Dasatinib discontinuation in patients with chronic-phase chronic myeloid leukemia and stable deep molecular response: the DASFREE study

Neil P. Shah, Valentin García-Gutiérrez, Antonio Jiménez-Velasco, Sarah Larson, Susanne Saussele, Delphine Rea, François-Xavier Mahon, Moshe Yair Levy, Maria Teresa Gómez-Casares, Fabrizio Pane, Franck-Emmanuel Nicolini, Michael J. Mauro, Oumar Sy, Patricia Martin-Regueira, and Jeffrey H. Lipton

*Department of Medicine/Hematology-Oncology, UCSF School of Medicine, San Francisco, CA, USA; Servicio Hematología y Hemoterapia, Hospital Universitario Ramón y Cajal, IRYCIS, Madrid, Spain; Hospital Universitario Carlos Haya, Malaga, Spain; David Geffen School of Medicine at UCLA, Los Angeles, CA, USA; III, Med. Clinic, Medizinische Fakultät Mannheim der Universität Heidelberg, Mannheim, Germany; Department of Hematology, Hôpital Saint-Louis, Paris, France; Department of Hematology, Institut Bergonié, University of Bordeaux, Bordeaux, France; Baylor Charles A. Sammons Cancer Center, Dallas, TX, USA; Hospital Universitario de Gran Canaria Dr. Negrín, Las Palmas de Gran Canaria, Spain; Dipartimento di Medicina clinica e Chirurgia, Università degli Studi di Napoli Federico II, Naples, Italy; HématoLOGIC Clinique, Centre Léon Bérard, Lyon, France; Myeloproliferative Neoplasms Program, Memorial Sloan Kettering Cancer Center, New York, NY, USA; Bristol-Myers Squibb, Princeton, NJ, USA; Department of Medical Oncology and Hematology, Princess Margaret Cancer Centre, University of Toronto, Toronto, ON, Canada

ABSTRACT
Treatement-free remission (TFR) in patients with chronic myeloid leukemia in chronic phase (CML-CP) is considered a feasible option, especially with the ability of second-generation tyrosine kinase inhibitors to induce higher rates of sustained deep molecular response (DMR). DASFREE is an open-label, single-arm, multicenter phase II trial assessing TFR after dasatinib discontinuation in patients with CML-CP (N = 84). At 2 years, TFR was 46% in all patients. Multivariate analyses revealed statistically significant associations between 2-year TFR and duration of prior dasatinib (≥ median; p = .0051), line of therapy (first line; p = .0138), and age (>65 years; p = .0012). No disease transformation occurred, and the most common adverse events experienced off treatment were musculoskeletal (observed in 30 patients); however, dasatinib withdrawal events were reported in nine patients (11%) by the investigator. Overall, these findings support the feasibility of discontinuing dasatinib for patients with CML-CP in sustained DMR in the first line and beyond.

Introduction
Tyrosine kinase inhibitors (TKIs) have vastly improved long-term outcomes for patients with chronic myeloid leukemia in chronic phase (CML-CP). In particular, second-generation TKIs have been shown to induce higher rates of deep molecular responses (DMR) and a more rapid decline in BCR-ABL1 transcript levels compared with imatinib in newly diagnosed patients [1–3]. Consequently, DMR is now increasingly being considered as being correlative of disease burden reduction and also the most relevant clinical endpoint for patients wishing ultimately to stop treatment [4–6]. A reduction in leukemic clone burden is associated with reduced rates of transformation to accelerated phase (AP) or blast crisis (BC) CML; however, it is not clear if the absence of detectable BCR-ABL1 transcripts is synonymous with a cure for CML [4–6]. Despite the persistence of the leukemic clone in such cases, a functional cure might still be possible, and the need for lifelong TKI treatment is now being challenged [7–22]. Furthermore, patients might be motivated to stop therapy for reasons that include toxicity, a desire for improvement in quality of life, and the financial burden associated with indefinite TKI treatment [23–25].

