



## **Effectiveness of mogamulizumab in patients with Mycosis Fungoides or Sézary syndrome. A multicentre, retrospective, real-world French study**

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## ORIGINAL ARTICLE

# Effectiveness of mogamulizumab in patients with Mycosis Fungoides or Sézary syndrome: A multicentre, retrospective, real-world French study

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## Abstract

**Background:** Efficacy and safety of mogamulizumab, a monoclonal antibody directed against C-C chemokine receptor 4, were demonstrated in a previous multinational clinical trial conducted in patients with previously treated cutaneous T-cell lymphoma (CTCL): Sézary syndrome (SS) or Mycosis Fungoides (MF).

**Objectives:** The real-world French OMEGA study aimed to describe effectiveness and tolerability of mogamulizumab in adult patients with CTCL, overall and according to the disease (SS or MF).

**Methods:** In this retrospective study, patients treated with mogamulizumab for SS or MF were included from 14 French expert centres. The overall response rate (ORR) under treatment was described (primary criterion), as well as treatment use and safety data.

**Results:** The 122 analysed patients (69 SS, 53 MF) were aged  $66.6 \pm 12.1$  years at mogamulizumab initiation, and their median disease duration was 2.5 years (IQR: 1.3–5.6). Prior to treatment start, they received a median of three systemic CTCL therapies (2–5). Overall, 77.8% of patients suffered from advanced disease (Stage IIB–IVB), with frequent blood (B1/B2) involvement (67.5%). Over the treatment period

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(median: 4.6 months, 2.1–7.2), 96.7% of patients received all the planned mogamulizumab infusions. Among the 109 patients evaluable for effectiveness, ORR was 58.7% (95% CI [48.9–68.1]) overall, 69.5% [56.1–80.8] in SS and 46.0% [31.8–60.7] in MF. Compartmental response in the blood was observed in 81.8% [69.1–90.9] of SS patients. Skin responses were observed in 57.0% [47.0–66.5] of patients overall, 66.7% [52.9–78.6] in SS and 46.0% [31.8–60.7] in MF. The most common serious adverse drug reactions were rash (8.1% of patients) and infusion-related reactions (2.4%) which led to treatment discontinuation in 7.3% and 0.8% of patients, respectively. One patient with SS died from mogamulizumab-related tumour lysis syndrome.

**Conclusions:** This large French study confirmed the effectiveness and tolerability of mogamulizumab in SS and MF patients in routine medical practice.

## INTRODUCTION

Mycosis Fungoides (MF) and Sézary syndrome (SS) are the most studied forms of cutaneous T-cell lymphoma (CTCL), together accounting to up two-thirds of cases.<sup>1,2</sup> MF generally follows an indolent course, characterized by patches and plaques; in advanced stages, patients can present with extracutaneous involvement of the blood, lymph nodes and viscera.<sup>3–5</sup> SS is rare but more aggressive and is characterized by a triad of erythroderma, lymphadenopathy and high levels of circulating atypical lymphocytes (Sézary cells).<sup>1–6</sup> The extent of cutaneous lesions, presence of extracutaneous manifestations, advanced age (over 60 years old), increased lactate dehydrogenase (LDH) level and cytologic large cell transformation have all been identified as poor prognostic factors, associated with reduced survival of patients with MF/ and SS.<sup>3,7</sup> Patients with advanced-stage MF (IIB–IVB) or SS have a median overall survival of 1.4–4.7 years.<sup>7</sup> Furthermore, blood involvement has prognostic significance, independently from cutaneous and nodal involvements.<sup>8–10</sup>

Several systemic treatments are available for advanced-stage of MF and SS, and for early-stage MF (IA–IIA) that is refractory to skin-directed therapies.<sup>4,5</sup> However, there is currently no curative treatment for MF and SS except for haemopoietic stem cell transplantation,<sup>4</sup> and patients often experience disease progression under therapy or become resistant to ongoing treatments.

