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► To cite this version:

Alizée Bozonnat, Marie Beylot-Barry, Olivier Dereure, Michel d’Incan, Gaëlle Quereux, et al.. Real-life efficacy of immunotherapy for Sézary syndrome: a multicenter observational cohort study. *EClinicalMedicine*, 2024, 73, pp.102679. 10.1016/j.eclinm.2024.102679 . hal-04747906

HAL Id: hal-04747906

<https://nantes-universite.hal.science/hal-04747906v1>

Submitted on 23 Oct 2024

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Real-life efficacy of immunotherapy for Sézary syndrome: a multicenter observational cohort study



Alizée Bozonnat,^{a,b,c} Marie Beylot-Barry,^d Olivier Dereure,^e Michel D'Incan,^f Gaëlle Quereux,^g Emmanuella Guenova,^h Marie Perier-Muzet,ⁱ Stephane Dalle,^j Florent Grange,^k Manuelle-Anne Viguier,^k Caroline Ram-Wolff,^a Laurence Feldmeyer,^l Helmut Beltraminelli,^l Nathalie Bonnet,^m Florent Amatore,^m Eve Maubec,ⁿ Nathalie Franck,^o Laurent Machet,^p François Chasset,^q Florence Brunet-Possenti,^r Jean-David Bouaziz,^{a,b,c} Maxime Battistella,^{b,c,s} Marie Donzel,^t Anne Pham-Ledard,^d Claudia Bejar,ⁿ Hélène Moins-Teisserenc,^{c,u} Samia Mourah,^{b,c,v} Philippe Saïag,^w Ewa Hainaut,^x Catherine Michel,^y Guido Bens,^z Henri Adamski,^{aa} François Aubin,^{ab} Serge Boulinguez,^{ac} Pascal Joly,^{ad} Billal Tedbirt,^{ad} Isabelle Templier,^{ae} Laura Troin,^{af} Henri Montaudie,^{af} Saskia Ingen-Housz-Oro,^{ag} Sarah Faiz,^{ah} Laurent Mortier,^{ah} Gabor Dobos,^{ai} Martine Bagot,^{a,b,c} Matthieu Resche-Rigon,^{b,c,aj} Claire Montlahuc,^{aj} Arnaud Serret-Larmande,^{b,c,aj} and Adèle de Masson,^{a,b,c,*} Cutaneous Lymphomas French Study Group

^aDepartment of Dermatology, Saint-Louis Hospital, AP-HP, Paris, France

^bINSERM U976, Institut de Recherche Saint-Louis, Paris, France

^cUniversité Paris Cité, Paris, France

^dDepartment of Dermatology, CHU de Bordeaux, BoRdeaux Institute of Oncology, BRIC INSERM U1312, INSERM BoRdeaux Institute of Oncology, Team 5, Université de Bordeaux, Bordeaux, France

^eDepartment of Dermatology, University of Montpellier, Montpellier, France

^fDepartment of Dermatology, CHU de Clermont-Ferrand, Clermont-Ferrand, France

^gDepartment of Dermatology, Nantes University Hospital, CIC 1413, Inserm UMR 1302/EMR6001 INCIT, F-44000 Nantes, France

^hDepartment of Dermatology, University Hospital Lausanne, Faculty of Biology and Medicine, University of Lausanne, Lausanne, Switzerland

ⁱDepartment of Dermatology, Hospices Civils de Lyon, Lyon, France

^jDepartment of Dermatology, CH de Valence, France

^kDepartment of Dermatology, Université Reims-Champagne Ardenne, EA7509-IRMAIC, Reims, France

^lDepartment of Dermatology, Inselspital, Bern University Hospital, University of Bern, Bern, Switzerland

^mDepartment of Dermatology, CHU de Marseille, Marseille, France

ⁿDepartment of Dermatology, Avicenne Hospital, AP-HP, Bobigny, France

^oDepartment of Dermatology, CHU Cochin, Paris, France

^pDepartment of Dermatology, CHU de Tours, Tours, France

^qDepartment of Dermatology, CHU Tenon, Faculty of Medicine, Sorbonne University, Paris, France

^rDepartment of Dermatology, CHU Bichat, Paris, France

^sPathology Laboratory, Saint-Louis Hospital, AP-HP, Paris, France

^tPathology Laboratory, Hospices Civils de Lyon, Lyon, France

^uHematology Laboratory, Saint-Louis Hospital, AP-HP, Paris, France

^vDepartment of Pharmacogenomics and Oncogenetics, Saint-Louis Hospital, AP-HP, Paris, France

^wDepartment of Dermatology, Ambroise-Paré Hospital, AP-HP, & EA 4340 "Biomarkers in Cancerology and Hemato-Oncology", UVSQ, Université Paris-Saclay, 92104, Boulogne-Billancourt, France

^xDepartment of Dermatology, CHU de Poitiers, Poitiers, France

^yDepartment of Dermatology, CH Mulhouse, Groupe Hospitalier Mulhouse Sud Alsace, Mulhouse, France

^zDepartment of Dermatology, CHU Orléans, Orléans, France

^{aa}Department of Dermatology, CHU Pontchaillou, Rennes, France

^{ab}Department of Dermatology, CHU de Besançon, Besançon, France

^{ac}Department of Dermatology, CHU de Toulouse, Toulouse, France

^{ad}Department of Dermatology, CHU de Rouen, Rouen, France

^{ae}Department of Dermatology, CHU de Grenoble, Grenoble, France

^{af}Department of Dermatology, CHU de Nice, Nice, France

^{ag}Department of Dermatology, Henri Mondor Hospital, APHP, Créteil, France

^{ah}Department of Dermatology, CHU Lille, Lille, France

^{ai}Department of Dermatology, Charité Hospital, Berlin, Germany

^{aj}Department of Biostatistics, Saint-Louis Hospital, AP-HP, Paris, France

*Corresponding author. Department of Dermatology, National Reference Center for Cutaneous Lymphomas, Saint-Louis Hospital, 1 avenue Claude Vellefaux, F-75010, Paris, France.

