

January 18, 2018



Submission Request

National Comprehensive Cancer Network® (NCCN®)

RE: Clinical Evidence in Support of Treatment Discontinuation with Tasigna® (nilotinib) in Eligible Patients with Chronic-phase Philadelphia Chromosome-positive Chronic Myeloid Leukemia (Ph+ CML-CP)

Name: Neilda Baron, MD
Company/Organization: Novartis Pharmaceuticals Corporation
Address: One Health Plaza, Building 345
East Hanover, NJ 07936
Phone: 1-862-778-5494
E-mail: neilda.baron@novartis.com
Date of request: January 18, 2018
NCCN Guidelines Panel: Chronic Myeloid Leukemia (CML)

To Whom It May Concern:

As the NCCN CML Panel reviews the NCCN Clinical Practice Guidelines in Oncology® (NCCN Guidelines®) for CML v.3.2018 and the associated Drugs and Biologics Compendium™, we have enclosed data regarding Tasigna® (nilotinib) for your consideration:

- 96-week data from two large clinical trials to support consideration of treatment discontinuation of nilotinib in eligible first- or second-line patients with Ph+ CML-CP who have achieved a sustained molecular response (MR4.5)
- On December 22, 2017, the FDA included information in the Tasigna Prescribing Information (PI) on patient eligibility for treatment discontinuation, monitoring guidelines, and when to reinstitute therapy in the event of loss of molecular remission

* * * * *

Treatment-free remission with nilotinib in eligible patients with Ph+ CML-CP

This request is for the Panel to consider including nilotinib as the preferred tyrosine kinase inhibitor (TKI) that may be considered for discontinuation (or treatment-free remission [TFR]) as appropriate in first- and second-line patients in the CML Guidelines® and the associated NCCN Drugs and Biologics Compendium™ based on the quality and consistency of evidence. To identify patients who may be considered for TFR, the feasibility and safety with nilotinib have been shown in two clinical studies with efficacy based on 96-week analysis data cutoff dates:

- ENESTfreedom: 190 adult Ph+ CML-CP patients treated with nilotinib in first-line for at least 2 years achieved MR4.5, sustained deep molecular response, were enrolled for an additional 52 weeks (consolidation phase) and entered the TFR phase after a documented sustained deep molecular response
- ENESTop: 163 adult Ph+ CML-CP patients treated with a TKI or TKIs for at least 3 years (imatinib as initial TKI therapy for more than 4 weeks without documented MR4.5 on imatinib at the time of switch to nilotinib, then switched to nilotinib for at least 2 years), and who achieved a sustained deep molecular response (MR4.5) on nilotinib, were enrolled for an additional 52 weeks (consolidation phase) and entered the TFR phase after a documented sustained deep molecular response

On December 22, 2017, the FDA included information in the Tasigna PI on patient eligibility for treatment discontinuation, monitoring guidelines, and when to reinstitute therapy in the event of loss of

molecular remission based on these trials.

The 96-week data were presented at the 2017 European Hematology Association meeting and have been submitted for publication. The journal manuscripts will be submitted to the Panel upon publication.

Specific changes recommended for the Guidelines & Compendium

- Based on the quality and consistency of evidence, please consider modifying CML-E and related discussion sections to include nilotinib as the preferred TKI where discontinuation (or TFR) may be considered for eligible CML patients.
- Please consider amending the recommended criteria for patient eligibility for nilotinib discontinuation, monitoring guidelines, and when to reinitiate nilotinib in the event of loss of molecular remission based on the clinical evidence to further clarify safe and appropriate treatment discontinuation.
- Please consider amending the general criteria for TKI discontinuation to reflect the evidence available for each specific treatment option.