Accordingly, treatment-free remission (TFR) has become a treatment goal for many patients with CML-CP in DMR. Typically, TFR is attempted in selected patients in the context of DMR, as measured by a reduction in BCR-ABL1 transcript levels on the International Scale (IS), ranging from ≤0.01% (MR4) to ≤0.0032% (MR5).
Successful TFR has been demonstrated in several clinical trials, the majority of which have included patients discontinuing long-term imatinib treatment. These studies have shown that nearly half of patients with sustained DMR successfully maintained major molecular response (MMR) after discontinuing treatment [9–12,14–16,19,21]. In nearly all cases, patients who relapsed in these trials remained sensitive to TKIs and regained MMR upon re-treatment [7–22]. Based on these findings, the National Comprehensive Cancer Network [27] and the European Society for Medical Oncology [28] suggest the possibility of stopping TKI therapy in selected patients, in the context of frequent monitoring and availability of standardized laboratory testing.

The consensus on the use of TFR in clinical practice, however, is still evolving. Results from ongoing TFR trials will help to provide more confirmatory data on long-term outcomes. Furthermore, many clinical trials on TFR have been unable to identify strong predictors of successful TKI discontinuation consistently. The optimal duration of DMR before entering TFR also remains to be determined.

DASFREE (NCT01850004) is the largest clinical trial to date of patients with CML-CP and sustained dasatinib-induced DMR (specifically MR4.5) who discontinued dasatinib across all lines of therapy. In this ongoing, open-label, single-arm phase 2 study, the primary objective was to assess the rate of TFR (defined herein as the maintenance of MMR following treatment cessation) at 1 year. Herein we report findings for this primary objective and additional pre-specified analyses for patients with a minimum of 2 years of follow-up after stopping dasatinib.

Materials and methods

Study design and eligibility

Patients aged ≥18 years with CML-CP who received dasatinib treatment (as first- or subsequent-line therapy) for a minimum of 2 years at the time of enrollment and had confirmed dasatinib-induced DMR (specifically MR4.5) who discontinued dasatinib across all lines of therapy. In this ongoing, open-label, single-arm phase 2 study, the primary objective was to assess the rate of TFR (defined herein as the maintenance of MMR following treatment cessation) at 1 year. Herein we report findings for this primary objective and additional pre-specified analyses for patients with a minimum of 2 years of follow-up after stopping dasatinib.

Study endpoints and assessments

Once all eligibility criteria were met, dasatinib was discontinued. The primary objective was the rate of TFR (proportion of subjects who maintained MMR \(\text{BCR-ABL} < 0.1\%\)) at 1 year following dasatinib discontinuation without restarting treatment. If MMR was lost, patients resumed dasatinib at the last dose received prior to stopping treatment. Key secondary endpoints include event-free survival (EFS; survival with no loss of MMR), \(\text{BCR-ABL}1\) kinetics, rate of transformation to CML-AP/BC, and progression-free survival (PFS). Patients who discontinued from the study were censored on the date of their last molecular assessment. PFS was defined as survival without progression to CML-AP/BC or death due to any cause. Time in prior MR4.5 was assessed retrospectively; consent for 10 patients could not be collected, thus information is available for only 74 of the 84 patients enrolled in the trial. Both intolerance and resistance were determined by the investigator. Additional study endpoints and further information on assessments and molecular testing are shown in the Online Supplementary Material.

Key exploratory endpoints included the frequency of adverse events (AEs) and serious AEs (SAEs) occurring off treatment after discontinuing and after restarting on dasatinib, the rate of MMR recapture after reinitiating dasatinib, and identification of prognostic factors in relation to TFR maintenance. AEs and SAEs were assessed according to the National Cancer Institute’s Common Terminology Criteria for Adverse Events version 4.03 [29]. Withdrawal events were defined as any AE occurring and/or worsening due to treatment cessation, as determined by the investigator.

The primary objective was presented as a percentage with an exact 95% Clopper–Pearson confidence interval (CI). Additional statistical analyses are provided in the Online Supplementary Material. Data for the primary endpoint are based on a cutoff date of October 2017, at which time all patients who discontinued dasatinib had 1 or more years of follow-up. Data presented herein are based on a cutoff date of December 2018, at which time patients had a minimum follow-up of 2 years.

Ethics

All patients provided written informed consent in accordance with the Declaration of Helsinki and local guidelines before study entry. The study protocol was approved by all Institutional Review Boards of each
participating center, as well as each center’s Ethics Committee and competent national authority.