E-mail address: adele.demasson@aphp.fr (A. de Masson).

Summary

Background Sézary syndrome is an extremely rare and fatal cutaneous T-cell lymphoma (CTCL). Mogamulizumab, an anti-CCR4 monoclonal antibody, has recently been associated with increased progression-free survival in a randomized clinical trial in CTCL. We aimed to evaluate OS and prognostic factors in Sézary syndrome, including treatment with mogamulizumab, in a real-life setting.

Methods Data from patients with Sézary (ISCL/EORTC stage IV) and pre-Sézary (stage IIIB) syndrome diagnosed from 2000 to 2020 were obtained from 24 centers in Europe. Age, disease stage, plasma lactate dehydrogenases levels, blood eosinophilia at diagnosis, large-cell transformation and treatment received were analyzed in a multivariable Cox proportional hazard ratio model. This study has been registered in ClinicalTrials (SURPASSe01 study: NCT05206045).

Findings Three hundred and thirty-nine patients were included (58% men, median age at diagnosis of 70 years, Q1-Q3, 61–79): 33 pre-Sézary (9.7% of 339), 296 Sézary syndrome (87.3%), of whom 10 (2.9%) had large-cell transformation. One hundred and ten patients received mogamulizumab. Median follow-up was 58 months (95% confidence interval [CI], 53–68). OS was 46.5% (95% CI, 40.6%–53.3%) at 5 years. Multivariable analysis showed that age ≥ 80 versus <50 (HR: 4.9, 95% CI, 2.1–11.2, $p = 0.001$), and large-cell transformation (HR: 2.8, 95% CI, 1.6–5.1, $p = 0.001$) were independent and significant factors associated with reduced OS. Mogamulizumab treatment was significantly associated with decreased mortality (HR: 0.34, 95% CI, 0.15–0.80, $p = 0.013$).

Interpretation Treatment with mogamulizumab was significantly and independently associated with decreased mortality in Sézary syndrome.

Funding French Society of Dermatology, Swiss National Science Foundation (IZLIZ3_200253/1) and SKINTEGRITY.CH collaborative research program.

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Keywords: Cutaneous T-cell lymphoma; Sézary syndrome; Mogamulizumab; Monoclonal antibody; Immunotherapy

Research in context

Evidence before this study

Sézary syndrome accounts for around 5–10% of cutaneous T-cell lymphomas and is the leukaemic and most aggressive form, with a median overall survival of 1–5 years. In 2018, mogamulizumab was approved for the treatment of subsets of patients with cutaneous T-cell lymphoma, including Sézary syndrome, who received at least one previous systemic therapy on the basis of a randomized, open-label phase 3 study showing superior efficacy on progression-free survival over vorinostat, a histone deacetylase inhibitor. Patients with Sézary syndrome had the best responses to monoclonal antibodies, compared to other cutaneous T-cell lymphoma subtypes, such as mycosis fungoides.

Added value of this study

To our knowledge, this is the first study to report increased overall survival associated with the use of mogamulizumab in

Sézary syndrome. We used high-quality data from 24 European reference centers of the French Cutaneous Lymphomas Study Group network. This allowed us to analyze the current treatment landscape of Sézary syndrome, and to study prognostic variables associated with overall survival in this rare and aggressive disease.

Implications of all the available evidence

Our study suggests that the use of mogamulizumab is associated with increased overall survival in patients with Sézary syndrome, independently of other prognostic variables including age, ISCL/EORTC disease stage, plasmatic levels of lactate dehydrogenases, and presence of large-cell transformation. This study is encouraging for countries with access to this innovative drug, and strongly calls for a larger and early access to this immuno-oncology agent for Sézary patients worldwide.

Introduction

Cutaneous T-cell lymphomas (CTCL) are a heterogeneous group of extranodal non-Hodgkin lymphomas, with approximately 500 new cases diagnosed in France each year.¹ Sézary syndrome is a rare subtype,

accounting for 5.4% of all cases of cutaneous lymphomas² characterized by erythroderma, lymphadenopathy, and leukemic involvement.³

Patients with Sézary syndrome commonly have severe pruritus, infections,⁴ and body disfigurement

