Società Italiana di Ematologia

FORMAZIONE SIE

I linfomi: un nome con almeno 40 sfaccettature!

25 giugno 2026

Bologna
Royal Hotel
Carlton

Linfomi primitivi cutanei di derivazione B-linfocitaria

Serena Rupoli

Clinica di Ematologia, Ancona

Disclosures of Serena Rupoli

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
I have no disclosures in this field							

PCBCL- Overview

B-cell lymphomas (BCLs) of the skin represent a rare and heterogeneous group of extranodal non-Hodgkin lymphomas. These neoplasms, albeit infrequent, are clinically significant in dermatology, oncology, hematology, and pathology, due to their diagnostic and therapeutic complexity. Lymphomas of the skin are classified as primary cutaneous (PCL), when *confined* to the skin at diagnosis, and secondary cutaneous (SCL), when the skin is involved following dissemination from systemic or nodal lymphomas.

The incidence of PCBCL has increased over recent decades, now affecting approximately **4 per million individuals**.

PCBCLs account for roughly 25% of PCL and demonstrate a higher prevalence in male, non-Hispanic White individuals, and adults aged over 50 years.

Barbati ZR & Yann CJ. Cancers 2025

PCBCL-References

Hematol Oncol. 2024 Jan;42(1):e3215. doi: 10.1002/hon.3215. Epub 2023 Aug 30.

Identifying and addressing unmet clinical needs i primary cutaneous B-cell lymphoma: A consensus based paper from an ad-hoc international panel

Pietro Quaglino [1], Nicola Pimpinelli [2], Pier Luigi Zinzani [3 4 5], Marco Paulli [6], Stefano Pileri [7], Emilio Berti [8 9], Lorenzo Cerroni [10], Joan Guitart [11], Youn H Kim [12], Serena Rupoli [13], Marco Santucci [14 15], Gabriele Simontacchi [16], Maarten Vermeer [17], Richard Hoppe [18], Barbara Pro [19], Steven H Swerdlow [20], Giovanni Barosi [21]

NCCN National Comprehensive Cancer Network®

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

Primary Cutaneous Lymphomas

Version 2.2025 — April 1, 2025

NCCN.org

NCCN recognizes the importance of clinical trials and encourages participation when applicable and available. Trials should be designed to maximize inclusiveness and broad representative enrollment.

NCCN Guidelines for Patients® available at www.nccn.org/patients

cancers

MDPI

Review

Unveiling Primary Cutaneous B-Cell Lymphomas: New Insights into Diagnosis and Treatment Strategies

Zachary R. Barbati [1] and Yann Charli-Joseph [2,*]

Cancers 2025, 17, 1202 https://doi.org/10.3390/cancers17071202

Eur J Haematol. 2025 Oct 28;116(2):116-128. doi: 10.1111/ejh.70053

Primary Cutaneous B-Cell Lymphomas: An Updated Portrait of Classification, Biology, and Clinical Management

A Bernardelli [1], E Carazzai [2], B Bugnotto [2], F Bellinato [3], M Krampera [1,2], C Visco [1,2]

Classification

Table 1: Classification of Cutaneous B-Cell Lymphomas

WHO-EORTC classification for Primary Cutaneous Lymphomas (2018)	The International Consensus Classification (ICC) of Mature Lymphoid Neoplasms (2022)	WHO Classification of Hematolymphoid Tumors: Lymphoid Neoplasms (5th edition, 2024)
Cutaneous B-Cell Lymphomas	**Mature B-cell Neoplasms**	**Mature B-cell Neoplasms**
Primary cutaneous marginal zone lymphoma	Primary cutaneous marginal zone lymphoproliferative disorder	Marginal zone lymphoma • Primary cutaneous marginal zone lymphoma
Primary cutaneous follicle center lymphoma	Primary cutaneous follicle center lymphoma	Cutaneous follicle center lymphoma • Primary cutaneous follicle center lymphoma
Primary cutaneous DLBCL, leg type	Primary cutaneous DLBCL, leg type	Large B-cell lymphomas • Primary cutaneous DLBCL, leg type • Intravascular large B-cell lymphoma
Intravascular large B-cell lymphoma	Intravascular large B-cell lymphoma	
EBV+ mucocutaneous ulcer (provisional)	EBV-positive mucocutaneous ulcer	Lymphoid proliferations and lymphomas associated with immune deficiency and dysregulation • EBV-positive mucocutaneous ulcer

Table 2: Classification of Cutaneous T-Cell Lymphomas (ST-2)

PCBCL are currently classified into three major subtypes by both the 5th edition of the World Health Organization (5-WHO) Classification of Hematologic Neoplasms and the 2022 International Consensus Classification (2022-ICC) of Mature Lymphoid Neoplasms: primary cutaneous **follicle center lymphoma** (PCFCL), **primary cutaneous marginal zone lymphoma or lymphoproliferative disorder** (PCMZL/LPD), and primary cutaneous **diffuse large B-cell lymphoma**, **leg type (PCDLBCL,LT).** These subtypes are further categorized based on clinical behavior and prognosis, with **PCFCL** and **PCMZL/LPD** being **low-grade/indolent**, and **PCDLBCL,LT** classified as a **high-grade/intermediate-to aggressive neoplasm.**

Notable differences with previous classifications include the categorization of **MZL/LPD** as a separate entity from the broad group of extranodal marginal zone lymphomas of mucosa-associated lymphoid tissue (**MALT lymphoma**), its **downgrading to an LPD** (in the 2022-ICC), and the recognition that **PCFCL may be composed of large cells**, and regardless, should not be categorized as PCDLBCL (even when occurring on the legs), with the diagnosis relying on its characteristic germinal center B-cell immunophenotype and defining molecular features.

Barbati ZR & Yann CJ. Cancers 2025

PCBCL- Overview

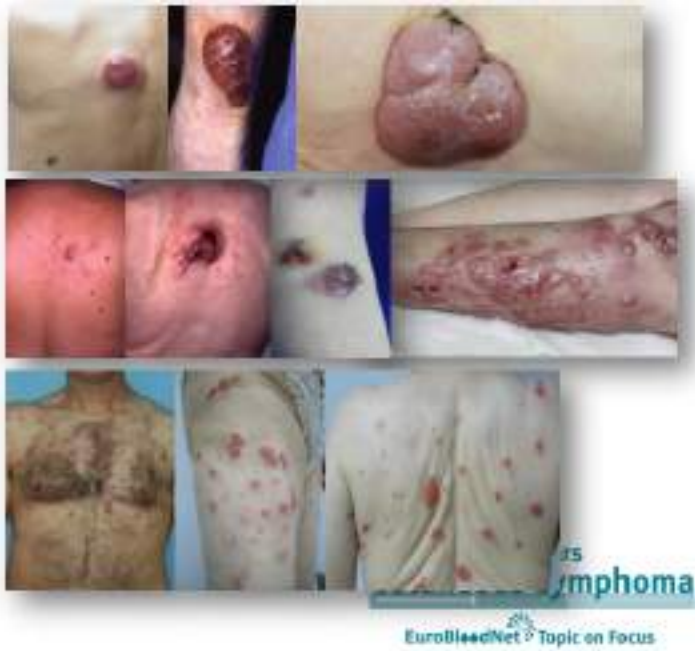
Secondary cutaneous B-cell lymphomas (SCBCLs) share numerous overlapping features with PCBCL, making it essential to **differentiate between primary and secondary cutaneous involvement in all suspected PCBCL cases**. Diagnostic workup for PCBCL follows the tumor, node, metastasis (**TNM**) **staging system** endorsed by the International Society for Cutaneous Lymphomas (ISCLs) and the European Organization for the Research and Treatment of Cancer (EORTC). A thorough evaluation should include **clinical assessment for B-symptoms and organ-specific signs**.

Barbati ZR & Yann CJ. Cancers 2025

NCCN Guidelines Version 2.2025
Primary Cutaneous B-Cell Lymphomas

TNM CLASSIFICATION OF CUTANEOUS LYMPHOMA OTHER THAN MF/SS[a,b]

TNM		Size/location of lesions		
T				
	T_0*	Absence of clinically suspicious lesions		
	T_1	Solitary lesion	T_{1A}	Solitary lesion <5 cm diameter
			T_{1B}	Solitary **≥5 cm** diameter
	T_2	Multiple lesions limited to 1 body region or 2 contiguous body regions[b]	T_{2A}	All disease encompassing in a <15-cm-diameter circular area
			T_{2B}	All disease encompassing a **15 to <30 cm** diameter circular area
			T_{2C}	All disease encompassing a **≥30 cm** diameter circular area
	T_3	Generalized skin involvement	T_{3A}	Multiple lesions involving 2 noncontiguous body regions[b]
			T_{3B}	Multiple lesions involving ≥3 body regions[b]
N				
	N_0	No clinical or pathologic LN involvement		
	N_1	Involvement of 1 peripheral LN region[c] that drains an area of current or prior skin involvement: biopsy positive for lymphoma		
	N_2	Involvement of >2 peripheral LN regions[c] or involvement of any LN region that does not drain an area of current or prior skin involvement: biopsy positive for lymphoma		
	N_3	Involvement of central lymph nodes: biopsy positive for lymphoma		
	N_X	Clinically abnormal peripheral or central LN but no pathologic determination. Other surrogate means of determining involvement may be determined by Tri-Society consensus		
M				
	M_0	No visceral involvement		
	M_1	Visceral involvement		
	M_X	Visceral involvement is neither confirmed nor refuted by available pathologic or imaging assessment		



Società Italiana di Ematologia

DIAGNOSIS[a,b]

ESSENTIAL:

- Biopsy of suspicious skin sites
  - Multiple biopsies may be necessary to capture the pathologic variability of disease at diagnosis
- Review of a sufficient number of slides with adequate material to perform a comprehensive workup as described below and/or at least one paraffin block representative of the tumor should be done by a pathologist with expertise in the diagnosis of PCBCL. Rebiopsy if pathological findings are non-diagnostic and/or discordant with the clinical presentation
- Adequate biopsy (by punch, incisional, excisional) of all types of clinical lesions present will aid in final diagnosis
- Adequate immunophenotyping to establish diagnosis[c]
  - Immunohistochemistry (IHC) panel may include: CD20, CD3, CD10, BCL2, BCL6, IRF4/MUM1

USEFUL IN CERTAIN CIRCUMSTANCES:

- Additional immunohistochemical studies to establish lymphoma subtype
  - IHC panel may include: Ki-67, CD5, CD43, CD21, CD23, cyclin D1, kappa/lambda, MYC (IHC or ISH)
  - Assessment of IgM,[d] IgD, and FOXP1 expression (to further help in distinguishing PC-DLBCL, leg type from PCFCL)
- EBER-ISH
- Cytogenetics (FISH and karyotype): t(14;18) if systemic FL is suspected; FISH for *BCL2* and *BCL6* rearrangements if MYC (IHC or ISH) is positive
- If adequate biopsy material is available, flow cytometry or molecular analysis to detect IgH gene rearrangement can be useful in determining B-cell clonality
- Next generation sequencing (NGS) for *MYD88*[d] and *CD79B* mutations (to further help in distinguishing PC-DLBCL, leg type from PCFCL)

WORKUP

ESSENTIAL[e]:

- History and physical exam, including complete skin exam
- CBC with differential
- Comprehensive metabolic panel
- Lactate dehydrogenase (LDH)
- Chest/abdominal/pelvic CT with contrast and/or FDG-PET/CT scan (may be omitted if clinically indicated)
- Pregnancy testing in patients of childbearing potential (if chemotherapy or RT planned)

USEFUL IN CERTAIN CIRCUMSTANCES:

- Bone marrow biopsy[f]
- Peripheral blood flow cytometry, if complete blood count (CBC) demonstrates lymphocytosis
- SPEP/quantitative immunoglobulins for PCMZL
- HIV testing
- Hepatitis B and C testing[g]
- Discuss fertility preservation[h]

→ PCMZL (CUTB-2)

→ PCFCL (CUTB-2)

→ PC-DLBCL, Leg Type (See NCCN Guidelines for B-Cell Lymphomas - DLBCL)

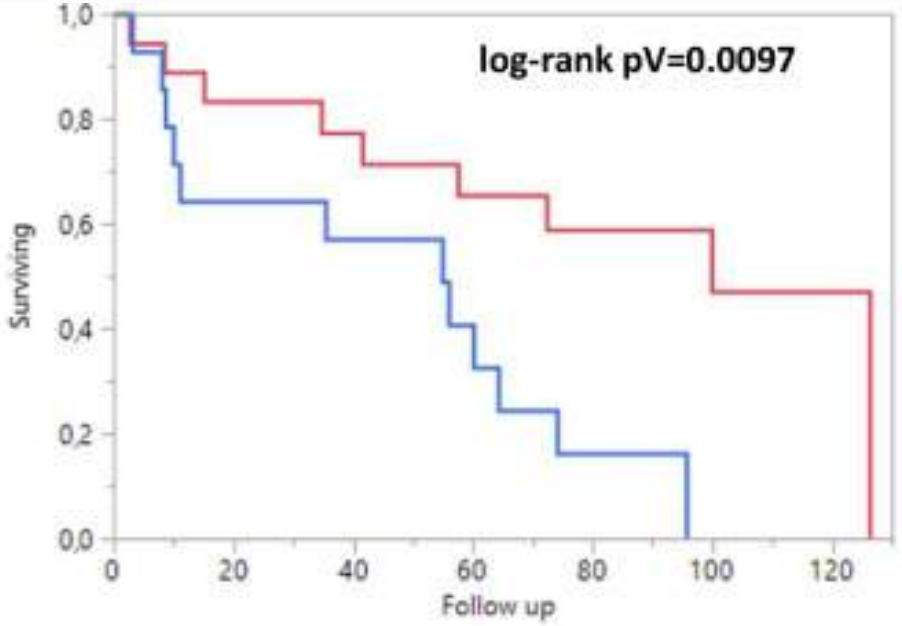
[d] IgM expression should be checked if *MYD88* mutations are identified since these are the cases likely to have systemic involvement.
[e] Rule out drug-induced cutaneous lymphoid hyperplasia.
[f] Often reserved for patients with unexplained cytopenias or if there is clinical

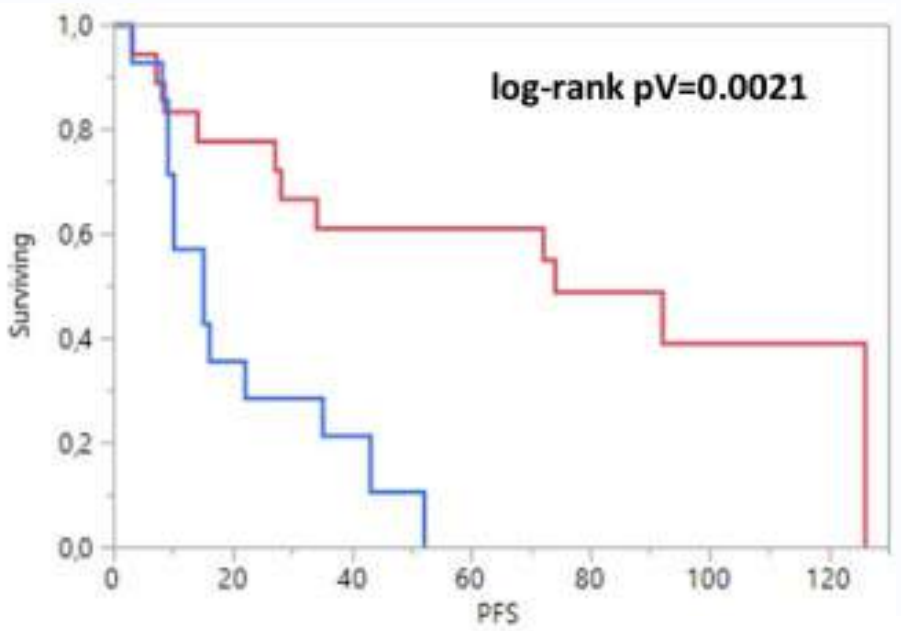
PCBCL- Overview

Additionally, **blood count with differential**, a metabolic panel with lactate dehydrogenase (**LDH) levels**, and imaging studies (e.g., **PET/CT or CT-SCAN** with intravenous contrast of the chest, abdomen, pelvis, and neck if applicable) are performed, except in cases of PCMZL/LPD, where they are unnecessary given its growing recognition as an indolent lymphoproliferative disorder.

Bone marrow biopsy, peripheral blood flow cytometry, and protein electrophoresis (to rule out monoclonal gammopathy) are optional and of limited value in indolent/low-grade PCBCL (especially in PCMZL/LPD) but are **indicated in patients with systemic symptoms, widespread disease, unexplained cytopenias or leukocytosis and are mandatory in patients with PCDLBC,LT**, where additional screening for infections (hepatitis B and C, human immunodeficiency virus, latent tuberculosis) is paramount before initiating systemic therapy.

Barbati ZR & Yann CJ. Cancers 2025





PCDLBCL
SCDLBCL

It essential to **differentiate between primary and secondary cutaneous involvement** in all suspected PCBCL cases

	Median OS, months (95% C.I.)	Median PFS, months (95% C.I.)
PCDLBCL	99 (41-126)	74 (27-126)
SCDLBCL	54 (8-64)	15 (9-35)

ELSEVIER

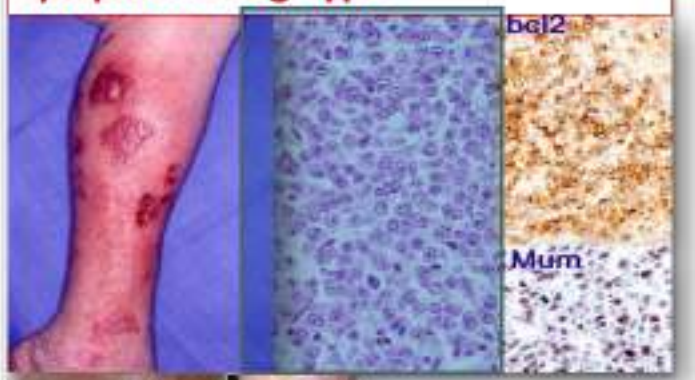
Human Pathology
Volume 136, June 2023, Pages 44-55

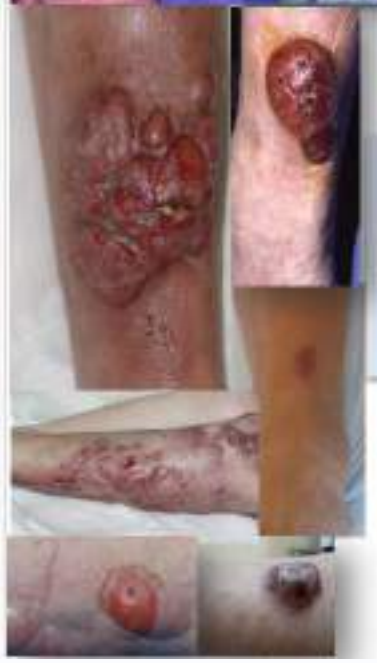
Original contribution

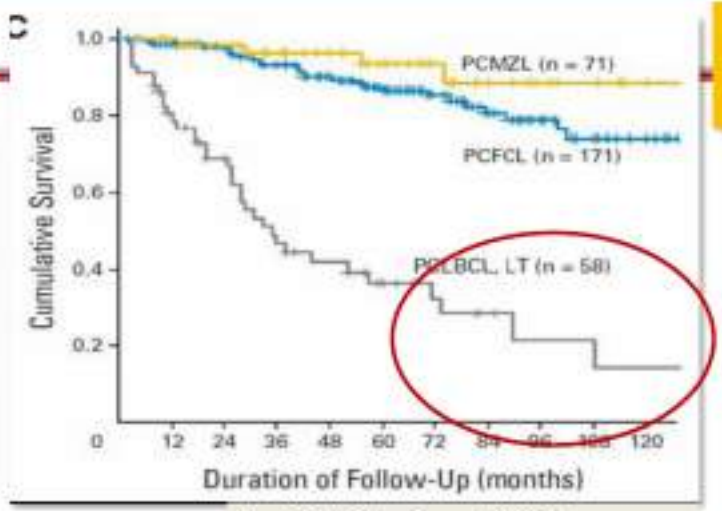
Clinicopathological, cytogenetic, and molecular profiles of primary cutaneous diffuse large B-cell lymphomas ☆, ☆☆

Silvia Uccella MD, PhD [a 1], Gaia Goteri MD, PhD [b 1], Antonino Maiorana MD [c], Valentina Donati MD [d], Maria Grazia Tibiletti BS [e], Francesca Magnoli MD, PhD [e], Sofia Facchi BS [f], Deborah Merchiori MD [f], Erika Morsia MD [g], Robel Papotti BS, PhD [c h i], Stefania Bettelli BS [j], Elisa Forti BS [j], Sara Galimberti MD [k], Serena Rupoli MD [g], Alessandra Filosa MD, PhD [b], Dimitri Dardanis MD [k], Riccardo Bomben BS [h], Luca Braglia BS, PhD [c], Samantha Pozzi MD [c], Stefano Sacchi MD [c]

Primary cutaneous large-B cell lymphoma leg-type

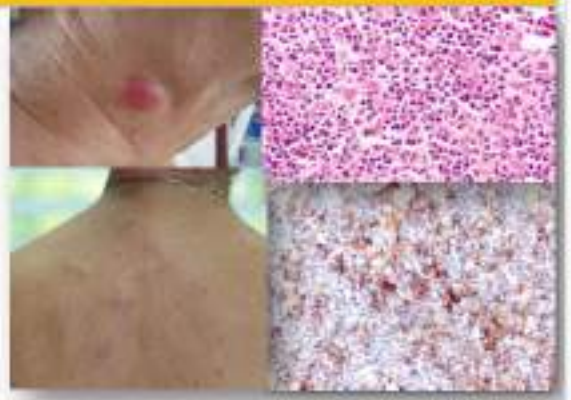




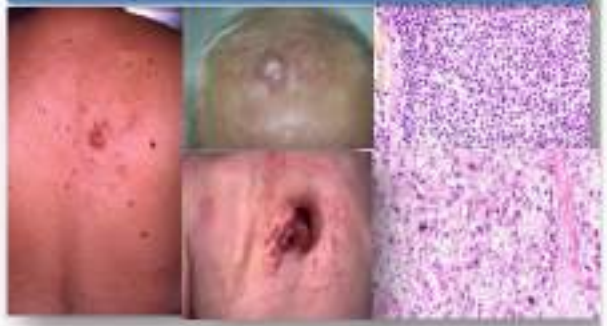


Senff, J Clin Oncol 2007

Primary cutaneous marginal zone lymphoma



Primary cutaneous follicle center lymphoma



30-50% skin recurrences
40% extracutaneous spreading : nodes, central nervous system
5-year survival ≈ 50

Adequate diagnosis is crucial for an adapted treatment

Webinars
Cutaneous Lymphoma
EuroBloodNet Topic on Focus

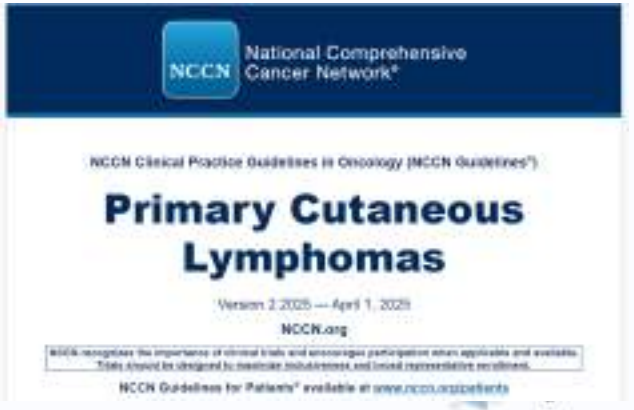
PCFCL

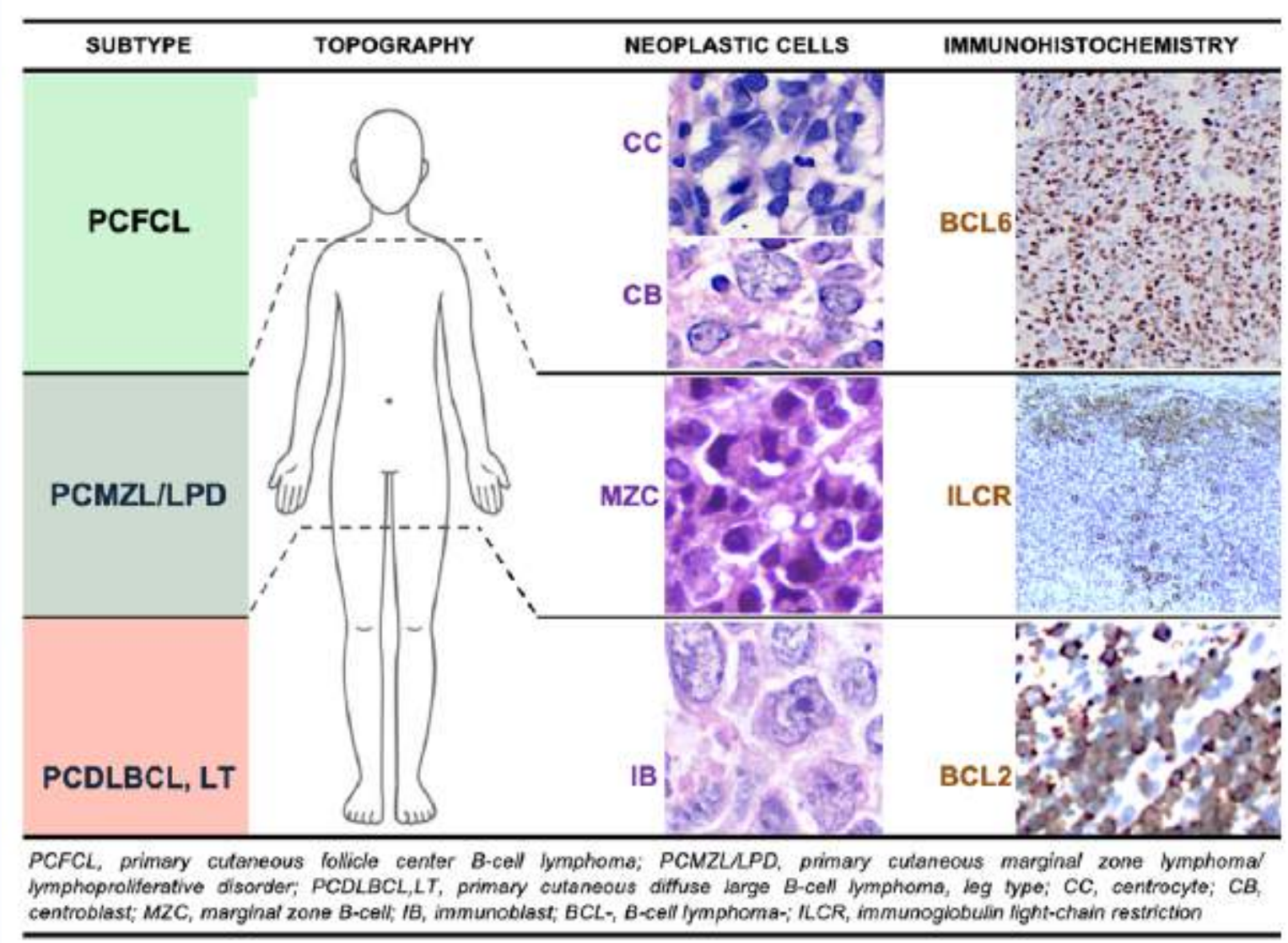
Bernardelli A et al. European Journal of Haematology, 2026

TABLE 1 | Features of primary cutaneous B-cell lymphomas.

