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The importance of assessing blood tumour burden in cutaneous T-cell lymphoma*

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Summary

Mycosis fungoides (MF) and Sézary syndrome (SS) are the best-studied subtypes of cutaneous T-cell lymphoma. The level of blood tumour burden in patients is important for diagnosis, disease staging, prognosis and management, as well as assessing treatment response. Until recently, the assessment of blood involvement was made using manual counts of morphologically atypical T cells (Sézary cells), but this approach may be subjective, and is affected by interobserver variability. Objective and consistent approaches to accurately quantifying blood involvement are required to ensure appropriate stage-related management of patients and to improve our understanding of the prognostic implications of blood tumour burden in these diseases. While assessment of blood involvement is common in SS and advanced-stage MF, an improved understanding of the implications of blood involvement at early disease stages could help identify patients more likely to progress to late-stage disease, and hence guide treatment decisions and frequency of follow-up assessment, ultimately improving patient outcomes. This concise review discusses the development of flow cytometry-based classifications for assessing blood involvement in MF and SS, and summarizes current recommendations for blood classification and assessment of blood response to treatment.

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Cutaneous T-cell lymphoma (CTCL) encompasses a broad spectrum of extranodal, T-cell-derived, non-Hodgkin lymphomas. The best-studied forms of CTCL are mycosis fungoides (MF) and Sézary syndrome (SS), which account for approximately 60% and < 5% of all cases of CTCL, respectively.[1–3] For MF, the initial presentation involves localized skin lesions in the form of patches or plaques, but tumour cells can also be present in the peripheral blood, lymph nodes and viscera.[1] MF generally follows an indolent disease course, with minimal impact on life expectancy for many patients. However, over time, up to 34% of patients experience disease progression to advanced-stage MF, which drastically reduces overall survival (overall survival is 15·8 years for patients with stage IIA disease vs. 4·7 years for those with stage IIB).[4] A more aggressive, leukaemic CTCL subtype, SS, is characterized by significant blood involvement, erythroderma and generalized lymphadenopathy; survival from diagnosis is generally ≤ 5 years.[2]

Disease stage is the major predictor of outcome for patients with MF or SS, and contributes to treatment decisions.[5] The first tumour–node–metastasis (TNM) classification and clinical staging system for CTCL was developed by the Mycosis Fungoides Cooperative Group (MFCG) in 1979.[6] According to these initial criteria, blood involvement in MF and SS was described as 'not present' (B0) or 'present' (B1), but the blood involvement rating did not impact clinical staging.[6]

Subsequent advances in our understanding of the pathology of CTCL have demonstrated that the level of peripheral blood involvement has important prognostic significance in MF and SS,[7–10] with significant blood involvement being found to have prognostic value independently of a patient's level of cutaneous and nodal involvement.[10] This development led the

European Organisation for Research and Treatment of Cancer (EORTC) and the International Society for Cutaneous Lymphomas (ISCL) to collaborate in a 2007 revision of the staging criteria to include blood class, effectively creating a tumour–node–metastasis–blood (TNMB) staging system for MF and SS.[11] By contrast, blood classification is not included in non-MF/SS CTCL or cutaneous B-cell lymphoma staging.

Blood tumour burden in MF and SS has since been validated as an independent predictor of both reduced survival and increased risk of disease progression[4] and, to date, blood involvement and classification have been included in MF and SS disease-staging criteria for more than 10 years. But what have we learnt about the impact of blood involvement on patient diagnosis, prognosis and management since this inclusion? This review provides a summary of the most recent evidence on the importance of blood involvement and classification in the staging, prognosis and assessment of treatment response in patients with MF or SS.

Evolving classification of blood involvement: towards objective measurements

The initial TNM classification for CTCL included only two levels of blood involvement. These were based on manual morphological assessment for, and counts of, characteristic malignant T cells with hyperconvoluted, cerebriform nuclei (Sézary cells): B0 ('not present'; < 5% circulating Sézary cells) and B1 ('present'; > 5% circulating Sézary cells).[6] In 1997, the guidelines were updated to include the presence of an expanded $CD4^+$ T-cell population with a CD4/CD8 ratio of > 10 and evidence of clonal T cells in the peripheral blood as more objective criteria for diagnosing SS. However, concerns that these criteria were too strict and did not allow recognition of early SS prompted the ISCL to formulate a new set of diagnostic criteria for SS, which were subsequently included (with some modifications) in the World Health Organization (WHO)–EORTC classification of cutaneous lymphomas (2005)[12] and the 2008 revision to the WHO classification of myeloid neoplasms and acute lymphomas.[13]

