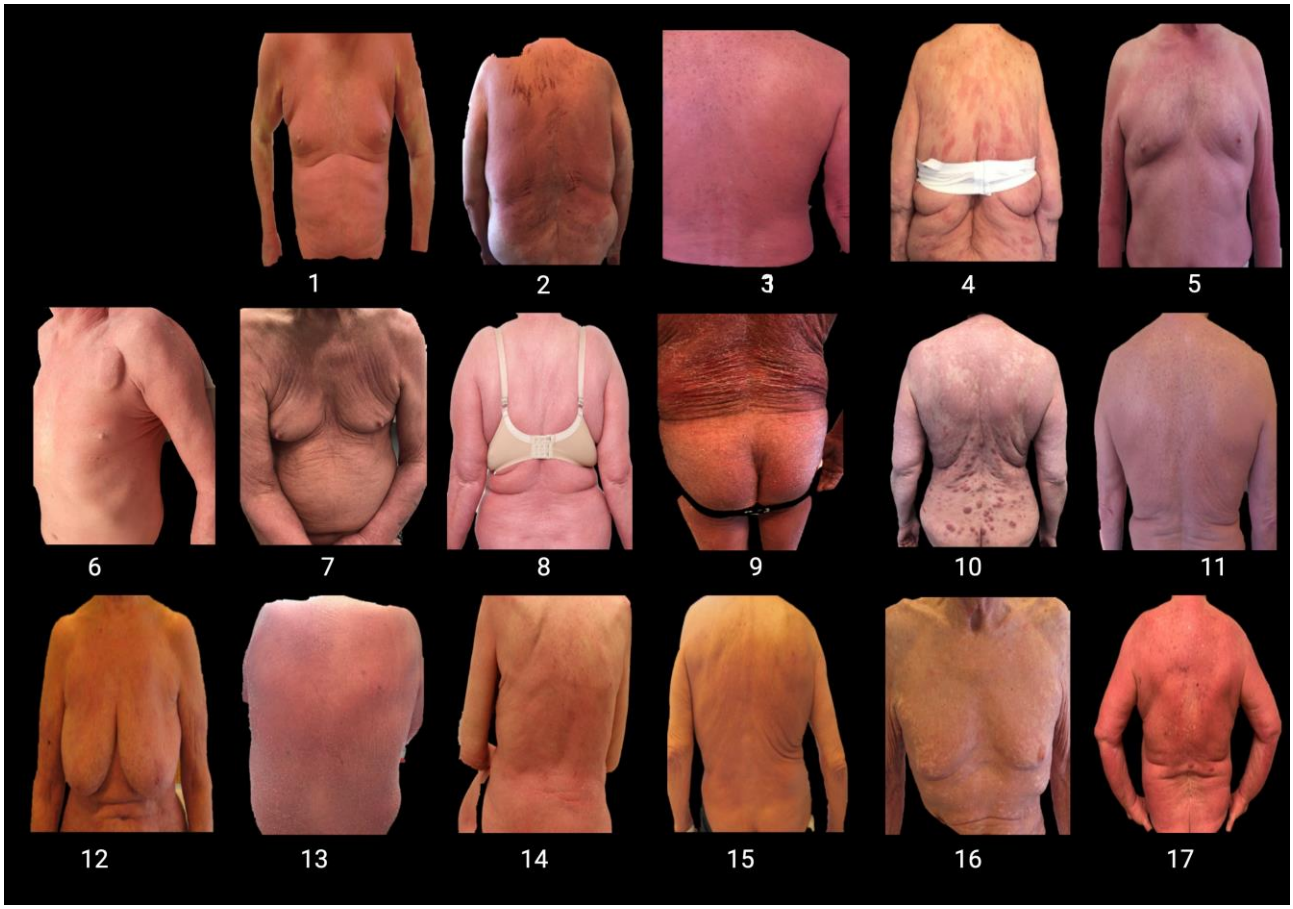
Background

Sézary syndrome is a rare variant of primary cutaneous T-cell lymphoma with a poor prognosis and no cure despite various treatment options. Enhanced descriptive research is urgently needed to improve the understanding and treatment of Sézary syndrome. This study aimed to outline demographic characteristics, investigate clinical, histopathological, and molecular findings, and assess treatment effectiveness, focusing on time to next treatment (TTNT) and disease progression.

Methods

Data for this retrospective study on 17 Sézary syndrome patients was obtained from the Primary Cutaneous Lymphoma Register in West Sweden, covering the period from 2012 to 2024.



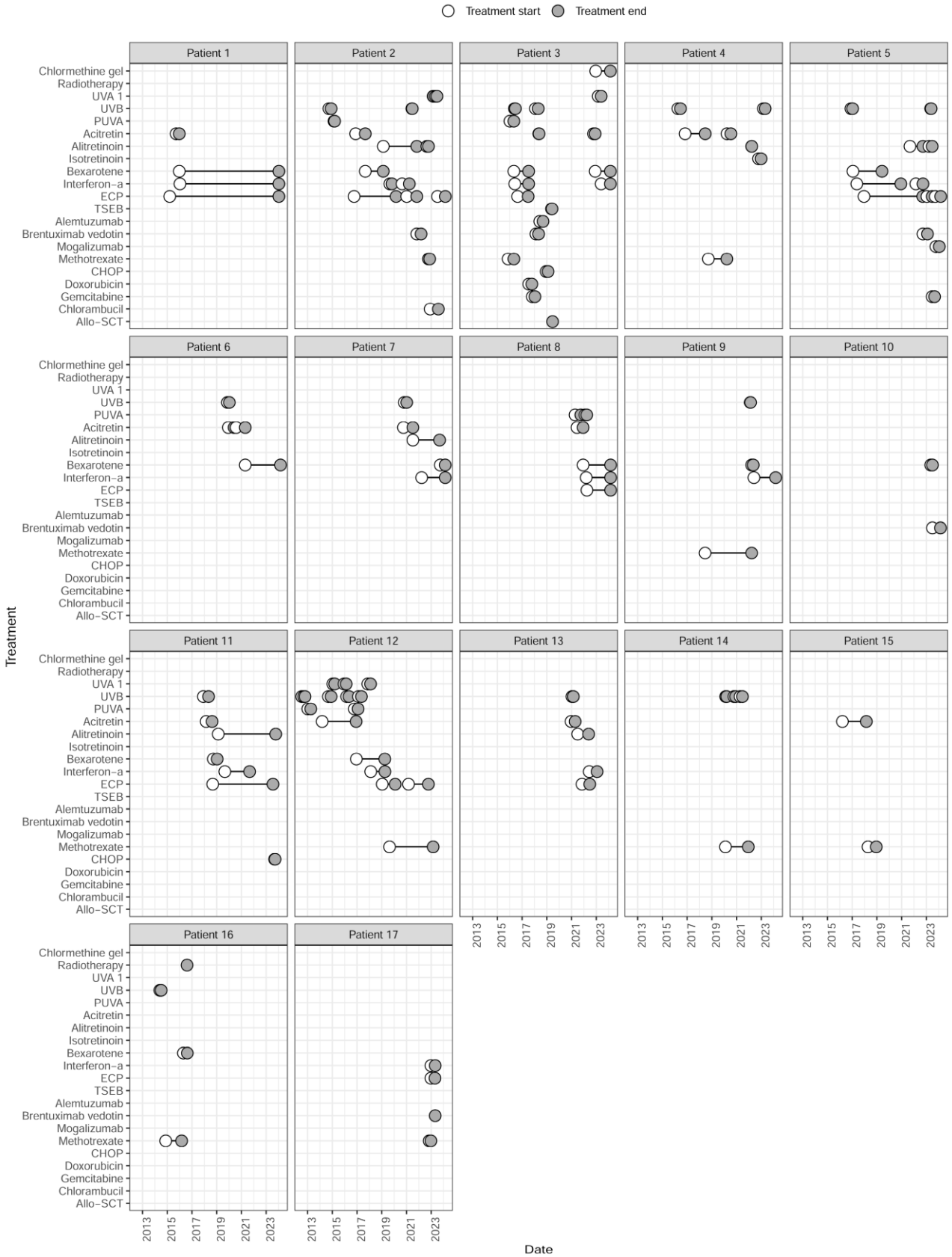
Photographs representing seventeen unique patients (1-17) diagnosed with Sézary syndrome.

Results

The findings revealed that only 35% of patients presented with the classic triad of symptoms at diagnosis, suggesting a need for personalized diagnostic approaches.

The median survival of 2.1 years reflects the aggressive nature of Sézary syndrome.

No significant difference in TTNT was found among different treatment lines.



Treatments received by 17 patients with Sézary syndrome between 2012 and 2024, including former and current regimens after B2 involvement in blood.

Various treatments were utilized, but combination therapies generally offered better median survival than single treatments. Specifically, triple therapy of retinoids, interferon alpha, and extracorporeal photopheresis (ECP) had the longest median time to the next treatment at 14.1 months. Early ECP initiation did not improve outcomes.

Conclusions
This study highlights the complexity of Sézary syndrome and the significance of combination therapy for better outcomes and underscores the need for future research to identify optimal treatment approaches.

A-257

Small Medium Pleomorphic T cell lymphoproliferative disorder – 20 years of experience from a specialist centre

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Background
Small medium pleomorphic T cell lymphoproliferative disorder (SM-PTLPD) is a rare subtype of lymphoproliferative disease. It has been established that this disease behaves in an indolent fashion; the treatment, investigations and follow up protocol remain up for debate. Using our large patient population, we aimed to establish the utility of investigations, efficacy of management and risk of relapse.

Methods
We performed a retrospective analysis of patients diagnosed at our institution with small medium pleomorphic T-cell lymphoproliferative disorder between 2005 and 2024. As well as overall survival and progression free survival, we analysed response to treatment and risk factors for relapse.

Results
86 patients (39F, 47M), mean age 60.82, were diagnosed with small medium T cell lymphoproliferative disorder. The vast majority (85%) presented with a solitary lesion, most often affecting the head and neck (58%). The median follow up was 3.1 years (1.2 - 4.9 IQR). 81 out of 86 patients had imaging at initial work up (CTAP/PET: 44/37) which confirmed no evidence of nodal or systemic involvement in 100% of cases and indeed no patient went on to develop systemic involvement during follow up. 47 patients had a diagnostic biopsy and 39 had a complete excision. Of those undergoing diagnostic biopsy, 16 patients had monitoring only. Of the remaining 31 patients, topical steroids were added for 20, 10 were treated with radiotherapy and one opted for no further monitoring nor management. 6 (12.8%) patients had relapse, 3 of which were in the radiotherapy group. For those who had an excision biopsy, 33 had monitoring only and 6 had radiotherapy. Four relapsed (10.3%) with 2 in the monitoring group and 2 in the radiotherapy group. The radiotherapy dose used was 8Gy in 2 fractions in the majority of patients, other schedules used were 30Gy in 15 fractions, 15Gy in 5 fractions. Patients initially presenting with multiple lesions (9 out of 13) were more likely to relapse compared to solitary lesions (1 of 73) ($p<0.001$). All patients are in CR at last follow up except 1. 3 patients died during follow up from unrelated illnesses. The mean and median progression free survival is 3.2 and 3.3 years respectively.
Conclusions
SMPTCLPD carries an excellent prognosis, especially for those presenting with a solitary lesion. The overall relapse rate was 12% following initial monitoring or treatment. Staging scans may no longer be required for these patients.

A-221

The effect of Anthracycline treatment on primary cutaneous T-cell lymphoma cells

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Background
Anthracyclines are widely used in the treatment of various hematologic malignancies and solid tumors. Anthracyclines work through poisoning topomerase II which induce double stranded breaks (DSB) and chromatin damage by histone eviction. However, anthracyclines can cause severe side effects in patients, such as dose-dependent irreversible cardiotoxicity which is mainly attributed to induction of DSB. Aclarubicin (acla), is a chemically modified anthracycline that has been shown to evict histones but fails to induce DBS and consequently has a more favourable side effect profile.
Cutaneous T-cell Lymphomas (CTCL) are a rare group of extra-nodal mature T-cell-derived lymphomas originating in the skin of which mycosis fungiodes (MF) and Sézary syndrome (SS) are the most studied types. Several treatment modalities are available for early stage disease, however more advanced disease is difficult to treat and requires new therapeutic options.

Methods
6 CTCL patients were selected from the LUMC Dermatology out-patient clinic, these patients all had both normal and aberrant (T-cell) populations present in their blood at the time of the experiment. From peripheral blood CD4+ T cells were isolated and seeded in 96-well plates. Cells were treated for 2 hours with anthracyclines (Doxorubicin, Daunorubicin, Aclarubicin, DiMethyl-Doxorubicin) and the effect of treatment was assessed after 72 hours. The overall cell metabolism was evaluated by a CellTiter-Blue assay and the components of healthy, aberrant, and dead cells were assessed using spectral flow cytometry.

Results
Cells from each patient show decreased metabolic activity when treated with acla at 0,3 to 1 µM, while with other anthracyclines this was only seen at concentrations higher than 3 µM. The flow cytometry data showed that both normal and aberrant cells die from the same concentration of anthracycline treatment.

Conclusions
We found that aclarubicin has therapeutic activity against neoplastic cells in CTCL with therapeutic efficacy at lower concentrations than other anthracyclines. These findings suggest that acla could be an effective treatment in CTCL patients. Given the absence of cardiotoxic side effects of aclarubicine, this treatment warrants further investigation for CTCL patients.

A-207

Towards guidelines for clinical management of cutaneous lymphoproliferative disorders: an 2024 update

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Background
In recent classifications several low-grade malignant CTCL and CBCL have been reclassified as lymphoproliferative disorder (LPD). These include primary cutaneous CD4-positive small/medium T-cell LPD (PCSM-TCLPD), primary cutaneous acral CD8+ T-cell LPD (acral CD8+ TCLPD) and primary cutaneous marginal zone LPD (PCMZLPD). Survey among 30 cutaneous lymphoma centres on the effects of this new terminology on clinical management revealed considerable heterogeneity in clinical practise and emphasized the need to develop uniform guidelines for management and treatment of these disorders. In this presentation the current status of this project will be reported.

Methods
interin analysis

Results
Primary cutaneous CD4-positive small/medium T-cell LPD
PCSM-TCLPD is considered as a benign condition by 80% of the cutaneous lymphoma centres. Most centres agree that in typical cases staging is not required. Treatment should be non-aggressive. In most centres surgical excision is the first choice of treatment. After successful treatment or spontaneous complete remission a single control visit after 3-6 months suffices.

Primary cutaneous acral CD8+ T-cell LPD
This condition shows diffuse infiltrates of highly atypical clonal T-cells with an aberrant phenotype suggesting an aggressive lymphoma, although with a very indolent clinical behaviour. Interestingly, more than 50% of the centres suggests that this is a benign process. There is growing consensus that in typical cases staging is not required. Treatment be non-aggressive with surgical excision and radiotherapy as first choice of treatment. In view of the rarity and lack of long-term follow-up data a follow-up period of two years following successful treatment is advised. (90)

Primary cutaneous marginal zone lymphoma/LPD
PCMZL(PD) is still considered as a low-grade malignant lymphoma by 75% of the centres. There is discussion whether CT scans are still indicated, but final recommendations can only be made after evaluation of PCMZL with alleged nodal involvement during follow-up. Treatment is non-aggressive and personalized and depends on the presence of solitary or mutifocal skin lesions. Patients need to be monitored regularly as long as new lesions develop.

Conclusions
The results of this interim analysis form the basis for further discussions aimed to develop definite guidelines for the management and treatment of these cutaneous LPD.

A-147

Transcriptomic and Genomic Profiling as Diagnostic and Prognostic Markers in CTCL Patients with a History of Atopic Dermatitis

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Background
Chronic benign inflammatory skin diseases, such as atopic dermatitis (AD) and psoriasis, may precede or mimic cutaneous T-cell lymphoma (CTCL), obscuring diagnosis and delaying treatment. This study investigates the molecular and microenvironmental relationship between AD and CTCL to improve diagnostic accuracy and gain insights into CTCL development.

Methods
A retrospective analysis was conducted on patients diagnosed with Mycosis Fungoides (MF) and Sezary Syndrome (SS) with a history of AD before their MF/SS diagnosis, identified via our cutaneous lymphoma biorepository. Six full-thickness tissue samples were collected from three patients (2 MF, 1 SS), each providing two biopsies: one before CTCL diagnosis favoring spongiotic or psoriasiform dermatitis, and one confirming CTCL. These biopsies underwent spatial transcriptomic and genomic profiling using high-plex Xenium in-situ analysis.

Results
Patients had a median age of 65 years at CTCL diagnosis, including one patient with early-stage disease (IA-IIA) and two with late-stage disease (IIIA-IVA). The average time between AD and MF diagnosis was 37.3 months (SD ± 15.0). One patient had a history of dupilumab use for AD treatment before their MF diagnosis. Spatial transcriptomic profiling showed gene expression patterns linked to increased CD8+ T-cells, Th2 inflammation, and keratinocyte proliferation in pre-CTCL diagnosis biopsies. Increased expression of LCK, CXCR4, and PCDH7, genes related to T-cell receptor signaling, migration, and tumor development, were noted in biopsies pre- and post-CTCL diagnosis. Shared expression of oncogenesis-related genes, such as JAG1, TP63, and IGFBP3, were observed before and after CTCL diagnosis, suggesting tumorigenesis pathways.

Conclusions
The identification of key molecular and oncogenesis pathways in pre- and post-CTCL biopsies highlights potential targets for early intervention and therapeutic strategies. Four additional patients have been identified, and their samples are being analyzed to validate our findings. Next steps include quality control and normalization using Seurat, clustering and differential gene expression (DGE) analysis, and comparing specific tissue regions. This involves analyzing all pre-CTCL versus subsequent CTCL biopsies to identify biomarkers for early diagnosis and malignant transformation. Leveraging Xenium's profiling in larger cohorts and controls will offer novel insights into CTCL progression, potentially revealing new mechanisms and personalizing treatment.

