Treatment-free Remission (TFR) in Patients With Chronic-phase Chronic Myeloid Leukemia (CML-CP) and Stable Deep Molecular Response (DMR) Discontinuing Dasatinib (DASFREE)

CML-044

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Introduction

- In clinical practice, there is growing interest in the feasibility and practicality of discontinuing TKI therapy in patients with CML-CP[1]
- TFR is currently being evaluated in patients with CML-CP and stable deep molecular response (DMR); however, the exact molecular response eligibility criteria across these clinical trials varies[2]
- Roughly 40%-60% of patients discontinuing TKIs maintain their molecular responses[2]
  - Almost all patients who relapse regain their response after restarting treatment
- Dasatinib, a second-generation TKI, induces high rates of early, deep, and sustained molecular responses, making it an effective option for patients who are considering TFR[3]

Objective

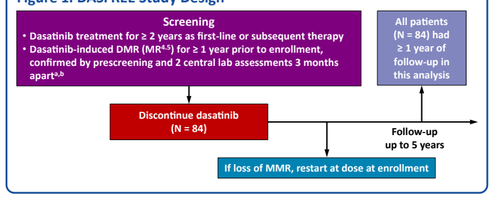
- To investigate TFR in patients with CML-CP and sustained DMR for ≥ 1 year discontinuing dasatinib in the first line and beyond

Methods

Study Design

- DASFREE (CA180-406/NCT01850004) is a phase 2, open-label, single-arm study conducted in North America and Europe (**Figure 1**)

Figure 1. DASFREE Study Design



[a]Adults with dasatinib-induced stable DMR for ≥ 9 months, documented by ≥ 3 assessments conducted 2 to 6.5 months apart at a local lab were screened.[9] For any patient not eligible for enrollment because both assessments at the central lab did not confirm DMR, rescreening was allowed ≥ 9 months after the last central lab screening failure.

DMR = deep molecular response; IS = International Scale; MMR = major molecular response; MR4.5 = *BCR-ABL1* ≥ 0.0032% on the IS.

Study Endpoints

- The primary endpoint is the rate of MMR maintenance 1 year following dasatinib discontinuation
- Key secondary endpoints
  - *BCR-ABL1* kinetics
  - Molecular relapse-free survival (MRFS or event-free survival; survival with no loss of MMR)
  - Relapse-free survival (RFS; survival with no loss of MMR, complete cytogenetic response [CCyR], or complete hematologic response [CHR]; or progression to CML in accelerated/blast phase [AP/BP])
  - Rate of transformation to CML-AP/BP
  - Progression-free survival and overall survival
- Key exploratory analyses
  - Frequency of adverse events (AEs) after discontinuation and during dasatinib treatment upon reinitiation
  - Rate of MMR recapture after reinitiating dasatinib, and time to molecular re-response
  - Identification of predictive factors after discontinuation and after reinitiating treatment

Results

- Baseline patient characteristics are presented in **Table 1**

Table 1. Baseline Patient Characteristics

	Enrolled Patients (N = 84)
Median age, years (range)	52 (24-80)
Male, n (%)	47 (56)
ECOG PS, n (%)	
0	68 (81)
1	11 (13)
Not reported	5 (6)
Line of therapy, n (%)	
First	37 (44)
Subsequent	47 (56)
Resistant	25 (53)
Intolerant	18 (38)
Other	4 (9)
Prior treatment, n (%)	
Imatinib	44 (52)
Ponatinib	1 (1)
Imatinib + nilotinib	2 (2)
IFN	0
Sokal score, n (%)	
Low	54 (64)
Intermediate	24 (29)
High[a]	5 (6)
Unknown	1 (1)
Median time from diagnosis to discontinuation, months (range)	69 (29-244)
Median dose at discontinuation, mg (range)	100 (20-150)

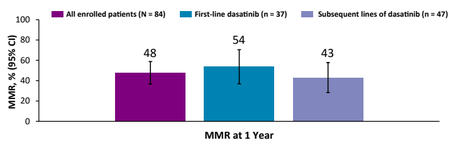
[a]After 35 patients were enrolled, the protocol was amended to allow for enrollment of patients with high Sokal scores.
ECOG = Eastern Cooperative Oncology Group; IFN = interferon; PS = performance status.

- Two patients discontinued the study while maintaining MMR off treatment, both due to relocation
- Three patients discontinued the study on treatment
  - Two withdrew consent at month 18; 1 was noncompliant with study protocol, and discontinued the study after restarting treatment and having only 1 follow-up polymerase chain reaction (PCR) assessment

TFR 1 Year Following Dasatinib Discontinuation

- TFR 1 year after dasatinib discontinuation was 48% in all enrolled patients (**Figure 2**)
  - 54% in patients on first-line and 43% in patients on subsequent lines of dasatinib

Figure 2. TFR 1 Year Following Discontinuation

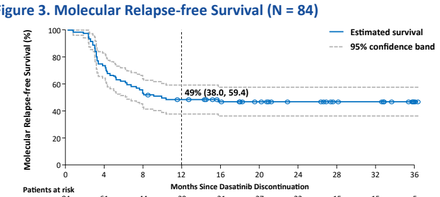


- 1 year after dasatinib discontinuation, TFR was 40% (95% confidence interval [CI]: 21.1, 61.3) for patients resistant to prior TKI therapy (n = 25) and 50% (95% CI: 26.0, 74.0) for patients intolerant of prior TKI therapy (n = 18)

Molecular Relapse-free Survival

- At 1 year, MRFS in all enrolled patients was 49% (**Figure 3**)
- No patients lost CCyR or CHR
- No transformation events or deaths occurred

Figure 3. Molecular Relapse-free Survival (N = 84)