Mogamulizumab is a first-in-class defucosylated monoclonal antibody, selectively binding to C-C chemokine receptor 4 (CCR4) with enhanced antibody-dependent cellular cytotoxicity activity. The CCR4 receptor is over-expressed on the malignant T-cells in the skin and peripheral blood of patients with MF and SS. Efficacy of mogamulizumab has been evidenced in an open-label, multinational, phase 3, randomized controlled trial comparing mogamulizumab with vorinostat, an oral histone deacetylase inhibitor and antineoplastic agent, among patients with refractory or relapsed MF and SS (MAVORIC, NCT01728805). It was shown that mogamulizumab significantly prolonged progression-free survival (PFS) compared with vorinostat (hazard ratio: 0.53, 95% CI [0.41–0.69],  $p < 0.0001$ ).<sup>11</sup> Based on these positive findings,

mogamulizumab was approved in 2018 in the European Union for adult patients with MF and SS who have received at least one prior systemic therapy.<sup>12</sup>

However, only few data were available on mogamulizumab outcomes in routine clinical practice, and none in a large non-selected population. In this context, this retrospective real-world study mainly aimed to describe the real-life effectiveness of mogamulizumab in patients suffering from MF or SS. This study also allowed describing the characteristics of treated MF or SS patients, the use of mogamulizumab and its safety profile.

## MATERIALS AND METHODS

### Study design

This non-interventional, multicentre, retrospective ('OMEGA') study was conducted in 14 expert centres of the French Study Group of Cutaneous lymphoma (<https://www.gfcl.org/>). Eligible patients were adults who received mogamulizumab at least once for MF or SS until March 2020. Patients previously enrolled in the MAVORIC trial could be included if they were alive at the end of this interventional study. The study protocol was approved by an independent Ethics Committee (*Sud-Est VI, Clermont-Ferrand*). According to the French law regarding retrospective studies, all included patients alive at the time of data collection were informed about the study content and had no objections to their personal data being processed. Data were retrospectively collected from patients' medical records until March 2020.

### Data collected

The following retrospective data were collected: Patient characteristics, type of CTCL, MF or SS, disease history, previous therapies for MF or SS, disease stage at diagnosis and mogamulizumab initiation, use of mogamulizumab including temporary and permanent discontinuations, response to treatment from mogamulizumab initiation to discontinuation or end of study (complete response [CR],

partial response [PR], stable disease [SD] or disease progression [DP]). Treatment response was collected overall and by compartment (skin, lymph nodes, viscera and blood in SS patients) according to European guidelines for response,<sup>6,13</sup> at any time and for no pre-specified duration from mogamulizumab initiation. Adverse events assessed as related to mogamulizumab (adverse drug reactions, ADRs) were also collected.

## Statistical methods

For this retrospective non-interventional study based on available patient medical files, no sample size calculation was requested. Descriptive analysis was performed. Study parameters were assessed using mean and standard deviation or median and interquartile range for continuous variables, and proportions for categorical variables. Two-sided tests with type I error  $\alpha=0.05$  were applied when relevant and were considered significant at  $p<0.05$ . Missing data were not replaced. Statistics were carried out using SAS® software (SAS Institute), version 9.4.

The safety population comprised all included patients having received at least one dose of mogamulizumab. Patients of the safety population who met all inclusion criteria were retained in the overall analysis population, and in patient groups MF or SS. Considering the retrospective non-interventional design of the study, primary effectiveness analysis (ORR calculation derived from CR and PR) was performed in the overall analysis population (and patient groups) who had available data on the disease stage at mogamulizumab initiation and during patient follow-up under treatment (effectiveness evaluable population). Overall response rate (ORR, primary criterion), defined as the proportion of patients with CR or PR under mogamulizumab, was described in the effectiveness evaluable population and by patient groups (primary criterion) with its associated 95% confidence interval (CI). We also described the time to reach CR or PR under mogamulizumab treatment. Compartmental response was also described for those patients with compartmental involvement at mogamulizumab initiation (blood, skin, lymph nodes and/or viscera in SS patients; skin, lymph nodes and/or viscera in MF patients). Additionally, the disease control rate (DCR; proportion of patients with CR, PR or stable disease [SD]) was presented in the effectiveness evaluable population.

Assuming that disease progression and patient death were a priori always recorded in patient medical files, PFS (time to disease progression or death from any cause, whatever comes first), assessed by physicians, was estimated from mogamulizumab initiation in the overall analysis population and by patient groups, using the Kaplan–Meier method. A similar analysis was performed for patient overall survival (OS, time to death from any cause).

Patient and disease characteristics were described in the overall analysis population, as well as the use of mogamulizumab. ADRs were described in the safety population.