resulting in altered quality of life.⁵ Median overall survival (OS) ranges from 1 to 5 years.⁶ Therapeutic strategies include immunomodulatory treatments such as extracorporeal photopheresis^{7,8} or interferon alfa,⁹ which are usually considered as first-line treatments in the American and European guidelines.^{10,11} Available therapeutic monoclonal antibodies (mAbs) include alemtuzumab (anti-CD52),^{12,13} lacutamab (anti-KIR3DL2),¹⁴ pembrolizumab (anti-PD1)¹⁵ and atezolizumab (anti-PDL1)¹⁶ which have been studied in CTCL including Sézary syndrome in prospective, open-label phase 1 and 2 studies. Given the rarity of long-lasting remissions in Sézary syndrome, time-to-next treatment (TTNT) has been proposed as a meaningful endpoint in this disease.⁷⁻⁹ In particular, immunomodulatory strategies such as extracorporeal photopheresis^{7,8} or interferon alfa⁹ have been associated with longer TTNT, as compared to chemotherapies. The current American guidelines recommend the use of therapeutic mAbs in Sézary syndrome among other treatments such as extracorporeal photopheresis, methotrexate, bexarotene, peginterferon-alfa-2a, HDAC inhibitors.¹⁰ There is limited published real-world data on the association of early use of mAbs with OS in Sézary syndrome. In 2018, mogamulizumab (anti-CCR4 mAb) was approved in Europe and the USA for the treatment of subsets of patients with CTCL, including Sézary syndrome, who received at least one previous systemic therapy on the basis of a randomized, open-label phase 3 study showing superior efficacy on progression-free survival over vorinostat, an histone deacetylase (HDAC) inhibitor.¹⁷ Mogamulizumab depletes tumor cells, as well as peripheral regulatory T cells in CTCL, and induces local activation of the antitumor immunity in responders,¹⁸ long-term responses and immune-mediated side effects.¹⁷⁻²² Patients with Sézary syndrome had the best responses to mogamulizumab¹⁷ compared to other CTCL subtypes such as mycosis fungoides. Long-term remissions, which are rare in Sézary syndrome, have been observed after treatment with mogamulizumab^{17,19} as well as allogeneic hematopoietic stem cell transplantation²³ suggesting the role of immunomodulation in the induction of long-lasting remissions in this disease. We hypothesized that the use of mogamulizumab was associated with increased overall survival in patients with Sézary syndrome. Here, we took advantage of a large cohort of 339 patients with Sézary syndrome treated at 24 French and Swiss reference centers of the Cutaneous Lymphomas French Study Group network to study the association of immunomodulatory treatments with OS in a real-life setting.

Methods

Study design and patients

Cases of patients included in the present study were retrieved from the database of the French Cutaneous

Lymphoma study group. This database currently comprises >20,000 prospectively included cases of cutaneous lymphomas from 42 centers in France, Belgium and Switzerland, over a 25-year time period. To limit the amount of missing data in the present study, the information on prognostic variables and follow-up were retrospectively curated from electronic medical records. Inclusion criteria were: (i) adult patients over 18 years old (ii) Sézary (stage IV) or pre-Sézary (stage IIIB) syndrome diagnosed between 2000 and 2020. Non-inclusion criteria were (i) patient opposition to research, (ii) patient under guardianship or curatorship, unable to express his/her opposition.

The main objective of the study was to describe the prognosis of patients with Sézary syndrome. The primary outcome was 5-year OS. The secondary objective was to study factors associated with OS at 5 years in this population and especially the association of treatments with OS. Since TTNT has recently been proposed as a valuable endpoint in CTCL,⁷⁻⁹ we performed TTNT analyses as post-hoc analyses.

In this registry-based study, data from patients with Sézary syndrome (defined as B2 blood involvement, IV) or pre-Sézary syndrome (T4 stage with B1 blood involvement, IIIB) according to the International Society of Cutaneous Lymphomas (ISCL)/European Organization for Research and Treatment of Cancer (EORTC) staging guidelines²⁴ were obtained to analyze OS and prognostic factors. Patients were included if diagnosed after the date of computerization of medical records, in order to avoid survivorship bias (i.e. enrolling only patients who survived until the date of computerization of medical records). Patients with loss of follow-up were censored at the time of last visit. Missing data was not replaced.

The data included patient-level and tumor-level characteristics—namely, sex, date of diagnosis, age at diagnosis, ISCL/EORTC TNMB classification and disease stage²⁴ at diagnosis, presence of clinical folliculotropism, presence of histological large-cell transformation at diagnosis or during follow-up, defined by the presence of >25% of large cells on histological examination, blood Sézary cell count (cytological examination) and flow cytometric parameters of B2 blood stage (absolute count of CD4+CD26-and CD4+CD7- T cells/mm³),^{24,25} plasma levels of lactate dehydrogenase (LDH) and blood eosinophil count at diagnosis, successive treatment lines and disease responses, date of last follow-up, disease status at last-follow-up, date and cause of death, if any. This study has been registered in ClinicalTrials (SURPASSe01 study: NCT05206045).

Ethics statement

This study was approved by the institutional review board of Paris Nord University, Paris, France (CER-2021-96) and the ethics committee of Canton Bern, Switzerland (BASEC-Nr: 2021-01405) and was

conducted in accordance with the current version of the Helsinki declaration. Written informed consent was obtained from patients prior to the start of the study.

Statistical analysis

Quantitative variables were described by medians and interquartile ranges, and qualitative variables by numbers and percentages. Time (in months) between the date of diagnosis and the date of death or the last visit, whichever occurred first, was calculated. Survival curves were estimated using Kaplan–Meier estimator. OS is presented as estimate and 95% confidence interval (95% CI) and association of factors with survival in terms of hazard ratio (HR) (95% confidence interval, CI). The primary endpoint was OS at 5-year. We divided the study period into 4 parts: before 2010, 2010–2013, 2014–2017 and since 2018, because mogamulizumab was first used in 2014 as part of the MAVORIC clinical trial¹⁷ and approved in 2018.

Associations between OS and age, disease stage, plasma lactate dehydrogenase (LDH) levels, large-cell transformation⁶ and eosinophilia²⁶ were studied because these factors were previously described as independently associated with OS in advanced-stage CTCL. The treatments received by the patients, and large-cell transformation were treated as time-dependent variables. Exposure to a given treatment was defined as the time period from the start of that treatment until the commencement of the subsequent treatment. Univariable analyses were first carried out using a Cox proportional hazard model. A multivariable analysis including the mentioned factors and the received treatments was subsequently conducted. The multivariable model was stratified on the number of received treatment lines, accounting for changes of the baseline instantaneous risk as the disease progressed. Because most patients treated with mAbs were treated with mogamulizumab (83%) whereas the use of other mAbs was marginal, and because mogamulizumab is the only approved mAb in the treatment of CTCL in Europe and USA, the analysis focused on the use of mogamulizumab. Additionally, we conducted a sensitivity analysis of the 5-year OS on the subset of patients who underwent at least five lines of treatment, who represent a group with a more uniform follow-up duration and disease severity. We assessed the proportional hazards assumptions by analyzing scaled Schoenfeld residuals and testing the slope of time-dependent coefficients for each model covariate. The ‘disease stage’ variable showed non-proportional hazards. We thus stratified our model on this variable, allowing to account for its differential impact on survival across various stages without assuming a constant proportional effect over time. A secondary analysis using TTNT as endpoint was conducted. TTNT was defined as the time from the start of the treatment to initiation of subsequent line of therapy or death, whichever occurred

first. Univariable and multivariable analyses, similar to the ones described for OS, were conducted.

