roflumilast is <7% that of apremilast in Denmark, with generic versions already available in some countries. Furthermore, experimental studies have found roflumilast to be up to 90 times more potent in inhibiting PDE4 isoforms compared with apremilast.[8] In contrast to biologic therapy, oral roflumilast treatment does not require routine laboratory monitoring, and with proven efficacy in COPD and weight loss commonly reported during treatment, roflumilast may also work directly on associated HS comorbidities.[5]

In the present case, we observed considerable improvements in clinical HS presentation and quality-of-life measures with oral roflumilast therapy. In addition, the patient achieved a 10% weight loss, which may have contributed to the reduction of disease burden.[1] Roflumilast could represent a novel and convenient treatment option for all severity stages of HS as well as associated comorbidities. To expand upon the rather limited treatment options in HS, larger studies investigating the long-term efficacy and safety of oral PDE4 inhibitors are warranted.

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References

1 Jemec GBE. Clinical practice. Hidradenitis suppurativa. *N Engl J Med* 2012; **366**:158–64.
2 Miller IM, Ellervik C, Vinding GR *et al.* Association of metabolic syndrome and hidradenitis suppurativa. *JAMA Dermatol* 2014; **150**:1273–80.
3 Kimball AB, Okun MM, Williams DA *et al.* Two phase 3 trials of adalimumab for hidradenitis suppurativa. *N Engl J Med* 2016; **375**:422–34.
4 Ring HC, Maul JT, Yao Y *et al.* Drug survival of biologics in patients with hidradenitis suppurativa. *JAMA Dermatol* 2022; **158**:184–8.
5 European Medicines Agency. Daxas [roflumilast]. Summary of product characteristics. Available at: https://www.ema.europa.eu/documents/product-information/daxas-epar-product-information_en.pdf (last accessed 6 July 2022).
6 Egeberg A, Meteran H, Gyldenløve M, Zachariae C. Complete clearance of severe plaque psoriasis with 24 weeks of oral roflumilast therapy. *Br J Dermatol* 2021; **185**:1251–2.
7 Vossen ARJV, van Doorn MBA, van der Zee HH, Prens EP. Apremilast for moderate hidradenitis suppurativa: results of a randomized controlled trial. *J Am Acad Dermatol* 2019; **80**:80–8.
8 Walsh N. Comparison of the modes of action of apremilast and roflumilast. PhD thesis, University of Glasgow, 2015. Available at: http://theses.gla.ac.uk/7427 (last accessed 6 July 2022).

Large-cell transformation is an independent poor prognostic factor in Sézary syndrome: analysis of 117 cases

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Dear Editor, Sézary syndrome (SS) is a rare cutaneous T-cell lymphoma (CTCL) grouped with mycosis fungoides (MF) in the international classification and staging criteria of CTCL.[1,2] Large-cell transformation (LCT) has been widely described in MF and associated with reduced overall survival, suggesting the importance of early and sequential histological screening of LCT in MF.[3] However, LCT has never been studied and characterized in a large cohort of SS. Another concern is that LCT in MF was defined in the 1980s using diagnostic criteria for LCT in follicular lymphoma.[4] Although widely used since, the reliability of these criteria has never been specifically studied in SS. Additionally, the presence of large circulating Sézary cells (SCs) based on cytomorphological and flow cytometry analysis was independently associated with poor outcome and might predict LCT occurrence in skin.[5,6] Nevertheless, the prognostic impact of structure parameters [forward scatter (FSC) and side scatter (SSC)] of circulating cells in cytometry and correlation with LCT remains to be determined in SS.

The main objective of our study was to characterize LCT in SS. All patients with SS diagnosed at Saint-Louis hospital (Paris, France) between 1998 and 2020 according to European Organisation for Research and Treatment of Cancer–World Health Organization criteria were included. The gating strategy of KIR3DL2+ SC among lymphocytes was previously described.[7] Circulating KIR3DL2+ SC $\geq$ 200 mm^{-3} was used to define KIR3DL2-positive status.[8] For each patient, all skin biopsy samples performed were included. LCT was histologically defined by the presence in the lymphocytes' infiltrate of > 25% or aggregates/nodules of large cells (more than four times the diameter of a small lymphocyte).[3,4] Haematoxylin-, eosin- and safran-stained slides were then digitized and an analysis using HALO software was performed. All blood samples from patients with flow cytometry data between 2015 and 2020 were included for FSC/SSC analysis. This study received the Institutional Review Committee agreement (LYMPHOTEQ reference: CPP 2019-AO1158-49).

