CCR4 in cutaneous T-cell lymphoma: therapeutic targeting of a pathogenic driver

Authors: Jan P. Nicolay [1,2,3]; Jana D. Albrecht[1,2,3]; Silvia Alberti-Violetti[4]; Emilio Berti[4]

Author affiliations: [1]Department of Dermatology, University Medical Centre Mannheim, University of Heidelberg, Mannheim, Germany; [2]Skin Cancer Unit, German Cancer Research Center (DKFZ), Heidelberg, Germany; [3]Section of Clinical and Experimental Dermatology, Medical Faculty Mannheim, Heidelberg University, Mannheim, Germany; [4]Dipartimento di Medicina Interna, UOC Dermatologia, IRCCS Ca' Granda Foundation – Ospedale Maggiore Policlinico, Milan, Italy

Corresponding author: Jan P. Nicolay

Department of Dermatology, Venereology and Allergy, University Medical Center Mannheim, Ruprecht-Karls-University of Heidelberg, Mannheim, Germany

Division of Immunogenetics, German Cancer Research Center (DKFZ), Heidelberg, Germany

Jan.Nicolay@umm.de

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List of abbreviations:

ADCC	antibody-dependent cellular cytotoxicity
AE	adverse event
ATLL	adult T-cell leukemia/lymphoma
CAR	chimeric antigen receptor
CCL	C-C motif chemokine ligand
CCR4	C-C chemokine receptor 4
CI	confidence interval
CLA	cutaneous lymphocyte antigen
CTCL	cutaneous T-cell lymphoma
DC	dendritic cell
ECP	extracorporeal photopheresis
EPOCH	etoposide prednisolone oncovin cyclophosphamide hydroxyaunorubicin
HDAC	histone deacetylase
HLA	human leukocyte antigen
HR	hazard ratio

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IFN	interferon
Ig	immunoglobulin
IL	interleukin
ITT	intent to treat
LC	Langerhans cell
MF	mycosis fungoides
Mo	month
NK	natural killer
ORR	overall response rate
PFS	progression-free survival
PTCL	primary T-cell lymphoma
PUVA	psoralen ultraviolet A
SS	Sezary syndrome
T_{CM}	central memory T cell
TEAE	treatment emergent adverse event
T_{RM}	resident memory T cell
Treg	regulatory T cell
TSEB	total skin electron beam
TTNT	time to next treatment

Abstract

New treatments are needed for patients with cutaneous T cell lymphoma (CTCL), particularly for advanced mycosis fungoides (MF) and Sezary syndrome (SS). The immunopathology of MF and SS is complex, but recent advances in tumor microenvironment understanding have identified CCR4 as a promising therapeutic target. CCR4 is widely expressed on malignant T cells and regulatory T cells (Tregs) in the skin and peripheral blood of patients with MF and SS. The interaction of CCR4 with its dominant ligands CCL17 and CCL22 plays a critical role in the development and progression of CTCL, facilitating the movement into, and accumulation of, CCR4-expressing T cells in the skin and recruiting CCR4-expressing Tregs into the tumor microenvironment. Expression of CCR4 is upregulated at all stages of MF and in SS, increasing with advancing disease. Several CCR4-targeted therapies are being evaluated, including 'chemotoxins' targeting CCR4 via CCL17, CCR4-directed chimeric antigen receptor-modified T cell therapies, small-molecule CCR4 antagonists,

and anti-CCR4 monoclonal antibodies. Only one is currently approved: mogamulizumab, a defucosylated, fully-humanized anti-CCR4 monoclonal antibody for the treatment of relapsed/refractory MF and SS. Clinical trial data confirm that mogamulizumab is an effective and well-tolerated treatment for relapsed/refractory MF or SS, demonstrating the clinical value of targeting CCR4.

Introduction

Cutaneous T-cell lymphoma (CTCL) represents a heterogeneous group of rare, extranodal non-Hodgkin's lymphomas caused by clonally derived, skin-homing T cells. CTCL usually presents primarily as localized lesions in the skin, but there can also be evidence of the disease in the blood, lymph nodes, and visceral organs [1]. The most common form of CTCL is mycosis fungoides (MF), which accounts for between 50% and 70% of CTCL and usually presents as localized skin disease characterized by patches, plaques and tumors, often accompanied by scaling and severe pruritus [1- 3]. In its early stages, characterized by limited plaques and patches, MF is an indolent disease with a favorable prognosis and limited impact on life expectancy that is often mistaken for benign dermatoses like eczema or psoriasis [1]. In many patients the disease does not progress, but in about one-third of patients the skin involvement will gradually spread and the disease becomes more advanced, with the potential for development of skin tumors and generalized erythroderma [3]. Sezary syndrome (SS) is a more aggressive, leukemic form of CTCL which in addition to erythroderma, is characterized by malignant lymphocytes with cerebriform nuclei and a typical surface marker profile (mainly loss of CD26 and/or CD7, with expression of CD158k and/or PD-1) [4-6]. Patients with SS represent approximately 5% of CTCL-cases [7] and have the most severe symptoms and poor prognosis [8, 9].

Depending on the disease type and stage, treatment for CTCL may include skin-directed therapies such as topical medication (e.g. topical corticosteroids, nitrogen mustard, topical retinoid), phototherapy (e.g. UVB, psoralen and UVA) total skin electron beam therapy) and localized radiation therapy or a systemic therapy [8, 10]. Systemic therapies include extracorporeal photopheresis, and treatment with interferons, systemic retinoids, histone deacetylase inhibitors (e.g. vorinostat or romidepsin), methotrexate or novel biologic therapies (e.g. brentuximab vedotin or mogamulizumab). Conventional systemic chemotherapy has only modest activity in CTCL and is therefore used only for patients with more advanced disease [8].

Although CTCL is well characterized, there is a lack of awareness and understanding of the disease — particularly in terms of its immunopathogenesis. New treatment options are urgently needed for patients with advanced MF or SS, as the majority of these patients have a very poor quality of life due to their disease and an expected survival of less than 5 years [2, 9]. In recent years, C-C chemokine receptor 4 (CCR4) and its ligands

have been shown to play a central role in the pathogenesis of several diseases including allergic asthma, atopic dermatitis, neurologic autoimmune disorders, and several hematologic and non-hematologic malignancies including CTCL [11]. CCR4 expression is elevated at all stages of CTCL [12-16]and increased numbers of CCR4-positive T cells are correlated with a poor disease prognosis [17]. Therefore, CCR4 has emerged as a potential disease marker and promising therapeutic target. In this review we provide an update of the role of CCR4 and its ligands in CTCL and review the development of new CCR4-targeting treatments for MF and SS.