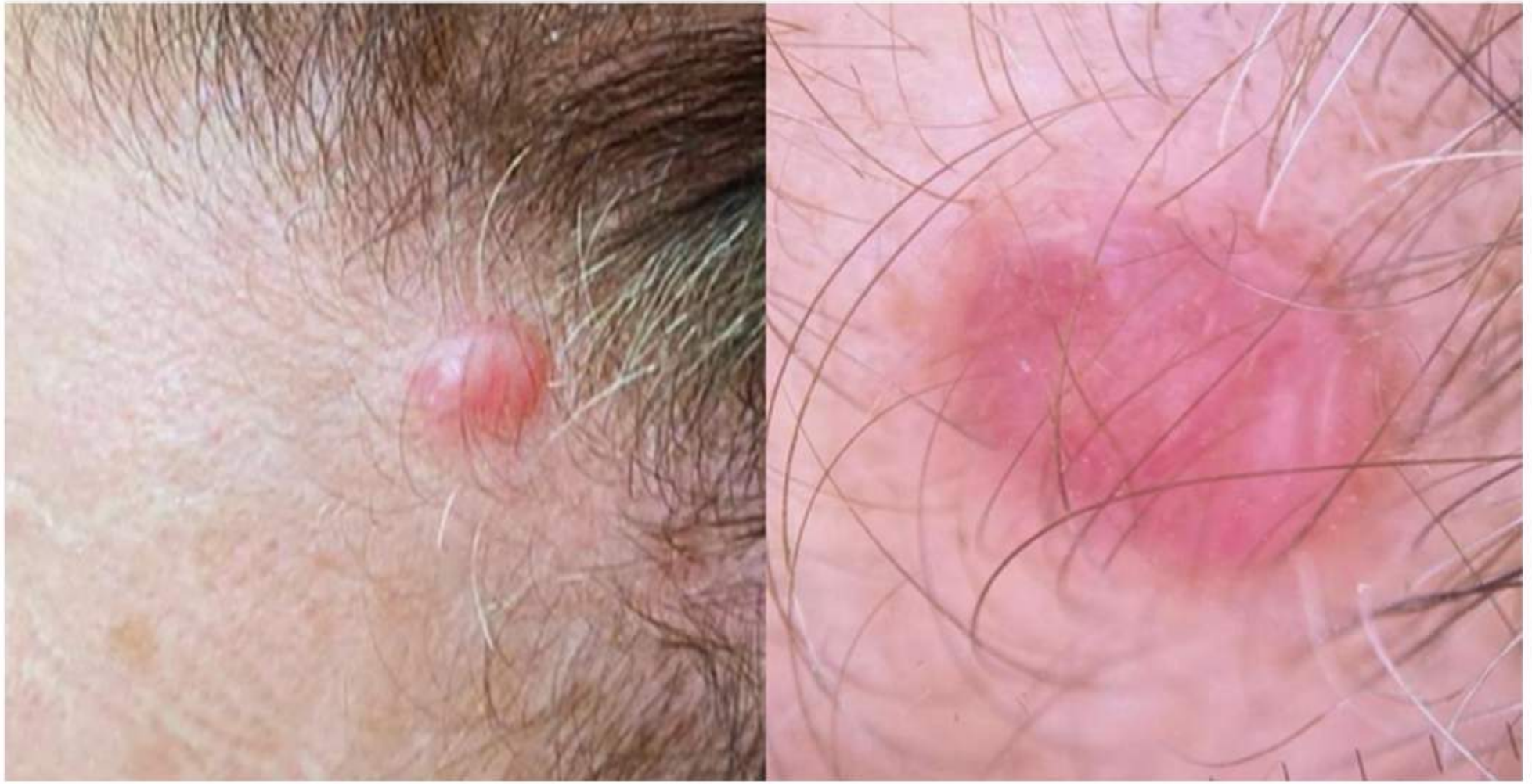
	PCFCL	PCMZL	PCDLBCL-LT	IVLBCL	EBVMCU
Epidemiology					
Mean age of onset	5–6th decade	5–6th decade	7–8th decade	7th decade	7th decade
Sex predominance	Male	Male	Female	Female	Female
% cases of PCBCL	30%–50% (in Caucasians)	25%–30%	20%–40%	Rare (more often in Caucasians)	Rare
Clinical features	Asymptomatic and localized plaques and nodules	Asymptomatic or slightly pruritic, solitary or multiple clustered plaques and nodules	Solitary or multiple, rapidly growing, multifocal nodules and tumors	Mild to severe symptoms, heterogeneous single or multiple skin lesions	Solitary, well-circumscribed ulcerative lesion
Frequent sites	Head or trunk	Trunk, arms or head	Lower extremities	Skin, frequent CNS involvement	Skin, oropharyngeal mucosa, or gastrointestinal tract

- Most common subtype of PCBCL (**57%**), located primarily in the scalp, face, forehead, and trunk, usually with indolent course and **excellent prognosis (5-year overall survival [OS] rate is >95%).**
- Multifocal skin lesions are seen in 15% of cases. Ulceration is rare.
- Dissemination to extracutaneous sites is extremely uncommon; cutaneous recurrences occur near the initial site in approximately 30% of cases.





Barbati ZR & Yann CJ. Cancers 2025



PCFCL

Asymptomatic and localized plaques and nodules

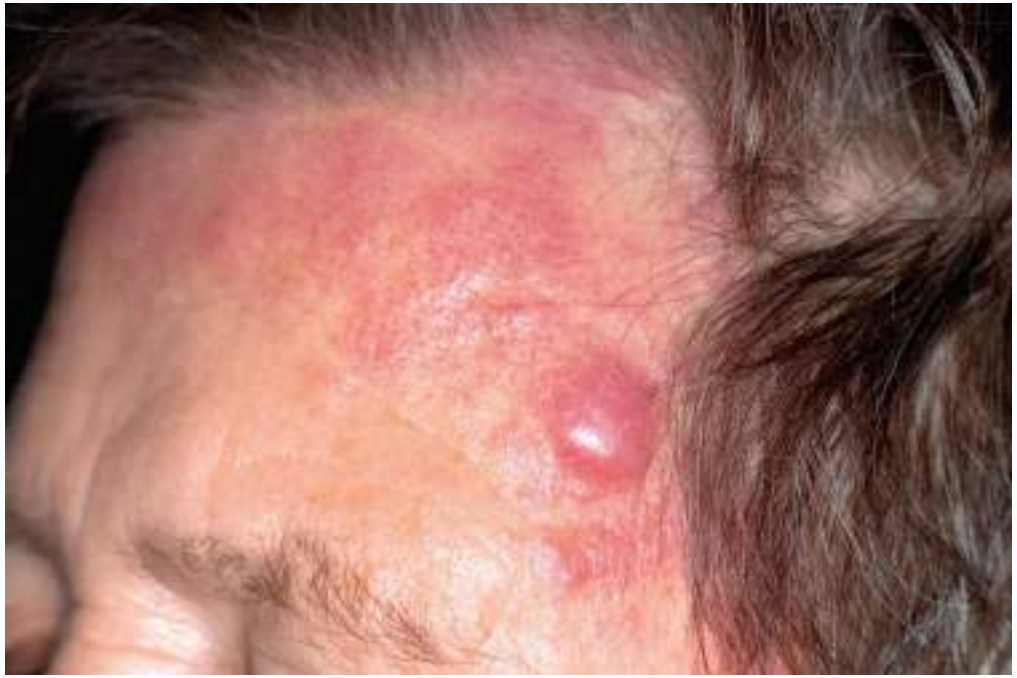
Head or trunk

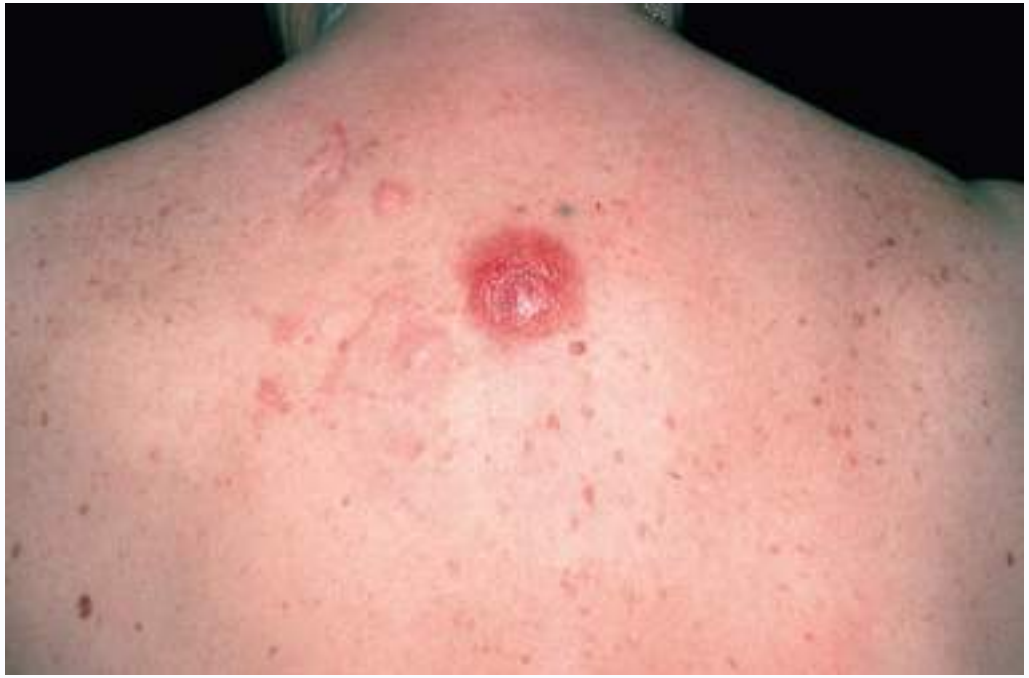
Figure 2. Primary cutaneous follicle center lymphoma presenting on the head. Clinical and dermoscopic (4×) images.

Barbati ZR & Yann CJ. Cancers 2025

B-Cell Lymphomas of the Skin

DERMATOLOGY / SEPTEMBER 13, 2023 / DERMATOLOGY





Atypical manifestations have been described in the literature and may mimic facial dermatoses such as lupus tumidus, granulomatous rosacea, lupus miliaris disseminates faciei, B-cell pseudolymphoma, IgG4 related disease but also solid organ metastasis. Scalp involvement may lead to alopecia. A clinical variant, historically known as "Crosti's lymphoma" or "reticulohistiocytoma of the dorsum", is characterized by figurate, annular, concentric plaques with peripheral macules or papules on the trunk

Bernardelli A et al. European Journal of Haematology, 2026

cancers

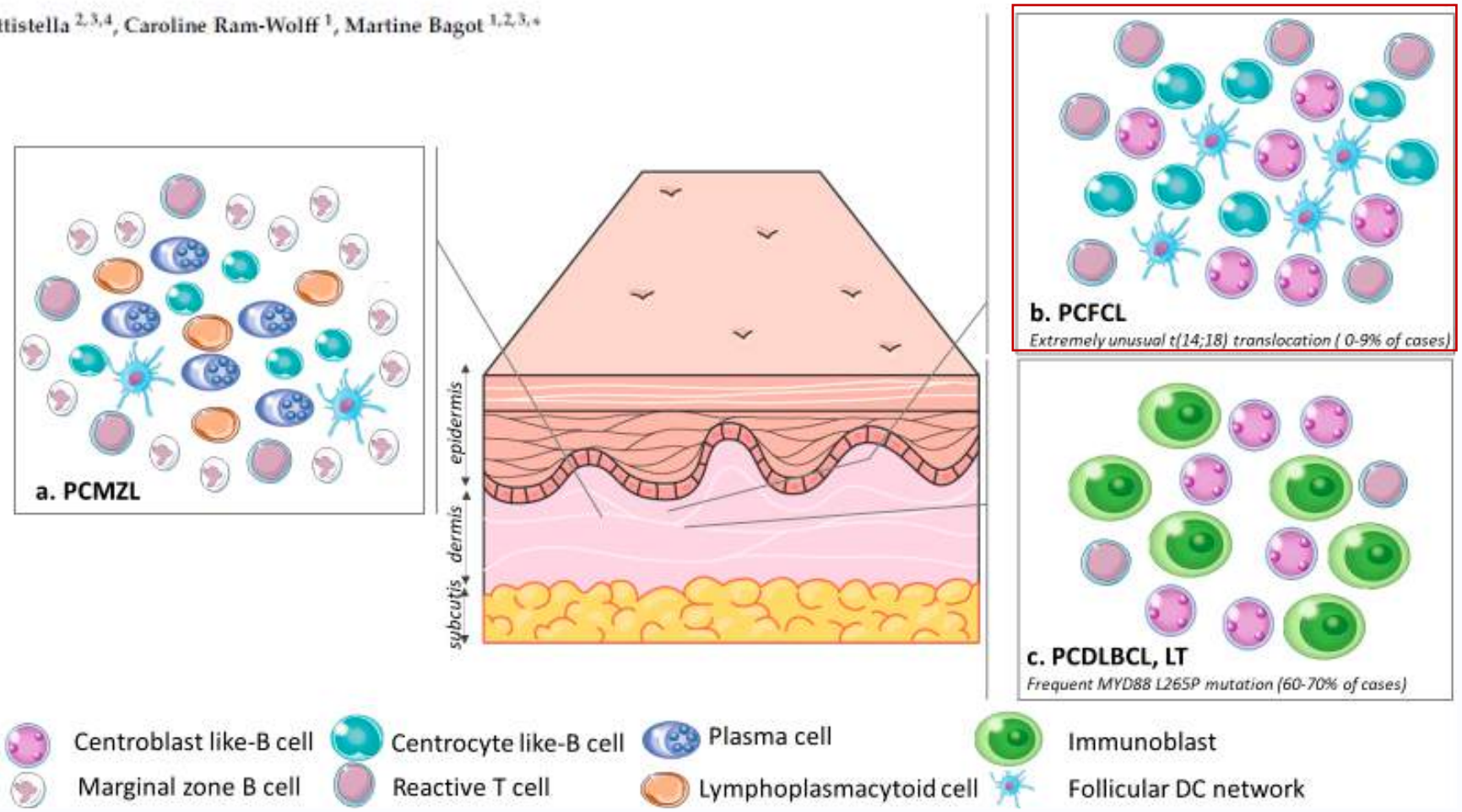
MDPI

Cancers 2020, 12(6), 1497

Review

Diagnosis and Treatment of Primary Cutaneous B-Cell Lymphomas: State of the Art and Perspectives

Maëlle Dumont [1,2,3], Maxime Battistella [2,3,4], Caroline Ram-Wolff [1], Martine Bagot [1,2,3,4] and Adèle de Masson [1,2,3,4]



PCFCL

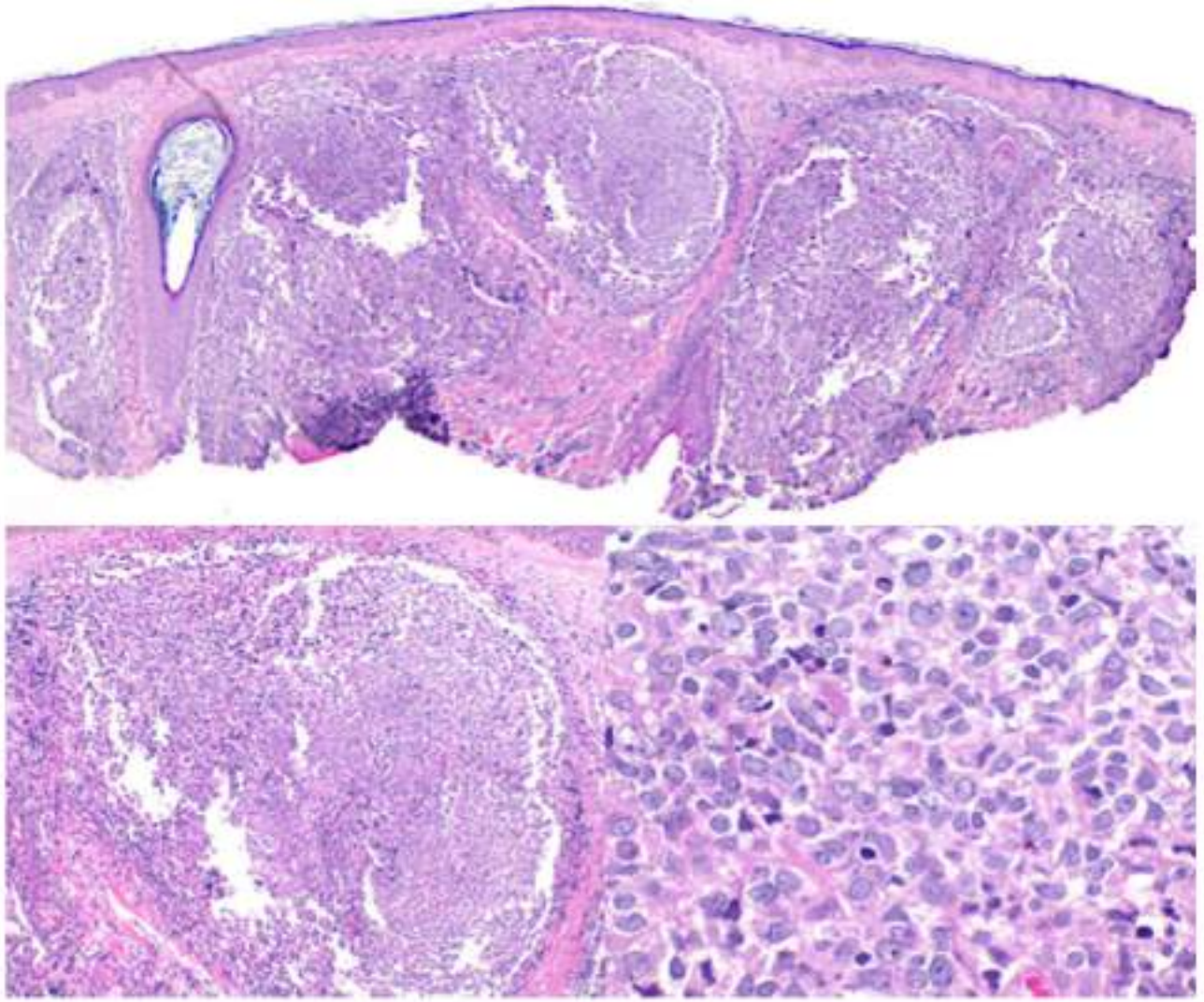


Figure 3. Primary cutaneous follicle center lymphoma. Hematoxylin and eosin-stained sectio
40×, and 400×.

Dermal or subcutaneous mixture of centrocytes and large centrocytes infiltrates in follicular, follicular and diffuse or diffuse growth patterns; background fibrosis and sclerosis with stromal reaction; without a normal mantle zone

Barbati ZR & Yann CJ. Cancers 2025

PCFCL

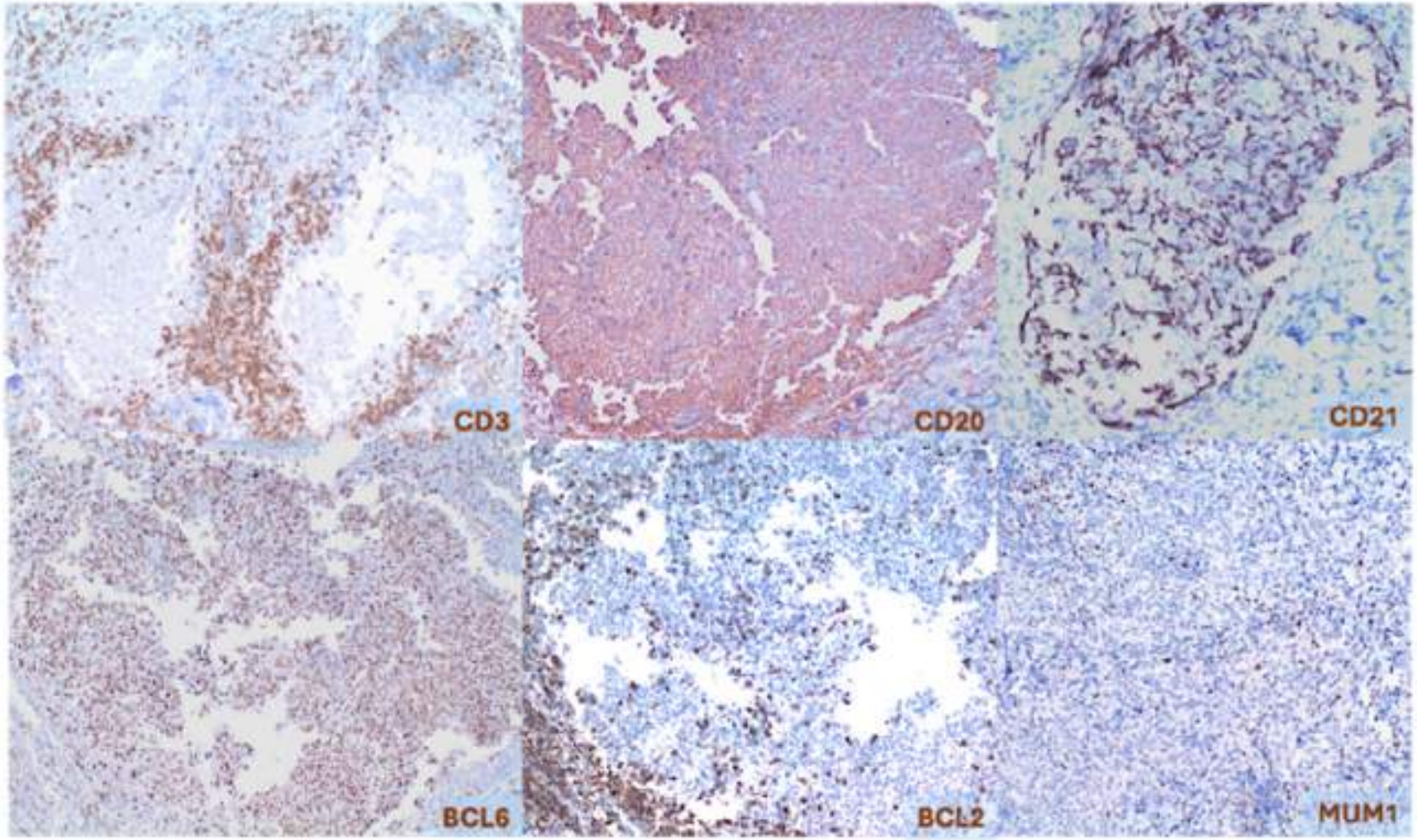


Figure 4. Primary cutaneous follicle center lymphoma. Immunohistochemistry, 40×.

