CORRESPONDENCE OPEN

Check for updates

Switching TKIs during CML therapy is frequent, mostly driven by intolerance, and does not affect survival: a prospective Quebec registry study

Blood Cancer Journal (2025)15:35 ; https://doi.org/10.1038/s41408-025-01242-8

Dear Editor

Tyrosine kinase inhibitors (TKI) targeting the *BCR::ABL1* fusion gene have dramatically improved the prognosis of patients with chronic myeloid leukemia (CML) to the point where most patients can enjoy a normal life expectancy [1]. Outside of clinical trials, the use of different TKIs in 1 L is largely influenced by drug accessibility, toxicity profile [2], and treatment-free remission (TFR) as the therapeutic goal [3]. However, there is a paucity of information on how therapeutic choices are made in the real-world (RW) setting, and on how resistance and tolerance drive switching compared to published clinical trials [4]. This study aimed to document treatment patterns and outcomes from a large provincial CML registry that includes 20 oncology centers, comprising both academic and community-based hospitals, reflecting a broad general treatment population.

This prospective observational study used data from the registry of the Quebec CML Research Group (GQR LMC-NMP). All patients signed an informed consent, and the study protocol was approved by the institutional review board of all participating centers. Data were extracted from medical charts and then transferred to a database by a limited number of trained data managers, ensuring consistency. The registry was initiated in 2009 and is actively recruiting new patients. Clinical data predating 2009 were collected retrospectively, thereafter all data were collected prospectively. Patients with a clinical diagnosis of CML, aged 18 years or older, and able to provide informed consent were included in the registry. Exclusion criteria for this analysis were a diagnosis prior to 2008, life expectancy inferior to 3 months due to a condition unrelated to CML, accelerated or blast phase at diagnosis, and ponatinib or bosutinib as 1 L treatment. Data used for the current analysis were extracted from the registry in April of 2024. Choice of TKI was at the discretion of the physician, however, local regulatory approvals impacted on the choice of 1 L therapy.

Switching was defined as a change of a specific TKI to another TKI or hematopoietic cell transplant (HSCT). Reasons for switching were categorized as resistance, intolerance, or other. Serial switchers were defined as individuals switching TKI ≥2 consecutive times for the same reason (intolerance or resistance). Event-free survival (EFS) was calculated from the date of TKI initiation until TKI switching, HSCT, or death. Patients ending treatment for an attempt at treatment-free remission (TFR) were censored at the time of TKI cessation for analysis. Details concerning statistical methods are available in the supplementary appendix.

At the time of data extraction, 661 patients were eligible for the analysis. Characteristics of the study population are available in Table S1 (supplementary). Imatinib was the preferred choice overall: 474 (71.7%) were on imatinib, 113 (17.1%) on nilotinib, and 74 (11.2%) on dasatinib. Switching was frequent in 1 L across all TKI, with 326 (49.3%) patients transitioning to 2 L. Switching from 2 L to 3 L line occurred in 141 patients, representing 21.3% of the total population and 43.3% of the patients who made a first switch. Finally, switching from 3 L to fourth line (4 L) TKI occurred in 54 patients (8.2% of the total population and 38.3% of the patients receiving 3 L therapy). The complexity of switching patterns is illustrated in Fig. S1 (supplementary).

A total of 504 switches to another TKI occurred either for intolerance or resistance from 1 L to 4 L of treatment. Intolerance was the reported cause in 65.9% of those switches compared to 34.1% for resistance ($p < 0.01$). In 1 L, intolerance led to switching in 185 (27.2%) patients, and resistance led to switching in 127 (19.2%) patients ($p < 0.01$). The proportion of intolerance (27.3%) was higher than resistance (7.0%) for patients on 2 G TKI in 1 L. In 2 L, intolerance led to switching in 105 (32.2%) patients, and resistance led to switching in 33 (10.1%) patients ($p < 0.01$). Treatment discontinuation by TKI and by line of treatment is depicted in Fig. S2 (supplementary). Across lines of treatment, there were 3.6 times more serial switchers (2 or more switches) for intolerance ($n = 77$) than serial switchers for resistance ($n = 21$).