In total, 117 patients were included with a median follow-up of 41 months (interquartile range 1–81). Overall, 6% (six of 100) and 16% (18 of 112) of patients were diagnosed with LCT on skin biopsy samples at diagnosis and during follow-up, respectively. Interobserver reliability between two independent pathologists was excellent [k = 0·88; 95% confidence interval (CI) 0·78–0·98]. Considering all skin biopsy

samples at diagnosis, CD30 > 10% and Ki67 > 20% was more frequent in LCT+ samples than in LCT− samples (67% vs. 9%; P = 0·003 and 100% vs. 22%; P = 0·016, respectively).

We then compared visual histopathological analysis with digital pathology analysis of skin biopsy samples (n = 189). Mean cell surface was significantly higher in LCT+ than in LCT− skin biopsy sample images [27 μm^2 (SD 3·3) vs. 22 μm^2 (SD 2·3); P < 0·001].

Subsequently, we compared cell size between blood and skin compartments on 231 blood samples from 112 patients with SS. The maximal mean FSC value of circulating tumour cells in patients who were LCT+ prior to LCT occurrence was not significantly higher than that found in patients who were LCT− [561 273 (SD 99 359) vs. 531 839 (SD 68 040)] (P = 0·37). Among patients with a maximum mean FSC value < 600 000 during follow-up, 17% (10 of 60) subsequently presented LCT vs. 14% (one of seven) of patients with a maximum mean FSC value ≥ 600 000 (P > 0·99). We obtained similar results for SSC.

Finally, median overall survival was shorter in patients who were LCT+ than in those who were LCT− at diagnosis (35 months vs. 80 months) (HR 9·5, 95% CI 1·9–47·1; P = 0·006). In multivariate analysis, age > 60 years (HR 4·46, 95% CI 1·14–17·41; P = 0·031), elevated LDH level (HR 2·63, 95% CI 1·03–6·72; P = 0·044), CD4 + CD26− circulating cell ≥ 10 000 mm^{-3} (HR 3·71, 95% CI 1·23–11·19; P = 0·020) and LCT at diagnosis (HR 4·77, 95% CI 1·11–20·4; P = 0·035) were independently associated with shorter overall survival (Table 1). During follow-up, median overall survival after LCT occurrence was 21 months, with a 5-year survival of 12% (95% CI 1–38).

In conclusion, our study characterized for the first time LCT in a large homogeneous cohort of patients with SS using histological, digital pathology and flow cytometry

Table 1 Univariate and multivariate survival analysis

				Univariate analysis		Multivariate analysis	
Variables	No. of patients with complete data	No. of patients (%)	Median survival, months	HR (95% CI)	P-values	HR (95% CI)	P-values
Sex	117			1·3 (0·67–2·4)	0·470		
Male		53 (45)	77			–	–
Female		64 (56)	150				
Age, years	117			3·3 (1·7–6·3)	**< 0·001**	4·46 (1·14–17·41)	**0·031**
> 60		38 (32)	62				
≤ 60		79 (68)	258				
Stage	103			7·4 (1·3–41·3)	**0·022**	0·66 (0·16–2·7)	0·562
IVA2		10 (9)	39				
IVA1		93 (91)	80				
LDH	97			2·4 (1·2–5·1)	**0·018**	2·63 (1·03–6·72)	**0·044**
Elevated		43 (44)	42				
Normal		54 (56)	92				
Circulating KIR3DL2+ SC mm^{-3}	87			5·9 (1·3–26·2)	**0·036**	–	–
≥ 10 000		7 (8)	39				
< 10 000		80 (92)	75				
Circulating CD4 + CD26− cells mm^{-3}	83			6·8 (1·7–27·7)	**0·007**	3·71 (1·23–11·19)	**0·020**
≥ 10 000		12 (14)	35				
< 10 000		71 (86)	75				
FSC baseline	96			1·6 (0·4–6·4)	0·537	–	–
≥ 600 000		9 (9)	NR				
< 600 000		87 (91)	109				
Large-cell transformation at diagnosis	100			9·5 (1·9–47·1)	**0·006**	4·77 (1·11–20·4)	**0·035**
Yes		6 (6)	35				
No		94 (94)	80				
CD30 expression in skin at diagnosis	63			0·8 (0·3–2·2)	0·649	–	–
> 10%		9 (14)	45				
≤ 10%		54 (86)	43				
Ki67 in skin at diagnosis	52			1·7 (0·5–6·3)	0·323	–	–
> 20%		14 (27)	41				
≤ 20%		38 (73)	55				