QUALITY OF LIFE

A-105

A Retrospective comparison between Home and In-office NB-UVB Efficacy for patients with Mycosis Fungoides

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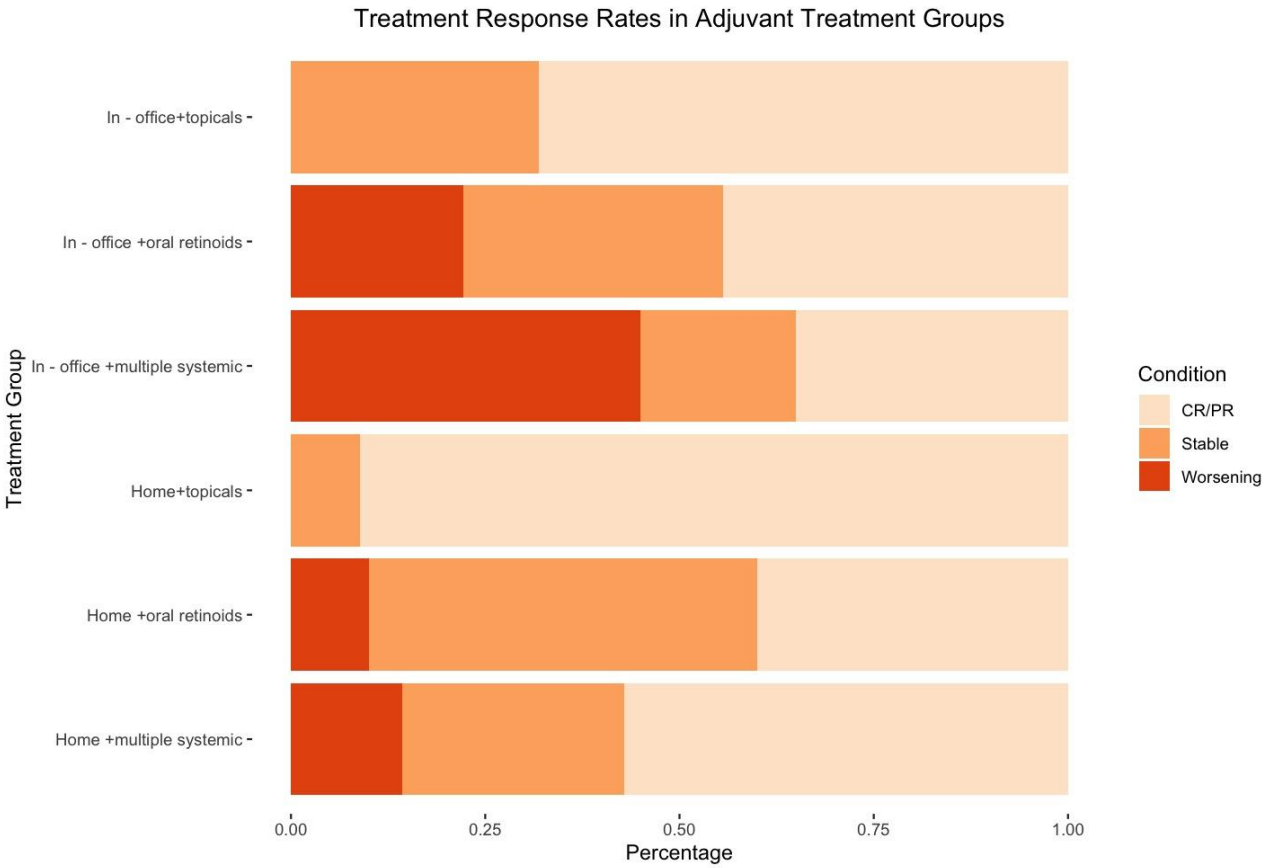
Background
[1]This study addresses the gap in research comparing the effectiveness between home and in-office narrowband ultraviolet B (NB-UVB) phototherapy for treatment of mycosis fungoides (MF). Elderly and disabled patients with this condition disproportionally lack access to home units due to insurance denial.[1]

Methods
A retrospective review included patients diagnosed with MF or Sezary syndrome who underwent either in-office or home UVB between 2016 and 2023. Patients were excluded if they were not diagnosed with MF or SS, not seen since initiating treatment, or not using NB-UVB phototherapy. Clinical characteristics were obtained from physician notes at clinic visits. Phototherapy treatment outcome was measured once the patient achieved complete response or reached their maximum tolerable dose of NBUVB. Treatment response was

obtained from clinic notes and was documented according to guidelines laid out by the EORTC, USCLC, and ISCL. Home unit coverage and reason for patient's lapse or discontinuation of treatment were also recorded. Statistical analyses were performed using SAS institute inc. (v.9.4) and R (v4.3.3). Significance was determined at the $p<0.05$ level.

Results



Treatment response rates between groups on adjuvant therapies. Full category titles are as follows: NB-UVB + topical steroids (Clobetasol, triamcinolone, etc.), NB-UVB + oral retinoids (acitretin), and NB- UVB + other systemic therapies (radiation, Brentuximab, IFN, etc.).

Characteristics	Home + topicals, N = 45	Home + Multiple Systemic, N = 35	Home + Oral retinoids, N = 10	In-office + topicals, N = 47=	In-office + Multiple Systemic, N = 20	In-office + Oral retinoids, N = 9
Age, years	55 (17.3)	61 (12.5)	47 (15.6)	62 (16.2)	69 (12.8)	66 (14.9)
Sex						
F	21 (47%)	18 (51%)	7 (70%)	28 (60%)	8 (40%)	4 (44%)
M	24 (53%)	17 (49%)	3 (30%)	19 (40%)	12 (60%)	5 (56%)
Stage at diagnosis						
IA	27 (60%)	8 (23%)	3 (30%)	31 (66%)	8 (40%)	4 (44%)
IB	17 (38%)	22 (63%)	6 (60%)	16 (34%)	5 (25%)	4 (44%)
IIA - IIB	0 (0%)	4 (11%)	1 (10%)	0 (0%)	4 (20%)	1 (11%)
III+	1 (2%)	1 (3%)	0 (0%)	0 (0%)	3 (15%)	0 (0%)

Summary characteristics between groups with adjuvant therapies. Mean (SD)

In our retrospective review, 90 patients used home NB-UVB, while 76 used in-office. No significant differences between sex, ethnicity, stage at diagnosis, and response to treatment were observed. There was no significant difference in response rates between home and in-office NB-UVB phototherapy ($P = 0.08$). Subgroup analysis based on adjuvant treatment revealed a significant difference in clinical response rates for patients using NB-UVB with topicals ($P = 0.006$) and NB-UVB with multiple systemic therapies ($P = 0.04$). 54 of the

in-office group were unable to switch to home treatment due to insurance denial or copay cost (71%). NB-UVB phototherapy treatments continued beyond our study for (84%,76) and (33%, 25) of the home group and in-office group, respectively. Financial and time constraints were the most common cause of treatment discontinuation for in-office patients (29%, 22).

Conclusions
The effectiveness of home NB-UVB treatment is comparable, if not superior, to in-office treatment, likely attributed to treatment ease in access and compliance.[2] Medicare and other health insurance companies should expand coverage to include home-based phototherapy for patients with MF, a potentially fatal cancer with a relative paucity of effective alternate therapies

References:

[1] Kim A, Insley A, West L, Woodworth Goff H. , (2021), Need for Expansion of Coverage for Narrowband UVB Phototherapy in Mycosis Fungoides and Sézary Syndrome, Am Health Drug Benefits. , 131-132, 14(4), https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8844638/
[2] Hum M, Kalia S, Gniadecki R. , (2019), Prescribing Home Narrowband UVB Phototherapy: A Review of Current Approaches, J Cutan Med Surg, 91-96, 23(1), https://pubmed.ncbi.nlm.nih.gov/30221998/

A-223

AI-assisted Evaluation of CD4/CD8-Ratio in Mycosis fungoides

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Background
Mycosis fungoides (MF) is the most frequently diagnosed cutaneous T-cell lymphoma. Early detection of the disease can impact prognosis and survival but remains a diagnostic challenge due to the great similarity of early MF to common benign inflammatory dermatoses. Parapsoriasis is a diagnosis often made in patients who present with lesions that could also be considered an early form of mycosis fungoides. There are no definitive criteria for differentiation between these entities, and some of those proposed, such as the CD4:CD8 ratio, are subject to interobserver variability. We sought to examine whether an AI-assisted workflow could provide a similarly accurate measurement to that of human pathologists and improve the objectivity of the assessment.

Methods
Manual measurement of the CD4:CD8 ratio was performed by three board-certified dermatopathologists on 18 samples from MF patients that had been stained for CD4 and CD8. The slides were then scanned and analyzed using a semi-automated AI-assisted workflow in QuPath that consisted of manual annotation of the regions of interest and automated cell segmentation using StarDist. Cell positivity was determined using an object classifier trained within QuPath.

Results
The workflow achieved mostly accurate cell segmentation and separation of positive from negative cells. Preliminary results show a strong positive correlation between the manual and AI-assisted measurements (Pearson-R 0.9).

Conclusions
Despite its limitations, such as imperfect cell detection, this pilot workflow shows promise considering its excellent performance in the test scenario. More research will be necessary to test interlaboratory reproducibility and to examine the utility of the workflow, or an expanded version thereof, that considers more histological criteria, in distinguishing between inflammatory dermatosis, parapsoriasis, and early MF.

A-188

Correlation of skin barrier function, bacterial colonization, and inflammation in Mycosis Fungoides and Sézary Syndrome

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Background
The main subtypes of cutaneous T-cell lymphomas (CTCLs) are mycosis fungoides (MF) and Sézary Syndrome (SS). MF presents as patches, plaques, or tumors on the skin, while SS causes erythroderma and involves malignant T cells in both skin and blood. Previous studies, often small-scale and limited to early-stage MF, reported impaired skin barrier function and increased bacterial colonization. However, correlations of trans-epidermal water loss (TEWL) with broad bacterial colonization and inflammation have not been performed until now. This study comprehensively analyzes skin barrier function, bacterial colonization, and erythema (used as a proxy for inflammation) in a large cohort of CTCL patients, encompassing all stages of MF and SS.

Methods
In this prospective, observational, cross-sectional study, 35 patients with MF (patches N=16, plaques N=12, non-ulcerative tumors N=7), 8 patients with SS, and 10 healthy volunteers (HV) were included. Patients who used antibiotic treatment were excluded. To assess skin barrier function, TEWL was evaluated in both lesional skin (LS) and non-lesional skin (NLS) using the GPSkin Barrier Pro-1. Swabs were taken from the nostril, LS, and NLS, followed by the evaluation of bacterial colonization through culturing and sequencing. Erythema was assessed using multispectral imaging and clinical scores.

Results
In all stages of CTCL, TEWL was significantly increased in LS compared to NLS and HV. In MF, TEWL increased significantly from 17.2 in patches to 34.4 in plaques to 47.2 in tumors. Increased TEWL was significantly correlated (r=0.58) with enhanced erythema in all stages of CTCL. Bacterial colonization in MF was higher in LS compared to NLS, and was predominantly observed in the tumor stage (*Staphylococcus aureus* frequency 43%). Subtyping of bacterial strains is ongoing and will be presented at the conference.

Conclusions
The present study demonstrates that decreased barrier function, increased bacterial colonization, and enhanced inflammation are observed in LS versus NLS and HV, and increase with progression of the disease stage. These observations are in line with previous studies suggesting bacterial colonization as a factor in the progression of CTCL and as a target for therapeutic intervention. Further investigation, including ongoing bacterial sequencing, will provide deeper insights into the microbiome composition and its role in the pathogenesis of MF and SS.

A-142

Cutaneous T-cell lymphoma in pregnancy: disease activity and outcomes

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Background
Mycosis Fungoides (MF) and Sezary syndrome (SS), types of non-Hodgkins's lymphoma (NHL), are the most common variants of cutaneous T-cell lymphoma (CTCL).

Objective
Our aim was to understand the impact of pregnancy on disease activity and outcomes in patients with MF/SS.

Methods
Patients followed during pregnancy, or the postpartum period were identified from an institutional cutaneous lymphoma database for retrospective review.

Results
Fifty-four patients with MF were followed during 62 pregnancies or in the immediate postpartum period.
In 42 cases where patients had a diagnosis of MF prior to a pregnancy, 50% (21/42) of cases reported stable or improved disease during pregnancy or the postpartum period, while 50% (21/42) noted worsening disease.
Four patients (10%) experienced advancement in stage after pregnancy. All pregnancies, except one, resulted in viable deliveries.
In 20 cases where patients were diagnosed with MF during a pregnancy or in the postpartum period, 25% (5/20) had advanced-stage disease at diagnosis. All pregnancies, except three, resulted in viable deliveries.
Five-year overall survival from diagnosis was 95%.

Limitations: This is a single-center retrospective study. Pregnancy status was not queried in all patients seen.

Conclusions

Conclusion: In 50% of cases, MF during pregnancy or the postpartum period may be characterized by worsening skin disease, and in 9.5% cases may result in stage progression after pregnancy. Interventions such as abortion and systemic anticancer agents may have to be considered in those with advanced disease during pregnancy, hence pregnancy is not advised in these patients. There is a high risk of treatment discontinuation during pregnancy hence close followup with gynecology and a CTCL specialist to reassess and reoptimize MF management after pregnancy, especially due to the mentioned risk of worsening skin disease and stage progression, is warranted.

A-141

Dysbiosis of the skin microbiome in patients with Mycosis fungoides

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Background

[1]Mycosis fungoides (MF) is the most frequent subtype of primary cutaneous T-cell lymphomas. Early stages of MF have a favourable prognosis, while advanced stages have a worse prognosis. There is a clinical unmet need to find potential biomarkers for progression of the disease. Previous studies have shown that *Staphylococcus aureus* may play a role in the progression of MF. *Cutibacterium acnes* is a common commensal bacterium that is important for maintaining a healthy skin microbiome and a normal skin barrier function, but its prevalence and role in the skin microbiome of MF is largely unexplored. The aim of this study was to investigate the skin microbiome and the skin barrier function in patients with MF compared to a healthy control group (1).

Methods

Patients with MF were classified according to TNMB classification. The absolute quantification of gene copies of *Staphylococci* and *Cutibacterium acnes* in the skin microbiome were analysed using dd-PCR. Skin barrier function was measured by transepidermal water loss (TEWL). Blood samples were analysed for interleukins, thymus and activation-regulated chemokine (TARC/CCL17) and total immunoglobulin E**.**

Results

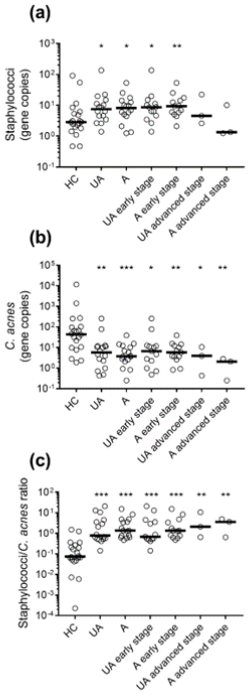

Figure 1. Gene copies of Staphylococci (a) and C. acnes (b) and the Staphylococci/C. acnes ratio (b) in affected and unaffected skin in

patients with Mycosis fungoides and in the healthy control group.
Seventeen patients with MF and 20 healthy controls were enrolled from 2021 to 2023. Affected skin of patients with MF had a significantly higher quantity of *Staphylococci* and a lower quantity of *Cutibacterium acnes* compared to healthy controls ($P<0.05$ and $P<0.001$, respectively) (Figure 1). TEWL was significantly higher in affected skin of patients with MF compared to healthy controls ($P<0.001$). TARC/CCL17 was significantly higher in patients with advanced stages of MF compared to early stages ($P<0.05$).

Conclusions

This study showed an increase in the quantity of gene copies of *Staphylococci* in the affected skin compared to healthy controls, which is in line with previous studies. This study also found a significant loss of gene copies of *Cutibacterium acnes* in affected skin compared to healthy controls, implying that the loss of *Cutibacterium acnes* might be of importance in the progression of MF; thus, this needs further investigations.

References:

[1] Belfrage E, Ek S, Johansson Å, Brauner H, Sonesson A, Drott K., (2024), Predictive and prognostic biomarkers in patients with Mycosis fungoides and Sézary syndrome (BIO-MUSE): Protocol for a translational study. , JMIR Res Protoc, Apr 4;13:e55723.

A-224

Evaluating the Impact of Phototherapy on Cardiovascular Risk in Cutaneous T-Cell Lymphoma: A Retrospective Analysis

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Background

Chronic inflammation in cutaneous T-cell lymphoma (CTCL) may increase the risk of cardiovascular (CV) events. While some studies suggest that phototherapy protects against adverse CV events in vitiligo patients, the effects of narrowband ultraviolet B (NB-UVB) and psoralen plus ultraviolet A (PUVA) phototherapies on CV risk in CTCL patients are not well studied.[Reference1]

Methods

A retrospective analysis of 621 adult CTCL patients diagnosed and treated at Johns Hopkins Hospital was conducted. Patients were divided into three cohorts based on their CTCL treatment regimen: 28 patients treated only with PUVA or NB-UVB phototherapy ('phototherapy-only'), 276 treated with phototherapy plus other treatment(s) ('phototherapy +'), and 317 who never received phototherapy ('no phototherapy'). CV events studied included myocardial infarction, stroke, peripheral arterial occlusive disease, abdominal aortic dissection, peripheral vascular disease, and cardiovascular disease. Statistical analysis was performed in R.

Results

Figure 1: Demographic factors in the three experimental cohorts

	'Phototherapy-only'	'Phototherapy +'	'No Phototherapy'	P-value*
Number of Patients	28	276	317	
Median Age at Diagnosis	49.3 years	55.0 years	59.7 years	p = 0.023[a], 1.0[a]
Gender				
Male	42.9%	43.8%	53.3%	p = 0.387[b], 0.025[b]
Female	57.1%	56.2%	46.7%	
Race				
White	50.0% (14)	52.5% (145)	57.7% (183)	p = 0.143[b], 0.541[b]
Black	46.4% (13)	45.3% (125)	41.1% (130)	
Asian	3.6% (1)	0.7% (2)	0.3% (1)	
Other or Unknown	0% (0)	1.5% (4)	0.9% (3)	
Max Staging				
IA	46.4% (13)	26.1% (72)	37.9% (120)	p < 0.01[b], p < 0.01[b]
IB	50.0% (14)	44.6% (123)	28.1% (89)	
IIA	0.0% (0)	2.9% (8)	2.5% (8)	
IIB	3.6% (1)	6.2% (17)	6.6% (21)	
IIIA	0.0% (0)	4.7% (13)	4.7% (15)	
IIIB	0.0% (0)	6.5% (18)	2.2% (7)	
IVA	0.0% (0)	7.9 % (22)	14.5% (46)	
IVB	0.0% (0)	1.1% (3)	3.5% (11)	

*First value corresponds to comparison between 'Phototherapy-only' and 'No Phototherapy.' The second p-value corresponds to the comparison between 'Phototherapy +' and 'No Phototherapy'
[a]P-value calculated using Independent T-test
[b]P-value calculated using Chi-squared test

The risk of adverse CV events was not significantly decreased in 'phototherapy-only' patients (P = .343) or 'phototherapy +' patients (P = .450) when compared to the 'no phototherapy' cohort. Notably, there were no CV events recorded in the 'phototherapy-only' cohort. This finding, however, may be limited by the group's small sample size. The median time to an adverse CV event was 61.97 months for the 'phototherapy +' cohort and 40.44 months for the 'no phototherapy' cohort (P = .157). A history of congestive heart failure significantly increased the odds of having an adverse CV event for 'phototherapy +' patients (P < .001). Additionally, a history of hyperlipidemia or coronary artery disease (CAD) were

significant comorbidities for developing a future adverse CV event in the 'no phototherapy' cohort ($P < .001$ for both conditions).

Conclusions

We observed that phototherapy for CTCL, when used alone or in combination with other treatments, did not significantly reduce the overall risk or delay the onset of adverse CV events. These findings underscore the complexity of managing CV risk in CTCL patients. Given the significant impact of specific comorbidities on increasing CV events, personalizing treatment plans to each patient's individual needs is essential. Next steps include validating our internal data with an open-source dataset to better understand the cardiovascular implications of phototherapy in CTCL.

References:

[Reference1] Bae, J.M., et al., (2021), Both cardiovascular and cerebrovascular events are decreased following long-term narrowband ultraviolet B phototherapy in patients with vitiligo: a propensity score matching analysis, J Eur Acad Dermatol Venereol, 222-229, 10.1111/jdv.16830

A-166

Health-related quality of life in primary cutaneous B-cell lymphoma following local radiotherapy

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Background

Primary cutaneous B-cell lymphomas (pcBCL) belong to a rare subset of lymphoproliferative neoplasms. Studies on health-related quality of life (HRQOL) in patients with pcBCL lacked the impact of local radiotherapy on HRQOL.

Methods

In this prospective cohort, the influence of local radiotherapy (RT) on the quality of life in patients with pcBCL is determined and compared before and after radiotherapy. Forty-seven patients with primary cutaneous B-cell lymphomas (CBCL), thereof 18 primary cutaneous marginal zone lymphomas (PCMZL), 22 primary cutaneous follicle center lymphoma (PCFCL), and 7 primary cutaneous diffuse large B-cell lymphoma (DLBCL)-leg type were treated between 2017 and 2024. The median radiotherapy (RT) dose was 36 Gy (range, 4-50). The median follow-up period was 42 months. The 3-year local control rate was 97±3%, and the median freedom from progression was 93±5%. At the time of analysis, six patients had deceased. The treated cases completed the Skindex-29 and European Organization for the Research and Treatment of Cancer Quality of Life C30 (EORTC-QLQ-C30) questionnaire before (first day of radiation) and after treatment (3 months after radiation).

Results

When comparing Skindex-29 scores before and after RT, Skindex-29 global scores reduced after treatment with a mean difference (mDiff) of 1.33 (P=0.2). In subgroup analysis, only patients with T3 lesions significantly improved the emotions subscale after treatment (mDiff=-2, P=0.04). However, the overall Skindex-29 scores significantly improved in younger patients (mDiff=2.10, P=0.036). Regarding the site of RT, there was a significant enhancement in Skindex-29 overall scores in locations other than head and neck (mDiff=2.38, P=0.017). We could not detect any significant dissimilarity in the EORTC-QLQ-C30 questionnaire (P > 0.05). In subgroup analysis, the physical subscale seems to improve after treatment of head and neck lesions (mDiff=1.782, P=0.07) and T3 lesions (mDiff=1.732, P=0.08). Patients who received more than 30 Gy have a non-significant trend towards emotional distress (mDiff=1.539, P=0.1) and a worse global health score subscale (mDiff=1.543, P=0.1).

