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Review

EORTC consensus recommendations for the treatment of mycosis fungoides/Sézary syndrome – Update 2023

Johanna Latzka [a,b,*], Chalid Assaf [c,d,e], Martine Bagot [f], Antonio Cozzio [g], Reinhard Dummer [h], Emmanuella Guenova [i], Robert Gniadecki [j,k], Emmilia Hodak [l], Constanze Jonak [m], Claus-Detlev Klemke [n], Robert Knobler [m], Stephen Morrris [o], Jan P. Nicolay [p], Pablo L. Ortiz-Romero [q], Evangelia Papadavid [r], Nicola Pimpinelli [s], Pietro Quaglino [t], Annamari Ranki [u], Julia Scarisbrick [v], Rudolf Stadler [w], Liisa Väkevä [u], Maarten H. Vermeer [x], Ulrike Wehkamp [y,z], Sean Whittaker [aa], Rein Willemze [x], Franz Trautinger [a,b]

[a] Department of Dermatology and Venereology, University Hospital of St. Pölten, Karl Landsteiner University of Health Sciences, St. Pölten, Austria
[b] Karl Landsteiner Institute of Dermatological Research, Department of Dermatology and Venereology, University Hospital of St. Pölten, St. Pölten, Austria
[c] Department of Dermatology, HELIOS Klinikum Krefeld, Krefeld, Germany
[d] Institute for Molecular Medicine, Medical School Hamburg, University of Applied Sciences and Medical University, Hamburg, Germany
[e] Department of Dermatology, HELIOS Klinikum Schwerin, University Campus of The Medical School Hamburg, Schwerin, Germany
[f] Department of Dermatology, Hopital Saint Louis, Université Paris Cité, INSERM U976, Paris, France
[g] Department of Dermatology and Allergology, Kantonspital St. Gallen, St. Gallen, Switzerland
[h] Department of Dermatology, University of Zurich, Zurich, Switzerland
[i] Department of Dermatology, University Hospital of Lausanne and Faculty of Biology and Medicine, University of Lausanne, Lausanne, Switzerland
[j] Department of Dermatology, University of Copenhagen, Copenhagen, Denmark
[k] Division of Dermatology, Department of Medicine, University of Alberta, Edmonton, Alberta, Canada
[l] Cutaneous Lymphoma Unit, Davidoff Cancer Center, Rabin Medical Center, Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel
[m] Department of Dermatology, Medical University of Vienna, Vienna, Austria
[n] Hautklinik, Städtisches Klinikum Karlsruhe, Karlsruhe, Germany
[o] Guy's and St Thomas' NHS Foundation Trust, Guy's Hospital, London, UK
[p] Department of Dermatology, Venereology and Allergology, University Medical Center Mannheim, Mannheim, Germany
[q] Department of Dermatology, Hospital Universitario 12 de Octubre, Institute i+12, CIBERONC, Medical School, University Complutense, Madrid, Spain
[r] National and Kapodistrian University of Athens, 2nd Department of Dermatology and Venereology, Attikon General Hospital, University of Athens, Chaidari, Greece
[s] Department of Health Sciences, Division of Dermatology, University of Florence, Florence, Italy
[t] Department of Medical Sciences, Section of Dermatology, University of Turin, Turin, Italy
[u] Department of Dermatology and Allergology, Inflammation Center, Helsinki University Central Hospital, Helsinki, Finland
[v] Department of Dermatology, University Hospital Birmingham, Birmingham, UK
[w] University Department of Dermatology, Venereology, Allergology and Phlebology, Skin Cancer Center, Johannes Wesling Medical Centre Minden, Ruhr University Bochum, Bochum, Germany
[x] Department of Dermatology, Leiden University Medical Center, Leiden, the Netherlands
[y] Department of Dermatology, University Hospital Schleswig-Holstein, Campus Kiel, Kiel, Germany
[z] Medical Department, Medical School of Hamburg, Hamburg, Germany
[aa] St. John's Institute of Dermatology, School of Basic and Medical Biosciences, Faculty of Life Sciences and Medicine, King's College London, London, UK

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ABSTRACT

On behalf of the EORTC Cutaneous Lymphoma Tumours Group (EORTC-CLTG) and following up on earlier versions published in 2006 and 2017 this document provides an updated standard for the treatment of mycosis fungoides and Sézary syndrome (MF/SS). It considers recent relevant publications and treatment options introduced into clinical practice after 2017.

Consensus was established among the authors through a series of consecutive consultations in writing and a round of discussion. Treatment options are assigned to each disease stage and, whenever possible and clinically useful, separated into first- and second line options annotated with levels of evidence.

* *Corresponding author*: Department of Dermatology and Venereology, University Hospital of St. Pölten, Dunant-Platz 1, A-3100 St. Pölten, Austria.
E-mail address: johanna.latzka@stpoelten.lknoe.at (J. Latzka).

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Immunotherapy
Retinoids
Corticosteroids

Major changes to the previous version include the incorporation of chlormethine, brentuximab vedotin, and mogamulizumab, recommendations on the use of pegylated interferon α (after withdrawal of recombinant unpegylated interferons), and the addition of paragraphs on supportive therapy and on the care of older patients.

Still, skin-directed therapies are the most appropriate option for early-stage MF and most patients have a normal life expectancy but may suffer morbidity and impaired quality of life. In advanced disease treatment options have expanded recently. Most patients receive multiple consecutive therapies with treatments often having a relatively short duration of response. For those patients prognosis is still poor and only for a highly selected subset long term remission can be achieved with allogeneic stem cell transplantation. Understanding of the disease, its epidemiology and clinical course, and its most appropriate management are gradually advancing, and there is well-founded hope that this will lead to further improvements in the care of patients with MF/SS.

1. Introduction

In 2004 the European Organisation of Research and Treatment of Cancer (EORTC) Cutaneous Lymphoma Task Force (now Cutaneous Lymphoma Tumour Group) organised a workshop to initiate the development and publication of a European consensus on the treatment of mycosis fungoides (MF) and Sézary Syndrome (SS). This effort resulted in the publication of the first EORTC-consensus recommendations for the treatment of MF/SS in 2006 to be revised and updated in 2017. Since then, the disease classification has again been refined, existing treatment regimens modified or removed and novel modalities introduced, necessitating another update, which is presented here [1–3].

Maintaining its original structure (stage-wise recommendations, separated into first- and second line options, wherever appropriate), reference to the previous version of the recommendations will be made whenever possible to avoid redundancy and duplication. At the same time some parts of the previous version will again be included to maintain readability and the use as an aid to clinical decision making.

Current definition of cutaneous T-cell lymphomas (CTCL), a group of rare non-Hodgkin lymphomas, follows the 5th edition of the WHO classification of haematolymphoid tumours, that largely incorporates the WHO-EORTC classification for cutaneous lymphomas published in 2019 (Table 1) [2,4]. Since MF (including its variants) is the most common entity among CTCL and since it shares many features with the much rarer SS, including pathological and clinical similarities, a common staging system and overlapping treatment options, both disorders are addressed in this paper. For recent data on epidemiology of CTCL and its subtypes see Cai et al., Dobos et al. and Vermeer et al. [5–7].

In addition to a correct diagnosis appropriate staging is fundamental to choose the best therapeutic approach for each individual patient. The current Tumor (skin) Lymph nodes Metastasis (viscera) Blood (TNMB)-staging classification is provided in Tables 2 and 3. For a detailed description of the clinical and pathological characteristics of MF and its variants and of SS see earlier published reviews [2,8,9].

Finally, before going into detail of therapeutic options and before considering who should be treated how, it is still and of unchanged importance to keep in mind that, although appropriate treatment will be effective in most patients, therapy in MF/SS is generally palliative and should follow a step wise, stage-adapted approach giving priority to maintenance of quality of life [10]. Remarkable exceptions to this principle are allogeneic stem cell transplantation (alloSCT) in advanced disease and the anecdotal patient with long term remission after skin-directed therapy (SDT) in localised early stages, where the primary intention of treatment is curative.

In an orphan condition and with evidence from larger randomised controlled trials still rare, guidelines developed by various national and international groups help with decision making [11–15]. The treatment recommendations provided here represent an updated consensus

Table 1
Classification of cutaneous T-cell lymphomas [2,4].

