Response to Campbell et al.'s comments on our study "Real-life efficacy of immunotherapy for Sézary syndrome: a multicenter observational cohort study"

Alizée Bozonnat,[a,b,c] Arnaud Serret-Larmande,[b,c] Marie Beylot-Barry,[d] Martine Bagot,[a,b,c] and Adèle de Masson,[a,b,c,*] Cutaneous Lymphomas French Study Group

[a]Department of Dermatology, Saint-Louis Hospital, AP-HP, Paris, France
[b]INSERM U976, Institut de Recherche Saint-Louis, Paris, France
[c]Université Paris Cité, Paris, France
[d]Department of Dermatology, CHU de Bordeaux, BoRdeaux Institute of Oncology, BRIC INSERM U1312, INSERM BoRdeaux Institute of Oncology, Team 5, Université de Bordeaux, Bordeaux, France

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We thank Campbell et al. for their relevant comments[1] on our study "Real-life efficacy of immunotherapy for Sézary syndrome: a multicenter observational cohort study".[2] They mention the low utilization of allogeneic hematopoietic stem cell transplantation (HSCT) in our study compared to the study by Campbell et al.[3] The details on the recruitment of the 339 patients in our study and of patients who received allogeneic HSCT are provided in Table 1 below. Seventeen patients (5%) received allogeneic HSCT in our study: 7 patients from Saint-Louis Hospital (Paris), 2 from Clermont-Ferrand, 2 from Lille, 2 from Rennes, and 4 patients from Bordeaux, Montpellier, Cochin Hospital (Paris), Henri-Mondor Hospital (Créteil). All participating centers offered allogeneic HSCT, either directly at the center or at a center nearby. We believe that this low utilization of allogeneic HSCT is related to the fact that our study spanned a two-decades period of time (patients were diagnosed between 2000 and 2020) and allogeneic HSCT was, in our experience, rarely offered to patients with advanced cutaneous T-cell lymphomas in the early 2000s, since the published evidence on this treatment was still scarce in this indication.[4] By contrast, the study by Campbell et al. enrolled patients newly diagnosed between 2012 and 2020, which could explain this discrepancy.[3]

Regarding the impact of allogeneic HSCT on survival and if mogamulizumab improved survival independently of allogeneic HSCT, we provided in Table 2 below an updated version of the main analysis. As a reminder, the main analysis modelized the overall survival using a Cox proportional hazard model, stratified on the number of lines, disease stage, and included mogamulizumab, age at inclusion, large-cell transformation, LDH increase and eosinophilia as covariates. We added the variable "allogeneic HSCT" to this model to study its impact on the results. The adjusted hazard ratio (HR) remained mostly unchanged when including the

	Total number of patients enrolled (%)	Number of patients who received allogeneic HSCT (%)
Inclusion center		
Bern	7 (2.1%)	
Besançon	10 (2.9%)	
Bordeaux	30 (8.8%)	1
Clermont-Ferrand	24 (7.1%)	2
Grenoble	11 (3.2%)	
Lille	15 (4.4%)	2
Lyon	22 (6.5%)	
Montpellier	28 (8.3%)	1
Nantes	29 (8.6%)	
Nice	1 (0.3%)	
Orléans	2 (0.6%)	
Paris–Cochin	6 (1.8%)	1
Boulogne–Ambroise Paré	1 (0.3%)	
Paris–Avicenne	4 (1.2%)	
Paris–Bichat	2 (0.6%)	
Créteil–Mondor	9 (2.7%)	1
Paris–Tenon	2 (0.6%)	
Paris–Saint-Louis	86 (25.4%)	7
Reims	13 (3.8%)	
Rennes	10 (2.9%)	2
Rouen	10 (2.9%)	
Toulouse	10 (2.9%)	
Tours	5 (1.5%)	
Valence	2 (0.6%)	

Table 1: **Details on the recruitment of the 339 patients in the study and 17 patients who received allogeneic hematopoietic stem cell transplantation.**

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*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).