The main adverse events (AE) leading to switching in 1 L were diverse but in-line with the known safety profile of specific TKIs: pleural effusion for dasatinib, cardiovascular abnormalities for nilotinib, and several different AEs for imatinib, including GI toxicity. Adverse events leading to TKI switching in 1 L are available in Table S2 (supplementary). For resistance in 1 L, 98 patients (77.2% of the 1 L resistant population) were switched after losing MMR while on treatment: 14 patients (11.0%) were switched because they did not achieve the milestones, seven patients (5.5%) because the physician was not satisfied with the depth of response, and data were incomplete for eight patients.

In 1 L, EFS was significantly better for dasatinib with an HR = 0.54 (95% CI: 0.38–0.77, $p < 0.01$) and for nilotinib with an HR = 0.55 (95% CI: 0.38–0.77, $p < 0.01$) compared to imatinib when adjusted for age, gender, and comorbidities (Fig. 1). EFS was not statistically significantly different in 2 L ($p = 0.46$) and in 3 L ($p = 0.12$) between available TKIs. In multivariate analysis, dasatinib (SHR = 0.26 (95% CI: 0.11–0.60, $p < 0.01$)) and nilotinib (SHR = 0.19 (95% CI: 0.09–0.42, $p < 0.01$)) were

Received: 11 November 2024 Revised: 20 January 2025 Accepted: 20 February 2025
Published online: 11 March 2025