FDA status

Tasigna is a TKI indicated for the treatment of newly diagnosed adult patients with Ph+ CML in chronic phase and for the treatment of chronic phase and accelerated phase Ph+ CML in adult patients resistant to or intolerant to prior therapy that included imatinib.¹

Eligible first-line patients with Ph+ CML-CP who have received nilotinib for a minimum of 3 years and have achieved a sustained molecular response (MR4.5) and second-line patients with Ph+ CML-CP resistant or intolerant to imatinib who have received nilotinib for at least 3 years and have achieved a sustained molecular response (MR4.5) may be considered for treatment discontinuation.¹

In order to be considered for treatment discontinuation, patients must have typical BCR-ABL transcripts. An FDA-authorized test with a detection limit below MR4.5 must be used to determine eligibility for discontinuation.¹

During the treatment-free phase, patients must be frequently monitored by the FDA-authorized test to detect possible loss of remission. First-line patients must reinitiate nilotinib therapy within 4 weeks of a loss of major molecular response (MMR, corresponding to MR3.0 or = BCR-ABL/ABL \leq 0.1%IS). Second-line patients must reinitiate nilotinib therapy within 4 weeks of a loss of MMR or confirmed loss of MR4.0 (two consecutive measures separated by at least 4 weeks showing loss of MR4.0, corresponding to = BCR-ABL/ABL \leq 0.01%IS). For patients who fail to achieve MMR after 3 months of treatment reinitiation, BCR-ABL kinase domain mutation testing should be performed.¹

Rationales for recommended change

- Based on the recent FDA-approved label and clinical evidence from the 96-week updates from ENESTfreedom and ENESTop, treatment discontinuation with nilotinib may be considered as the preferred TKI in eligible first- or second-line patients with Ph+ CML-CP who have achieved a sustained molecular response (MR4.5).
- In considering patient safety, the eligibility for treatment discontinuation, the frequency of BCR-ABL monitoring with a sensitive and reliable test, and guidance on when to reinitiate treatment in the event of loss of molecular remission should be based on evidence generated from clinical trials, which has been reviewed by the FDA and included within the US approved label.
- There are no citations included within the discussion section, nor ongoing clinical trials, providing evidence in support of TKI discontinuation with ponatinib or bosutinib. Patients utilizing agents in the third-line setting after treatment failure with other TKIs may not be appropriate for TKI discontinuation.

While the NCCN Guidelines are a statement of consensus of the authors regarding their views on currently accepted approaches to cancer treatment, we would respectfully request that the committee consider the following topics in the next Panel meeting:

1. Clarification around the generalization of TKI discontinuation as a class effect when at the time of this submission:
 - a. There are currently no TFR studies conducted in bosutinib or ponatinib
 - b. The current evidence does not support TFR consideration in patients receiving greater than second-line therapy
 - c. The current Sprycel[®] (dasatinib) PI states, "The effect of stopping treatment on long-term disease outcome after the achievement of a cytogenetic response (including complete cytogenetic response [CCyR]) or major molecular response (MMR and MR4.5) has not been established."
 - d. The current Guidelines include "no history of resistance to any TKI" as part of the criteria; however, ENESTop demonstrated TFR with nilotinib in patients who had previously been resistant or intolerant to imatinib
2. The definition and qualification of a CML Specialty Center, and its role in determining appropriateness of TFR. In speaking with community practicing hematologists who review the Guidelines, this was not well understood.
3. Reporting of CML progression or significant AE related to discontinuation to NCCN and existence of an NCCN safety monitoring Panel or committee.

Literature support

1. Tasigna [prescribing information]. East Hanover, NJ: Novartis Pharmaceuticals Corp; 2017.
2. Ross D, Masszi T, Gomez Casares M, et al. Durable treatment-free remission following frontline nilotinib in patients with chronic myeloid leukemia in chronic phase: ENESTfreedom 96-week update. Poster presented at: European Hematology Association (EHA); June 22-25 2017; Madrid, Spain. Poster P601.
3. Hughes T, Boquimpani C, Takahashi, et al. Durable treatment-free remission after stopping second-line nilotinib in patients with chronic myeloid leukemia in chronic phase: ENESTop 96-week update. Poster presented at: European Hematology Association (EHA); June 22-25 2017; Madrid, Spain. Poster P257.

* * * * *

We appreciate the opportunity to provide this additional information specific to nilotinib for consideration by the NCCN CML Panel. If you have any questions or require additional information, please do not hesitate to contact me at 1-862-778-5494 or via e-mail at neilda.baron@novartis.com.

Thank you for your time and consideration.

Sincerely,

Neilda Baron, MD
Executive Director, Medical Information Oncology
Novartis Pharmaceuticals Corporation

Enclosures: Copy of Tasigna PI and referenced primary literature; author disclosures included within references

SPRYCEL is a registered trademark of Bristol-Myers Squibb Company.