Results

Accrual and patient characteristics

A total of 84 patients enrolled between February 2014 and June 2016 at 22 study centers in six countries discontinued dasatinib treatment. Baseline patient characteristics are presented in Table 1. Thirty-seven patients (44%) who were receiving first-line dasatinib and 47 patients (56%) who were receiving dasatinib in subsequent lines prior to stopping treatment were enrolled. Of those on later lines, 53% were deemed resistant to their first-line TKI and 38% were considered intolerant of a prior TKI by the investigator, including two patients (2%) on prior imatinib and nilotinib. Four patients (9%) on later lines of dasatinib were not classified as resistant to or intolerant of prior therapy by the investigator; the status of two of these patients is unknown, while one patient switched to dasatinib following closure of a first-line ponatinib trial and the other switched from imatinib to dasatinib due to out-of-pocket costs. In 74 patients with available information on duration of prior time in MR$^{4.5}$, the median duration of MR$^{4.5}$ prior to discontinuation was 28 months (range, 13–116 months) and was similar regardless of line of therapy (Supplementary Figure S1). The median time from CML diagnosis to discontinuation was 69 months (range, 29–244 months), and the median dose received prior to stopping dasatinib was 100 mg (range, 20–150 mg) once daily. With a minimum follow-up of 2 years, 11 patients (13%) discontinued the study (Supplementary Table S1). Two patients discontinued the study (while maintaining MMR) due to relocation, one patient was non-compliant with study visits and discontinued the study before undergoing molecular assessments, and one patient discontinued after being diagnosed with a metastatic malignancy unrelated to CML.

Efficacy

At 1 year, TFR was 48% (95% CI: 37, 59) in all enrolled patients (Supplementary Figure S2). By line of dasatinib, TFR at 1 year was maintained in 54% (95% CI: 37, 71) of first-line patients and 43% (95% CI: 28, 58) of subsequent line patients (broken down further, TFR was 40% [95% CI: 21, 61] in patients resistant to prior TKI therapy and 50% [95% CI: 26, 74] in patients intolerant of prior TKI therapy. At 2 years, TFR was 46% (95% CI: 36, 57) in all patients, 51% (95% CI: 35, 67) in first-line patients, and 42% (95% CI: 28, 57) in subsequent-line patients (Figure 1). TFR was maintained in 44% (95% CI: 25, 64)
of patients resistant to prior TKI and 44% (95% CI: 22, 67) of patients intolerant of prior TKI.

In total, 46 patients (55%) lost MMR 2 years after discontinuation (Figure 2). Of the 45 patients (98%) who restarted dasatinib, 44 (98%; 95% CI: 88, 100) regained MMR after a median of 2 months (range, 1–4) and 43 (96%; 95% CI: 85, 100) regained MR4.5 after a median of 3 months (range, 2–18). One patient on first-line dasatinib for 41 months prior to discontinuation lost MMR at month 39 and had not restarted therapy at the time of this analysis. Additionally, one patient who lost MMR and discontinued the study after restarting treatment was lost to follow-up after having only one follow-up molecular assessment. Of the 40 evaluable patients in MR4.5 who remained in MMR after dasatinib discontinuation, 14 (35%) patients maintained MR4.5, while 26 (65%) patients lost MR4.5 but did not lose MMR at 12 months after dasatinib discontinuation.

At 2 years, PFS was 99% (95% CI: 96, 100) in all patients, 100% (95% CI: 100, 100) in first-line patients, and 98% (95% CI: 93, 100) in subsequent-line patients. No patients progressed to CML-AP/BC. However, one patient was diagnosed with ovarian cancer, discontinued the study, and died 1 month later. This patient was categorized as having discontinued due to death for this database lock and is thus reflected in the survival results.