The ISCL/EORTC revisions to the MFCG staging system in 2007 expanded the classification of blood involvement in MF and SS to include three stages of blood involvement: B0 (no significant blood involvement: ≤ 5% Sézary cells; includes subgroups B0a, T-cell clone negative, and B0b, T-cell clone positive), B1 (low blood tumour burden: > 5% Sézary cells but does not meet criteria for B2) and B2 (high blood tumour burden: ≥ 1000 Sézary cells per μL and T-cell clone positive) (Table 1).[6,11,14] In these revised guidelines, blood classification definitions were updated to include flow cytometry criteria, although it was acknowledged that manual Sézary cell counts were routinely used at that time.[11] However, when relying on the identification and visual assessment of atypical cell morphology alone to determine the level of blood involvement, counts may suffer from subjective bias.[11] Several research groups have reported that there is poor correlation between manual Sézary cell counts and absolute counts as provided by flow cytometry.[15,16] A prospective evaluation of the merits of morphological review, flow cytometry immunophenotyping and molecular genetic analysis (e.g. T-cell-receptor sequencing) as methods of quantifying blood involvement in SS found that determining Sézary cell counts based on morphology alone underestimated tumour burden compared with counts obtained using flow cytometry.[16]

In 2011, the ISCL, the US Cutaneous Lymphoma Consortium, and the Cutaneous Lymphoma Task Force (CLTF) of the EORTC published consensus guidelines for defining clinical endpoints. These recommended that, in clinical trials, an absolute count of $CD4^+$ $CD26^-$ cells (or $CD4^+$ $CD7^-$ in $CD26^+$ patients) assessed using flow cytometry should be used to determine the level of blood involvement.[17] Moreover, because the ISCL–EORTC 2007 classification of B2 was determined by absolute numbers of Sézary cells per μL (≥ 1000 per μL), it was suggested that B0 should be defined by an absolute count of < 250 per μL $CD4^+$ $CD26^-$ or $CD4^+$ $CD7^-$ T cells by flow cytometry, or < 250 per μL Sézary cells by manual cell count (this value allowing for a 15% upper limit of normal for $CD4^+$ $CD26^-$ or $CD4^+$ $CD7^-$ cells; loss of CD26 or CD7 can occur at lower levels in normal populations and benign dermatoses).[17] These new flow cytometry-based definitions were included in the most recent EORTC–CLTF recommendation for classifying blood involvement and response in MF and SS, which further highlight the need for objective and standardized measurements of lymphocyte counts using flow cytometry.[14]

Accordingly, there has been a shift in blood measurement methods from manual Sézary cell counts to flow cytometry methodologies in many CTCL treatment centres. However, it should be noted that recommended cutoff values have not been validated in prospective clinical studies and a greater degree of standardization is required. Also required are more consistent definitions for blood classification by flow cytometry that will allow for adequate comparison of epidemiological and outcome data and assessment of treatment response.[18] Implementation of consistent definitions for blood classification will also improve the comparability of endpoint data from clinical studies such as the ongoing Prospective Cutaneous Lymphoma International Prognostic Index (PROCLIPI) study, which is collecting data on prognostic factors, staging, survival outcomes and treatment in patients with early-stage MF.[14]

Furthermore, the EORTC's Cutaneous Lymphoma Working Group is collaborating with EuroFlow in a study aimed at resolving shortcomings in blood classification methodologies by developing a standardized, fast, accurate and highly sensitive flow cytometry protocol for identifying Sézary cells in patients with CTCL. EuroFlow is a consortium of over 20 diagnostic research groups that has developed a range of protocols and standard operating procedures in flow cytometry as applied to haematological malignancies.[19–21] Accurate measurement of circulating tumour cells combined with follow-up will help in defining optimal cutoff points for blood staging.