Cutaneous T-cell lymphoma	ICD-O-3 (morphology)
Mycosis fungoides (MF)	9700/3
MF variants and subtypes:	
Folliculotropic MF	
Pagetoid reticulosis	
Granulomatous slack skin	
Sézary syndrome (SS)	9701/3
Primary cutaneous CD30-positive lymphoproliferative disorders:	
Primary cutaneous anaplastic large cell lymphoma	9718/3
Lymphomatoid papulosis	9718/1
Subcutaneous panniculitis-like T-cell lymphoma	9708/3
Primary cutaneous peripheral T-cell lymphoma, unspecified	9709/3
Primary cutaneous CD8+ aggressive epidermotropic cytotoxic T-cell lymphoma	9709/3
Primary cutaneous γ/δ T-cell lymphoma	9726/3
Primary cutaneous CD4+ small/medium T-cell lymphoproliferative disorder	9709/1
Primary cutaneous acral CD8+ T-cell lymphoproliferative disorder*	9709/3

* The condition was recently reconsidered a lymphoproliferative disorder rather than an overt lymphoma [239]. This is not yet recognised in International Statistical Classification of Diseases and Related Health Problems (ICD)-0-3.

Table 2
TNMB staging for mycosis fungoides and Sézary syndrome [1].

Skin	
T1	Limited patches, papules, and/or plaques covering <10% of the skin surface. May further stratify into T1a (patch only) versus T1b (plaque +/- patch).
T2	Patches, papules, or plaques covering ≥10% of the skin surface. May further stratify into T2a (patch only) versus T2b (plaque +/- patch).
T3	One or more tumours (≥ 1-cm diameter)
T4	Confluence of erythema covering ≥80% body surface area
Node	
N0	No clinically abnormal peripheral lymph nodes; biopsy not required
N1	Clinically abnormal peripheral lymph nodes; histopathology Dutch grade 1 or National Cancer Institute (NCI) LN_{0-2} N1a Clone negative N1b Clone positive
N2	Clinically abnormal peripheral lymph nodes; histopathology Dutch grade 2 or NCI LN_3 N2a Clone negative N2b Clone positive
N3	Clinically abnormal peripheral lymph nodes; histopathology Dutch grades 3–4 or NCI LN_4; clone positive or negative
Nx	Clinically abnormal peripheral lymph nodes; no histologic confirmation
Visceral	
M0	No visceral organ involvement
M1	Visceral involvement (must have pathology confirmation and organ involved should be specified)
*Blood**	
B0	Absence of significant blood involvement: ≤5% of peripheral blood lymphocytes are atypical (Sézary) cells
B0a	Clone negative
B0b	Clone positive
B1	Low blood tumour burden: >5% of peripheral blood lymphocytes are atypical (Sézary) cells but does not meet the criteria of B2
B1a	Clone negative
B1b	Clone positive
B2	High blood tumour burden: ≥1000/μl Sézary cells with positive clone

SS is staged as T4 N2/3/x M0 B2.

* Blood staging for MF/SS is further defined as B0 = <250/ml of $CD4^+/CD26^-$ or $CD4^+/CD7^-$ cells, B1 = does not meet criteria for B0 or B2, and B2 = ≥1000/ml of $CD4^+/CD26^-$ or $CD4^+/CD7^-$ cells or other aberrant population of lymphocytes identified by flow cytometry [3,240].

Table 3
Clinical stages (5-year disease free survival [DSS] according to Olsen et al. [1]).

Stage	T	N	M	B	5-year DSS (%)
IA	1	0	0	0,1	98
IB	2	0	0	0,1	89
IIA	1,2	1,2	0	0,1	89
IIB	3	0–2	0	0,1	56
IIIA	4	0–2	0	0	54
IIIB	4	0–2	0	1	48
IVA1	1–4	0–2	0	2	41
IVA2	1–4	3	0	0–2	23
IVB	1–4	0–3	1	0–2	18

developed by a panel of European experts specifically considering medicinal products and therapies available and in use in Europe. Thus, histone deacetylase inhibitors, although approved by the United States Food and Drug Administration for CTCL, will not be covered. Modalities which are considered experimental and for which only minor published evidence is available are also excluded.

2. Development process of recommendations

The development of the consensus followed the same process as published earlier [13]. In short, after earlier authors and additional experts were invited and had agreed to participate, comments and suggestions for update to the past recommendations were collected in writing starting with May 2021. This initial survey was followed by an interactive personal discussion of its results at the EORTC CLG Annual Clinical Meeting in October 2021 and a further final collection of feedback by email until a unanimous consensus was reached. Since beyond clinical presentation and patient history, the choice of treatment is largely based on availability and institutional experience, the order of options within each category does not represent a recommendation for the order of use: Thus, unless specifically stated, options within a category should be considered equivalent. The final version of the manuscript was approved by all authors.

These recommendations were developed without external funding. Individual authors' potential conflicts of interest are disclosed in a separate section at the end of the manuscript.

3. Levels of evidence

As in the previous version, the Revised Levels of Evidence published by The Oxford Centre for Evidence-Based Medicine (OCEBM) in 2011 are used (Table 4) [16]. When interpreting these recommendations readers should keep in mind the initial sentence of OCEBM's accompanying introductory document: 'No evidence ranking system or decision tool can be used without a healthy dose of judgement and thought.' [17].

Table 4
Detail from: Oxford centre for evidence-based medicine 2011 levels of evidence [16].

Question: Does this intervention help?	Level*
Systematic review of randomised trials or *n*-of-1 trials	1
Randomised trial or observational study with dramatic effect	2
Non-randomised controlled cohort/follow-up study**	3
Case series, case-control studies, or historically controlled studies**	4
Mechanism-based reasoning	5

* Level may be graded down on the basis of study quality, imprecision, indirectness (study Population, Intervention, Control, and Outcomes (PICO) does not match questions PICO), because of inconsistency between studies, or because the absolute effect size is very small; Level may be graded up if there is a large or very large effect size.

** As always, a systematic review is generally better than an individual study.

4. Management options and treatment modalities considered for inclusion in the consensus recommendations

4.1. Expectant policy (watch and wait)

In patients with stage IA disease 'Expectant Policy' remains a legitimate management option. These patients have a low risk of progression and a life expectancy similar to the general population [18–21]. Careful monitoring is mandatory when using this option as some patients will eventually progress. Patients presenting with plaque disease (T1/2b) seem to be at higher risk and 'watch and wait' should thus be offered mainly to informed T1a patients [1,19,22–24]. An ongoing prospective multicenter international web-based data collection study (Prospective cutaneous lymphoma international prognostic index study, PROCLIPI) for early-stage MF analysed so far 395 newly diagnosed patients with early-stage MF and showed that expectant observation was the chosen management option in 7.3% [25]. Expectant policy does not mean no therapy and treatments to control symptoms such as itch, depression, insomnia are important to improve patients quality of life.

4.2. Skin-directed therapy

Skin-directed therapies (SDT) are recommended first-line in early stages of MF but may also be used in combination with systemic options in advanced stages to control symptoms and improve skin tumour burden. PROCLIPI has recently reported on 395 early stage patients. SDT have been used as first line in 81.6% of these patients with an overall response rate of 73% and significant improvement of health related quality of life. SDT are listed here in no particular order of preference.

4.2.1. Topical corticosteroids

Although widely used, the use of topical corticosteroids for the treatment of MF is still supported by little evidence [26,27]. In a recent retrospective single centre study Kartan et al. confirmed the efficacy and safety of topical clobetasol propionate monotherapy in 37 MF patients showing a high response rate (81%) in early-stage MF (stage IA/IB) [28].

Since no further relevant published evidence exists, the advice to prefer high potency steroids with consideration of measures to reduce the risk of skin atrophy is maintained.

4.2.2. Topical chlormethine

Chlormethine (2-chloro-*N*-(2-chloroethyl)-*N*-methylethan-1-amine, mechlorethamine) is an alkylating agent that received its initial approval in the US for the topical treatment of MF in 1949. Its use in various compounded formulations has a long history documented in several uncontrolled studies [29–32]. Based on the results of a pivotal phase 2 study [33] that showed non-inferiority of a commercial gel containing 0.02% chlormethine hydrochloride (corresponding to 0.016% chlormethine) to a compounded ointment of the same strength, the gel preparation was approved by the US Food and Drug Administration (FDA) in 2013 for 'the topical treatment of stage IA and IB mycosis fungoides-type cutaneous T-cell lymphoma in patients who have received prior skin-directed therapy' and – with a broader indication – in 2017 by the European medical agency (EMA) 'for the topical treatment of mycosis fungoides-type cutaneous T-cell lymphoma in adult patients' [33–35]. A post hoc analysis of the above-mentioned study showed that clinical response at 1 month was modest with a steady increase in response rates to peak at 10 months [36]. Early, intermittent, and late response patterns were observed. Another post hoc analysis of the same study found the gel to be more effective compared to the ointment specifically in stage IA patients and provisional evidence that the emergence of contact dermatitis might be an indicator for clinical response [37].