Pathophysiology of MF/ SS, and the role of CCR4

Etiology

The etiologies of MF and SS are largely unknown, and epidemiological studies have not been able to establish any clear environmental or genetic risk factors (or identify any viral infections) associated with an increased risk of CTCL [18]. Several studies have suggested that some drugs, such as hydrochlorothiazide, may be associated with reversible, antigen-driven T cell lymphoproliferation that mimics, and may trigger, MF [18], and that discontinuation of hydrochlorothiazide should be carefully evaluated in patients whose use of this drug preceded their MF. There have also been rare reports of familial clustering of MF, and clustering of specific human leukocyte antigen (HLA) class II alleles in sporadic and familial MF. Consequently, a genetic component may be involved in the development of some CTCL [18]. To date, however, collective clinical evidence shows only that the genetic background of CTCL is heterogeneous, with no clear links to specific somatic mutations, fusion proteins or copy number variants [3, 19]. Nonetheless, genomic studies of patients with MF or SS have identified somatic mutations in genes involved in various cellular processes (including DNA damage response, epigenetic regulation, cell cycle control, programmed cell death) and signaling pathways (including T cell receptor signaling, and immune signaling pathways), indicating that there may be a wide variety of possible underlying causes [3].

Origin of malignant T cells and immunopathogenesis in CTCL

The skin microenvironment is crucial to the pathogenesis of CTCL. During the development (and through the progression) of MF, a disruption in the balance of the skin's immune-surveillance response allows the migration of malignant T cells to the skin [2]. In healthy individuals, when naive T cells encounter antigen-presenting cells within the lymph nodes, they are activated as part of the adaptive immune response. Activated T cells subsequently undergo clonal expansion, followed by differentiation into subsets with varying roles. Antigen-specific central memory T cells (T_{CM}) form a reservoir within the lymph nodes to provide long-term immune surveillance, whereas effector memory T cells express the E-selectin ligand cutaneous lymphocyte

antigen (CLA) and chemokine receptors (such as CCR4, CCR8, and CCR10) that facilitate extravasation of T cells into the skin [2, 18-20]. Thus, in healthy skin, most of the T cells are skin-homing resident memory T cells (T_{RM}) localized within the dermis and circulation (**Fig. 1a**) [21-23]. Effector memory T cells migrate outside the lymph system to multiple sites, including the skin, where a residual number will remain as tissue-T_{RM} [18].

In patients with MF, the clonal malignant T cells that accumulate within the dermis and epidermis are commonly derived from T_{RM} and express high levels of skin-homing receptors such as CLA and CCR4; this explains why they often remain localized within the skin (**Fig. 1b**) [18]. T_{RM} are CD69-positive cells which express CD103 mainly in the epidermis, where their effector function is greater, but their proliferative capacity is lower compared to CD103-negative T_{RM} which is found mainly in the dermis [20]. In contrast, malignant T cells in SS and in cases of MF with secondary leukemic progression, appear to be derived from T_{CM} due to their co-expression of L-selectin and CCR7. T_{CM}, which have a long life, are resistant to apoptosis and have the ability to circulate from the peripheral blood to the skin and lymph nodes [18]. Another subset of malignant T cells are migratory memory T cells (T_{MM}): T_{MM} are characterized by an intermediate cytokine-production profile that is between that of T_{RM} and T_{CM} [20]. Compared to T_{CM}, T_{MM} recirculate relatively slowly between the blood and skin [20]. T_{MM} are associated with lesions with ill-defined borders and have been identified in both advanced cases of MF and in SS [18].

CTCL pathophysiology involves aberrant trafficking of malignant T cells from the blood to the skin (**Fig. 1c, Fig. 1d**), and, as the disease progresses, to the lymph nodes and viscera [3]. Regulatory T cells (Tregs) are also important in the pathogenesis of CTCL: Tregs can suppress anti-tumor responses through the release of chemokines into the tumor microenvironment, resulting in an immunosuppressive tumor microenvironment in which tumor cells are able to escape from immune surveillance, which in turn allows tumor growth, especially in late stages of CTCL [24].

The correlation between Treg numbers and MF stage is controversial discussed in the literature. Expression of FOXP3, a master regulator of Treg, was found highly expressed in early-stage MF compared to advanced stages and unspecified CTCL. It correlates with an improved survival and its expression declined with tumor progression [25, 26]. In contrast, others could not confirm this correlation between Treg number and MF stage or progression nor MF diagnosis itself [27, 28]. In SS, expression of FOXP3 was found on malignant cells in the skin and blood of some patients, suggesting they indicate a subset of Sézary patients [29]. In addition, the suppressive function and typical marker profile of Treg has been found to be altered in many MF and SS

patients [28]. These varied findings could be explained by dividing T cells with Treg properties in MF and SS into four subsets as described in Table 1 [30].

Other cytokines and signaling pathways have been intensively investigated in CTCL. For example, the proinflammatory cytokine IL-17 has been seen to be expressed by malignant T cells in a subset of CTCL and its upregulation through the JAK/STAT3 pathway may have a role in disease progression [31, 32]. Aberrantly activated JAK/STAT3 signaling itself has also been found to play an important role in CTCL cell survival and proliferation in CTCL patient cells and a mouse model [33, 34]. Furthermore, in recent years, the cutaneous microbiome and bacterial colonization of the skin gained increasing focus in CTCL pathogenesis. Especially colonization of the skin with Staphylococcus aureus has been found to be involved in the development and progression of CTCL, which could be confirmed in CTCL patients and mouse models [33, 34]. Malignant T cells are able to escape immune surveillance and enable disease progression through aberrant ligand expression on the cell surface, e.g. cytotoxic T lymphocyte antigen-4 (CTLA-4) and programmed death- ligand 1 (PD-L1) [35, 36]. These ligands compete to bind with immune receptors on antigen-presenting cells (APCs) and in this way are able to downregulate T cell activation and reduce the immune response to the malignant cell.

