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Submission Request
National Comprehensive Cancer Network® (NCCN®)

RE: Clinical Evidence in Support of Achieving Deep Molecular Response with Frontline Tasigna® (nilotinib) in Newly Diagnosed Patients With Chronic-Phase Philadelphia Chromosome-Positive Chronic Myeloid Leukemia

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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.1.2019 and the associated Drugs and Biologics Compendium™, we have enclosed recent data relating to achieving early deep molecular response (DMR; defined as MR4 [BCR-ABL1^{IS} ≤0.01%] or MR4.5 [BCR-ABL1^{IS} ≤0.0032%]) with nilotinib as frontline treatment of CML in the chronic phase (CP) in newly diagnosed patients. The data support DMR as a goal of therapy at 2 years.

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DMR with frontline nilotinib for the treatment of newly diagnosed Ph+ CML-CP patients
This request is for the Panel to consider data supporting achieving early DMR as a goal of therapy with frontline nilotinib use in patients with newly diagnosed CML-CP at 2 years.

ENESTnext, an open-label, single-arm, multicenter, Phase IV trial in the US (NCT01227577) evaluated the rate of MR4.5 by two years for newly diagnosed CML patients receiving nilotinib (N = 128). The primary endpoint was rate of confirmed MR4.5 with up to two years of on-study nilotinib. Thirty-four (26.6%) patients achieved MR4.5 by two years. Among patients who achieved confirmed MR4.5, 74% did so by 12 months and median time to confirmed MR4.5 was 8.3 months with a median duration of confirmed MR4.5 of 13.9 months. Safety results, including cardiovascular events (CVEs), were consistent with other nilotinib trials. Overall, the most common Grade 3/4 adverse events were increased lipase (n = 16; 12.5%), thrombocytopenia (n = 11; 8.6%) and neutropenia (n = 8; 6.3%). Six patients died during the study: two during study treatment, one after 30-day follow-up and three during post-treatment survival follow-up.[1] In the European Phase IIIb, single-arm, open-label, ENEST1st study that evaluated efficacy and safety of nilotinib as first-line treatment in patients with newly diagnosed CML-CP (N = 1089), the primary endpoint rate of DMR (MR4) at 18 months was achieved by 38.4% (404/1052) of patients who had received ≤ 3 months of prior imatinib. Safety profile of nilotinib was consistent with previous studies. Ischemic CVEs occurred in 6% of patients.[2]

With five years follow-up, the pivotal Phase III ENESTnd trial demonstrated that more patients receiving frontline nilotinib 300 mg twice daily achieved MR4.5 than those receiving imatinib 400 mg daily (54% vs. 31%; *P*<0.0001). Among patients with low, intermediate and high Sokal risk scores, rates of MR4.5 for patients receiving nilotinib 300 mg twice daily vs imatinib 400 mg once daily were 53.4% vs. 36.5%, 60.4% vs. 32.7% and 44.9% vs. 23.1%, respectively. Overall and within each Sokal risk group, more patients achieved MR4.5 with nilotinib vs imatinib. Overall, safety results remained consistent with those from previous reports. Numerically more CVEs occurred in patients receiving nilotinib vs imatinib, and elevations in blood cholesterol and glucose levels were more frequent with nilotinib. In contrast to high mortality rate associated with CML progression, few deaths in any arm were associated with CVEs, infections or pulmonary diseases.[3]

Specific changes recommended for the Guidelines
Please consider modifying CML-2 to prefer nilotinib to imatinib (or generic imatinib) in low-risk patients.

FDA status
Tasigna is a kinase inhibitor indicated for the treatment of:[4]

- Adult and pediatric patients greater than or equal to 1 year of age with newly diagnosed Ph+ CML-CP
- Adult patients with chronic phase and accelerated phase Ph+ CML resistant to or intolerant to prior therapy that included imatinib
- Pediatric patients greater than or equal to 1 year of age with Ph+ CML-CP resistant or intolerant to prior tyrosine kinase inhibitor (TKI) therapy.

Rationale for recommended change

- DMR has been associated with long-term clinical benefits, such as high rates of failure-free survival, progression-free survival, and overall survival. None of the patients receiving imatinib in the CML-IV study who achieved MR4.5 experienced disease progression. Additionally, sustained DMR is a key requirement for attempting treatment-free remission.
- The NCCN Guidelines for CML v1.2019 already indicate that second generation TKIs are preferred for patients with an intermediate- or high-risk Sokal or Hasford score, especially young women whose goal is to achieve a deep and rapid molecular response and eventual drug discontinuation of TKI therapy for fertility purposes (CML-2).
- The Guidelines also indicate BCR-ABL1 of 0.1% at 12 months is associated with a very low probability of subsequent disease progression and a high likelihood of achieving a subsequent MR4.0, which may facilitate discontinuation of TKI therapy (CML-3).
- Achieving MR4 or MR4.5 with frontline nilotinib was demonstrated in ENEST1st and ENESTnext, and with the ENESTnd 5-year follow-up, across all patients, including low-risk patients.

Literature support

1. Berdeja JG, Heinrich MC, Dakhil SR, et al. Rates of deep molecular response by digital and conventional PCR with frontline nilotinib in newly diagnosed chronic myeloid leukemia: a landmark analysis. Leukemia & Lymphoma (2019) [Epub ahead of print]; doi: 10.1080/10428194.2019.1590569
2. Hochhaus A, Rosti G, Cross NCP, et al. Frontline nilotinib in patients with chronic myeloid leukemia in chronic phase: results from the European ENEST1st study. Leukemia (2016) 30, 57-64; doi:10.1038/leu.2015.270.
3. Hochhaus A, Salio G, and Hughes TP, et al. Long-term benefits and risks of frontline nilotinib vs imatinib for chronic myeloid leukemia in chronic phase: 5-year update of the randomized ENESTnd trial. Leukemia (2016) 30, 1044–1054; doi:10.1038/leu.2016.5.
4. Tasigna [prescribing information]. East Hanover, NJ: Novartis Pharmaceuticals Corp; 2018.

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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,

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