CD20+, BCL6+,
CD21+, CD43+,
monotypic Igs,
CD10- (<25% +),
BCL2-(weak+),
MUM1/IRF4 —

Barbati ZR & Yann CJ. Cancers 2025

PCFCL

	PCFCL	PCMZL	PCDLBCL-LT	IVLBCL	EBVMCU
Molecular and cytogenetic findings					
BCL2 rearrangement/t(14;18)	Negative (10%–40% positive)	Negative	Negative	Negative	Negative
BCL6 or MYC rearrangement	Negative	Negative	Positive (30% BCL6, 30% MYC)	Rare MYC rearrangement	Negative
Other	< 10% of cases mutation in epigenetic modifiers	t(14;18)(q32,q21) (27%), FAS mutations (60%)	*MYD88* (60%), *CD79B* (20%)	MYD88 L265P (44%); CD79B (26%)	—

Bernardelli A et al. European Journal of Haematology, 2026

Hematol Oncol. 2024 Jan;42(1):e3215. doi: 10.1002/hon.3215. Epub 2023 Aug 30.

PCFCL

Identifying and addressing unmet clinical needs in primary cutaneous B-cell lymphoma: A consensus-based paper from an ad-hoc international panel

Pietro Quaglino [1], Nicola Pimpinelli [2], Pier Luigi Zinzani [3 4 5], Marco Paulli [6], Stefano Pileri [7], Emilio Berti [8 9], Lorenzo Cerroni [10], Joan Guitart [11], Youn H Kim [12], Serena Rupoli [13], Marco Santucci [14 15], Gabriele Simontacchi [16], Maarten Vermeer [17], Richard Hoppe [18], Barbara Pro [19], Steven H Swerdlow [20], Giovanni Barosi [21]

Recommendations and proposals

The presence of a vaguely residual nodular pattern (usually detectable at low mangnification), a residual often disrupted follicular dendritic cell meshwork, an intense intermingled reactive T-cell infiltrate, weak to absent BCL2 expression, favour a PCFCL whereas large cohesive sheets of centroblasts and immunoblasts without dendritic cell aggregates favours PCDLBCL.

Patients with BCL2 expression should be staged extensively (including bone marrow biopsy, unless PET-CT scan is available) to exclude extra-cutaneous involvement.

Those patients and patients with localization on the legs and/or FOXP1 expression should be anyway followed aggressively with 3-4 times a year clinical follow-up and restaging on relapse.

PCMZL

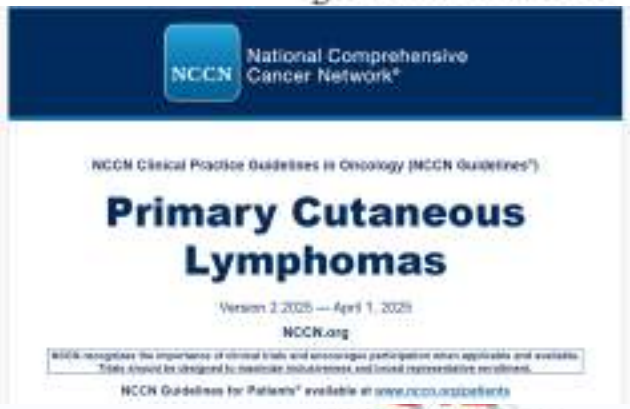
Bernardelli A et al. European Journal of Haematology, 2026

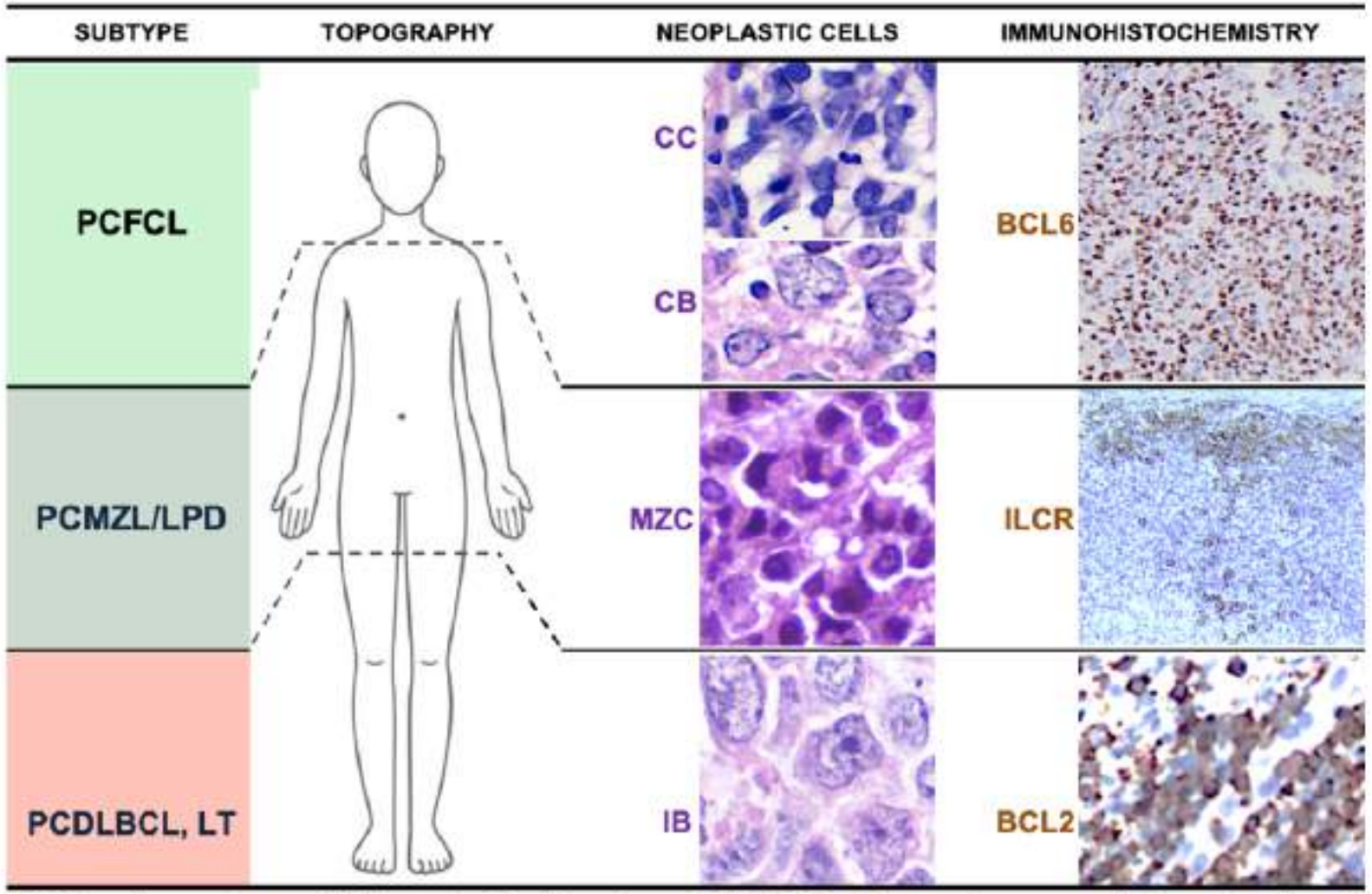
TABLE 1 | Features of primary cutaneous B-cell lymphomas.

	PCFCL	PCMZL	PCDLBCL-LT	IVLBCL	EBVMCU
Epidemiology					
Mean age of onset	5–6th decade	5–6th decade	7–8th decade	7th decade	7th decade
Sex predominance	Male	Male	Female	Female	Female
% cases of PCBCL	30%–50% (in Caucasians)	25%–30%	20%–40%	Rare (more often in Caucasians)	Rare
Clinical features	Asymptomatic and localized plaques and nodules	Asymptomatic or slightly pruritic, solitary or multiple clustered plaques and nodules	Solitary or multiple, rapidly growing, multifocal nodules and tumors	Mild to severe symptoms, heterogeneous single or multiple skin lesions	Solitary, well-circumscribed ulcerative lesion
Frequent sites	Head or trunk	Trunk, arms or head	Lower extremities	Skin, frequent CNS involvement	Skin, oropharyngeal mucosa, or gastrointestinal tract

Primary cutaneous marginal zone lymphoma (PCMZL) (WHO5)/Primary cutaneous marginal zone lymphoproliferative disorder (ICC)

- Second most common subtype of PCBCL (**24%–31%**) with distribution primarily on the trunk, upper extremities, and head. Typically presents as solitary or multiple erythematous to violaceous papules, small nodules, plaques, or tumors with indolent course and **excellent prognosis** (**5-year survival rate is 99%**).
- Relapses in the skin occur in 50% of patients.



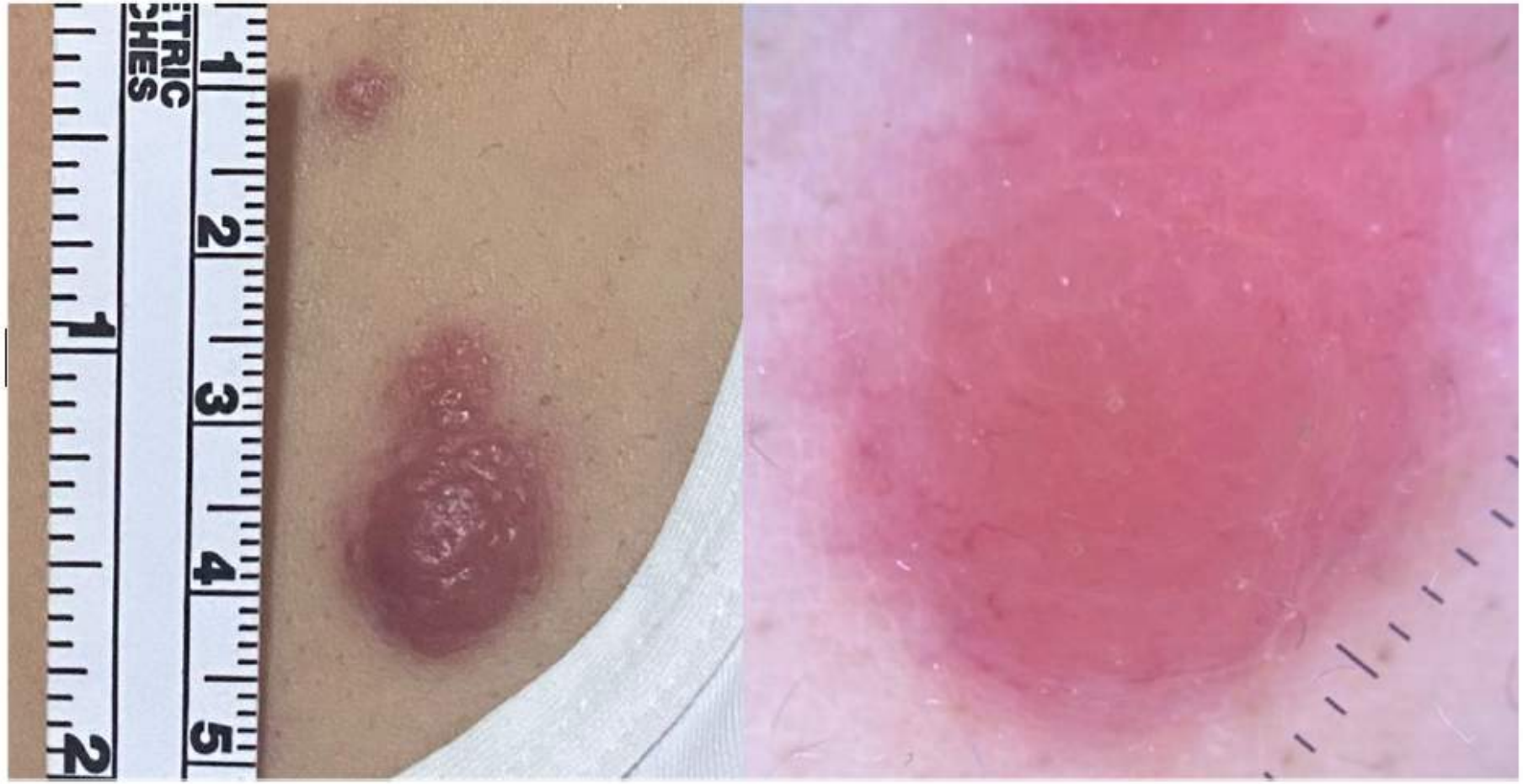


PCFCL, primary cutaneous follicle center B-cell lymphoma; PCMZL/LPD, primary cutaneous marginal zone lymphoma/ lymphoproliferative disorder; PCDLBCL,LT, primary cutaneous diffuse large B-cell lymphoma, leg type; CC, centrocyte; CB, centroblast; MZC, marginal zone B-cell; IB, immunoblast; BCL-, B-cell lymphoma-; ILCR, immunoglobulin light-chain restriction

Barbati ZR & Yann CJ. Cancers 2025

PCMZL

Barbati ZR & Yann CJ. Cancers 2025



Asymptomatic or slightly pruritic, solitary or multiple clustered plaques and nodules

Trunk, arms or head

Figure 5. Primary cutaneous marginal zone lymphoma/lymphoproliferative disorder presenting on the trunk: clinical and dermoscopic (4×) images.

cancers

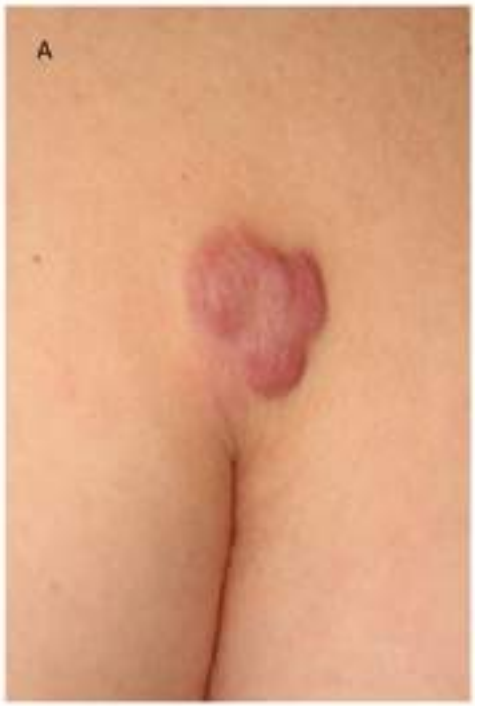
MDPI

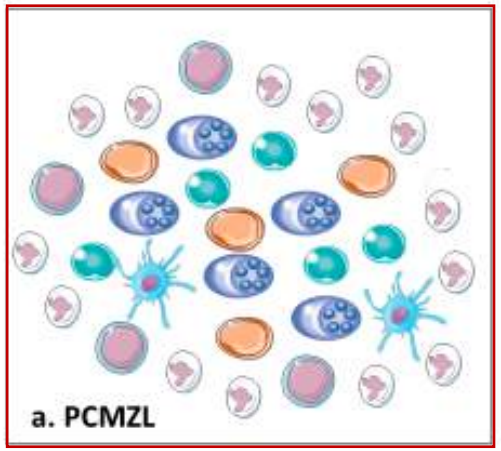
Cancers 2020, 12(6), 1497

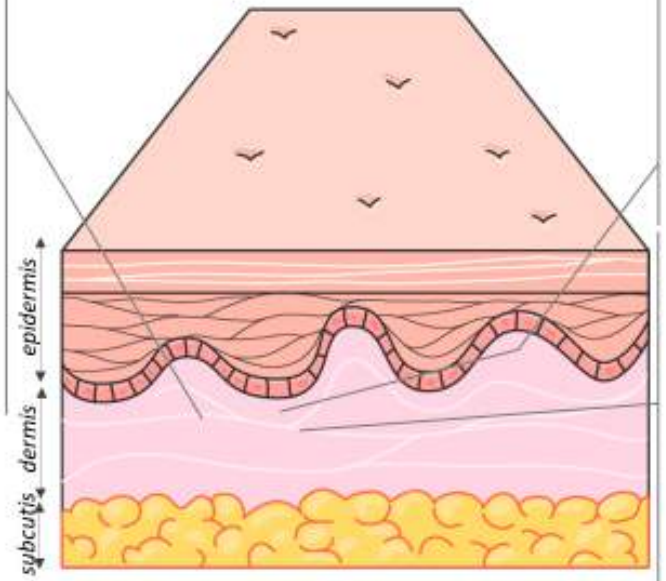
Review

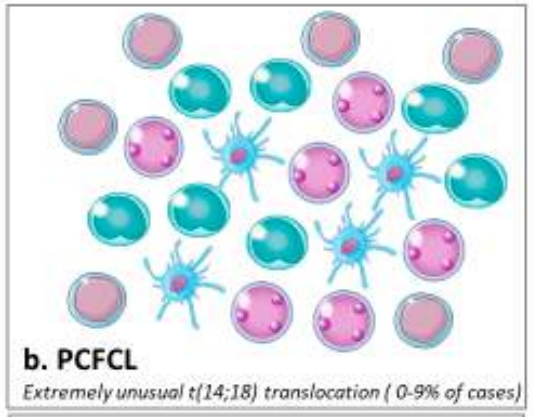
Diagnosis and Treatment of Primary Cutaneous B-Cell Lymphomas: State of the Art and Perspectives

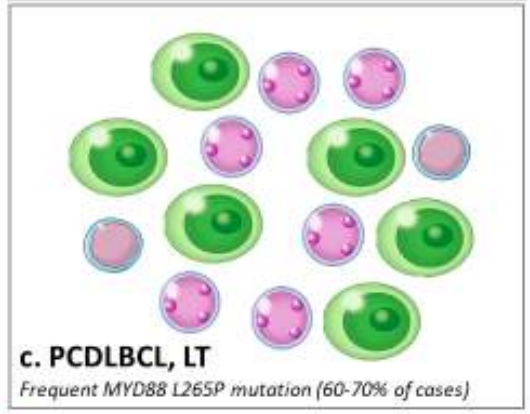
Maëlle Dumont [1,2,3], Maxime Battistella [2,3,4], Caroline Ram-Wolff [1], Martine Bagot [1,2,3,4] and Adèle de Masson [1,2,3,4]





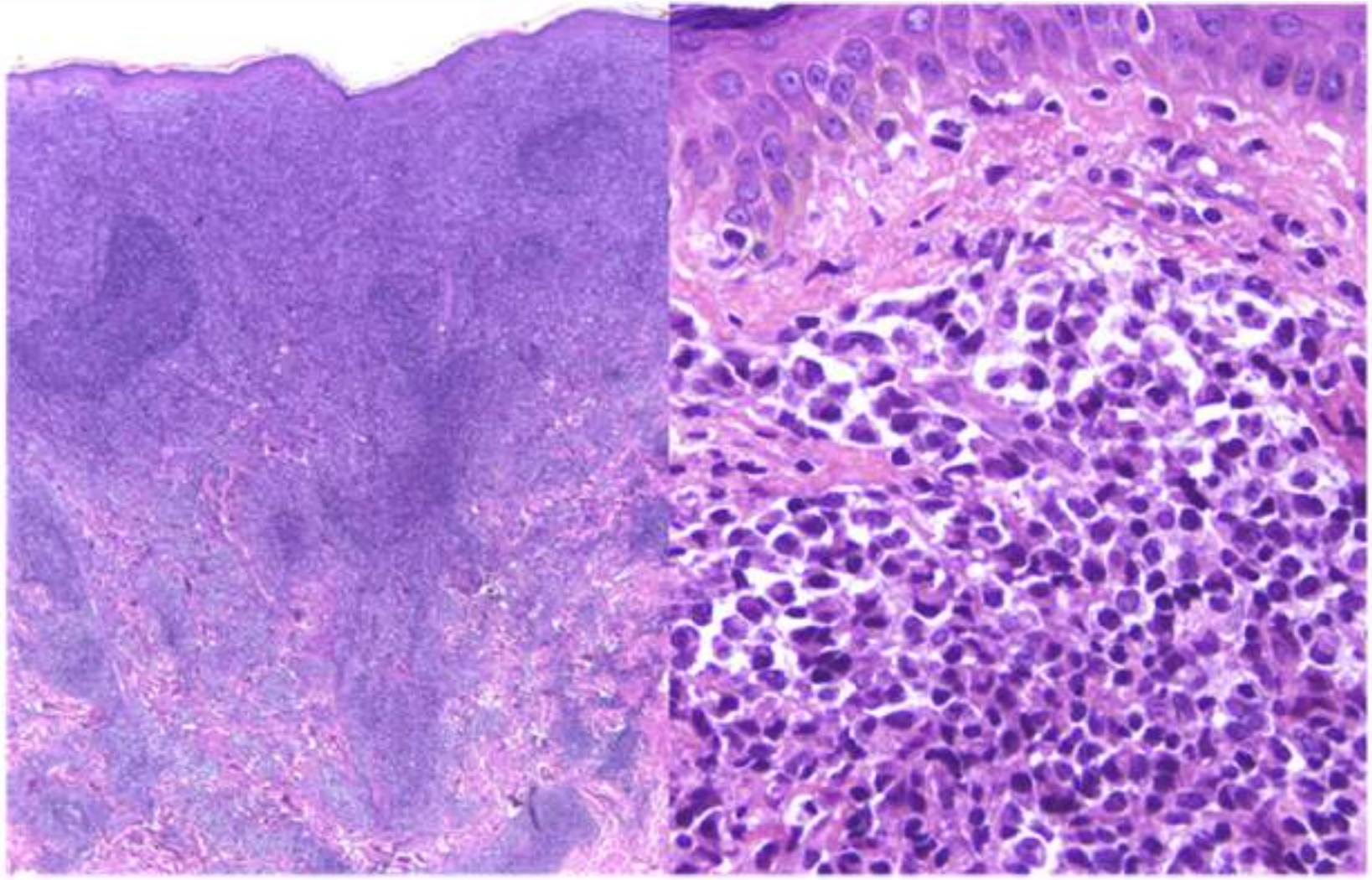






Centroblast like-B cell
Centrocyte like-B cell
Plasma cell
Immunoblast
Marginal zone B cell
Reactive T cell
Lymphoplasmacytoid cell
Follicular DC network

PCMZL

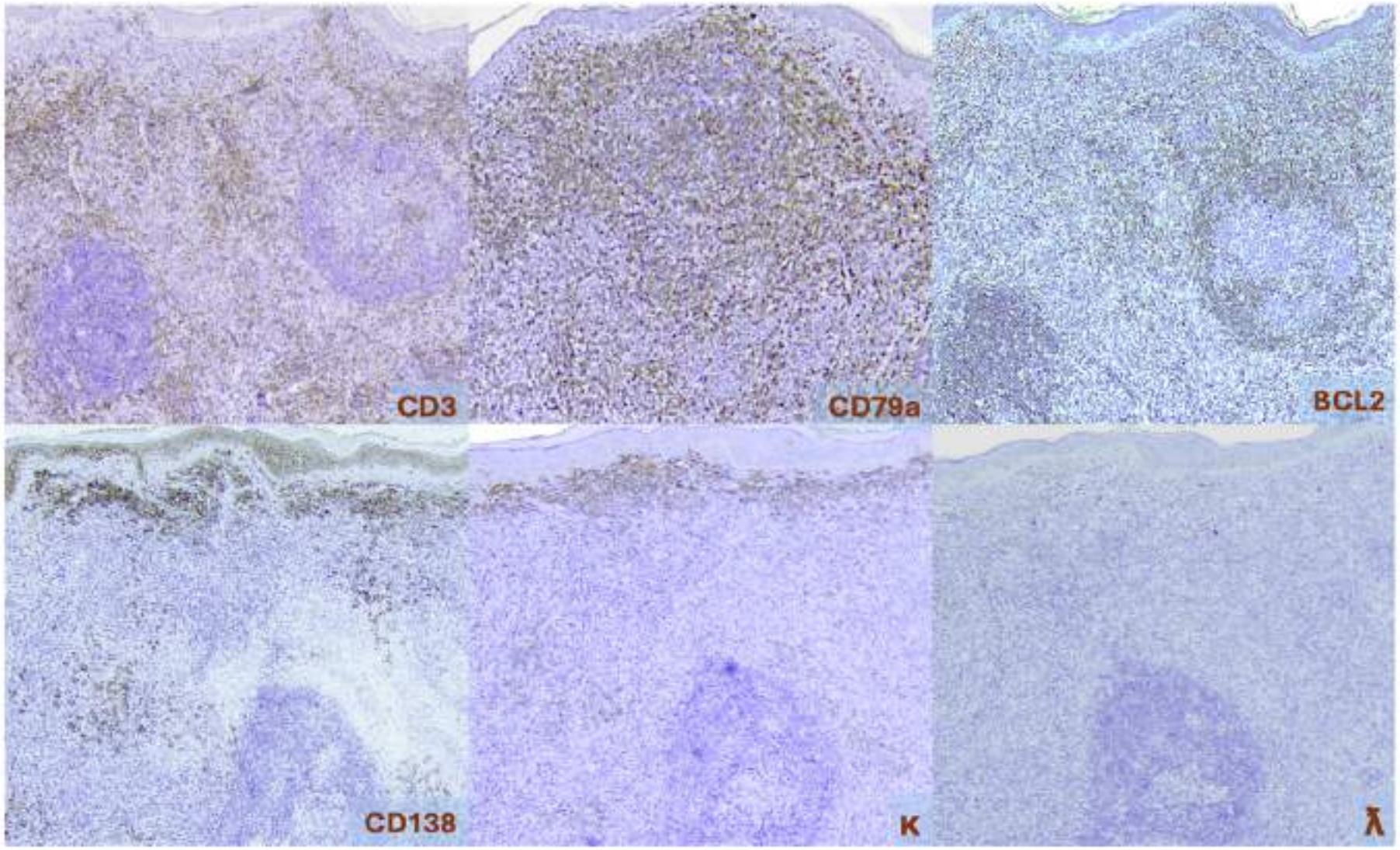


Polymorphus. Nodular or diffuse dermal infiltrate composed of small to medium-sized lymphocytes ("centrocyte-like"), with monocytoid B-cells, plasma cells, reactive T-cells; no stromal reaction

Figure 6. Primary cutaneous marginal zone lymphoma/lymphoproliferative disorder. Hematoxylin and eosin-stained sections 20× and 400×.

