

Safety and efficacy of switching to nilotinib 400 mg twice daily for patients with chronic myeloid leukemia in chronic phase with suboptimal response or failure on front-line imatinib or nilotinib 300 mg twice daily

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1 **Supplementary Appendix.**

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3 **Safety and efficacy of switching to nilotinib 400 mg twice daily for patients with chronic**
4 **myeloid leukemia in chronic phase with suboptimal response or failure on frontline**
5 **imatinib or nilotinib 300 mg twice daily**

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12 **Detailed methods**

13 *Evaluating Nilotinib Efficacy and Safety in Clinical Trials—Newly Diagnosed Patients (ENESTnd) Core*
14 *Study: Patients, Study Design, and Treatments*

15 The study design of the phase 3, randomized, open-label ENESTnd trial has been previously reported.¹⁻³

16 Briefly, newly diagnosed patients with Philadelphia chromosome–positive (Ph+) chronic myeloid
17 leukemia in chronic phase (CML-CP) were randomized 1:1:1 to receive nilotinib 300 mg twice daily,
18 nilotinib 400 mg twice daily, or imatinib 400 mg once daily. Randomization was stratified according to
19 Sokal risk score⁴ at the time of diagnosis. Patients enrolled in the imatinib arm of ENESTnd who had
20 suboptimal response or treatment failure were allowed to undergo dose escalation of imatinib from 400
21 mg once daily to 400 mg twice daily, if tolerable. Dose escalation of nilotinib was not permitted in the
22 core study.

23

24 *ENESTnd Core Study: Analysis of Suboptimal Response and Treatment Failure*

25 Definitions of suboptimal response and treatment failure in ENESTnd were based on those recommended
26 by the European LeukemiaNet,⁵ with some modifications. Suboptimal response was defined as follows:

27 less than a complete hematologic response (CHR) at 3 months, less than a partial cytogenetic response
28 (PCyR; > 35% Ph+ cells) at 6 months, less than a complete cytogenetic response (CCyR; > 0% Ph+ cells)
29 at 12 months, less than a major molecular response (MMR; BCR-ABL on the international scale [BCR-
30 ABL^{IS}] ≤ 0.1%) at 18 months or later, or loss of MMR at any time. Loss of MMR required confirmation
31 by a second assessment unless it was associated with loss of CHR, loss of CCyR, progression to
32 accelerated phase/blast crisis (AP/BC), or CML-related death.

33
34 Treatment failure was defined as follows: less than CHR or no cytogenetic response (CyR; > 95% Ph+
35 cells) at 6 months, less than PCyR at 12 months, less than CCyR at 18 months, or loss of CHR, loss of
36 PCyR, loss of CCyR, or progression to AP/BC at any time. Loss of CHR required confirmation unless it
37 was associated with progression to AP/BC or CML-related death; loss of PCyR or CCyR was confirmed
38 by a second cytogenetic analysis ≥ 4 weeks later unless it was associated with loss of CHR, progression to
39 AP/BC, or CML-related death.

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41 Incidences of suboptimal response and treatment failure were reported cumulatively by 6, 12, and 18
42 months. For each patient, only their worst response at or before each time point was counted (eg, a patient
43 who satisfied the criteria for treatment failure at 6 months and suboptimal response at 12 months was
44 considered to have treatment failure by 12 months).

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