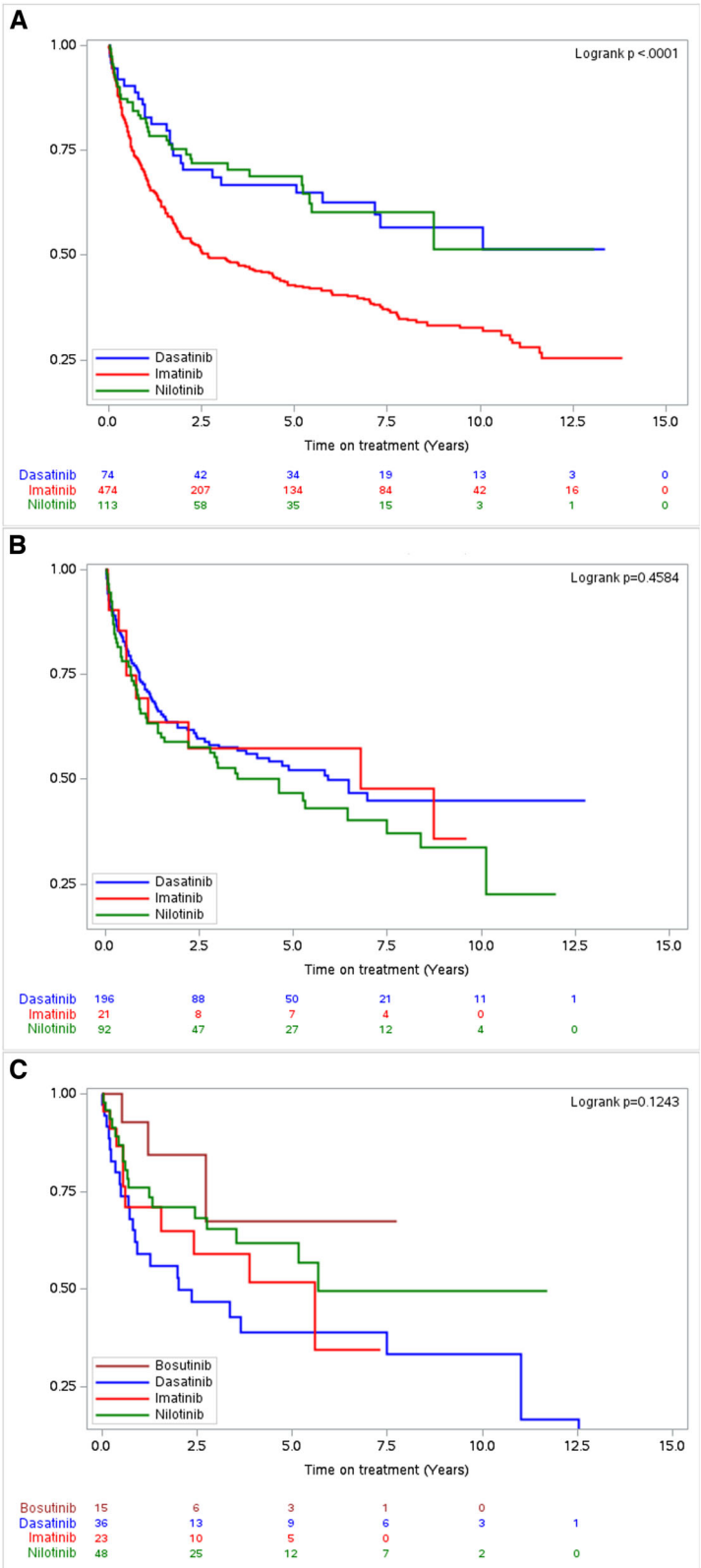

Fig. 1 Event-free survival. This figure shows the probability of event-free survival according to the TKI used (imatinib = red, dasatinib = blue, nilotinib = green, bosutinib = burgundy). **A** is 1 L of treatment, **B** is 2 L of treatment, and **C** is 3 L.

associated with less resistance 1 L compared to imatinib. Age <50 years and male sex negatively impacted EFS due to resistance in 1 L. There was no statistically significant difference for EFS due to intolerance between dasatinib or nilotinib and imatinib in 1 L in multivariate analysis. Age >65 years, female sex, and having >3 comorbidities at diagnosis all negatively impacted EFS due to intolerance (Table S3 supplementary). The cumulative incidence of intolerance and

