# Durable Treatment-Free Remission Following Frontline Nilotinib in Patients With Chronic Myeloid Leukemia in Chronic Phase: ENESTfreedom 96-Week Update

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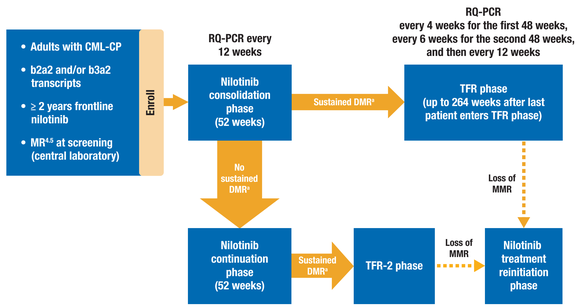
## Introduction

- Discontinuation of tyrosine kinase inhibitor therapy for treatment-free remission (TFR) in patients with chronic myelogenous leukemia in chronic phase (CML-CP) and a sustained deep molecular response is an emerging treatment goal[1-6]
- ENESTfreedom is the first study to investigate TFR in patients who achieved a sustained deep molecular response with frontline nilotinib[2]
  - In the primary analysis of ENESTfreedom, the rate of TFR at 48 weeks was 51.6%, similar to rates reported in studies of TFR following imatinib despite a shorter duration of prior therapy (median of 3.6 years in ENESTfreedom vs ≈ 5-7 years in prior studies)[2-6]

## Methods

- ENESTfreedom (NCT01784068) is an ongoing, single-arm, phase 2 study (**Figure 1**)

**Figure 1. ENESTfreedom Study Design**



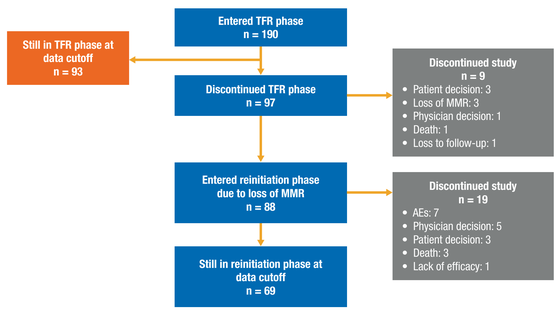

DMR, deep molecular response; IS, International Scale; MMR, major molecular response (*BCR-ABL*$^{IS}$ ≤ 0.1%); MR$^{4.5}$, *BCR-ABL*$^{IS}$ ≤ 0.0032%; RQ-PCR, real-time quantitative polymerase chain reaction (standardized to the IS).
[a]Sustained DMR defined as the following (in the last 4 quarterly PCR assessments): MR$^{4.5}$ in the last assessment, no assessment worse than MR$^{4}$ (*BCR-ABL*$^{IS}$ ≤ 0.01%), and ≤ 2 assessments between MR$^{4}$ and MR$^{4.5}$.

- Here we present updated results from ENESTfreedom based on a cutoff date of 31 October 2016, at which time all patients who entered the TFR phase had completed 96 weeks of TFR, entered the reinitiation phase, or discontinued from the study
- Building on results from the primary analysis reported previously,[2] the current report provides longer-term efficacy and safety updates
  - Updated efficacy analyses include the rate of patients remaining in TFR (with MMR) at 96 weeks and evaluation of potential predictors of TFR success at 48 weeks
  - Updated safety analyses include the characterization of safety during TFR over time for the subset of patients who remained in the TFR phase for > 48 weeks

## Results

- Of 190 patients who entered the TFR phase, 93 (48.9%) remained in TFR at the data cutoff; of the 88 patients who reinitiated nilotinib due to loss of MMR, 69 (78.4%) remained in the reinitiation phase at the data cutoff (**Figure 2**)

**Figure 2. Patient Flow and Disposition**




AE, adverse event.

- At diagnosis, 32.6%, 26.3%, and 14.7% of patients had low, intermediate, and high Sokal risk scores, respectively; Sokal risk scores at diagnosis were not available for 26.3% of patients (**Table 1**)
- At the data cutoff date, the median duration of follow-up in the TFR phase was 75.9 weeks (range, 8.4-133.0 weeks)

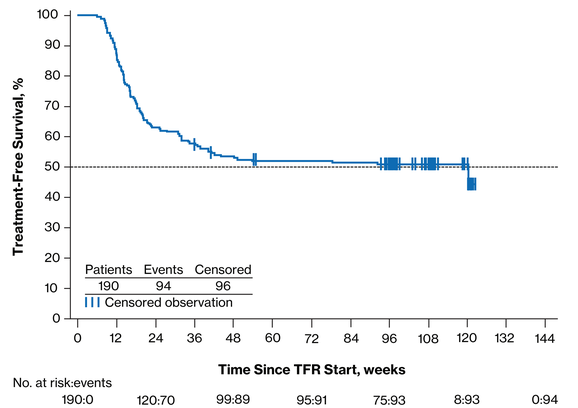
**Table 1. Patient Characteristics in the TFR Population**

| | TFR Population (n = 190) |
|---|---|
| Median age at study entry (range), years | 55 (21-86) |
| Sokal risk score at diagnosis, n (%) | |
| Low | 62 (32.6) |
| Intermediate | 50 (26.3) |
| High | 28 (14.7) |
| Missing | 50 (26.3) |
| Median time from first MR$^{4.5}$ until TFR entry (range), months | 30.4 (12.3-83.0) |
| Median total nilotinib duration prior to TFR (range), months | 43.5 (32.9-88.7) |

