Durable Treatment-Free Remission After Stopping Second-Line Nilotinib in Patients With Chronic Myeloid Leukemia in Chronic Phase: ENESTop 96-Week Update

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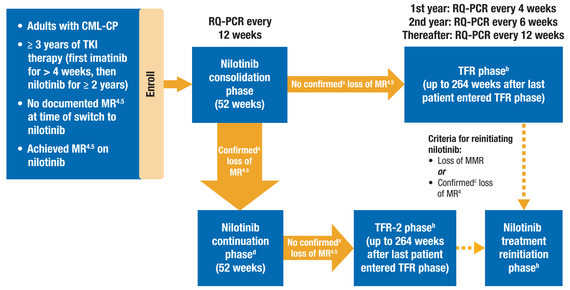
Introduction

- An emerging treatment goal for patients with chronic myeloid leukemia in chronic phase (CML-CP) is treatment-free remission (TFR)—ie, treatment cessation without loss of response
- ENESTop (NCT01698905) is the first study evaluating TFR after stopping nilotinib specifically in patients who achieved a sustained deep molecular response after switching from imatinib[1,2]
- In the primary analysis, the TFR rate at 48 weeks was 57.9% (95% CI, 48.8%-66.7%)[1,2]
- Updated data from the 96-week follow-up in ENESTop are presented here

Methods

- ENESTop is an ongoing, single-arm, phase 2 study (**Figure 1**)
- Enrolled patients continued nilotinib treatment during a 1-year consolidation phase
- Patients without a confirmed loss of MR[4.5] (*BCR-ABL1* ≤ 0.0032% on the International Scale [IS]) during the consolidation phase were eligible to stop nilotinib in the TFR phase
- Patients with a loss of major molecular response (MMR; *BCR-ABL1*^{IS} ≤ 0.1%) or a confirmed loss of MR[4] (*BCR-ABL1*^{IS} ≤ 0.01%) during the TFR phase reinitiated nilotinib

Figure 1. ENESTop Study Design



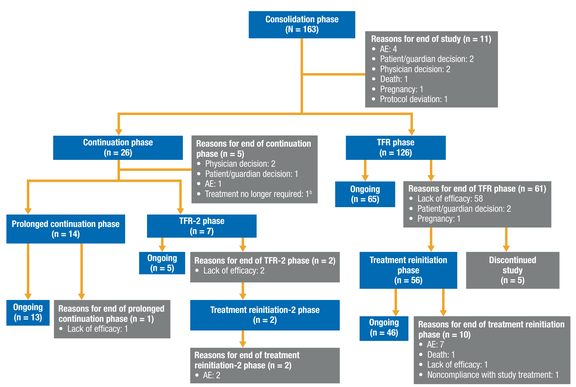
RQ-PCR, real-time quantitative polymerase chain reaction (standardized to the IS); TKI, tyrosine kinase inhibitor.
[a] Confirmed loss of MR[4.5] was defined as *BCR-ABL1*^{IS} > 0.0032%, confirmed in a second assessment within 4 weeks. [b] The end of the study was 264 weeks after the last patient entered the TFR phase. [c] Confirmed loss of MR[4] was defined as *BCR-ABL1*^{IS} > 0.01%, confirmed in a second assessment within 4 weeks. [d] Patients with confirmed loss of MR[4.5] during the continuation phase continued nilotinib treatment in the prolonged continuation phase until 264 weeks after the last patient entered the TFR phase or until discontinuation due to unacceptable toxicity, disease progression, investigator discretion, or withdrawal of consent.

- The primary endpoint (previously reported)[1,2] was the proportion of patients in TFR (defined as no loss of MMR, no confirmed loss of MR[4], and no treatment reinitiation) at 48 weeks
- The results reported here are based on a data cutoff date of 7 November 2016, when all patients who entered the TFR phase had completed 96 weeks of TFR, reinitiated treatment, or discontinued from the study
- Efficacy results are reported for all patients who entered the TFR phase (ie, the TFR population)
- Safety results are reported for the subset of the TFR population who remained in the TFR phase for > 48 weeks

Results

- Of 163 enrolled patients who entered the consolidation phase, 126 (77.3%) were eligible to stop nilotinib in the TFR phase (**Figure 2**)

Figure 2. Patient Disposition[a]



AE, adverse event.
[a] As of the data cutoff date of 7 November 2016.
[b] This patient was not eligible to attempt TFR according to protocol criteria and, with physician approval, discontinued from the study in order to attempt TFR off trial.