The product should be applied once daily to all affected areas of the skin. For widespread disease application to the whole body surface is possible and safe. Contact dermatitis occurs in over 50% of patients

resulting in withdrawal in 20.3% and 17.3% of patients (gel versus ointment, respectively) in the pivotal trial [33]. In many patients skin toxicity can be managed by treatment interruption and reintroduction with longer intervals between applications and by combination with topical corticosteroids. Options for the management of chlormethine-induced dermatitis with the goal of allowing for treatment continuation have been described in a number of prospective and retrospective studies, reviews, reports on real world experience and consensus statements [38–48]. Allergic and irritative mechanisms have been speculated to cause dermatitis upon exposure of the skin to chlormethine. A currently closed EORTC-sponsored trial, the REACH study (NCT04218825), aims to determine the etiology of chlormethine induced skin drug reaction and its association with clinical response.

No evidence for systemic absorption of the drug after topical application has been found and no systemic toxicity observed [33,49]. Moreover, during a 24 months observation period (12 months treatment and 12 months follow-up) no excess skin cancer was observed in the treatment areas. Within the limitations of the observation period and uncontrolled confounding variables, these data together with the long historical safety record do not support an obvious association between the development of skin cancer and the topical use of chlormethine.

Chlormethine gel is recommended as 1st line treatment of early stage disease (stages IA to IIA).

4.2.3. Topical options without recommendation

4.2.3.1. Topical retinoids. Bexarotene gel is approved by the FDA for topical treatment of cutaneous lesions in patients with CTCL (stage IA and IB) who have refractory or persistent disease after other therapies or who have not tolerated other therapies. Since the last update of this recommendations no relevant new information on its use in CTCL has been published and the product is still not approved in Europe. Thus, again no recommendation as to the use of bexarotene gel is included in the current report.

Tazarotene is another retinoid available for topical use and approved in the US for the treatment of psoriasis and acne. In two small trials it has demonstrated efficacy and safety in early stage MF [50,51]. However, these results have not been followed up and the product has been discontinued in Europe, precluding its use and its inclusion as a treatment option in this report.

4.2.3.2. Topical calcineurin inhibitors. Tacrolimus and pimecrolimus are calcineurin inhibitors initially developed and widely used for the topical treatment of atopic dermatitis. While on the use of tacrolimus in MF only a single case report is available [52] pimecrolimus has been investigated recently in a single-arm, multicentre phase 2 trial (Pim-To-MF) [53]. Thirty nine patients with early-stage MF were included and an overall response rate of 56% was reported (one complete response, 21 partial responses) without adverse events other than transitory mild itch or burning. The authors conclude that, although promising, the described results should be interpreted with caution until efficacy and safety of pimecrolimus in MF is confirmed in controlled trials with longer follow-up. Thus, so far no recommendation as to the use of topical calcineurin inhibitors in MF can be made.

4.2.3.3. Others. The Toll-like receptor agonist imiquimod has been successfully used for the treatment of MF in case reports [54–56] and its successor drug resiquimod has shown safety and efficacy in a phase 1 trial in patients with early-stage MF [57].

Other topical pharmaceuticals that have been tried in small studies in MF are methotrexate combined with the penetration enhancer laurocapram [58] and 5-fluorouracil (5-FU) [59]. The purine nucleoside phosphorylase (PNP) inhibitor peldesine (BCX-34) has been tried in a phase III, randomised, double-blind, placebo-controlled study and was not superior to placebo [60].

In summary, all of these topicals are either not (yet) available or not supported by sufficient data to recommend their use in MF.

4.2.4. Ultraviolet (UV) phototherapy

Both, 8-Methoxypsoralen plus UVA (320–400 nm, Psoralen plus ultraviolet-A (PUVA)) and narrowband UVB (311–312 nm, nbUVB) not only have a longstanding history in the treatment of MF but continue to be a mainstay in disease management able to induce high response rates in early-stage MF and improve patients' psychological well-being and quality of life [61].

As already mentioned before, broadband UVB (290–320 nm, bbUVB) has disappeared from photodermatology offices and wards due to its disadvantages compared to nbUVB in the treatment of psoriasis and will thus not be further recommended. In MF nbUVB appears to be similarly effective as bbUVB even in skin types III and IV as shown in a small retrospective study [62]. Excimer sources (308 nm) and UVA1 (340–400 nm) are other phototherapeutic options that have been tried in MF with a number of recent reports adding additional evidence as to their potential benefit [63–67]. However, only PUVA and nbUVB will be considered here, since only for those a sufficient body of evidence together with broad accessibility is available [68,69].

A recent review and meta-analysis by Phan et al. compared efficacy and adverse effects of PUVA and nbUVB including seven studies with a total of 778 patients with histologically confirmed early-stage MF, defined as stages IA, IB and IIA [70]. Confirming earlier findings the authors conclude that PUVA is a potential alternative to nbUVB in the management of early-stage MF. Specifically, one of the studies included in the meta-analysis showed retrospectively in 227 early-stage MF patients that PUVA might lead to better responses and longer relapse-free intervals than nbUVB [71]. Another retrospective analysis of the use of nbUVB in 117 early-stage patients even concluded that over half of stage I patients remained disease free for more than 5-years, constituting a potential 'cure' [72]. These and other publications in the field demonstrate the general difficulty in interpreting studies in dermatological phototherapy with their inherent inconsistency in general methodology, trial design, and reporting.

In bath PUVA 8-methoxypsoralen is applied topically through immersion of the patient in a bathtub of medicated water. The procedure has been developed for the treatment of psoriasis. Its efficacy has been reported also in early-stage MF and confirmed in recent retrospective case series [73,74]. However, its use is still not generally recommended because with bath PUVA the head is usually not exposed to the photosensitizer and might be a site of early relapse.

Combination of phototherapy with systemic pharmaceuticals (most commonly retinoids or interferon α) can be considered upon clinical need and will be covered below [75]. Another option to prolong remission in phototherapy is the continuation of treatment beyond complete or almost complete response (maintenance therapy, see below).

Apart from UV-induced erythema and phototoxic reactions phototherapy carries a potential risk of skin carcinogenicity as documented for PUVA in patients with psoriasis and emergent keratinocyte derived skin cancer [76,77]. For nbUVB such an association has not yet been confirmed. In MF evidence from similar studies is lacking and the risk for phototherapy induced skin cancer unknown but obviously too low to become apparent so far.

Recently, in the search for mutational signatures in CTCL two groups independently found that tumour cells in MF and in SS often carry a mutational UV-signature associated with a high tumour mutational burden and suggesting a role for exposure to UV radiation in their pathogenesis [78,79]. Considering that UV is the most abundant environmental skin carcinogen, this is not surprising, but might challenge the long-standing and successful history of phototherapy in MF. As a result, future studies will have to examine the role of UV-mutagenesis in contributing to clonal transformation of skin resident memory T-cells and whether phototherapy, with its obvious benefits documented in a large body of evidence, may also have potentially adverse effects on clinical outcomes in early stage disease, for which we have no clinical or epidemiological evidence to date.

Taken together, earlier reviews and consensus statements on the topic remain valid and recommendations unchanged [80–82].

4.2.5. Photodynamic therapy

In photodynamic therapy (PDT) a photosensitizer (PS) is applied to the target organ and then activated by light of the appropriate wavelength and intensity, resulting in the formation of cytotoxic oxygen free radicals only in the exposed area, sparing surrounding tissue. PDT is used mainly in oncology to target tumour cells but also to treat infections (antimicrobial PDT) and inflammatory skin diseases. In dermatology, topically applied (methyl-)aminolaevulinic acid (ALA, MAL; prodrugs that are metabolised to protoporphyrin IX in the target cells) is most commonly used in combination with red light for the treatment of superficial keratinocyte derived skin cancer.

The successful use of PDT in MF is described in various case studies recently summarised by Hooper et al. [83]. Complete response (CR) was achieved in 67.3%, partial response (PR) in 13.5%, and no response (NR, defined as <50% clinical response) in 3.8% of all included cases. Stable disease (SD) was reported in 3.8% and clinical response data were not available (NA) in 11.5% of cases. The mean treatment number in this analysis was 9.5 (range 1–46) showing that serial PDT is likely required for the successful treatment of MF.