CCR4 has been identified as an important therapeutic target for the treatment of CTCL [3]. Studies comparing patients with MF or SS to healthy individuals have shown that CCR4 is highly expressed on malignant T cells taken from the blood and skin of patients with MF or SS and that primary CCR4 ligands are also abundant in skin lesions of these patients [12, 37]. It has recently been reported that MF / SS –patients, who have high levels of CCR4 expression, have a poor survival prognosis [17], providing further validation for CCR4 as an important biomarker of disease progression and potential treatment target. Importantly, CCR4 is expressed at high levels on malignant T cells at all stages of CTCL (patch, plaque, and tumor) and facilitates the migration of skin-homing malignant T cells into the dermis and epidermis. It has been shown that in CTCL, CCR4 is upregulated due to increased activity of the transcription factor *FRA-2* [11]. CCR4 may also harbor mutations in its C-terminal that cause truncation and leads to a gain in receptor function due to increased migration towards the CCR4-associated C-C chemokine receptor ligands (CCLs) CCL17 and CCL22 and impaired internalization of CCR4 [38]. The proportion of CCR4-positive malignant T cells increases as the disease becomes more advanced, accompanied by dynamic changes in the skin microenvironment [21-23]. The early stages of MF are characterized by a Th1 cytokine environment with elevated levels of interleukin (IL)-2, IL-12 and interferon-gamma. However, as CTCL becomes more advanced and malignant T cells accumulate within the skin, the microenvironment becomes Th2 dominant (this is particularly the case in SS), with high levels of the cytokines

IL-17, IL-13, and IL-26, creating a proinflammatory environment that also indirectly supports tumor growth. The shift from Th1 to Th2 cytokine expression is accompanied by an increase in CCR4 and CCR10 expression on malignant T cells [39]. Therefore, the advanced stages of MF and SS are characterized by a migration of CCR4- and CCR10-positive malignant T cells to the skin, driven by increased expression of the CCL17 and CLA ligands on Langerhans cells and keratinocytes, respectively (**Fig. 2**) [40]. In the 'tumor' stage of MF and in SS, the lymphatic homing receptor CCR7 is also expressed, promoting migration of malignant T cells into the lymphatic system, leading to metastasis and blood involvement [23].

Among the various T cell subsets, CCR4 is predominantly expressed by Th2 cells, CD4-positive cells, CLA-positive skin-homing T cells and Tregs [27, 41]. CCR4 has several CCLs: CCL3, CCL5, CCL17 and CCL22. The most important CCLs for the pathogenesis of CTCL, and the primary ligands for CCR4, are CCL17 (also known as *thymus and activation regulated chemokine* or TARC) and CCL22 (also known as *macrophage-derived chemokine* or MDC) [41]. With regard to the other CCR4-associated CCLs, CCL3 (also known as *macrophage inflammatory protein-1 alpha*) is involved in recruiting immune cells to tumors, regulating the homing of dendritic cells to lymph nodes, and inducing antigen-specific T cell responses [42]. CCL5 (also known as *regulated on activation, normal T cell expressed and secreted* or RANTES) is involved in leukocyte recruitment to inflammatory sites, and in the activation and proliferation of natural killer (NK) cells [43]. Thus, both of these are also relevant in the pathogenesis and the microenvironment of CTCL.

The CCR4–CCL17/CCL22 axis in CTCL

CCL17 and CCL22 are skin-derived CCLs of CCR4 that are upregulated in the skin of patients with MF or SS [12, 21]. CCL17 is produced by dendritic cells, endothelial cells, keratinocytes, and fibroblasts [44], and facilitates recognition of circulating malignant CCR4- and CLA-expressing T cells, promoting their attachment to the endothelial surface [45]. CCL22 is produced by dendritic cells and macrophages, and works in concert with CCL17 to tether malignant T cells to the epidermis/dermis and guide their subsequent migration through the endothelium [41]. Importantly, CCL22 is also involved in the recruitment of Tregs into the tumor microenvironment, which facilitates the avoidance of immune surveillance by suppressing tumor-specific effector T cell-mediated immunity [46]. Moreover, early studies have demonstrated that the cytotoxic activity of NK cells is decreased in patients with MF and SS [47, 48], possibly related to increased Treg activity. Studies have shown that high expression levels of CCL22 by Langerhans cells in the epidermis may be involved in the aggregation of CCR4-positive malignant T cells in the skin, leading to the development of the Pautrier's microabscesses that are characteristically observed in patients with MF [12]. Overall, during the pathogenesis of

CTCL, the parallel increases in CCL17 and CCL22 expression, combined with upregulated expression of CCR4 on malignant T cells, facilitate trafficking of cells into the skin and promote disease progression [12, 21].

Expression and upregulation of CCR4 and its ligands at the different stages of CTCL

CCR4

The expression of CCR4 is upregulated in epidermotropic cells of the skin during the 'patch' and 'plaque' stages of CTCL, and subsequently in large transformed cells at the 'tumor' stage of the disease [12, 21, 37]. In recent studies, CCR4 immunostaining was observed in 34% of MF and 42% of SS cases [17]. The level of CCR4 expression, however, appears to vary widely, with studies reporting a range of immunohistochemical expression in the skin of patients with CTCL of between 14% and 97% [49]. This might, at least in part, be explained by methodological limitations and heterogeneity of methods used for the CCR4 detection in different publications. Nevertheless, it has to be stated that in clinical studies in which the CCR4 expression on CTCL patient T cells was measured by sensitive immunohistochemistry on paraffin samples, the expression ranged between 90% and 100% and was thus almost universal. This data reflects the real-life situation best due to its superior method and the high patient numbers [49]. It has also been shown that high levels of CCR4 expression correlate with the risk of disease progression [22] and that the number of CCR4-positive T cells increases in the later, more aggressive stages of CTCL [3]. In addition, and when compared to those with inflammatory erythroderma or healthy controls, CCR4 expression on CD4-positive T lymphocytes in the blood is significantly higher in patients with SS [39]. A possible explanation for this may be related to the different T memory cell subsets, as described by Watanabe et al [20]. Blood analyses have shown very high levels of CCR4 expression on the malignant T cells and Tregs of patients with MF or SS [14, 16]. For example, for patients with relapsed/refractory MF or SS in the phase 3 MAVORIC study of mogamulizumab, CCR4 expression was observed in 97% of patients, with a median percentage of CCR4-positive cells of 80% [16].