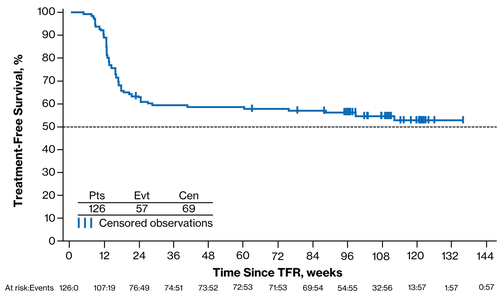
- The median duration of follow-up in the TFR phase through the data cutoff date was 99.0 weeks (range, 6.0-147.0 weeks)
- Patient characteristics for the TFR population are reported in **Table 1**

Table 1. Baseline Characteristics and TKI Treatment Prior to TFR Phase Entry

Parameter	TFR Population (n = 126)
Baseline characteristics	
Age, median (range), years	56.0 (21-86)
Female, n (%)	70 (55.6)
Time from CML diagnosis to study entry, median (range), months	77.9 (37-268)
Time from achievement of MR[4.5] with nilotinib to TFR phase entry, median (range), months	32.1 (11-89)
TKI therapy prior to TFR phase entry	
Duration of TKI therapy, median (range), months	87.7 (49-171)
Duration of nilotinib therapy, median (range), months	53.0 (37-109)
Daily dose of nilotinib, n (%)	
300 mg	1 (0.8)
400 mg	21 (16.7)
450 mg	1 (0.8)
600 mg	37 (29.4)
800 mg	66 (52.4)
Actual nilotinib dose intensity during consolidation phase, median (25th-75th percentile), mg/day	771.8 (596.7-800.0)

- At 96 weeks from the start of the TFR phase, 67 of 126 patients (53.2% [95% CI, 44.1%-62.1%]) remained in TFR
- Of 73 patients who were in TFR at 48 weeks, 6 were considered nonresponders for the analysis of TFR at 96 weeks
  - Four patients had confirmed loss of MR[4] and reinitiated treatment at 60, 72, 90, and 96 weeks, respectively
  - Two patients discontinued from the study between 48 and 96 weeks
    - One due to pregnancy (last *BCR-ABL1*^{IS} on study of 0.0035% at 60 weeks)
    - One due to patient decision (patient maintained MR[4.5] through 90 weeks)
- In a Kaplan-Meier analysis of treatment-free survival (TFS), the curve appeared to plateau after 24 weeks, and the median duration of TFS was not reached by the data cutoff (**Figure 3**)

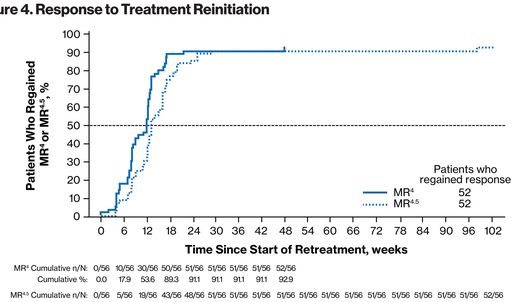
Figure 3. Kaplan-Meier Estimate of TFS[a]



Cen, censored; Evt, events; Pts, patients.
[a] TFS was defined as the time from the start of TFR until the earliest of any of the following: loss of MMR, confirmed loss of MR[4], reinitiation of nilotinib for any reason, progression to accelerated phase/blast crisis, or death due to any cause.

- Of 56 patients who reinitiated nilotinib by the data cutoff, 52 (92.9%) regained MR[4] and MR[4.5] (**Figure 4**)
  - The times by which 50% of patients regained MR[4] and MR[4.5] were 12.0 and 13.1 weeks, respectively
  - Among the 4 patients who did not regain MR[4]:
    - Two were ongoing in the treatment reinitiation phase: 1 had regained MMR, but not MR[4], with a retreatment duration of 87.9 weeks, and the other, who reinitiated treatment due to confirmed loss of MR[4], had a retreatment duration of 6.9 weeks
    - Two had discontinued from the study before 48 weeks (1 due to not regaining MMR after 20 weeks of retreatment and 1 due to an AE after regaining MMR, as previously described[1,2])

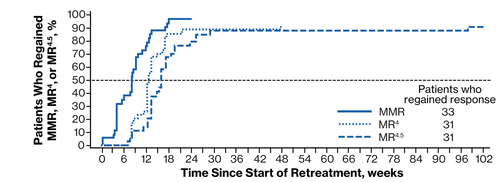
Figure 4. Response to Treatment Reinitiation