Variable	adjusted HR	95% CI	p. value
Treated with mogamulizumab	0.34	0.15; 0.80	0.013
Diagnosis age (years): 50–59	0.86	0.34; 2.16	0.74
Diagnosis age (years): 60–69	1.39	0.59; 3.31	0.45
Diagnosis age (years): 70–79	2.49	1.07; 5.76	0.03
Diagnosis age (years):≥80	4.91	2.10; 11.46	<0.001
Cytologic transformation (diagnosis or follow-up)	2.82	1.57; 5.07	<0.001
LDH increase	1.07	0.65; 1.76	0.80
Eosinophilia	1.59	0.96; 2.64	0.07
Allogeneic hematopoietic stem cell transplantation	1.04	0.34; 3.19	0.94

Abbreviations: LDH, serum levels of lactate dehydrogenases; HR, hazard ratio; CI, confidence interval. Hazard ratios (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), allogeneic stem cell transformation and eosinophilia as covariables.

Table 2: **Multivariable model on overall survival including allogeneic hematopoetic stem cell transformation as covariable.**

Variable	HR	95% CI	p. value
Treated with mogamulizumab	0.57	0.41; 0.77	0.00033
Diagnosis age (years): 50–59	1.40	0.99; 1.99	0.05485
Diagnosis age (years): 60–69	1.79	1.28; 2.51	0.00061
Diagnosis age (years): 70–79	1.69	1.20; 2.37	0.00249
Diagnosis age (years):≥80	1.62	1.10; 2.38	0.01484
Cytologic transformation (diagnosis or follow-up)	2.51	1.97; 3.21	<1e-05
LDH increase	1.26	1.03; 1.56	0.02663
Eosinophilia	0.98	0.77; 1.24	0.85856
Number of treatment lines received	1.27	1.19; 1.36	<1e-05

Abbreviations: LDH, serum levels of lactate dehydrogenases; HR, hazard ratio; CI, confidence interval.

Table 3: **Multivariable model on time to next treatment using the number of received treatment lines as covariable.**

allogeneic HSCT in the model. Therefore, being treated with mogamulizumab showed a statistically significant association with overall survival independently of allogeneic HSCT.

In our study, the time-to-next treatment (TTNT) "clock" ended, indeed, when end-of-life care commenced. Sixty-six patients received mogamulizumab as last line of treatment, excluding rechallenges. To avoid re-treatment bias in patients experiencing treatment-efficacy and tolerance, we conducted an updated TTNT analysis, censoring patients when they were exposed to mogamulizumab a second time. There were 8 patients in such a case, they were therefore censored at the time of their second exposure. The median TTNT of mogamulizumab in this analysis was unchanged: 24.5 months [95% confidence interval (CI): 18; 28]. Of note, Cox proportional hazard model departs from the assumption of uninformative censorship. However, given the little loss of information these censors represented, it did lead to only minor changes in the results, and mogamulizumab remained significantly associated with longer TTNT in multivariate analysis (HR = 0.51 [0.36; 0.74]; $p < 0.01$).

There was no significant impact of combination therapies on TTNT in our study in multivariable analysis (HR, 0.89, 95% CI 0.73; 1.09, $p = 0.26$). This could potentially be explained by the heterogeneity of the combination therapies received by the patients. Regarding the association between the number of treatment lines received by the patient and the TTNT, the number of treatment lines was used as a stratification factor in the survival analyses using a Cox proportional hazard model, given that the baseline hazard was increasing with more advanced disease.[2] Nonetheless, running a Cox proportional hazard model showed a statistically significant association between treatment lines count and the TTNT (HR = 1.27 [1.19; 1.36], $p \leq 0.001$, Table 3), underscoring, as expected, the shorter TTNT experienced by patients with more advanced diseases.

Contributors

AB performed data collection, ASL performed data analysis, MBB and MBag participated in data interpretation and writing, ADM participated in data interpretation and wrote the manuscript. All authors reviewed the manuscript.

Declaration of interests

ADM declares honoraria and consulting fees from Almirall, Takeda, Recordati, Helsinn, Kyowa.

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

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AB and ASL declare no conflict of interest.

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