CCR4 expression is also upregulated in a subset of suppressive CD4-positive Tregs that also express the transcription factor FoxP3, and which are associated with tumor escape from host immunity in CTCL [2, 18]. A subset of SS patients has been identified with a Treg-like clone, although the prognostic significance of this observation is not yet understood [18]. Novel CTCL treatments targeting CCR4 are expected to act by depleting these effector Tregs, which could potentially improve anti-tumor response and clinical outcomes by restoring immune surveillance.

CCL17 and CCL22

Alongside the increased expression of CCR4, CCR4-associated CCL17 and CCL22 are also overexpressed during the 'patch', 'plaque', and 'tumor' stages of MF, with higher levels having been observed in patients with more aggressive disease [21]. Production of CCL17 and CCL22 by endothelial cells and dendritic cells, respectively, has been shown to be upregulated both in inflamed skin and in the blood of patients with MF and SS [12, 21]. In addition to promoting the aggregation of CCR4-positive skin-homing T cells in skin lesions at the initial stages of CTCL [12], CCL17 and CCL22 may have other cancer-promoting effects. These cytokines may attract Tregs, immunosuppressive inhibitory macrophages, and NK T cells into the tumor microenvironment, thereby facilitating the escape of malignant T cells from normal immune surveillance, and promoting tumor cell proliferation [50]. Additionally, *in vitro* studies of cells derived from patients with MF suggest that CCL17 and CCL22 may enhance the survival of malignant T cells, further supporting the importance of the CCR4–CCL17/CCL22 axis in the pathophysiology of CTCL [51] and its validity as a therapeutic target in CTCL.

Therapeutic approaches targeting CCR4 in CTCL

Several strategies for targeting CCR4 have been developed. An early approach that attempted to target CCR4 using a 'chemotoxin' was the fusion of CCL17 to a neurotoxin or truncated exotoxin. The aim was to deliver the toxin into the cytoplasm of malignant T cells via CCR4 [49]. *In vitro* studies and preclinical studies in mice have demonstrated the effectiveness of this approach in killing CTCL malignant T cells [50]. Following the success of treating B-cell lymphomas with chimeric antigen receptor (CAR)-modified T cells, another approach is to target CCR4 with CAR-modified T cells [49]. Donor T cells modified *ex vivo* with a CCR4-targeted CAR have been shown to lyse patient-derived tumor cell lines *in vitro* and in a mouse xenograft model. This possible future treatment option warrants further preclinical study [52].

Small-molecule CCR4 antagonists

Significant research effort has also been expended in trying and develop small-molecule CCR4 antagonists as new treatments for CTCL. However, CCR4 pharmacology is highly complex and CCR4 exhibits multifaceted biological responses to its dominant ligands, CCL17 and CCL22. These factors have led to some unexpected findings during early preclinical research into small-molecule CCR4 antagonists – for example, although the agents disrupted cytokine signaling with CCR4, opsonization did not occur with some of the CCR4 inhibitors [11]. Two classes of small-molecule CCR4 inhibitors are currently being studied: arylsulfonamides, and amine antagonists [11]. Arylsulfonamides, appear to be unable to induce CCR4 internalization, unlike the amine

antagonists, which have this ability due to a different CCR4 binding site [11]. Thus, despite the initial promise of this class of agents, to date only one small-molecule CCR4 inhibitor has made it to clinical trial: FLX475.

FLX475

A small-molecule CCR4 antagonist designed to inhibit the migration of Tregs into tumors, FLX475 is currently being evaluated in a phase 1/2 study as monotherapy and in combination with the checkpoint inhibitor pembrolizumab in different advanced malignancies (**Table 2**) [53, 54].

Monoclonal antibodies targeted to CCR4

The most successful CCR4-targeted treatment approach to date has been the development of monoclonal antibodies targeted to CCR4, which induce antibody-dependent cellular cytotoxicity (ADCC) by recruiting the body's own immune cells to induce lysis of malignant T cells [49]. So far, only one antibody has already advanced to clinical use: mogamulizumab.

Mogamulizumab

Mogamulizumab is a fully humanized, defucosylated anti-CCR4 antibody that was approved in 2018 by the US Food and Drug Administration (FDA) for the treatment of relapsed/refractory MF and SS after at least one prior systemic therapy [55] and by the European Medicines Agency (EMA) for adult patients with MF or SS who have received at least one prior systemic therapy [56].

Mogamulizumab has a high affinity for the N-terminus of CCR4. Once bound to CCR4, mogamulizumab is not internalized, and does not drive complement-dependent cytotoxic activity or induce apoptosis of tumor cells. Instead, mogamulizumab exerts potent anti-tumor effects through ADCC, inducing cell-mediated lysis of CCR4-expressing malignant T cells and Tregs [57]. Analyses of peripheral blood from patients with previously treated, advanced MF or SS who participated in the phase 1 and 2 clinical trials of mogamulizumab showed high levels of positivity for CCR4 in circulating malignant T cells and Tregs before mogamulizumab treatment [14]. Following mogamulizumab treatment, decreased levels of malignant T cells and Tregs were observed, accompanied by an increase in NK cells and NK cytotoxicity, suggesting a post-treatment improvement in immune function [14].

The safety and efficacy of mogamulizumab have been established in several clinical studies (**Table 2**) [16, 57, 58]. An open-label, multicenter phase 1/2 study of mogamulizumab, 1.0 mg/kg per week, in patients with previously treated MF (22 patients) or SS (19 patients) reported durable clinical responses with an overall response rate of 36.8% after 4 weeks of treatment; a higher response was observed in patients with SS vs MF (47.1% vs 28.6%, respectively) [57]. The exact reasons for this difference are not yet known and are subject to

further study. Most patients in this study (~65%) had stage IV disease, the most advanced stage of disease [57]. Mogamulizumab was well tolerated, with no hematologic adverse events reported [57]. Drug-related skin rash was the most common reason for discontinuation of mogamulizumab [57]. Similar results were obtained after 8 weeks of mogamulizumab, 1.0 mg/kg once weekly, in a Japanese multicenter phase 2 study of patients with CCR4-positive relapsed CTCL or peripheral T-cell lymphoma [58]. In this study, an overall response rate of 38% was observed in the CTCL group; mogamulizumab was well tolerated, and most adverse events were mild and reversible [58].