## RESULTS

### Populations, patient and disease characteristics at mogamulizumab initiation

All the 124 included patients received at least one dose of mogamulizumab and entered the safety population. Among these 124 patients, 122 patients with a clear diagnosis (53 with MF and 69 with SS) met all the selection criteria and were retained in the overall analysis population, including 20 patients (16.9%) previously enrolled in the MAVORIC interventional study having assessed mogamulizumab efficacy and safety. Of these 122 patients, 109 patients (89.3%, 50 with MF and 59 with SS) entered the effectiveness population. Reasons for exclusion of the 13 patients were as follows: missing disease stage ( $n=5$ ), missing response to treatment ( $n=8$ ), and/or unknown period of the treatment response (under mogamulizumab or after discontinuation,  $n=2$ ). Over this retrospective study, mogamulizumab was initiated between 19 February 2014 and 02 March 2020, which led to a duration of patient follow-up varying from 0.5 to 72.6 months.

Patient and disease characteristics at mogamulizumab initiation are detailed in Table 1. The mean age of patients was  $66.6 \pm 12.1$  years, with a balanced gender ratio. Patients with SS were older than patients with MF ( $\geq 65$  years: 66.7% vs. 54.7%). The median disease duration was 2.5 years (interquartile range, IQR [1.3–5.6]) prior to mogamulizumab initiation. At that time, the majority of patients (77.8%) had an advanced stage of disease (IIB–IVB), with frequent blood (B1/B2) involvement (67.5%). All but two SS patients received previous CTCL systemic therapies (median number: 3 [2–5]), including bexarotene (76.7%), methotrexate (72.5%), interferon (43.3%), gemcitabine (29.2%), interferon (42.6%) and/or extracorporeal photopheresis (48.8%).

### Effectiveness

For the 109 patients of the effectiveness evaluable population, the median durations of follow-up and mogamulizumab treatment were 8.7 months (IQR [4.0–15.0], range: 0.6–72.6) and 4.9 months (IQR [2.2–7.4], range: 0.5–71.6), respectively, until the end of the study period. On this basis, ORR under mogamulizumab treatment was 58.7% (95% CI [48.9–68.1]) (Figure 1). A higher response rate was observed in patients with SS compared to patients with MF (69.5% [56.1–80.8] and 46.0% [31.8–60.7], respectively). CR was reached in 10/59 SS patients (16.9%, 95% CI [8.4–29.0]), and in 4/50 MF patients (8.0%, [2.2–19.2]); PR was reached in 31/59 SS patients (52.5% [39.1–65.7]), and in 19/50 MF patients (38.0% [24.7–52.8]). The median time to response under treatment (CR or PR) was similar according to patient groups (3.1 months for SS and MF patients; respective ranges: 0.1–25.0, and 0.3–44.3 months).

According to compartments involved, blood response was achieved in 45 out of 55 (81.8%) patients with SS; skin