Table 1 Classification of peripheral blood involvement in patients with cutaneous T-cell lymphoma (mycosis fungoides or Sézary syndrome)

Original TNM classification[6]		ISCL/EORTC revised classification[11]		EORTC–CLWG updated blood classification[14]
B0	No Sézary cells circulating in peripheral blood (< 5%)	B0	No significant blood involvement: ≤ 5% of lymphocytes in peripheral blood are atypical	Recommend objective assessment of blood class using flow cytometry to assess absolute lymphocyte counts of either $CD4^+$ $CD7^-$ in $CD26^+$ patients or $CD4^+$ $CD26^-$
		B0a	T-cell clone negative[a]	
		B0b	T-cell clone positive	
B1	Sézary cells present in peripheral blood (> 5%); record the total white blood cell count, total lymphocyte count and number of Sézary cells per 100 lymphocytes	B1	Low blood tumour burden: > 5% peripheral blood lymphocytes are atypical but does not meet criteria for B2 class	B0 is defined as a count of < 250 cells μL^{-1} B1 is defined as a count of > 250 cells μL^{-1} up to 1000 cells μL^{-1}
		B1a	T-cell clone negative	
		B1b	T-cell clone positive	
		B2	High blood tumour burden: ≥ 1000 Sézary cells per μL or increased $CD4^+$ or $CD3^+$ cells with CD4/CD8 ratio of ≥ 10 or increased $CD4^+$ cells with an atypical phenotype (≥ 40% $CD4^+$ $CD7^-$ or ≥ 30% $CD4^+$ $CD26^-$) *and* a positive T-cell clone	B2 is defined as a count of ≥ 1000 cells μL^{-1} plus a positive T-cell clone

CLWG, Cutaneous Lymphoma Working Group; EORTC, European Organisation for Research and Treatment of Cancer; ISCL, International Society for Cutaneous Lymphomas; TNM, tumour–node–metastasis. [a]T-cell clone identified using polymerase chain reaction or Southern blot analysis of the T-cell-receptor gene. Adapted with permission from Bunn PA, Lamberg SI. Report of the committee on staging and classification of cutaneous T-cell lymphomas. *Cancer Treat Rep* 1979; **63**:725–8; Olsen E, Vonderheid E, Pimpinelli N *et al.* Revisions to the staging and classification of mycosis fungoides and Sézary syndrome: a proposal of the International Society for Cutaneous Lymphomas (ISCL) and the cutaneous lymphoma task force of the European Organization of Research and Treatment of Cancer (EORTC). *Blood* 2007; **110**:1713–22; and Scarisbrick JJ, Hodak E, Bagot M *et al.* Blood classification and blood response criteria in mycosis fungoides and Sézary syndrome using flow cytometry: recommendations from the EORTC cutaneous lymphoma task force. *Eur J Cancer* 2018; **93**:47–56.

However, until standardized definitions and methodologies are available and implemented, any comparison of results obtained using different methodologies will be both difficult and of limited value, further limiting our understanding of the prognostic significance of blood tumour burden, and of the implications of movement between blood classes during disease progression or treatment.

Flow cytometry can also be supported by T-cell-receptor gene sequencing methods, which can increase the sensitivity of detection and accuracy of blood classification, and can be particularly valuable in patients with a low tumour burden or minimal residual disease.[22–24] It has also been suggested that multiparameter flow cytometry with cluster analysis could be of value in detecting small Sézary cell populations, and that the full panel of T-cell aberrations should be reported, rather than only assessing $CD4^+$ $CD7^-$ or $CD4^+$ $CD26^-$ T-cell populations.[25]

International guidelines for flow cytometric analysis of peripheral blood in patients with suspected MF or SS have recently been published.[26] While the details of these guidelines are outside the scope of this concise review, the guidelines specify that flow cytometry analyses for MF and SS should include CD3, CD4, CD7, CD8, CD26 and CD45 antibodies, as a minimum, and must be able to detect Sézary cell populations reliably, even if they are $CD3^-$, $CD45^-$ or an atypical phenotype.[26] It is recommended that gating strategies to identify Sézary cells be based on the identification of T-cell subsets that have distinct, homogeneous immunophenotypes that differ from normal T-cell populations, and that blood concentrations of atypical cells be determined either by direct count or using dual-platform methodology, and fully reported.[26]

Blood involvement in diagnosis and staging of mycosis fungoides and Sézary syndrome

CTCL is chronic for many patients, and effective disease management is important to optimize treatment and reduce symptom burden. Staging of MF and SS using TNMB classification should be carried out at diagnosis by assessing each of the four disease 'compartments' (skin, blood, lymph nodes and viscera); scores for these compartments can then be used to derive a clinical stage (stage I–IV) (Table 2).[1,11]

