ORIGINAL REPORT

Systemic Targeted Therapies in Patients with Relapsed/Refractory Advanced Stage Cutaneous T-cell Lymphoma: A Real-world Single-centre Case Series

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Cutaneous T-cell lymphomas are a heterogeneous group of non-Hodgkin lymphomas. Early stages are often controlled with skin-directed therapy, such as topical corticosteroids, topical chlormethine gel, or UV therapy, whereas advanced stages often warrant a more aggressive approach with systemic antibody targeted therapy including mogamulizumab, brentuximab vedotin, or alemtuzumab. A retrospective cohort case series of 27 patients from Aarhus University Hospital, Denmark is presented, evaluating real-world outcomes of patients with cutaneous T-cell lymphomas treated with intravenous systemic targeted therapies from 2013 to 2023. The median age was 72 and the majority had Sézary syndrome or mycosis fungoides. All patients had relapsed/refractory advanced stage cutaneous T-cell lymphoma. Six patients received mogamulizumab, 12 patients received brentuximab vedotin, and 15 patients received alemtuzumab. Six patients received more than 1 of the systemic targeted treatments. Overall response rates were 78% for mogamulizumab, 65% for brentuximab vedotin, and 61% for alemtuzumab. Median time to progression was 2.5, 4, and 11 months, respectively. In conclusion, this paper offers a unique perspective on the complexities of clinical practice when managing advanced-stage cutaneous T-cell lymphomas and demonstrates the effectiveness of the therapies described, with particular emphasis on the promising results observed with alemtuzumab administered in a low-dose protocol.

Key words: alemtuzumab; brentuximab vedotin; cutaneous T-cell lymphoma; mogamulizumab; mycosis fungoides; Sézary syndrome.

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SIGNIFICANCE

Cutaneous T-cell lymphomas (CTCLs) are a heterogeneous group of rare cancers originating from malignant transformed T-lymphocytes. The diseases encompass various clinical presentations and prognoses. The overall prognosis of CTCL in early stages is good and can often be managed with skin-directed therapies, including topical steroids or UV therapy. However, advanced stages present a higher disease burden and mortality, therefore necessitating more aggressive approaches with treatments targeted towards the abnormal T-lymphocytes. The present study evaluates the treatment efficacy of 27 patients with advanced stage CTCL treated with systemic antibody targeted treatment at Aarhus University Hospital, Denmark, from 2013 to 2023.

Cutaneous T-cell lymphomas (CTCLs), including mycosis fungoides (MF) and Sézary syndrome (SS), are a rare group of cancers of skin-homing T-cells. Patients often suffer from severe pruritus, cutaneous pain, and infections affecting the quality of life. The prognoses vary depending on subtype and disease stage, with advanced stage disease (stage IIB–IVB) having a median survival of less than 5 years (1).

Systemic treatments with monoclonal antibodies targeting surface proteins on the malignant T-cells have been investigated and described in prospective controlled studies, demonstrating increased progression-free survival in advanced CTCLs (2, 3).

Mogamulizumab, a humanized anti-CCR4 antibody, has been investigated in the MAVORIC trial as one of the promising therapies in advanced CTCLs (3, 4). Similarly, brentuximab vedotin (BV), a humanized anti-CD30 antibody, has been investigated in the ALCANZA study demonstrating significant effects outperforming methotrexate and bexarotene (2). A retrospective study from 2022 also found favourable overall response rates in patients with advanced stage mycosis fungoides (MF) treated with BV (5).

Alemtuzumab, a monoclonal anti-CD52 antibody, has also been reported as an effective treatment option, in particular for patients with leukaemic CD52-positve CTCL (6, 7). Alemtuzumab induces lymphocyte apoptosis, thereby causing long-term lymphocyte suppression (8, 9). Due to pronounced lymphocyte depletion. Alemtuzumab is associated with a considerable risk of infectious complications when administrated at high doses. However, when administrated at lower doses, side effects including infections are much more tolerable (9).

The heterogeneous nature of this disease poses a significant therapeutic challenge. The aim of this retrospective assessment was to evaluate the effect of the 3 systemic targeted treatments mogamulizumab, brentuximab vedotin, and alemtuzumab among patients with advanced stage relapsed/refractory CTCLs within a real-world clinical setting at Aarhus University Hospital, Denmark.