**TABLE 1** Patient and disease characteristics at mogamulizumab initiation.

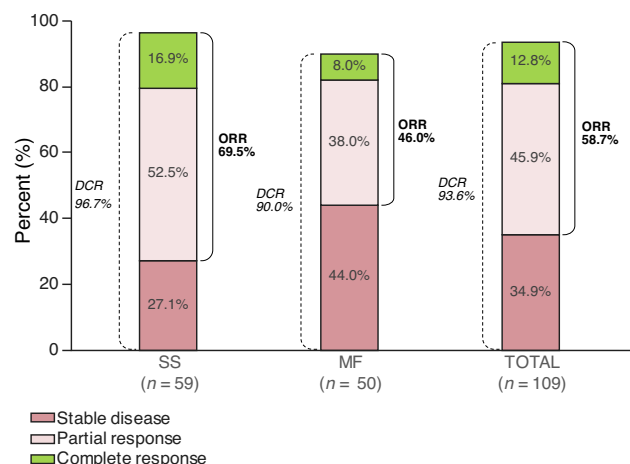
|   | Sézary syndrome (N= 69) | Mycosis Fungoides (N= 53) | Overall analysis population (N= 122) |
|---|-------------------------|---------------------------|--------------------------------------|
| Age, years  |                         |                           |                                      |
| Mean ± SD   | 67.3 ± 11.5             | 65.8 ± 13.0               | 66.6 ± 12.1                          |
| ≥65 years   | 46 (66.7%)              | 29 (54.7%)                | 75 (61.5%)                           |
| Male sex  | 34 (49.3%)              | 27 (50.9%)                | 61 (50.0%)                           |
| Time from initial diagnosis, years – median [IQR]     | 2.0 [1.1–3.0]           | 4.0 [1.7–7.9]             | 2.5 [1.3–5.6]                        |
| CTCL stage  |                         |                           | N= 117                               |
| IA-IB-IIA   |                         |                           | 26 (22.2%)                           |
| IIB   |                         |                           | 7 (6.0%)                             |
| IIIA  |                         |                           | 8 (6.8%)                             |
| IIIB  |                         |                           | 7 (6.0%)                             |
| IVA <sub>1</sub>                                      |                         |                           | 59 (50.4%)                           |
| IVA <sub>2</sub>                                      |                         |                           | 8 (6.8%)                             |
| IVB   |                         |                           | 2 (1.7%)                             |
| TNMB stages   | N= 66                   | N= 51                     | N= 117                               |
| T involvement   |                         |                           |                                      |
| T1  | 1 (1.5%)                | 2 (3.9%)                  | 3 (2.6%)                             |
| T2  | 5 (7.6%)                | 25 (49.0%)                | 30 (25.6%)                           |
| T3  | 1 (1.5%)                | 9 (17.6%)                 | 10 (8.5%)                            |
| T4  | 59 (89.4%)              | 15 (29.4%)                | 74 (63.2%)                           |
| N involvement   |                         |                           |                                      |
| N0  | 31 (47.0%)              | 30 (58.8%)                | 61 (52.1%)                           |
| N1  | 5 (7.6%)                | 4 (7.8%)                  | 9 (7.7%)                             |
| N2  | 8 (12.1%)               | 4 (7.8%)                  | 12 (10.3%)                           |
| N3  | 6 (9.1%)                | 2 (3.9%)                  | 8 (6.8%)                             |
| Nx  | 16 (24.2%)              | 11 (21.6%)                | 27 (23.1%)                           |
| M involvement   |                         |                           |                                      |
| M0  | 64 (97.0%)              | 51 (100.0%)               | 115 (98.3%)                          |
| M1  | 2 (3.0%)                | 0 (0.0%)                  | 2 (1.7%)                             |
| B involvement   |                         |                           |                                      |
| B0  | 0 (0.0%)                | 38 (74.5%)                | 38 (32.5%)                           |
| B1  | 0 (0.0%)                | 13 (25.5%)                | 13 (11.1%)                           |
| B2  | 66 (100.0%)             | 0 (0.0%)                  | 66 (56.4%)                           |
| Previous cutaneous T-cell systemic lymphoma therapies |                         |                           |                                      |
| At least one  | 67 (97.1%)              | 53 (100.0%)               | 120 (98.4%)                          |
|   | N= 67                   | N= 53                     | N= 120                               |
| Median number [IQR] (n= 120)                          | 3.0 [2–5]               | 4.0 [3–5]                 | 3 [2–5]                              |
| Previous systemic treatments <sup>a</sup>             |                         |                           |                                      |
| Conventional chemotherapy <sup>b</sup>                | 28 (41.8%)              | 28 (52.8%)                | 56 (46.7%)                           |
| Bexarotene  | 50 (74.6%)              | 42 (79.2%)                | 92 (76.7%)                           |
| Methotrexate  | 50 (74.6%)              | 37 (69.8%)                | 87 (72.5%)                           |
| Interferon  | 30 (44.8%)              | 22 (41.5%)                | 52 (43.3%)                           |
| Romidepsin  | 10 (14.9%)              | 8 (15.1%)                 | 18 (15.0%)                           |
| Brentuximab vedotin                                   | 7 (10.4%)               | 7 (13.2%)                 | 14 (11.7%)                           |
| Systemic glucocorticoids                              | 9 (13.4%)               | 4 (7.5%)                  | 13 (10.8%)                           |
| Vorinostat  | 5 (7.5%)                | 8 (15.1%)                 | 13 (10.8%)                           |
| Extracorporeal photopheresis                          | 47 (70.1%)              | 11 (20.8%)                | 58 (48.8%)                           |
| Other   | 11 (16.4%)              | 16 (30.2%)                | 27 (22.5%)                           |

Abbreviations: CTCL, cutaneous T-cell lymphoma; IQR, interquartile range; SD, standard deviation; TNMB, tumour node, metastasis, blood.