In a recent single-arm, prospective open-label study PDT combining ALA and blue light was investigated in 11 patients with MF defined as refractory to skin directed and at least one systemic therapy [84]. PDT was applied for up to 6 monthly cycles with increasing ALA incubation times. Depending on the outcome measure, response rates where between 18% and 36% with no complete remission or progressive disease. The poorer outcome compared to earlier reports might be explained by differences in the treatment protocol (ALA versus MAL, blue versus red light), patients' characteristics, and clinical end-points highlighting the need for future trials to optimise PDT protocols in relation to lesion type, thickness, and location. Furthermore, it must be considered that PDT is a local therapy for limited areas of the skin with no practical option for treatment of large areas of the body surface or total skin exposure. Thus, currently no recommendation as to the use of PDT for the treatment of MF can be made.

4.2.6. Total skin electron beam therapy

In total skin electron beam therapy (TSEB) radiation from linear accelerators, attenuated to penetrate the skin but avoid toxicity to internal organs, including the bone marrow, is used to target the patients' whole body surface. TSEB has a long history in the treatment of MF and a number of reviews and consensus statements as to its indication and use have been published [85–89]. Traditionally, a standard treatment course consists of a total dose of 30–36 Gy applied over a period of 8–10 weeks and in selected patients TSEB has been successfully repeated upon relapse after initial response without significant additional toxicity. As clinically indicated TSEB can be combined with nodal and localised skin irradiation [90–92]. To minimise the dose-dependent toxicity of TSEB to the skin and adnexal structures low-dose regimens (8–12 Gy) have recently been increasingly reported [90,93–96].

The introduction of a low dose TSEB schedule (12 Gy in ,eight fractions over a period of 2 weeks) in the UK was accompanied by a prospective study [97]. One hundred and three patients with MF were included, of which 54 had stage IB, 33 stage IIB, 12 stage III, and 4 stage IV. The complete response rate was 18%, the partial response rate was 69%, stable disease was achieved in 8%, and progression was observed in 5%. Median response duration was 11.8 months and median time to relapse after complete response was 7.3 months. Median progression-free survival for all patients was 13.2 months and stage-dependent (stage IB: 26.5 months, stage IIB 11.3 months, stage III: 10.2 months).

Further recent prospective data on low dose TSEB is provided by Song et al. who investigated in a prospective cohort study efficacy and safety of a novel condensed low-dose TSEB therapy in 25 MF patients [98]. They delivered 12 Gy per six fractions, three fractions per week, with boosts to shadowed sites at risk between treatments (perineum, inframammary folds, soles, scalp, and pannus). The overall response rate was 88% with complete response in six patients (24%). The median duration of response was 17.5 months (3.5–44.2), and the median time to response was 2 months (range, 0.9–4.1). No patients had toxicity of grade 3 or greater and a significant improvement in quality of life (QoL) and disease burden was observed.

In a small prospective, randomised trial including patients with MF or SS Georgakopoulos et al. directly compared conventional (36 Gy, n = 6) to low-dose (12 Gy, n = 8) TSEB [99]. Both arms showed excellent overall response rates: 100% for the 36 Gy group (four complete remissions) and 87.5% for the 12 Gy group (two complete remissions). Duration of response did not differ significantly between the two groups (10.5 versus 9.25 months in conventional and low dose TSEB, respectively). Toxicity was mild in both groups, except one case of grade 3 erythema in the 36 Gy group.

Retrospective comparisons between conventional- and low-dose TSEB are reported by Dault et al. including 26 patients with MF stages IB to IVA and by Taverniers et al. (n = 26, MF stages IA to IVA) [100,101]. In both reports the low dose regimen consisted of 12 Gy and was compared to the conventional dose of 36 Gy [100] and to what the authors called 'middle-dose' of 25 Gy [101]. Considering the risk of bias in retrospective analysis, where treatment allocation is not randomised, results of both reports confirm the finding of better tolerability of lower total doses with the potential of retreatment compared to higher response rates and a tendency to longer remission free survival with higher dosage.

Skin carcinogenicity secondary to TSEB is a concern particularly relevant for patients in early stages of the disease with long life expectancy and for patients with an already high underlying skin cancer risk from chronic sun exposure and/or immunosuppression. The issue was addressed in a retrospective study from Israel including 197 patients with MF treated with TSEB (n = 104) and other systemic and skin-directed options (n = 93) and observed over a time period of up to 36 years [102]. Emergent skin cancer rates were compared with those of patients receiving other therapies than TSEB and of a matched cohort of the Israel National Cancer Registry. The authors found the skin cancer rates in MF patients to be increased in comparison to the general population (6.7-fold in males and 13.1-fold in females). Malignant melanoma was observed in eight patients after radiotherapy and in one patient without irradiation. Skin cancer rate was generally higher after irradiation (p = 0.011, compared to patients never irradiated) with a history of PUVA and/or nitrogen mustard (chlormethine) constituting an additional risk factor. These results, however, must be read with caution as the cohort was not prospectively recruited and followed-up and the results might be influenced by inherent bias and lack of statistical power so that the skin cancer risk associated with TSEB is still to be defined.

Regretfully, clinically useful biomarkers to predict response to TSEB are currently not available. A recent study investigating the value of peripheral blood CD4:CD8 ratio as prognosticator for response to TSEB found a high ratio being an independent predictor of a poor response to TSEB warranting further prospective investigation [103].

In summary, based on published data TSEB is an effective and well-tolerated treatment option in MF with low dose regimens (defined as a total dose of 12 Gy) providing a number of advantages over conventional dose (36 Gy). Literature on the use of TSEB in SS is scarce and its benefit in this condition is controversial [90,104–106]. Individual decisions on which TSEB schedule to choose in which patient must consider patient history, age and functional capacities, individual treatment goals, QoL, and disease stage and associated prognosis.

4.2.7. Localised radiotherapy

Since the publication of the previous version of these recommendations only little has been published to change clinical practice. It is still

valid that localised, superficial radiotherapy provides effective palliative treatment for individual lesions, including special sites as the face and genitalia, and may even induce long term remission in unilesional disease. In a model study from the US localised radiotherapy proved to be the most cost-effective treatment for limited disease [107]. Photons as well as electrons can be used, and doses may range from 0.7 to 35 Gy. Low dose regimens have the advantage of allowing areas to be retreated. Combinations with other skin directed and systemic therapies are possible [89,108–114].

Strong support for the use of radiotherapy early-on in MF comes from a translational study by OMalley et al [115]. To assess whether remissions achieved by skin-directed therapy are associated with malignant T-cell clone depletion at treated sites and – if yes – if clone-ablative therapy is associated with improved overall survival, they performed pre- and post-treatment biopsies in 18 patients (20 lesions) with MF, treated either with low dose radiotherapy (n = 16) or topical corticosteroids (n = 4). Upon radiotherapy clones were eradicated in five and reduced by more than 90% in 11 lesions. In contrast, topical corticosteroids lead to clinical improvement but with clonal persistence. The amount of residual malignant T cells was a predictor of lesion recurrence. Furthermore, the authors did a retrospective chart review in a prospectively defined cohort of 210 early-stage MF patients and found that among patients (n = 45) with >25% of clonal cells in their lesion, but not in the general cohort, a history of radiotherapy was associated with significantly better overall survival.

4.3. Systemic therapies

Systemic therapies are recommended in early stage disease refractory to SDT and in advanced stages of MF and SS. Response rates and durations are typically short and time to next treatment may provide a useful surrogacy of real life drug benefit [116]. Systemic treatments are listed here in no particular order of preference.

4.3.1. Retinoids (including bexarotene)

Since publication of the previous version of these recommendations no new retinoids have been approved for clinical use and the group still consists of all-trans retinoic acid, isotretinoin, etretinate, acitretin, alitretinoin and bexarotene, the latter standing out as a substrate of the retinoid-X-receptor (thus termed a 'rexinoid') and as it is the only retinoid specifically developed and approved for the treatment of CTCL. Historically the most used substances are acitretin and isotretinoin. The successful use of alitretinoin is described in recent retrospective studies, but without comparison to other treatments and without obvious benefits compared to other retinoids than the substance specific differences in adverse events and associated requirements for monitoring [117–131].

Bexarotene received approval for the treatment of CTCL in Japan in 2016 (17 years after its initial approval in the US) based on existing evidence and on a phase I/II study in Japanese patients, that followed the established dose recommendations and confirmed the results in terms of response, tolerability and adverse events from existing evidence. After approval follow up-studies were published: A large post-marketing surveillance study from 2022 identified 294 Japanese patients treated with bexarotene. Of these 267 could be included in the safety analysis and 175 in the efficacy analysis of which 139 had MF [132]. A significant difference in objective response rates was detected between patients who started with bexarotene at 300 mg/m^2 (61.6%) and those who started with less. Ninety two patients with MF were treated with a combination of bexarotene plus photo(chemo)therapy and a significantly better objective response rate was observed for the combination compared to bexarotene alone. Emergent adverse events did not differ from what is known from published evidence and from long-standing clinical practice out of Japan and included dose dependent hypothyroidism (85.8%), hypertriglyceridemia (68.5%), hypercholesterolaemia (43.8%), and neutropenia (21.3%). Remarkably, and in contrast to a recommendation from a group of European experts the authors conclude that bexarotene should be started according to its label at 300 mg/m^2[125].