In a sensitivity analysis, we addressed missing data for three key variables—disease stage, age category, and LDH increase—using multiple imputation by chained equations.

An alpha risk of 5% was used for all the statistical analyses. All statistical analyses were performed with R software version 4.2.2. Survival analyses and time-dependent covariates modelling have been carried out using the ‘survival’ package version 3.5.7, and missing data imputation relied on the ‘mice’ package version 3.16.0.

Role of the funding source

The funders of the study had no role in study design, data collection, analysis, data interpretation, writing of the manuscript or the decision to submit the paper for publication. All authors had access to all study data. All authors agreed to submit for publication.

Results

Patients and baseline clinical characteristics

During the study period, 339 patients met the inclusion criteria and were included in the analysis (58% men, median age at diagnosis of 70 years, Q1–Q3, 61–79): 33 pre-Sézary (stage IIIB–9.7% of 339), 296 Sézary syndrome (stage IV 87.3%), and 10 (2.9%) had Sézary with large-cell transformation at diagnosis (Table 1). Five patients had confirmed visceral involvement at diagnosis. Thirty-five patients presented with clinical folliculotropism at diagnosis. The median number of Sézary cells at diagnosis (measured by cytological examination of peripheral blood smears or flow cytometry) was 2429/mm³ [Q1–Q3: 1242–5407]. Elevated blood LDH at diagnosis were present in 72.3% of patients, and blood eosinophilia (>500/mm³) in 22.6%.

One hundred thirty-two patients (39.1%) were treated with a mAb at least in one therapeutic line, including 110 patients with mogamulizumab (32.5% of the cohort and 83.3% of patients treated with a mAb). Fourteen (4.1%) patients were treated with alemtuzumab, 22 (6.5%) patients with lacutamab, and 2 (0.6%) patients with cusatuzumab in one therapeutic line (Table 2).

One hundred and twelve patients (33.1% of 339) received at least one depleting mAb in the first five therapeutic lines: eleven patients were treated with alemtuzumab (3.2%), 95 (28%) patients with mogamulizumab, 13 (3.9%) patients with lacutamab, and 2 (0.6%) patients with cusatuzumab.

Most common first-line treatments, used alone or in combination, included low-dose methotrexate (n = 113, 33.4% of 339), extracorporeal photopheresis (n = 103, 30.5%), oral retinoid (n = 71, 21.0%), subcutaneous interferon alfa (n = 37, 11.0%).

Characteristic	Overall (n = 339)
Sex, n (%)	
Female	144 (42.5%)
Male	195 (57.5%)
Age at diagnosis (years)	
Missing, n	1
Median (IQR)	70 (61-79)
Diagnosis, n (%)	
Pre-Sézary syndrome (stage IIIB)	33 (9.7%)
Sézary syndrome (stage IV)	296 (87.3%)
Sézary with LCT	10 (2.9%)
ISCL/EORTC stage at diagnosis	
Missing, n	3
IIIB, n (%)	33 (9.8%)
IVA1, n (%)	256 (76.2%)
IVA2, n (%)	42 (12.5%)
IVB, n (%)	5 (1.5%)
Sézary cells concentration (/mm³)	
Median (IQR)	2429 (1242, 5406)
Plasma LDH increase at diagnosis	
Missing, n	68
No	75 (27.7%)
Yes	196 (72.3%)
Eosinophilia at diagnosis (>500/mm³)	
Missing, n	52
No	222 (77.4%)
Yes	65 (22.6%)
Large cell transformation	
Missing, n	3
No, n (%)	326 (97%)
Yes, n (%)	10 (3%)

Abbreviations: IQR: interquartile range, ISCL/EORTC: International Society of Cutaneous Lymphomas/European Organization for Research and Treatment of Cancer, LDH: lactate dehydrogenase.

Table 1: Baseline characteristics of the study population.

Regarding mogamulizumab, only 3 patients received it as front-line treatment. Twenty-four received it as second line, 30 as third line, 22 as fourth line and 16 as fifth line.

Primary endpoint: 5-year overall survival

A total of 185 deaths were observed during the study period. The median follow-up was 58 months (95% CI: 53–68) and the median overall survival was 56 months (95% CI, 47–65). OS was 46.5% (95% CI, 40.6–53.3) at 5 years and 16.4% (10.8%–24.9%) at 10 years (Fig. 1a).

Seventy-six patients died of progressive CTCL (41% of 185).

Causes of death included infection in 46 cases (24.9%). Two patients died of a complication of allogeneic hematopoietic stem cell transplantation (pulmonary graft-versus-host disease and hepatocellular insufficiency). Two patients died of a second cancer, five of cardiovascular disease and 46 from equivocal causes.

We first analyzed OS as a function of date of diagnosis, dividing our study group into 4 time periods: before 2010, 2010–2013, 2014–2017 and since 2018. There was no significant difference in overall survival according to the time period of inclusion (respectively 71 months (95% CI: 50; 90); 56 (30; 81), 52 (44; 63) and not reached, $p = 0.70$) (Fig. 1b).