Conclusions

The present analysis shows that local RT was not associated with the quality of life deterioration in CBCL. In contrast, selected patients with CBCL receiving local RT might experience clinically meaningful health-related quality of life changes.

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Is there microbial dysbiosis in CTCL? A pilot study.

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Background
Analysis of the skin microbiome has deepened our understanding of the deleterious role of microbial dysbiosis in a range of skin conditions, and previous studies have implicated dysbiosis in promoting lymphoma-associated immune dysregulation in patients with cutaneous T cell lymphoma (CTCL).
We are a group of Early career/Young Investigators in CTCL being mentored by leaders from the EORTC. We have designed a multicentre study investigating the epidermal and dermal microbiome in CTCL.
The aim of this pilot study is to investigate, using whole genome sequencing (WGS), the epidermal and dermal microbiome in patients with mycosis fungoides (MF) and Sezary Syndrome (SS), with comparison made to control patients.

Methods
This pilot study will include ten controls and twenty patients with MF (patch/plaque/tumour stage disease) and patients with SS from four European centres. Enrolled patients will provide one skin swab and one 6mm punch biopsy.
Skin is swabbed for 60 seconds with a sterile FLOQswab® moistened with 0.9% sodium chloride. A 6mm punch biopsy is taken and divided into epidermal and dermal compartments. Biopsy samples are deep frozen at -80°C. DNA is subsequently extracted using the QIAamp DNA Microbiome Kit (Qiagen) as per manufacturer's instructions.
Library preparation is being completed using purified and quantified gDNA (1 ng) in the Illumina Nextera XT library preparation kit. We will utilize an assembly-based bioinformatics workflow to analyze our shotgun metagenomics data. Data elaboration and analyses will be performed using R, and data visualization will be performed using ggplot2 and pheatmap.
Clinical metadata will be analysed with descriptive statistics, frequency distribution and tests for normality. Alpha and beta microbiome diversity will be assessed using the vegan package in R.

Results
Our first samples are currently undergoing 16S and WGS in the US. We will present our detailed bioinformatic analysis of patient MF/SS samples and normal controls.

Conclusions
A preserved dermal microbiome across CTCL patients will be an exciting and highly relevant finding. The data from this pilot study will pave the way for future skin microbiome studies in patients with MF/SS e.g. (1) Longitudinal analysis of the changes that occur in the microbiome with disease progression; (2) Interventional trials evaluating the use of decolonisation regimens for patients with microbial dysbiosis; (3) Might therapeutic use of autologous microbiome transplantation be of potential use in CTCL?

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A-201

Patient-reported symptoms and HRQL of MF and SS patients receiving mogamulizumab over 24 weeks: interim results from the PROSPER study.

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Background
Cutaneous T-cell lymphomas (CTCLs) are non-Hodgkin lymphomas with Mycosis fungoides (MF) and Sezary syndrome (SS) sub-types accounting for ~65% of all cases. Patients can experience high symptom burden including disfiguring lesions, pruritis and sleep problems, which significantly impacts their health-related quality of life (HRQL). Mogamulizumab, an anti-CCR4 monoclonal antibody, improved HRQL in the phase 3 MAVORIC trial. PROSPER aims to measure patient-reported symptoms and HRQL during mogamulizumab treatment in real world clinical practice.

Methods
PROSPER is a prospective, observational, non-interventional study enrolling MF and SS patients between November 2022 and August 2024 from 19 sites across Europe, the US, and UAE. Using a bespoke symptom diary, patients rated the severity of their skin symptoms (itch, flaking, redness and pain) using 0-10 numerical rating scales and frequency of sleep problems and difficulties regulating body temperature using a Likert scale (Never, Rarely, Occasionally, Frequently and Every Night/ Always). Patients completed the Brief Fatigue Inventory (BFI) and the MF/SS CTCL-QoL every 12 weeks. Here we present the first 20 patients followed for up to 24 weeks. Data were analysed descriptively.

Results
Of the first 20 patients enrolled, the majority were SS patients (60%), had advanced disease (90%) and blood involvement (65%). Symptom diary, BFI (total) and MF/SS CTCL-QoL (total) scores are shown in table 1. At baseline, skin itch scored highest (worst) amongst the skin symptoms, while approximately 50% reported sleep problems or difficulties regulating body temperature occurring frequently or every night/always. All 6 symptoms showed improvement by week 4, which was mostly maintained throughout the following 24 weeks. At baseline, patients experienced moderate fatigue (4-6) as measured using BFI global score. By week 12 and week 24 fatigue reduced to mild (1-3). The MF/SS-CTCL-QoL mean score decreased from moderate interference at baseline and week 12 to mild interference at week 24.

Patient-reported Outcome	Baseline	Week 4	Week 12	Week 24
Skin Itch (0-10) Mean ±SD n	6.63 ±3.02 19	4.44 ±2.99 16	4.06 ±2.74 16	4.94 ±2.41 16
Skin Pain (0-10) Mean ±SD n	4.00 ±3.25 19	3.38 ±2.39 16	1.75 ±1.92 16	2.63 ±2.80 16
Skin Redness (0-10) Mean ±SD n	6.21 ±3.05 19	4.27 ±2.52 15	3.80 ±2.37 15	4.13 ±2.55 16
Flaking Skin (0-10) Mean ±SD n	5.89 ±2.92 19	3.75 ±2.41 16	3.75 ±2.38 16	3.75 ±2.46 16
Sleep problems Frequently/every night, n(%) n	10 (56) 18	8 (53) 15	5 (31) 16	3 (19) 16
Difficulties regulating body temperature Frequently/always, n(%) n	9 (47) 19	3 (20) 15	2 (13) 16	4 (25) 16
BFI Global Score Mean ±SD n	3.76 ±2.04 19	NA	3.26 ±1.27 14	3.05 ±1.41 12
MF/SS CTCL-QoL Mean ±SD n	112.71 ±11.75 17	NA	107.23 ±11.34 13	105.33 ±10.67 9

Table 1. *Symptom diary, BFI and MF/SS CTCL-QoL results over 24 weeks. BFI categorized as mild (1-3), moderate (4-6) and severe (7-10) and MF/SS CTCL-QoL categorized as No to Low Interference (62-89), Mild Interference (91-105), Moderate Interference (106-117), Substantial Interference (118-133) and Severe Interference (135-154).*

Conclusions
Patients experienced a high symptom burden, moderate fatigue and moderate HRQL impact at baseline. Following treatment with mogamulizumab, patients report improved skin symptoms (pain, itch, flaking and redness), sleep problems and body temperature regulation within 4 weeks of treatment. Patient-reported fatigue and impact on HRQL both improved from moderate to mild within 24 weeks following treatment with mogamulizumab.

Keywords: mycosis fungoides, sezary syndrome, mogamulizumab

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Pruritus and Quality of Life in Patients with Cutaneous T-cell Lymphoma

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Background
In cutaneous T-cell lymphoma (CTCL), chronic pruritus affects up to 94% of patients. Traditional antipruritic treatment is not effective, underlining the relevance of pruritus as a major factor reducing quality of life (QoL). Routine pruritus assessment scores the severity on a numeric rating scale from 1-10. To date, pruritus as a symptom complex is often neglected in clinical practice. A better understanding of patient-specific pruritus perception is needed.

Methods
In this cross-sectional, single institution study, we developed a questionnaire assessing CTCL-associated pruritus including characterization, dynamics and modifying factors. QoL was evaluated with the Dermatology Life Quality Index (DLQI) and EORTC core quality of life questionnaire (QLQ-C30). Patients with early-stage Mycosis fungoides (MF) (n=16), late-stage MF (n=10) and Sézary syndrome (n=10), treated at the University Hospital of Zurich, completed the three questionnaires.

Results
A total of 80.5% (n=29/36) patients reported disease-associated pruritus. It was worsening with scratching (37.9%, n=11/29), stress (31.0%, n=9/29) and elevated temperature (24.1%, n=7/29). DLQI was associated with severity of skin involvement (ρ=0.44, p=0.01), worst experienced pruritus (ρ=0.42, p=0.02) and current perceived pruritus (ρ=0.60, p<0.01). Those three factors summarized in a Pruritus-Score correlated strongly with DLQI (ρ=0.71, p<0.01). This Pruritus-Score revealed strong correlation to QLQ-C30 global health status (ρ=-0.64, p<0.01) as well as fatigue (ρ=0.55, p<0.01).

Conclusions
Pruritus is a prevalent symptom in CTCL. Screening CTCL-patients with a Pruritus-Score outperforms unimodal assessment of current perceived pruritus to identify patients with pruritus-related impaired QoL and is associated with fatigue. Further investigation in larger patient cohorts are needed to assess the role of Pruritus-Score as a tool for symptom improvement and potentially influencing CTCL management.

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Quality of Life in Egyptian Mycosis Fungoides Patients Attending Cutaneous Lymphoma Clinic at Ain Shams University Hospitals: A Cross-Sectional Study

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Background
Mycosis Fungoides (MF) is a form of primary cutaneous T-cell lymphoma which may also involve the lymph nodes, blood, and visceral organs. Classic MF commonly presents with patches which may progress to plaques, tumors, or even erythroderma. However, it is frequently referred to as 'the great mimicker' owing to its capacity to emulate several other dermatoses, this results in a wide range of symptoms with a possible mild to severe impact on Quality of Life (QoL)

Methods
The study included 51 MF patients (22 males and 29 females with mean age 47.3±15.3 years) and 51 healthy controls (21 males and 30 females with mean age 46.4±13.2 years). Both groups completed the validated Arabic version of generic and oncology specific QoL tools [36-Item Short Form Health Survey (SF-36) and EORTC Core Quality of Life questionnaire (EORTC QLQ-C30)]. MF patients completed the validated Arabic version of Dermatology Life Quality Index (DLQI) which is a dermatology-specific tool. Total scores of the dermatology-specific and generic tools and the summary score of the oncology-specific tool were analyzed in relation to demographic data and clinical characteristics. Demographic data collected from both groups included age, gender, marital status and education. Clinical characteristics of interest in the MF group included time since diagnosis, time to diagnosis, MF type (classic/hypopigmented/other), disease stage, current treatment and presence of itching. Intensity of pruritus was assessed using VAS itch.

Results
Comparison of quality of life between the two groups revealed statistically significant lower scores of SF-36 and QLQC-30 in MF patients compared to control.
Regading DLQI, there was a statistically significant association between DLQI and marital status as married patients had higher scores.

In addition, A statistically significant association was observed between DLQI and MF type, stage and treatment. Classic type, Stages IIIA and IVA and patients on topical treatment or PUVA had the highest scores.

		DLQI		
		Mean rank	**Test value**	**P value**
Age		-	0.303	**0.031#**
Gender	**Male**	24.68	0.533	0.580^
	Female	27.00		
Marital status	**Married**	28.34	2.146	**0.032^**
	Single	17.50		
Education	**Uneducated**	33.83	2.263	0.323@
	Basic education	27.75		
	High education	23.57		

Table 1: Associations between DLQI and demographic data. #using Spearman correlation test, ^using Mann-Whitney test, @using Kruskal-Wallis test

		DLQI		
		Mean rank	**Test value**	**P value**
Time since diagnosis		-	-0.067	0.640#
Time to diagnosis		-	0.218	0.124#
VAS score		-	0.267	0.058#
Type	**Classic**	30.47	7.827	**0.020@**
	Hypopigmented	17.90		
	Other types	19.11		
Stage	**IA**	19	12.803	**0.025@**
	IB	27.6		
	IIA	26.35		
	IIB	28.50		
	IIIA	43.20		
	IVA	45.00		
Recurrence	**No**	27.46	0.606	0.739@
	Once	25.05		
	More than once	22.13		
Treatment	**PUVA**	29.10	8.662	**0.034@**
	NBUVB	11.10		
	Topical	31.25		
	Systemic	20.95		
Itching	**Present**	27.34	0.743	0.457^
	Absent	24.23		

Table 2: Associations between DLQI and clinical characteristics. #using Spearman correlation test, ^using Mann-Whitney test, @using Kruskal-Wallis test

There was no significant association between SF-36 and demographic data. However, stage IIIA had significantly lower SF-36 scores. There was no significant association between EORTC QLQ-C30 and demographic data or clinical characteristics.

Conclusions

Analysis of the data from the 3 instruments used revealed a significant negative impact on QoL in MF patients especially in married cases and advanced stages. Hypopigmented MF type and treatment with NBUVB were associated with better QoL.

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Single-cell multiomics identifies formation of immunologic memory in CTCL - transition from blood to skin

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Background
Cutaneous T-cell lymphoma (CTCL) is a malignancy characterised by neoplastic lymphocytes accumulating in the skin. In patients with the aggressive Sézary Syndrome, malignant T-cells with hyperexpanded TCR-Vβ clones are detected in both the circulation and skin lesions. Therefore, trafficking of T-cells can be studied in both local cutaneous and systemic environments. Circulating T-cells extravasate and accumulate in the skin where they form an immunologic memory. Using skin and blood of CTCL patients, we study formation of immunologic memory from the perspective of malignant T-cells and their interaction with the skin microenvironment potentially triggering skin homing and extravasation.

Methods
To study the formation of immunologic memory in CTCL, we employed multiomics single cell (sc) profiling. Cellular indexing of transcriptome and epitopes by sequencing (CITE-seq) and scATAC (the assay for transposase-accessible chromatin)-gene seq were employed to haracterize T-cells and the environment at a single cell level across 3 omics layers: surface proteome, whole transcriptome paired with scTCR repertoire and accessible chromatin regions. Key candidates were further validated using spatial analysis and orthogonal high throughput methods, such as flow cytometry and bulk proteome profiling.

Results
Using five independent readouts, we identified a phenotypically heterogeneous malignant population with a range of two central memory phenotypes in blood (n=8) and involved skin (n=10) across three omics layers. Quantification of transcriptional diversity at a single cell level revealed a differentiation potential, ranging from multipotent in blood to terminally differentiated in skin compartment. CellChat analysis identified multiple interactions involved in skin homing and Th2 polarization. Spatial distribution confirmed the proximity of the identified receptor -ligand pairs within the tissue architecture. Serum proteomics confirmed elevated levels of Th2 and skin homing cytokines in CTCL patients.

Conclusions
Spectrum of differentiation, identified receptor-ligand interaction and presence of terminally differentiated phenotype in skin supports the role of immunologic memory in skin homing and enhanced extravasation of malignant T-cells in CTCL. Disturbing some of those interactions could be a promising strategy in CTCL management.

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Skin-Limited Versus Extended Manifestation In BPDCN Patients: A Retrospective Multi-Centre Observational Study

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Background
Blastic plasmacytoid dendritic cell neoplasm (BPDCN) is a rare haematological malignancy, classified as its own distinct diagnostic entity by the World Health Organization in 2016, with an incidence of 0.04 per 100,000 individuals. Arising from plasmacytoid dendritic precursor cells, is has a poor prognosis, with a median overall survival (OS) of 8 to 12 months. Up to 90% of patients present initially with asymptomatic, bruise-like and/or violaceous skin lesions followed by systemic dissemination. Although it represents the earliest possible opportunity for intervention, the clinical significance of this initial phase of cutaneous manifestation is not well understood.

Methods
We conducted a retrospective multi-centre observational study to evaluate the survival and treatment outcomes of patients with BPDCN in relation to skin-limited versus extended disease manifestations at the time of hematopoietic stem cell transplantation.

Results
We observed no statistically significant difference in 5y-OS between patients with skin-limited and extended manifestation BPDCN at time of transplantation (n = 9, p = 0.17). However, there was a significant difference in overall OS between patients undergoing hematopoietic stem cell transplantation and those receiving chemotherapy, with the former showing superior outcomes (median OS: 93 vs. 6 months, p = 0.01).

Conclusions
Early diagnosis and treatment of BPDCN are critical, as they significantly improve the prognosis and survival outcomes for patients, regardless of skin limited or extracutaneous manifestation.

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Staphylococcus aureus induces drug resistance in cancer T cells in Sézary syndrome

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Background
Patients with Sézary syndrome (SS), a leukemic variant of cutaneous T-cell lymphoma (CTCL), are prone to *Staphylococcus aureus* infections and have a poor prognosis due to treatment resistance.

Methods
We utilised primary malignant cells from PBMCs isolated from blood donated by SS patients and performed flow cytometry.

Results
Here, we report that *S aureus* and staphylococcal enterotoxins (SE) induce drug resistance in malignant T cells against therapeutics commonly used in CTCL. Supernatant from patient-derived, SE-producing *S aureus* and recombinant SE significantly inhibit cell death induced by histone deacetylase (HDAC) inhibitor romidepsin in primary malignant T cells from patients with SS. Bacterial killing by engineered, bacteriophage-derived, *S aureus*–specific endolysin (XZ.700) abrogates the effect of *S aureus* supernatant. Similarly, mutations in major histocompatibility complex (MHC) class II binding sites of SE type A (SEA) and anti-SEA antibody block induction of resistance. Importantly, SE also triggers resistance to other HDAC inhibitors (vorinostat and resminostat) and chemotherapeutic drugs (doxorubicin and etoposide). Multimodal single-cell sequencing indicates T-cell receptor (TCR), NF-κB, and JAK/STAT signaling pathways (previously associated with drug resistance) as putative mediators of SE-induced drug resistance. In support, inhibition of TCR-signaling and Protein kinase C (upstream of NF-κB) counteracts SE-induced rescue from drug-induced cell death. Inversely, SE cannot rescue from cell death induced by the proteasome/NF-κB inhibitor bortezomib. Inhibition of JAK/STAT only blocks rescue in patients whose malignant T-cell survival is dependent on SE-induced cytokines, suggesting 2 distinct ways SE can induce drug resistance.

Conclusions
In conclusion, we show that *S aureus* enterotoxins induce drug resistance in primary malignant T cells. These findings suggest that *S aureus* enterotoxins cause clinical treatment resistance in patients with SS, and antibacterial measures may improve the outcome of cancer-directed therapy in patients harboring *S aureus*.

Abstract from Vadivel CK et al *Blood* (2024) 143 (15): 1496–1512.

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Update to the Cutaneous Lymphoma Application (CLApp v2.0) on iPhone. A resource tool for information and training for healthcare professionals.

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Background

Management of Mycosis Fungoides and Sezary Syndrome (MF/SS) is complex due to its rarity, the variation in rates of progression and the symptomatic nature of the disease. Whilst the nodes, viscera and blood components are more easily quantifiable with imaging and blood tests, the severity of skin involvement requires a more user dependent scoring system – the mSWAT score. We present an update to the current Cutaneous Lymphoma Application (CL App) on the iPhone. This contains the most up to date information resources and a new painting tool (iSWAT) to help in training and education for skin scoring.

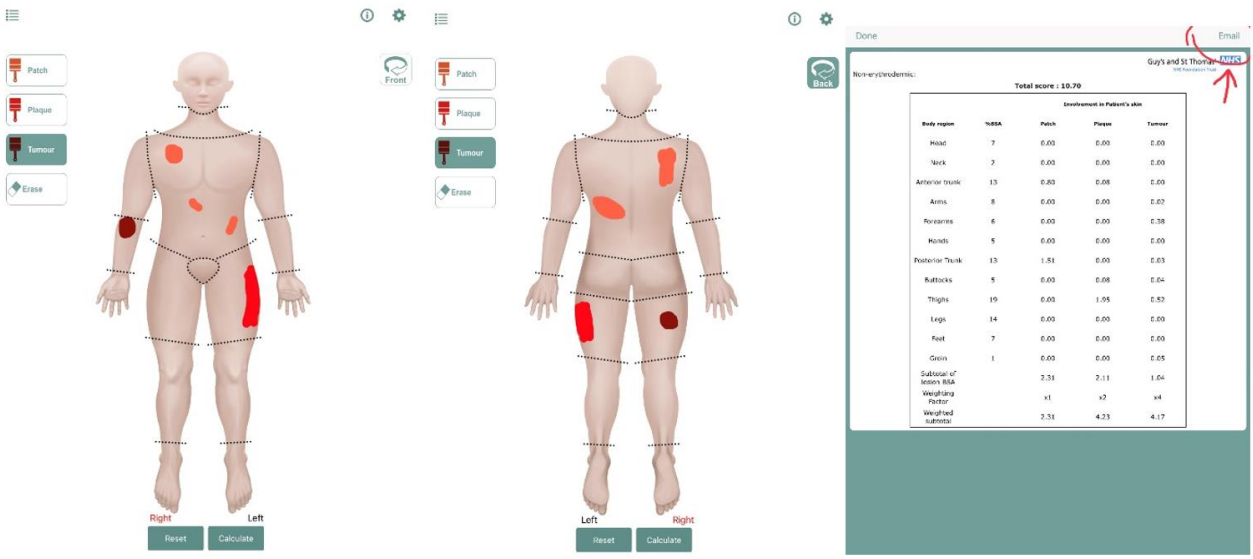
Methods

We have worked with the developers and the multi disciplinary team at the St Johns institute of Dermatology, London. The latest guidance and resources are now built in within the application and we have developed an online resource to update the resources continually. We re-designed the painting skin scoring tool iSWAT originally developed on the iPad and integrated it onto the iPhone app.