Most recently, in the open-label, randomized, active-controlled phase 3 MAVORIC study (NCT01728805), 372 patients with relapsed/refractory MF or SS were randomized to treatment with either mogamulizumab (186 patients) or the histone deacetylase inhibitor vorinostat (186 patients) [16]. Mogamulizumab was dosed at 1.0 mg/kg, and given intravenously once a week for the first 28-day cycle and then on days 1 and 15 of subsequent cycles until disease progression. Vorinostat was given orally at a dose of 400 mg/day. Patients treated with vorinostat who experienced intolerable toxicity or disease progression following two treatment cycles were able to cross over to the mogamulizumab treatment arm. Mogamulizumab treatment resulted in a significantly longer progression-free survival (median 7.7 months vs 3.1 months, respectively; hazard ratio 0.53, $P<0.0001$) and a significantly greater overall response rate compared to vorinostat (28% vs 5%, respectively; $P<0.0001$) [16]. Compartmental treatment responses were superior for mogamulizumab compared to vorinostat in the skin, peripheral blood, and lymph nodes. No difference was seen for viscera, but there was a very limited number of patients with visceral disease at baseline. Exploratory analyses showed no correlation between the levels of CCR4 expression in the skin and the overall response rate to mogamulizumab [16].

No new safety concerns were identified in the safety population (370 patients) of the MAVORIC study. In the mogamulizumab treatment group, infusion reactions, skin rash, and fatigue were the most common adverse events of any cause or grade, and skin rash was the most common cause of treatment discontinuation. Grade 3 or 4 ‘Any cause’ adverse events occurred in 75/184 patients (41%) in the mogamulizumab group and in 76/186 patients (41%) of the vorinostat group [16]. Treatment-related serious adverse events occurred in 35/184 patients (20%) in the mogamulizumab group, the most common of which were pneumonia (4/184 patients, 2%) and pyrexia (4/184 patients, 2%) [16]. Overall, the results from the MAVORIC study show that mogamulizumab provides an effective and well tolerated new treatment option for patients with previously treated MF or SS, supporting the validity of CCR4 as an important therapeutic target for CTCL.

In addition to being approved by the FDA (treatment of relapsed/refractory MF and SS ≥ one prior systemic therapy [55]) and EMA (adult MF/SS patients ≥ one prior systemic therapy), mogamulizumab was approved in Japan for adult T-cell leukemia/lymphoma in 2012 and for peripheral T-cell lymphoma and CTCL in 2014 [59]. In adult T-cell leukemia/lymphoma CCR4 is expressed abundantly, whereas for peripheral T-cell lymphoma expression seems to correlate with advanced or relapsed/refractory disease, in particular with blood involvement [59]. Mogamulizumab has also been evaluated in Phase 1 clinical trials for advanced solid tumors (including non-small-cell lung cancer, ovarian cancer and pancreatic cancer) in combination with other monoclonal antibodies: checkpoint inhibitors (nivolumab, durvalumab, tremelimumab) and a 4-1BB agonist (utomilumab). In all cases, a depletion of CCR4-expressing Tregs was seen [61-63]. It is suggested that combining an anti-PD-1 monoclonal antibody with mogamulizumab provides an antitumor activity and a potentially effective option in cancer immunotherapy [62]. Acceptable safety profiles were also demonstrated, providing further support for the evaluation of mogamulizumab in other diseases associated with the expression of CCR4 [61-63]. Of course, these results have to be confirmed in Phase II and III trials, as they only reflect the phase I study experience. Especially with respect to efficacy and long-term outcomes, it is too early to make definite statements on the use of combination therapies with anti-CCR4. Nevertheless, the preclinical data, the mechanistic rationale and the first early clinical study data promote Mogamulizumab as a promising agent in targeted combination therapies in different tumor entities, especially CTCL and ATLL [64-67, 69-71]. Potential combination partners include skin-directed therapies, etoposides, immunotherapy, HDAC inhibitors, chemotherapy and engineered T cells. In contrast, preclinical data indicate, that bexarotene, a third-generation retinoid X-receptor-selective retinoid (‘rexinoid’) that is a standard therapy already in wide use in the treatment of CTCL, might be a less suitable candidate for combination therapy as it suppresses CCR4 expression in SS-cells *in vitro*, although a recent case report showed a successful use of bexarotene and mogamulizumab combination therapy [68, 76] (**Fig. 3**).

Conclusions

An improved understanding of the complex biological processes in which CCR4 is involved, supported by a greater understanding of the role of CCR4, CCL17 and CCL22 in the immunopathology of CTCL, has led to its identification as an important and promising therapeutic target. As such, a new treatment option for patients with MF and SS — a group of patients for who treatment remains a clinical challenge — has been identified. Accumulating evidence confirms that CCR4 is expressed to varying degrees on malignant T cells and Tregs across all stages of CTCL, and at consistently higher levels in patients with later stage, more aggressive disease. Consequently, this makes CCR4 even more appealing as a target for patients with advanced MF and SS. In

addition, studies are ongoing to establish CCR4 expression as a prognostic marker, meaning anti-CCR4 targeted treatments in development could hold significant promise for improved outcomes in patients with CTCL across the spectrum of the disease.

In terms of the currently available treatment options, the monoclonal antibody mogamulizumab has emerged as the first CCR4-targeted therapy to demonstrate potent anti-tumor effect, with clinical trial data confirming that it is an effective and well-tolerated treatment option for patients with previously treated or relapsed/refractory MF or SS and demonstrating the clinical value of targeting CCR4 to provide novel treatment options for all patients with CTCL.

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Conflicts of interest

J. P. Nicolay has received travel and congress participation funding from TEVA and Novartis as well as consulting fees from TEVA, Almirall, Biogen, Novartis, Kyowa Kirin, Innate Pharma, Takeda and Actelion. J. D. Albrecht has no conflicts to disclose. S. Alberti-Violetti received travel grants from Takeda and consulting fees from Kyowa Kirin. E. Berti has received travel grants from Takeda.