MATERIALS AND METHODS

Study population

The study was conducted as a single-centre retrospective cohort study. The study population consisted of adult individuals >18 years of age with histopathologically confirmed CTCLs according to the current WHO classification, diagnosed by an experienced expert team of haemato-dermato-pathologists. Patients, who received treatment with mogamulizumab, BV, or alemtuzumab in the period from december 2013 to november 2023, were included. Mogamulizumab was administered according to protocol, i.e., intravenously 1 mg/kg every 4 weeks. Regarding BV, 1 series of treatment comprising 1.8 mg/kg was administered as an intravenous infusions every 3 weeks and for up to 6 infusions in total. In some cases, the dosage was reduced for clinical issues to 1.2 mg/kg, e.g., due to clinically significant peripheral neuropathy. Alemtuzumab was administered subcutaneously at a low-dose protocol, i.e., 10 mg × 3 per week for up to 12 weeks. Throughout the course of alemtuzumab treatment, all patients received prophylaxis against viral, fungal, and pneumocystis infections with Sulfatrim (sulfamethoxazole and trimethoprim), Acyclovir and Fluconazole.

Clinico-pathologic features and patient-specific data were extracted from the electronic medical record system of Aarhus University Hospital, Aarhus, Denmark. Information on the study population is summarized in **Table I**.

Response criteria

Project-specific data were recorded in a REDCap database (https://project-redcap.org/) at Aarhus University. Patients were classified according to the World Health Organization (WHO)–European Organization of Research and Treatment of Cancer (EORTC) classification criteria (10). Tumour-node-metastasis (TNM) staging was determined following the guidelines provided by the International Society for Cutaneous Lymphomas (ISCL) and the Cutaneous Lymphoma Task Force of the EORTC (11, 12). Response to treatment was evaluated according to the standard

Table I. Patient characteristics and treatment responses

Factor	Mogamulizumab	Brentuximab vedotin	Alemtuzumab
Patients receiving the treatment, *n*	6	12	15
Age at targeted treatment start, years, median (range)	64.5 (59–74)	73 (59–84)	73 (59–82)
Sex, *n* (%)			
Male	3 (50)	9 (75)	10 (83)
Female	3 (50)	3 (25)	5 (17)
CTCL subtype, *n* (%)			
Mycosis fungoides	1 (17)	8 (67)	5 (33)
Patch/plaque	–	2 (17)	2 (13)
Folliculotropic variant pcALCL	–	1 (8)	–
Sézary syndrome	5 (83)	1 (8)	7 (47)
Sézary phenotype with B1	–	–	1 (7)
Stage, *n* (%)			
IIB	1 (17)	4 (33)	3 (20)
IIIA	1 (17)	4 (33)	–
IIIB	3 (50)	–	6 (40)
IVA	1 (17)	2 (17)	3 (20)
IVB	–	2 (17)	3 (20)
Time from diagnosis to targeted treatment, years, median (range)	1 (0–3)	3 (0–20)	1 (0–18)
Comorbidities, *n*			
Cardiac/vascular disease	2	8	8
Diabetes	–	2	–
Secondary haematologic malignancy	1	3	5
Secondary non-haematologic malignancy	–	4	4
Other	2	4	2
No. of previous systemic treatment regimens, median (range)	2 (1–4)	3 (0–6)	2 (1–6)
Involvement, *n* (%)			
Skin only	1 (17)	8 (67)	2 (13)
Extracutaneous disease (blood, lymph nodes, bone marrow, viscera)	5 (83)	4 (33)	13 (87)
Blood involvement, *n*			
B0	1	10	4
B1	–	1	4
B2	5	1	7
Treatment duration, months, median (range)	16 (2–72)	–	–
No. of treatment series, median (range)	–	1 (1–3)	1 (1–2)
Responses, *n*	9	17	18
Complete response	1	7	4
Partial response	6	4	7
No response to therapy	2	6	7
Overall response rate, *n* (%)	7 (78)	11 (65)	11 (61)
No progression, *n* (%)	3 (33)	2 (12)	4 (22)
Time to progression, months, median (range)	2.5 (2–8)	4 (3–96)	11 (4–48)
MAR, *n* (%)	3 (50)	–	–
PN, *n* (%)	–	3 (25)	–