	MRFS, % (95% CI)
Patients on first-line dasatinib (n = 37)	54 (38.0, 70.1)
Patients on subsequent lines of dasatinib (n = 47)	45 (30.2, 58.7)
Resistant (n = 25)	44 (24.5, 63.5)
Intolerant (n = 18)	50 (26.9, 73.1)

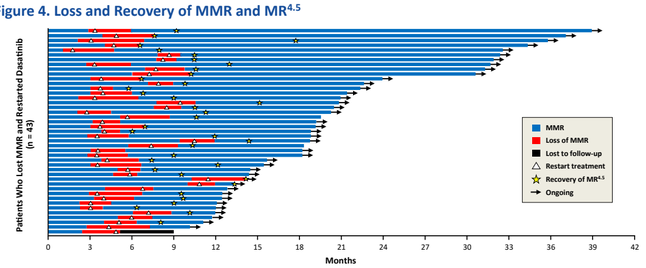
Kinetics of Loss and Recovery of MMR and MR4.5

- All evaluable patients (n = 42) regained MMR in a median of 1.9 months after restarting dasatinib (**Figure 4**)

Univariate Analysis of RFS and Covariates

- A univariate analysis revealed that patients aged < 65 years were less likely to maintain RFS at 1 year than patients aged ≥ 65 years (hazard ratio [95% CI]: 2.376 [1.004, 5.625]; *P* = 0.0489)
  - Additional statistical analyses revealed no significant association between RFS and duration of prior TKI therapy and line of therapy

Figure 4. Loss and Recovery of MMR and MR4.5



	Patients Who Lost MMR (n = 44)
Median time from discontinuation to loss of MMR, months (range)	3.93 (1.1-15.6)
Patients losing MMR and restarting treatment, n (%)	43 (98)[a]
Patients evaluated for molecular response after restarting dasatinib, n (%)	42 (95)[b]
Patients who regained MMR	42 (100)
Patients who regained MR4.5	38 (90)
Median time to regain MMR, months (range)	1.89 (0.9-3.7)
Median time to regain MR4.5, months (range)	3.25 (1.9-14.7)

[a]One patient lost MMR and had not restarted therapy prior to data cut. [b]One patient lost MMR and restarted treatment. This patient discontinued the study after only 1 follow-up PCR assessment.

Time on TKIs Prior to Dasatinib Discontinuation

- The range of time on prior treatment was similar for patients who lost or maintained MMR
  - For patients on first-line dasatinib, median time on prior dasatinib was 35 months (95% CI: 28, 87) for those who lost MMR and 46 months (95% CI: 28, 89) for those who maintained MMR
  - For patients on subsequent lines of dasatinib, median time on prior dasatinib was 55 months (95% CI: 26, 149) for those who lost MMR and 70 months (95% CI: 28, 125) for those who maintained MMR
  - For patients on subsequent lines of dasatinib, median time on prior TKIs was 100 months (95% CI: 34, 221) for those who lost MMR and 101 months (95% CI: 44, 154) for those who maintained MMR

All-causality Adverse Events of Special Interest

- AEs were consistent with the known safety profile of dasatinib (**Table 2**), and no AEs led to discontinuation

Table 2. All-causality Adverse Events of Special Interest

	Patients off Treatment After Discontinuing Dasatinib (n = 84)		Patients on Treatment After Restarting Dasatinib (n = 43)	
Patients with AEs, n (%)	Any Grade	Grade 3-4	Any Grade	Grade 3-4
Musculoskeletal and connective tissue disorders	19 (23)	0	8 (19)	0
Arthralgia	8 (10)	0	4 (9)	0
Myalgia	6 (7)	0	3 (7)	0
Pain in extremity	4 (5)	0	1 (2)	0
Back pain	3 (4)	0	1 (2)	0
Musculoskeletal pain	3 (4)	0	2 (5)	0
Vascular disorders	6 (7)	1 (1)	2 (5)	0
Hypertension	6 (7)	1 (1)	1 (2)	0
Cardiac disorders	2 (2)	1 (1)	1 (2)	0

Dasatinib-related Withdrawal Events

- Fifteen withdrawal events were experienced in 8 patients off treatment (**Table 3**)

Table 3. Dasatinib-related Withdrawal Events

	Patients With Withdrawal Events (n = 8)
Withdrawal events,[a] n	15
Median time from discontinuation to withdrawal event onset/worsening, months (range)	3 (< 1-6)
Withdrawal events resolved, n	9[b]
Resolution before restarting dasatinib	4
Resolution on or after restarting dasatinib	5
Spontaneous resolution without medication (other than a TKI)	7
Resolution after non-TKI/nonanalgesic medication[c]	2
Median time from withdrawal event onset to resolution, months (range)	3 (1-9)

[a]AEs occurring and/or worsening after dasatinib was discontinued were considered withdrawal events, as determined by the investigator. [b]At the time of analysis, all 6 unresolved withdrawal events were grade 1 and did not require therapy. [c]One withdrawal event was an arterial hypertension event that resolved with antihypertensive therapy.

Conclusions

- In patients with CML-CP in DMR discontinuing dasatinib, 48% maintained TFR 1 year after discontinuation
  - MMR rates at 1 year were similar for patients on first-line (54%) and subsequent lines of dasatinib (43%)
- 100% of evaluable patients who lost MMR quickly regained their response after therapy was reinitiated
  - Median time to regain MMR was 1.9 months
- AEs reported here were consistent with the known safety profile of dasatinib
- Only 9.5% of patients reported symptoms of dasatinib withdrawal, and most events resolved without concomitant therapy
- This largest dasatinib discontinuation trial to date strongly supports the feasibility of TFR in patients with CML-CP in DMR treated in the first line and beyond

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