Most patients with MF are diagnosed with early-stage disease (stages I–IIA), which has been estimated to have a prevalence of 4·8–6·6 cases per 100 000 population.[27] However, it is estimated that around one-quarter to one-third of patients with early-stage disease eventually progress to more advanced, late-stage disease, and that accurate staging of patients with early, stable disease can serve as a clinical baseline against which to compare future measurements when the disease progresses.[4,28] Equally, staging of patients with more advanced or

Table 2 Impact of blood involvement on disease staging based on the revised International Society for Cutaneous Lymphomas–European Organisation for Research and Treatment of Cancer 2007 classification and staging of mycosis fungoides and Sézary syndrome[1,11]

	T (skin)	N (node)	M (viscera)	B (peripheral blood)
IA	1	0	0	0, 1
IB	2	0	0	0, 1
IIA	1, 2	1, 2	0	0, 1
IIB	3	0–2	0	0, 1
III	4	0–2	0	0, 1
IIIA	4	0–2	0	0
IIIB	4	0–2	0	1
IVA1	1–4	0–2	0	2
IVA2	1–4	3	0	2
IVB	1–4	0–3	1	0–2

Adapted with permission from Olsen E, Vonderheid E, Pimpinelli N *et al.* Revisions to the staging and classification of mycosis fungoides and Sézary syndrome: a proposal of the International Society for Cutaneous Lymphomas (ISCL) and the cutaneous lymphoma task force of the European Organization of Research and Treatment of Cancer (EORTC). *Blood* 2007; **110**:1713–22; and National Comprehensive Cancer Network. NCCN CTCL Guidelines version 2, 2019. Available at: https://www.nccn.org/professionals/physician_gls/pdf/primary_cutaneous.pdf (last accessed July 2020).

progressive disease may rationalize a certain treatment approach based on scores in each compartment.

A diagnosis of SS requires a B2 classification of blood involvement with generalized erythroderma and positive circulating T-cell clones identical to those observed in the skin.[2,12,14] However, B2 blood involvement can also be seen in patients with MF, including those with only T1 disease, although this is very uncommon.[29] A recent study suggested that patients with nonerythrodermic SS with a B2 blood class may have a survival time from diagnosis of just 3·6 years.[30]

Objective assessment of tumour burden by flow cytometry of the peripheral blood is currently recommended for all MF stages.[11,14,31] However, the clinical significance of blood involvement in early-stage disease has yet to be fully characterized.[14]

Prognostic value of blood classification in cutaneous T-cell lymphoma

Blood involvement has been found to be both an independent prognostic factor and a criterion escalating the clinical stage that itself carries prognostic significance; therefore, blood involvement may not simply be a surrogate marker for more advanced disease stage.[11] For patients with erythrodermic (T4) MF, blood classification determines whether they are designated stage IIIA (B0) or stage IIIB (B1), whereas for patients with patch (T1a/T2a), plaque (T1b/T2b) or tumour (T3) MF, disease stage is unaffected by movement between B0 and B1.[14] However, patients with B2-level blood involvement are classed as stage IV regardless of their degree of skin involvement, and an increase from B1 to B2 may indicate that the patient has significant blood involvement that fulfils the (diagnostic) criteria for SS.[14] It has been reported that patients in either B1 or B2 stage have a 4·6-fold greater risk of disease progression than those in B0 ($P < 0{\cdot}001$ for B1 vs. B0 and for B2 vs. B0). Furthermore, the median survival of patients with B1 or B2 blood involvement is considerably affected compared with B0, independently of disease stage, where median survival for B0 is 6·9–24·5 years (dependent on presence or absence of a peripheral blood T-cell clone), and 3·2 years and 3·1 years for B1 and B2, respectively.[4]

That being said, the role of blood involvement in early-stage MF is not yet fully understood, as many patients with early-stage disease are often not routinely tested for blood involvement. Consequently, information is lacking on the prognostic impact of B0 and B1 classification in patients with early-stage disease, and the implications of movement between B0 and B1 are not known.[14] However, what is clear is that escalating levels of blood involvement (particularly B2 classifications) are associated with a poorer prognosis. Although patients with B2 blood class and T1 disease are rare,[29] the latest guidelines from the EORTC state that patients with B2 and patch, plaque or tumour MF should be regularly monitored.[14]

The presence of an identical positive T-cell clone in the skin and blood has been shown to be independently associated with a poor prognosis, even in the absence of evidence of blood involvement (i.e. B0 classification).[4] In a recent study that used high-throughput sequencing to determine tumour clone frequency in the skin, tumour clone frequency > 25% was found to be a stronger predictor of aggressive early-stage MF than currently established prognostic factors, and it has been suggested that this could help identify patients who would benefit from allogeneic haematopoietic stem cell transplantation and prevent disease progression to the point of refractory disease.[32]