MAR: mogamulizumab-associated rash; PN: peripheral neuropathy (clinically significant).

definitions, i.e., complete remission (CR) defined as no evidence of lymphoma; partial remission (PR) – clearance of at least 50% of skin lesions from baseline; no response to therapy (NRT) defined as no decrease in disease burden or progression during treatment. Blood involvement was evaluated with flowcytometry of peripheral blood following criteria proposed by ISCL/EORTC (13). We defined blood involvement as: detection of abnormal T-lymphocytes ($CD3^+/CD4^+$, $CD7^-$) by flowcytometry, expressed as a percentage of the total T-lymphocyte count. We examined the abnormal T-lymphocytes for CD30 and CD52 expression by flowcytometry. It was not possible for us to examine CCR4-expression on T-cells routinely. Treatment decisions were taken at multidisciplinary team (MDT) conferences based on the patient's symptomatology, clinical presentation, and comorbidities. The criteria for systemic antibody targeted therapy were as follows: brentuximab vedotin treatment necessitated the systemic involvement of MF or primary cutaneous anaplastic large cell lymphoma (pcALCL) expressing CD30, while alemtuzumab required systemic involvement of CTCLs expressing CD52. Mogamulizumab therapy could be considered for patients not meeting the criteria for either brentuximab vedotin or alemtuzumab, particularly following the failure of other systemic treatment regimens.

Endpoints

The endpoints were overall response rate (ORR), defined as percentage of patients achieving CR or PR; and time to progression (TTP), i.e., the time from end of treatment until documented progression of CTCL. Progression was evaluated by expert dermatologists through a comprehensive assessment that included clinical observations, biochemical analyses, histological examinations, and radiological imaging evidence. Overall survival (OS) was defined as the overall survival rate in our cohort from treatment initiation, and described by Kaplan–Meier curves. The quantity of responses was documented in each patient after every treatment regimen. Likewise, the TTP was documented after each documented response to treatment.

Statistical analysis

We used descriptive statistics to summarize patient demographics, baseline characteristics, and treatment outcomes. ORR and TTP were calculated as frequencies and percentages, representing the proportion of patients achieving a given response. We performed a descriptive analysis presenting medians and associated distribution measures, depending on distribution symmetry. Categorical variables were expressed as absolute numbers and percentages. A Kaplan–Meier survival curve was conducted using Stata statistical software (StataCorp LLC, College Station, TX, USA).

Approvals

Living patients at the time of inclusion provided written informed consent for study enrolment, while for deceased patients a specific permit was acquired from the Central Region of Denmark with approval number: 1-45-70-5-23. The study was approved by the Danish Data Protection Agency: 1-16-02-477-22.

RESULTS

Patient characteristics and treatment responses are summarized in Table I. In total, 27 patients were included in the study. Six patients were treated with more than 1 of the specified systemic targeted treatments, and some of these patients also had more than 1 treatment series with the same targeted treatment agent. Male to female ratio was 20:7. The median age at treatment initiation was 72 years. Eight patients had SS, 13 had patch/plaque MF, 4 had folliculotropic MF, and 1 had pcALCL. One patient with SS phenotype presented with generalized erythroderma, lymphadenopathy, palmoplantar keratoderma, and ectropion but only B1 blood stage and therefore did not formally fulfil the EORTC criteria for SS (10). This patient was enrolled as the administration of systemic targeted therapies relies on clinical features rather than exclusively on blood involvement. Follow-up ranged from 0.5 to 118 months, yielding a median follow-up of 19 months. **Fig. 1** demonstrates OS by a Kaplan–Meier curve for the entire cohort ($n=27$). **Fig. 2** provides a summary of treatment responses and ORR for each treatment group.