Taken together, still, according to published evidence, no conclusion as to superiority of one retinoid over the other can be made. All substances are generally well tolerated sharing some common, class specific adverse effects (most notably teratogenicity, dryness of skin and mucous membranes, hyperlipidemia) and are at the same time characterised by substance specific toxicity profiles (e.g. central hypothyroidism with bexarotene) and individual pharmacokinetics, the prescribing physician has to be aware of. As again confirmed by the above mentioned recent study from Japan, only moderate response rates can be achieved with retinoid monotherapy in MF/SS. The substances thus are commonly used in combination (see below) or in maintenance (see below) [64,75,120,133–135].

4.3.2. Interferon (IFN)-α

The interferons (IFN-α, IFN-β, IFN-γ) have a long history in the treatment of in CTCL [136]. Among those substances, only recombinant IFN- α was approved and recommended for this indication and was widely used alone and in various regimens and combinations [13,136]. Since publication of the last version of this consensus, both previously available formulations of recombinant IFN- (IFN-α 2a, IFN-α 2b) have been withdrawn from the market by the suppliers. After review of the available evidence the authors agreed that, as IFN-α is essential in the treatment of MF and SS, the withdrawn preparations should be replaced with the only remaining available pharmacological variant, namely pegylated IFN-α 2a (peg-IFN-α 2a). Recently, Patsatsi et al. reported on the use of peg-IFN-α 2a in a retrospective cohort of 31 MF patients with MF across all stages and alone or in combination (with bexarotene, acitretin, methotrexate, and topical chemotherapy) [137]. The initial dose was 135–180 μg/week, subcutaneously, with dose reduction in eight of 31 patients due to intolerance. An overall response rate of 54.8% (17/31) was observed (CR 9.7%, PR 45.2%). Main adverse effects were neutropenia, fatigue, and anaemia. Earlier, the safety, tolerability, and efficacy of peg-IFN-α 2a has been prospectively investigated by Schiller et al. in patients with MF (stages IB to III) in an open-label, multicenter, dose-escalation study [138]. Peg-IFN-α 2a was administered subcutaneously at 180 (n = 4), 270 (n = 6), or 360 μg (n = 3) once weekly for 12 weeks. Peg-IFN-α 2a was generally well tolerated, the most common AEs were fatigue, acute flu-like symptoms, and hepatotoxicity. Dose reductions or withholding because of adverse events were rarely required (n = 1, n = 4, n = 0 in the 180-, 270-, and 360-μg/week groups, respectively). Response rates (CR or PR) between 50% and 66% were observed, without a clear dose-response relationship. Additional evidence comes from studies on the use of peg-IFN-α 2a in melanoma. [139–141]. In this indication its toxicity profile was found to be similar to that of recombinant INF-α. Adverse events are dose dependent and include flu-like symptoms, elevated transaminases, leukopenia, thrombocytopenia, and - probably previously under-recognised with non-pegylated IFN-α - mental depression, cardiac arrhythmias and thyroid dysfunction [142]. Two variants of pegylated IFN- (peg-IFN-α 2a and - 2b) have shown to be equally effective in the treatment of chronic hepatitis B and C with differences in pharmacokinetics and dosing [143,144]. In the previous version of this paper no difference was made between the non-pegylated recombinant IFN-α variants. However, due to the larger (although still limited) body of evidence with pegylated IFN-α 2a compared to - 2b and the differences in dosing, it is recommended to prefer the former over the latter when treating MF/SS. Dose equivalents of pegylated and non-pegylated IFN-α have not been established for either efficacy or toxicity. However, the pertinent literature has not yet demonstrated any clinically relevant differences from previously used IFN variants (including the heterogeneity in recommended doses), and in accordance with the literature cited above and expert opinion, treatment should start with 135–180 μg/week subcutaneously with clinical and laboratory monitoring and dose adaptation as required.

4.3.3. Combinations

As mentioned in the previous version of this consensus statement various combinations of systemic and skin directed therapies have been reported in the literature and are commonly used. Except for one small pilot trial exploring the combination of pegylated IFN-α 2b and phototherapy in seven patients with advanced stage MF (IIB-IVB) no new relevant literature on combination therapies in MF/SS have been reported since then [145]. The dose of pegylated IFN-α 2b in the mentioned trial was escalated up to 9 μg/kg body weight with PUVA or nbUVB given concomitantly three times weekly. Although treatment was reported to be highly effective (5/7 patients responding, 1 CR), median PFS was short (3.5 months, range 0.5–10.0 months) with limiting toxicity and progression observed in all patients. Six of 7 patients died within a median observation period of 34 months.

Thus, as summarised previously, accumulated evidence confirms the clinical applicability of IFN-α- retinoid combinations and of combinations of both substances with phototherapy [75]. Whether this also applies to pegylated IFN has not been shown but might be inferred from its pharmacodynamics and the mentioned pilot study. Ample, albeit retrospective, evidence exists for combinations of most systemic and all forms of SDT with extracorporeal photochemotherapy (ECP, see below). Further, and as mentioned above, localised radiotherapy can be used in combination with other therapies for the palliation of individual, particularly tumorous lesions. Concomitant application of topical corticosteroids is commonly prescribed as is – more recently – the use of topical chlormethine for individual recalcitrant lesions [146].

In general, however, the superiority over monotherapy has not been shown for any combination. Thus, current evidence does not support the use of combinations as first line options in MF/SS. Combinations might be useful in the individual patient when monotherapy proved insufficient and should be applied based on institutional and personal experience.

4.3.4. Chemotherapy

The use of conventional single agent and combination cytostatic chemotherapy has been described in the previous report with only limited, confirmatory additional evidence published since [13,147]. Recently, single-centre experience with pegylated liposomal doxorubicin for induction (20 mg/m^2 biweekly) and maintenance (20 mg/m^2, treatment intervals individually extended for up to 4 weeks) was retrospectively described in a group of 36 patients (34 with MF, stages IIA – IVB, two with SS) with a high overall response rate (78% CR + PR, median duration of response 31 weeks) and a safety profile comparable to what has been reported earlier [148,149].

Gemcitabine is another cytostatic drug recommended for the treatment of advanced stage MF and SS. Two recent retrospective studies described its use in regimens with reduced dosage compared to what is recommended in other indications. In a German multicenter study 37 patients with MF (stage $\geq$ IIB) and 11 with SS were included who had received gemcitabine in cumulative doses from 1800 to 2000 mg/m^2 per monthly cycle. An overall response rate of 62% (CR + PR) was reported with a median progression free survival of 12 months [150]. Similarly, a single centre from Italy reported on the treatment of nine patients with MF (stages IIB-IVA) and 13 with SS with gemcitabine at cumulative monthly doses of 2000 to 3000 mg/m^2. Overall response rate was 54.5% with a median progression free survival of 17 months [151]. Treatment was well tolerated in both studies with mainly haematological toxicity of CTCAE grades 1–2 and rarely grade 3.

Other chemotherapeutic agents included in these recommendations are chlorambucil and methotrexate. Chlorambucil is used in SS in combination with low dose prednisone with no new evidence recently published. Prolonged exposure is associated with a risk of leukaemia and thus should be avoided [13]. Due to the introduction of mogamulizumab with high efficacy in the treatment of SS confirmed by high level evidence (see below), the use of chlorambucil is limited to individual patients and resource-poor settings.

Recommendations also remain unchanged for methotrexate as no new evidence on its use in MF/SS has become available. Recommended doses range from five to 25 mg once weekly.

4.3.5. Targeted immunotherapy

Alemtuzumab, a humanised recombinant IgG1 monoclonal antibody against CD52 was initially developed for the treatment of lymphoid malignancies. No new primary evidence has appeared since the previous version of this report. A systematic review from 2018 confirmed earlier findings of its efficacy in SS and of reduced toxicity with low dose regimens [152]. Similarly to what is said above for chlorambucil, after the introduction of mogamulizumab (see below) the use of alemtuzumab will be limited to individual cases.