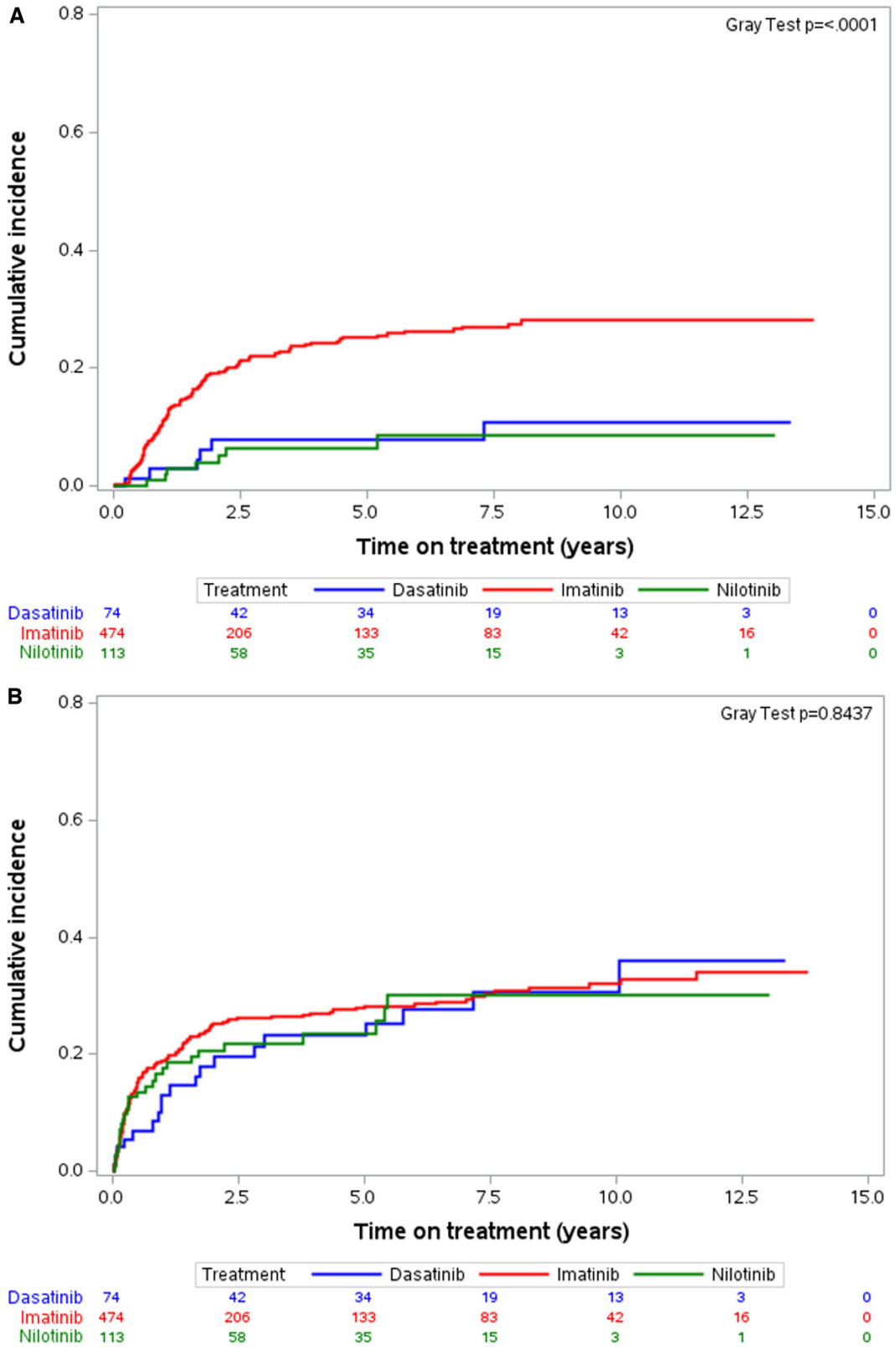

Fig. 2 Cumulative incidence of failure in the first line of treatment. This figure shows the cumulative incidence of failure in 1 L of treatment according to the TKI used (imatinib = green, dasatinib = blue, nilotinib = green). Panel **A** shows a cumulative incidence of resistance leading to switching in 1 L. Panel **B** shows the cumulative incidence of intolerance leading to switching in 1 L.

resistance leading to switching in 1 L using a competing risk model is shown in Fig. 2.

Estimated median OS was not different and not reached for those who never switched and for those who switched only 1 time or many times ($p = 0.90$) (Fig. S3, supplementary).

In this RW study, we examined routine TKI prescription patterns with a focus on therapy switching. We benefit from one of the largest worldwide registries that includes the majority of CML patients in the province of Québec in Canada. We confirm and further characterize previous observations and identify the tolerability as a main target to optimize CML management. In comparison to the pivotal frontline randomized trials [5–7], the rates of discontinuation for AE of the given TKI were lower than the switching rates for intolerance observed in our study. The maturity of our registry allowed us to have meaningful data beyond 1 L. Intolerance was the most frequent cause for switching in all lines of treatment for all TKI and the difference was more pronounced in 2 L and 3 L. It is important to note that in this study, we did not look at the prevalence of AEs, but only at those that led to TKI switching. Factors which may explain the disparate rates of switching in real life include less stringent and more heterogeneous definitions of intolerance. It may be that access to multiple 2 L options weighs in favor of changing treatments rather than attempting to palliate the side effects. However, the observation that a significant proportion of patients are serially intolerant supports the notion that for some, it may be due to a drug class effect. The introduction of a non-ATP-binding TKI, such as asciminib, has already led to improved tolerability [8–11].

We used EFS a surrogate marker of global efficacy, which encompasses optimal disease control for the hematologist and acceptable tolerance for the patient. In 1 L, dasatinib and nilotinib were associated with significantly better EFS than imatinib. This global advantage of 2 G in 1 L is mainly driven by better efficacy. The TKIs had similar failure rates for intolerance in 1 L. All TKI fared the same for EFS in 2 L and 3 L, suggesting that at these timepoints, there was not a globally superior TKI. That said, a given patient may benefit from one molecule over the other when comorbidities are considered.

This study demonstrates that the CML patient journey is more complex than suggested by clinical trials, and that although the overall survival of these patients is excellent [1], the tolerance to the medication is the major driver of therapy changes in all lines of treatment; this occurs more frequently than in clinical trials. We speculate that intolerance may be a factor limiting eligibility for treatment-free remission, and that better-tolerated treatment strategies would lead to more sustained deep molecular response which is a prerequisite for TFR attempt. For example, lower starting doses of dasatinib [12], weekend holiday schedules [13], and (C) min titration [14] have been shown to be more tolerable and at least equally effective than the 100 mg daily approved dosing.