<sup>a</sup>One patient could receive more than one previous cutaneous T-cell systemic lymphoma treatment.

<sup>b</sup>Conventional chemotherapy includes chemotherapy that might have been used as monotherapy or in combination with other agents: gemcitabine (n=35), pegylated liposomal doxorubicin (n=28), chlorambucil (n=9), bendamustine (n=6), cyclophosphamide-doxorubicin-vincristine-prednisolone (CHOP, n=4; mini-CHOP, n=1), gemcitabine-oxaliplatin (GEMOX, n=3), ifosfamide-etoposide (n=3), cyclophosphamide-vincristine-prednisolone (COP, n=1), cyclophosphamide-doxorubicin-etoposide-vincristine-prednisolone (CHEOP, n=1), and/or vinorelbine (n=1).





**FIGURE 1** Overall response rate and disease control rate under mogamulizumab treatment. DCR, disease control rate; MF, Mycosis Fungoides; ORR, overall response rate; SS, Sézary syndrome.

overall response was achieved in 38 out of 61 (66.7%) patients with SS and in 23 out of 50 patients with MF (46.0%) (Table 2). ORR was significantly higher ( $p=0.0030$ ) in patients with blood involvement (69.5% for B2 [SS patients] and 75.0% for B1 [MF patients] vs. 36.8% for B0 [MF patients]) (see Table S1).

In the overall analysis population ( $n=122$ ), the median PFS was estimated at 15.0 months (95% CI [9.0–50.8]). It was longer in SS patients than in MF patients (20.3 months [11.7 – not reached] vs. 8.8 months [4.6–43.0]) but no significant difference between patient groups was shown ( $p=0.0542$ ) (Figure 2). At 12 months, the PFS rates were estimated at 56.3% (95% CI [44.9–66.3]) in the overall analysis population, 63.1% [46.8–75.7] in SS patients, and 47.6% [31.5–62.1] in MF patients. Over patient follow-up, the median OS was not reached in the overall analysis population as well as in both patient groups. At 12 and 18 months, OS rates were estimated at 95.8% (95% CI [89.1–98.4]) and 85.3% [83.2–97.4], respectively in the overall analysis population, while quite similar OS rates were observed at the same time-points in SS and MF patients (96.1% [85.0–99.0] and 95.4% [82.7–98.8] at 12 months, 83.7% [56.8–84.5] and 87.5% [59.2–96.6] at 18 months).

## Use of mogamulizumab

Patients of the overall analysis population were treated with mogamulizumab during a median period of 4.6 months (IQR [2.1–7.2], range: 0.5–71.6) over the study period. Overall, 96.7% of patients received all the planned infusions of mogamulizumab during the treatment period. A total of 13 patients (10.7%) experienced at least one temporary treatment discontinuation, and 71 patients (58.2%) permanently discontinued mogamulizumab treatment during follow-up, mainly due to disease progression (43 patients, 60.6% of the cases) or ADR (15 patients, 21.1%). Few patients discontinued treatment upon remission achievement (4/71, 5.6%).

**TABLE 2** Compartmental response rates with mogamulizumab treatment.

|                      | SS (N = 59)   | MF (N = 50)   | Total (N = 109) |
|----------------------|---------------|---------------|-----------------|
| Blood, n/N (%)       | 45/55 (81.8%) | NA            | NA              |
| 95% CI               | [69.1–90.9]   |               |                 |
| Skin, n/N (%)        | 38/57 (66.7%) | 23/50 (46.0%) | 51/107 (57.0%)  |
| 95% CI               | [52.9–78.6]   | [31.8–60.7]   | [47.1–66.5]     |
| Lymph nodes, n/N (%) | 9/15 (60.0%)  | 5/19 (26.3%)  | 14/34 (41.2%)   |
| 95% CI               | [32.3–83.7]   | [9.1–51.2]    | [24.6–59.3]     |
| Viscera, n/N (%)     | 0/2 (0.0%)    | 2/8 (25.0%)   | 2/10 (20.0%)    |
| 95% CI               | NA            | [3.2–65.1]    | [2.5–55.6]      |

Abbreviations: CI, confidence interval; MF, Mycosis Fungoides; NA, not applicable; SS, Sézary syndrome.