Results

Latest guidance and resources for diagnosis and management of Mycosis Fungoides/ Sezary Syndrome (MF/SS) and Cutaneous B cell lymphoma (CBCL) are now built in within the application. This includes the WHO EORTC classification 2018 [1], MF/SS staging according to Olsen 2022[2], UKCLG/ BAD guidelines and the EORTC guidelines for CBCL. An online application to allow continuous updates to the information resources has been developed which will go live with the launch of the app update.

The iSWAT painting function has now been integrated into the CL App. An evaluation training study carried out at GSTT previously show that the iSWAT assessment improves the median time for assessment. (iSWAT 2.3mins vs mSWAT 3.0 mins). Using the grid counting method, the quantification of involvement of affected skin on the iSWAT app can be correlated with the mSWAT standard method for training and education. The mSWAT images and scores are exportable for future use and training.



1(a) 1(b) 1(c)

Image 1(a) and 1(b) showing distribution of disease and type that can easily be painted on. Image 1(c) shows a summary of the MSWAT score calculated in real time. All images are exportable via email.

Conclusions

The new application acts as a one stop resource for skin lymphoma and may be used as an educational and training tool.

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αEβ7 Integrin (CD103) expression in both early and advanced stage of Cutaneous T cell Lymphoma's (CTCL)

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Background

αEβ7 Integrin (CD103) is thought to play a critical role in T cell migration and localization within the epidermis. CD103 is a marker for tissue resident memory T cells (T_{RM}). A previous report states that CD103 is mostly expressed by cancer cells in the early stages of Mycosis Fungoides (MF), and not in the advanced stages of MF [1]. The expression of CD103 on cutaneous T cells parallels the degree in epidermotropism in both neoplastic and inflammatory disorders of the skin. It is not known how the interaction between CD103 and other cellular subsets facilitate the trafficking of T cells into the epidermis. Imaging Mass Cytometry (IMC) provides the opportunity to quantify and identify immune cell clusters in the skin, and, most importantly, elucidate the spatial context and cellular interactions. Here, we construct a CTCL specific immune phenotyping panel with IMC to investigate CD103+ T^{RM} in the immune architecture in CTCL on formalin fixed paraffin embedded (FFPE) material. We aim to reveal differences in the composition and interactions of immune cell subsets and CD103+ T^{RM} in early and advanced stage CTCL.

Methods

Biopsies were selected from MF patients with early-stage (n=13) and advanced-stage (n=15) disease. An in-house developed IMC panel with 43 antibodies was used. The antibodies were initially tested for performance by immunohistochemical staining (IHC) on human skin and tonsil. Subsequently, antibodies with an appropriate signal intensity were conjugated to lanthanide metals. Advanced data analysis tools were used to identify immune cell clusters and elucidate their cellular interactions.

Results

Preliminary results show CD103 expression in both early and advanced stage MF. Further analyses of specific immune cell subsets is ongoing.

Conclusions

Here we apply IMC to characterize the composition and interactions of various immune cell subsets and CD103+ T^{RM} in CTCL. Our initial results show expression of CD103 in not only early stage MF, as expected, but also in advanced stage MF. We are now pursuing its interactions with the surrounding reactive immune cells, e.g. subsets of macrophages and dendritic cells.
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TREATMENTS

A-193

A Prospective, US-based Study Assessing Mogamulizumab-Associated Rash in Patients Diagnosed with Mycosis Fungoides or Sézary Syndrome and Treated with Standard of Care Mogamulizumab

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Background
Mogamulizumab (moga) is a humanized defucosylated IgG1κ monoclonal antibody with enhanced antibody-dependent cell mediated cytotoxicity that targets chemokine receptor type 4 (CCR4) for the treatment of adults with relapsed/refractory MF and SS who have failed at least 1 prior systemic therapy. CCR4 is a transmembrane chemokine receptor for CCL22 and CCL17 and acts as a chemotaxis mediator for T helper type 2 cells, regulatory T cells (Treg), and cutaneous lymphocyte antigen-positive skin-homing T-cells. Treatment can be complicated by the occurrence of inflammatory skin reactions (moga-associated rash, or MAR) that may be triggered due to depletion of $FOXP3^{+}CCR4^{+}$ Tregs, allowing a therapeutic antitumor immune response and an exaggerated immune response to occur. Retrospective analyses have suggested MAR may also be associated with a positive response to moga although this has not been prospectively investigated.

Methods
This is a multi-center, prospective, observational study being conducted in the United States that will enroll patients with MF or SS who are starting treatment with standard-of-care moga (N=100, maximum follow up: 1 year). The primary objective is to assess the incidence of MAR and its association with overall response while secondary objectives include describing the characteristics and treatment patterns of patients with MAR and the outcome of MAR interventions, to assess clinical outcomes and serious adverse events among patients treated with moga, and to assess the association of MAR with duration of response, time-to-next treatment, and progression-free survival. Exploratory endpoints will examine the CTCL microenvironment using paired single-cell RNA and T-cell receptor analysis and biomarkers that potentially predict clinical outcomes. Biomarkers that will be investigated include profiles of M1/M2 tumor-associated macrophages, Tregs, T-cell subsets, and chemokines as well as CCR4 expression and mutations in tissue and blood. Health-related quality of life will be assessed using the Skindex-29 and numerical rating scale for pruritus.

Conclusions
This study will provide prospective data on the relationship between MAR and clinical outcomes and may identify risk factors predictive of rash. It will also collect data on biomarkers that can potentially be used to assess response in patients undergoing treatment with moga. The study is currently enrolling patients with readout expected in 2026.
This study is in collaboration with Kyowa Kirin, Inc

A-174

Acitretin as a noninferior retinoid alternative to bexarotene in the management of mycosis fungoides.

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Background
Studies to establish the efficacy of acitretin as a retinoid agent in the treatment of mycosis fungoides are limited. The goal of this study was to determine if acitretin is at least as equally efficacious as the FDA-approved retinoid, bexarotene, in the management of mycosis fungoides.

Methods
We employed a single center retrospective chart review that captured 81 patients diagnosed with biopsy-confirmed mycosis fungoides stages 1A through 3B and treated with acitretin at any time during disease course between 02/25/2009 to 12/13/2023; comparison was made to patients enrolled in stage 2 and 3 bexarotene clinical trials. Patients received oral acitretin at weekly doses of 25 mg to 175 mg in addition to any number of concurrent treatment modalities to manage cutaneous manifestations of their disease. The primary end point was classification of response to therapy as determined by the Physician's Global Assessment of Clinical Condition. Reductions in body surface area over time and side effect profiles were secondary outcomes.

Results
Overall, 71.6% of patients were male; 59.26% of patients were white and 32.1% were black. When comparing rates of response to rates of progressive disease among patients taking either low, moderate, or high doses of each drug, respectively, results showed a statistically significant difference in the low-dose groups (p=0.0498) - with more acitretin patients demonstrating response and fewer demonstrating progressive disease - and lack of statistically significant difference in the moderate (p=0.747) and high dose groups (p=0.0805). When comparing overall rates (in all dose groups) of related adverse events consistently observed in practice in the use of both retinoids, there were statistically significant differences in the occurrence of headaches, leukopenia, elevated LDL, and elevated

triglycerides, with lower rates of all observed in those taking acitretin compared to bexarotene.

Conclusions
Our primary conclusion is that acitretin offers a noninferior alternative to bexarotene as a retinoid therapeutic agent in the management of cutaneous manifestations of mycosis fungoides with a different side effect profile that notably does not include the need for patients to begin taking thyroid hormone supplementation. Acitretin can be considered in mycosis fungoides patients who have contraindications or intolerability to bexarotene yet could benefit from the incorporation of a retinoid into their treatment regimen.

A-297

Acneiform Case of Mogamulizumab-associated rash

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Background
Mogamulizumab-associated rash (MAR) is one of the most frequent adverse events of the CCR4-antibody Mogamulizumab, which is approved as second-line therapy for the treatment of mycosis fungoides and Sézary Syndrome. MAR can present in a variety of clinical and histological types but can be difficult to distinguish from the underlying disease. Clinically MAR demonstrates in 4 predominant patterns: folliculotropic MF–like scalp plaques with alopecia, papules and/or plaques, photo accentuated dermatitis, and morbilliform dermatitis. Regarding histologic reaction patterns, Wang et al. identified 3 major patterns: spongiotic/psoriasiform dermatitis, interface dermatitis, and granulomatous dermatitis. This case report presents a patient with acneiform MAR that has not been previously described.

Results
We report a 42-year-old male patient with stage IIB mycosis fungoides. After initial therapy with bexarotene, we started therapy with mogamulizumab due to disease progression. After 12 doses of mogamulizumab, the patient reported the appearance of new skin changes, while the tumour nodules and plaques regressed significantly. Clinically, he presented with pustules and abscesses, especially nuchal, on the arms and legs, as well as on the décolleté. Skin samples were taken and showed a histiocyte-rich inflammatory reaction with a strong CD8-positive component, consistent with MAR. We started treatment with topical steroids while continuing mogamulizumab. As there was no improvement, we switched to doxycycline 100 mg twice a day. Two weeks after starting doxycycline, the patient reported a significant reduction in skin changes and pruritus.

Conclusions
An acneiform variant of MAR has not yet been described in the literature. MAR can present clinically and histologically in many different ways, which is why diagnosis can be challenging. Current data analysis suggest that MAR is associated with a significantly better response to treatment, making the distinction from disease progression particularly important. In the management of MAR, it should always be kept in mind that there is evidence that the occurrence of MAR is associated with a better prognosis for the underlying disease, making the distinction from disease progression particularly important.

A-245

Brentuximab vedotin as second-line treatment for primary cutaneous CD8+ aggressive epidermotropic T-cell lymphoma

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Background
Primary cutaneous CD8+ aggressive epidermotropic T-cell lymphoma (PCAECTL) is a rare, aggressive and poorly characterized variant of cutaneous lymphoma, with limited and unsatisfactory treatment options. CD30+ cases pose a diagnostic and therapeutic challenge.

Methods
We describe a case of PCAECTL with CD30 positivity with a partial response to brentuximab vedotin (BV) as second-line treatment.

Results
A 41-year-old man, smoker and active user of IV drugs, presented with a 3-month history of widespread large cutaneous ulcers with no spontaneous regression. He complained of local pain but had no systemic symptoms. He also had active hepatitis C, untreated due to loss of follow-up. In the first evaluation, multiple papulonodular (some keratotic) lesions and disseminated ulcers (1-3cm) were seen. Initial clinical hypotheses included *lues maligna*, ecthyma, Mucha-Habermann disease and perforating dermatosis. Syphilis serologies were negative. Transaminases were slightly elevated and HCV was positive. MRSA was cultured from skin lesions and he was firstly medicated accordingly but, after lack of improvement, two skin biopsies were performed. Histopathological analysis showed a CD8+ T lymphoproliferative disease, markedly epidermotropic, with a superficial pattern similar to pagetoid reticulosis. In the clinical context of this patient, the main differential diagnoses were PCAECTL and type D lymphomatoid papulosis (LP). While the presence of numerous CD30-positive cells supported the second hypothesis, clinicopathological correlation and subsequent staging led to the final diagnosis of PCAECTL. He received 6 cycles of polychemotherapy with CHOP, as well as treatment for hepatitis C. Unfortunately, cutaneous response was poor, and the pathological clone was also identified in the blood, bone marrow and ganglia. He was then referred to our department, where serial skin biopsies persistently showed CD30+. After multidisciplinary discussion and literature review, we decided to start brentuximab vedotin (BV). The patient completed 16 cycles with good tolerance and partial cutaneous and systemic response. He is alive 34 months after the diagnosis.

Conclusions
While CD30 positivity is mostly present in mimickers of PCAECTL (such as LP type D), it was also identified in 13% of PCAECTL in the largest study to date. In PCAECTL patients with a poor response to first-line therapy, treatment with BV can be considered.

A-159

Characteristics and Outcomes for Granulomatous Mycosis Fungoides in 80 Patients

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Background
Granulomatous mycosis fungoides (GMF) is a rare variant of cutaneous T-cell lymphoma (CTCL) that is characterized by the formation of granulomas. GMF poses a diagnostic challenge due to its shared clinical characteristics with both CTCL variants as well as inflammatory granulomatous dermatoses. This single-center, retrospective study reviewed clinical, histopathological, and immunophenotypic features of patients with GMF to characterize factors that may aid in diagnosis and management of this rare cohort.

Methods
In this retrospective cross-sectional study, patients diagnosed with GMF from 1980 to 2023 were identified using our institutional database. Clinical data, including demographic information, clinical manifestations of disease, histopathological findings, treatment, and outcomes, were extracted from the electronic medical records.

Results
80 patients with GMF, including 48 men and 32 women (male to female ratio of 1.5:1), were included for analysis. The median age at diagnosis was 58 years (range, 4-81 years). At the time of MF diagnosis, 57 patients (71%) had early-stage disease (stage IA-IIA), and 23 patients (31%) were diagnosed with advanced-stage disease (IIB-IVB). Although clinical characteristics were variable, most patients presented with patches or plaques (n=67,84%). Twelve patients (15%) presented with tumors. Most patients had multifocal involvement of the head/neck, trunk, and extremities (n=49, 61%). Other patients presented with locoregional involvement of the trunk (n=10, 11%) and extremities (n=17, 21%), while isolated involvement of the head/neck was seen in only three patients (3%). Patients underwent a median of four treatments. Localized radiotherapy (median dosage=14 Gy; range, 6-50 Gy) was used in many patients (n=34, 43%) which resulted in a response in nearly all patients (n=33/34, 97%). Median follow-up time of our cohort was 7 years (range, 2 months - 30 years). Overall survival was 71%.

Conclusions
This study highlights clinical characteristics of patients with GMF. Low-dose localized radiotherapy appears to be an effective therapy and should be considered first-line, especially in those with limited disease. Overall survival is still low for these patients. Further exploration into effective management for these patients is needed.

A-268

Chlormethine Treatment Effectively Targets the Tumor Micro-Environment in Early-stage Mycosis Fungoides Patients

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Background

Previous studies established the efficacy of topical chlormethine treatment in mycosis fungoides (MF), but understanding is limited of the treatment-associated inflammation and how these changes in the tumor micro-environment (TME) can contribute to therapeutic success. In this study, we investigated chlormethine treatment-associated changes in the TME to optimize treatment strategy and patient outcomes.

Methods

In this exploratory, open-label study, 21 patients with early-stage (IA – IIA) MF were treated with chlormethine gel 160µg/g QD for 16 weeks. Suction blister exudates and skin punch biopsies were collected pre-treatment from lesional and non-lesional skin, and optionally during inflammation reactions at the application sites, as well as after 16 weeks of treatment from lesional skin. Blister exudate was analyzed on cellular composition using flow cytometry, and its proteome was analyzed using high-throughput proteomics (OLINK panels immuno-oncology and inflammation). Biopsies were analyzed on cellular composition of the TME by means of cell-neighborhood analyses using imaging mass cytometry (IMC).

Results

After 16 weeks of treatment, 8 (38.1%) patients had a mean significant decrease in mCAILS (µ:-10.5±3.4, $p<0.0001$), differing from 13 non-responding patients (µ:-2.1, ±2.9, $p<0.0001$). Inflammation of application-site reactions correlated to mCAILS relative change from baseline (CFB, $r=0.59$, $p<0.001$) and time to inflammation correlated with time to treatment response ($r=0.49$, $p=0.03$). Lesional blister exudate and biopsies taken after 16 weeks of treatment showed significantly fewer T-cells including lower numbers of aberrant T-cells, regulatory T cells, and non-activated and activated cytotoxic T-lymphocytes. In parallel, prevalence of IL-33, ARG1, CCL20, CXCL11, GZMB and IFN-ɣ decreased to levels similar to normal skin. These changes in protein signature were most prominent in clinical responders. Preliminary results from IMC studies show that these changes in inflammatory proteins are accompanied by a normalization of T-cell infiltrate in skin as well.

Conclusions

Our results demonstrate that a cytotoxic T-cell inflammatory reaction correlates with chlormethine application site reactions and that treatment response after 16 weeks of treatment correlates with a normalization of the proteome and cellular infiltrate in the TME. Combined, these observations suggest that an activated cytotoxic T-cell reaction contributes to the clinical effect of topical chlormethine therapy.

A-254

Comparing Responses to Romidepsin Monotherapy and the Sequential Treatment of Romidepsin Followed by Mogamulizumab for Advanced Cutaneous T-cell Lymphoma

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*Contributed equally

Background

Current therapies for advanced cutaneous T-cell lymphoma (CTCL) may not provide durable responses and often have negative side effects, underscoring a need for investigation into novel therapies and treatment combinations. Romidepsin, a class I selective histone deacetylase inhibitor, and mogamulizumab, a novel monoclonal antibody directed against C-C chemokine receptor 4, have shown to be moderately effective in treating advanced CTCL[1][2]. Long-term use of romidespin may be limited by toxicities, resulting in a transition to more well-tolerated therapies, including mogamulizumab. The efficacy of this treatment sequence has not been studied.

Methods

We conducted a retrospective IRB-approved single-center database analysis at Columbia University Medical Center to identify patients with advanced CTCL who received sequential treatment with romidepsin and mogamulizumab. We compared the skin, blood, lymph node, and global responses to romidepsin monotherapy with the responses to sequential therapy with romidepsin and mogamulizumab. Treatment response was determined as per Olsen 2011 Criteria.

Results

A total of 814 patients with CTCL were identified, from which 18 patients treated sequentially with romidepsin followed by mogamulizumab were selected for analysis. Nine of 18 patients (50%) initiated mogamulizumab within 30 days of romidepsin termination, and nine of 18 (50%) received mogamulizumab more than 30 days after romidepsin termination. The global response to romidepsin monotherapy was 67% [2 complete response (CR) (11%), 10 partial response (PR) (56%), 2 stable disease (SD) (11%), and 3 progressive disease PD (17%)]. While the global response to sequential therapy with romidepsin and mogamulizumab was also 67%, more patients achieved CR, and there was one fewer PD [4 CR (22%), 8 PR (44%), 4 SD (22%), 2 PD (11%)]. Notably, this increased CR rate was only observed in patients who initiated mogamulizumab within one month of romidepsin discontinuation. Similar observations were seen when comparing patients' skin, blood, and lymph node responses. These findings suggest that treatment with romidepsin followed by mogamulizumab may maintain or improve patients' responses to romidepsin.

Conclusions

Sequencing treatment with romidespin followed by mogamulizumab may be an effective therapeutic strategy, with the results suggesting improved responses with a treatment interval of one month. Further research is needed to confirm these observations and characterize mechanisms of potential syngergy.