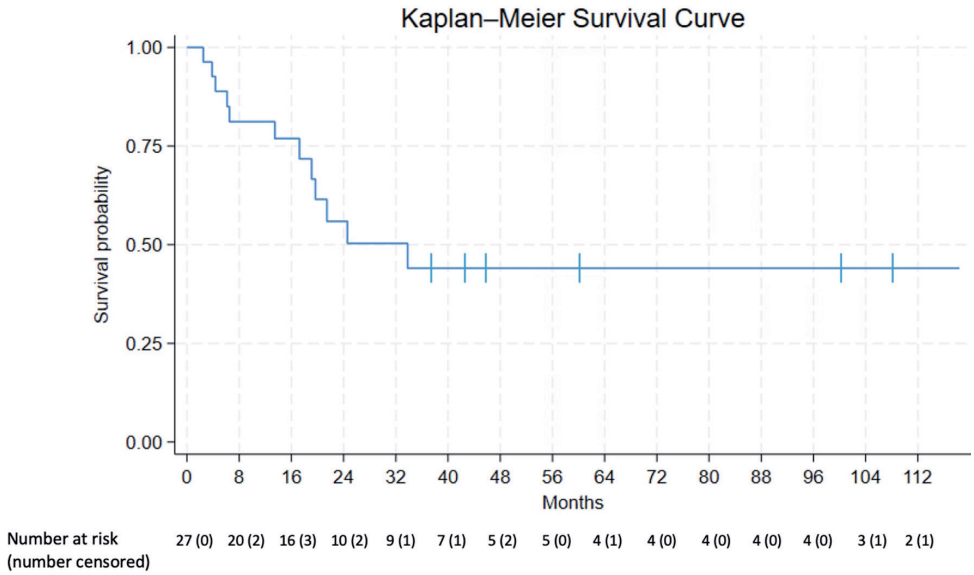

Fig. 1. Overall survival months after initiation of systemic targeted therapy based on the entire cohort of patients ($n=27$). In this study, a marked decrease in survival rates is observed early on; however, this trend stabilizes after 48 months, suggesting that the remaining patients experience a period of prolonged survival.