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Table 1. Subsets of T cells determined by Treg properties and markers

Cell Type	**Cell Function**	**Reference**
Functional Suppressor	T cell immune response is physiologically suppressed	28
Malignant	CTCL cells themselves express Treg markers	28
Tumor-killing	High Treg counts correlate with improved overall survival	28
Incompetent	Tregs function poorly and contribute to the appearance of autoimmune symptoms	28

Table 2. Outcomes of clinical trials involving CCR4-targeting therapeutics

Trial	Purpose	Short-term outcomes	Long-term outcomes	Reference
FLX475 **NCT03674567**	• Phase 1/2 trial on dose escalation and cohort expansion, examining use both as monotherapy and in combination with pembrolizumab	• Estimated study completion date August 2021	• N/A	51, 52
Mogamulizumab **NCT00888927**	• Phase 1/2 trial to investigate the maximum safe dose for subjects with previously treated PTCL or CTCL	• Majority of TEAEs were grade 1/2 • No significant hematological effects were seen • ORR was 36.8% in 38 evaluable patients (MF: 28.6%[21/38], SS: 47.1%[17/38]) • Complete responses seen in 11 patients	• N/A	55
Mogamulizumab **NCT01192984**	• Phase 2 trial to investigate overall response rate in patients with relapsed CCR4-positive PTCL or CTCL	• Clinically meaningful antitumor activity was seen • Toxicity profile was acceptable	• N/A	56
Mogamulizumab **(MAVORIC**	• Phase 3 trial to compare mogamulizum	• Superior investigator-assessed PFS	• AE type and frequency were consistent with	14, 57

study) **NCT01728805**	ab treatment with vorinostat treatment in CTCL patients	for mogamulizumab compared with vorinostat (median 7·7 mo [95% CI 5·7–10·3] vs 3·1 mo [2·9–4·1]; HR 0·53, 95% CI 0·41–0·69; *P*<0·0001) (Kim 2018) • Grade 3–4 AEs were similar between treatment arms (41% [75/184] of patients vs 41% [76/186] of patients in the mogamulizumab and vorinostat groups, respectively) (Kim 2018) • In the ITT population, median TTNT was longer for mogamulizumab patients at 11 mo (95% CI, 8.8-12.6) compared to vorinostat at 3.5 mo and consistently longer for MOGA vs VORI across disease stage grouping or by disease type. (TTNT -	those in the primary analysis in both treatment arms. • AE types and frequencies considered attributable to mogamulizumab (per Investigator assessment) included infusion-related reaction (33.2% [61/184]), drug eruption (23.9% [44/184]), and fatigue (18.5% [34/184]), and for vorinostat, diarrhea (55.4% [103/186]), nausea (38.2% [71/186]), and fatigue (33.3% [62/186]). • For patients who crossed over from vorinostat to mogamulizumab (n=135), the AEs most frequently reported and attributable to mogamulizumab were infusion-related reaction (37.8% [51/135]), drug eruption (24.4% [33/135]), fatigue (7.4% [10/135]), increased	

		Kim 2019) • Median TTNT was 10 mo (95% CI: 8.0-12.6) for patients who crossed over from vorinostat to mogamulizumab. (TTNT - Kim 2019)	alanine aminotransferase (7.4% [10/135]), and increased aspartate aminotransferase (7.4% [10/135]). • Similar discontinuation rates due to AEs were seen between both treatment arms and crossover patients (mogamulizumab, 21.7% [40/184]; vorinostat, 23.7% [44/186]; crossover, 25.9% [35/135]). • The most common AEs which led to discontinuation were: mogamulizumab, drug eruption (7.1% [13/184]) and vorinostat, fatigue (4.3% [8/186]). • Similar drug-related serious TEAEs rates were seen between both treatment arms and crossover patients (mogamulizuma	

			b, 19.6% [36/184]; vorinostat, 16.7% [31/186]; crossover, 11.9% [16/135]).	

AE, adverse event; CI, confidence interval; CTCL, cutaneous T-cell lymphoma; HR, hazard ratio; ITT, intent to treat; MF, mycosis, fungoides; mo, month; ORR, overall response rate; PFS, progression-free survival; PTCL, primary T-cell lymphoma; TEAE, treatment emergent adverse event; TTNT, time to next treatment; SS, Sezary syndrome.