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A-156

Current State and Therapeutic Potential of CCR4 Therapies in Cutaneous T-Cell Lymphomas

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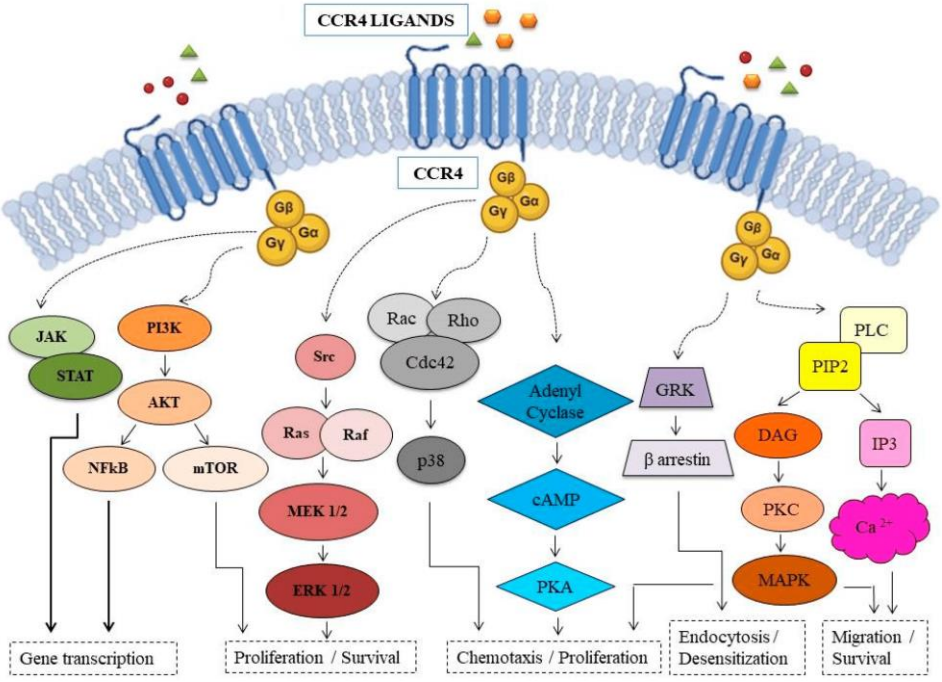
Background

Our work provided a brief overview of the therapeutic landscape surrounding CCR4 targeting in T-cell malignancies



Schematic representation of the molecular pathways activated by CCR4

. We aimed to report therapies already validated, in development, currently being tested, or about to be tested around CCR4, which appears to be a fundamental signalling pathway for the development and malignancy of cutaneous lymphomas (CTCLs)[1].

Methods
We have gathered data from the literature through the main medical database, including monoclonal antibodies, small molecule inhibitors, and chimeric antigen receptor (CAR) T-cell therapy.

Results
Except for the well-known mogamolizumab, for which real-life data remain solid and promising[2], there are few CCR4-targeted therapies with at least promising clinical trials.
A series of small soluble inhibitory molecules capable of binding effectively to the receptor are emerging, but in most cases, they do not go beyond pre-clinical studies. However, CAR-T therapy with engineered CCR4 holds significant promise, offering a beacon of hope in the treatment of T-cell malignancies. The potential of chloroquine towards this receptor seems exclusively theoretical. Finally, some real-life data on mogamolizumab associated with checkpoint inhibitors are reported, but it remains a currently controversial therapy.

Conclusions
As of now, the only therapy with a solid basis for CCR4-based oncological treatment remains mogamolizumab. CAR-T therapy, with its promising potential, is on the horizon. However, in the short term, we do not expect the release of therapies based on soluble antagonists.
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A-192

Deciphering reliable mycosis fungoides-specific diagnostic classifiers and personalized therapeutic regimens through spatial single-cell type proteomics in tissues

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Background
Mycosis fungoides (MF), the most common type of cutaneous T-cell **lymphoma**, presents unique challenges for diagnosis and personalized treatment. These challenges include: 1) a lack of tumor **cell-specific** diagnostic markers, 2) an incomplete understanding of the mechanisms underlying MF **progression**, 3) the absence of methods addressing the spatial homing (**epidermotropism**) of malignant T cells to the epidermis, and 4) the need for **personalized** interventions due to the clinical variability of MF. This study aims to identify reliable diagnostic markers for MF and propose potential druggable targets.

Methods
We developed Deep Visual Proteomics (**DVP**), incorporating high-resolution **staining and imaging** on FFPE sections, AI-driven single-cell phenotyping, automated single-cell laser **microdissection**, and ultrasensitive **mass spectrometry** (MS). DVP effectively addresses the challenges through: 1) unbiased MS-based **proteomics** analysis to differentiate reactive and malignant T cells, identifying diagnostic markers, 2) **longitudinal** proteome comparisons to explore MF progression, 3) **spatial proteome** comparisons of T cells in the epidermis, papillary dermis, and reticular dermis to elucidate mechanisms of epidermotropism, and 4) integration of **multi-omics** data to support clinical decision-making in **personalized oncology**.

Results
Key findings include: 1) the identification of approximately 5000 protein groups from a cellular volume of 175,000 μm^3, equivalent to only 400 single cells, 2) the discovery of potential early diagnostic markers, such as Mini-Chromosome Maintenance proteins, 3) significant upregulation of specific proteins in advanced MF stages, including those involved in cell adhesion, immune response regulation, and the EGF/EGFR signaling pathway, 4) the upregulated proteins in epidermal malignant T cells involved in cell-cell adhesion, cytoskeleton organization, protein folding, and signal transduction, with VEGFA-VEGFR2 pathway suggesting angiogenic factors promoting T cell migration to the epidermis. 5) the identification of molecular alterations pointing towards potential therapeutic targets, such as inhibitors of EGFR and VEGF.

Conclusions

Our study applies DVP to address key diagnostic and therapeutic challenges associated with MF. Our approach provides insights into the mechanisms of MF progression and epidermotropism. Moving forward, we aim to integrate multiplex imaging-powered DVP and transcriptomics to gain deeper insights into the tumor microenvironment dynamics of MF.

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Drug-induced mimics of Mycosis Fungoides: Two case reports and a systemic literature review

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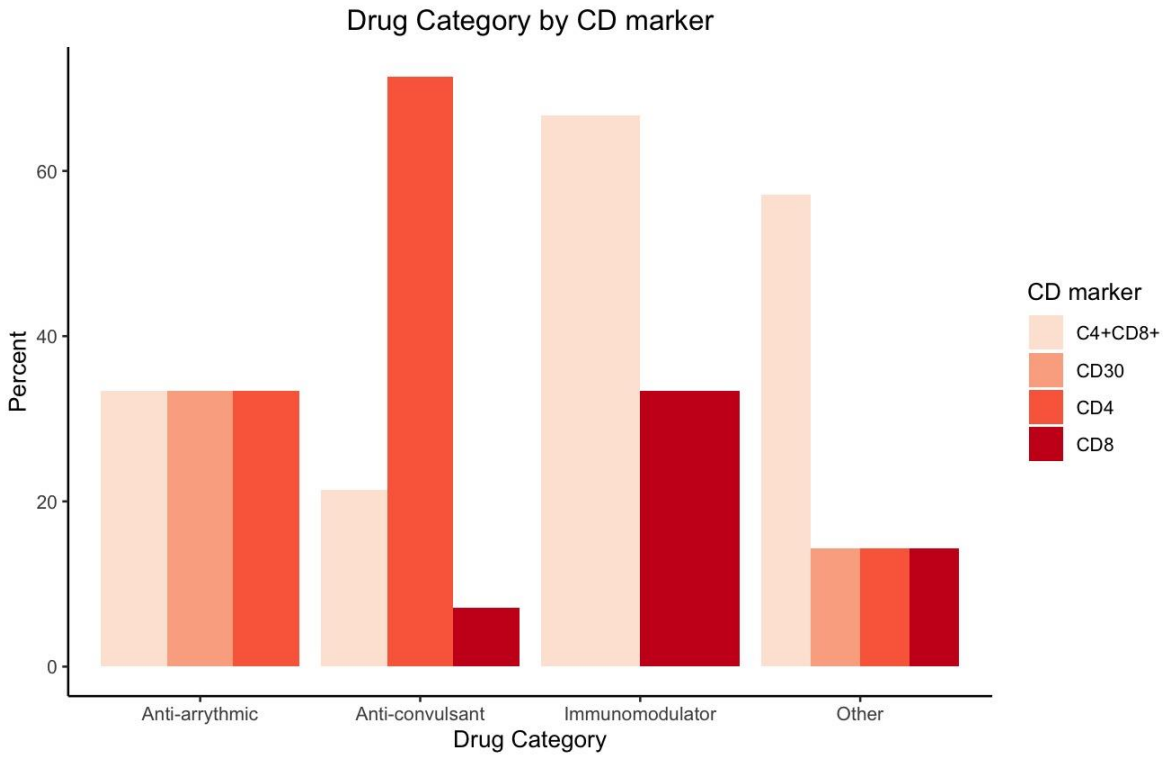
Background

Mycosis fungoides (MF) is the most common type of cutaneous T-cell lymphoma, often presenting diagnostic challenges due to its resemblance to benign dermatoses, particularly drug-induced eruptions. This study aims to examine cases where drug-induced eruptions mimic MF and provide insights into clinical evaluation for improvement of diagnostic approach.

Methods

A comprehensive literature review following PRISMA guidelines was conducted using PubMed, Embase, and Scopus databases, focusing on case reports and series published after 1990 that involved histologic mimickers of MF. Data on demographics, clinical presentation, implicated drugs, histologic findings, and treatment outcomes were collected and analyzed using descriptive statistics and fishers exact tests for significance.

Results



CD markers of T-lymphocytes detected/identified in skin biopsy of drug induced mimickers of MF by drug category

From 46 articles rendered, a total of 25 were included in our study that yielded forty cases to analyze. The average age of patients was 56 years and 58% were males. Anticonvulsants were the most frequently implicated drugs (58%), followed by anti-arrhythmic medications (10%) and immunomodulators (8%). Other category medications made up 25% of reported cases. Clinical presentations varied, with hypersensitivity-like reactions being common in patients on anticonvulsants (59%) and immunomodulators (67%), while MF-

like lesions were more frequent in other category medications (56%). Histologically, atypical lymphocytes and epidermotropism were common findings, particularly in patients on anticonvulsants. Immunohistochemical analysis revealed significant difference in CD markers and drug class (P = 0.04), as shown in Figure 1. Discontinuation of the offending drug often led to clinical remission, with an average resolution time of 61 days.

Conclusions

Diagnosing MF requires careful consideration of the full clinicopathologic picture, especially when drug-induced mimics are suspected. Histologic and immunohistochemical evaluations, such as positivity for both CD4 and CD8 T-cells in the lymphocytic infiltrate, can be giveaways to a drug-induced etiology. Repeat biopsies after drug cessation can be particularly valuable in distinguishing true MF from drug-induced pseudo-lymphomas. These findings highlight the importance of considering drug-induced etiologies in MF-like presentations son that unnecessary treatments can be avoided and appropriate patient management is ensured.

A-167

Durable disease control with low-dose total skin electron beam therapy combined with maintenance treatment for patients with erythrodermic mycosis fungoides and Sézary syndrome

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Background

Systemic and skin-directed treatments for patients with erythrodermic mycosis fungoides (eMF) and Sézary syndrome (SS) are frequently associated with late onset and non-lasting clinical benefits. Limited radiotherapy trials include eMF and SS patients. This analysis evaluates the efficacy of low-dose total skin electron beam therapy (TSEBT) ± maintenance therapy in patients with eMF and SS.

Methods

Thirty-five total patients with eMF and SS received TSEBT. The overall response rate (ORR), health-related quality of life (Skindex-29), and median time to next treatment (TTNT) were analyzed. This study is registered with TrialSearch.WHO.int, DRKS00030375.

Results

21 SS and 14 eMF patients pre-treated with a median of 3 previous systemic agents were included. The median age was 68 years (range, 48-88) and the median radiation dose was 12 Gy (range, 8-12). The overall response rate (ORR) after 3 months was 89% with 17 very good partial response/complete responses (49%). Twenty-five (71%) patients received maintenance therapy after TSEBT. The median time to next treatment (TTNT) of the whole cohort was 20 months (95%-CI: 10-30). The median TTNT was 20 months (95% CI: 5-35) for patients in the maintenance therapy group versus 4 months (95% CI: 3-5) for patients without maintenance therapy (hazard ratio [HR] 0.191, 95% CI 0.068-0.534; p<0.002). The median progression-free survival (PFS) of the whole cohort was 14 months (95%-CI: 4-24). The median PFS was 23 months (95% CI: 10-36) for patients in the maintenance therapy group versus 4 months (95% CI: 3-5) for patients without maintenance therapy (hazard ratio [HR] 0.174, 95% CI 0.064-0.473; p<0.001). A substantial reduction in the itching scale, skin disease burden, Skindex-29 score, and EORTC QLQ-C30 global score improvement has been detected. The rate of grade ≥3 toxicity was 6%. In the translational part of the study, various potential biomarkes in the peripheral blood were assessed from baseline to the first follow-up.

Conclusions

The analysis showed that TTNT and PFS were increased in the TSEBT plus maintenance therapy cohort compared with low-dose TSEBT alone in patients with eMF or SS. Moreover, low-dose TSEBT for SS patients significantly reduced blood tumour burden and improved the quality of life.

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Erythrodermic Folliculotropic Mycosis Fungoïdes successfully treated with Bexaroten plus nbUVB and chlormethine gel

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Background

Cutaneous T-cell lymphoma (CTCL) are a group of non-Hodgkin's lymphomas (NHL) characterized by monoclonal proliferation of malignant T-cells in the skin. Around three-fourths are represented by Mycosis fungoides (MF). Among them, Folliculotropic mycosis fungoides (FMF) represents the most common subtype of MF and is characterized by specific clinical-pathologic features. Bexarotene has been approved to treat advanced stage cutaneous T-cell lymphomas (CTCL) since 1999 in patients refractory to at least 1 systemic treatment, but its use in FMF and as a first line systemic treatment is poorly described

Methods

A 53-year-old female, presented at universitary hospital with diffuse patches and plaques covering more than 80% of body surface area, severe hair loss and acneiform lesions on the cheeks. She was diagnosed a MF 4 years ago and did not respond to UVA and nbUVB therapy.

Results

She was classified as FMF stage IIIA(T4N0M0B0) and treated with bexaroten 300mg/m^2 per day in combination with Chlormethine gel and nbUVB. Time to response was 3 months and after 12 months of treatment, we observed almost complete hair regrowth and a decrease of the mSWAT score from 72.8 to 4.5. Treatment was well tolerated, hypertriglyceridemia and central hypothyroidism were managed with fenofibrate and levothyroxine.

Conclusions

This case highlights the effectiveness of bexarotene in FMF patients. Expression of RXRs in pilosebaceous units suggests that retinoids play a physiologic role in the function of the sebaceous gland and hair follicle. We postulate that activation of RXR by bexarotene may lead to its beneficial effects on FMF.
This patient also received concomitant therapy, suggesting that bexarotene and nbUVB may have a greater therapeutic effect as suggested in a previous study. The effect of the combination of Chlormethine gel with bexarotene or nbUVB is still unclear.
Regarding the large number of treatment options and high treatment resistance of FMF compared to classical MF, specific guidelines are desirable to ensure significant and clear evidence on the treatments to be preferred in this peculiar variant.

A-169

Establishment of a special electron beam therapy system for the treatment of mycosis fungoides

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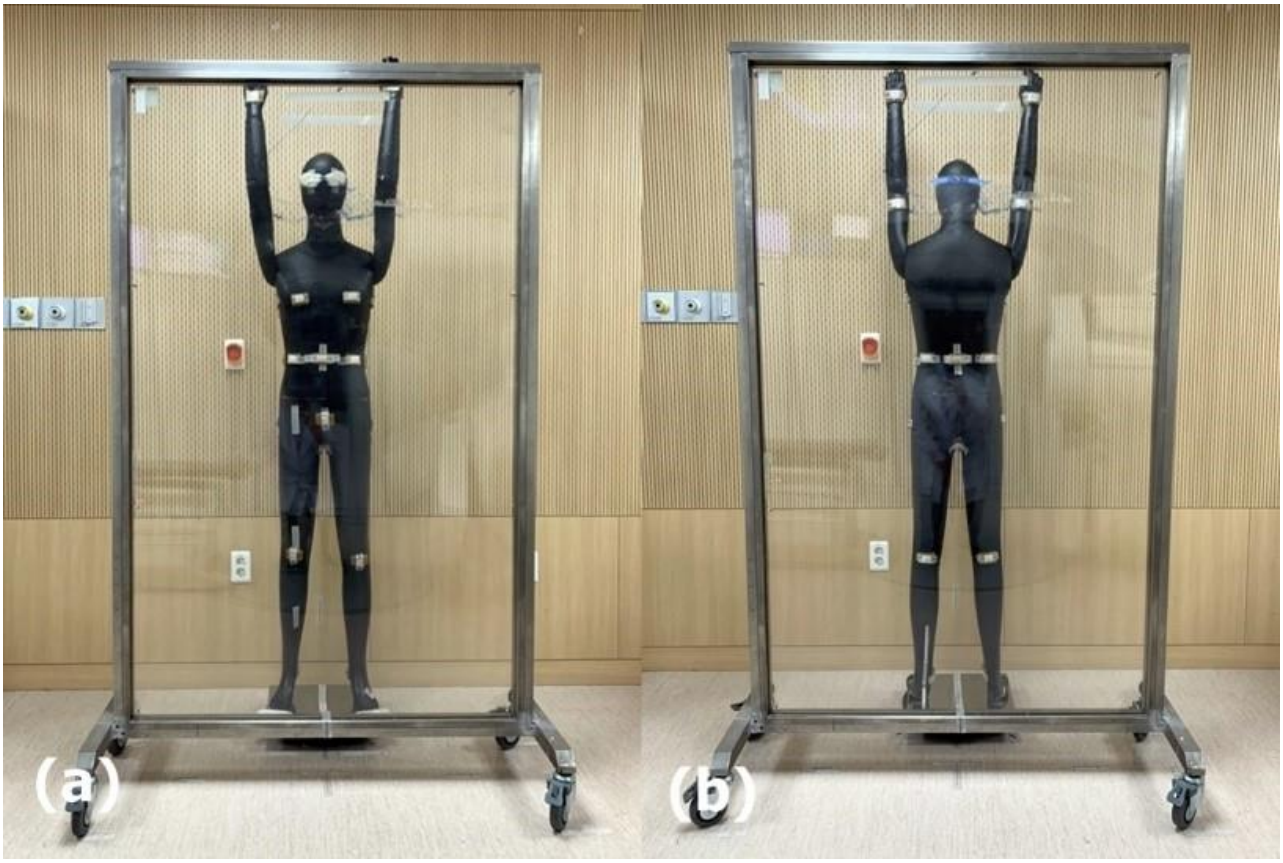
Background

Mycosis Fungoides (MF) is the most common type of cutaneous T-cell lymphoma, accounting for 50% of all cutaneous lymphomas [1]. However, total skin electron irradiation (TSEI), one of the treatment option for MF, has complex procedures and limitations (impossibility to evaluate pre-treatment dose, long treatment time, low posture reproducibility, uneven distribution of treatment dose) for various reasons. The purpose of this study is to establish a standardized system for the special electron beam treatment of MF.

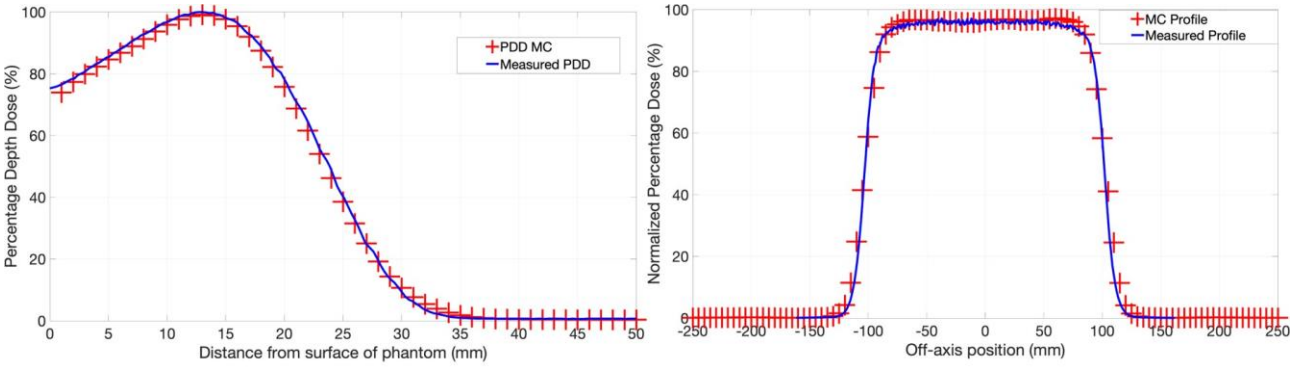
Methods

Phantom set up positon of RTSEI: (a) AP, (b) PA
To apply the Rotating-TSEI (RTSEI) method, a device equipped with a rotating plate that rotates the object at a constant speed was applied (figure1). In addition, we acquired the surface information of the human phantom using a 3D scanner and established a system to evaluate the pre-treatment dose through a dose calculation program using Monte Carlo simulation (MCs). Currently, TSEI treatment is an approach that can overcome this drawback because it is impossible to calculate the dose in advance by first taking a CT scan.