Mogamulizumab is a defucosylated humanised IgG1 κ monoclonal antibody directed against C-C chemokine receptor 4 (CCR4) with enhanced antibody-dependent cellular cytotoxicity activity. CCR4, which is involved in cell trafficking of lymphocytes to skin, is consistently expressed on the surface of tumour cells of cutaneous T-cell lymphoma (including MF and SS), adult T-cell leukaemia-lymphoma, and peripheral T-cell lymphoma [153]. The drug is approved in Europe for the treatment of adult patients with MF or SS who have received at least one prior systemic therapy. Safety and efficacy of mogamulizumab was shown in a large open-label, randomised, controlled phase 3 trial (MAVORIC trial) where 372 patients (204 with MF and 168 with SS) were randomly assigned to receive mogamulizumab (n = 186) or vorinostat (n = 186) [154]. Mogamulizumab significantly prolonged median progression free survival (PFS, the primary end-point in MAVORIC) compared to vorinostat (7.7 versus 3.1 months) with a superior objective response rate (ORR). Analysis of predefined subgroups revealed that efficacy is superior in SS compared to MF and stage III/IV disease compared to stages IB/II.

A post hoc analysis evaluated the effect of baseline blood tumour burden on patients' response and identified blood involvement (B1 and B2) as predictor of response to mogamulizumab for all end-points, including PFS, ORR, time to next treatment (TTNT) and skin involvement (mSWAT). Mogamulizumab induced rapid and sustained reductions in $CD4^+$ $CD26^-$ cell counts and CD4:CD8 ratios. The rate of treatment-emergent adverse events was independent of B-class [155]. A further post hoc analysis showed that prior systemic therapies did not affect ORR, PFS and DOR (duration of response) to mogamulizumab [156].

The most common mogamulizumab related treatment-emergent adverse events (TEAE) in MAVORIC were infusion-related reactions, drug rash, diarrhoea, and fatigue [154]. Mogamulizumab-associated rash (and probably also other immune-mediated toxicity) is presumed to be related to the depletion by mogamulizumab of regulatory T-cells in the skin allowing cytotoxic T-cells to cause inflammation and skin disease [157]. The resulting rash is highly variable, can clinically resemble MF/SS and was the most common TEAE leading to treatment discontinuation. Differentiation of mogamulizumab-associated rash from persistent/progressive MF/SS is essential to prevent premature drug discontinuation. Skin rashes have been reported to be associated with higher overall survival [158]. Recommendations as to their characterisation and management have been published recently [159].

Brentuximab vedotin is an antibody-drug conjugate consisting of an anti-CD30 IgG1 antibody attached to monomethyl auristatin E, a microtubule-disrupting agent, through a protease-cleavable linker [160]. Based on the results of the ALCANZA trial (see below) the drug is approved in Europe for the treatment of adult patients with CD30+ cutaneous T-cell lymphoma (CTCL) after at least one prior systemic therapy.

The safety and efficacy of brentuximab vedotin in CTCL was shown in an international, open-label, randomised, phase 3, multicentre trial (ALCANZA) [161]. Ninety seven adult patients with CD30-positive mycosis fungoides (stages IA to IVB and defined by $\geq$10% of CD30 positive malignant cells in at least one biopsy) who had received at least

one previous systemic therapy (and 31 adult patients with CD30-positive pcALCL) were enroled and randomly assigned 1:1 to receive brentuximab vedotin or physician's choice (oral methotrexate or oral bexarotene). The primary end-point was the percentage of patients achieving an objective response lasting for at least 4 months (ORR4) and was reached in 50% (brentuximab vedotin) versus 10% (physician's choice) of patients with MF. The complete response (CR) rates were 10% and 0% and median progression free survival 15.9 and 3.5 months, respectively. Subgroup analysis showed that the superiority of brentuximab vedotin over physician's choice was consistent across all stages of MF. Peripheral sensory neuropathy was the most frequently described treatment emergent adverse event in 44 of 66 patients (67%) in the brentuximab vedotin group [161].

In the overall population (MF and pcALCL), the final analysis of this trial after a median follow up of 45.9 months demonstrated an ORR4 of 54.7% versus 12.5% with CR in 17.2% versus 1.6% of patients (brentuximab vedotin versus physician's choice, respectively). In the MF group median PFS was 16.1 versus 3.5 months, respectively. Of 44 patients in the brentuximab vedotin arm who experienced any-grade peripheral neuropathy, 86% had complete resolution or improvement to grades 1 and 2. Peripheral neuropathy was ongoing in 18 patients (all grades 1–2) [162].

Other smaller single arm phase 2 studies of brentuximab vedotin in relapsed/refractory CTCL included patients with CTCL subtypes not studied in ALCANZA such as SS and lymphomatoid papulosis (LyP) as well as patients with levels of CD30 positivity down to 0%. Also in these studies brentuximab vedotin demonstrated clinical activity in treatment-refractory or advanced MF, SS or LyP over a wide range of CD30 expression levels [163–168].

Regarding the practical issue of choosing the appropriate patients for treatment with brentuximab vedotin, it must not only be taken into account that the cut-off value as used in the ALCANZA study (10% positivity) was defined arbitrarily and that there is evidence that significant responses can also be achieved at lower positivity levels, but also that CD30 expression can vary within individuals. This was shown in a retrospective survey evaluating 135 biopsy specimens of 95 patients with MF for the expression of CD30 by immunohistochemistry. The authors show that not only can CD30 be detected in 90% of samples (with $\geq$10% positivity in 60%) but also that in patients with multiple biopsies (69 samples) highly variable CD30 expression was found, especially in biopsies taken at different time points. CD30 expression was more common in advanced disease stage. The authors conclude that investigation of multiple tissue samples improves the assessment of CD30 expression status in MF and may help reduce the risk of inadequate treatment assignment [169].

4.3.6. Other immunotherapies

Since the initial reports on their efficacy in the treatment of metastatic melanoma T-cell checkpoint inhibitors have revolutionised treatment in a number of solid cancers. Specifically anti-programmed-cell-death protein 1 (PD1) and anti-PD1-ligand (PD-L1) antibodies can induce durable responses in a high percentage of patients with acceptable (mainly immune-mediated) toxicity. In CTCL the results of only few early phase studies have so far been reported [170–172] with trials ongoing. From the currently available results of these studies no conclusion on the clinical value of anti-PD1/PD-L1 can be made. Caution should be exercised with their use in patients with T-cell malignancies out of clinical trials, as – in contrast to solid cancer – the malignant tumour cell may at the same time act as an immunological effector cell with the risk of unexpected effects upon checkpoint inhibition [173–176].

KIR3DL2, a member of the KIR family of natural killer (NK) cell Ig-like receptors, has been found to be aberrantly expressed in tumour cells of most patients with SS and other CTCL [177]. In addition to its use in diagnosis, follow-up and as a prognostic biomarker, targeting KIR3DL2 with IPH4102, a therapeutic monoclonal antibody, was reported to be safe and clinically active in a first-in-human phase 1 study in CTCL [178]. 44 patients with CTCL (35 with SS, eight with MF, and one with CTCL, not otherwise specified). Responses were observed mainly in patients with SS. A subsequent, open label, multi-cohort, and multi-centre phase II study (NCT03902184, the TELLOMAK trial), evaluating the clinical activity and safety of IPH4102 alone or in combination with chemotherapy in patients with advanced T cell lymphoma is ongoing.

4.3.7. Extracorporeal photochemotherapy

Since our last report an expert panel of the European Dermatology Forum has published an updated version of their guidelines on the use of extracorporeal photochemotherapy (ECP; also variously called photopheresis, extracorporeal photopheresis or extracorporeal photoimmunotherapy) in various indications including MF/SS [179]. Furthermore a small number of retrospective studies on the use of ECP in MF/SS have been published confirming previous evidence [180–182] and one investigating a modified treatment schedule [183], without implications for a change in current clinical practice. There may be an emerging role of ECP in early stage MF but data is limited and no recommendation is currently possible [184,185].

It thus still applies that ECP can be safely applied alone or in combination with other systemic and skin directed therapies and its use is recommended mainly in erythrodermic MF and SS without high level evidence on superiority of one combination over the other or over ECP alone.

4.3.8. Hematopoietic stem cell transplantation

Apart from the rare situation of local radiotherapy for monolocalised MF (see above) allogeneic stem cell transplantation (alloSCT) is the only option in MF/SS with curative intention in patients with advanced disease. Autologous stem cell transplantation, on the other hand, has been abandoned in MF/SS due to invariable relapse in all patients reported [13].