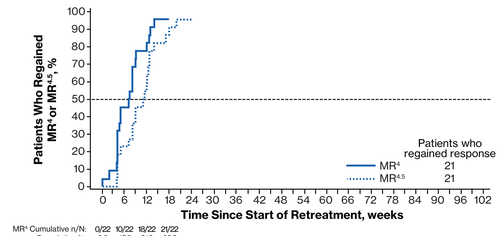
- Response to treatment reinitiation was also analyzed in subsets of patients who reinitiated treatment due to loss of MMR or confirmed loss of MR[4] (**Figure 5**)
  - The time by which 50% of patients regained MR[4.5] was shorter among patients who reinitiated treatment due to confirmed loss of MR[4] (n = 22; 11.0 weeks) vs loss of MMR (n = 34; 16.0 weeks)
  - Among the 34 patients who reinitiated treatment due to loss of MMR, 4 did not regain MR[4.5] within 48 weeks (1 subsequently regained MR[4.5] at week 102)
  - Among the 22 patients who reinitiated treatment due to confirmed loss of MR[4], 1 did not regain MR[4.5] within 24 weeks (patient did not regain MR[4.5] by the data cutoff, with a retreatment duration of ≈ 7 weeks)

Figure 5. Response to Retreatment by Criterion for Reinitiating Treatment

Loss of MMR



Confirmed Loss of MR[4]



Safety

- Among 73 patients who remained in the TFR phase for > 48 weeks, the overall incidences of AEs (any grade) during the first and second 48 weeks of TFR were 82.2% and 63.0%, respectively, vs 79.5% during consolidation (**Table 2**)

Table 2. AEs Reported in > 5% of Patients in Any Study Period

	Consolidation Phase (n = 73)[a]		First 48 Weeks of TFR Phase (n = 73)[a]		Second 48 Weeks of TFR Phase (n = 73)[a]	
AE, n (%)	Any Grade	Grade 3/4	Any Grade	Grade 3/4	Any Grade	Grade 3/4
Any AE	58 (79.5)	14 (19.2)	60 (82.2)	10 (13.7)	46 (63.0)	12 (16.4)
Nasopharyngitis	7 (9.6)	0	3 (4.1)	0	2 (2.7)	0
Headache	5 (6.8)	0	2 (2.7)	0	4 (5.5)	1 (1.4)
Hypertension	5 (6.8)	2 (2.7)	4 (5.5)	0	4 (5.5)	0
Pain in extremity	5 (6.8)	0	6 (8.2)	0	1 (1.4)	0
Constipation	4 (5.5)	1 (1.4)	0	0	2 (2.7)	0
Urinary tract infection	4 (5.5)	0	2 (2.7)	0	1 (1.4)	0
Diarrhea	3 (4.1)	1 (1.4)	5 (6.8)	0	0	0
Influenza	3 (4.1)	1 (1.4)	4 (5.5)	0	2 (2.7)	0
Myalgia	3 (4.1)	0	13 (17.8)	0	3 (4.1)	0
Upper respiratory tract infection	3 (4.1)	0	1 (1.4)	0	4 (5.5)	1 (1.4)
Arthralgia	2 (2.7)	0	19 (26.0)	1 (1.4)	6 (8.2)	0
Musculoskeletal pain	2 (2.7)	0	7 (9.6)	0	3 (4.1)	0
Cough	1 (1.4)	0	5 (6.8)	0	1 (1.4)	0
Oral herpes	0	0	4 (5.5)	0	0	0
Weight increased	0	0	4 (5.5)	0	7 (9.6)	1 (1.4)

[a] Incidences are reported for the 73 patients who remained in the TFR phase for > 48 weeks.

- In an analysis of AEs based on groupings of terms (among patients who remained in the TFR phase for > 48 weeks), the incidence of musculoskeletal pain–related events decreased from 47.9% during the first 48 weeks of TFR to 15.1% during the second 48 weeks of TFR, compared with 13.7% during consolidation (**Table 3**)
- Among the 126 patients who entered the TFR phase, 57 had ≥ 1 musculoskeletal pain–related AE by the 96-week data cutoff, with 3 patients having a musculoskeletal pain–related AE after the 48-week data cutoff
  - The majority (46 of 57) of these AEs began during the first 24 weeks of the TFR phase
- Incidences of cardiovascular events (CVEs) were low across study periods (**Table 3**)

Table 3. Clinically Notable AE Groupings

	Consolidation Phase (n = 73)[a]		First 48 Weeks of TFR Phase (n = 73)[a]		Second 48 Weeks of TFR Phase (n = 73)[a]	
AE Grouping, n (%)	Any Grade	Grade 3/4	Any Grade	Grade 3/4	Any Grade	Grade 3/4
Musculoskeletal pain	10 (13.7)	0	35 (47.9)	2 (2.7)	11 (15.1)	1 (1.4)
Rash	3 (4.1)	0	0	0	2 (2.7)	1 (1.4)
CVEs	2 (2.7)	1 (1.4)	0	0	2 (2.7)	0
Ischemic heart disease	1 (1.4)	1 (1.4)	0	0	0	0
Peripheral arterial occlusive disease	1 (1.4)	0	0	0	1 (1.4)	0
Other	0	0	0	0	1 (1.4)[b]	0
Fluid retention[c]	2 (2.7)	0	9 (12.3)	0	7 (9.6)	1 (1.4)

[a] Incidences are reported for the 73 patients who remained in the TFR phase for > 48 weeks. [b] The patient had an AE of arteriosclerosis.
[c] Specific AEs reported were: consolidation phase, edema peripheral (n = 2); first 48 weeks of TFR, weight increased (n = 4), edema peripheral (n = 2), face edema (n = 2), and eyelid edema (n = 1); second 48 weeks of TFR, weight increased (n = 7).