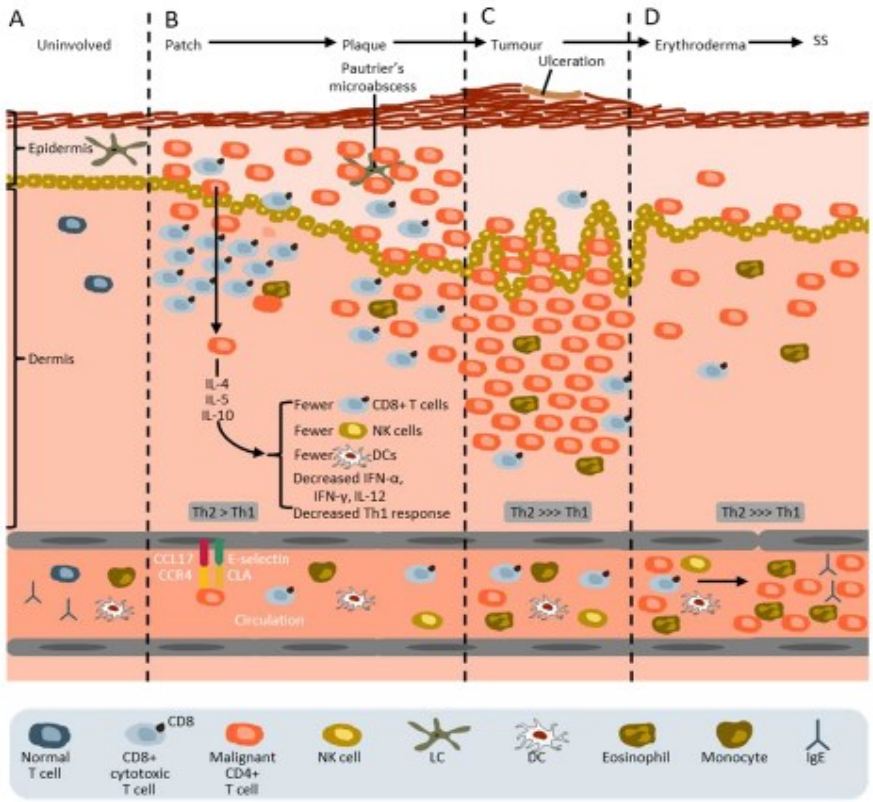


Fig. 1 Summary of the pathogenesis of MF and SS. It should be noted that MF and SS might be independent forms of CTCL. Additionally, there is an increase in the proportion of CCR4-positive malignant T cells as the disease advances [19-21]. a.) Normal skin with only skin-homing T cells in dermis and in circulation. b.) Patch and plaque MF: more, especially malignant, T cells home to the skin via interaction of expressed CCR4 and CLA with CCL17 and E-selectin, instigating an immune response. These CTCL cells influence their microenvironment: Th2 cytokine production increases and Th1 cytokine production decreases. The Th2 increase leads to an increase in IL-4, IL-5 and IL-10 which in turn leads to a decrease in CD8+ T cells, NK cells, DCs, IFN-α, IFN-γ and IL-12, as well as other cytokines. c.) In Tumor MF, this effect escalates, so that the infiltrate is comprised mainly of malignant T cells and some CD8-positive cells, an increase in eosinophils, and greatly enhanced Th2 cytokine production. d.) Erythroderma in MF and SS, with detectable circulating, but fewer malignant T cells, again with an increase in eosinophils and greatly enhanced Th2 cytokine production. DC, dendritic cell; IFN, interferon; Ig, immunoglobulin; IL, interleukin; LC, Langerhans cell. *Adapted with permission from Kim EJ, et al (2005). J Clin Invest 115:798-812. doi: 10.1172/JCI24826 © 2005, American Society for Clinical Investigation.*

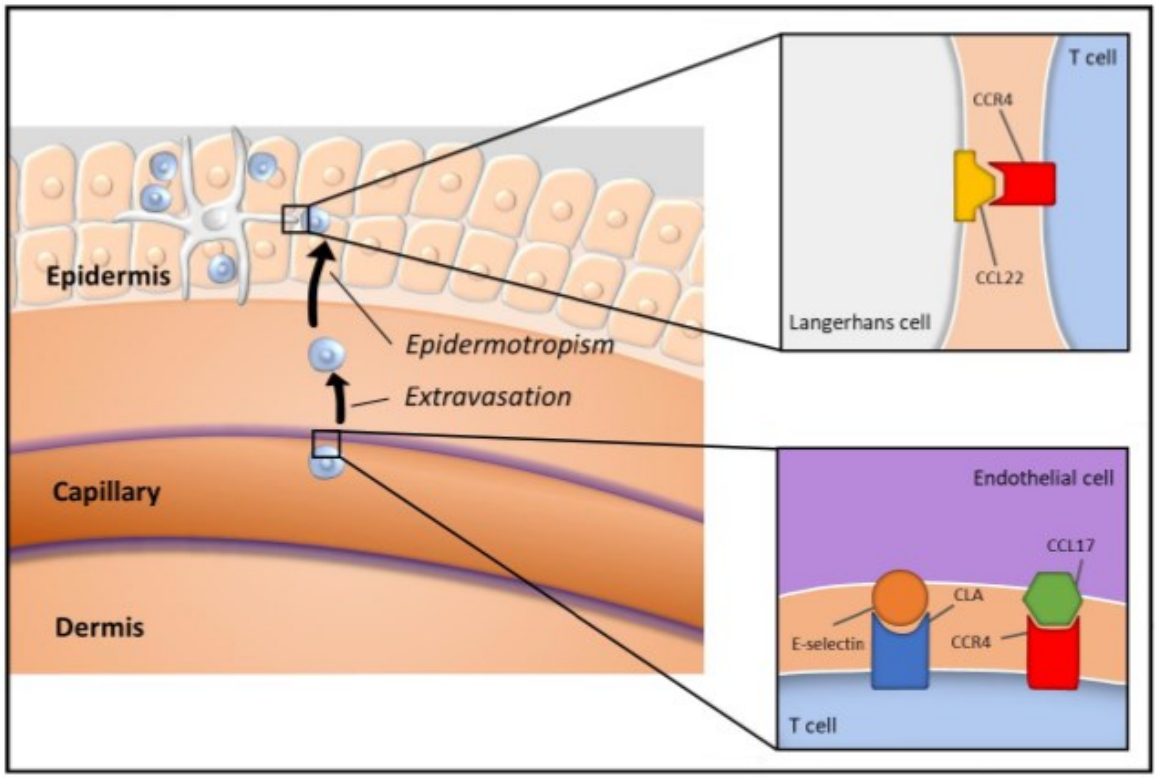


Fig. 2 Extravasation of malignant T cell to the epidermis. Migration of malignant CTCL cells from the blood vessel into the epidermis follows a two-step process, with CCR4 and its interaction partners involved in both of these steps: 1. Extravasation occurs through malignant T cells expressing CCR4 and CLA which bind to CCL17 on endothelial cells and E-selectin, respectively, allowing them to leave the capillary and enter the dermis. 2. Trafficking of the T cells through the endothelium to the epidermis, epidermotropism, is then mediated by CCL22 (present on Langerhans cells in the epidermis) which binds to a separate site on CCR4.
Based on Girardi M, et al (2004). N Engl J Med. 2004;350(19):1978-1988. doi:10.1056/NEJMra032810

