October 20, 2021

Submission Request
National Comprehensive Cancer Network® (NCCN®)

RE: Clinical Evidence in Support of Asciminib for Ph+ CML-CP After ≥2 Prior TKIs or T315I Mutation

Name:	Neilda Baron, MD
Company/Organization:	Novartis Pharmaceuticals Corporation
Address:	One Health Plaza East Hanover, NJ 07936
Phone:	862-210-0112
E-mail:	Neilda.Baron@novartis.com
Date of request:	October 20, 2021
NCCN Guidelines Panel:	Chronic Myeloid Leukemia

To Whom It May Concern:

As the Panel reviews the NCCN Clinical Practice Guidelines in Oncology® (NCCN Guidelines®) for Chronic Myeloid Leukemia (CML) Version 1.2022 and the associated Drugs & Biologics Compendium®, we are enclosing data from the Phase III ASCEMBL and Phase I CABL001X2101 studies for your consideration[1,2,3]:

- Data to support the use of asciminib in adult patients with Philadelphia chromosome-positive chronic myeloid leukemia (Ph+ CML) in chronic phase (CP), previously treated with two or more tyrosine kinase inhibitors (TKIs) or harboring the T315I mutation

Specific Changes

- **[CML-2]:** Please consider including asciminib as a treatment option for patients with Ph+ CML-CP who have failed two or more TKIs and update the treatment algorithm.
- **[CML-5]:** Please consider including asciminib as a treatment option for Ph+ CML-CP patients with the T315I mutation and update the chart.
- **[CML-G]:** Please consider adding asciminib to the list of CML treatments and creating a corresponding management of toxicities/drug interactions page for asciminib.
- **Discussion:** Please add a summary of asciminib to the discussion section accordingly.

*****

Asciminib for the Treatment of Ph+ CML-CP After ≥2 Prior TKIs or T315I Mutation
ASCEMBL (NCT03106779)

ASCEMBL is a randomized, open-label, active-controlled, multicenter Phase III study that evaluated patients with CML-CP previously treated with two or more TKIs and were randomized (2:1) and stratified by major cytogenetic response (MCyR) status to either[1]:

- Asciminib 40 mg twice daily (n = 157)
- Bosutinib 500 mg once daily (n = 76)

Eligible patients must have failed treatment with a second-line TKI as defined in the 2013 European LeukemiaNet (ELN) recommendations or were intolerant to their most recent TKI treatment. The primary endpoint was the rate of major molecular response (MMR; BCR-ABL1^{IS} ≤0.1%) at week 24. The median follow-up for all patients randomized was 14.9 months. At baseline, 68 (29.2%) of patients in the asciminib arm and 22 (28.9%) of patients in the bosutinib arm were in MCyR.[1]

The study met its primary objective with an MMR rate at week 24 of 25.5% with asciminib vs 13.2% with bosutinib. After adjusting for MCyR status at baseline, the difference in MMR rates at week 24 between asciminib and bosutinib was 12.2% (95% CI:2.19 – 22.30; 2-sided *P* = .029). The complete cytogenetic response rate (CCyR) at week 24 was 40.8% with asciminib vs 24.2% with bosutinib. The difference in CCyR between the treatment arms, after adjusting for MCyR status at baseline, was 17.3% (95% CI:3.62 – 30.99). The median duration of exposure for asciminib and bosutinib was 43.4 (range, 0.1 – 129.9) weeks and 29.2 (range, 1.0 – 117.0) weeks, respectively. The percentage of

patients with treatment ongoing with asciminib and bosutinib were 61.8% and 28.9%, respectively. [1]

The most common adverse events of all grades regardless of relationship to study drug (≥10% incidence; asciminib arm vs bosutinib arm respectively) were[1]:

- thrombocytopenia (28.8% vs 18.4%)
- neutropenia (21.8% vs 21.1%)
- headache (16.0% vs 13.2%)
- diarrhea (11.5% vs 71.1%)
- hypertension (11.5% vs 3.9%)
- nausea (11.5% vs 46.1%)
- fatigue (10.3% vs 9.2%)
- rash (7.1% vs 23.7%)
- vomiting (7.1% vs 26.3%)
- abdominal pain (4.5% vs 14.5%)
- ALT increase (3.8% vs 27.6%)
- AST increase (3.8% vs 21.1%)