### Treatment-Free Remission

- Ninety-three of 190 patients (48.9%; 95% CI, 41.6%-56.3%) remained off treatment and in MMR at week 96 of the TFR phase
  - Eighty-eight of 190 patients also had MR$^{4.5}$
- Five of the 98 patients who were in TFR at 48 weeks were no longer in TFR at 96 weeks
  - Three patients lost MMR after 48 weeks (at 54, 78, and 92 weeks)
  - Two patients discontinued from the study without loss of MMR (due to patient decision and loss to follow-up)
- The estimated rate of treatment-free survival (TFS) at 96 weeks was 50.9% (95% CI, 43.6%-57.8%; **Figure 3**)

**Figure 3. Kaplan-Meier–Estimated TFS[a,b]**

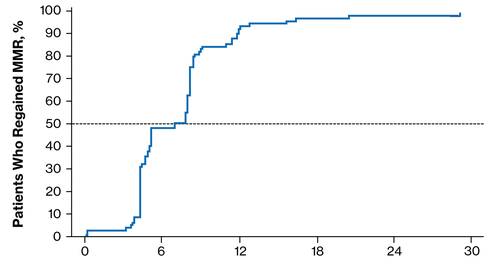



[a]TFS was defined as the time from the start of TFR until the earliest of any of the following: loss of MMR, reinitiation of nilotinib for any reason, progression to accelerated phase/blast crisis, or death due to any cause. [b]By the data cutoff date, 1 patient lost MMR at week 120, at which time only 8 patients were considered to be at risk, resulting in the artificial drop seen at the end of the curve.

### Response to Retreatment

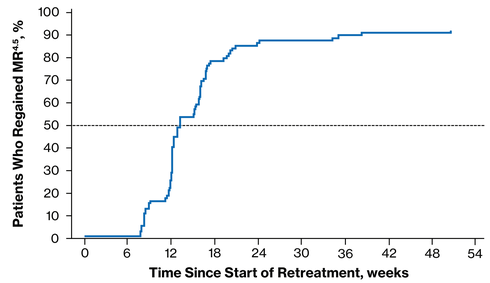
- Of the 88 patients who reinitiated nilotinib due to loss of MMR:
  - Eighty-seven (98.9%) regained MMR (**Figure 4**)
    - The remaining 1 patient discontinued from the study (due to patient decision) without regaining MMR 7.1 weeks after reinitiating nilotinib
  - Eighty-one (92.0%) regained MR$^{4.5}$ by the data cutoff date (**Figure 5**)
    - Of the patients who regained MMR but not MR$^{4.5}$, 1 remained on study, and 5 discontinued from the study by the data cutoff date 5 to 25 weeks after reinitiation of nilotinib (2 patients due to AEs, 1 patient due to lack of efficacy, and 2 patients due to individual decisions)

**Figure 4. Cumulative Incidence of MMR Regained After Nilotinib Reinitiation**




| | | | | | | |
|---|---|---|---|---|---|---|
| Cumulative n/N | 0/88 | 42/88 | 81/88 | 85/88 | 86/88 | 87/88 |
| Cumulative % | 0.0 | 47.7 | 92.0 | 96.6 | 97.7 | 98.9 |

**Figure 5. Cumulative Incidence of MR$^{4.5}$ Regained After Nilotinib Reinitiation**




| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Cumulative n/N | 0/88 | 0/88 | 25/88 | 69/88 | 76/88 | 77/88 | 79/88 | 80/88 | 80/88 | 81/88 |
| Cumulative % | 0.0 | 0.0 | 28.4 | 78.4 | 86.4 | 87.5 | 89.8 | 90.9 | 90.9 | 92.0 |

- Patients with low Sokal risk scores at diagnosis and patients with MR$^{4.5}$ in all assessments during the consolidation phase remained in TFR at higher rates than other patients (**Table 2**)

**Table 2. TFR Rates According to Sokal Risk and MR$^{4.5}$ Stability**

| TFR Rate at 48 Weeks, n/N (%; 95% CI) | TFR Population (n = 190) |
|---|---|
| Sokal risk score at diagnosis | |
| Low | 39/62 (62.9; 49.7-74.8) |
| Intermediate | 25/50 (50.0; 35.5-64.5) |
| High | 9/28 (32.1; 15.9-52.4) |
| *BCR-ABL*$^{IS}$ level in the consolidation phase | |
| ≤ 0.0032% in all assessments | 90/170 (52.9; 45.2-60.6) |
| > 0.0032% in ≥ 1 assessment | 8/20 (40.0; 19.1-63.9) |