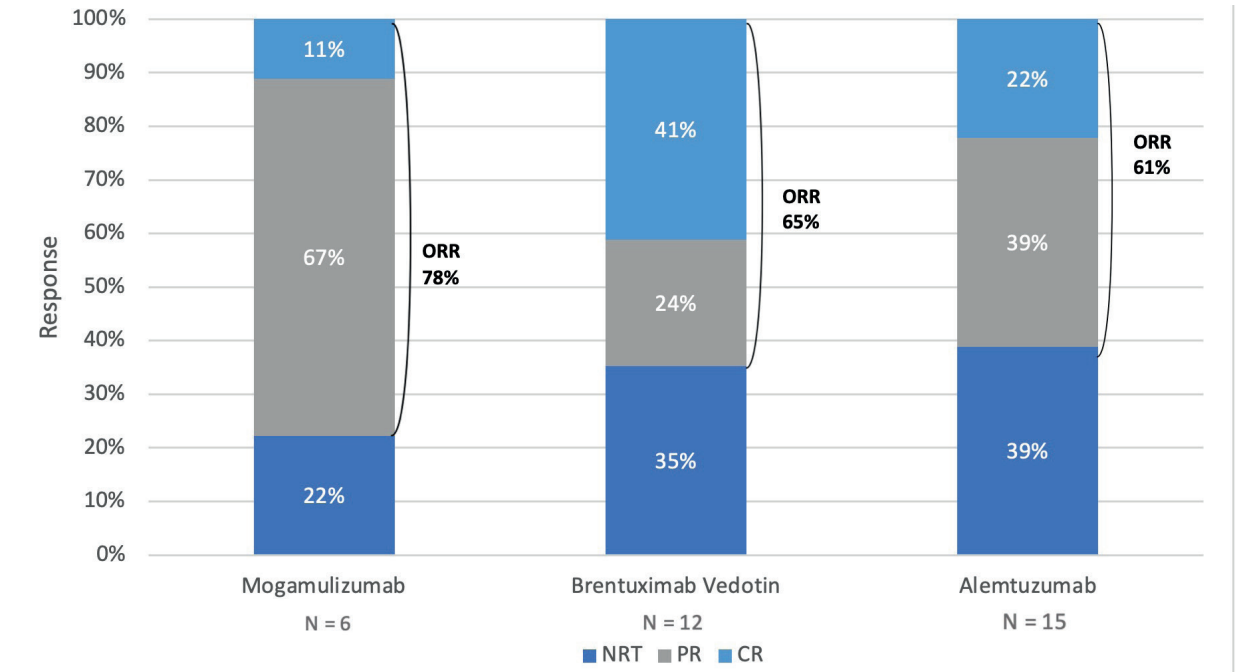

Fig. 2. Overall response rate according to systemic targeted treatment. Bars show the percentage of patients achieving complete response (CR, dark blue), partial response (PR, grey), or no response to Therapy (NRT, light blue). Overall response rates (ORR: CR + PR) are 78% for mogamulizumab ($n = 6$), 65% for brentuximab vedotin ($n = 12$), and 61% for alemtuzumab ($n = 15$). ORR values are labelled within each bar.

Patient outcomes with mogamulizumab

Six patients in total were treated with mogamulizumab. In this group, 5 patients had SS while 1 patient had MF. The average treatment duration was 16 months (range: 2–72 months). Prior to this, the patients had a median of 2 previous systemic treatment regimens (range: 1–4). Responses to mogamulizumab were 1 CR, 6 PR, and 2 classified as NRT, resulting in an ORR of 78%. After treatment termination sustained CR was observed in 33%. The median time to progression was 2.5 months (range: 2–8 months) and 50% experienced mogamulizumab-associated rash (MAR) during treatment. See Table I under "mogamulizumab" for reference.

Patient outcomes with brentuximab vedotin

Twelve patients received brentuximab vedotin including patch/plaque MF ($n = 8$), folliculotropic MF ($n = 2$), pcALCL ($n = 1$), and SS ($n = 1$). The patients were typically treated with brentuximab vedotin in a cycle of 6 treatments administered every third week. The median number of treatment series in this cohort was 1 (1–3 treatment series). Prior to this, patients had a median of 3 previous systemic treatment regimens (range 0–6). A total of 17 treatment responses to brentuximab vedotin were recorded, resulting in an ORR of 65% with 7 CRs, 4 PRs, and 6 NRT. Sustained CR was observed in 12%. Median time to progression was 4 months (3–96 months). Clinically significant peripheral neuropathy was documented in 25% of the patients. See Table I under "brentuximab vedotin" for reference.

Patient outcomes with alemtuzumab

Fifteen patients were treated with alemtuzumab including SS ($n = 7$), patch/plaque MF ($n = 5$), folliculotropic MF ($n = 2$), and SS phenotype with blood stage B1 ($n = 1$). The median number of treatment series in this cohort was 1 (1–2 series). The median number of previous systemic targeted treatments was 2 (range: 1–6 treatments). Responses to alemtuzumab were 4 CR, 7 PR, and 7 NRT, resulting in an ORR of 61%. Among these responses, 22% had sustained CR. The median time to progression was 11 months (range: 4–48 months). See Table I under "alemtuzumab" for reference. Despite application of a low-dose alemtuzumab protocol, we observed sustained lymphocyte depletion in patients up to 2 years post treatment. We illustrate this lymphocyte depression and infections associated with alemtuzumab treatment in **Fig. 3**. Notably, 47% of patients treated with alemtuzumab experienced bacterial infections requiring hospitalization and intravenous antibiotics. None of these infections had a fatal outcome.

DISCUSSION

Cutaneous T-cell lymphomas constitute a heterogeneous group of diseases with diverse clinical presentations and prognoses. However, advanced stage CTCL is a distressing condition with high morbidity, mortality, and markedly impaired quality of life for the patients. Initial stages of CTCL are typically managed through skin-directed therapies. Applied targeted treatment approaches