Similarly, another group reported using high-throughput sequencing of the T-cell receptor β gene to identify two different subsets of CTCL, with differentiation based on whether the same top (most frequently detected) clone was present in skin tissues and blood.[33] Patients with the same top clone in both the skin and blood had a worse prognosis than those with different clones in each location, which suggests identifying this in early disease stages could help with disease management.[33] The prognostic value of blood involvement also differs between MF and SS. For example, a change in blood class in a patient with SS is more likely to correlate positively with changes in skin scores than is movement between B0 and B1 in a patient with MF.[34] Analyses from ongoing studies (such as the PROCLIPI study) will provide further insights into prognostic factors in MF.[35]

Measuring treatment response in cutaneous T-cell lymphoma

To date, blood classifications used in published studies have varied.[14] However, in MF and SS, use of standardized

objective definitions of blood involvement is essential if we are to formulate comparable endpoints that will allow us to assess response to treatment in clinical trials and clearly evaluate therapeutic management in clinical practice. The EORTC–CLTF guidelines on clinical trial endpoints indicate that, in patients with MF or SS, an absolute $CD4^+$ $CD26^-$ T-cell count obtained using flow cytometry is the most reasonable objective measure for quantifying blood involvement, and thereby blood response to treatment.[17] Assessment of $CD4^+$ $CD7^-$ count is the suggested alternative in patients who are $CD26^+$.[17] These recommendations were updated by the EORTC–CTLF in 2018 (Table 3).[14,17] Notable changes to the 2011 recommendations are that movement between blood classes B0 and B1 should not be considered when assessing treatment response, and, in patients who are in B2, an increase in T-cell count of $\geq 50\%$ should be considered progressive disease, with no requirement for ≥ 5000 Sézary cells per μL.[14]

Table 3 Recommendations from the European Organisation for Research and Treatment of Cancer Cutaneous Lymphoma Task Force for assessment of disease response using blood classification[14,17]

Disease response	Blood class definition
Complete response (CR)	B2 improvement to B0
	B2 to B1 has unclear significance so not classed as CR
	B1 to B0 is not considered a CR
Partial response (PR)	50% reduction in absolute count of Sézary cells in patients with B2
	Relevance of change from B1 to B0 not known so not classed as PR
Stable disease (SD)	Failure to meet criteria for CR, PR or PD
Progressive disease (PD)	Change from B0 or B1 to B2 class with an increase of $\geq 50\%$ in absolute T-cell count (no requirement for ≥ 5000 Sézary cells μL^{-1})
	Increase of $\geq 50\%$ in absolute T-cell count in B2
	Loss of response accompanied by increase in the absolute count of Sézary cells of ≥ 1000 cells μL^{-1} and an increase of $\geq 50\%$ from nadir
Relapse	An increase in absolute count of Sézary cells of ≥ 1000 cells μL^{-1} in patients with CR
	Change from B0 to B1 should not be considered a relapse

Adapted with permission from Olsen EA, Whittaker S, Kim YH *et al.* Clinical endpoints and response criteria in mycosis fungoides and Sézary syndrome: a consensus statement of the International Society for Cutaneous Lymphomas, the United States Cutaneous Lymphoma Consortium, and the Cutaneous Lymphoma Task Force of the European Organization for Research and Treatment of Cancer. *J Clin Oncol* 2011; **29**:2598–607; and Scarisbrick JJ, Hodak E, Bagot M *et al.* Blood classification and blood response criteria in mycosis fungoides and Sézary syndrome using flow cytometry: recommendations from the EORTC cutaneous lymphoma task force. *Eur J Cancer* 2018; **93**:47–56.

There are important limitations associated with using absolute lymphocyte counts to determine response to therapy. Some drugs used in treatment may induce unspecific lymphopenia or leucopenia, without reducing the malignant T-cell count. A differentiation between unspecific lymphopenia and specific reduction in the malignant lymphocyte population is therefore essential for evaluating treatment response and a patient's prognosis. In this context, it would be valuable to develop a standardized method to detect minimal amounts of tumour cells in blood; this would be particularly relevant to the assessment of patients who undergo allogeneic haematopoietic stem cell transplantation.