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Safety

AEs of any grade and cause occurred in 67% of patients off treatment and 76% of patients after restarting treatment. All-cause AEs reported in >4% of patients off treatment following dasatinib discontinuation or on treatment after restarting dasatinib are

Figure 1. TFR in all enrolled patients at 2 years (N = 84). CI: confidence interval; NE: not estimable; TFR: treatment-free remission.
Figure 2. Loss and recovery of MMR and MR4.5 at 2 years. A 52-year-old male with low-risk CML treated with first-line dasatinib 100 mg once daily for 40 months discontinued the study after 33 months in MR4.5. This patient maintained BCR-ABL1 transcript levels between 0.0017 and 0.01 for 3 years and had an increase to 0.1% in month 39, which was confirmed on a second occasion in month 42 (0.11%). One patient lost MMR and restarted treatment. This patient discontinued the study after only one follow-up molecular assessment and therefore was not considered evaluable for molecular response. CML: chronic myeloid leukemia; MMR: major molecular response; MR4.5: \textit{BCR-ABL1} ≤ 0.0032% on the International Scale.

| Patients who lost MMR, \( n (\%) \) | 46 (55) |
| Median time from discontinuation to loss of MMR, months (range) | 4 (1–39) |
| Patients who lost MMR and restarted treatment, \( n (\%) \) | 45 (98) |
| Patients who regained MMR | 44 (98) |
| Patients who regained MR4.5 | 43 (96) |
| Median time to regain MMR, months (range) | 2 (1–4) |
| Median time to regain MR4.5, months (range) | 3 (2–18) |

Figure 3. Multivariate analysis of TFR and covariates at 2 years. CI: confidence interval; MR4.5: \textit{BCR-ABL1} ≤ 0.0032% on the International Scale; TFR: treatment-free remission; TKI: tyrosine kinase inhibitor.
### Table 2. All causality adverse events in ≥4% of enrolled patients and withdrawal events in all enrolled patients.

| Patients with AEs, n (%) | Patients off treatment after discontinuing dasatinib (n = 84) | Patients on treatment after restarting dasatinib (n = 45) |
|------------------------|-------------------------------------------------------------|----------------------------------------------------------|
|                        | Any grade | Grade 3–4 | Any grade | Grade 3–4 |
| Blood and lymphatic disorders | 3 (4) | 0 | 7 (16) | 1 (2) |
| Neutropenia | 0 | 0 | 3 (7) | 1 (2) |
| Gastrointestinal disorders | 12 (14) | 0 | 13 (29) | 0 |
| Upper abdominal pain | 1 (1) | 0 | 2 (4) | 0 |
| Constipation | 1 (1) | 0 | 3 (7) | 0 |
| Diarrhea | 1 (1) | 0 | 4 (9) | 0 |
| Dyspepsia | 1 (1) | 0 | 2 (4) | 0 |
| Abdominal pain | 0 | 0 | 2 (4) | 0 |
| Dry mouth | 0 | 0 | 3 (7) | 0 |
| General disorders | 11 (13) | 0 | 15 (33) | 0 |
| Peripheral edema | 3 (4) | 0 | 2 (4) | 0 |
| Asthenia | 2 (2) | 0 | 5 (11) | 0 |
| Fatigue | 2 (2) | 0 | 8 (18) | 0 |
| Pyrexia | 2 (2) | 0 | 2 (4) | 0 |
| Pain | 0 | 0 | 2 (4) | 0 |
| Investigations | 8 (18) | 3 (7) | 12 (14) | 2 (2) |
| Increased blood creatinine | 0 | 0 | 2 (4) | 0 |
| Metabolic disorders | 6 (7) | 0 | 9 (20) | 0 |
| Hypercholesterolemia | 0 | 0 | 3 (7) | 0 |
| Hypokalemia | 0 | 0 | 2 (4) | 0 |
| Hypophosphatemia | 0 | 0 | 2 (4) | 0 |
| Infections and infestations | 18 (21) | 2 (2) | 15 (33) | 2 (4) |
| Nasopharyngitis | 7 (8) | 0 | 5 (11) | 0 |
| Sinusitis | 4 (5) | 0 | 2 (4) | 0 |
| Urinary tract infection | 2 (2) | 0 | 2 (4) | 0 |
| Cellulitis | 0 | 0 | 2 (4) | 0 |
| Pharyngitis | 0 | 0 | 2 (4) | 0 |
| Pneumonia | 0 | 0 | 2 (4) | 0 |
| Musculoskeletal and connective tissue disorders | 30 (36) | 2 (2) | 11 (24) | 0 |
| Arthralgia | 11 (13) | 0 | 4 (9) | 0 |
| Back pain | 6 (7) | 0 | 2 (4) | 0 |
| Myalgia | 6 (7) | 0 | 4 (9) | 0 |
| Arthritis | 4 (5) | 0 | 0 | 0 |
| Pain in extremity | 4 (5) | 0 | 2 (4) | 0 |
| Musculoskeletal pain | 3 (6) | 0 | 2 (4) | 0 |
| Nervous system disorders | 12 (14) | 0 | 13 (29) | 3 (7) |
| Headache | 8 (10) | 0 | 6 (13) | 0 |
| Dizziness | 1 (1) | 0 | 3 (7) | 0 |
| Memory impairment | 0 | 0 | 2 (4) | 0 |
| Syncope | 0 | 0 | 2 (4) | 2 (4) |
| Respiratory disorders | 6 (7) | 0 | 11 (24) | 0 |
| Depression | 1 (1) | 0 | 3 (7) | 0 |
| Insomnia | 0 | 0 | 2 (4) | 0 |
| Anxiety | 2 (2) | 0 | 2 (4) | 0 |
| Respiratory disorders | 5 (6) | 0 | 9 (20) | 1 (2) |
| Dyspnea | 1 (1) | 0 | 2 (4) | 0 |
| Dyspnea exertional | 1 (1) | 0 | 2 (4) | 0 |
| Pleural effusion | 1 (1) | 0 | 3 (7) | 1 (2) |
| Cough | 0 | 0 | 2 (4) | 0 |
| Skin and subcutaneous tissue disorders | 15 (18) | 0 | 6 (13) | 0 |
| Rash | 4 (5) | 0 | 2 (4) | 0 |
| Vascular disorders | 9 (11) | 2 (2) | 2 (4) | 0 |
| Hypertension | 9 (11) | 2 (2) | 1 (2) | 0 |