Barbati ZR & Yann CJ. Cancers 2025

PCMZL



CD20+, CD79a+,
PAX5+, BCL2+, CD5-,
CD10-, BCL6—

Figure 7. Primary cutaneous marginal zone lymphoma/lymphoproliferative disorder. Immunohistochemistry, 40×.

Barbati ZR & Yann CJ. Cancers 2025

PCMZL

Can be **divided into 2 groups** with different prognosis based on the immunoglobulin heavy chain IgH gene rearrangement:

- **CXCR3-negative** and Ig class-switched subtype (IgG, IgA, and IgE) characterized by nodular infiltrates of plasma cells
- A less common subtype that is **CXCR3-positive** and IgM positive (non class switched), which may have extracutaneous extension
- IgG class-switched subtype is a clonal chronic lymphoproliferative disorder (LPD), with indolent course

Barbati ZR & Yann CJ. Cancers 2025

PCMZL

	PCFCL	PCMZL	PCDLBCL-LT	IVLBCL	EBVMCU
Molecular and cytogenetic findings					
BCL2 rearrangement/t(14;18)	Negative (10%–40% positive)	Negative	Negative	Negative	Negative
BCL6 or MYC rearrangement	Negative	Negative	Positive (30% BCL6, 30% MYC)	Rare MYC rearrangement	Negative
Other	< 10% of cases mutation in epigenetic modifiers	t(14;18)(q32,q21) (27%), FAS mutations (60%)	*MYD88* (60%), *CD79B* (20%)	MYD88 L265P (44%); CD79B (26%)	—

Bernardelli A et al. European Journal of Haematology, 2026

PCMZL

- As in other extranodal MZL, a link with chronic antigenic stimulation has also been suggested for PCMZL, including bacterial and viral agents, tattoo pigments, vaccines and iatrogenic agents (fluoxetine). *Borrelia burgdorferi infection* has been associated with PCBCL, including the PCMZL type, according to studies from some European countries (Scotland and Austria); however, other studies, mostly from Asia and the U.S.A., did not confirm such an association, suggesting geographic variability.
- Other infections possibly associated with the development of PCMZL are herpes simplex virus type 1 and hepatitis virus. Notably, hepatitis C virus (HCV) infections have been found in association with up to 43% of PCMZL, according to one Italian study, and rare cases responding to antiviral therapy have been reported. PCMZL may also arise in an autoimmune disease setting, such as Sjögren syndrome or Hashimoto's thyroiditis.

Lucioni M et al. Hemato 2022

> Hematol Oncol. 2024 Jan;42(1):e3215. doi: 10.1002/hon.3215. Epub 2023 Aug 30.

Identifying and addressing unmet clinical needs in primary cutaneous B-cell lymphoma: A consensus-based paper from an ad-hoc international panel

Pietro Quaglino [1], Nicola Pimpinelli [2], Pier Luigi Zinzani [3 4 5], Marco Paulli [6], Stefano Pileri [7], Emilio Berti [8 9], Lorenzo Cerroni [10], Joan Guitart [11], Youn H Kim [12], Serena Rupoli [13], Marco Santucci [14 15], Gabriele Simontacchi [16], Maarten Vermeer [17], Richard Hoppe [18], Barbara Pro [19], Steven H Swerdlow [20], Giovanni Barosi [21]

PCMZL

Recommendations and proposals

PCMZL and CLH often share histopathological features…

Ancillary studies may corroborate a lymphoma diagnosis, documenting clonal IGH rearrangements.. However it is important to stress that clonal rearrangements may occur also in some reactive lymphoid infiltrates.

A definitive diagnosis **may not always be achieved**, even after a judicious integration of pathological and clinical data. In these cases only clinical follow-up and repeated biopsy may finally confirm the lymphoma diagnosis.

PCDLBCL-LT

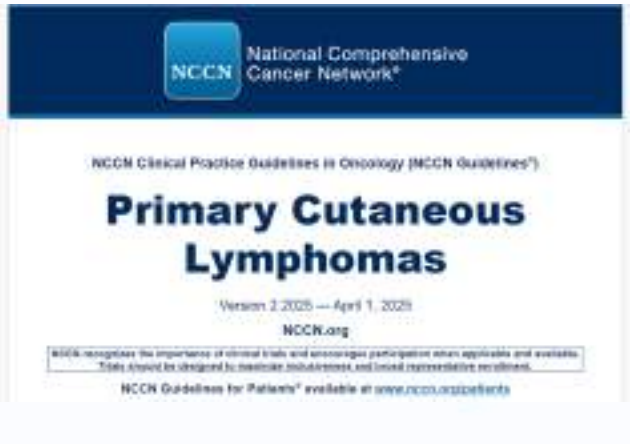
Bernardelli A et al. European Journal of Haematology, 2026

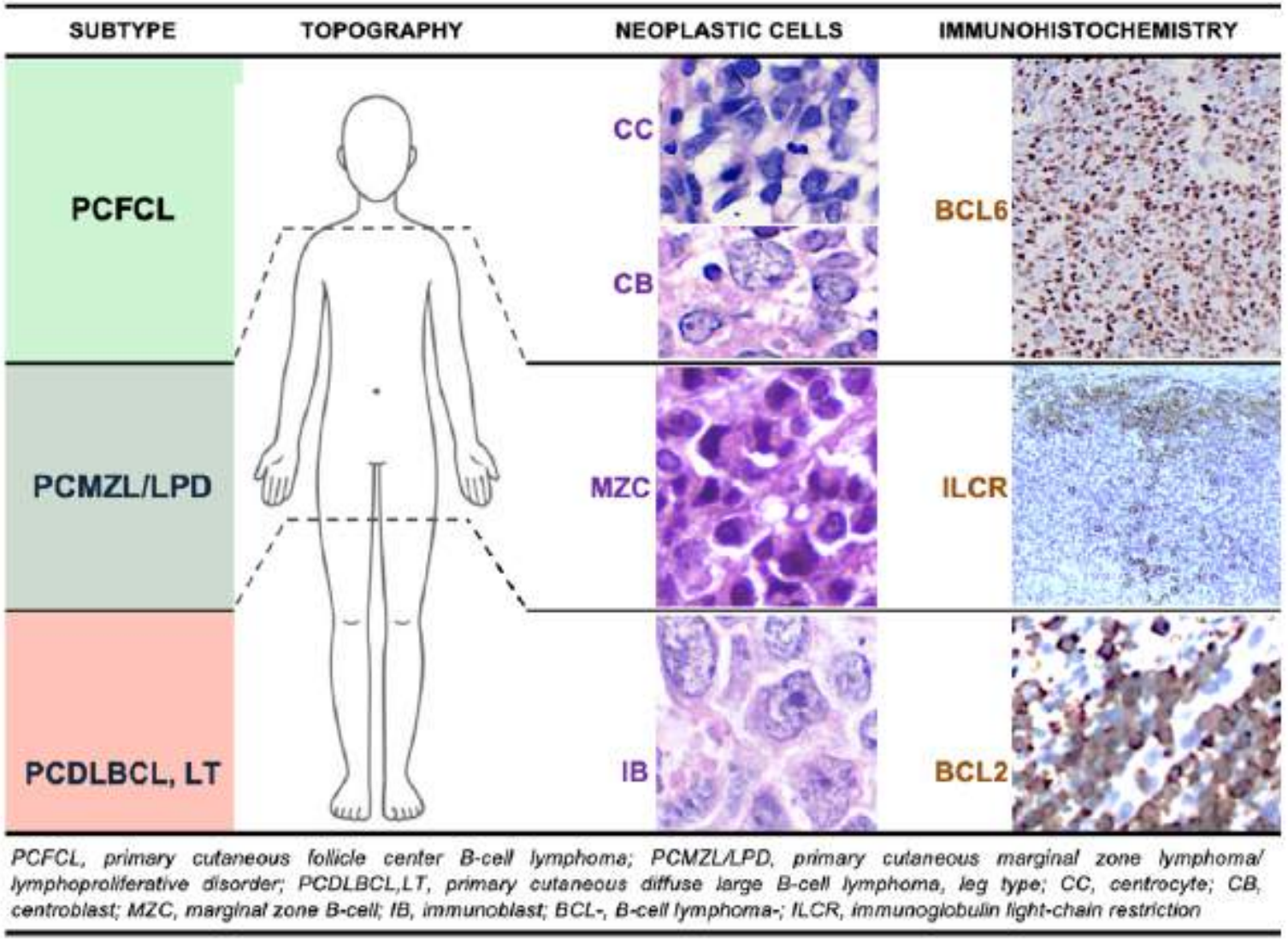
TABLE 1 | Features of primary cutaneous B-cell lymphomas.

	PCFCL	PCMZL	PCDLBCL-LT	IVLBCL	EBVMCU
Epidemiology					
Mean age of onset	5–6th decade	5–6th decade	7–8th decade	7th decade	7th decade
Sex predominance	Male	Male	Female	Female	Female
% cases of PCBCL	30%–50% (in Caucasians)	25%–30%	20%–40%	Rare (more often in Caucasians)	Rare
Clinical features	Asymptomatic and localized plaques and nodules	Asymptomatic or slightly pruritic, solitary or multiple clustered plaques and nodules	Solitary or multiple, rapidly growing, multifocal nodules and tumors	Mild to severe symptoms, heterogeneous single or multiple skin lesions	Solitary, well-circumscribed ulcerative lesion
Frequent sites	Head or trunk	Trunk, arms or head	Lower extremities	Skin, frequent CNS involvement	Skin, oropharyngeal mucosa, or gastrointestinal tract

The **rarest subtype of PCBCL** (**11%–19%),** constituting 4% of all primary cutaneous lymphomas. It is distributed mostly to the leg, but not uncommonly (10%–15%) can be found in other sites.

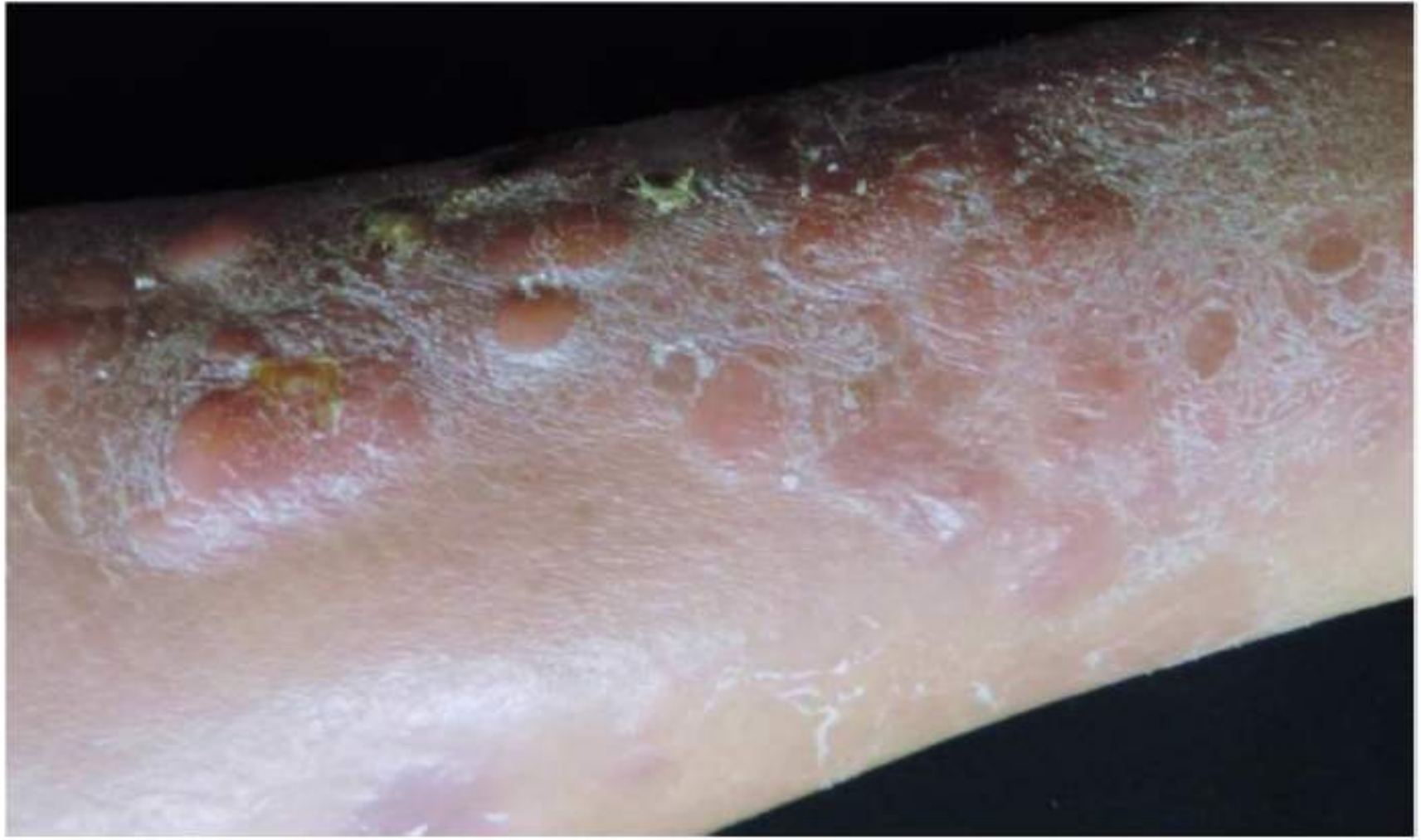
- Typical clinical presentation is red to bluish plaques or tumors located on one or both legs that can ulcerate.
- It is usually aggressive and associated with a poor prognosis (high frequency of extracutaneous relapses) (**5-year OS rate is 50%).**
- Multiple skin lesions, inactivation of CDKN2A, and MYD88 L265P associated with inferior prognosis





Barbati ZR & Yann CJ. Cancers 2025

PCDLBCL-LT



Solitary or multiple, rapidly growing multifocal nodules and tumors

Lower extremities

Figure 9. Primary cutaneous diffuse large B-cell lymphoma, leg type. Clinical image.

Barbati ZR & Yann CJ. Cancers 2025

Cancers 2020, 12(6), 1497

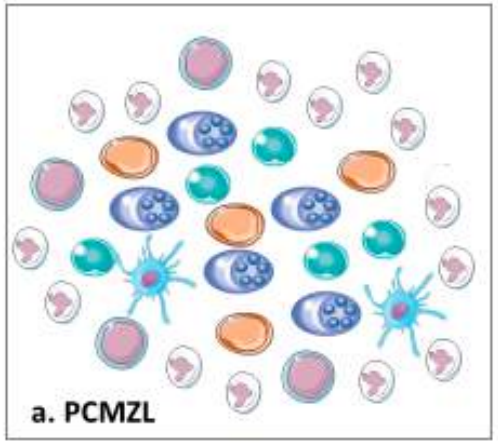
cancers

MDPI

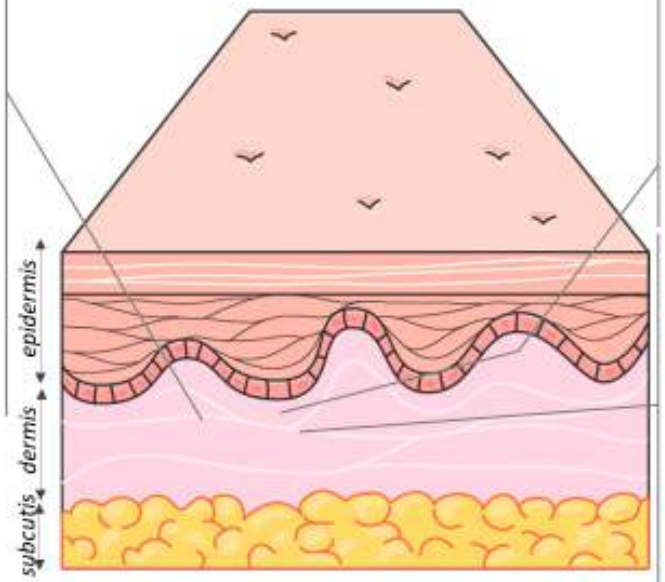
Review

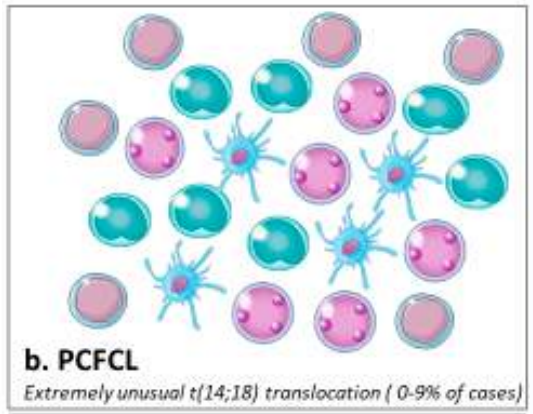
Diagnosis and Treatment of Primary Cutaneous B-Cell Lymphomas: State of the Art and Perspectives

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



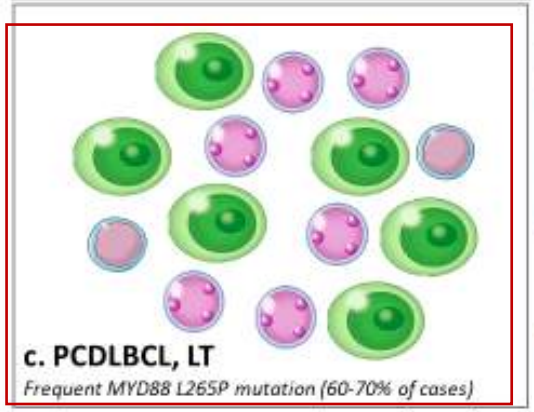
a. PCMZL





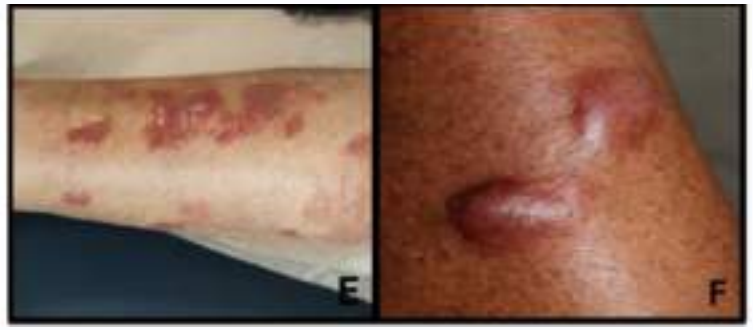
b. PCFCL

Extremely unusual t(14;18) translocation (0-9% of cases)



c. PCDLBCL, LT

Frequent MYD88 L265P mutation (60-70% of cases)



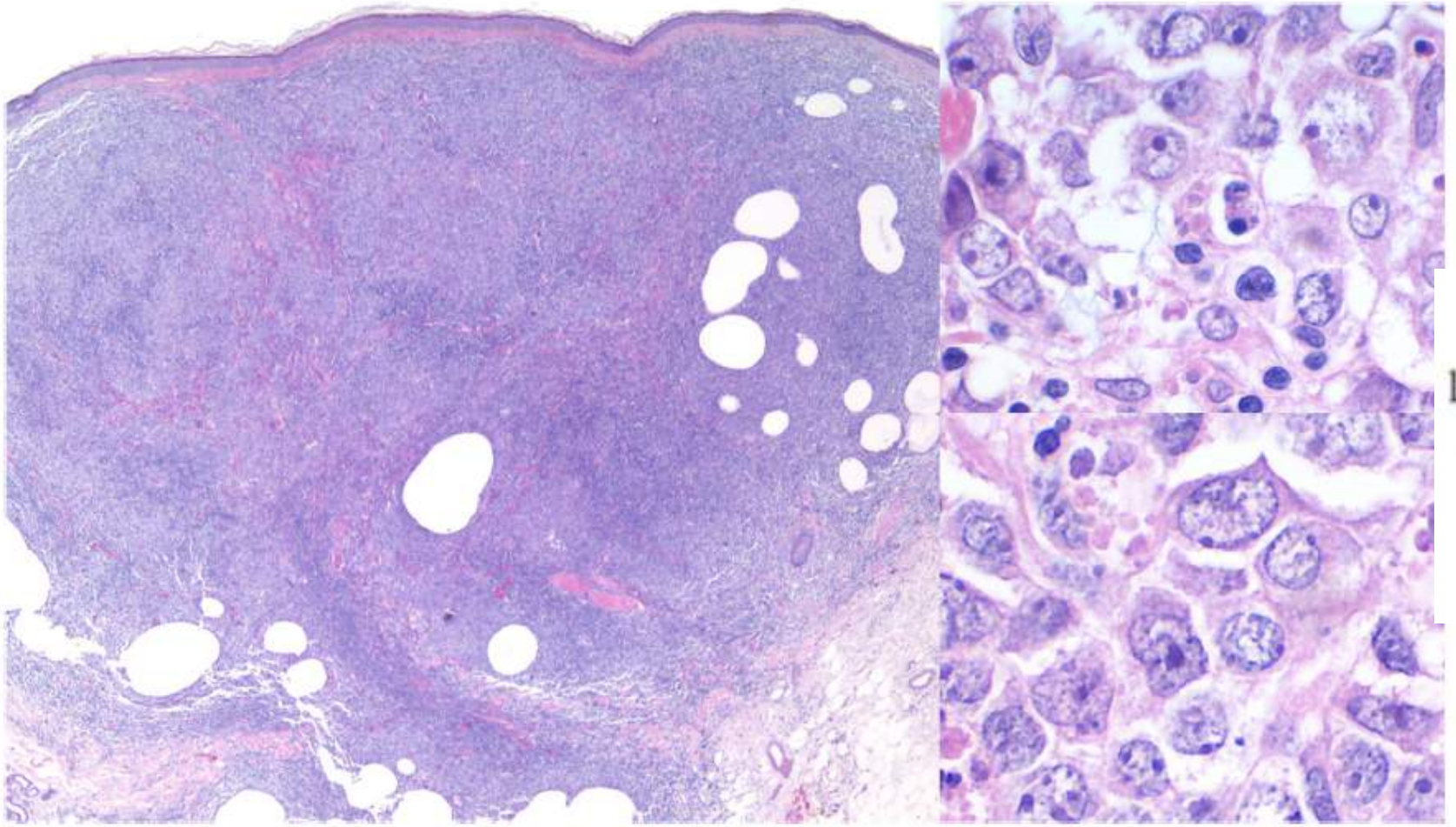
Centroblast like-B cell
Centrocyte like-B cell
Plasma cell
Immunoblast
Marginal zone B cell
Reactive T cell
Lymphoplasmacytoid cell
Follicular DC network