Results

MCs calculated a percentage depth dose (PDD) that matched the measured value within 1.79% / 1 mm and a side profile within 0.79% of the measured data. The measured and calculated results matched 2%. The optimal angles of 73° and 107° were identified in the dual field settings.



The measured and calculated (a) PDD, (b) profile curves for a 36 × 36 cm2 field.

Conclusions

In this study, we demonstrated the feasibility of a novel approach utilizing MCs in a phantom study for treatment of MF. By employing MCs in RTSEI, we can pre-assess the dose distribution similar to other radiation treatments. This ensures precise and safe treatment for patients while alleviating the workload for healthcare providers. Furthermore, this method could also be applied to other electron beam treatment of small tumors such as keloids.

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A-214

Evaluation of Sézary cell marker expression and cell death behavior upon in vitro treatment by flow cytometry in Sézary Syndrome patients

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Background
The diagnosis of Sézary syndrome relies on the identification of blood Sézary cells (SC) by different markers *via* flow cytometry, but is yet to be clarified which of these markers characterizes the malignant cell population best. Treatment of SS is challenging since its pathogenesis is characterized by cell death resistance rather than hyperproliferation. Therefore, restoration of cell death sensitivity and subsequent cell death induction is a central therapeutic approach.

Methods
In this study, peripheral blood samples collected from 20 SS patients were analyzed for the SC marker expression (CD7, CD26, CD158k, and PD1) and cell death behavior both spontaneously and upon *in vitro* treatment with the CTCL therapeutics dimethyl fumarate (DMF), bexarotene, and mitomycin c.

Results
In the SS patients, CD7 loss was detected in 65% of the samples, CD26 loss in 95%, and CD158k gain in 70% of the patient samples. Strikingly, 100% of the SC patient samples expressed PD1. MF and psoriasis patients were measured as controls; in MF, a CD7 loss was detected in 7%, CD26 loss and PD1 gain in 14% respectively, while no MF patient expressed CD158k. In psoriasis, no CD4+CD7-, CD4+CD26-, CD4+CD158k+, and CD4+PD1+ cells were detected. Consequently, SS patients with high and low blood tumor burden were compared. We found the percentage of marker-positive patient samples very similar in the CD4+ and Vβ-clonal populations in patients with high tumor load, while in patients with low tumor burden, we found higher variability in the percentage of marker-positive cells for CD7, CD26, and CD158k between both analyses. Then, cell death behavior was analyzed. The cells were treated *in vitro* with the above-mentioned therapeutics and the difference in cell death was measured. We found DMF to significantly induce specific cell death in the CD7- and CD158k+ and thus SS-typical cell populations compared to the respective marker-negative cell populations. Bexarotene significantly induced cell-death in the CD7-, CD158k+, and the PD1+ cell populations, while mitomycin C only induced cell death in the PD1+ cell population.
Conclusions
Our novel integrated approach enables us to differentially investigate cell death in putative malignant and benign T cell populations and is a first step towards therapeutic stratification. CTCL treatments can be evaluated *in vitro* to individually identify the treatment with high efficacy in the malignant population while leaving the benign bystanders unaffected.

A-260

Extracorporeal photopheresis leads to short-term, but not long-term changes in peripheral blood count analysis of patients with cutaneous T-cell lymphoma

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Background
Extracorporeal photopheresis (ECP) is frequently used for the treatment of cutaneous T-cell lymphoma, i.e. mycosis fungoides and Sézary syndrome. Little is known about short-term and long-term changes in blood counts due to ECP.

Methods
This retrospective study analysed blood counts in patients receiving ECP for mycosis fungoides and Sézary syndrome at the Medical University of Graz.

Results
wenty-eight patients (8 women and 20 men) were enrolled in the study with a mean age (standard deviation, SD) of 61.4 (14.9 years). The median (range) of applied ECP cycles was 17 (3-116). There were significant changes in the mean (SD) total leukocyte count from 8.87 x 10^9/L (4.88) to 7.95 x 10^9/L (4.48) (p=0.001) when comparing blood count from directly before first ECP exposure to the count one day later immediately before the second ECP exposure of the 2-day-treatment cycle. Additionally, the mean (SD) total leukocyte count changed significantly from 8.61 x 10^9/L (4.77) to 8.24 x 10^9/L (4.67) (p=0.006) when taking together and comparing in the very same way the means of all ECP cycles that a patient had received. However, there were no significant changes in leukocyte counts comparing values immediately before the first and before the last applied ECP exposure. Similar changes were observed for levels of erythrocytes, thrombocytes and neutrophile granulocytes, but not lymphocytes, which did not differ in either short-term or long-term analysis.

Conclusions
ECP has short-term effects on peripheral leukocytes but not lymphocytes, primarily due to the depletion of neutrophiles. However, there is no long-term effect on these cells. These findings support the notion that ECP exerts its effect likely through an immunomodulatory mechanism (on lymphocytes) rather than cell depletion and destruction.

A-138

Indolent systemic mastocytosis: A severely symptomatic case – need for mast cell depleting therapy?

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Background
Case description: We present a case of a 49-year-old woman with indolent systemic mastocytosis (ISM). The patient exhibited extensive skin involvement with confluent red-brown maculae/plaques and positive Darier sign (urticaria pigmentosa). A haematological workup revealed 25% infiltration of the bone marrow with atypical mast cells, KIT D816V mutation positive. In the peripheral blood, the mutation load was 1.8%. Serum tryptase was around 80µg/l. There were no B-/ C-findings or associated hematologic neoplasm.

Methods
Symptoms: Main complaints of the patient were severe migraines and gastrointestinal complaints with pain and diarrhoea, resulting in a highly impaired quality of life

Results
Course of therapy: Basic symptomatic therapy for ISM included non-sedating antihistamines, montelukast, cimetidine, and oral cromoglycate. Migraine therapy consisted of triptans, metoclopramide, ibuprofen, metamizole, and erenumab as a prophylaxis. Patient also followed a histamine-reduced diet, noting a correlation between histamine-rich meals and the severity of her migraines. Despite all these therapies, she still suffered from 2-3 migraine attacks per week, accompanied by worsening gastrointestinal symptoms and increased itching and redness of pre-existing urticaria pigmentosa. In November 2023 a therapy with omalizumab was started, which led to an improvement in migraine severity and duration, but not frequency.

Conclusions
Discussion: Headache is a frequent symptom of ISM patients. However, it remains unclear if migraines are directly linked to ISM and mast cell activation or if they are an independent entity. Newly available therapies like avapritinib (tryosinkinase inhibitor with high affinity to KIT D816V mutation), leading to a (KIT D816V mutated) mast cell depletion, represent new therapeutic options for such highly symptomatic IDM patients and could shed further light to pathophysiological mechanisms.

A-219

Italian expert opinion on the treatment of mycosis fungoides with chlormethine gel: results of a Delphi consensus

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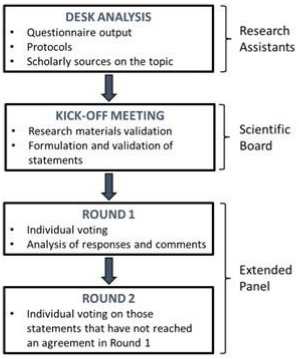
Background

Mycosis fungoides (MF) is the most common form of a rare cutaneous T-cell lymphoma, often present with patches or plaques on the skin and characterized of malignant T cell infiltration.[1][2]. Topical Chlormethine (CL) gel has been approved as monotherapy for treatment of adult patients with MF. In clinical practice, chlormethine (CL) gel is often combined with other skin-directed or systemic therapies to optimize response and target recalcitrant lesions.

Objective: Increase knowledge, identify and discuss the use of CL gel on MF lesions in clinical practice with the aim of improving patients health-related quality of life (QoL).

Methods

In the present study a modified Delphi methodology (Fig. 1) is used. A panel of 7 experts (the Scientific Board) was selected to identify 22 statements to be voted by the extended panel (28 expert Italian dermatologists) and consensus was reached on most of the points discussed.



Overall flow of the Delphi process employed in this study

Results

In case of early stages of the disease, it was stated the use of CL gel is recommended in stages IA-IIA. The panel agreed in supporting the acceptable tolerability of CL gel in combination with other topical or systemic therapies, paying attention to the type of lesion treated (stage) and emphasizing the fact that it is a very useful adjuvant drug for persistent or refractory lesions. It was also stated by the panel that maintenance therapy after a partial response is suggested until complete remission.

Conclusions

The experts unanimously support how CL gel is characterized by speed of action and flexibility in its application and also has safety features in cases of early and advanced lesions, giving to the patient an improvement of Quality of Life (QoL).

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A-173

Long-Lasting Remission in a Patient with Sézary Syndrome Treated with Anecdotal Low Doses of Triple Therapy

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Background
Sézary syndrome (SS) patients comprise less than 5 % of all patients with cutaneous T-cell lymphoma. There are still no clinical signs or biomarkers to predict treatment response. The aim of this report is to present a patient with a history of long-lasting disease remission achieved after triple treatment with extracorporeal photopheresis (ECP), pegylated interferon alpha and Targretin.

Methods
This is a case report. A 66-y old man with a history of hypertension, inguinal hernia, and myocardial infarction was diagnosed with SS in November 2014 (skin biopsy showing typical presentation of SS, blast cells 10-20%, Ki67-40%, TCR β+γ +).

Results
After an initially ineffective treatment with Acitretin, the patient started on Targretin (150mg /m^2) then pegylated interferon alfa (135 µg/week), and ECP (initially 2 consecutive days every second week). The patient responded well to the triple therapy, achieving complete remission within 1 year. Due to the side effects, including decreased blood parameters and increased lever function enzymes, the therapy was subsequently tapered to 90 µg pegylated interferon alfa every 6^{th} week, Targretin 1 capsule (75 mg) every 3^{rd} day, and ECP every 12^{th} week. The patient responded well to this treatment strategy, achieving complete blood resolution within 1,5 years and resolution of skin symptoms within 3 years. Complete resolution of SS with this low dose of triple therapy has lasted since 2019, with no signs of skin or blood involvement. The patient is now requesting a futher reduction in ECP cycles, preferable to every 16^{th} week. Allogenic stem cell transplantation has been discussed at many appointments. However, the patient has resisted this option, which might offer a cure but also carries risks of complications and treatment-related morbidity.

Conclusions
This patient illustrates that low dosages of triple therapy (Bexaroten + pegylated interferon alpha + ECP) with dosage adjustments based on clinical response and tolerability, might be an effective and cost-saving treatment option for some patients with SS.

A-299

Long-term management of advanced mycosis fungoides:Challenges in routine clinical practice

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Background
Folliculotropic Mycosis Fungoides (FMF) and tumor-stage Mycosis Fungoides (MF) are variants of cutaneous T-cell lymphoma often requiring sequential and multi-modal treatment. We herein present the history of two patients, highlighting the complexity of treatment in advanced MF.

Methods
Patient 1: A 50-year-old male with histologically confirmed FMF (ISCL/EORTC stage IIB), CD30-positive, first presented to our department in 2018. Previous treatments comprised oral methotrexate, alongside with extracorporeal photopheresis, and 4 doses of doxorubicin. None of these therapies had led to improvement, thus we initiated brentuximab vedotin. After 9 months, brentuximab

treatment was discontinued due to lack of response. The patient subsequently received total skin electron beam therapy (TSEB, 36 Gy) leading to complete remission. In 2022, nodular erythematous lesions appeared on his left upper eyelid. Biopsy revealed mixed B- and T-cell infiltrates, consistent with FMF. This site proved to be particularly refractory to local steroids. Hence, multiple surgical interventions including a tarsal wedge resection of the right eye were conducted leading to temporary disease control. Currently, local brachytherapy is considered due to repeated recurrence.

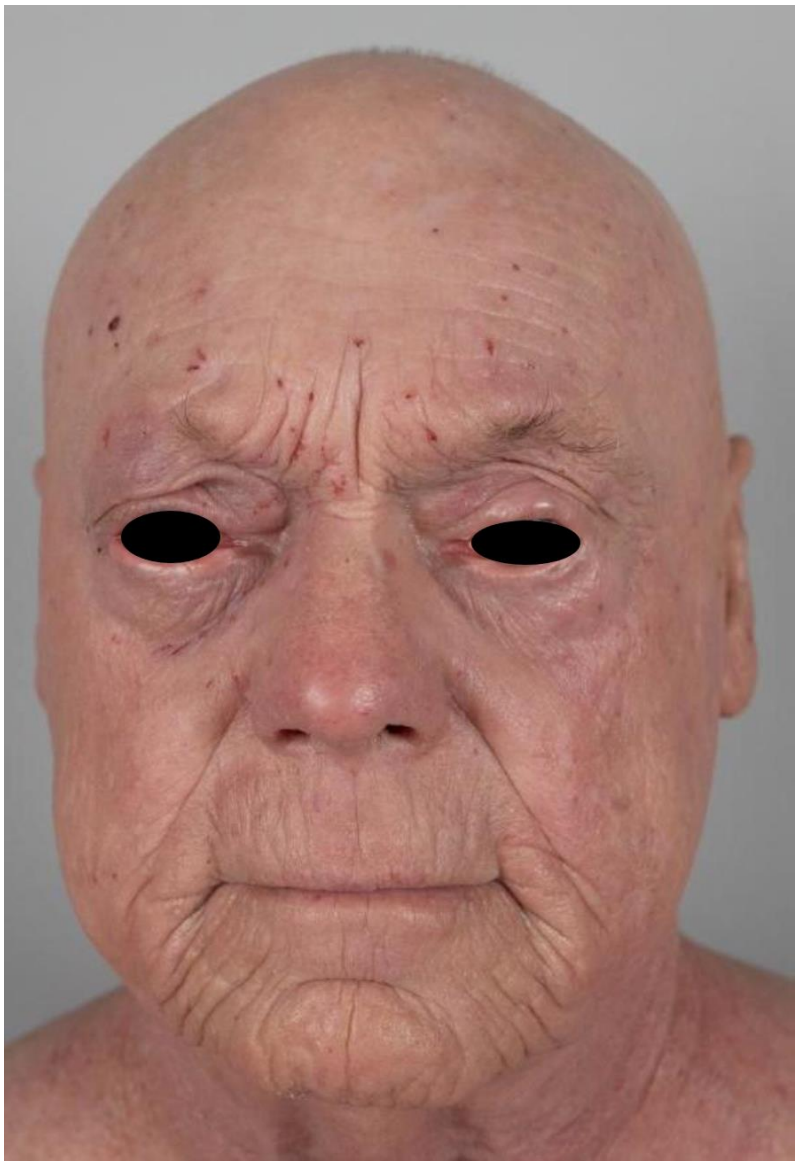

Figure 1

Results

Patient 2: A 79-year-old female was diagnosed with tumor-stage MF (IIB, T3NxB1b) in 2020, featuring a positive TCRR and <1% CD30 positivity on immunohistochemistry.

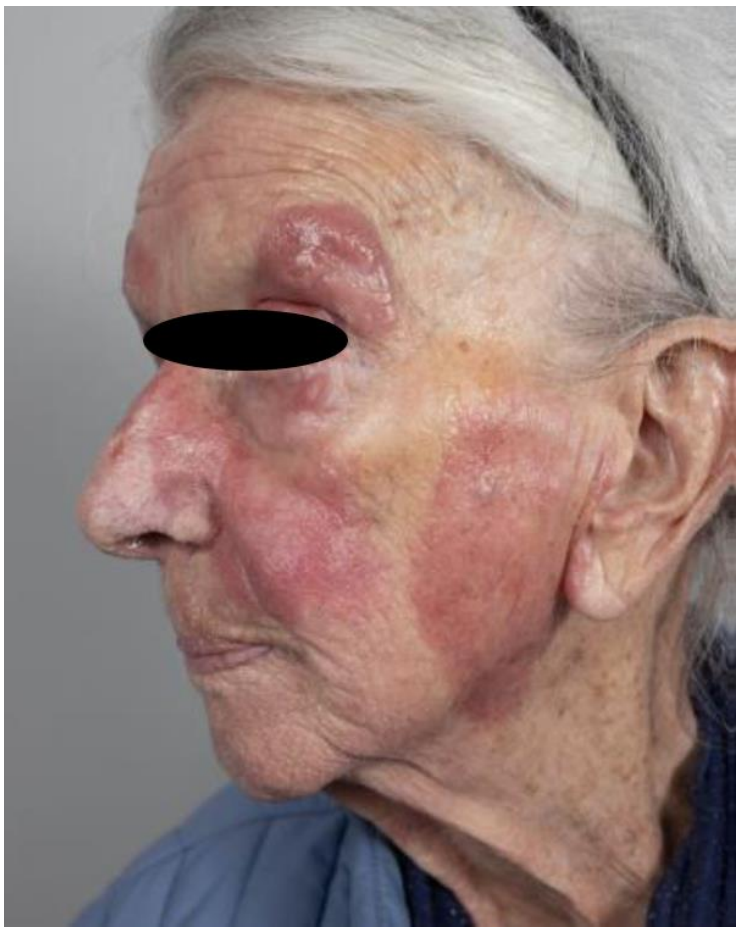

Figure 2
UVB therapy and bexaroten treatment showed no significant improvement of the skin lesions. Progressive lymphadenopathy led to the initiation of mogamulizumab, resulting in partial response, also in the skin. After 18 doses, the therapy was discontinued due to disease progression. Subsequent electrochemotherapy provided only slight improvement of an ulcerated parieto-occipital tumor. The patient then received seven doses of brentuximab vedotin, which was halted in August 2023 due to lack of response and increasing hair loss. Most recently, pegylated interferon alfa did not influence rapid disease progression with development of numerous ulcerated tumors, which is why cytotoxic chemotherapy is considered as the next line of treatment.

Conclusions
Primary and secondary treatment resistance as well as adverse effects are challenges in the treatment of advanced MF, explaining the frequent need for several lines of treatment in clinical practice. Our cases illustrate the need for continuous reassessment and treatment adaptation to achieve optimal patient outcomes.

A-272

Mogamulizumab-induced lymph node enlargement mimicking micosis fungoides progression

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Background
Cutaneous T-cell lymphomas are lymphoproliferative disorders with an estimated annual incidence of 0.5 cases per 100,000 people. The most common type is Mycosis Fungoides (MF)s. Mogamulizumab is a monoclonal antibody approved for MF treatment after at least one prior systemic therapy. A wide spectrum of Mogamulizumab-associated rash (MAR) have been reported, as far as we know limited to the skin.

Methods
In this case report we present a patient with MF treated with mogamulizumab who experienced apparent malignant lymph node progression based on imaging tests, but were histologically free of malignant disease. Additionally, the patient developed new skin

lesions consistent with Mogamulizumab-associated rash (MAR) and later he maintained complete remission and good overall condition with continued mogamulizumab treatment.

Results
The patient is a 70-year-old male with MF with large cell transformation, basal mSWAT score of 70 and 40% lymphocytes (82 cells/uL) displaying pathological inmunophenotype (CD2+, CD3+, CD4+, CD7-, CD26-), therefore at T4N2M0B2 stage.
Mogamulizumab was initiated with prompt complete haematological and cutaneous remission at 4th infusion. Two months after starting mogamulizumab (7th infusion), imaging tests showed multiple new enlarged adenopathies with increased metabolism. Simultaneously, hethe patient developed new skin lesions different from pre-treatment ones. Lymphoma progression was suspected, and histological study was performed. Lymph node biopsy revealed dermopathological changes without a lymphoproliferative process, with isolated non-necrotizing granulomas. Likewise, the skin biopsy showed sarcoid granulomatous dermatitis. Both biopsies showed a predominace of CD8 cells over CD4. No evidence of lymphoma was found in any other department, and patient kept an excellent overall condition. Mogamulizumab infussions were spaced to every 3 weeks, maintaining clinical and radiological stability after 1 year.