Patients with withdrawal events (n = 9)

| Withdrawal events\(^a\), n | 15 |
|----------------------------|----|
| Time from discontinuation to withdrawal event, onset/worsening, median (range), months | 4 (1–18) |
| Withdrawal events resolved, n | 9 |
| Spontaneous resolution without medication, (other than a TKI) | 7 |
| Resolution after non- TKI/nonanalgesic medication | 2 |
| Time from withdrawal event onset to resolution, median (range), months | 5 (1–12) |

\(^a\)Withdrawal events were defined as any adverse event occurring and/or worsening due to treatment cessation, as determined by the investigator.

AE: adverse event; TKI: tyrosine kinase inhibitor.
reported an estimated overall rate of TFR was 44% at 3 years [11,14]. Findings for other second-generation TKIs have been similar: the ENESTfreedom and ENESTop trials with first- and second-line nilotinib reported TFR rates of 47% and 48%, respectively, at 144 weeks [9,12,15,19]. Finally, in STOP 2 G-TKI (dasatinib and nilotinib discontinuation), 63% of patients remained in TFR at 1 year [16]. It is important to note, however, that the capability to make an in-depth, comprehensive comparison of results across all discontinuation trials is limited by differences in eligibility criteria and varying DMR and molecular relapse definitions.

Although several TKI discontinuation trials have sought to identify prognostic factors that could help predict successful TFR [7,30], a consensus has yet to be reached. In this study, duration of prior dasatinib (≥median; \( p = .0051 \)), line of therapy (first line; \( p = .0138 \)), and age (>65 years; \( p = .0012 \)) represent three prognostic factors for 2-year TFR. Although prior line of therapy is considered a prognostic factor for TFR, these findings suggest that TFR is certainly achievable regardless of the line of discontinued therapy. Identification of these factors adds to the growing body of evidence in delineating key prognostic factors for successful TFR. Similar findings were also observed for age in the Imatinib Suspension and Validation (ISAV) study, where an inverse relationship between patient age and risk of relapse was reported (95% of patients aged <45 years relapsed vs 42% of patients aged ≥45 to <65 years; 33% of patients aged ≥65 years), although this may be an effect of a smaller patient population [30]. In addition, other discontinuation trials have established the presence of imatinib resistance as a significant risk factor for molecular relapse [14,16]. This association was particularly evident in the DADI trial, in which imatinib-resistant patients relapsed more quickly and with a significantly shorter doubling time of BCR-ABL1 transcript levels [14]. In DASFREE, however, an important proportion of resistant patients (42%) were able to maintain TFR at 2 years. Although some prognostic factors were identified in this study, other ongoing trials are seeking to identify additional factors predictive of TFR outcomes, including the possible effect of pleural effusion [22].