Eur J Haematol. 2025 Oct 28;116(2):116-128. doi: 10.1111/ejh.70053

Primary Cutaneous B-Cell Lymphomas: An Updated Portrait of Classification, Biology, and Clinical Management

A Bertuzzelli [1], E Canozzi [1], B Buonomo [2], F Bellinato [3], M Hrampsava [1,2], C Visco [1,2,*]

PCDLBCL-LT

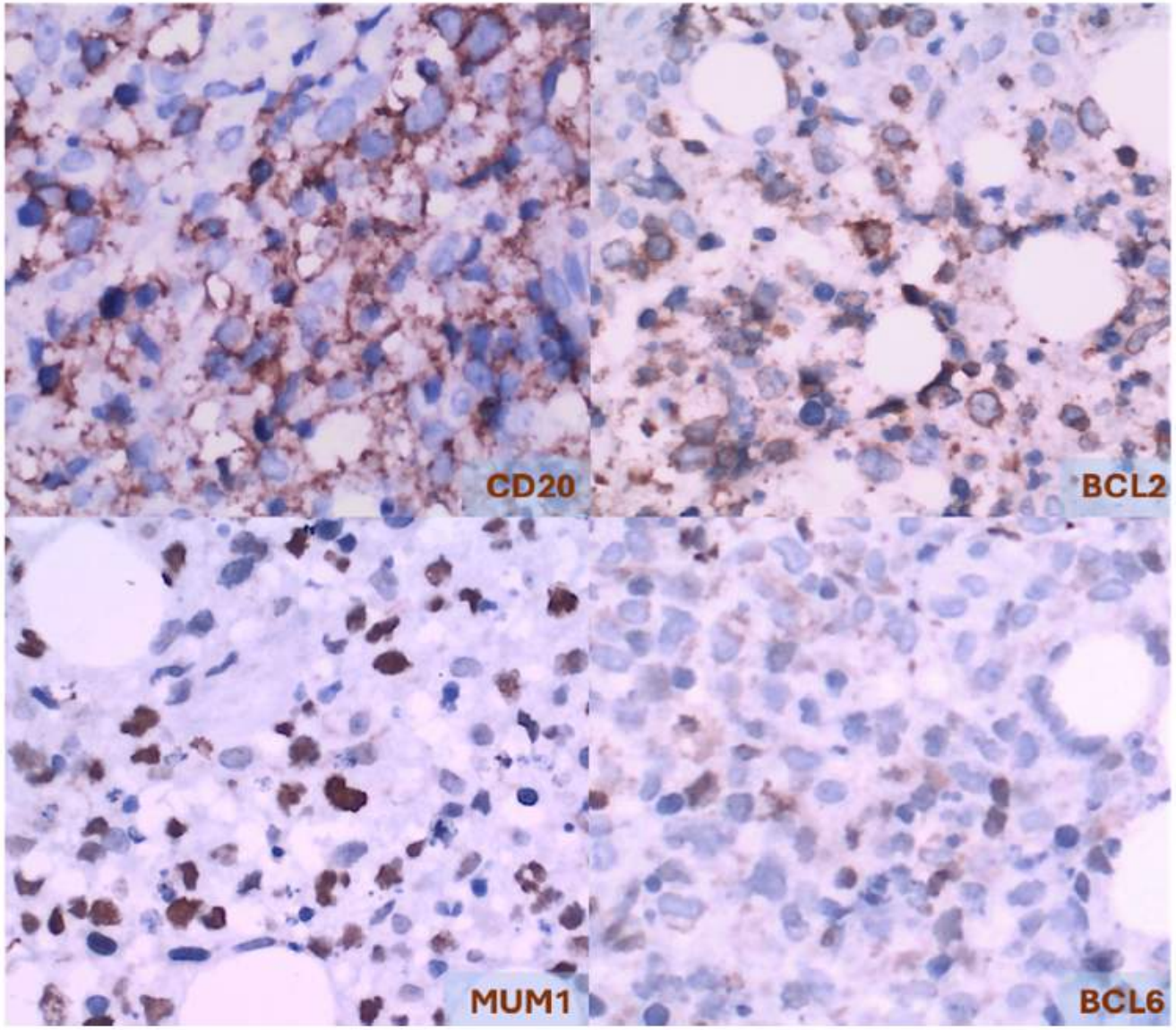


Diffuse, dense infiltrate of large atypical lymphoid cells predominantly involving the dermis and frequently extending into the subcutaneous tissue; no stromal reaction

Figure 10. Primary cutaneous diffuse large B-cell lymphoma, leg type. Hematoxylin and eosin-stained sections 20×, 400× and 600×.

Barbati ZR & Yann CJ. Cancers 2025

PCDLBCL-LT



CD20+, CD79a+, BCL6+/−, PAX5+, IgM+, BCL2+, MUM1/IRF4+, CD10—

Figure 11. Primary cutaneous diffuse large B-cell lymphoma, leg type. Immunohistochemistry, 400×.

Barbati ZR & Yann CJ. Cancers 2025

PCDLBCL-LT

Bernardelli A et al. European Journal of Haematology, 2026

	PCFCL	PCMZL	PCDLBCL-LT	IVLBCL	EBVMCU
Molecular and cytogenetic findings					
BCL2 rearrangement/t(14;18)	Negative (10%–40% positive)	Negative	Negative	Negative	Negative
BCL6 or MYC rearrangement	Negative	Negative	Positive (30% BCL6, 30% MYC)	Rare MYC rearrangement	Negative
Other	< 10% of cases mutation in epigenetic modifiers	t(14;18)(q32,q21) (27%), FAS mutations (60%)	*MYD88* (60%), *CD79B* (20%)	MYD88 L265P (44%); CD79B (26%)	—

Immunophenotype – cells express CD20, CD79a, monotypic immunoglobulins, BCL2 (strong), IRF/MUM1, FOXP1, IgM, and occasionally MYC. CD10 staining is usually negative. Immunophenotype may vary with poor correlation with Hans algorithm, but most cases are positive for MUM1 and BCL2 with variable expression of other markers.

Gene expression profiling: PCDLBCL, leg type has been demonstrated to be most commonly activated B-cell (ABC) subtype.

Gain-of-function mutations in MYD88 and CD79B co-occur in the so-called "MCD" subtype, and are specific to PCDLBCL, leg type

Hematol Oncol. 2024 Jan;42(1):e3215. doi: 10.1002/hon.3215. Epub 2023 Aug 30.

Identifying and addressing unmet clinical needs in primary cutaneous B-cell lymphoma: A consensus-based paper from an ad-hoc international panel

Pietro Quaglino [1], Nicola Pimpinelli [2], Pier Luigi Zinzani [3 4 5], Marco Paulli [6], Stefano Pileri [7], Emilio Berti [8 9], Lorenzo Cerroni [10], Joan Guitart [11], Youn H Kim [12], Serena Rupoli [13], Marco Santucci [14 15], Gabriele Simontacchi [16], Maarten Vermeer [17], Richard Hoppe [18], Barbara Pro [19], Steven H Swerdlow [20], Giovanni Barosi [21]

PCDLBCL-LT

Recommendations and proposals

The presence of a vaguely residual nodular pattern (usually detectable at low mangnification), a residual often disrupted follicular dendritic cell meshwork, an intense intermingled reactive T-cell infiltrate, weak to absent BCL2 expression, favour a PCFCL whereas large cohesive sheets of centroblasts and immunoblasts without dendritic cell aggregates favours PCDLBCL.

Molecular analyses can also be useful as PCDLBCL variably carry MYC and/or BCL6 translocations, and amplification of MALT1 and BCL2.

Table 2. Differential diagnosis between PCFCL, PCDLBCL NOS and PCDLBCL-LT.

Lucioni M et al. Hemato 2022

Characteristics	PCFCL	PCDLBL NOS	PCDLBCL-LT
Age	50–60	60	70–80
Sex	M>F	M>F	F>M
Site	head, trunk, leg	trunk, head-neck, lower limbs, upper limbs	leg, trunk, head-neck, upper extremities
Clinical features	plaque, nodule, tumour	nodule, plaque	tumour, nodule
Single/multiple lesions	usually single	single	single or multiple
Histology			
Cells morphology	centrocytes (prevalent) and centroblasts	centroblasts with <10% of medium sized cells	centroblast and/or immunoblast
Pattern	nodular, nodular and diffuse, diffuse	diffuse, vaguely nodular	diffuse
Skin ulceration	Absent	present or absent	mostly present
Necrosis	no	rare	yes
Adnexal effacement	usually absent	May be present	mostly present
Reactive T-cell CD3+ infiltrate	present, abundant	present, mild to moderate	few or absent
Dendritic meshwork	present/absent	absent	absent
Immunophenotype	CD20+, CD79a+, Bcl6+, CD10+, Bcl2-(73%)	CD20+, CD79a+, Bcl6+, CD10+/−, MUM1+/−, IgM+/−, c-Myc+/−, bcl2-/+	CD20+, CD79a+, Bcl2+, MUM1+, Bcl6+, c-myc+, IgM+, CD10-
Ki67	usually low (up to 30%)	moderate (40%)	high (>70%)
DE phenotype	no	infrequent	>60% of cases
Molecular features	rarely translocation IGH-BCL2, up to 40% BCL2 aberrations	rearrangements of BCL6 or MYC, rarely BCL2 alterations	IGH clonal rearrangements, translocations involving BCL6, MYC and IGH, $MYD88^{L265P}$ mutations
DH/TH status	no	DH status reported in literature (one case)	yes
Prognosis	indolent	less aggressive than PCDLBCL-LT, GC cases more similar to PCFCL, Non-GC cases in between PCFCL and PCDLBCL-LT	aggressive

Human Pathology
Volume 136, June 2023, Pages 44-55

Original contribution

Clinicopathological, cytogenetic, and molecular profiles of primary cutaneous diffuse large B-cell lymphomas ☆, ☆☆

Silvia Uccella MD, PhD [a 1], Gaia Goteri MD, PhD [b 1], Antonino Maiorana MD [c], Valentina Donati MD [d], Maria Grazia Tibiletti BS [e], Francesca Magnoli MD, PhD [e], Sofia Facchi BS [f], Deborah Merchiori MD [f], Erika Morsia MD [g], Robel Papotti BS, PhD [c h i], Stefania Bettelli BS [j], Elisa Forti BS [j], Sara Galimberti MD [k], Serena Rupoli MD [g], Alessandra Filosa MD, PhD [b], Dimitri Dardanis MD [k], Riccardo Bomben BS [h], Luca Braglia BS, PhD [c], Samantha Pozzi MD [c], Stefano Sacchi MD [c]

Our study comprehensively analyzed the clinicopathological and molecular features of PCDLBCL-LT, PCDLBCL-NOS, and SCDLBCL, underlining the differences among them and the importance of properly identifying these entities at the time of diagnosis.

PCDLBCL-LT, 10 cases and PCDLBCL-NOS, 8 cases

- Immunohistochemistry for Hans' algorithm markers, BCL2, and MYC was performed.
- The molecular study included the determination of the cell of origin (COO) by Lymph2Cx assay on NanoString platform, FISH analysis of IgH, BCL2, BCL6, and MYC genes, as well as the mutation analysis of MYD88 gene.

- In immunohistochemistry analysis, **BCL2 and MYC hyperexpression was more frequent in LT than in NOS cases** and, according to Hans' algorithm, PCDLBCL-LTs were mostly of the non-GC type (8/10), whereas in PCDLBCL-NOS, the GC type prevailed (6/8).
- The determination of COO using Lymph2Cx supported and further confirmed these results. In FISH analysis, all but one LT cases versus 5 of 8 PCDLBCL-NOS showed at least one gene rearrangement among IgH, BCL2, MYC, or BCL6. In addition, **MYD88 mutations were more frequently present in LT than in NOS subtypes.** Interestingly, MYD88-mutated patients were older, with a non-GC phenotype and had worse OS, compared to MYD88 WT cases. Overall, SCDLBCL did not show, at the genetic and expression level, different profiles than PCDLBCL, even if they bear a significantly worse prognosis. At survival analysis, the most important prognostic factors in patients with PCDLBCL were age and MYD88 mutation, whereas relapse and high Ki-67 expression were relevant in patients with SCDLBCL.

Uccella S et al. Human Pathology 2023

PCDLBCL-NOS

Hematol Oncol. 2024 Jan;42(1):e3215. doi: 10.1002/hon.3215. Epub 2023 Aug 30.

Identifying and addressing unmet clinical needs in primary cutaneous B-cell lymphoma: A consensus-based paper from an ad-hoc international panel

Pietro Quaglino [1], Nicola Pimpinelli [2], Pier Luigi Zinzani [3 4 5], Marco Paulli [6], Stefano Pileri [7], Emilio Berti [8 9], Lorenzo Cerroni [10], Joan Guitart [11], Youn H Kim [12], Serena Rupoli [13], Marco Santucci [14 15], Gabriele Simontacchi [16], Maarten Vermeer [17], Richard Hoppe [18], Barbara Pro [19], Steven H Swerdlow [20], Giovanni Barosi [21]

Proposals

The identification of PCDLBCL, not otherwise specified (**PCDLBCL-NOS**) as a distinct entity with intermediate features between PCDLBCL leg type and PCFCL is still debated.

Survival of these patients would be strongly dependent on the cell of origin: good and similar to that of PCFCL in those with germinal center (GC) profile, or viceversa, poorer and similar to that of PCDLBCL leg type in those with activated B-cell (ABC) profile.

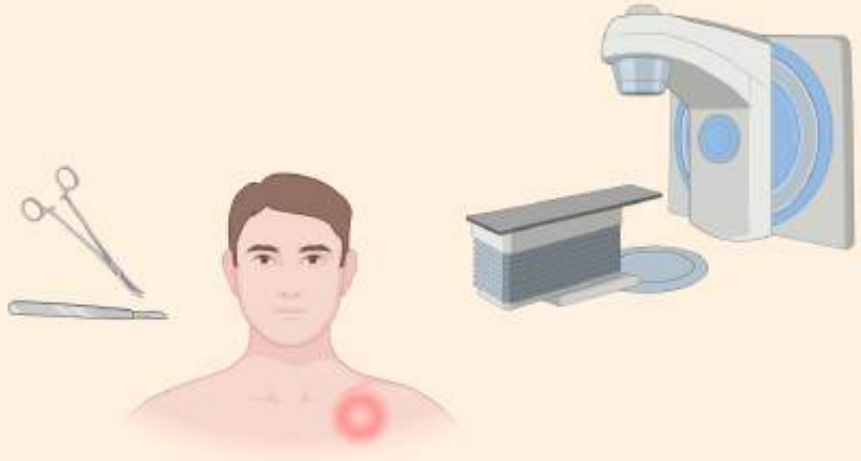
.**Treatment of Indolent/**Low-Grade Primary Cutaneous B-Cell Lymphomas/ Lymphoproliferative Disorders

Barbati ZR & Yann CJ. Cancers 2025

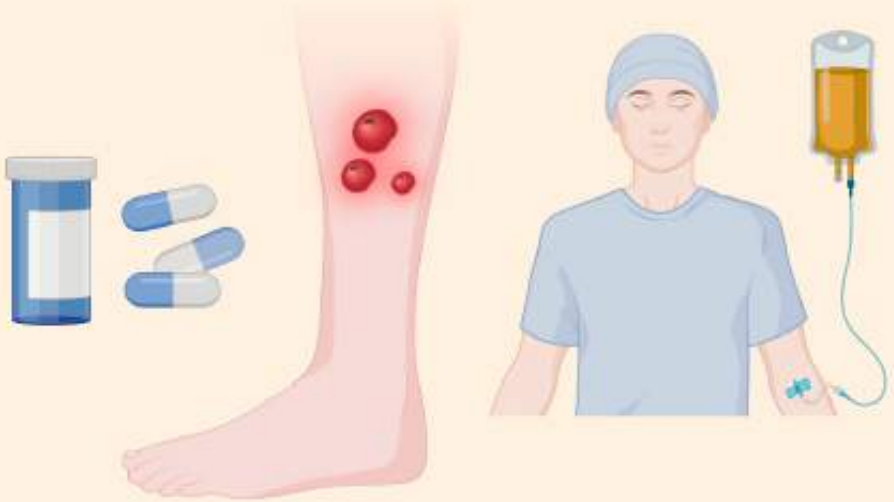
INDOLENT PCBCL (PCFCL; PCMZL/LPD)	**Localized disease** (T1-2)	**ISRT** - *preferred* *or in select cases* **Surgical excision** *or* Intralesional steroids *or* Intralesional rituximab	***Relapsed disease***	**Treat as before**
	Multifocal disease (T3)	**ISRT** or **surgical excision** + **Intravenous rituximab**		
AGGRESSIVE PCBCL (PCDLBCL,LT)	(T1-3)	**R-CHOP + ISRT** *or* Clinical trial	***Relapsed*** *or* ***Refractory disease***	**2nd line chemoimmunotherapy for DLBCL** *or* **CAR T-cell therapy** *or* **Clinical trial** *or* **Transplant** *or* Palliative ISRT *or* Supportive care

Figure 8. Simplified treatment approach for skin-limited indolent and aggressive primary cutaneous

Primary cutaneous follicle centre lymphoma and marginal zone lymphoma/lymphoproliferative disorder



Primary cutaneous diffuse large B-cell lymphoma, leg type



In PCBCLs, indolent subtypes (PCFCL, PCMZL/LPD) are effectively managed with localised therapies, whereas PCDLBCL-LT requires systemic chemo-immunotherapy and, increasingly, immune- and pathway-directed approaches in relapse.

lymphatics

MDPI

Review

Dermatologic Perspectives on Primary Cutaneous Lymphomas: Clinicopathologic Spectrum, Molecular Insights, and Evolving Treatment Paradigms

Orsola Crespi [1,*], François Rosset [2], Umberto Santaniello [1], Valentina Pala [1], Cristina Sarda [1], Martina Accorinti [1], Pietro Quaglino [1] and Simone Ribero [1]

Treatment of Indolent/Low-Grade Primary Cutaneous B-Cell Lymphomas/Lymphoproliferative Disorders

Given the generally favorable prognosis of indolent/low-grade PCBCL, a conservative therapeutic approach should always be prioritized when clinically appropriate.

This may include a "wait and see" strategy for **solitary PCMZL/LPD**, which, while acceptable, is often not preferred by patients and necessitates close surveillance.

For both PCMZL/LPD and PCFCL with solitary or limited lesions, the treatment modalities of choice are typically involved-site radiation therapy (ISRT) and, less commonly, surgical excision.

ISRT is often favored due to its lower morbidity and excellent outcomes, particularly in older adults, or in anatomic areas where surgical excision may result in suboptimal cosmetic outcomes or healing difficulties, such as the face and lower leg, respectively.

Barbati ZR & Yann CJ. Cancers 2025

Treatment of Indolent/Low-Grade Primary Cutaneous B-Cell Lymphomas/Lymphoproliferative Disorders

While **both surgical excision and ISRT can provide complete responses (CRs) in nearly all cases**, **relapses are common, and optical surgical margins remain ill-defined.**

Reported **surgical margins** are generally **less than 1 cm,** while **ISRT typically employs margins ranging from 1 to 5 cm**.

Regarding ISRT, there is no consensus on the optimal radiation doses for indolent PCBCL, with treatment regimens varying widely. Success has been reported from very low-dose ISRT (VLD-IRST; 2–4 Gy in 2 fractions) to **standard-dose ISTR** (SD-IRST; **24–40 Gy in 12–20 fractions**). Both regimens have demonstrated similar efficacy (CRs), but VLD-ISRT is associated with a significantly lower incidence of side effects (15.7% vs. 78.4%, $p < 0.0001$), making it an attractive option for treating indolent PCBCL.

Although some cohorts suggest a higher relapse rate following excisional surgery compared to ISRT, statistically significant differences have not been established. Nevertheless, excision is typically only favored in select cases, where small lesions may be removed with minimal non-disfiguring surgery.

Barbati ZR & Yann CJ. Cancers 2025

Treatment of Indolent/Low-Grade Primary Cutaneous B-Cell Lymphomas/Lymphoproliferative Disorders

Barbati ZR & Yann CJ. Cancers 2025

Alternative treatment strategies for solitary or limited lesions of indolent PCBCL include intralesional corticosteroids, particularly for small lesions of PCMZL/LPD, though the CR rate is suboptimal at approximately 44% and multiple treatment cycles are often required.

Systemic antibiotics such as cephalosporins and tetracyclines may be effective for lesions associated with Borrelia burgdorferi infection (especially in endemic regions of Europe).

Other therapies include intralesional interferon-alpha (though not available in many countries) and intralesional rituximab, a chimeric monoclonal antibody targeting CD20.

Intralesional rituximab has shown high CR rates (60–80%) but is often impractical due to the need for multiple injections, associated pain, wheal-like reactions (both at the injection site and distant sites), and mild, albeit bothersome, adverse events, such as urticaria, exanthem, fever, nausea, and malaise. Importantly, rituximab can lead to rare, but potentially serious reductions in B-cell counts, even with low cumulative doses.

.**Treatment of Indolent/**Low-Grade Primary Cutaneous B-Cell Lymphomas/ Lymphoproliferative Disorders

Barbati ZR & Yann CJ. Cancers 2025

INDOLENT PCBCL (PCFCL; PCMZL/LPD)	**Localized disease** (T1-2)	**ISRT** - *preferred* *or in select cases* **Surgical excision** *or* Intralesional steroids *or* Intralesional rituximab	***Relapsed disease***	**Treat as before**
	Multifocal disease (T3)	**ISRT** or **surgical excision** + **Intravenous rituximab**		
AGGRESSIVE PCBCL (PCDLBCL,LT)	(T1-3)	**R-CHOP + ISRT** *or* Clinical trial	***Relapsed*** *or* ***Refractory disease***	**2nd line chemoimmunotherapy for DLBCL** *or* **CAR T-cell therapy** *or* **Clinical trial** *or* **Transplant** *or* Palliative ISRT *or* Supportive care

Figure 8. Simplified treatment approach for skin-limited indolent and aggressive primary cutaneous

Treatment of Indolent/Low-Grade Primary Cutaneous B-Cell Lymphomas/Lymphoproliferative Disorders

In patients with **multiple disseminated lesions**, or in select cases (i.e., **PCFCL** with extensive scalp lesions, where IRST may lead to long-standing alopecia), intravenous rituximab (325 mg/m2 weekly for 4–8 infusions) has proven effective, with reported 98% overall response rates (ORRs), 64% CRs, a median progression free survival (PFS) of 58 months, and a median time to next treatment (TTNT) of 60 months in the largest series of 25 cases of **PCMZL/LPD**.

In a similar cohort of 29 patients with **PCFCL,** systemic rituximab achieved an ORR of 96%, a CR of 72%, a median **PFS** of 78 months, and a median TTNT of 85 months.

In both cohorts, adverse events, mostly grade 1–2, occurred in approximately 32–38% of cases.

Barbati ZR & Yann CJ. Cancers 2025

Treatment of Indolent/Low-Grade Primary Cutaneous B-Cell Lymphomas/Lymphoproliferative Disorders

However, rare cohorts of multiagent chemotherapy in **PCMZL/LPD** have demonstrated CR rates of approximately 85%, though relapses occur at similar rates to those observed with other treatment modalities.

Similarly, a systematic review of multi-agent chemotherapy in **PCFCLs** found CR rates in 85% of patients, with a relapse rate of 44%.

The cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) regimen has been the most commonly used chemotherapy protocol, often with or without the addition of rituximab and/or ISRT.

However, experience with these combined approaches remains limited by the relatively small patient populations treated with such regimens.

Barbati ZR & Yann CJ. Cancers 2025

Hematol Oncol. 2024 Jan;42(1):e3215. doi: 10.1002/hon.3215. Epub 2023 Aug 30.