Secondary endpoints

Univariable analysis on overall survival

Treatments. The median number of consecutive treatment lines received by the patients was 4 (range, 0 to 14).

Treatment with mAb in the first 5 lines of treatments (analysed in the subgroup of patients who had received at least 5 successive lines of treatments) was significantly associated with higher OS compared to patients

Treatment	Patient count (%) All lines (n = 339)	Patient count (%) First line (n = 339)
Oral retinoid	211 (62.43%)	71 (21.01%)
Methotrexate	180 (53.25%)	113 (33.43%)
Phototherapy	48 (14.20%)	25 (7.40%)
Histone Desacetylase Inhibitor	44 (13.02%)	0 (0%)
Monochemotherapy	153 (45.27%)	21 (6.21%)
Polychemotherapy	63 (18.64%)	12 (3.55%)
Antibody-drug conjugate	41 (12.13%)	1 (0.30%)
Immunomodulatory treatments		
Interferon-alfa	95 (28.11%)	37 (10.95%)
Extracorporeal photopheresis	207 (61.24%)	103 (30.47%)
Allogeneic hematopoietic stem cell transplantation	17 (5.03%)	0 (0%)
Monoclonal antibodies		
Anti-CD158k (lacetumab)	22 (6.51%)	0 (0%)
Anti-CD70 (cusatumab)	2 (0.59%)	0 (0%)
Anti-CCR4 (mogamulizumab)	110 (32.54%)	3 (0.89%)
Anti-CD52 (alemtuzumab)	14 (4.14%)	2 (0.59%)

Table 2: Characteristics of the main treatments received by the patients.

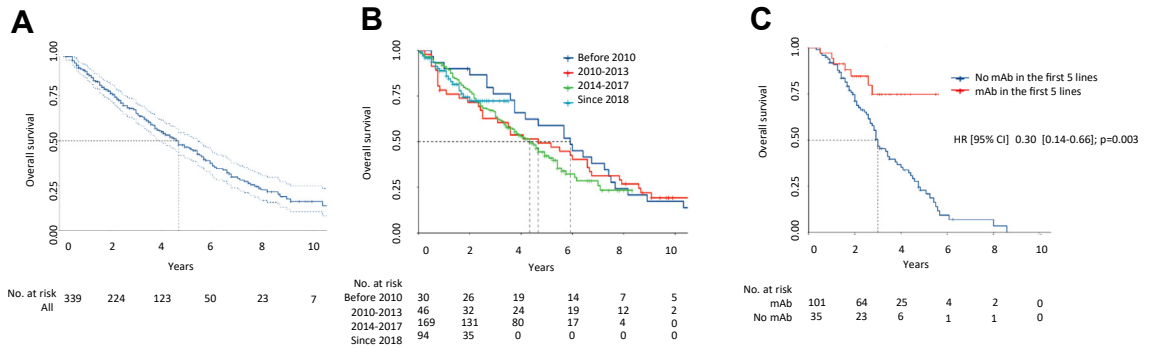


Fig. 1: Overall survival in the whole cohort of 339 patients, according to the time period and to the use of monoclonal antibodies in the first five lines of treatments. A. Overall survival in 339 patients. Overall survival was estimated from the date of diagnosis by the Kaplan–Meier method (dashed lines, 95% confidence interval). B. Overall survival in 339 patients according to the period of diagnosis. No significant difference was observed in terms of overall survival according to the time period. C. Overall survival according to the use, or not, of a therapeutic monoclonal antibody in the first 5 lines of treatments, analyzed in the subgroup of patients who had received at least 5 successive lines of treatments. The median number of consecutive treatment lines received by the patients was 4 (range, 0 to 14).

who had not received any mAb in the first 5 lines of treatments (median OS, 36 months versus not reached, HR = 0.30 (95% CI, 0.14–0.66, p = 0.003, Fig. 1c).

In the whole cohort of 339 patients, treatment with mogamulizumab was significantly associated with OS in univariable analysis (median OS, 92 months versus 55 months, HR = 0.60, 95% CI 0.36–1.0, p = 0.049, Fig. 2a and Table 3).

All other treatments were analyzed as time-dependent variables for their association with OS in univariable analysis. The only other treatments associated with longer OS were extracorporeal photopheresis (median OS, 66 months versus 44, HR = 0.68, 95% CI 0.50–0.92, p = 0.012, Fig. 2b) and interferon alfa (median OS, 68 months versus 52, HR = 0.68, 95% CI 0.43–0.89, p = 0.009, Fig. 2c).

Other prognostic variables. Age >80 years (versus <50, HR = 4.4, 95% CI 2.4–8.1, p = 0.001, Table 3),

eosinophilia (>500/mm³, HR = 1.5, 95% CI, 1.0–2.1, p = 0.041), and large-cell transformation (HR = 4.1, 95% CI, 2.9–5.9, p = 0.001) were significantly associated with shorter OS in univariable analysis.

Multivariable analysis on overall survival

Treatment with mogamulizumab, age, plasma lactate dehydrogenase (LDH) levels, large-cell transformation and eosinophilia were used as covariables because the latter clinical variables were previously described as independently associated with OS in advanced-stage CTCL.

Mogamulizumab treatment was an independent factor associated with an increased OS in multivariable analysis (HR: 0.34, 95% CI, 0.15–0.80, p = 0.013). Age and the presence of large-cell transformation remained significantly associated with OS in multivariable analysis.

The summary of the univariable and multivariable survival analyses are shown in Table 3.

