NOVARTIS ONCOLOGY

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Submission Request
National Comprehensive Cancer Network

RE: Clinical Evidence in Support of Tasigna® (nilotinib) in CML

Name:	Neilda Baron, MD
Company/Organization:	Novartis Pharmaceuticals Corporation
Address:	One Health Plaza, Building 345 East Hanover, NJ 07936
Phone:	862-778-5494
Email:	Neilda.baron@novartis.com
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NCCN Guidelines Panel:	Chronic Myelogenous 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.2.2016 and the associated Drugs & Biologics Compendium™, we have enclosed data relating to treatment of CML with Tasigna® (nilotinib):

Five-year data to further support the use of nilotinib in newly diagnosed Philadelphia chromosome-positive (Ph+) CML in chronic phase (CP) patients across all Sokal risk groups, and in particular longer term data demonstrating improved outcomes with nilotinib use versus imatinib in patients with intermediate- and high-Sokal risk scores.

Nilotinib for the treatment of newly diagnosed Ph+ CML-CP patients
This request is for the Panel to consider updating the NCCN Guidelines® to reflect the 5-year data available from ENESTnd to further support the frontline use of nilotinib in those with intermediate- and high-risk Sokal scores.

ENESTnd 5-year estimated OS, PFS rates and outcomes according to Sokal risk score[1]

	Nilotinib 300mg BID	Nilotinib 400mg BID	Imatinib 400mg once daily
Estimated OS* on study, % (95%CI)	93.7 (90.8-96.6)	96.2 (93.9-98.5)	91.7 (88.3-95.0)
P vs imatinib**	.4881	.0266	-
Estimated PFS on study, % (95%CI)	92.2 (89.0-95.4)	95.8 (93.4-98.3)	91.0 (87.5-94.4)
P vs imatinib**	.2032	.0260	-
Low Sokal risk, n	103	103	104
MR4.5 by 5 years, n (%)	55 (53.4)	64 (62.1)	38 (36.5)
Estimated 5-yr PFS on study, %	96.0	99.0	100
Estimated 5-yr OS on study, %	97.0	99.0	100
Intermediate Sokal risk, n	101	100	101
MR4.5 by 5 years, n (%)	61(60.4)	50(50.0)	33(32.7)
Estimated 5-yr PFS on study,%	92.9	96.9	87.9
Estimated 5-yr OS on study,%	93.8	96.9	88.5
High Sokal risk, n	78	78	78
MR4.5 by 5 years, n (%)	35 (44.9)	33 (42.3)	18 (23.1)
Estimated 5-yr PFS on study,%	86.2	90.0	82.6
Estimated 5-yr OS on study,%	88.8	91.5	84.2

BID, twice daily; OS, overall survival; PFS, progression-free survival
*Median rates for overall survival were not yet reached at the time of the 60- month analysis.

**Nominal two-sided P- values for descriptive purposes only without multiplicity adjustments; therefore, no formal statistical claim can be made and statistical interpretation should be made with caution

Overall, the 5-year safety results have been consistent with previous study reports; more cardiovascular events occurred in patients receiving nilotinib and elevations in blood cholesterol and glucose levels were more frequent with nilotinib versus imatinib.

Specific changes recommended for the Guidelines and Compendium

- Update the Chronic Phase CML Primary Treatment section (CML-1) and footnote 'g' in the Workup for Primary Treatment based on the 5-year data available for nilotinib use in patients with intermediate- and high-risk Sokal scores.
- Update the Frontline Therapy section with the nilotinib 5-year estimated overall survival and progression-free survival data within the discussion section.
- Correct the 5-year MR4.5 rate for imatinib high Sokal risk score patients from 27% to 23% within the discussion section.

FDA status

Nilotinib is approved for the treatment of newly diagnosed adult patients with Ph+ CML-CP and for the treatment of Ph+ CML-CP and accelerated phase adult patients resistant to or intolerant to prior therapy that included imatinib.

Rationale for recommended change

Based on the 5-year ENESTnd reported rates for MR4.5 by 5-years, estimated 5-year OS rate, and estimated 5-year PFS on study, nilotinib 300mg twice daily has demonstrated better outcomes compared to imatinib including the subset of intermediate- and high-risk patients.

Literature support

1. Hocchaus 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.

We appreciate the opportunity to provide this additional information 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

Enclosure: A copy of the referenced primary literature