- A total of 3 deaths were reported
  - One occurred during the consolidation phase prior to the 48-week data cutoff due to arterial hemorrhage following a preplanned angioplasty (previously reported[1,2])
  - After the 48-week data cutoff, an additional 2 patients died during posttreatment follow-up > 30 days after discontinuing from the treatment reinitiation phase
    - One death was due to cardiopulmonary failure 111 days after the patient discontinued retreatment due to an AE
    - The other was due to adenocarcinoma metastasis of occult primary 77 days after the patient discontinued retreatment due to initiation of chemotherapy for this secondary malignancy
- Hematologic and biochemical laboratory abnormalities occurring in ≥ 10% of patients in any study period are reported in **Table 4**

Table 4. Laboratory Abnormalities Reported in ≥ 10% of Patients in Any Study Period

	Consolidation Phase (n = 73)[a]		First 48 Weeks of TFR Phase (n = 73)[a]		Second 48 Weeks of TFR Phase (n = 73)[a]	
Parameter, n (%)	Grade 1/2	Grade 3/4	Grade 1/2	Grade 3/4	Grade 1/2	Grade 3/4
Hematologic						
Hemoglobin decreased	19 (26.0)	0	16 (21.9)	0	15 (20.5)	0
Lymphocytes decreased	13 (17.8)	0	9 (12.3)	0	11 (15.1)	0
Platelets decreased	10 (13.7)	0	12 (16.4)	0	6 (8.2)	0
Leukocytes decreased	3 (4.1)	0	11 (15.1)	0	9 (12.3)	0
Biochemical						
ALT increased	36 (49.3)	0	15 (20.5)	0	10 (13.7)	1 (1.4)
AST increased	35 (47.9)	0	10 (13.7)	0	6 (8.2)	1 (1.4)
Glucose increased	32 (43.8)	3 (4.1)	23 (31.5)	2 (2.7)	24 (32.9)	1 (1.4)
Creatinine increased	26 (35.6)	0	22 (30.1)	0	23 (31.5)	0
Bilirubin increased	24 (32.9)	0	2 (2.7)	0	1 (1.4)	1 (1.4)
Phosphate decreased	23 (31.5)	1 (1.4)	2 (2.7)	1 (1.4)	10 (13.7)	0
Calcium decreased	16 (21.9)	0	3 (4.1)	0	2 (2.7)	0
Uric acid	15 (20.5)	3 (4.1)	29 (39.7)	0	32 (43.8)	2 (2.7)
Alkaline phosphatase increased	14 (19.2)	0	8 (11.0)	0	13 (17.8)	0
Triacylglycerol lipase increased	12 (16.4)	5 (6.8)	8 (11.0)	3 (4.1)	9 (12.3)	2 (2.7)
Glucose decreased	11 (15.1)	0	10 (13.7)	0	13 (17.8)	0

ALT, alanine aminotransferase; AST, aspartate aminotransferase.
[a] Incidences are reported for the 73 patients who remained in the TFR phase for > 48 weeks.

Conclusions

- In this updated analysis of ENESTop, 53.2% of patients (67/126 [95% CI, 44.1%-62.1%]) remained in TFR at 96 weeks after stopping nilotinib
  - Only 4 patients reinitiated treatment (all due to confirmed loss of MR[4]) between 48 and 96 weeks of the TFR phase
- Among patients who reinitiated treatment, 92.9% regained MR[4] and MR[4.5]
- The overall incidence of AEs was lower during the second vs the first 48 weeks of TFR (63.0% vs 82.2%, respectively)
- The incidence of musculoskeletal pain–related AEs decreased from 47.9% during the first 48 weeks of TFR to 15.1% during the second 48 weeks of TFR, similar to the incidence observed during the consolidation phase (13.7%)
  - This suggests that musculoskeletal pain–related AEs, which have also been reported following imatinib cessation,[3,4] are transient and manageable
- In summary, longer follow-up in ENESTop demonstrated the stability and durability of the TFR rate at 96 weeks after stopping second-line nilotinib

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