[Correction added on 12 June 2023, after first online publication: The authors have revised the data for Viscera in Table 2.]

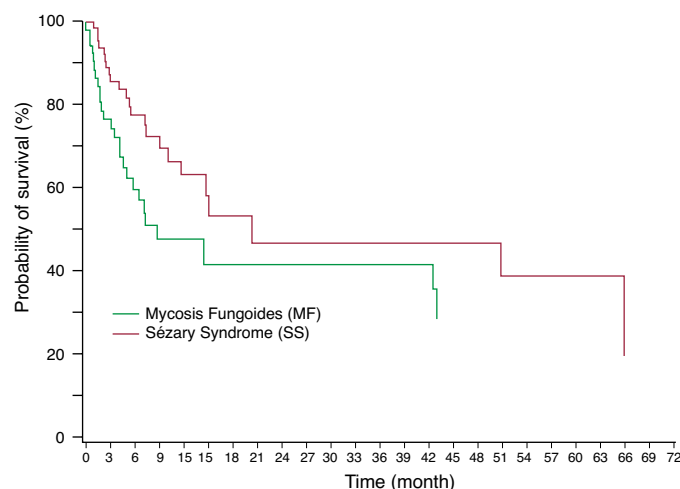
## Safety

At least one treatment-emergent ADR was reported in 70 out of the 124 patients of the safety population (56.5%). Among the 203 ADRs reported, the most common events were lymphopenia (reported in 23.4% of patients), asthenia (17.7%), rash (14.5%) and infusion-related reaction (IRR, 12.1%) (Table 3). These four subsets of ADRs were more frequently reported in SS patients than in MF patients (lymphopenia: 30.4% vs. 15.1%; asthenia: 23.2% vs. 11.3%; rash: 18.8% vs. 9.4%; IRR: 15.9% vs. 7.5%).

Serious ADRs were reported in 23 patients (18.5%), mainly as rash (10 patients, 8.1%), and vitiligo (3 patients, 2.4%). Among the 15 patients (12.1%) with ADRs leading to permanent discontinuation of mogamulizumab, rash (nine patients, 7.3%), was the most reported event. Treatment stop occurred 60 days in median after the first mogamulizumab infusion. The 17 IRRs reported under mogamulizumab in 15 patients were limited to the first treatment cycle, and they occurred at the first infusion in 15/17 cases. The most reported symptoms associated with IRRs were chills (eight patients) and pyrexia (six patients). For three patients (2.4%), IRRs were assessed as serious, and one patient (0.8%) discontinued mogamulizumab due to IRRs at the first infusion. Among the seven deceased patients during follow-up, a 78-year-old patient with SS experienced a serious ADR, with three episodes of tumour lysis syndrome, 3, 6 and 8 weeks after the first infusion of treatment, that led to patient death within 3 weeks, despite hydration and antihyperuricemic treatment with resburicase.

## DISCUSSION

After the previous MAVORIC multinational pivotal trial,<sup>11</sup> this real-world retrospective French study provided complementary mogamulizumab effectiveness and safety data in 109 and 124 patients, respectively, with SS or MF. Very recently, data from a French study involving 21 SS and MF patients conducted with a similar design were published.<sup>14</sup>



| Time (mo) | 0  | 3  | 6  | 9  | 12 | 15 | 18 | 21 | 24 | 27 | 30 | 33 | 36 | 39 | 42 | 45 | 48 | 51 | 54 | 57 | 60 | 63 | 66 | 69 | 72 |
|-----------|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|
| At risk   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |
| MF        | 53 | 36 | 22 | 14 | 11 | 7  | 7  | 7  | 7  | 7  | 7  | 7  | 7  | 7  | 7  | 4  | 4  | 3  | 3  | 2  | 2  | 2  | 1  | 1  | 1  |
| SS        | 69 | 50 | 36 | 25 | 19 | 11 | 8  | 7  | 7  | 6  | 6  | 6  | 6  | 6  | 6  | 6  | 6  | 5  | 5  | 4  | 4  | 3  | 2  | 1  | 0  |