The published evidence on alloSCT in CTCL until recently came from retrospective studies and case series comprising a total of approximately 400 patients and describing the use of full- and reduced intensity conditioning regimens [186–200]. Comprehensive reviews have been published recently [201,202]. In the only prospective, controlled trial on alloSCT in MF or SS 99 patients with advanced disease were enroled at 17 centres in France. A propensity score matched group of patients without a compatible donor served as controls. The primary end-point was PFS with a significant benefit for the alloSCT group (median PFS of 9.0 months after alloSCT versus 3.0 months in the matched control group). At the time of publication, median overall survival was 26.9 months in controls and not reached in the alloSCT group. Serious adverse events were more common in the alloSCT group. The authors conclude that alloSCT should be provided to patients with high-risk, advanced-stage MF/SS and pre-transplant disease remission [203].

Summarising the pertinent evidence, alloSCT has the potential to induce prolonged remissions in advanced MF/SS in a substantial proportion of patients (reported 2–7 years overall survival between 79% and 32%). It is, however, associated with a high risk for post-transplant relapse, procedure-associated mortality and severe morbidity from graft-versus-host disease and infections. AlloSCT should be considered only in patients with advanced disease and poor prognosis but without significant comorbidity. For best results, complete or near complete remission should be achieved prior to transplantation. Therefore, alloSCT is optimally not used as a 'last resort' when all other options have failed, but rather in patients who are at high risk of progression and death from their disease but are not yet refractory to the most effective therapeutic options.

4.4. Maintenance

Maintenance therapy can be defined as continuous exposure to a skin

directed or systemic therapy once remission has been achieved with the aim to maintain response and prevent relapse and progression. As a consequence, to qualify for the use as maintenance modalities treatments must be selected to be effective, palliative, available, and easy to apply, that is, have an excellent safety profile and not or only minimally interfering with quality of life [13] (Table 10). The use of maintenance therapy in MF/SS is supported by little evidence [204,205].

A recent prospective study demonstrated potential benefit for continuing low-dose, low-frequency PUVA in early stage MF after remission has been achieved [206]. The use of topical chlormethine for maintenance has been reported from single centres [207,208]. However, due to heterogeneity and the potential bias associated with retrospective data no conclusion as to the optimal mode of application and potential benefit of chlormethine for maintenance is possible. Furthermore, a recent report describes the long-term use of pegylated liposomal doxorubicin in individual patients [148] and a prospective trial aiming to study lenalidomide maintenance after debulking chemotherapy in advanced CTCL failed to reach its target due to insufficient recruitment [209]. An ongoing multicenter, double-blind, placebo controlled trial evaluates the use of the histone deacetylase inhibitor resminostat for maintenance in patients with advanced MF or SS that have achieved disease control with systemic therapy (the RESMAIN Study, NCT02953301) and results have to be awaited.

In practice, maintenance is commonly performed with tapering of the remission-inducing treatment (e.g. phototherapy, retinoids, IFN-α, ECP, and others) or with the introduction of a maintaining agent after remission achieved with a method that has dose-limiting toxicity, for example, TSEB and systemic chemotherapy [135]. In summary, it still applies that no guiding evidence exists on the indication and selection of maintenance in MF/SS. It should be considered mainly in patients ≥ IB (T2b) with high risk of relapse and/or progression following the principles described above and after careful counselling.

4.5. Supportive care

Supportive care in oncology is defined as health care that relieves symptoms caused by cancer or its treatment and improves quality of life [210]. Skin-specific symptoms going along with MF and SS are mainly pruritus and burning or painful skin sensations with impact on quality of life [211–213]. Furthermore, skin colonisation with Staphylococcus aureus has been described in MF and SS, possibly contributing to disease flares [214–218]. Thus, commonly applied measures to reduce staphylococcal colonisation and the risk for opportunistic infection will also be included here. Due to lack of evidence the following is a summary of expert-based practice without recommendations as to general or specific use of described measures. Decisions must be made on an individual basis and further research into this important component of patient care in CTCL is encouraged.

Table 5a
Recommendations for first-line treatment of MF stages IA, IB, and IIA.

Expectant policy (mainly T1a)		level 4
SDT	Topical corticosteroids (mainly T1a and T2a)	level 3
	Topical chlormethine	level 2
	nbUVB (mainly T1a and T2a)	level 2
	PUVA*	level 2
	Localised RT (for localised MF including pagetoid reticulosis)	level 4

MF, mycosis fungoides; SDT, skin-directed therapy.
* See text for details onrecommendations as to the use of oral, topical, and bath PUVA.

Table 5b
Recommendations for second-line treatment of MF stages IA, IB, and IIA.

Systemic therapies*	
Retinoids**	level 2
IFN-α***	level 2
TSEB (mainly T2b)	level 2
Brentuximab vedotin****	level 2
Mogamulizumab****	level 2
Low-dose MTX	level 4

MF, mycosis fungoides; TSEB, total skin electron beam therapy.
* The following agents are most commonly combined with PUVA, combinations with other modalities and with each other are also widely used.
** Including Retinoic acid receptor (RAR) and Retinoid X receptor (RXR) agonists.
*** Recombinant IFN-α has been withdrawn from the market. Replacement with peg-IFN-α is recommended. See text for details.
**** Only after failure of at least one prior systemic therapy. On the requirement of CD30 expression for brentuximab vedotin, see text.

Table 6a
Recommendations for first-line treatment of MF stage IIB.

Systemic therapies*	
Retinoids**	level 2
IFN-α***	level 2
TSEB	level 2
Brentuximab vedotin****	level 2
Mogamulizumab****	level 2
Monochemotherapy (pegylated liposomal doxorubicin, gemcitabine, pegylated liposomal doxorubicin)	level 4
Low dose MTX	level 4
Localised RT*****	level 4

MF, mycosis fungoides; TSEB, total skin electron beam therapy.
* The following agents are most commonly combined with PUVA, combinations with other modalities and with each other are also widely used.
** Including RAR and RXR agonists.
*** Recombinant IFN-α has been withdrawn from the market. Replacement with peg-IFN-α is recommended. See text for details.
**** Only after failure of at least one prior systemic therapy (i.e. during treatment of early stage disease). On the requirement of CD30 expression for brentuximab vedotin, see text.
***** Used as add-on treatment in combination with systemic and other skin directed therapies.

Table 6b
Recommendations for second-line treatment of MF stage IIB.

(Poly-)chemotherapy*	level 3
Brentuximab vedotin**	level 2
Mogamulizumab**	level 2
Allogeneic stem cell transplantation***	level 2

MF, mycosis fungoides; TSEB, total skin electron beam therapy.
* Cyclophosphamide Hydroxydaunorubicin (Doxorubicin) Oncovin (Vincristin) Prednisone (CHOP) is the most widely used regimen with a number of variants and other combinations available. Monochemotherapy may also be used in second-line.
** Only after failure of at least one prior systemic therapy (i.e. second-line after first-line TSEB is not recommended). On the requirement of CD30 expression for brentuximab vedotin, see text.
*** Should be restricted to exceptional patients, see text for details.

Table 7a
Recommendations for first-line treatment of MF stage IIIA and B.

Systemic therapies*	
Retinoids**	level 2
IFN-α***	level 2
ECP****	level 3
Brentuximab vedotin*****	level 2
Mogamulizumab*****	level 2
low dose Methotrexate (MTX)	level 4
TSEB	level 2

ECP, extracorporeal photochemotherapy; MF, mycosis fungoides; TSEB, total skin electron beam therapy.
* The following agents are most commonly combined with PUVA, combinations with other modalities and with each other are also widely used.
** Including RAR and RXR agonists.
*** Recombinant IFN-α has been withdrawn from the market. Replacement with peg-IFN-α is recommended. See text for details.
**** ECP is most commonly used in combination with skin directed and other systemic therapies.
***** Only after failure of at least one prior systemic therapy (i.e. during treatment of an earlier disease stage). On the requirement of CD30 expression for brentuximab vedotin, see text.

Table 7b
Recommendations for second-line treatment of MF stage IIIA and B.

Monochemotherapy (gemcitabine, pegylated liposomal doxorubicine)	level 3
Brentuximab vedotin*	level 2
Mogamulizumab*	level 2
Allogeneic stem cell transplantation**	level 2

MF, mycosis fungoides; TSEB, total skin electron beam therapy.
* Only after failure of at least one prior systemic therapy (i.e. second-line after first-line TSEB is not recommended). On the requirement of CD30 expression for brentuximab vedotin, see text.
** Should be restricted to exceptional patients, see text for details.

Table 8
Recommendations for treatment of MF stages IVA and IVB*.