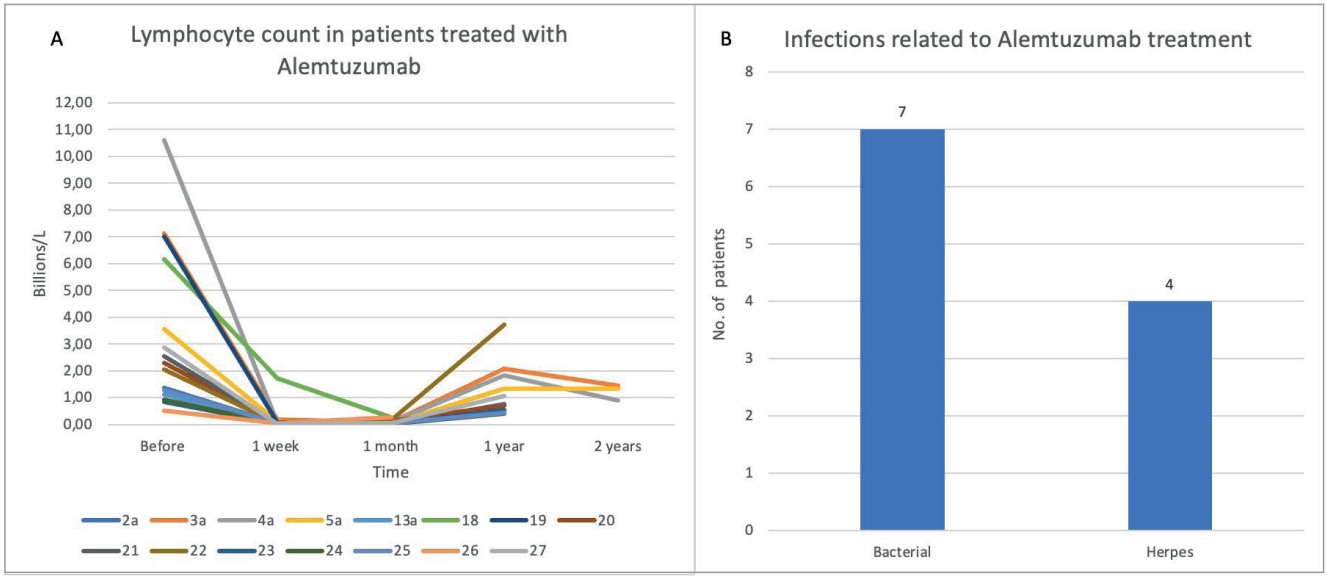

Fig. 3. Overview of lymphocyte count and infections related to alemtuzumab treatment. Significant and prolonged lymphocyte depletion associated with alemtuzumab treatment. One week following the initial infusion, lymphocyte counts dropped sharply and remained suppressed for up to 2 years. Notably, blood samples at the two-year mark were available for only three patients. Fig. 3B shows that 7 patients (47%) experienced at least 1 infection requiring hospitalization within the first year after alemtuzumab treatment ended. Additionally, 4 patients (27%) developed either primary infections or reactivations of herpes viruses, including human herpes virus 6 (HHV-6) or cytomegalovirus (CMV).

include the 3 monoclonal antibodies mogamulizumab, brentuximab vedotin, or alemtuzumab.

The efficacy of mogamulizumab in patients with relapsed or refractory CTCL has been described in a recent multi-centre retrospective analysis from France (OMEGA study) (14). The authors report an ORR of 58.7% among 122 patients over a treatment duration varying from 0.5 to 71.6 months. In the MAVORIC trial, 186 patients received mogamulizumab treatment, resulting in an ORR of 28% (3). In our study, we observed an ORR of 78%, indicating a response level similar to the level reported in the OMEGA study, but considerably better than the level reported in the MAVORIC study. It is important to note that our comparatively smaller sample size may contribute to this observed difference in response rates. Furthermore, the difference in ORR may be explained by a stricter response definition (confirmed CR or PR at $\geq$2 consecutive assessments spaced $\geq$8 weeks) in the MAVORIC trial and less patient selection bias. The use of mogamulizumab in a non-protocol setting may vary, potentially introducing discrepancies in our findings. This could pose a challenge for comparative analysis with studies such as OMEGA and the MAVORIC trial.