**FIGURE 2** Progression-free survival from mogamulizumab initiation.

**TABLE 3** Adverse drug reactions ( $N=124$ ).

|  | Adverse drug reactions (ADRs) |                           |                             | Serious ADRs                | ADRs leading to treatment discontinuation |
|--|-------------------------------|---------------------------|-----------------------------|-----------------------------|---|
|  | Sézary syndrome (N= 69)       | Mycosis Fungoides (N= 53) | Total <sup>a</sup> (N= 124) | Total <sup>a</sup> (N= 124) | Total <sup>a</sup> (N= 124)               |
| Blood and lymphatic system disorders                 |                               |                           |                             |                             |   |
| Lymphopenia  | 21 (30.4%)                    | 8 (15.1%)                 | 29 (23.4%)                  | 0 (0.0%)                    | 0 (0.0%)                                  |
| Thrombopenia   | 3 (4.3%)                      | 1 (1.9%)                  | 4 (3.2%)                    | 3 (2.4%)                    | 1 (0.8%)                                  |
| Gastrointestinal disorders                           |                               |                           |                             |                             |   |
| Diarrhoea  | 3 (4.3%)                      | 2 (3.8%)                  | 5 (4.0%)                    | 0 (0.0%)                    | 0 (0.0%)                                  |
| Nausea   | 1 (1.9%)                      | 2 (2.9%)                  | 4 (3.2%)                    | 0 (0.0%)                    | 0 (0.0%)                                  |
| General disorders and administration site conditions |                               |                           |                             |                             |   |
| Asthenia   | 16 (23.2%)                    | 6 (11.3%)                 | 22 (17.7%)                  | 0 (0.0%)                    | 0 (0.0%)                                  |
| Pyrexia  | 2 (2.9%)                      | 3 (5.7%)                  | 5 (4.0%)                    | 1 (0.8%)                    | 0 (0.0%)                                  |
| Injury, poisoning and procedural complications       |                               |                           |                             |                             |   |
| Infusion-related reaction                            | 11 (15.9%)                    | 4 (7.5%)                  | 15 (12.1%)                  | 3 (2.4%)                    | 1 (0.8%)                                  |
| Musculoskeletal and connective tissue disorders      |                               |                           |                             |                             |   |
| Myalgia  | 1 (1.4%)                      | 2 (3.8%)                  | 3 (2.4%)                    | 0 (0.0%)                    | 0 (0.0%)                                  |
| Skin and subcutaneous tissue disorders               |                               |                           |                             |                             |   |
| Rash   | 13 (18.8%)                    | 5 (9.4%)                  | 18 (14.5%)                  | 10 (8.1%)                   | 9 (7.3%)                                  |
| Vitiligo   | 3 (4.3%)                      | 0 (0.0%)                  | 3 (2.4%)                    | 3 (2.4%)                    | 0 (0.0%)                                  |

Note: Data are  $n$  patients (%). ADRs that occurred in  $\geq 2\%$  of patients and all serious ADRs in that occurred in these patients. Serious ADRs (Sézary syndrome, Mycosis Fungoides): thrombopenia (3.0), pyrexia (0.1), infusion-related reaction (3.0), rash (8.2), vitiligo (3.0); ADRs leading to treatment discontinuation: thrombopenia (1.0), infusion-related reaction (1.0), rash (5.4).

<sup>a</sup>Including two patients for whom the diagnosis (Sézary syndrome or Mycosis Fungoides) was not clearly established.

We confirm the efficacy of mogamulizumab in heavily pre-treated patients (median of 3 prior CTCL systemic therapies) in routine medical practice, with an ORR of 58.7% over a median treatment duration varying from 0.5 to 71.6 months. ORR was 28% in the MAVORIC study and

a median follow-up duration of 17 months.<sup>11</sup> This lower ORR may be partly due to a stricter response definition in this interventional study (confirmed CR or PR at  $\geq 2$  consecutive assessments spaced  $\geq 8$  weeks) and to less selective patient characteristics. Based on a meta-analysis of nine

interventional studies, the pooled ORR was 43% for patients treated with mogamulizumab monotherapy.<sup>15</sup>

In the OMEGA study, the response rate was higher in patients with SS than in patients with MF (69.5% and 46.0%, respectively) as was observed in the MAVORIC trial (37% and 21%, respectively). The rapid effectiveness of mogamulizumab was confirmed in a real-life setting (median time to treatment response: 3.1 months in OMEGA and 3.3 months in MAVORIC). Better effectiveness outcomes were observed in patients with blood involvement (B2) at treatment start: highest ORR in these SS patients (81%) which was consistent with findings from the previous MAVORIC trial (68%),<sup>11</sup> and improved treatment response with increasing blood involvement, as previously shown in patients with MF and SS.<sup>16,17</sup> However, in this study the effectiveness was also observed in the MF patients without blood involvement.