### Safety

- Three new deaths were reported since the 48-week analysis; an overall total of 8 deaths were reported in the study by the data cutoff (**Table 3**)

**Table 3. Deaths**

| Deaths, n (%) | Consolidation Phase (N = 215) | TFR Phase (n = 190) | Reinitiation Phase (n = 88) | Post-treatment Follow-Up[a] |
|---|---|---|---|---|
| Total | 2 (0.9) | 1 (0.5) | 3 (3.4) | 2 |
| Cardiac arrest | 1 (0.5) | 0 | 0 | 0 |
| Suicide | 1 (0.5) | 0 | 0 | 0 |
| Acute myocardial infarction | 0 | 0 | 1 (1.1) | 0 |
| Respiratory failure | 0 | 0 | 1 (1.1)[b] | 0 |
| Other cancers | 0 | 0 | 0 | 2[a,b] |
| Unknown cause | 0 | 1 (0.5) | 1 (1.1) | 0 |

[a]Deaths were reported > 30 days after patients discontinued from the study. [b]New deaths reported since the 48-week analysis.

- Safety analyses included the subgroup of patients remaining in TFR for > 48 weeks (n = 100)
- Fewer patients in this subgroup had AEs during the second 48 weeks of TFR (62.0%) vs the first 48 weeks of TFR (76.0%) or the 1-year consolidation phase (85.0%)
- The frequency of cardiovascular events reported in each study period are shown in **Table 4**
- The incidence of AEs in the musculoskeletal-pain grouping increased during the TFR phase vs the consolidation phase, but decreased over time in the TFR phase (**Table 5**)

**Table 4. Cardiovascular Events (all grades)[a,b]**

| Patients, n (%) | Consolidation Phase (n = 100) | TFR Phase | |
|---|---|---|---|
| | | First 48 Weeks (n = 100) | Second 48 Weeks (n = 100) |
| Cardiovascular events | 3 (3.0) | 2 (2.0) | 1 (1.0) |
| Ischemic cerebrovascular events | 1 (1.0) | 1 (1.0) | 0 |
| Ischemic heart disease | 1 (1.0) | 0 | 1 (1.0) |
| Peripheral arterial occlusive disease | 1 (1.0) | 1 (1.0) | 0 |

[a]Among patients who remained in TFR for > 48 weeks (n = 100). [b]Each listed AE group includes a predefined set of individual AEs. Reported frequencies include all patients with ≥ 1 new or worsening AE in the group reported during the indicated study period.

**Table 5. Musculoskeletal Pain and Other Clinically Notable AE Groups (all grades)[a,b]**

| Patients, n (%) | Consolidation Phase (n = 100) | TFR Phase | |
|---|---|---|---|
| | | First 48 Weeks (n = 100) | Second 48 Weeks (n = 100) |
| Musculoskeletal pain | 17 (17.0) | 34 (34.0) | 9 (9.0) |
| Fluid retention | 3 (3.0) | 4 (4.0) | 4 (4.0) |
| Edema and other fluid retentions | 2 (2.0) | 3 (3.0) | 4 (4.0) |
| Severe | 1 (1.0) | 1 (1.0) | 0 |
| Hepatotoxicity | 2 (2.0) | 2 (2.0) | 0 |
| Cardiac failure | 0 | 1 (1.0) | 0 |
| Rash | 5 (5.0) | 1 (1.0) | 1 (1.0) |
| Myelosuppression (thrombocytopenia) | 1 (1.0) | 0 | 0 |
| Pancreatitis | 1 (1.0) | 0 | 0 |
| Significant bleeding | 0 | 0 | 1 (1.0) |
| Gastrointestinal hemorrhage | 0 | 0 | 1 (1.0) |

[a]Among patients who remained in TFR for > 48 weeks (n = 100). [b]Each listed AE group includes a predefined set of individual AEs. Reported frequencies include all patients with ≥ 1 new or worsening AE in the group reported during the indicated study period.

## Conclusions

- 48.9% of patients who had a sustained deep molecular response with frontline nilotinib therapy remained in remission at 96 weeks after stopping treatment
- Ninety-six-week results from ENESTfreedom were consistent with the previously reported results at the time of the primary analysis
  - Five patients discontinued from the TFR phase between 48 and 96 weeks; only 3 of these patients discontinued TFR due to loss of MMR
  - Of patients who reinitiated nilotinib due to loss of MMR, 98.9% regained MMR, and 92.0% regained MR$^{4.5}$
  - The frequency of AEs, including musculoskeletal-pain AEs, decreased during the second 48 weeks of TFR
- In this study, low Sokal risk at diagnosis and continuous MR$^{4.5}$ in the consolidation phase appeared to be associated with higher TFR rates; however, these results must be interpreted with caution due to small patient numbers in some subgroups
- These results support use of TFR for patients in sustained deep molecular response with frontline nilotinib

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