In recent years, several new T-cell biomarkers have been identified that could be used to assess treatment response in MF and SS. Flow cytometry studies have identified CD158k as a potential tool for assessing tumour burden in peripheral blood,[36] and, more recently, CD164 has emerged as a potential disease-specific biomarker for SS. Additionally, genes described as 'Sézary signature genes' (*PLS3*, *GATA3*, *FCRL3*, *TOX*, miR-214) have been found to be more highly expressed in $CD164^+$ $CD4^+$ T cells (compared with $CD26^-$ $CD4^+$ T cells).[37,38] A high level of *TOX* expression was observed in patients with SS across all levels of blood classification, while *FCRL3* and miR-124 were strongly associated with advanced disease and B2 blood classification.[37]

High-throughput sequencing of T-cell receptors is another technique that can be used to measure patient response to treatment by assessing malignant T-cell populations before and after treatment. However, this method is not dependent on measuring malignant T cells in the blood and can be used with punch biopsies to evaluate malignant T cells present in the skin.[23,39]

Impact of blood involvement on patient care

Current treatment guidelines are based on disease stage, and available therapies can be broadly divided into early-stage (stage IA–IIA) and late-stage (stage IIB–IVB) treatments.[1,40,41] The only potentially curative treatment option is allogeneic haematopoietic stem cell transplantation, but a wide range of treatments are available, including skin-directed therapies (e.g. topical corticosteroids, topical retinoids, phototherapy, local radiation therapy), systemic treatments including chemotherapy, and novel targeted therapies (e.g. brentuximab vedotin, mogamulizumab).[1,40] Some guidelines, such as those published by the National Comprehensive Cancer Network, recommend systemic treatment for patients with persistent T1 disease and for early-stage MF that is refractory to multiple skin-directed therapies, and that treatments for erythrodermic (stage III) disease be considered for patients with very early-stage MF (stage IA) where there is B1 blood involvement.[1]

A better understanding of which patients with early-stage disease will go on to develop advanced disease is particularly important in this context, as it will help guide treatment choices, the use of maintenance therapy, recommendations for stem cell transplantation and the frequency of follow-up

assessments. Improving the methodology and extent of blood testing for patients with early-stage MF to establish the proportion of patients with B1- or B2-level blood involvement in stage I–IIA disease is crucial in determining the risk for disease progression in patients with less advanced disease.

Conclusions

Objective, consistent, quantifiable measures of blood involvement are a requirement if we are to stage MF and SS accurately at diagnosis, as is currently recommended. The implementation of such measures will benefit our understanding of the prognostic impact of blood involvement across disease stages, and improve between-trial assessments and comparisons of treatment response. Flow cytometry is the currently recommended method for objective assessment of malignant T-cell counts, and can be supported by T-cell-receptor gene sequencing to provide further prognostic information in patients with low disease burden or unusual T-cell clonal immunophenotypes. To improve standardization, the EORTC–CLTF has published consensus guidelines defining the levels of blood involvement as determined using flow cytometry, and further guidance on using these measures to assess blood response to treatment. Prospective, multicentre studies (such as the EuroFlow consortium and EORTC–CLTF's collaborative initiative) are in progress, aimed at developing a standardized protocol with validated cutoff values for assessing blood involvement in patients with CTCL. A greater understanding of the prognostic implications of blood classification in early-stage MF is required, and the results of initiatives such as the PROCLIPI study will provide further insights into the role of blood involvement in these patients.

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Appendix

Conflicts of interest

M.H.V. has received consulting fees from Kyowa Kirin, Innate Pharma and Piqur; and has received research funding from Kyowa Kirin and Takeda. J.P.N. has received travel and congress participation funding from Teva and Novartis; and consulting fees from Teva, Almirall, Biogen, Novartis, Kyowa Kirin, Innate Pharma, UCB Pharma, Takeda and Actelion. J.J.S. has received honoraria from 4SC, Kyowa Kirin, Mallinckrodt and Takeda; serves as a consultant or advisor for 4SC, Innate Pharma, Kyowa Kirin, Mallinckrodt and Takeda; and has received research funding from Kyowa Kirin and Takeda. P.L.Z. has received consultancy, advisory and/or speakers bureau fees from Verastem, Celltrion, Gilead, Janssen-Cilag, Bristol Myers Squibb, Servier, Sandoz, Merck Sharp & Dohme, Immune Design, Celgene, Portola, Roche, EUSA Pharma, Kyowa Kirin and Sanofi.