In summary, this RW study of a large cohort of CML patients identify that TKI switching is frequent in all lines of treatment and mainly driven by intolerance. An event-free survival analysis demonstrated that 2 G are superior to imatinib in 1 L owing to less resistance, but that all TKI are globally equivalent in later lines of treatment. Overall survival was the same regardless of whether patients remained on their first TKI or switched. Our results suggest that the most important unmet medical need in CML is better-tolerated treatment strategies.

Lambert Busque[1,2,3,16]✉, Marc-Étienne Beaudet[1,2,16], Michaël Harnois[3], Hanane Moussa[3], Natasha Szuber[1,2,3], Luigina Mollica[1,2,3], Robert Delage[3,4,5], Harold Olney[2,3,6], Pierre Laneuville[3,7,8], Ghislain Cournoyer[3,9], Inès Chamakhi[2,3,10], Marc Lalancette[3,4,5], Danielle Talbot[3,11], Vincent Ethier[3,12,13], Pierre Desjardins[3,13,14] and Sarit Assouline[3,8,15]✉

[1]Institut universitaire d'hémato-oncologie et de thérapie cellulaire (IHOT), Hôpital Maisonneuve-Rosemont, Montréal, QC, Canada. [2]Université de Montréal, Montréal, QC, Canada. [3]Groupe Québécois de recherche en LMC-NMP (GQR LMC-NMP), Montréal, QC, Canada. [4]Department of Hemato-oncology, Centre Hospitalier Universitaire de Québec (CHU de Québec), Montréal, QC, Canada. [5]Université Laval, Québec, QC, Canada. [6]Department of Hemato-oncology, Centre Hospitalier Universitaire de Montréal (CHUM), Montréal, QC, Canada. [7]Department of Hematology, McGill University Health Center (MUHC), Montréal, QC, Canada. [8]McGill University, Montréal, QC, Canada. [9]Department of Hemato-oncology, Hôpital regional de St-Jérôme, Montréal, QC, Canada. [10]Department of Hemato-oncology, Hôpital du Sacré-Cœur de Montréal, Montréal, QC, Canada. [11]Department of Hemato-oncology, Hôpital de la Cité-de-la-Santé, Montréal, QC, Canada. [12]Department of Hemato-oncology, Centre Hospitalier Universitaire de Sherbrooke (CHUS), Montréal, QC, Canada. [13]Université de Sherbrooke, Sherbrooke, QC, Canada. [14]Department of Hemato-oncology, Hôpital Charles-Lemoyne, Montréal, QC, Canada. [15]Department of Hematology, Jewish General Hospital, Montréal, QC, Canada. [16]These authors contributed equally: Lambert Busque, Marc-Étienne Beaudet.
✉email: lambert.busque.med@ssss.gouv.qc.ca; sarit.assouline@mcgill.ca

DATA AVAILABILITY

Datasets analyzed during the current study are available from the corresponding author according to the bylaws of the GQR LMC-NMP.

REFERENCES

1. Bower H, Björkholm M, Dickman PW, Höglund M, Lambert PC, Andersson TM. Life expectancy of patients with chronic myeloid leukemia approaches the life expectancy of the general population. J Clin Oncol. 2016;34:2851–7.
2. Lipton JH, Brümmendorf TH, Gambacorti-Passerini C, Garcia-Gutiérrez V, Deininger MW, Cortes JE. Long-term safety review of tyrosine kinase inhibitors in chronic myeloid leukemia - What to look for when treatment-free remission is not an option. Blood Rev. 2022;56:100968.
3. Atallah E, Sweet K. Treatment-free remission: the new goal in CML therapy. Curr Hematol Malig Rep. 2021;16:433–9.
4. Held N, Atallah EL. Real-world management of CML: outcomes and treatment patterns. Curr Hematol Malig Rep. 2023;18:167–75.
5. Saglio G, Kim DW, Issaragrisil S, le Coutre P, Etienne G, Lobo C, et al. Nilotinib versus imatinib for newly diagnosed chronic myeloid leukemia. N Engl J Med. 2010;362:2251–9.
6. Kantarjian HM, Shah NP, Cortes JE, Baccarani M, Agarwal MB, Undurraga MS, et al. Dasatinib or imatinib in newly diagnosed chronic-phase chronic myeloid leukemia: 2-year follow-up from a randomized phase 3 trial (DASISION). Blood. 2012;119:1123–9.
7. Cortes JE, Kim DW, Kantarjian HM, Brummendorf TH, Dyagil I, Griskevicius L, et al. Bosutinib versus imatinib in newly diagnosed chronic-phase chronic myeloid leukemia: results from the BELA trial. J Clin Oncol. 2012;30:3486–92.
8. Réa D, Mauro MJ, Boquimpani C, Minami Y, Lomaia E, Voloshin S, et al. A phase 3, open-label, randomized study of asciminib, a STAMP inhibitor, vs bosutinib in CML after 2 or more prior TKIs. Blood. 2021;138:2031–41.
9. Hochhaus A, Rea D, Boquimpani C, Minami Y, Cortes JE, Hughes TP, et al. Asciminib vs bosutinib in chronic-phase chronic myeloid leukemia previously treated with at least two tyrosine kinase inhibitors: longer-term follow-up of ASCEMBL. Leukemia. 2023;37:617–26.