Identifying and addressing unmet clinical needs in primary cutaneous B-cell lymphoma: A consensus-based paper from an ad-hoc international panel

Pietro Quaglino [1], Nicola Pimpinelli [2], Pier Luigi Zinzani [3 4 5], Marco Paulli [6], Stefano Pileri [7], Emilio Berti [8 9], Lorenzo Cerroni [10], Joan Guitart [11], Youn H Kim [12], Serena Rupoli [13], Marco Santucci [14 15], Gabriele Simontacchi [16], Maarten Vermeer [17], Richard Hoppe [18], Barbara Pro [19], Steven H Swerdlow [20], Giovanni Barosi [21]

Recommendations and proposals

Patients with PCMZL or PCFCL presenting with solitary or localized skin lesions should be managed with **excision and/or local RT with curative intent.**

As second line or when lesions are difficult to treat with RT or surgery, intralesional (IL) high-potency corticosteroids and IL rituximab, are options.

Alternative topical therapies (e.g. clobetasol, nitrogen mustard, imiquimod and photodynamic therapy) may also be considered in selected situations.

In **multifocal disease**, local RT, **intravenous rituximab monotherapy**, IFN-alpha, oral chlorambucil, are all acceptable palliative choices.

Clinical observation or limiting treatment to symptomatic lesions can be acceptable in patients with multifocal indolent disease.

Similar approach can be adopted to treat relapses.

Clinical trials should be considered in appropriate cases.

.Treatment of **Aggressive PCBCL (PCDLBCL, LT)**

Barbati ZR & Yann CJ. Cancers 2025

INDOLENT PCBCL (PCFCL; PCMZL/LPD)	**Localized disease** (T1-2)	**ISRT** - *preferred or in select cases* **Surgical excision** *or* Intralesional steroids *or* Intralesional rituximab	***Relapsed disease***	**Treat as before**
	Multifocal disease (T3)	**ISRT** or **surgical excision** + **Intravenous rituximab**		
AGGRESSIVE PCBCL (PCDLBCL,LT)	(T1-3)	**R-CHOP + ISRT** *or* Clinical trial	***Relapsed*** *or* ***Refractory disease***	**2nd line chemoimmunotherapy for DLBCL** *or* **CAR T-cell therapy** *or* **Clinical trial** *or* **Transplant** *or* Palliative ISRT *or* Supportive care

Figure 8. Simplified treatment approach for skin-limited indolent and aggressive primary cutaneous

.Treatment of **Aggressive PCBCL (PCDLBCL, LT)**

The standard first-line treatment for PCDLBCL,LT involves polychemotherapy with the **R-CHOP regimen**.

The **addition of ISRT** has been shown to enhance local control and **prolong PFS**, with a median PFS of 58 months when combined with R-CHOP, compared to 14 months with R-CHOP alone.

Importantly, localized treatment alone is typically inadequate for effective disease management.

In patients who are unable to tolerate the standard R-CHOP regimen due to advanced age or significant comorbidities, alternative reduced-intensity regimens or the combination of rituximab with pegylated liposomal doxorubicin (PLD) may be considered.

The use of PLD is advantageous as it has a reduced risk of cardiotoxicity compared to conventional doxorubicin.

Barbati ZR & Yann CJ. Cancers 2025

ORIGINAL ARTICLE

Efficacy and safety of pegylated liposomal doxorubicin in primary cutaneous B-cell lymphomas and comparison with the commonly used therapies

Stefano Pulini[1], Serena Rupoli[2], Gaia Goteri[3], Nicola Pimpinelli[4], Renato Alterini[5], Alberta Bettacchi[6], Simonetta Mulattieri[2], Paola Picardi[2], Angela Tassetti[7], Anna Rita Scortechini[2], Giuseppe Fioritoni[1], Pietro Leoni[2]

[1]Clinical Hematology, Department of Hematology, 'Spirito Santo' Civic Hospital, Pescara, Italy; [2]Clinic of Hematology, Polytechnic University of Marche, Ancona, Italy; [3]Institute of Pathology, Polytechnic University of Marche, Ancona, Italy; [4]Department of Dermatological Sciences, University of Florence, Florence, Italy; [5]Department of Hematology, University of Florence, Florence, Italy; [6]Division of Dermatology, Macerata, Italy; [7]Division of Internal Medicine, Civitanova Marche, Italy

Among our patients, all the five with aggressive forms (PCLBCL-LT) **showed a CR in a short period**, which was long lasting in two of them (69 and 63 months respectively), even if one of them had a refractory, relapsing disease (Patient 2).

The particular skin-tropism of Peg-Doxo probably accounts for the high rate of CR in such very aggressive cutaneous lymphoma.

European Journal of Haematology 2008

Table 1 Clinico-pathological characteristics of the patients before starting Peg-Doxo treatment, response and follow-up

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5
Gender	F	M	M	M	M
Age (yrs)	38	55	53	75	55
Disease history (months)	23	35	10	2	2
WHO/EORTC histological type	PCMZL	PCLBCL-LT	PCLBCL-LT	PCLBCL-LT	PCLBCL-LT
Pretreatment	R; Gem	R; R-CVP	R	None	None
Type of lesions	Nodules and plaques	Nodules and plaques	Nodules and plaques	Nodules and plaques	Nodules
Body regions	HN, RLAH, LLAH, RUL, RLLF, LUL	C, AG	UB	C, UB, RLLF, LLLF	RUA, RLAH LUA, LLAH
TNM	T3b, N0, M0	T2c, N0, M0	T2b, N0, M0	T3b, N0, M0	T3b, N0, M0
PS	0	0	1	1	0
No. infusions	4	8	8	6	6
LDH	Normal	Normal	High	High	High
$\beta_2$microglobulin	Normal	Normal	Normal	High	Normal
Itching	No	Yes	No	No	Yes
Max response (months)	2	2	3	4	3
Response	Complete	Complete	Complete	Complete	Complete
Toxicity (grade and type)	No	No	No	III neutropenia	I neurotoxicity
Relapse (months)	Yes (8)	No	No	Yes (11)	No
Post-treatment	IFN; Rit	–	–	CBVD; Rit	–
Status at last follow-up	AW; CR	AW; CR	AW; CR	DOD	AW; CR
Follow-up (months)	52	69	5	25	63

Pulini S et al. European Journal of Haematology 2008

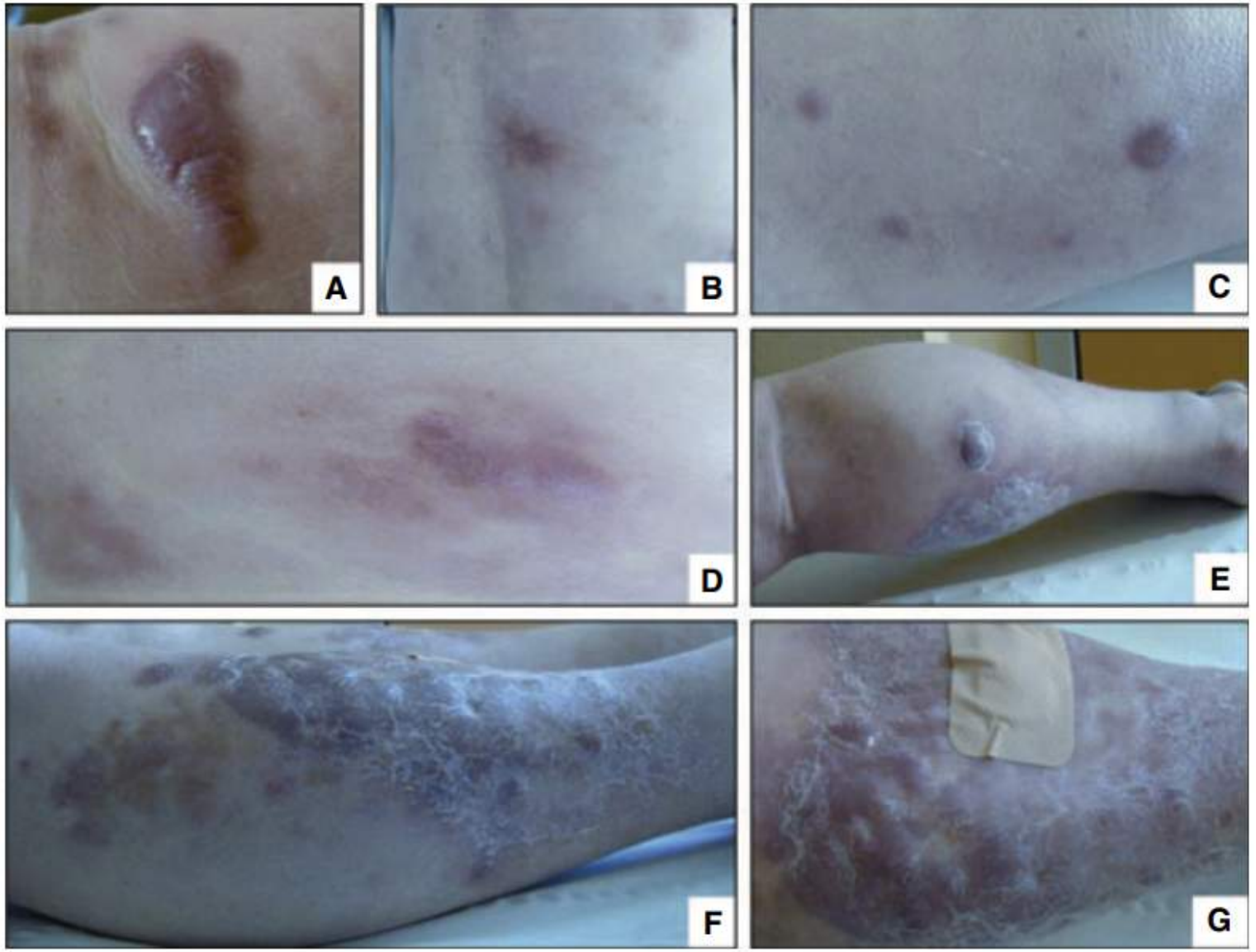
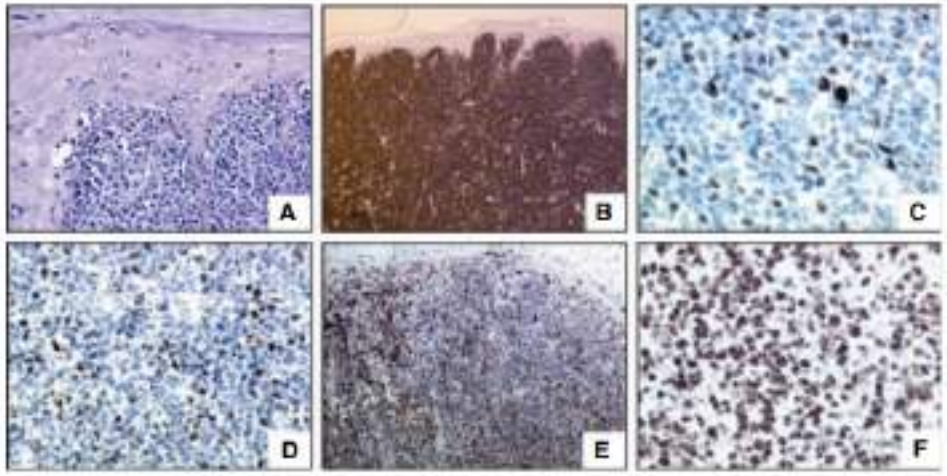


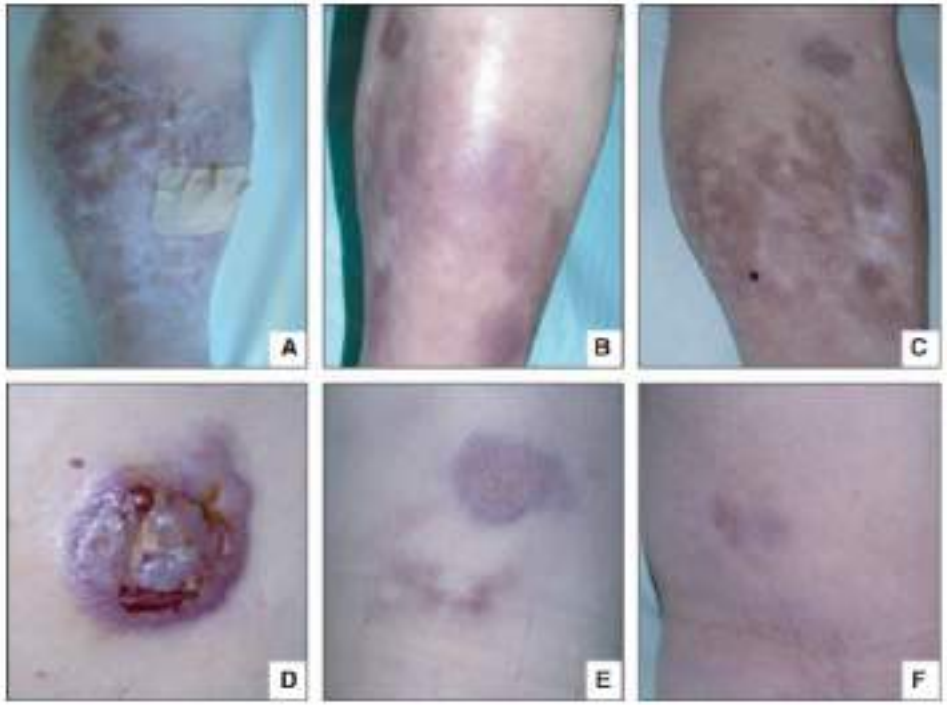
Figure 1 Patient number 4: PCLBCL-LT. A 75-yr-old man presented multifocal rapidly growing infiltrating plaques and tumours of 3–4 cm on the trunk (A, B, D) and both lower legs (C, E, F, G).

Pulini S et al. European Journal of Haematology 2008



Pulini S et al. European Journal of Haematology 2008

Figure 2 Patient number 4: PCLBCL-LT. Diffuse large B-cell lymphoma involving the skin and infiltrating the epidermis; cells are large blasts with immunoblastic appearance (H and E) (A). Blasts are diffusely positive for CD20 (B), negative for CD10 (C), positive for BCL6 (D), BCL2 (E), and highly proliferating with Mib-1 immunostaining (F).



The patient 4 died for relapsing and progressive disease. He constitutes **a rare example of extracutaneous recurrence in the central nervous system (CNS).** The overall risk of secondary CNS involvement in NHL is about 5%. With regards to PCLs, this complication is mainly reported in patients with PCTCL, mostly in stage IV B Mycosis Fungoides and, among B histological types, in intravascular lymphoma, but very rarely in other PCBCL, which accounts for 2% of cases and is related to death, according to the published data from the Dutch Cutaneous Lymphoma Registry.

Figure 3 Patient number 4: PCLBCL-LT. At diagnosis (A, D), after two cycles of Peg-Doxo monotherapy (B, E), after four cycles of Peg-Doxo (C, F). A, B, C: lower legs; D, E, F: trunk.

.Treatment of **Aggressive PCBCL (PCDLBCL, LT)**

Barbati ZR & Yann CJ. Cancers 2025

INDOLENT PCBCL (PCFCL; PCMZL/LPD)	**Localized disease** (T1-2)	**ISRT** - *preferred or in select cases* **Surgical excision** *or* Intralesional steroids *or* Intralesional rituximab	***Relapsed disease***	**Treat as before**
	Multifocal disease (T3)	**ISRT** or **surgical excision** + **Intravenous rituximab**		
AGGRESSIVE PCBCL (PCDLBCL,LT)	(T1-3)	**R-CHOP + ISRT** *or* Clinical trial	***Relapsed*** *or* ***Refractory disease***	**2nd line chemoimmunotherapy for DLBCL** *or* **CAR T-cell therapy** *or* **Clinical trial** *or* **Transplant** *or* Palliative ISRT *or* Supportive care

Figure 8. Simplified treatment approach for skin-limited indolent and aggressive primary cutaneous

Hematol Oncol. 2024 Jan;42(1):e3215. doi: 10.1002/hon.3215. Epub 2023 Aug 30.

Identifying and addressing unmet clinical needs in primary cutaneous B-cell lymphoma: A consensus-based paper from an ad-hoc international panel

Pietro Quaglino [1], Nicola Pimpinelli [2], Pier Luigi Zinzani [3 4 5], Marco Paulli [6], Stefano Pileri [7], Emilio Berti [8 9], Lorenzo Cerroni [10], Joan Guitart [11], Youn H Kim [12], Serena Rupoli [13], Marco Santucci [14 15], Gabriele Simontacchi [16], Maarten Vermeer [17], Richard Hoppe [18], Barbara Pro [19], Steven H Swerdlow [20], Giovanni Barosi [21]

Recommendations and proposals

For PCDLBCL-LT, the Panel argued that the preferred frontline approach should be referral to a major academic centre for consideration of disease dedicated clinical trials.

If trials are not available, therapy strategy for PCDLBCL-LT should be derived from the results of clinical trials in diffuse large B-cell lymphoma.

CHOP-like regimens associated with rituximab and local RT, are used as initial treatment, even for solitary and localized tumors.

As possible alternative for elderly and unfit patients is RT alone, rituximab monotherapy with/without RT, the association of rituximab with pegylated liposomal doxorubicin.

Lenalidomide, an oral immunomodulating agent, represents a therapeutic option in relapsed/refractory PCDLBCL-LT, although the clinical benefit appears restricted to a subset of patients without the MYD88L265 P mutation.

The Panel considered an **urgent need** that more extensive trials with lenalidomide in this setting should confirm preliminary data.

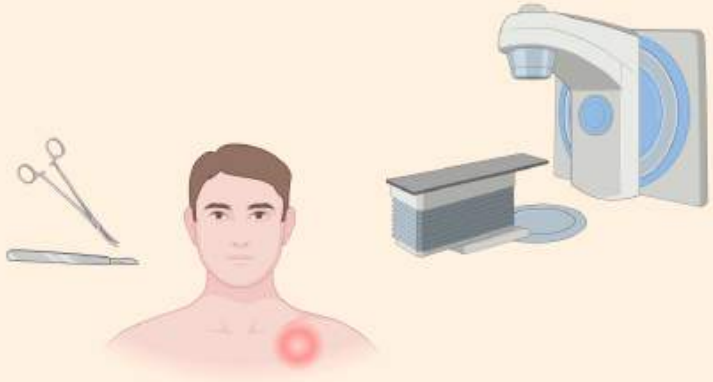
Even with R-Chemo: 40% recurrences

- Therapeutic choice in case of recurrence or progression
- Further complicated in already treated, advanced age patients, co-morbilities?

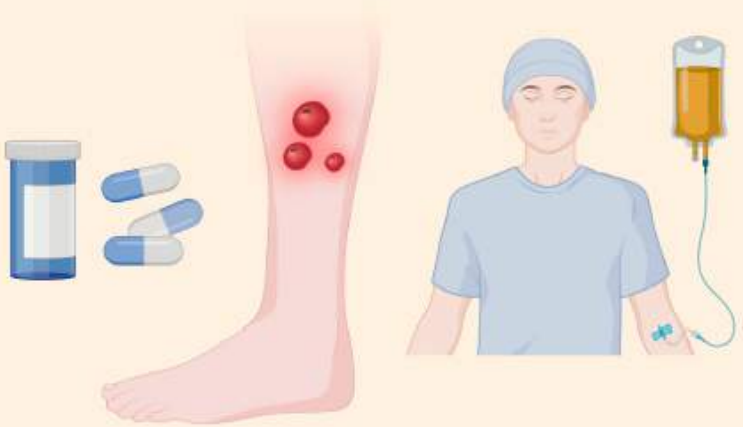
New therapeutic options and strategies

Predictive markers for response or recurrences?

Primary cutaneous follicle centre lymphoma and marginal zone lymphoma/lymphoproliferative disorder



Primary cutaneous diffuse large B-cell lymphoma, leg type



lymphatics

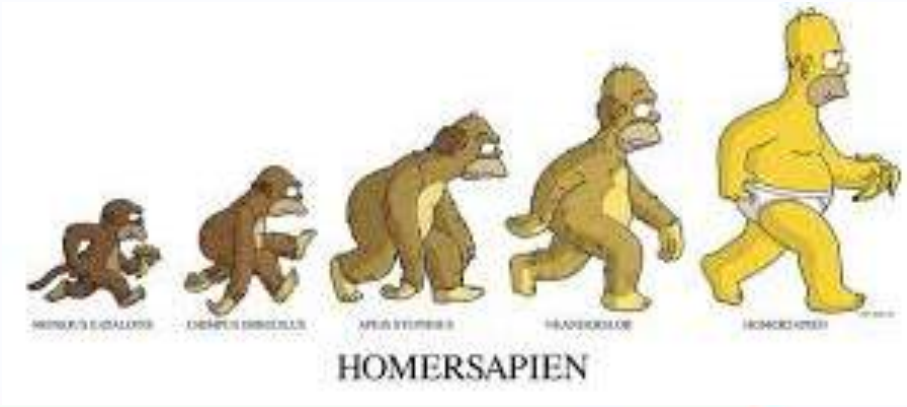
MDPI

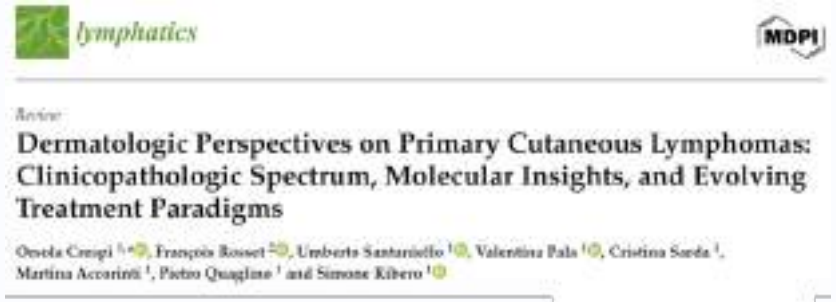
Review

Dermatologic Perspectives on Primary Cutaneous Lymphomas: Clinicopathologic Spectrum, Molecular Insights, and Evolving Treatment Paradigms

Orsola Crespi [1,*], François Rosset [2], Umberto Santaniello [1], Valentina Pala [1], Cristina Sarda [1], Martina Accorinti [1], Pietro Quaglino [1] and Simone Ribero [1]

PCDLBCL-LT requires systemic chemo-immunotherapy and, increasingly, **immune- and pathway-directed approaches in relapse.**




lymphatics

MDPI

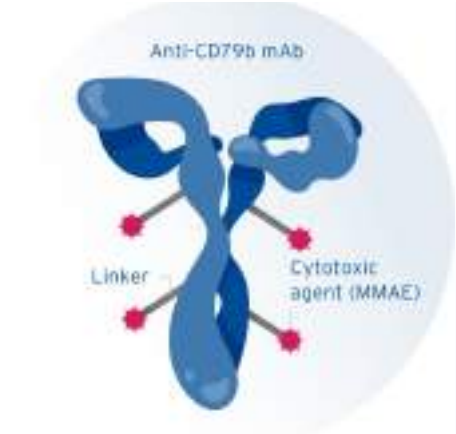
Review

Dermatologic Perspectives on Primary Cutaneous Lymphomas: Clinicopathologic Spectrum, Molecular Insights, and Evolving Treatment Paradigms

Ornela Crespi, François Rosset, Umberto Santaniello, Valentina Pala, Cristina Sorda, Martina Accorinti, Pietro Quaglino and Simone Ribero

- Beyond conventional chemoimmunotherapy, therapeutic innovation in PCDLBCL-LT has increasingly drawn on advances developed for nodal diffuse large B-cell lymphoma (DLBCL).
- Case reports and small series describe responses to ADCs (such as CD79b-targeted polatuzumab vedotin) and other novel agents in multiply relapsed PCDLBCL-LT, particularly in patients harbouring MYD88 and BCR-pathway mutations
- Although clinical data remain limited, the biological parallels between PCDLBCL-LT and activated B-cell-type DLBCL—especially their addiction to the **BCR–MYD88–NF-κB axis**—support further exploration of ADCs and related targeted approaches in this setting.