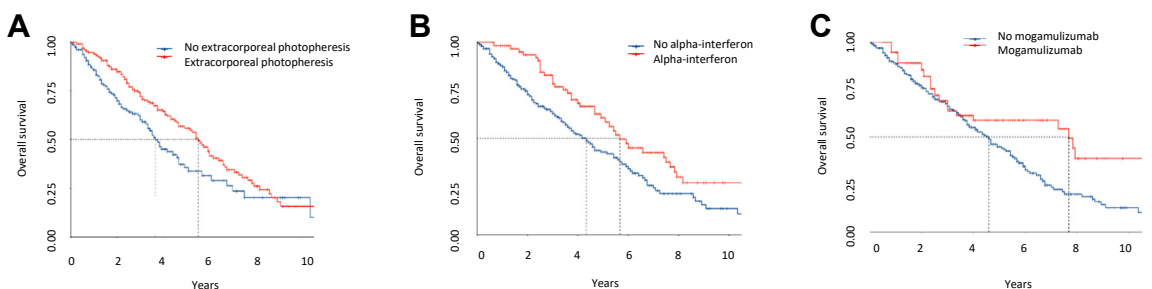


Fig. 2: Overall survival according to the treatments received by the patients. A. Overall survival according to the use, or not, of mogamulizumab at any time point during the course of the disease. B. Overall survival according to the use, or not, of extracorporeal photopheresis at any time point during the course of the disease. C. Overall survival according to the use, or not, of interferon alfa at any time point during the course of the disease. Treatments were analyzed as time-dependent variables and numbers at risk not indicated for this reason. Hazard ratios, 95% confidence intervals and p-values are from univariable Cox analysis.

Variable	Univariable			Multivariable		
	HR	95% CI	p.value	adjusted HR	95% CI	p.value
No mogamulizumab treatment	1			1		
Treated with mogamulizumab	0.60	0.36; 1.00	0.049	0.34	0.15; 0.80	0.013
Diagnosis age (years): <50	1			1		
Diagnosis age (years): 50–59	1.41	0.72; 2.77	0.316	0.85	0.34; 2.16	0.70
Diagnosis age (years): 60–69	1.67	0.92; 3.06	0.094	1.38	0.59; 3.21	0.50
Diagnosis age (years): 70–79	2.37	1.31; 4.28	0.004	2.47	1.09; 5.58	0.03
Diagnosis age (years): ≥ 80	4.38	2.37; 8.07	<0.0001	4.88	2.13; 11.19	0.001
No eosinophilia	1			1		
Eosinophilia	1.46	1.02; 2.10	0.041	1.59	0.96; 2.64	0.07
No LDH increase	1			1		
LDH increase	1.35	0.91; 1.99	0.133	1.07	0.65; 1.75	0.80
No large cell transformation	1			1		
Large cell transformation	4.12	2.91; 5.85	<0.0001	2.83	1.58; 5.06	0.001

Abbreviations: HR: hazard ratio, CI: confidence interval, LDH: lactate dehydrogenase. HRs are estimated using Cox proportional hazard regressions. Multivariable HRs are obtained using models stratified on the number of received lines and that include age, disease stage, plasma lactate dehydrogenase (LDH) levels, large-cell transformation (time-dependent covariable) and eosinophilia as covariables.

Table 3: Uni and multivariable analysis on overall survival in the whole cohort of 339 patients.

Extracorporeal photopheresis remained significantly associated with OS in multivariable analysis (HR: 0.68, 95% CI 0.50–0.92, $p = 0.012$), but not interferon alpha (HR: 0.89, 95% CI 0.49–1.64, $p = 0.72$).

Time-to-next treatment analysis

TTNT analyses were performed on all treatment types and summarized in [Table 4](#). Treatments with mogamulizumab, extracorporeal photopheresis, and allogeneic hematopoietic stem cell transplantation were associated with significantly higher TTNT in multivariable analysis, thus confirming the potential benefit associated with the use of immunomodulatory strategies in Sézary syndrome. As previously described (9), mono-

and polychemotherapy were associated with a trend towards shorter TTNT in the multivariable analysis (respectively adjusted $p = 0.008$ and $p = 0.055$).

A sensitivity analysis, addressing missing data for three key variables—disease stage, age, and LDH increase—using multiple imputation by chained equations, performed on OS and TTNT, provided the same conclusions ([Supplemental Tables S1 and S2](#)).

Discussion

To our knowledge, the present study is the largest to evaluate survival and prognostic factors specifically in Sézary syndrome.

Variable	Median TTNT (months) [95% CI]	Univariable HR [95% CI]	p.value	Multivariable HR [95% CI]	p.value
Not treated with ECP	6 [5; 7]				
Treated with ECP	17 [13; 20]	0.77 [0.66; 0.88]	0.001	0.78 [0.64; 0.95]	0.013
Not treated with MTX	6 [5; 8]				
Treated with MTX	13 [10; 17]	0.78 [0.68; 0.90]	0.001	0.94 [0.77; 1.15]	0.54
Not treated with allo HSCT	8 [7; 9]				
Treated with allo HSCT	41 [36; NA]	0.33 [0.16; 0.71]	0.004	0.26 [0.10; 0.66]	0.005
Not treated with interferon	7 [6; 9]				
Treated with interferon	13 [8; 20]	1.21 [1.03; 1.41]	0.02	1.42 [1.12; 1.79]	0.004
Not treated with moga	7.5 [7; 9]				
Treated with moga	24 [19; 28]	0.87 [0.68; 1.10]	0.24	0.51 [0.35; 0.73]	0.001
Not treated with monochemotherapy	8 [7; 10]				
Treated with monochemotherapy	7 [5; 10]	2.23 [1.91; 2.60]	<0.0001	1.41 [1.09; 1.81]	0.008
Not treated with polychemotherapy	8 [7; 10]				
Treated with polychemotherapy	6 [3; 10]	2.51 [2.02; 3.13]	<0.0001	1.44 [0.99; 2.08]	0.055

Abbreviations: ECP, extracorporeal photopheresis, MTX, low dose methotrexate, moga, mogamulizumab, CI, confidence interval, HR, hazard ratio. HRs are estimated using Cox proportional hazard regressions. Multivariable HRs are obtained using models stratified on the number of received lines and that include age, disease stage, plasma lactate dehydrogenase (LDH) levels, large-cell transformation (time-dependent covariable) and eosinophilia as covariables.