No significant association between TFR and duration of prior TKI therapy (other than dasatinib) or prior MR4.5 was identified in this study. However, treatment duration and duration of DMR have been identified in other studies as prognostic factors for TFR when a TKI is discontinued [11,30–34]. Results from the multicenter Stop Imatinib (STIM) trial, in which
40% of patients entering TFR with MR4.5 remained in remission at 18 months, indicated an imatinib treatment duration of ≥50 months as a prognostic factor of TFR [11]. In addition, prognostic analysis of patients in EURO-SKI (European Stop Tyrosine Kinase Inhibitor Study) suggested that the duration of DMR had the greatest impact on the success of stopping TKI treatment [21]. In EURO-SKI it was recommended that the patient should be in MR4 for 3 or more years before stopping [21]. Patients in DASFREE were required to be in MR4.5 for 1 or more years (Online Supplementary Figure S1) and on dasatinib for 2 or more years prior to enrollment, which might be considered aggressive in comparison to the treatment duration and duration of response criteria in similar discontinuation trials.

Patients considering TFR are not only concerned about the risk of relapse but also fear that their disease might not remain responsive to treatment following relapse. Across TFR trial reports, all patients who have relapsed after stopping treatment have remained sensitive to re-treatment and regained molecular responses ≥MMR [22]. However, one patient (in ENESTfreedom) with loss of MMR was found to have a detectable BCR-ABL1 mutation, though the significance of this finding is unclear because the mutation might have been present prior to stopping nilotinib [19]. In DASFREE, PFS was high (99%) at 2 years and no cases of disease progression to CML AP/BC were observed. All patients who relapsed and were evaluable for molecular assessment after restarting dasatinib regained MMR, and 93% regained MR4.5.

Withdrawal events after discontinuation of TKI therapy are well described in the current literature on TFR [7–22]. In DASFREE, only nine patients (11%) off treatment reported symptoms that investigators considered related to withdrawal, most of which resolved on their own without the use of concomitant therapy. Furthermore, AEs observed in patients who restarted treatment were found to be consistent with the known safety profile of dasatinib, with no new safety signals being reported in this study. To our knowledge, the specific definition of withdrawal events utilized in DASFREE (investigator assessed and defined as any AE occurring and/or worsening in severity after discontinuation and related to dasatinib discontinuation) is unique to this trial and unlike other discontinuation trials that defined withdrawal events to be solely musculoskeletal [16,21,22].

One limitation of this study is the retrospective manner in which some data were collected, which might account for some of the differences between DASFREE and other TFR studies. This might play a particularly important role with regard to the low rate of withdrawal events in this study, which might be associated with a definition of withdrawal that requires an investigator assessment of relatedness. Conversely, most patients discontinued treatment following the first published description of TKI withdrawal syndrome, so most investigators were aware of this phenomenon. A second possible limitation of this study, which is also characteristic of other discontinuation trials, is sample size. A better understanding of the long-term durability of TFR, including identification of definitive prognostic factors and longer follow-up, is needed before fully incorporating these findings into clinical decision-making, particularly given the apparently low risk of attempting TKI discontinuation. Long-term (5-year) follow-up is planned, including an assessment of the stability of MR4.5 achieved on dasatinib, recurrence rate, patients’ quality of life off treatment, and the ability to regain a molecular response in patients who relapse after discontinuation.

In summary, DASFREE results provide clinically relevant information on TFR for many patients with CML-CP who achieve stable DMR with dasatinib. Suggestions on appropriate treatment duration and duration of response criteria prior to discontinuing, as well as newly identified prognostic factors, are novel contributions to those considering TFR. Furthermore, these data support the practicality of TFR in patients with resistance to or intolerance of prior TKI treatment and, perhaps most importantly, confirm the feasibility and safety of dasatinib discontinuation in patients stopping first-line treatment.

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Data availability statement
BMS policy on data sharing may be found at https://www.bms.com/researchers-and-partners/independent-research/data-sharing-request-process.html.

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