Satoko Oka, Kazuo Ono & Masaharu Nohgawa




Home › Annals of Hematology › Article

Effective treatment with polatuzumab vedotin of relapsed and refractory primary cutaneous diffuse large B-cell lymphoma leg type

Letter to the Editor | Published: 09 August 2022

Volume 101, pages 2353–2354 (2022) Cite this article

Features	Primary Cutaneous (Leg Type)
Age (median)	7th decade
M:F	1:3 to 1:4
Tumor site	Legs
Therapy	R-CHOP, RT
5-year DSS	60–70%
Immunohistology	
CD10	–
BCL2	+
BCL6	+
CD21	–
FoxP1	+
MYC	+
Ki-67	>75%
MUM1	+
Genetics	
Putative oncogenes	*MYD88, CD79B, CCND3, STAT3, PIM1*
Tumor suppressor genes	*CDKN2A/B, NFKBIE, PRDM1, KMT2D, CD58, B2M, CIITA, HLA* genes
Gene rearrangements	*PDL1, PDL2, BCL6, IGH, MYC*
Pathways Involved	NF-κB, JAK/STAT, MAPK, PI3K, immune surveillance

https://doi.org/10.1007/s00277-025-06311-3

REVIEW

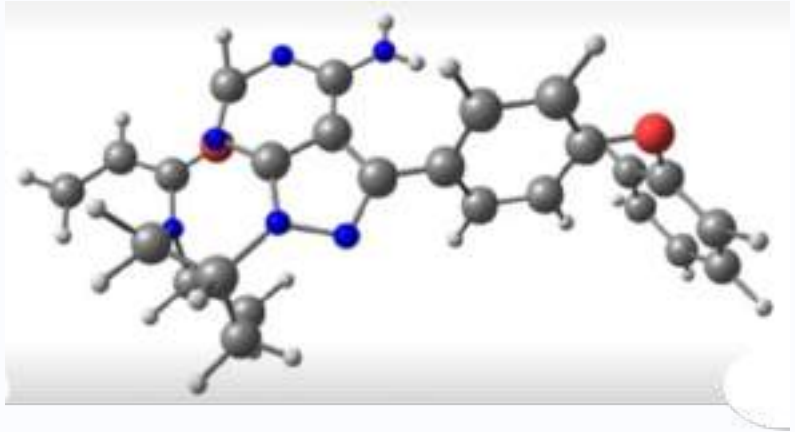
Advances in classification and treatment of primary cutaneous lymphomas

Hong Zheng[1] · Lihua Qiu[1] · Chang Liu[2] · Chen Tian[1]

Clinical and Molecular Features

Treatment strategies guided by molecular profiles

- Many mutations in PCDLBCL-LT occur in the NF-kB pathway.
- Although there are no direct inhibitors of the most frequently mutated proteins (e.g., MYD88 and CD79B), other targets in the NF-kB pathway have shown promising early results.
- For example, **ibrutinib**, which inhibits the kinase BTK **downstream of MYD88**, led to complete skin responses in three cases of PCDLBCL-LT (*Al-Obaidi et al., 2020; Fox et al., 2018; Gupta et al., 2015)*



Disease-Defining Molecular Features of Primary Cutaneous B-Cell Lymphomas: Implications for Classification and Treatment

Yue Zhang[1,2], Tessa M. LeWitt[1], Abner Louissaint Jr[3,4], Joan Guitart[1], Xiaolong Alan Zhou[1,5] and Jaehyuk Choi[1,2,3]

Journal of Investigative Dermatology 2023

▸ Rare Tumors. 2015 Dec 29;7(4):6067. doi: 10.4081/rt.2015.6067

Excellent Outcome of Immunomodulation or Bruton's Tyrosine Kinase Inhibition in Highly Refractory Primary Cutaneous Diffuse Large B-Cell Lymphoma, Leg Type

Eva Gupta [1,✉], Joseph Accurso [2], Jason Sluzevich [3], David M Menke [4], Han W Tun [1]

We report a case of PCDLBCL-LT with short lived responses to standard systemic DLBCL therapies, including high-dose chemotherapy and autologous stem cell transplantation. We achieved an excellent response to immunomodulatory therapy with lenalidomide followed by a long-lasting complete remission to Burton's tyrosine kinase inhibition with ibrutinib.

……**Ibrutinib 560 mg qd per os** was started in December 2013 with rapid improvement resulting in complete remission (CR).
He remains in CR at the time of this writing

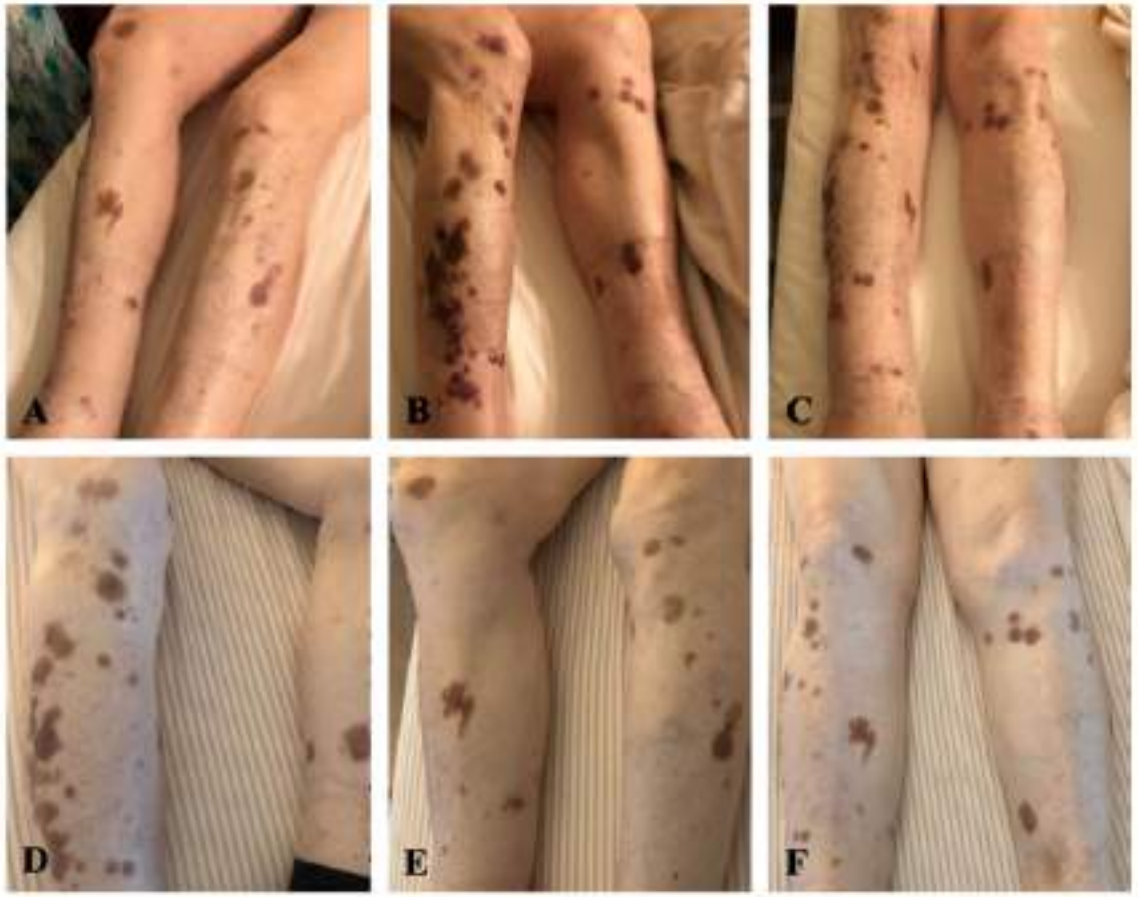


FIGURE 2: The clinical picture of primary cutaneous diffuse large B-cell lymphoma, leg type and its response to treatment.

(A-C) Multiple violaceous, raised skin lesions involving the right lower extremity, before starting ibrutinib therapy. (D-F) Dissipating skin lesions approximately six months after initiating ibrutinib therapy.

Primary Cutaneous Diffuse Large B-Cell Lymphoma, Leg Type: A Case Report

Ammar Al-Obaidi [1], Nathaniel A. Parker [1], Khalil Choucair [1], Daniel Lalich [2], Phu Truong [3]

Cureus 12(6) 2020: e8651. DOI 10.7759/cureus.8651

Fourth line ibrutinib therapy have shown CR and skin lesion regression, respectively.

Blood (2018) 132 (Supplement 1): 4237.

627. AGGRESSIVE LYMPHOMA (DIFFUSE LARGE B-CELL AND OTHER AGGRESSIVE B-CELL NON-HODGKIN LYMPHOMAS)-RESULTS FROM RETROSPECTIVE/OBSERVATIONAL STUDIES: POSTER III | NOVEMBER 29, 2018

Ibrutinib Can Induce Complete Remissions and Sustained Responses in Refractory Cutaneous or Leg-Type Diffuse Large B-Cell Lymphoma

Johannes Bloehdorn, MD, Stephanie Ellen Weissinger, MD, Anca Sindrilaru, MD, Stefan Schoensteiner, MD, Thorsten Peters, MD, Peter Moeller, MD, Ralf Marienfeld, PhD, Andreas Viardot, MD

Int J Mol Sci. 2018 Jun 13;19(6):1758. doi: 10.3390/ijms19061758

Molecular Mechanisms of Disease Progression in Primary Cutaneous Diffuse Large B-Cell Lymphoma, Leg Type during Ibrutinib Therapy

Lucy C Fox [1], Costas K Yannakou [1], Georgina Ryland [1], Stephen Lade [1], Michael Dickinson [1], Belinda A Campbell [1], Henry Miles Prince [1,*]

We describe the first case of novel genomic changes of PCDLBCL-LT that occurred while on ibrutinib, providing important mechanistic insights into both pathogenesis and drug resistance.

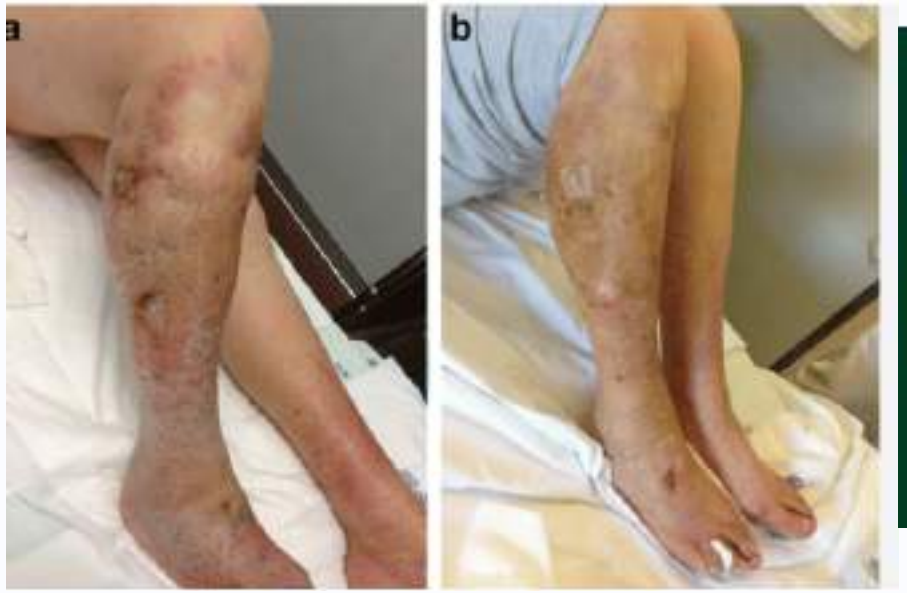
Treatment strategies guided by molecular profiles

Treatment with lenalidomide,which antagonizes transcription factors IRF4 and SPIB downstream of the NF-kB pathway, has also shown some benefits in PCDLBCL-LT

Disease-Defining Molecular Features of Primary Cutaneous B-Cell Lymphomas: Implications for Classification and Treatment

Yue Zhang[1,2], Tessa M. LeWitt[1], Abner Louissaint Jr[3,4], Joan Guitart[1], Xiaolong Alan Zhou[1,5] and Jaehyuk Choi[1,2,5]

Journal of Investigative Dermatology 2023

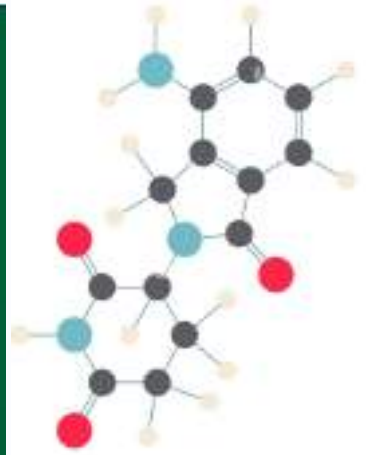


Home › Annals of Hematology › Article

Lenalidomide monotherapy in relapsed primary cutaneous diffuse large B cell lymphoma-leg type

Letter to the Editor | Published: 17 May 2013

Volume 93, pages 333–334 (2014) Cite this article



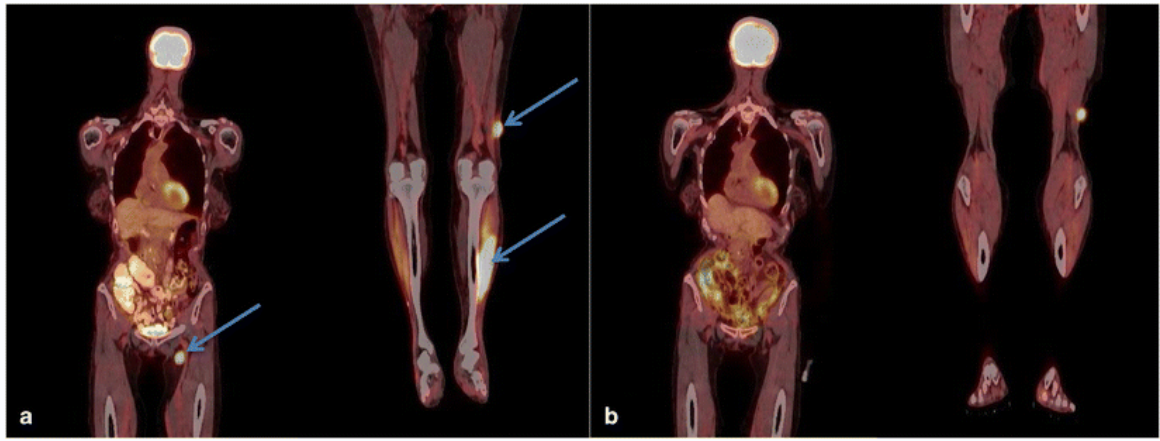
P. Savini, A. Lanzi, F. G. Foschi, G. Marano & G. F. Stefanini

Home › Annals of Hematology › Article

Remission induction with lenalidomide in a patient with relapsed diffuse large B cell lymphoma of the leg type

Letter to the Editor | Published: 15 November 2014

Volume 94, pages 895–896 (2015)



Abhisek Swaika, David M. Menke, Manoj K. Jain & Taimur Sher

A Single-Arm Phase II Trial of Lenalidomide in Relapsing or Refractory Primary Cutaneous Large B-Cell Lymphoma, Leg Type

Marie Beylot-Barry[1,2,19], Diane Mermin[1,19], Aline Maillard[3], Reda Bouabdallah[4], Nathalie Bonnet[5], Anne-Bénédicte Duval-Modeste[6], Laurent Mortier[7], Saskia Ingen-Housz-Oro[8], Caroline Ram-Wolff[9], Stéphane Barete[10], Stéphane Dalle[11], Eve Maubec[12,20], Gaelle Quereux[13], Isabelle Templier[14], Martine Bagot[9], Florent Grange[15], Pascal Joly[6], Béatrice Vergier[2,16], Pierre-Julien Vially[17], Audrey Gros[2,18], Anne Pham-Ledard[1,2], Eric Frison[3] and Jean-Philippe Merlio[2,18]

Journal of Investigative Dermatology 2018

Lenalidomide: **25 mg daily for 21/28 day-cycle**. Treatment maintained 12 months unless progression

Primary endpoint: overall response (OR = CR + PR) at 6 months.

19 patients, med age 79 ans (69-92), 18/19 : leg location, 16/19 : Relapse after CR; Stages: T1 (n=2), **T2 (n=13)**, T3 (n=4)

Median nbr of cycles = 5; 63% ORR

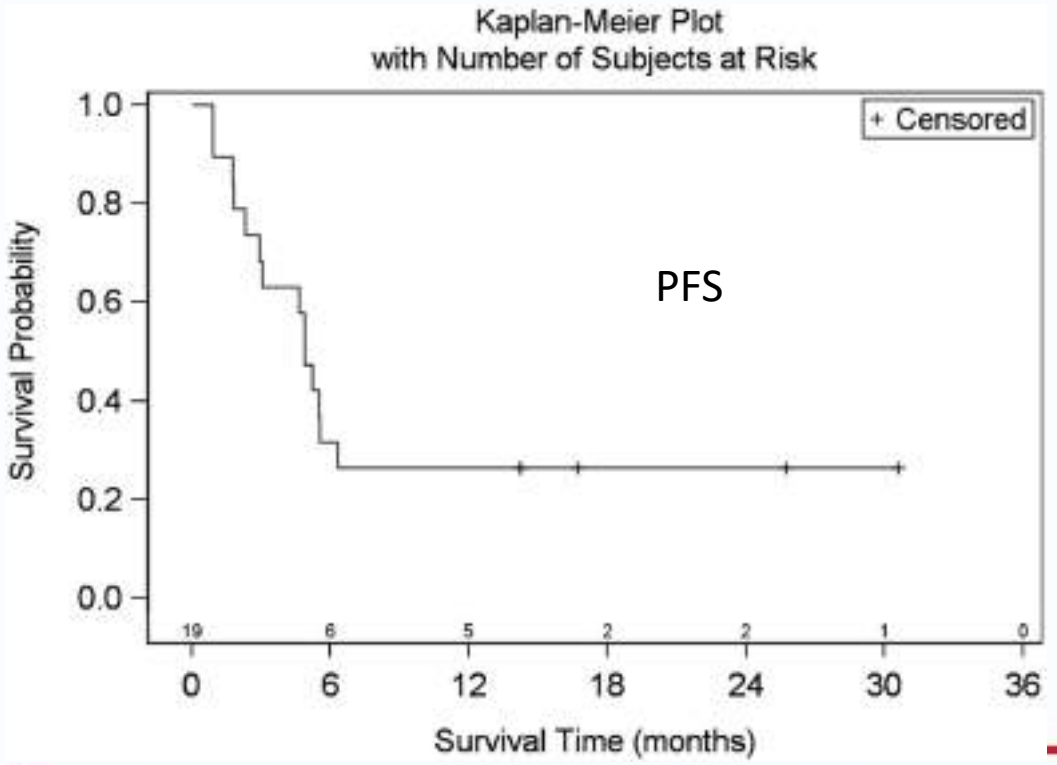
but **RR at 6 months = 26.3%** (11%-47.6%, 90%CI) including **4 CR** and 1 PR)

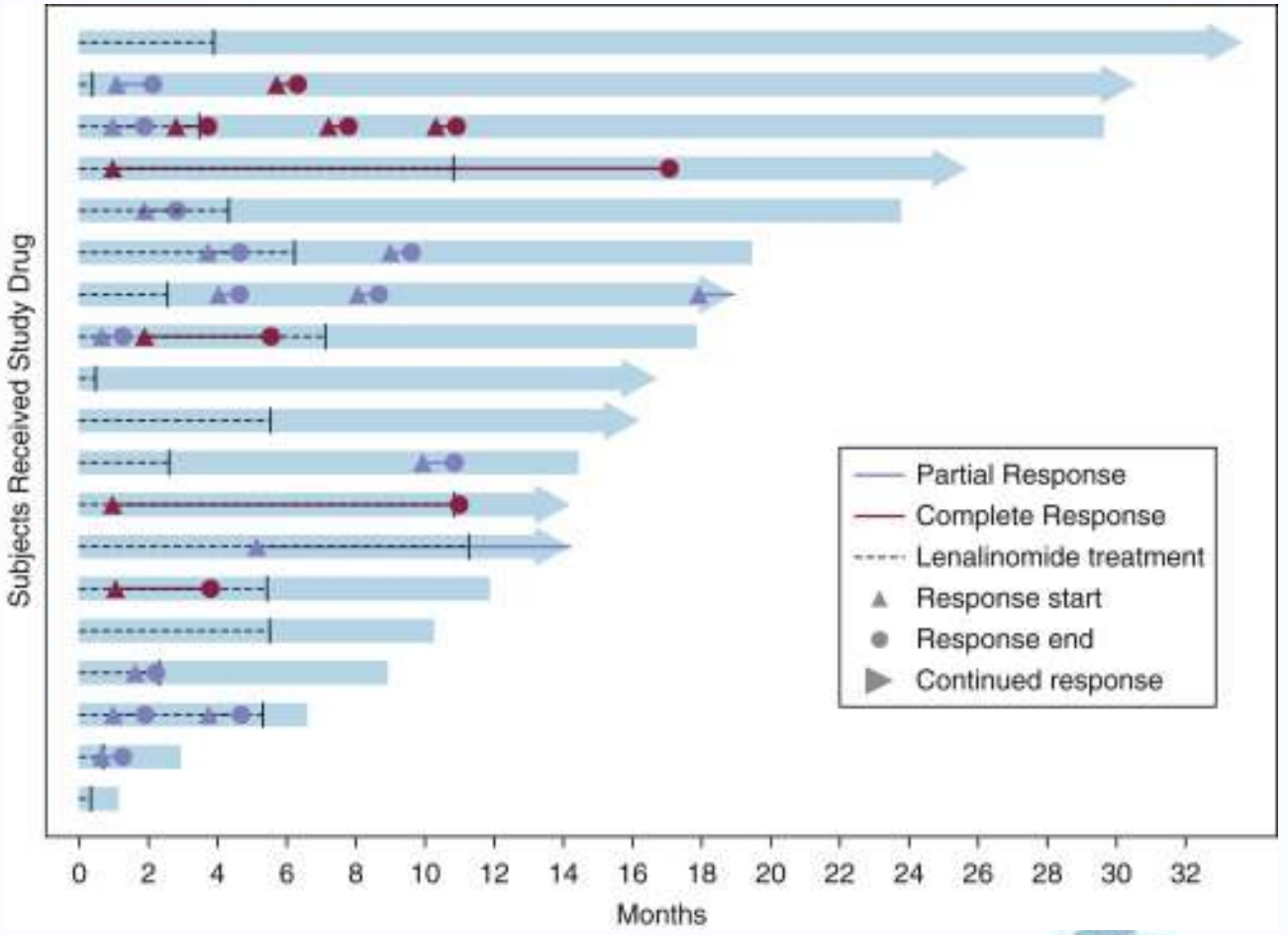
At 12 months, 3 still treated : 2 CR and 1 PR.

Median PFS = 5 months (1-31)

Overall survival 6 and 12 months : 89.5% and 68.4%

Median overall survival 19 months





Beylot-Barry M et al. J Invest Dermatol 2018

- **Severe AEs** (11 grade 3 in 7 patients and 2 deaths) and **dose reduction due to AEs in 7 patients** (cytopenia, thromboembolic)
- However, a prolonged response (including CR) was obtained in some patients:

- 60% of patients who achieved response at M6 had a durable response and were still responders at 12 months
- Patients treated in the second year of the trial vs first year:

- Doses reduced for AEs: 62.5% vs 36.4%
- Higher number of cycles: median =7 (5-12) vs 4 (1-5)
- Better survival, deaths= 25% vs 81.8%

Reduced doses tended to be associated with **higher 6-month overall response rate and progression-free survival.**
Absence of the MYD88L265P mutation was associated with a **higher overall response under treatment** (80.0% vs. 33.3%; P = 0.05).
Lenalidomide at reduced doses may allow prolonged responses in a few patients and represents a therapeutic option in relapsing/refractory primary cutaneous diffuse large B-cell lymphoma, leg type.