Conclusions
We suggest that mogamulizumab treatment may induce non-neoplastic adenopathy, mimicking lymphatic progression of primary lymphoma, leading to potential misdiagnosis and unnecessary discontinuation of medication. Histological confirmation of adenopathic progression is recommended alongside imaging tests. Furthermore, the presence of non-neoplastic adenopathy due to mogamulizumab may serve as a marker of a positive response to treatment. Recognizing these reactions will prevent misdiagnosis and unnecessary discontinuation of medication.

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Nb-UVB and PUVA Therapy for Early Mycosis Fungoides: A Cross-Sectional Study

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Background
Mycosis fungoides (MF) and Sezary Syndrome are the most common forms of cutaneous T-cell lymphoma[2]. Early-stage MF typically has an indolent course, and the EORTC guidelines recommend skin-directed therapies, such as phototherapy, over systemic treatments. Phototherapy, utilizing PUVA and narrowband UVB (nb UVB), is a popular treatment option. Although PUVA can have systemic effects and potential carcinogenic risks, nb UVB primarily affects the skin. Despite ongoing debates regarding UVB light's efficacy, in 2021, the Cutaneous Lymphoma Italian Study Group reached a consensus on technical protocols for Nb-UVB and PUVA in treating MF.

Methods
This study aimed to compare the efficacy of nb UVB and PUVA in early-stage MF patients. Patients diagnosed with stage IA/B MF between 31/12/2011 and 31/12/2021 were selected from our unit's cutaneous lymphoma database. Inclusion criteria were at least 12 months of follow-up, a minimum of 24 phototherapy sessions (PUVA or nb-UVB), and treatment only with topical steroids alongside phototherapy. Data analyzed included treatment number, time between cycles, total cumulative dose, mSWAT scores before and after each cycle, therapy response, and follow-up duration. PUVA treatments involved 8-methoxypsoralen (0.6 mg/kg) two hours before UVA exposure, administered three times weekly. Nb-UVB treatments were given two to three times weekly, with dosage adjustments based on skin phototype.

Results
Our findings support existing literature on nb UVB and PUVA efficacy. Nb-UVB showed a 71.7% complete response (CR) rate, aligning with previous reports. More patients received nb UVB, reflecting a trend favoring it for early-stage MF due to fewer side effects and lower carcinogenic risk. PUVA had a 73.1% CR rate, similar to literature data, but the small number of PUVA patients may explain the lack of a higher CR rate. When responses were stratified by disease stage, no significant differences emerged between nb-UVB and PUVA, suggesting that nb-UVB's efficacy in stage IA is comparable to PUVA's efficacy in stage IB.

Conclusions
Our data[1] and literature suggest nb-UVB as the preferred initial treatment for stage IA MF due to comparable efficacy to PUVA but with fewer adverse effects and lower carcinogenic risk. Thus, nb-UVB may be favored in early-stage MF treatment protocols.
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A-232

Outcome of cutaneous T-cell lymphomas after allogeneic hematopoietic stem cell transplantation : focus on relapses and their management

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Background
Prognosis for advanced cutaneous T-cell lymphoma (CTCL) is poor, despite the development of monoclonal antibodies. Allogeneic hematopoietic stem cell transplantation (HSCT) is the only potentially curative treatment, as recently shown by the prospective randomized CUTALLO trial. However, 47% of relapses occurred in the HSCT group vs. 86% in the control group and data on management and evolution of post-HSCT relapses are limited.

Methods
This single-center retrospective study included all patients who had HSCT for advanced-stage CTCL between 2016 and 2024. Pre- and post-HSCT data were collected : CTCL type, stage, number of pre-HSCT lines, status at the time of HSCT, type and time to recurrence, treatments performed, existence of GVH, status at last news and post-HSCT survival).

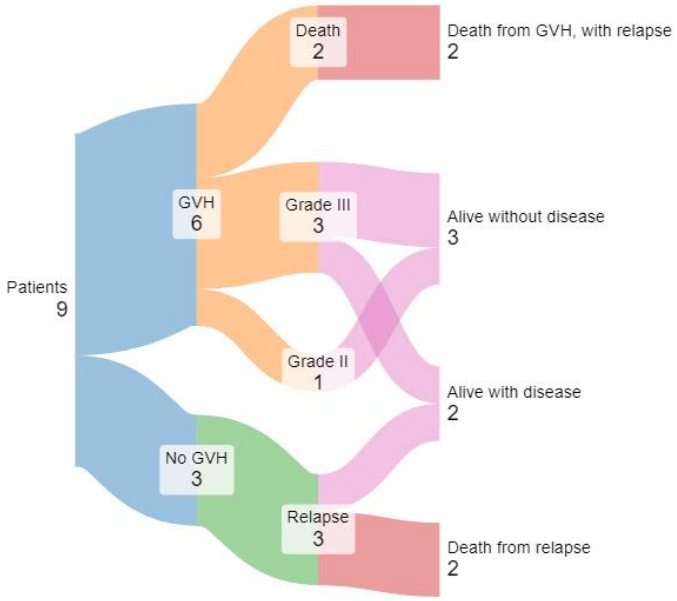
Results
Among the 9 patients included, median age 47 years [32-68]; 7 had transformed mycosis fungoides (T-MF), 1 Sézary syndrome (SS) and 1 cytotoxic CD8+ CTCL. Median time from initial diagnosis to HSCT was 24 months [4-121] and median number of pre-HSCT lines, 5 [1-8]; 4 patients were in complete response (CR) at the time of HSCT, 4 partial and one in progression. After a median follow-up of 48 months (4-99), 2 patients (1 MF, 1 SS) did not relapse, 6 had skin relapse, 1 both skin and brain relapse. Four patients died: 2 of CTCL and 2 of GVH after CTCL relapse. Median progression free survival (PFS) was 3 months [0-84], and overall survival (OR) 51 months [4-99]. Brentuximab +/- radiotherapy was the main strategy relapses management, and 1 patient achieved prolonged CR after initial relapse.

Sex/age	diagnosis	Time from diagnosis and HSCT (months)	Number of pre-HSCT lines	Total skin electronbeam before HSCT	Statud at the time of HSCT	Delay and type of relapse	relapse treatment	GVH	Current status and folow-up (months)
M/68	T-MF	6	1	no	PR	3/skin	Radiotherapy, bexarotene, methotrexate, brentuximab, Chemotherapy, DLI	no	Alive PR, 70
M/41	T-MF	42	5	yes	PR	2/skin	Radiotherapy, Bexarotene, Brentuximab	Grade III	Alive, PR, 51
M/44	Cytotoxic	19	5	yes	CR	1/skin	Chemoth	Grade IV	Dead

	CD8+ CTCL						erapy, DLI		from hepatic GVH after disease relapse, 18
M/55	SS	44	7	no	PR	none	none	Grade III	Alive, CR, 85
M/47	T-MF	16	4	no	PR	1/skin	Brentuximab, radiotherapy, DLI	Grade II	Alive, CR, 99
M/56	T-MF	24	8	yes	CR	17/skin	Radiotherapy, chemotherapy, brentuximab, iHDAC, DLI	no	Dead from disease, 81
M/42	T-MF	121	5	yes	CR	none	none	Grade III	Alive, CR, 8
M/52	T-MF	4	1	no	CR	12/skin	Bexarotene, UVB	Grade IV	Dead from digestive GVH after disease recurrence, 18
M/32	T-MF	32	6	yes	PD	0/skin-brain	radiotherapy	no	Dead from disease, 4

Characteristics of patients

Global outcome of patients (Sankey diagram)



Conclusions

Within the limits of its small size, our series suggests that the occurrence of grade II or III GVH appeared to be associated with better PFS, whereas conversely, those without GVH relapsed more severely. Interestingly, on patient was treated by photopheresis for GVH and did not relapsed from MFT to date, underlining the dual benefit of this approach on GVH and CTCL. The recurrences observed were mostly (6/7) exclusively cutaneous (6/7), manageable with a reduction of tumor burden comparing to pre-HSCT status, whereas it is likely that these patients would have died from the natural history of their CTCL without HSCT.

Despite the improvement in prognosis brought by HSCT in CTCL, we illustrate here the frequency of skin recurrences, less aggressive than the initial disease, and suggest local, immunomodulatory treatments, especially brentuximab, relevant in the therapeutic strategy.

A-295

Radiotherapy Dose for Primary Cutaneous Anaplastic Large Cell Lymphoma

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Background
Radiotherapy is very effective treatment for Primary cutaneous anaplastic large cell lymphoma (pcALCL). The current guidelines recommend conventional radiotherapy doses of 30 to 36 Gy. We have used lower dose radiotherapy schedules and report our experience.

Methods
We retrospectively reviewed the notes on patients diagnosed with pcALCL. We recorded demographics, treatment details, relapse, survival, relapse sites and relapse treatments. Relapses post radiotherapy were defined as local infield, edge of field, distant or systemic. We analysed the outcomes of the radiotherapy patients based on whether they received conventional 30-36Gy in 15-18 fractions, or our low dose schedules of 8-12Gy in 2-3 fractions.

Results
37 patients have been identified with confirmed pcALCL. The median follow up was 48 months. 35 patients had no systemic involvement and 2 patients had loco regional nodal involvement. The 2 patients with locoregional nodal involvement received CHOP chemotherapy. The modalities of treatment were observation n=1, topical therapy n=4, radiotherapy n=21, excision and observation n =9, chemotherapy n=2. All 37 patients are alive at last follow up in remission.
11 patients were treated with low dose radiotherapy, with a median follow up of 23 months. In these patients there were 4 distant skin relapses that were successfully treated with low dose radiotherapy.
10 patients were treated with conventional dose radiotherapy with a median follow up of 62 months. In these patients there were 4 relapses, 2 at distant skin sites and 2 with systemic node involvement.

Conclusions
Our preliminary experience confirms the excellent prognosis of pcALCL and shows some patients may be effectively treated with lower doses of radiotherapy.

A-121

Real-life evaluation of chlormethine gel in the treatment of stage IA-IVA2 mycosis fungoides: a single centre experience of 66 patients

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Background
Topical chlormethine gel (CG) is an anti-neoplastic alkylating agent, licenced in England since August 2021 for the treatment of MF in patients who have received prior skin-directed therapy. The aim of this study was to evaluate our experience of using CG in a single UK centre.

Methods
All patients who commenced topical chlormethine gel in our unit between January 2022 (when chlormethine gel was first available to us) and December 2023 were identified. An intention to treat, retrospective analysis of medical records was performed.

Results
66 patients (58% male) were identified with a mean age of 60.3 years (standard deviation 14.6). Multiple stages of MF (IA 35%, IB 47%, IIB 9%, III 2%, IVA1 2%, IVA2 6%) were represented; CG was applied to patches and plaques only. Prior to commencing chlormethine gel, all patients had used topical steroids; the majority of patients had received more than 5 (33%) or 2-4 (50%) prior treatment lines (superficial radiotherapy and TSEB 53; phototherapy 62; systemic therapy 50). 16% used CG as an adjuvant to specific lesions whilst continuing systemic or radiotherapy. The median duration of treatment with CG was 264 days; 64% of patients consider the treatment a success and continue ongoing episodic treatment or have stopped due to a complete or partial response. 2% stopped due to disease progression, 9% due to lack of response and 22% due to unacceptable side effects. The average duration of treatment for responders (complete or partial response) and non-responders (no response or worsening of skin disease) was 340 and 176 days respectively. 82% of all patients experienced toxicities; these were exclusively cutaneous: most commonly erythema (32%), pruritus (32%) and dermatitis (30%). Hyperpigmentation at treated sites was observed in 14% patients. The majority of these patients had a complete or

partial response to treatment; they had no other adverse events allowing for a longer duration of treatment. No serious adverse events were observed. Toxicities were largely managed with brief treatment breaks, emollients and topical steroid use immediately followed by gradual re-introduction of chlormethine at a lower frequency, enabling patients to continue treatment. 50% used emollients and topical steroids briefly to enable CG to be restarted.

Conclusions

We present real-life data on the use of topical CG in our cohort of MF patients and demonstrate that it is an effective, well-tolerated skin-directed therapy. Skin toxicities were managed conservatively.

A-133

Real-world evidence study of brentuximab vedotin retreatment in patients with cutaneous T-cell lymphoma

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Background

Cutaneous T-cell lymphoma (CTCL) is a rare tumor with limited treatment options; allogeneic stem cell transplant is the only available curative therapy, and many patients may require retreatment with a drug that has been used previously. Brentuximab vedotin (BV) has been approved for the treatment of adult patients with CD30+ CTCL who have received ≥1 prior systemic therapy. This approval was based on data from the phase III ALCANZA study which showed a treatment benefit for BV compared to physicians' choice in patients with CTCL. While results from real-world studies are consistent with the ALCANZA study [1][2], currently no multi-country data are available regarding the safety and effectiveness of BV retreatment in patients with CTCL. Here, we report an interim analysis of real-world data from a retrospective chart review of patients with CTCL in Europe.

Methods

This retrospective, multicenter chart review study included data from patients being treated at 8 clinical sites in Germany, Spain, and France between January and June 2024. Eligible patients had a confirmed diagnosis of CTCL and had relapsed or progressed after achieving a complete response, partial response, or stable disease upon previous treatment with BV. Patients were aged ≥18 years at the time of first BV treatment and received BV in ≥2 lines of therapy (≥3 cycles of BV during retreatment) with ≥4 months between first BV treatment and retreatment. Primary objectives were to describe the effectiveness of BV re-exposure in patients with CTCL (objective response rate [ORR]), progression-free survival, and time to next treatment), and safety outcomes (rates of peripheral neuropathy, neutropenia, and serious infections).

Results

A total of 12 patients with CTCL were included in this interim analysis (Table). The median (range) age at diagnosis was 54 years (12–73); 58% were male. The primary CTCL subtypes at diagnosis were mycosis fungoides (MF; 67%), Sézary syndrome (17%), and primary cutaneous anaplastic large cell lymphoma (17%). In patients who were tested (n=8), CD30 expression at diagnosis was <10% in 33%, 10–50% in 33%, and >50% in 17% of patients. At first and second BV treatment, 58% and 50% of patients, respectively, had skin symptoms. After first BV treatment, the ORR was 83%; at retreatment this was 64%.

	CTCL diagnosis (N=12)	First BV treatment (N=12)	Second BV treatment (N=12)
Age, years, median (range)	54 (12–73)	59 (29–80)	60 (30–83)
Sex, male, n (%)	7 (58%)	–	–
Primary CTCL subtype, n (%)			
Mycosis fungoides	8 (67%)	–	–
Folliculotropic MF*	3 (38%)	–	–
Classical type*	5 (63%)	–	–
Sézary syndrome	2 (17%)	–	–
Primary cutaneous anaplastic large cell lymphoma	2 (17%)	–	–
CD30 expression tested, n (%)			
Yes	8 (67%)	10 (83%)	8 (67%)
CD30 expressed†	6 (75%)	10 (100%)	8 (100%)
<10%	2 (33%)	2 (20%)	2 (25%)
10-50%	2 (33%)	6 (60%)	4 (50%)
>50%	1 (17%)	1 (10%)	–
Unknown	1 (17%)	1 (10%)	2 (25%)
No	–	1 (8%)	4 (33%)
Unknown	4 (33%)	1 (8%)	–
Comorbidities, n (%)			
Yes	3 (25%)	3 (25%)	3 (25%)
No	6 (50%)	9 (75%)	9 (75%)
Unknown	3 (25%)	–	–
Skin symptoms at the time of BV treatment, n (%)‡			
Yes	–	7 (58%)	6 (50%)
No	–	5 (42%)	6 (50%)

*Denominator is total number of patients with MF primary CTCL subtype
†Denominator is total number of patients with CD30 expression at CTCL diagnosis
‡Skin symptoms: rash, dry skin, pruritus/itching, redness, irritation, burning, scabbing, flaking, skin infection, erosions, skin induration and oozing

Table. Patient demographics and clinical characteristics

Conclusions
At interim analysis of this real-world retrospective chart review, 12 patients with CTCL were enrolled. Safety and further efficacy data will be presented.

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A-107

Severe relapses of cutaneous T-cell lymphoma after treatment of chronic graft-versus-host disease with ruxolitinib

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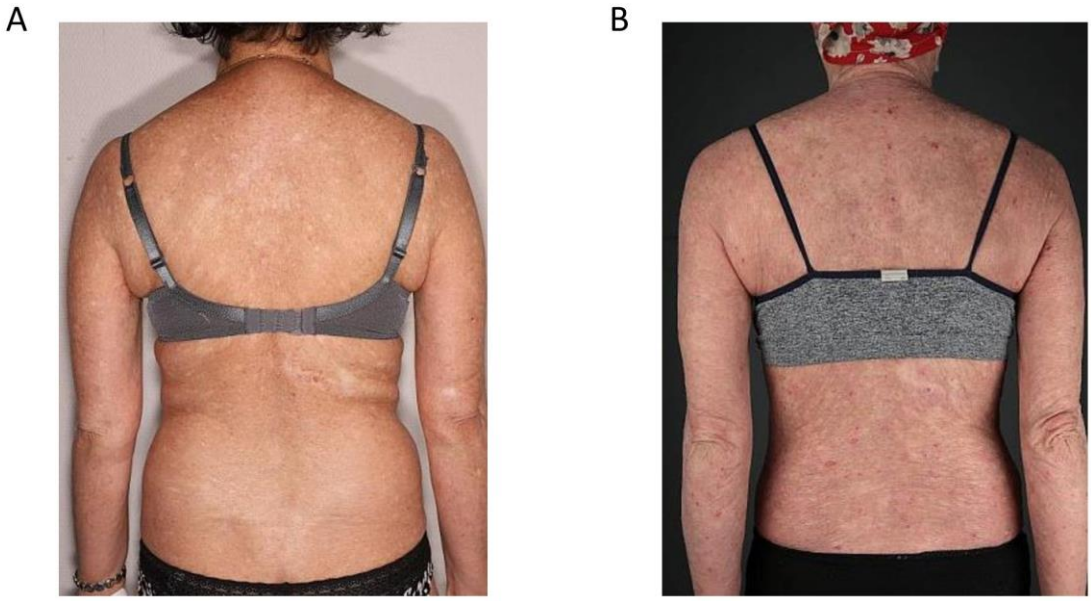
Background
A poor prognosis characterizes advanced-stage cutaneous T-cell lymphomas (CTCL) including tumor-stage mycosis fungoides (T-MF) and Sézary syndrome (SS). Allogeneic stem cell transplantation (aHSCT) is the only potential curative option in advanced CTCL, but is associated with complications, such as graft-versus-host disease (GVHD)[1]. Ruxolitinib, a JAK1/2 inhibitor, has shown efficacy in treating corticosteroid (CS)-refractory chronic GVHD, but has mainly been studied in context of myeloid malignancies.

Methods
We present two cases of patients who experienced dramatic worsening of CTCL after aHCST, after having received ruxolitinib for the treatment of GVHD.

Results

A 63-year-old (case-1) man with T-MF (T3N0M0B0) in excellent partial response (PR) after multiple treatments received an aHSCT, allowing a complete (C)R. He later developed a muscular GVHD effectively treated with several treatments including ruxolitinib. However, he developed erythroderma with skin tumors histologically consistent with a relapse of a large-cell transformed (LCT) CTCL, without evidence for extra-cutaneous involvement (T4N0M0B0). Ruxolitinib was progressively tapered and the patient received chemotherapy and total skin electron beam therapy with a PR.

A 53-year-old (case-2) female with LCT folliculotropic MF (T3N0M0B0) received an aHSCT inducing a CR. However, she subsequently developed severe chronic skin GVHD, treated with ruxolitinib and CS. She then experienced a cutaneous and blood relapse of LCT CTCL (**figure and table)**classified as SS (T4NxM0B2). Withdrawal of ruxolitinib and chemotherapy+ brentuximab-vedotin led to a skin and blood PR (**table**).