The median PFS was estimated at 15.0 months in OMEGA, with no significant differences between SS and MF patients. It was shorter in MAVORIC (7.7 months overall)<sup>11</sup> and longer in a recent French real-world study (22 months)<sup>14</sup>; such differences may be notably attributed to the patient and disease characteristics at treatment initiation. In OMEGA, the median OS was not reached after a median follow-up duration of 8.7 months which was consistent with findings from MAVORIC trial (median OS not reached after 17.0 months of patient follow-up<sup>11</sup>).

Regarding the safety profile of mogamulizumab, ADRs were reported in 56.5% of patients, that is, in a lower proportion than previously observed in the MAVORIC trial (84.8%).<sup>18</sup> Such an under-reporting of adverse events is regularly observed in non-interventional studies. Nevertheless, our results on serious ADRs were consistent with previous findings (reported in 18.5% of patients during follow-up vs. in 20% in the MAVORIC study<sup>11</sup>). As previously shown,<sup>11,15</sup> the most common ADRs were lymphopenia and rashes. According to literature data,<sup>15</sup> lymphopenia is explained by the pharmacologic effect of mogamulizumab, but no serious treatment-related lymphopenia was reported in the OMEGA study. As already shown,<sup>11,19</sup> mogamulizumab can induce rashes, and this event was the most reported ADR leading to treatment discontinuation (8% of patients) while it may be associated with positive clinical response.<sup>20–22</sup> As rash is difficult to clinically distinguish from relapse or disease progression,<sup>18,23,24</sup> skin biopsies could be useful and practice recommendations to assist healthcare providers in identifying and managing drug-related skin eruptions (with topical or even oral steroids for severe events) were recently proposed<sup>25</sup> which could prevent unnecessary discontinuation of mogamulizumab. Asthenia and IRRs were the most common non-hematologic ADRs (18% and 12% of patients, respectively), but no patients experienced serious asthenia and only 2.4% of patients had serious IRRs (2% in MAVORIC).<sup>11</sup> In addition, IRRs were limited to the first infusion of mogamulizumab in most cases, and only one patient discontinued treatment due to IRR. During follow-up, one patient died from related tumour lysis syndrome. This rare serious ADR<sup>16</sup> may be avoided by close monitoring at the treatment

initiation. Finally, this study highlights the acceptable safety profile of mogamulizumab in routine medical practice.

Our study had some limitations, mainly due to its non-interventional and retrospective design (no comparator, assessments available only when performed in routine clinical practice, and data available only when previously recorded in patients' medical files). In this retrospective study, the duration of patient follow-up strongly varied (ranging from 0.5 to 72.6 months depending on patients) which led to heterogeneous effectiveness population. Since 20 patients still alive at the end of the MAVORIC trial were included in the OMEGA study (i.e. 16% of our analysis population), there might be a survivor bias<sup>26</sup> with an overestimation of our effectiveness results.

Despite these limitations, our real-life data from a large French population of patients with Sézary syndrome or Mycosis Fungoides, less selective than in clinical trials, were consistent with previous findings and confirmed the effectiveness of mogamulizumab (high level and rapid onset of treatment response, in particular in patients with blood involvement), as well as its manageable safety profile.

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## CONFLICT OF INTEREST STATEMENT

MBB: Kyowa Kirin, Recordati, Takeda; GQ: Kyowa Kirin, Recordati Rare Diseases, Takeda; CN and SDR: None; OD, CRW, MDI, FG, and ABDM: Kyowa Kirin; GD: Kyowa Kirin, Recordati Rare Diseases; APL: Kyowa Kirin, Recordati; VB: Employee of Kyowa Kirin; MB: Helsinn/Recordati, Innate Pharma, Kyowa Kirin, Takeda.

## DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

## ETHICS STATEMENT

The study protocol was approved by an independent Ethics Committee (*Sud-Est VI, Clermont-Ferrand*). According to the French law regarding retrospective studies, all included patients alive at the time of data collection were informed about the study content and had no objections to their personal data being processed.

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## SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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