10. Atallah E, Mauro MJ, Hochhaus A, Boquimpani C, Minami Y, Maheshwari VK, et al. Matching-adjusted indirect comparison of asciminib versus other treatments in chronic-phase chronic myeloid leukemia after failure of two prior tyrosine kinase inhibitors. J Cancer Res Clin Oncol. 2023;149:6247–62.
11. Hochhaus, A, Wang, J, Kim, D-W, Kim, DDH, Mayer, J, Goh, Y-T, et al. Asciminib in newly diagnosed chronic myeloid leukemia. N Engl J Med. https://doi.org/10.1056/NEJMoa2400858.
12. Jabbour E, Sasaki K, Haddad FG, Issa GC, Skinner J, Dellasala S, et al. Low-dose dasatinib 50 mg/day versus standard-dose dasatinib 100 mg/day as frontline therapy in chronic myeloid leukemia in chronic phase: a propensity score analysis. Am J Hematol. 2022;97:1413–8.
13. La Rosée P, Martiat P, Leitner A, Klag T, Müller MC, Erben P, et al. Improved tolerability by a modified intermittent treatment schedule of dasatinib for patients with chronic myeloid leukemia resistant or intolerant to imatinib. Ann Hematol. 2013;92:1345–50.
14. Rousselot P, Mollica L, Guilhot J, Guerci A, Nicolini FE, Etienne G, et al. Dasatinib dose optimisation based on therapeutic drug monitoring reduces pleural effusion rates in chronic myeloid leukaemia patients. Br J Haematol. 2021;194:393–402.

ACKNOWLEDGEMENTS

The authors would like to thank the patients enrolled in the GQR LMC-NMP registry, the study coordinators in each participating centers and the dedicated data managers, Hanane Taoufiqi and Mahdiah Sabbahi. This study was funded by the GQR LMC-NMP, a registered non-for-profit organization.

AUTHOR CONTRIBUTIONS

LB, SA, and MH designed the study. HM, M-EB, and MH performed analyses. LB, NS, RD, LM, HO, PL, GC, IC, ML, DT, VE, PD, and SA recruited patients. M-EB and LB wrote the paper. SA, NS, and LM critically revised the paper. All authors revised the last version and approved the manuscript.

COMPETING INTERESTS

LB, GC, RD, ML, and VE participated in advisory boards for Novartis. LM, M-EB, DT, and IC have nothing to declare. NS is a clinician scientist of the FRQS.

ETHICAL APPROVAL

The study protocol was conducted in accordance with the principles of the Declaration of Helsinki (as revised in 2013) and approved by the Institutional Review Board (IRB) of all participating centers. The approbation is renewed every year with CÉR CIUSSS-EIMTL (ethics committee).

INFORMED CONSENT

All patients signed an informed consent.

ADDITIONAL INFORMATION

Supplementary information The online version contains supplementary material available at https://doi.org/10.1038/s41408-025-01242-8.

Correspondence and requests for materials should be addressed to Lambert Busque or Sarit Assouline.

Reprints and permission information is available at http://www.nature.com/reprints

Publisher's note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.