Table 4: Summary of time to next treatment analyses.

Large international studies have identified stage IV, age >60 years, large-cell transformation, and increased LDH as independent prognostic variables in CTCL in general⁶ but have not focused on Sézary syndrome patients and association of the use of specific treatments with OS. Immunomodulatory strategies such as extracorporeal photopheresis^{7,8} or interferon alfa⁹ have been associated with longer TTNT, as compared to chemotherapies and our study confirmed the benefit of immune modulation in Sézary syndrome: the only treatments associated with a significantly longer OS in our study were mogamulizumab, extracorporeal photopheresis and interferon alfa. Interestingly, the effect of mogamulizumab on OS was mainly visible after a few years (Fig. 2a), suggesting long-term effects possibly associated with the local activation of the immune responses, as previously described in responders.¹⁸ Additionally, TTNT analyses in the present study showed significantly higher TTNT associated with the use of mogamulizumab, allogeneic HSCT and extracorporeal photopheresis, also strengthening the hypothesis of a long-term benefit induced by immunomodulatory strategies in this disease.²³

This study assessed the 5-year OS of a large multicenter European cohort (n = 339) over a 20-year period. The results confirm the poor survival of these patients with a median survival of 56 months. A 2015 international study involving 29 centers and including all advanced-stage CTCL patients found similar data with a median OS of 47 months in patients with stage IVA disease⁶ and identified stage, age, large-cell transformation and elevated LDH levels as independent adverse prognostic factors of OS. Large-cell transformation is an identified poor prognostic factor in Sézary syndrome²⁷ whereas the absence of CD30 expression in transformed mycosis fungoides,²⁸ as well as other biological factors such as CAF-1/p60 overexpression²⁹ have been associated with shorter overall survival. There was no significant difference in terms of OS according to the study period, suggesting that differences in OS associated with the different specific treatments of Sézary syndrome were not simply reflecting improved supportive care over time (anti-infectious drugs, earlier diagnosis, for example).

Treatment with mogamulizumab was associated with increased OS in multivariable analysis. Our results are in agreement with the recent results of the MAVORIC study, which excluded patients with large-cell transformation, and found an increase in progression-free survival in the mogamulizumab group compared to the vorinostat group with an HR of 0.53, (95% CI: 0.41, 0.69) and suggested increased OS in a post-hoc analysis adjusted for cross-over and relying on a small number of patients.³⁰ A study including 16 Sézary syndrome and 5 mycosis fungoides patients treated with mogamulizumab, also showed the benefit of mogamulizumab in real life in the treatment of

advanced CTCL with a median progression-free survival of 22 months.³¹

In our study, a significant number of patients died of disease progression (76 patients or 41%) and 25% of sepsis; this was probably underestimated since some patients died from an equivocal cause. Sepsis remained a leading cause of death in our cohort, as previously described^{4,32} and this provides an additional argument supporting the use of immunomodulatory treatments, and not chemotherapies, in this disease.

The main limitation is the retrospective nature of this study and heterogeneity of the treatments received as a direct consequence of the multicentre retrospective setting of this study, which is usual in this disease since most patients receive several consecutive lines of treatments. The sequential treatments are tailored to each case in this disease and, guided by decisions in tumor boards, further add to the variability of therapeutic approaches. It is important to note that the availability of treatment options varied throughout the study period due to factors such as drug approvals and market withdrawals. While this could introduce bias, it also serves to reflect the authentic context of our investigation. Additionally, this variability aligns with the real-world conditions of advanced-stage CTCL care and enhances the external validity of our findings. We strived to limit the amount of missing data in this largest multicentre study ever published in this particularly rare disease. In our study, the number of complete cases, i.e. cases without any missing information, on the prognostic covariables in this disease (LDH levels, large-cell transformation, age and disease stage) was 249 (73% of 339 patients).

The strengths of our study are the multicenter setting, the use of international diagnostic and response criteria, and the size of the cohort (n = 339). It constitutes one of the largest published international series of patients with Sézary syndrome. Although relatively large compared to existing studies in the field of this extremely rare disease, our cohort was smaller than expected (700 initially expected patients), due to the fact that we enrolled only patients whose diagnosis date was posterior to the digitalization of medical records to avoid major survivorship bias. Among the subset of patients diagnosed before digitalization, only those who survived until digitalization are included in our cohort. Additionally, the protocol was written and collection of data began at the time of the 2018 diagnostic recommendations.³ Consequently, some patients diagnosed as Sézary with B2 criteria were later reclassified as Mycosis Fungoides without B2 phase and excluded from the analysis. We included only patients with B2 criteria according to the latest ISCL/USCLC/EORTC staging guidelines.²⁴ Our intention was to ensure homogeneity of the study group, enable a more accurate and clinically relevant classification of patients, and eventually improve the validity of our

results in the context of the existing staging guidelines. Nonetheless, this cohort represents one of the largest prospective international cohort of patients with Sézary syndrome. No study had yet studied the impact of mAbs and in particular mogamulizumab on OS in a large cohort of Sézary syndrome patients. This study is not without limitations. The findings are derived from an observational design, which is inherently prone to confounding bias. We attempted to mitigate this both at the data collection step (only including patients diagnosed after medical records digitization), and in the statistical analysis (using a multivariate, stratified, time-dependent Cox regression model). We reported the significance testing of various exposure factors, leading to type I error rate inflation, that is an increased likelihood of erroneously identifying results as statistically significant. Given these considerations, the results should be interpreted as exploratory.