Clinical presentation of patient 2 with cutaneous T-cell lymphoma A: Near complete response at the time of allogeneic hematological stem cell transplantation. B: Erythroderma at the time of post-transplant relapse, 9 months after starting treatment with ruxolitinib

Table. Patients' characteristics at diagnosis and evolution under treatment		
	Case 1	Case 2
Age (years) at diagnosis, sex	47, male	36, female
TNMB staging at CTCL diagnosis	T3N0M0B0	T2N0M0B0
Pre-transplant cutaneous large-cell transformation	Yes	Yes
CTCL treatment used before allo-HCST / best response / reason for discontinuation	PUVA therapy / SD / LE Clobetasol / SD / LE Acitretine / SD / LE Bexarotene / SD / LE Brentuximab-nivolumab / PR / AE PLD / PR / LE Romidepsin / PR / LE Etoposide-ifosfamide / PR / LE Bendamustine / PR	Chlormethine / PR / LE Carmustine / PR / LE PUVA therapy / PR /AE PLD / CR Bexarotene / PR /AE
Clinical pre-transplant response	PR	PR
B stage at time of transplant	B0	B0
Age (years) at time of transplant	60	49
Initial GVHD prophylaxis	Cs-A, MTX	Cs-A, MTX
Occurrence of acute GVHD	No	Yes: Skin, gut, liver
Organs involved by chronic GVHD	Muscle	Eyes, skin, mouth
Treatments of chronic GVHD	IgIV, prednisone, ruxolitinib	IgIV, prednisone, ruxolitinib
Ruxolitinib dosage	20 mg/day	30 mg/day
TNMB staging at relapse	T4N0M0B0	T4NxM0B2
Time between aHCST and CTCL relapse (months)	20	30
Cumulative time of ruxolitinib exposure at the time of CTCL relapse (months)	12	9
Therapeutic strategy to manage CTCL relapse	Withdrawal of ruxolitinib PLD	Withdrawal of ruxolitinib Bexarotene, PLD + brentuximab vedotin
CTCL: cutaneous T-cell lymphoma; allo-HCST: allogeneic hematopoietic stem cell transplantation; CR: complete response; PR: partial response; SD: stable disease; PD: progression of the disease; AE: adverse events; LE = lack of efficiency / MCD = maximum cumulative dose achieved; GVHD: graft-versus-host disease; ciclosporine A (Cs-A); methotrexate (MTX); pegylated liposomal doxorubicin (PLD)		

Patients' characteristics at diagnosis and evolution under treatment

Conclusions

As CTCLs exhibit dysregulation of JAK/STAT signaling, this pathway is considered as a novel target for CTCL. However, in a trial evaluating ruxolitinib in refractory T-cell lymphomas, one only out of 7 MF patients experienced a PR.[2]While relapses following transplantation are in most cases limited to skin, our two patients experienced an uncommonly explosive relapse with major blood involvement in one. Although the evaluation of JAK inhibitors to treat CTCL requires further investigation, these cases suggest a deleterious effect of ruxolitinib on CTCL after aHSCT possibly linked to the impairment of the graft versus leukemia response. This warrants prudent use of ruxolitinib to treat GVHD in patients with CTCL.

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A-111

Sub-analysis of the BELIEVE STUDY: Effectiveness and safety for re-treatment with Brentuximab-vedotin in relapsed/refractory (R/R) Cutaneous T Cell Lymphoma (CTCL): a retrospective medical chart review study in Spain. NCT:04998331

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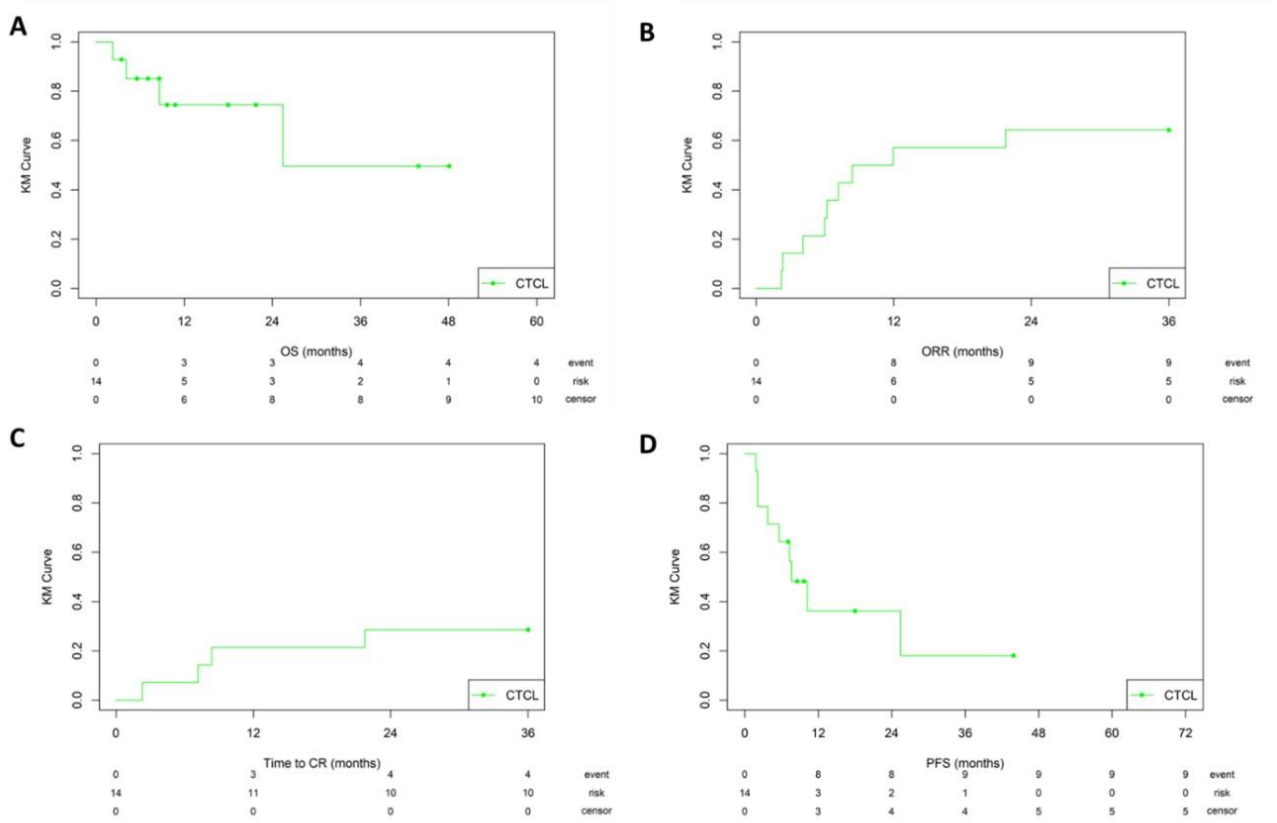
Background

Brentuximab vedotin (BV) is a CD30-directed antibody-drug conjugate. The efficacy and clinical benefit of BV in patients with CD30+ R/R malignancies has been shown in pivotal studies. The aim of this study was to describe effectiveness/safety of BV retreatment in R/R CD30+ patients in a real-world setting in Spain.

Methods

A noninterventional, retrospective chart review study conducted in 30 Spanish sites (collection:2014-2022). Adult patients with CD30+ malignancies who were treated with BV (evidence of objective response, OR) and having received ≥2 doses of BV as retreatment were included. Patients were followed up to ≥6 months or treatment discontinuation due to death or toxicity. Primary objectives were to assess safety/effectiveness of BV retreatment. Here we present the data related to mycosis fungoides (MF) and primary cutaneous anaplastic large cell lymphoma (pcALCL).

Results



Kaplan -Meier estimates of (A) Overall Survival, (B) time to OR, (C) CR and (D) PFS for CTCL patients

Of the 14 patients evaluable, 12MF /2pcALCL. At BV retreatment, >70% of patients had advanced disease (3 Stage IIB, 4 stage IIVA, 3 Stage IVB). Median age was 51 (34-76) years, 57% were male, and 90% had ECOG PS grade 0–1. The median number of treatments received before retreatment was 6.5 (2-30). The median time from 1st BV treatment to retreatment initiation was 11 (6–45) months. OR was 64.3%: 4 CR (28.6%) and 5 PR (35.7%); 3 progressed (21.4%). The median time to achieve CR: 8 months (2.3-21.7). The median PFS: 5.6 months (1.8-25.4). Four patients died due to progression providing a median OS of 25.4 (2.3-25.4) months (Fig. 1). The median number of cycles of the first BV treatment had been 8.5 (3-16) and during BV retreatment it was 7 (3-14). Four patients experienced adverse events (AEs) related to BV retreatment, mainly peripheral sensory neuropathy (PSN). Severe AEs were reported in 3 patients (21.4%) corresponding to PSN, neutropenia and bacteremia. No Grade 5 events were reported during retreatment.

Conclusions

The BELIEVE study is the first real word evidence study in Spain that assesses the role of BV as retreatment. BV retreatment seems to be promising and tolerable treatment strategy for CTCL patients.

A-251

Successful Treatment of Refractory Folliculotropic Mycosis Fungoides with Topical Ruxolitinib

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Background

The JAK/STAT pathway is activated in many subtypes of T-cell lymphomas and has been found to play an important role in the pathogenesis of mycosis fungoides (MF). Ruxolitinib is a JAK 1 and 2 inhibitor with efficacy demonstrated in T-cell lymphoma when administered orally.

Methods

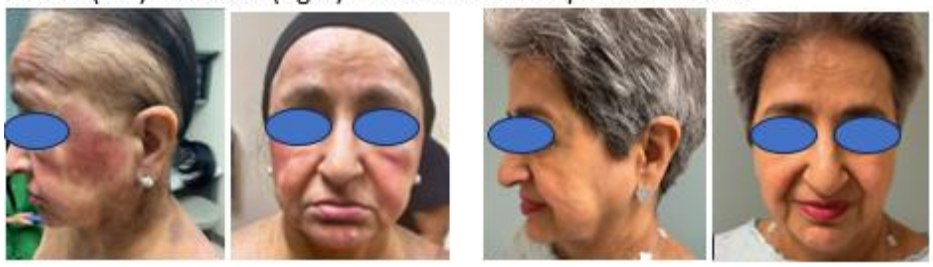
We present a patient with folliculotropic MF who presented with a persistent skin disease after both total skin electron beam therapy

(TSEBT) radiation and Brentuximab Vedotin (BV) but improved with topical ruxolitinib.

Results

The patient is a 72-year-old Hispanic female with a history of rash since 2013 and a diagnosis of MF in 2021. She was treated previously with topical steroids, bexarotene, methotrexate, and UVB phototherapy when she presented to our institution in January 2023 with progressive disease. She presented with patches and plaques on the skin with BSA 21.3 and mSWAT 23.8. Skin biopsy showed CD4+ atypical lymphoid infiltrate with epidermotropism and focal folliculotropism consistent with folliculotropic MF. PETCT and blood flow cytometry were negative for systemic involvement. She also had staphylococcus aureus infection at multiple sites on her skin. The patient received 12 Gy TSEBT in March 2023, and for the lack of complete response, TSEBT was shortly followed by several local radiation fields in April 2023. Pegylated interferon was added as an adjunct to radiation therapy, but patient was not able to tolerate it due to elevated liver enzymes. In May 2023, the patient presented with disease recurrence with patches and plaques on the face and trunk BSA 24.5 and mSWAT 32, and started on BV, given for six cycles with partial response. The patient had persistent patches on her face despite BV treatment. Desonide ointment to the face was initiated without improvement. Imiquimod caused worsening of lesions. Topical ruxolitinib cream 1.5% cream was initiated twice daily, given a history of previous use with benefit before MF diagnosis. She continued to apply the cream for six months to active areas of the face, achieving complete remission. No adverse effects were noted with the use of topical ruxolitinib.

Before (left) and After (right) Treatment with Topical Ruxolitinib



Conclusions

Topical ruxolitinib was effective in achieving complete response on this patient with folliculotropic MF. The treatment was well-tolerated and can be used on sensitive areas of the body such as the face. Topical JAK inhibitors may be an option for treatment for patients with MF with lower side effect profile compared to oral formulations.

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TCR Vβ repertoire analysis and immunophenotyping to detect target molecules in patients with mycosis fungoides and Sézary syndrome

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Background

Mycosis fungoides (MF) and Sézary syndrome (SS) are the most common cutaneous T-cell lymphomas (CTCLs). There is no definitive cure for either, and in advanced stages the prognosis is poor. Although a number of treatment options are available, achieving and maintaining durable remissions remains a challenge. Precise identification of targets for treatment should avoid unnecessary, potentially ineffective therapies. Quantitative determination of the TCR-Vβ repertoire of T lymphocytes by flow cytometry and subsequent immunophenotyping (TCR-IPT) of the clonal cells may help to identify specific targets for therapies.

Methods

The purpose of this case series is to demonstrate how the identification of potential targeted therapies for MF and SS is achieved. By developing a multiparametric analysis tool for the quantitative determination of the TCR Vβ repertoire of human T lymphocytes by flow cytometry, we are able to identify malignant clones from the blood of patients with T-cell lymphoma. Furthermore, we can examine CD52, CCR4, CTLA-4, CD30, KIR3DL2, and CLA expression by flow cytometric immunotyping of clonal cells, as demonstrated in three reported cases.

Results

A 95-year-old female patient with Sezary syndrome experienced massive skin deterioration during ongoing photopheresis therapy. A malignant clone with CD52 expression was detected by TCR-IPT and the patient was treated with 10 mg of alemtuzumab subcutaneously once a week. The skin changes improved very quickly.

A 75-year-old patient with granulomatous MF and stage IIB had progressive disease under treatment with PUVA and methotrexate and was subsequently treated with brentuximab vedotin due to CD 30 expression of the malignant clone detected by TCR-IPT, resulting in rapid improvement of the patient's condition and disappearance of all lesions.
A 60-year-old man with erythrodermic MF was treated with mogamulizumab after TCR-IPT detection of a malignant clone with expression of CCR4. He had previously received photopheresis (105 cycles), bexarotene, PUVA and interferon. His condition improved significantly after the second dose of mogamulizumab. After six treatments, the skin lesions had almost disappeared.

Conclusions
We report three cases in which precise identification of the target structures by TCR-IPT allowed targeted therapy with favorable outcomes.

A-225

The efficacy and safety of extracorporeal photopheresis (ECP) for treatment of mycosis fungoides and/or sézary syndrome in cutaneous T-cell lymphoma

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Background
Cutaneous T-cell lymphomas (CTCLs) are a rare, clinically heterogeneous group of non-Hodgkin's lymphomas. Mycosis fungoides (MF) and Sézary syndrome (SS) are the most common subtypes of CTCL. Extracorporeal photopheresis (ECP) has been used for the treatment of skin manifestations in patients with CTCL since its FDA approval in 1988. Despite its long history, a deeper understanding of the efficacy and safety of ECP in treating CTCL is needed.

Methods
The aim of the study was to review the efficacy and safety of ECP for the treatment of CTCL subtypes MF and/or SS. A systematic literature review was conducted in line with the PRISMA guidelines. Electronic database searches included Embase, MEDLINE, and Cochrane Library (data cut-off: 16th January 2024), as well as grey literature. Studies not specifying CTCL subtypes were excluded.

Results
30 studies, including 5 conference abstracts, assessing clinical efficacy and/or safety outcomes in patients with MF and/or SS receiving ECP were identified. All observational studies, except one prospective controlled trial. Despite various definitions, response to treatment was one of the most reported outcomes. The overall response rate was reportedly ranging from 42-81% for MF, 38 to 89% for SS, and 33-74% for mixed phenotype. Overall survival was reported in 17 studies with medium survival ranging from 43-72 months for MF, 34-65 months for SS, and 18-212 months for mixed phenotype. Time to next treatment was reported in 5 studies (SS and mixed phenotype), ranging from 5 to 26 months. Medium duration of ECP treatment ranged from 6 to 32 months.
The review identified 16 studies that assessed adverse events (AEs) in MF and/or SS patients undergoing ECP. ECP was well-tolerated amongst patients with most studies reporting no ECP related complications and/or no serious AEs, demonstrating a favorable safety profile.

Conclusions
The findings highlighted the heterogeneity in efficacy outcome amongst patients undergoing ECP, subject to subtypes, disease stages, and/or treatment lines. By contrary, favorable safety profile of ECP was consistently observed throughout the studies.

A-189

Treatment trends in advanced Mycosis fungoides and Sèzary syndrome: an update from the PROCLIPI study.

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Background
Advanced-stage MF/SS includes various manifestations, such as skin tumors (stage IIB), erythroderma (stage III), and blood, nodal, or visceral involvement (stages IVA1, IVA2, and IVB). Patients' treatment is challenging due to their exposure to multiple therapies and low likelihood of cure.

Methods
A total of 571 patients diagnosed with advanced MF/SS were recruited to the PROCLIPI study, with 493 having fully annotated, prospectively collected treatment data, including 166 IIB, 54 IIIA, 56 IIIB, 162 IVA1, 41 IVA2, and 15 IVB. This study aimed to 1) describe treatment approaches, 2) identify differences with the introduction of new drugs, 3) analyse response rates, response duration, and time to next systemic treatment (TTNsT). [1]

Results
At a median FU of 33 months, the most common first-line treatments were extracorporeal photopheresis (ECP) (21.7%), bexarotene (19.4%), methotrexate (17.0%), and interferon-alpha (16.2%), accounting for 74.3% of the total. The most common first-line agent varied by stage: bexarotene in IIB, methotrexate in IIIA-B, ECP in IVA1, and multi-agent chemotherapy in IVA2-IVB. Second-line therapies included bexarotene, interferon-alpha, and single-agent chemotherapy, followed by brentuximab vedotin and mogamulizumab (10.7%). The median TTNsT for all first-line systemic therapies was 14.0 months, while it was 18.1 for non-chemotherapy regimens. ECP, alone or in combination, achieved the longest TTNsT (median 36.6 months), followed by bexarotene and retinoids (15.2 and 20.8 months). Romidepsin and single-agent chemotherapy had the highest response rates (70%-80%) but shorter TTNsT (5.7-7.3 months). Combination regimens of ECP with other systemic agents had a longer TTNsT (36.6 months) compared to ECP monotherapy (25.5 months). For second-line therapy, mogamulizumab had the longest median TTNsT (18.6 months) and higher response rates, along with CHOP, brentuximab vedotin, and retinoids.

Conclusions
The wide array of initial systemic treatments highlights the lack of clear guidance for optimal therapy sequence. TTNsT confirms to be a reliable metric for therapeutic effectiveness. New drugs like brentuximab vedotin and mogamulizumab show favourable response rates and durable TTNsT, while chemotherapy regimens, despite high response rates, have shorter TTNsT. This prospectively gathered patient population offers valuable insights into the evolving treatment landscape for advanced MF/SS.
References:

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A-244

Ultrasound-guided intralesional therapies in tumour-stage mycosis fungoides.

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Background
Mycosis fungoides (MF) is the most common primary cutaneous lymphoma. Tumour-stage MF may have multiple approaches, depending on the number of tumours, involvement at other levels or patient's condition. For a limited number of tumours, options such as surgery or radiotherapy are useful. In case of a larger number of tumours, systemic therapies such as brentuximab or chemotherapy will play a more important role.
Intralesional treatments have been reported for tumour-stage MF with a limited number of lesions. They are usually not associated with systemic toxicity and tolerance is generally good.
Cutaneous ultrasound has become an increasingly used diagnostic tool in recent years. Ultrasound-guided infiltration of intralesional treatments allows for more precise control of the technique. In addition, ultrasound follow-up facilitates monitoring of the response to treatment.

Methods
We have collected all patients with tumoral lesions that have been treated with ultrasound-guided intralesional therapies in our hospital in the last two years.

Results
A total number of 15 tumors have been treated with ultrasound-guided intralesional therapy. Two intralesional treatments were used: brentuximab vedotin and pegylated interferon. All the patients were recieving skin-directed therapy or other systemic treatment. Response rates were acceptable, 70% of total or partial (more than 50% of the tumour) clearing. Tolerance was good, with no important adverse effects. Pain in the injection site was the most common side effect. Ultrasound follow-up was used as an objective

determination of treatment response.

Conclusions

Ultrasound-guided intralesional treatment in tumour-stage MF is a therapeutic option to be considered due to its effectivity and good tolerance. Ultrasound follow-up may be used as an objective determination of treatment response.