Fewer adverse events leading to treatment discontinuation occurred in the asciminib arm (5.8%) compared to the bosutinib arm (21.1%). The most common AEs leading to treatment discontinuation included thrombocytopenia (all-grade, 3.2%; Grade ≥3, 3.2%) with asciminib and increased alanine aminotransferase (ALT) (all-grade, 5.3%; Grade ≥3, 3.9%) with bosutinib. Two deaths occurred on treatment in the asciminib arm, one due to arterial embolism and one due to ischemic stroke. Two deaths due to CML occurred after asciminib discontinuation during the survival follow-up period. In the bosutinib arm, there was one death on treatment due to septic shock.[1]

CABL001X2101 (NCT02081378)

The Phase I CABL001X2101 first-in-human, multicenter, open-label study evaluated the efficacy and safety of asciminib in patients with Ph+ CML-CP or accelerated phase (AP) and those with or without the T315I mutation. Patients with the T315I mutations were eligible if they were treated with at least one other TKI and no other effective therapy was available. The primary objective of the study was to determine the maximum tolerated dose/recommended dose of asciminib. Asciminib was administered once or twice daily at doses ranging from 10 – 200 mg.[2,3]

Patients harboring the T315I mutation were assigned to various dose levels in Phase I and 200 mg twice daily was selected for the cohort expansion. Below is a summary (data cutoff: April 2, 2020) from the ASH 2020 presentation, specifically for the cohort of patients (Ph+ CML-CP and AP, n = 52) with the T315I mutation treated with asciminib 200 mg twice daily. The median duration of exposure was 68.4 weeks (range, 2 – 175). Among patients without MMR at baseline, 23/49 (46.9%) achieved MMR and 21/23 of these responders were still in MMR at the data cutoff. The median time to MMR was 12.1 weeks (range, 4 – 84).[3]

The most frequent all grade AEs regardless of study drug relationship (≥15% incidence) were[3]:

- fatigue (26.9%)
- nausea (26.9%)
- diarrhea (21.2%)
- increased lipase (21.2%)
- thrombocytopenia (19.2%)
- vomiting (19.2%)
- abdominal pain (15.4%)
- headache (15.4%)

On-treatment AEs leading to discontinuation were reported in four patients (7.7%; disease progression, Grade 2 thrombocytosis, Grade 3 lipase elevation, and Grade 4 pancytopenia [1 patient each]). Ischemic stroke and peripheral arterial occlusive disease were reported in one patient each and both patients had underlying cardiovascular disease. There were no on-treatment deaths reported.[3]

FDA Status
Asciminib is investigational and is currently under review. There is no guarantee that asciminib will become commercially available for the uses under investigation.

Rationale for Recommended Changes
Based on the efficacy and safety data from ASCEMBL and CABL001X2101 in adult patients with Ph+ CML-CP treated with two or more TKIs or who harbor the T315I mutation, if approved, asciminib may be considered a new treatment option for appropriate patients.

Literature Support

1. Réa D, et al. A phase 3, open-label, randomized study of asciminib, a STAMP inhibitor, vs bosutinib in CML after ≥2 prior TKIs. *Blood*. Published online August 18, 2021. doi:10.1182/blood.2020009984.

2. Hughes, et al. Asciminib in chronic myeloid leukemia after ABL kinase inhibitor failure. *N Engl J Med*. 2019 Dec 12;381(24):2315-2326. doi:10.1056/NEJMoa1902328.

3. Cortes, et al. Asciminib, a first-in-class STAMP inhibitor, provides durable molecular response in patients (pts) with chronic myeloid leukemia (CML) harboring the T315I mutation: primary efficacy and safety results from a phase 1 trial. *Blood*. 2020; 136 (Supplement 1): 47–50. doi:10.1182/blood-2020-139677.

The prescribing information and study results in the form of a published manuscript will be submitted when available.

*****

We appreciate the opportunity to provide this information for consideration by the NCCN Chronic Myeloid Leukemia Panel. If you have any questions or require additional information, please do not hesitate to contact me at 862-210-0112 or via email 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: Referenced primary literature; author disclosures included within references