The significantly and independently increased OS associated with mogamulizumab treatment at any time point, in a real-life setting, is encouraging for patients with Sézary syndrome. Further molecular studies and deep learning approaches, together with large-scale cohorts like this one or the Cutaneous Lymphoma International Consortium database³³ may help to better identify the best treatment for each patient at each time point during the course of the disease.

Contributors

A. Bozonnat participated in data curation, formal analysis, writing of the original draft and review & editing.

A. Serret-Larmande performed formal analysis and contributed to the methodology, writing of the original draft, review & editing.

C. Montlahuc and M. Resche-Rigon contributed to the methodology, review & editing.

A. de Masson supervised the study, participated in formal analysis, writing of the original draft and review & editing.

M. Beylot-Barry, O. Dereure, M. d Incan, G. Quereux, E. Guenova, M. Perier-Muzet, S. Dalle, F. Grange, M. Viguier, C. Ram-Wolff, L. Feldmeyer, H. Beltraminelli, N. Bonnet, F. Amatore, E. Maubec, N. Franck, L. Machet, F. Chasset, F. Brunet-Possenti, J.D. Bouaziz, M. Battistella, M. Donzel, A. Pham-Ledard, C. Bejar, H. Moins-Teisserenc, S. Mourah, P. Saiag, E. Hainaut, C. Michel, G. Bens, H. Adamski, F. Aubin, S. Boulinguez, P. Joly, B. Tedbirt, I. Templier, L. Troin, H. Montaudié, S. Ingen-Housz-Oro, S. Faiz, L. Mortier, G. Dobos, M. Bagot, participated in data collection, manuscript review & editing.

All authors contributed to manuscript review, approved the final draft for submission, and are accountable for accuracy and integrity of any part of the work. All authors had full access to all data in the study and agreed to submit for publication.

Data sharing statement

According to the French General Data Protection regulation at the time of publication, all proposals requesting access to anonymised individual participant data from the SURPASSE study will need to specify how the data will be used and for what purpose. Requests for access to data should be addressed to Adèle de Masson at adele.demasson@aphp.fr.

Declaration of interests

AdM declares nonfinancial support from Kyowa Kirin and Recordati Rare Diseases; fees from Takeda, Almirall and Recordati Rare Diseases, and research funding, outside the scope of this study, from Kyowa Kirin, Innate Pharma, Almirall and Takeda.

MB declares consultant fees from Innate Pharma, Kyowa Kirin, Takeda, BMS, Sanofi, Quantum Genomics, and research funding from Kyowa Kirin and Takeda, outside the scope of this study.

SM declares consultant fees outside the scope of this study, from Pierre Fabre, Sanofi, Novartis and Biocartis, and has received research funding from BMS, Novartis and Roche.

NF declares having received nonfinancial support from Kyowa Kirin.

PS received a research grant from Pierre Fabre, fees unrelated to this manuscript from Bristol-Myers Squibb, MSD, Merck-Serono, Pfizer, Roche-Genentech, Pierre Fabre, and Novartis; received nonfinancial support from Bristol-Myers Squibb, MSD, Roche-Genentech, Pierre Fabre, and Novartis outside of the scope of this study.

MBB declares consultant fees from Kyowa Kirin, Takeda and Recordati and research funding from Kyowa Kirin and Almirall outside the scope of this study.

HMT declares consultant fees outside from the scope of this study from Innate Pharma, and has received research funding, outside the scope of this study, from Kyowa Kirin.

SIHO declares consultant fees outside the scope of this study from Takeda and Recordati.

GD declares consultant fees outside of the scope of this study from Kyowa Kirin and Recordati.

EG declares consultant fees and/or grant support from Mallinckrodt, Helsinn, Takeda, Novartis and Kyowa Kirin unrelated to this work.

FG declares consultant fees from Recordati and Kyowa Kirin, outside from the scope of this study.

GQ declares consultant fees from Takeda, Recordati and Kyowa Kirin, outside the scope of this study.

CM declares nonfinancial support from MSD, Pfizer, Novartis, Bristol-Myers Squibb, Pierre Fabre, Leo Pharma, Sanofi Aventis, Janssen Cilag outside of the scope of this study.

SB declares having received nonfinancial support from Kyowa Kirin and Recordati.

MBag declares consulting fees from Kyowa Kirin, Takeda, Recordati.

HB declares consultant fees from Kyowa Kirin.

EH declares consultant fees outside the scope of this study from Bristol-Myers Squibb, Takeda, Sanofi, Janssen Cilag, Blueprint Medicines, AbbVie and nonfinancial support from Kyowa Kirin, MSD, UCB Pharma, Novartis, Almirall, Pierre Fabre.

The other authors declare that they have no conflict of interest.

Acknowledgements

This study was funded by the French Society of Dermatology, by the Swiss National Science Foundation (IZLIZ3_200253/1) and by the SKINTEGRITY.CH collaborative research program. We thank all the patients who participated in this study, and their families and caregivers. We also thank all the investigators for their contributions to the administration and execution of the study, as well as Marion Dubois and Razika Guizem for their excellent administrative support. The sponsor had no role in the study design, data collection, data analysis, interpretation of data, writing of the report, or the decision to submit the paper for publication.

Appendix A. Supplementary data

Supplementary data related to this article can be found at <https://doi.org/10.1016/j.eclim.2024.102679>.

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