Chemotherapy (gemcitabine, pegylated liposomal doxorubicine, CHOP and CHOP-like polychemotherapy)**	level 3
Radiotherapy (TSEB and localised)***	level 4
Brentuximab vedotin****	level 2
Mogamulizumab*****	level 2
Alemtuzumab (mainly in B2)	level 3
Allogeneic stem cell transplantation	level 2

MF, mycosis fungoides; SS, Sézary syndrome; TSEB, total skin electron beam therapy.
* For treatment of MF stage IVA1 recommendations for SS might apply.
** Monochemotherapy should be preferentially used.
*** Used alone or in combination with systemic therapies.
**** Only after failure of at least one prior systemic therapy. On the requirement of CD30 expression for brentuximab vedotin, see text.
***** Only after failure of at least one prior systemic therapy. Preferential option in B2.

4.5.1. Pruritus

Pruritus affects a large proportion of patients with CTCL and is significantly more severe in late- than in early-stage disease and in SS than in MF [219,220]. Few studies have addressed the management of CTCL-related pruritus and evidence for commonly used measures is largely extrapolated from experience with other pruritic conditions. Rare studies, case series, and other reports on anti-pruritic interventions in CTCL are heterogeneous regarding application, dose and dose-distribution and outcome measures.

A survey among the authors resulted in the following list of topicals and systemic agents that are variably used to provide comfort to the patient and relieve itch:

Topicals: various emollients; topical steroids of variable class, strength and formulation [221].

Systemic agents: antihistamines (sedating as well as H1-receptor specific agents), mirtazapine, selective serotonin reuptake inhibitors, gabapentinoids, naltrexone, and aprepitant. Among these agents only the antiemetic drug aprepitant, a neurokinin-1 receptor antagonist, has been investigated in more detail in CTCL: Although observational studies have supported its use, a small, randomised crossover trial has cast doubt on these observations, even showing increased itch with aprepitant compared to placebo [222]. In summary, as evidence is lacking careful consideration has to be given to potential adverse events

Table 9a
Recommendations for first-line treatment of SS.

ECP*	level 3
Systemic therapies in combination with ECP or PUVA	
Retinoids**	level 3
IFN-α***	level 3
Chlorambucil + prednisone	level 3
Low dose MTX	level 4

ECP, extracorporeal photochemotherapy; SS, Sézary syndrome.
* ECP can be used alone or in combination with skin directed and other systemic therapies.
** Including RAR and RXR agonists.
*** Recombinant IFN-α has been withdrawn from the market. Replacement with peg-IFN-α is recommended. See text for details.

Table 9b
Recommendations for second-line treatment of SS.

Mogamulizumab	level 2
Brentuximab vedotin*	level 2
Alemtuzumab	level 3
Chemotherapy (gemcitabine, pegylated liposomal doxorubicine, CHOP and CHOP-like polychemotherapy)	level 3
Allogeneic stem cell transplantation**	level 2

SS, Sézary syndrome.
* On the requirement of CD30 expression for brentuximab vedotin, see text.
** Should be restricted to exceptional patients, see text for details.

Table 10
Agents that can be used for maintenance after remission has been achieved in MF and SS*.

ECP
IFN-α**
Low-dose methotrexate
nbUVB
PUVA
Retinoids***
Topical chlormethine
Topical corticosteroids

MF, mycosis fungoides; SS, Sézary syndrome.
* Options are listed alphabetically and should be chosen to be effective, tolerable, easy to use, and efficient. See text for details.
** Recombinant IFN-α has been withdrawn from the market. Replacement with peg-IFN-α is recommended. See text for details.
*** Including RAR and RXR agonists.

and drug interactions before prescribing these agents in patients with MF/SS [223–226].

4.5.2. Antimicrobials

The prevalence of nasal and skin colonisation with Staphylococcus aureus (including methicillin-resistant strains) has been found to be increased in CTCL and is thought to contribute to disease progression and disease flares [214–218,227]. Colonisation was found to be highest in erythrodermic MF and SS patients [216,218]. Systemic and topical antibiotic treatment and local disinfectants were shown to reduce staphylococcal colonisation and were reportedly associated with improvement in CTCL skin involvement in a single centre retrospective review and a small prospective study, that provides translational evidence for S.aureus derived toxins as drivers of CTCL-cell proliferation [215,217]. Agents used include cephalosporins, metronidazole, amoxicillin and clavulanic acid and doxycycline. As topical antimicrobial treatments bleach and chlorhexidine baths and mupirocine containing ointment are applied by some centres [228]. Taken together, the current evidence, while intriguing, is insufficient to recommend antimicrobial treatment in MF/SS when no clinically obvious bacterial infection is present.

4.6. Treatment of elderly patients with mycosis fungoides/Sézary syndrome

From clinical practice, epidemiological and demographic data it can be assumed that a substantial proportion of patients with MF/SS are older than 65 years [22,229]. Consequently, the advances older adult oncology has made in the last decade should be incorporated in research and patient care also in CTCL and considered when applying these consensus recommendations.

We must make all efforts to make geriatric assessment the standard of care in elderly patients with MF/SS to identify those with highest risk for severe adverse events, to relate non-cancer life-expectancy with the risk of cancer related morbidity and mortality and support individualised treatment decisions considering the specific needs and perspectives of the elderly [230].

In MF/SS the situation is complicated by the fact that advanced age has been shown to be associated with a more advanced clinical stage at presentation as well as with a greater risk for disease progression, worse disease-specific survival and worse overall survival [22,23,229,231]. This may be the result of multiple factors including comorbidity, more limited treatment options (e.g. when treatment is physically demanding as with TSEB, or when it is travel intensive as with phototherapy). Further impairments might come from polypharmacy, impaired cognition, and a general increased risk of treatment-associated toxicities in this population. Moreover, CTCL patients over 60 were shown to have a higher risk for secondary haematologic malignancies, mainly Hodgkin lymphoma [232].

Due to lack of evidence, this consensus on treatment recommendations was developed and is presented in Tables 5a-9b without age-related considerations. Therefore, before use in the elderly it should be individually reconsidered based on the results of geriatric assessment and individual counselling.

Moreover, to date there is insufficient evidence for specific differences in therapeutic outcomes in elderly patients with MF/SS compared to the young. In recently published phase III trials about 50% of patients included were older than 65, corresponding well to the reported age distribution of CTCL (see above). In both trials, subgroup analyses were performed to compare responses in patients above or below 65 years of age. Reported results point to a more favourable response to brentuximab vedotin in the younger age group, while response to mogamulizmab was almost identical for both groups. Specific recommendations for oncological care in the elderly are provided by NCCN and EORTC [233,234].

5. Treatment recommendations by disease stage

Stagewise consensus recommendations for the selection of a treatment are laid out in Table 5a, 5b, 6a, 6b, 7a, 7b, 8, 9a and 9b, subdivided into first- and second-line options, where second line options should be reserved for patients who are refractory or have contraindications to first line therapy. In this context a patient is considered refractory to a specific treatment if he shows no or only minimal response and upon progression under treatment. In case of relapse after a successful course of a first line treatment patients should not be considered refractory and therapy can be reinitiated in most cases. As in the previous version of this report no division into first- and second-line options is made for stage IV disease as according to the opinion of the authors pertinent evidence as well as personal experience is insufficient to justify such a separation. The order of recommendations is based on the consensus opinion of the authors whenever possible. The individual choice of the appropriate therapy can differ and will depend on clinical presentation and treatment availability. Furthermore, in addition to clinical stage histological evidence of folliculotropism and large cell transformation can be associated with poorer outcome and more aggressive treatment might be considered [235–238].

6. Summary and conclusion

Following up on the initial report from the EORTC-CLTF on treatment of MF/SS we provide here a timely update based as before on a broad consensus among a representative group of experts from multiple European countries.

Although additional evidence has accumulated within the last 10 years, evidence levels supporting individual therapies are still low (with a few exceptions) and progress is gradual. The main changes regard newly licensed drugs (chlormethine gel, mogamulizumab, brentuximab vedotin), treatment schedules and dosages (e.g. TSEB) and the introduction of paragraphs on supportive care and considerations in elderly patients.

In general the principles on treatment selection in MF/SS as stated in the summary of the preceding version of this report still apply, namely that patients with early stage disease should primarily be treated with SDT and should they relapse to the skin receive further courses of the same or another SDT. Systemic therapy should be mainly considered for patients with advanced stages and for refractory cutaneous disease. Ideally, patients with advanced-stage disease should have the option to enter multicenter clinical trials. Finally, as treatment of MF/SS is still palliative in almost all cases maintenance of quality of life should be at the centre of therapeutic strategies and be considered alongside response rates in clinical research.

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