Beylot-Barry M et al. J Invest Dermatol 2018

Chemotherapy

Anticancer Section / Novel Insights from Clinical Practice

Chemotherapy 2024;69:23–26
DOI: 10.1159/000534784

Received: September 19, 2023
Accepted: October 20, 2023
Published online: November 1, 2023

Prolonged Complete Response with Lenalidomide in a Relapsed Diffuse Large B-Cell Lymphoma, Leg-Type: A Case Report

Sabrina Zoli[a, b] Cinzia Pellegrini[a] Beatrice Casadei[a] Alessandro Broccoli[a, b]
Lisa Argnani[b] Laura Nanni[a, b] Vittorio Stefoni[a, b] Pier Luigi Zinzani[a, b]

[a]IRCCS Azienda Ospedaliero-Universitaria di Bologna, Istituto di Ematologia "Seràgnoli", Bologna, Italy;
[b]Dipartimento di Scienze Mediche e Chirurgiche, Università di Bologna, Bologna, Italy

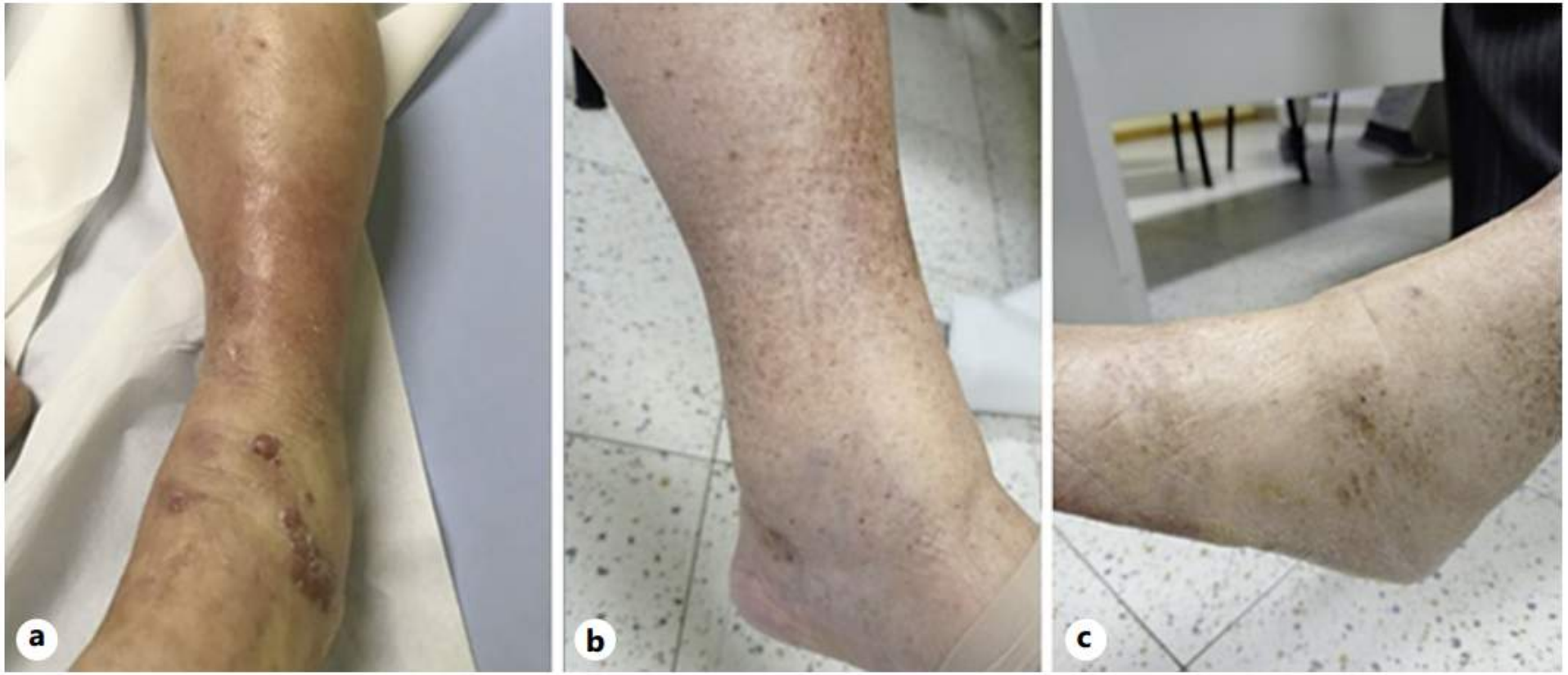


Fig. 1. a Left leg before starting lenalidomide. **b** Left leg after 8 cycles of lenalidomide. **c** Lateral side of left ankle after 8 cycles of lenalidomide.

…..On March 24, 2021, the patient was started on single-agent **lenalidomide (15 mg/day for 21 days in a 28-day cycle).**

Zoli S et al. Chemotherapy 2024

The patient achieved a clinical CR after approximately 4 cycles of therapy which was maintained for 16 months. Considering her optimal tolerance of the drug, we decided to prolong the treatment with lenalidomide even after the completion of the usual 12 cycles. Overall, the patient received 24 cycles of therapy without experiencing any relevant side-effects apart from asymptomatic skin lentigo and grade 4 neutropenia, which resolved with dose reduction

Open Access Review

Dermatologic Perspectives on Primary Cutaneous Lymphomas: Clinicopathologic Spectrum, Molecular Insights, and Evolving Treatment Paradigms

by Orsola Crespi [1,*], François Rosset [2], Umberto Santaniello [1], Valentina Pala [1], Cristina Sarda [1], Martina Accorinti [1], Pietro Quaglino [1] and Simone Ribero [1]

[1] Dermatologic Clinic, Department of Medical Science, University of Turin, 10126 Turin, Italy
[2] Department of Dermatology, Beauregard Hospital, Azienda USL della Valle d'Aosta, Via L. Vaccari 5, 11100 Aosta, Italy
* Author to whom correspondence should be addressed.

Lymphatics **2026**, *4*(1), 11; https://doi.org/10.3390/lymphatics4010011

Real-world case reports confirm the activity of lenalidomide, including impressive responses after multiple prior lines of therapy and in combination with rituximab, supporting its use as a palliative yet potentially disease-modifying option in selected patients.

Nonetheless, recent studies underline modest response durability and marked interpatient heterogeneity, reinforcing the **role of lenalidomide as part of combination or sequential strategies rather than as a standalone long-term solution**.

Rituximab, lenalidomide, and ibrutinib in relapsed/refractory primary cutaneous diffuse large B-cell lymphoma, leg type

To our knowledge, this is the first case series of PCDLBCL-LT treated with a combination of rituximab, lenalidomide, and ibrutinib.

We chose this triplet regimen based on the presence of the MYD88 L265P mutation in PCDLBCL-LT, the short duration of response with chemoimmunotherapy, and the favourable response rates observed in previous studies relative to that observed with lenalidomide/rituximab or ibrutinib monotherapy in relapsed/refractory DLBCL.

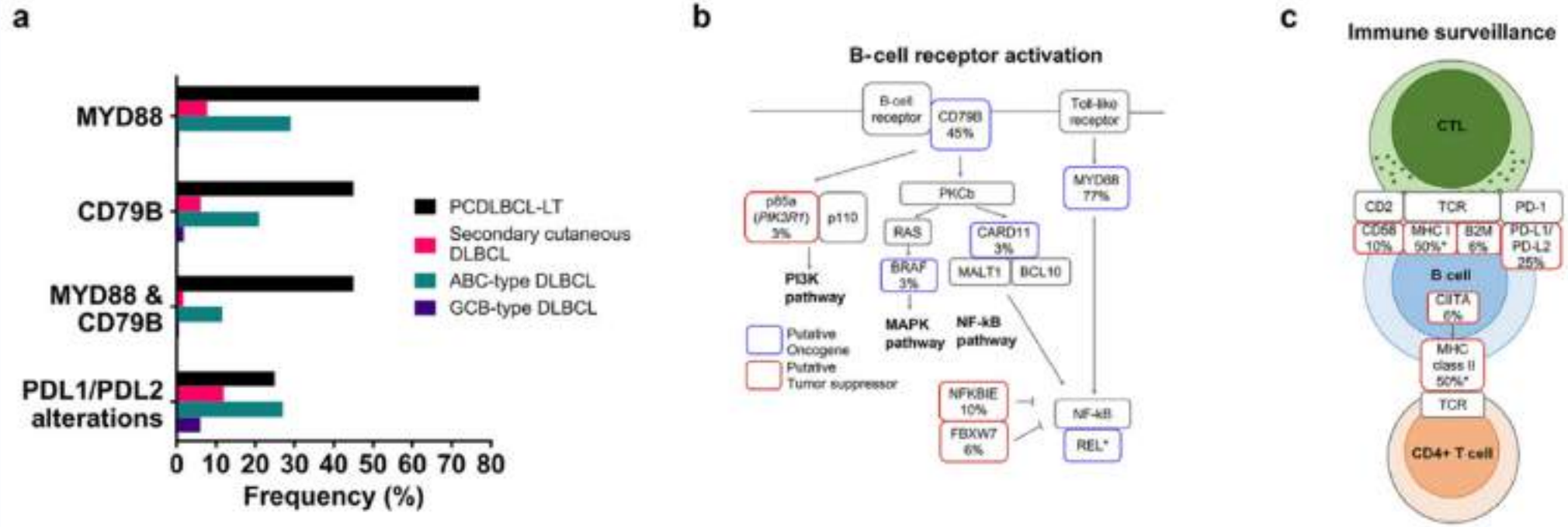
In conclusion, the combinationof **rituximab, lenalidomide, and ibrutinib** led to clinically meaningful responses in **two patients** with relapsed/refractoryPCDLBCL-LT and could potentially represent a novel therapeutic approach for patients with this rare aggressive subtypeof DLBCL harbouring MYD88 mutation.

Moore DC et al. British Journal of Haematology, 2022

Disease-Defining Molecular Features of Primary Cutaneous B-Cell Lymphomas: Implications for Classification and Treatment

Yue Zhang[1,2], Tessa M. LeWitt[1], Abner Louissaint Jr[1,3], Joan Guitart[1], Xiaolong Alan Zhou[1,5] and Jaehyuk Choi[1,2,5]

Journal of Investigative Dermatology 2023

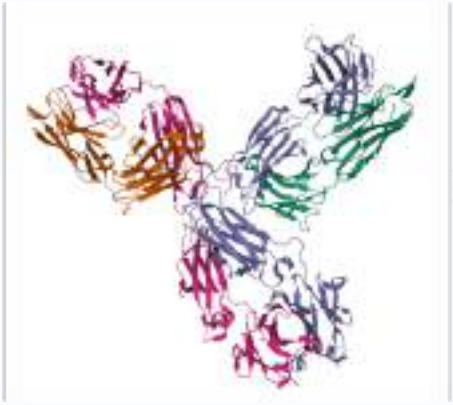


The occurrence of PDL1/PDL2 tumor mutations and near universal expression of PD-L1 in the tumor microenvironment of PCDLBCL-LT suggests the potential for **PD-1/PD-L1 inhibitors** in this devastating disease (Figure 1c).
PDL1/PDL2 copy number alterations and translocations have predicted clinical responses to PD-1/PD-L1 inhibitors in other lymphomas, including extranodal ABC-type DLBCLs….

Rituximab, lenalidomide and pembrolizumab in refractory primary cutaneous diffuse large B-cell lymphoma, leg type

Di Raimondo C et al. Br J Haematol 2019

…….In early 2019 patient was started on **rituximab 375 mg/m2 once weekly for the first 4 weeks**. **Lenalidomide (10 mg/day, days 1–21)** was added by the second rituximab administration and 1 month later **pembrolizumab** was started at the **dosage of 200 mg. This triple combination was repeated every 3 weeks for two cycles.**



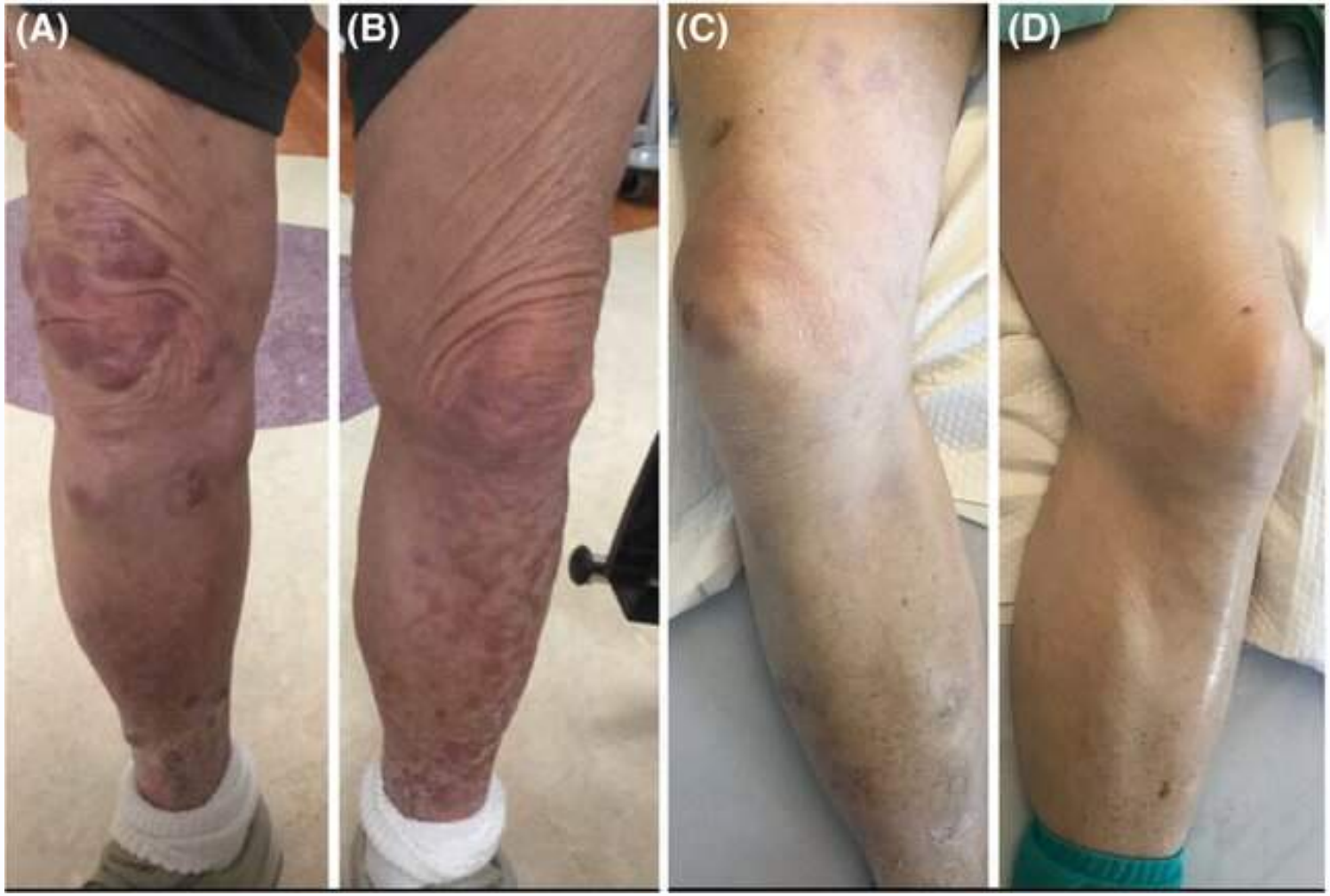
Pemprolizumab

Di Raimondo C et al. Br J Haematol 2019

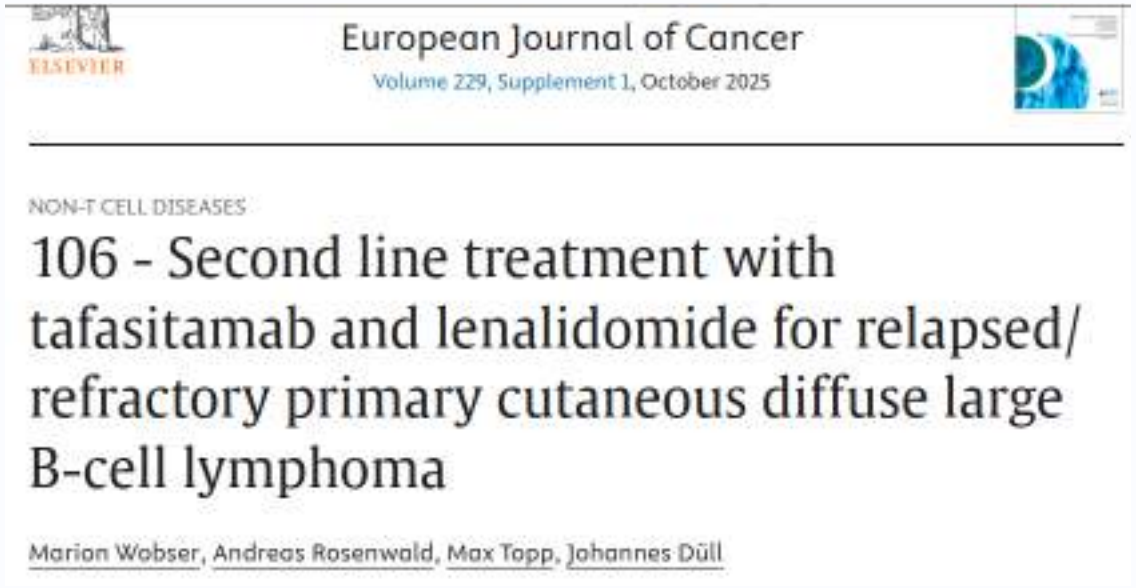
After only one administration of pembrolizumab, his skin lesions regressed with complete clinical remission (Fig 1B).

Treatment was complicated by transient neutropenia and associated pneumonia, which responded to antibiotics.

He has remained in complete remission for the last seven months, receiving lenalidomide 10 mg days 1–21, rituximab and pembrolizumab on a monthly basis.



Primary cutaneous anaplastic large cell lymphoma, leg type. (A, B) Clinical presentation with indurated red nodules on both legs.
(C, D) **Clinical regression after the administration of rituximab, lenalidomide and pembrolizumab**



European Journal of Cancer
Volume 229, Supplement 1, October 2025

NON-T CELL DISEASES

106 - Second line treatment with tafasitamab and lenalidomide for relapsed/ refractory primary cutaneous diffuse large B-cell lymphoma

Marion Wobser, Andreas Rosenwald, Max Topp, Johannes Düll

5 patients with PCDLBC (3 male, 2 female; age 82±5 years) were treated, having relapsed after first-line treatment with R-CHOP± local radiation (n=4) or radiation alone (n=1).

Tafasitamab 12mg/kg was given as a **weekly infusion** (interval prolongation after 3 cycles), **lenalidomide 25mg/m²** was administered daily for up to 12 months

Tafasitamab/lenalidomide induced **rapid response** (time to response ≤ 3 months) achieving **CR in 4/5** with response duration of 16±10 months (range 5-36 months)

Treatment was well tolerated, AEs mainly included hematological toxicities being attributed to lenadidomide.

.Treatment of **Aggressive PCBCL (PCDLBCL, LT)**

Barbati ZR & Yann CJ. Cancers 2025

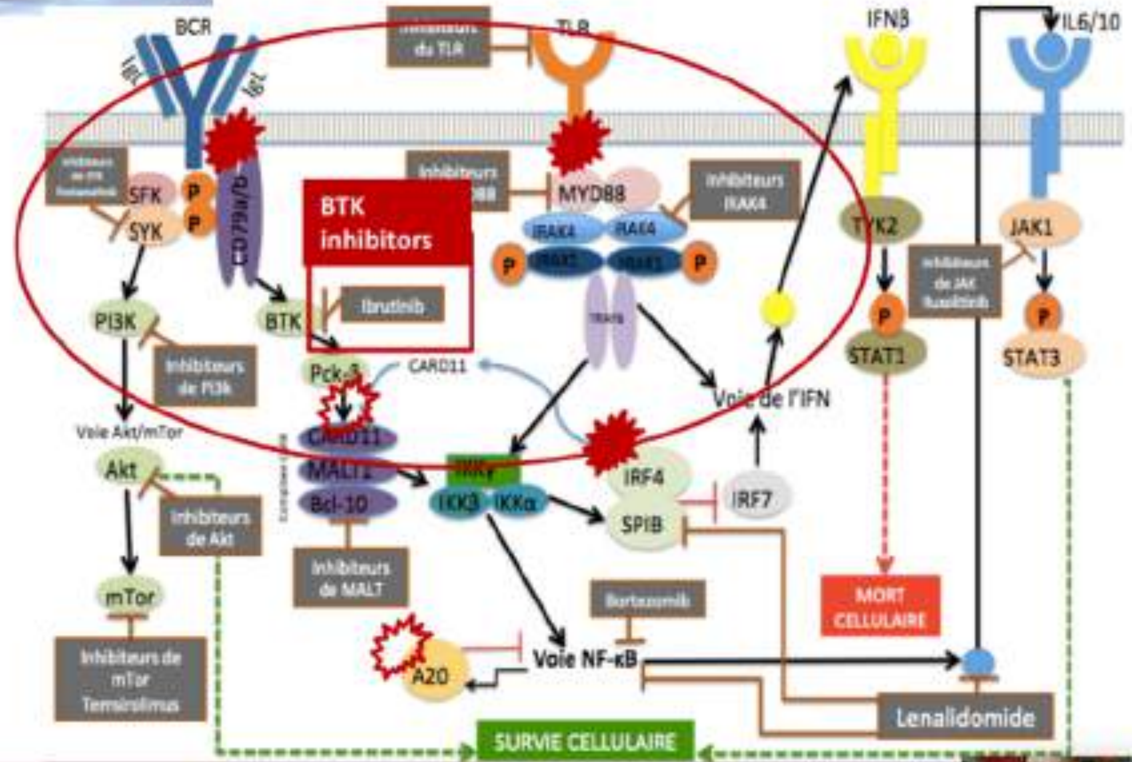
AGGRESSIVE PCBCL (PCDLBCL,LT)	(T1-3)	**R-CHOP + ISRT** *or* Clinical trial	***Relapsed*** *or* ***Refractory disease***	**2nd line chemoimmunotherapy for DLBCL** *or* **CAR T-cell therapy** *or* **Clinical trial** *or* **Transplant** *or* Palliative ISRT *or* Supportive care

Figure 8. Simplified treatment approach for skin-limited indolent and aggressive primary cutaneous

Currently, there are no robust clinical data specifically evaluating the efficacy of **other innovative therapies**—such as antibody–drug conjugates, bispecific antibodies, or chimeric antigen receptor T-cell (CAR-T) therapies—in the treatment of PCDLBCL-LT. These advanced therapeutic modalities have shown promising results in relapsed/refractory systemic DLBCL, particularly in high-risk or treatment-resistant cases. However, **their use in PCDLBCL-LT remains largely unstudied, and clinical experience is limited to anecdotal reports or extrapolation from systemic disease settings**.

To go further ?

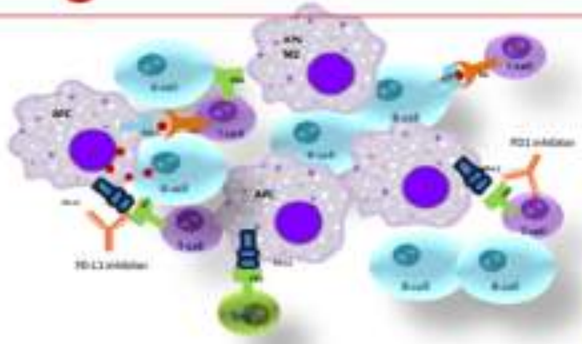
Cooperation / different pathways



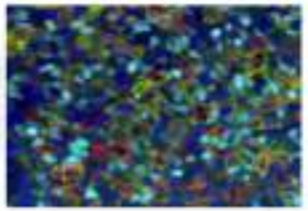
Cooperation between pathways ➔ Synergistic combined therapies ?

Walter HS. Et al. Ascopubs.org 2020 (Venetoclax anti-BCL2); Gupta E. et al. Rare Tumors 2015; Fox LC. Et al. Int J Mol Sci 2018 ; Pang A. et al. Ann Haeatol 2019; Di Raimondo C. et al. Br J Haematol 2019; Melani C. Best Pract Res

Target microenvironnement



PD-L1 PAX5 CD163



AmJ Surg Pathol. 2017

Tumor Microenvironment and Checkpoint Molecules in Primary Cutaneous Diffuse Large B-Cell Lymphoma—New Therapeutic Targets

Christina Mitteldorf, MD, Arbeneshe Berisha, BSc, Monique C. Pfaltz, PhD, Sigrid M.C. Broekaert, MD, Michael P. Schön, MD, Karin Kerl, MD, and Werner Kempf, MD

PD-L1 and PD-L2 Are Differentially Expressed by Macrophages or Tumor Cells in Primary Cutaneous Diffuse Large B-Cell Lymphoma, Leg Type

Sarah Menguy, MD, Marina Prochazkova-Carlotti, PhD, Marie Beylot-Barry, MD, PhD, Frédéric Saltel, PhD, Béatrice Vergier, MD, PhD, Jean-Philippe Merlio, MD, PhD, and Anne Pham-Ledard, MD, PhD

Journal of Investigative Dermatology (2018),

Genomic Analyses Identify Recurrent Alterations in Immune Evasion Genes in Diffuse Large B-Cell Lymphoma, Leg Type

Xiaolong Alan Zhou, Abner Louissaint Jr, Alexander Wenzel, Jingyi Yang, Maria Estela Martinez-Escala, Andrea P. Moy, Elizabeth A. Morgan, Christian N. Paxton, Bo Hong, Erica F. Andersen, Joan Guitart, Amir Behdad, Lorenzo Cerroni, David M. Weinstock and Jaehyuk Choi

Webinars Cutaneous Lymphoma
EuroBloodNet Topic on Focus

Il tratto sensibile. Personale diffusa di *Umberto Grati*

Riemersione nel prato