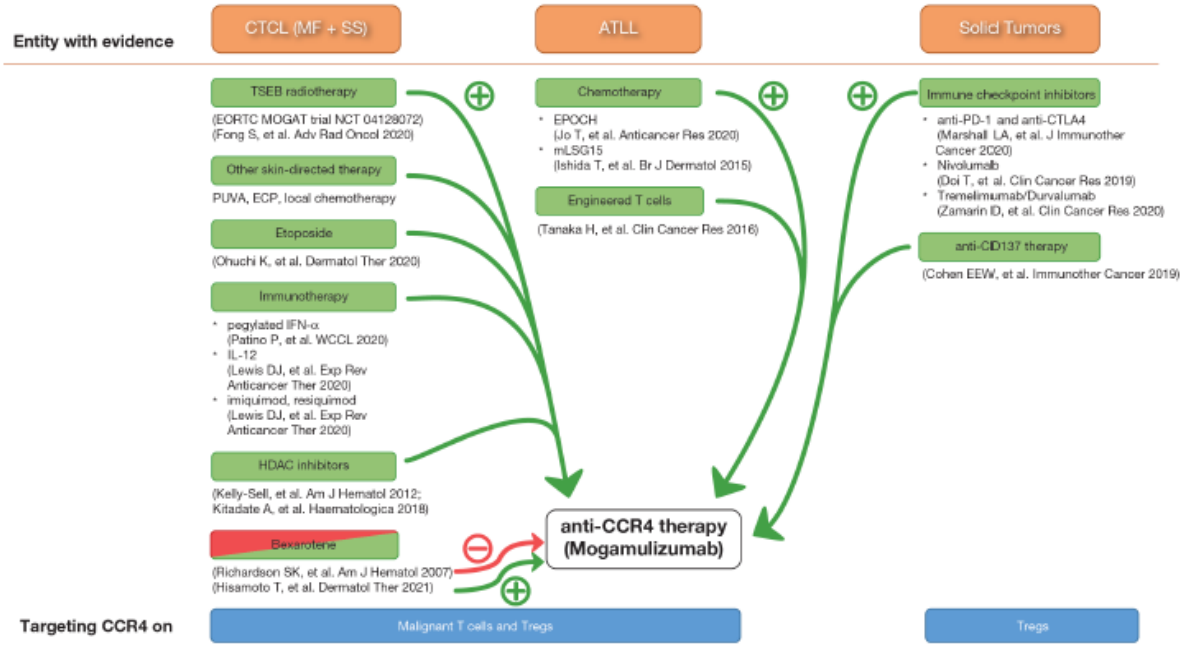
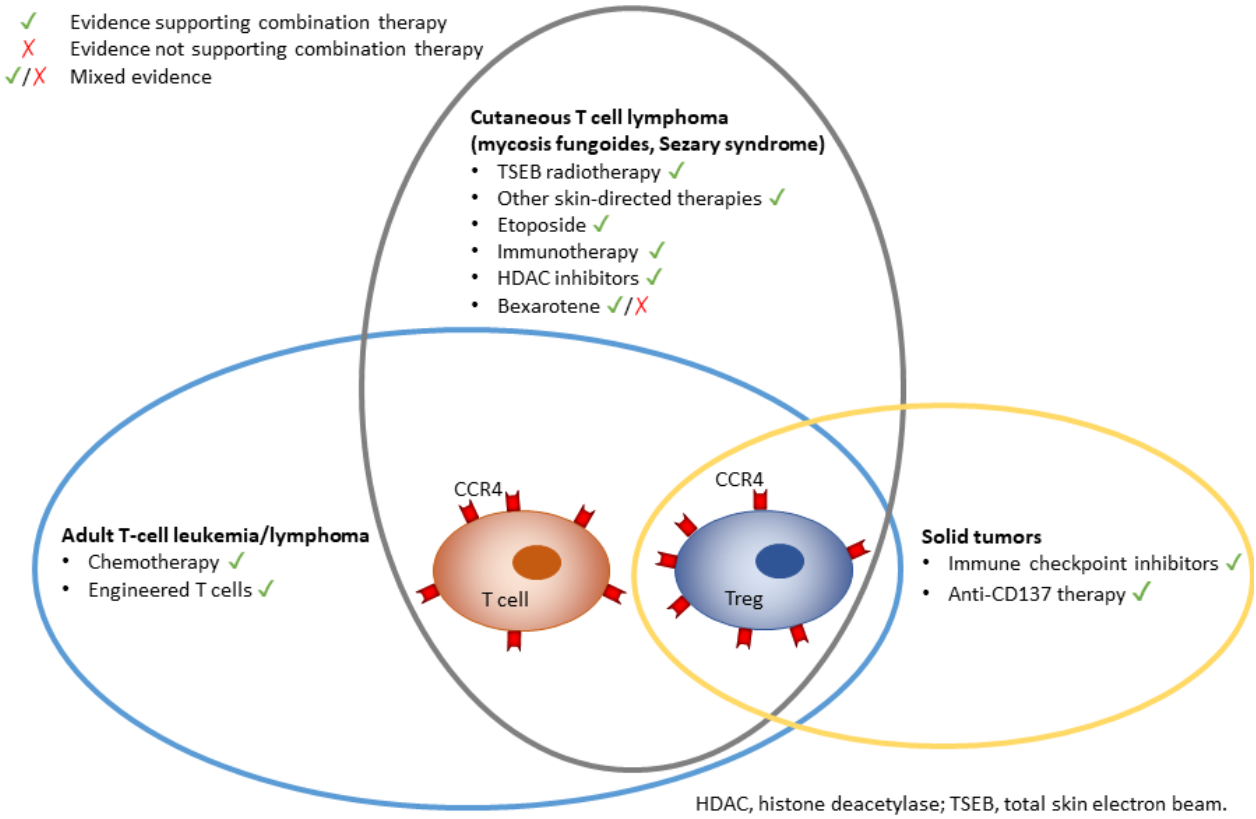


Fig. 3 Potential combination partners for anti-CCR4 therapy. There is currently evidence for potential therapeutic combination partners for anti-CCR4 therapy in CTCL (MF and SS), ATLL and solid tumors (including non-small-cell lung cancer, pancreatic cancer and ovarian cancer) from the current literature. For CTCL and ATLL, CCR4-expressing malignant T cells and Tregs are both targeted, whereas for solid tumors, mainly CCR4-expressing Tregs are targeted. There is evidence both for and against the use of bexarotene as a therapeutic partner. ATLL, adult T-cell leukemia/lymphoma; CCR4, C-C chemokine receptor 4; CTCL, cutaneous T-cell lymphoma; ECP, extracorporeal photopheresis; EPOCH, etoposide prednisolone oncovin cyclophosphamide hydroxyaunorubicin; HDAC, histone deacetylase; IFN, interferon; IL, interleukin; MF, mycosis fungoides; PUVA, psoralen ultraviolet A; SS, Sezary syndrome; TSEB, total skin electron beam.

Graphical abstract

C-C chemokine receptor 4 (CCR4) is expressed on malignant T cells in cutaneous T cell lymphoma (CTCL). CCR4 is also expressed on T regulatory cells (Tregs) and accumulation of Tregs by tumours is a known mechanism of immune escape in CTCL and other cancers. Anti-CCR4 therapy holds potential as an antitumour treatment both as monotherapy and in combination with other existing therapies.



HDAC, histone deacetylase; TSEB, total skin electron beam.