Our study found an ORR of 65% for the 12 patients treated with BV. A recent retrospective study from Spain demonstrated a similar ORR of 67% in 67 CTCL patients (5). This study determined the median progression-free survival (PFS) to be 10.3 months (range: 4.9–45.0). In comparison, our reported median time to progression was 4 months (range: 3–96 months). The ALCANZA trial investigated treatment with BV in 66 patients, demonstrating an ORR of 54.7% (2). PFS in the ALCANZA trial was 16.7 months, which was superior to the time to progression found in our study. However, the ALCANZA trial also included patients with early stage CTCLs (IA-IIA) and only investigated treatment with BV in patients with CD30+ MF or pcALCL. In our study, we included all patients with advanced stage CD30 positive CTCLs. This group of patients possess a higher mortality, and this may contribute to the observed discrepancy. Furthermore, our relatively small sample size should also be considered when comparing with other studies.

Alemtuzumab was investigated in a multicentre retrospective analysis from 2014 demonstrating an ORR of 51% and median TTP of 3.4 months in 39 patients, with highest response (70%) in the SS group compared with 25% in the MF group (15). In the study by de Masson et al. (15), patients were treated with a dose of 30 mg 2–3 times per week for 12 weeks, whereas patients in our study adhered to a low-dose protocol, receiving 10 mg 3 times per week for up to 12 weeks. The low-dose protocol regimen aimed to capitalize on Alemtuzumab's apoptotic effects while minimizing potential adverse events, such as infections, associated with higher doses. Patients in our study had an ORR of 61%. Within the SS subgroup, we observed 5 PR and 4 CR out of 11 total responses, yielding an ORR of 82%. Conversely, within the MF group we found an ORR of 29% (2 PR out of 7 collected responses). The impressive response rate and TTP of 11 months observed with the low-dose protocol of alemtuzumab in our study suggests promising potential for its future utilization, especially in CD52-expressing SS patients. In our study, we found that 47% patients experienced bacterial infections necessitating hospitalization,

while 62% of patients in de Masson et al. experienced a grade 3 or higher infection. These findings suggest that alemtuzumab may demonstrate efficacy in patients with SS, yet the pronounced lymphocyte depression raises concerns about potential life-threatening infections. Therefore, careful monitoring and control of such side effects are essential in the clinical management of patients undergoing alemtuzumab treatment.

Our study has limitations, primarily due to its non-interventional and retrospective design. Assessments were solely available when conducted as part of routine clinical practice, and data were confined to information previously recorded in patients' medical files. These constraints may have implications for the comprehensive evaluation of certain parameters and should be considered when interpreting the study findings. Despite these limitations, our study provides valuable insights into the real-world outcomes of relapsed/refractory advanced stage CTCLs patients treated with systemic targeted therapies and the associated treatment challenges. Notably, the efficacy of the 3 described systemic targeted treatment regimens exhibits considerable variability. Certain patients displayed robust responses while others exhibited limited, short-lived, or negligible responses. This indicates considerable biological heterogeneity and underlines the critical need for a better understanding of the underlying pathology in these diseases. Further investigation into the determinants explaining this variability in treatment response is warranted. Personalized and targeted treatment approaches have the potential to improve patient prognosis and therapeutic efficacy in CTCLs. Special emphasis is directed towards the promising results observed with alemtuzumab administered in a low-dose protocol. This finding may signal a potential direction for the future management of SS, highlighting the role of this drug in improving patient outcomes. Despite 47% of alemtuzumab-treated patients experiencing infection requiring admission to hospital, none of these infections had a fatal outcome. Additionally, infections are common in advanced stage CTCLs (16, 17).

In conclusion, our study demonstrates the effectiveness and tolerability of 3 antibody-based treatments in a real-world setting. Particularly noteworthy is the unique perspective this paper offers on the complexities of clinical practice when managing advanced-stage CTCL cases in Aarhus, Denmark. Understanding these challenges is crucial for tailoring treatment approaches to individual patients, considering factors such as disease stage, surface marker profile of the cutaneous T-cell lymphoma, and the malignant T-cell clone. Patients with relapsed/refractory advanced stage CTCL treated with mogamulizumab, brentuximab vedotin and alemtuzumab at Aarhus University Hospital, Denmark, demonstrated ORR of 78%, 65%, and 61% respectively. The median TTP was 2.5 months for mogamulizumab, 4 months for BV, and 11 months for alemtuzumab.

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