HR, hazard ratio; NR, not reached; LDH, lactate dehydrogenase; CI, confidence interval; FSC, forward scatter; SC, Sézary cell. P-values < 0·05 are provided in bold [log-rank (univariate) and Cox regression (multivariate) statistical test].

approaches. LCT incidence in SS is lower than for MF. Studies specifically investigating LCT in advanced-stage MF reported variable cumulative incidences ranging from 20% to 55% and large international cohorts have reported a variable incidence of LCT from 4·7% (all stages) to 20% (advanced stages) of MF/SS but without distinguishing the two entities.[2]

Moreover, we have shown that LCT at diagnosis was an independent unfavourable prognostic factor that could not be predicted by the presence of large circulating tumour cells. In parallel, patients with visually diagnosed LCT on skin biopsy had lymphoid cells with a significantly higher mean surface in digital pathology analysis. The criteria used in MF for LCT diagnosis proved reliable and reproducible.

Thus, histological evaluation of LCT in SS, assisted by digital pathology, is a major means of prognostic staging at diagnosis and during follow-up, allowing the early selection of patients that might benefit from therapeutic changes.

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References

1 Olsen E, Whittaker S, Willemze R *et al.* Primary cutaneous lymphoma: recommendations for clinical trial design and staging update from the ISCL, USCLC, and EORTC. *Blood* 2021; DOI: https://doi.org/10.1182/blood.2021012057.

2 Scarisbrick J, Prince H, Vermeer M *et al.* Cutaneous lymphoma international consortium study of outcome in advanced stages of mycosis fungoides and Sézary syndrome: effect of specific prognostic markers on survival and development of a prognostic model. *J Clin Oncol* 2015; **33**:3766–73.

3 Vergier B, de Muret A, Beylot-Barry M *et al.* Transformation of mycosis fungoides: clinicopathological and prognostic features of 45 cases. *Blood* 2000; **95**:2212–18.

4 Salhany KE, Cousar JB, Greer JP *et al.* Transformation of cutaneous T cell lymphoma to large cell lymphoma. A clinicopathologic and immunologic study. *Am J Pathol* 1988; **132**:265–77.

5 Clark RA, Shackelton JB, Watanabe R *et al.* High-scatter T cells: a reliable biomarker for malignant T cells in cutaneous T-cell lymphoma. *Blood* 2011; **117**:1966–76.

6 Vonderheid EC, Jakubowski J, Hou JS. High-scatter lymphocytes in the blood of erythrodermic cutaneous T-cell lymphoma: evidence for large-cell transformation? *Clin Lymphoma Myeloma Leuk* 2020; **20**:624–31.e2.

7 Moins-Teisserenc H, Daubord M, Clave E *et al.* CD158k is a reliable marker for diagnosis of Sézary syndrome and reveals an unprecedented heterogeneity of circulating malignant cells. *J Invest Dermatol* 2015; **135**:247–57.

8 Roelens M, de Masson A, Ram-Wolff C *et al.* Revisiting the initial diagnosis and blood staging of mycosis fungoides and Sézary syndrome with the KIR3DL2 marker. *Br J Dermatol* 2020; **182**:1415–22.

Differences in epidemiology, comorbidities and treatment choice between plaque psoriasis and pustular psoriasis: results from the BIOBADADERM registry

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Dear Editor, Pustular psoriasis is a group of inflammatory skin conditions characterized by clinically visible sterile pustules. It has been considered as a form of psoriasis vulgaris, but they are phenotypically different, respond differently to treatments and are genetically distinct. Variations in *IL36RN*, *CARD14*, *APIS3*, *MPO* and *SERPINA3* genes have been linked to generalized pustular psoriasis.[1,2] The European Rare and Severe Psoriasis Expert Network (ERASPEN) recently presented a consensus classification of clinical phenotypes of pustular psoriasis.[3] There are limited data on the differences between pustular and plaque psoriasis. Therefore, we aimed to compare the demographic characteristics, comorbidities and prescriptions between these clinical variants in clinical practice.

We used data from the BIOBADADERM registry, a previously described prospective multicentre cohort registry of patients with psoriasis treated with systemic drugs in Spain intended to detect adverse events related to systemic therapy.[4] Participants enter the cohort when they start a therapy that they have never used before. This study contains analysis of the data extracted from BIOBADADERM from October 2008 to December 2021. Therapy in the first 5 years of disease was described in a subset of patients with disease onset close to cohort entry. Plaque psoriasis (PP) was used as the reference group for all comparisons.

There were 3864 patients with PP, 41 patients with generalized pustular psoriasis (GPP) and 294 patients with