October 29, 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

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Date of request:	October 29, 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 V.1.2022 and the associated Drugs & Biologics Compendium®, we are enclosing data related to treatment with the recently FDA-approved Scemblix® (asciminib) for your consideration[1,2,3,4]:

- 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 with the T315I mutation

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Specific changes recommended for the Guidelines & Compendium

- **[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.

FDA status

Asciminib is a kinase inhibitor indicated for the treatment of adult patients with[1]:

- Philadelphia chromosome-positive chronic myeloid leukemia (Ph+ CML) in chronic phase (CP), previously treated with two or more tyrosine kinase inhibitors (TKIs) This indication is approved under accelerated approval based on major molecular response (MMR). Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial(s).
- Ph+ CML in CP with the T315I mutation.

Rationale

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[2]:

- 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. At baseline, 68 (29.2%) of patients in the asciminib arm and 22 (28.9%) of patients in the bosutinib arm were in MCyR.[2]

The study met its primary objective with an MMR rate at week 24 of 25% (95% CI: 19 – 33) with asciminib vs 13% (95% CI: 6.5 – 23) with bosutinib. After adjusting for MCyR status at baseline, the difference in MMR rates at week 24 between asciminib and bosutinib was 12% (95% CI: 2.2 – 22; two-sided P = 0.029). The complete cytogenetic response rate (CCyR) at week 24 was 41% (95% CI: 31 – 51) with asciminib (n = 103) vs 24% (95% CI: 14 – 37) with bosutinib (n = 62). The difference in CCyR between the treatment arms, after adjusting for MCyR status at baseline, was 17% (95% CI: 3.6 – 31).[1,2] The median duration of treatment was 67 weeks (range, 0.1 – 162 weeks) for patients treated with asciminib and 30 weeks (range, 1 – 149 weeks) for those treated with bosutinib. The MMR rate at 48 weeks was 29% (95% CI: 22 – 37) in patients receiving asciminib and 13% (95% CI: 6.5 – 23) in patients receiving bosutinib. With a median duration of follow-up of 20 months (range: 1 day to 36 months), the median duration of response had not yet been reached for patients with MMR at any time.[1]

The most common adverse reactions of all grades (≥10%) in patients who received asciminib (n = 156) vs bosutinib (n = 76), respectively, were[1]:

- Upper respiratory tract infection (26% vs 12%)
- Musculoskeletal pain (22% vs 16%)
- Headache (19% vs 15%)
- Fatigue (17% vs 11%)
- Rash (17% vs 30%)
- Hypertension (13% vs 5%)
- Arthralgia (12% vs 3.9%)
- Diarrhea (12% vs 71%)
- Nausea (12% vs 46%)
- Abdominal pain (10% vs 24%)

Serious adverse reactions occurred in 15% of patients who received asciminib. Serious adverse reactions in ≥ 1% included pyrexia (1.9%), cardiac failure congestive (1.3%), thrombocytopenia (1.3%), and urinary tract infection (1.3%). Permanent discontinuation of asciminib due to an adverse reaction occurred in 7% of patients. Adverse reactions which resulted in permanent discontinuation of asciminib in > 2% of patients included thrombocytopenia (3.2%) and neutropenia (2.6%). Two deaths occurred on treatment in the asciminib arm, one due to mesenteric artery thrombosis and one due to ischemic stroke.[1] 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.[2]

CABL001X2101 (NCT02081378)

The Phase I CABL001X2101 multicenter, open-label study evaluated the efficacy and safety of asciminib, including patients with Ph+ CML-CP with the T315I mutation. Patients with the T315I mutation were eligible if they were treated with at least one other TKI and no other effective therapy was available. Testing for T315I mutation utilized a qualitative p210 BCR-ABL mutation test using Sanger Sequencing. 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.[3,4]

Patients with T315I were assigned to various dose levels in Phase I and the 200 mg twice daily regimen was selected for the cohort expansion. Below is a summary for the cohort of Ph+ CML-CP patients with the T315I mutation treated with asciminib 200 mg twice daily. The median duration of treatment was 108 weeks (range: 2 – 215). Efficacy was based on 45 patients with Ph+ CML-CP with the T315I mutation who were treated with asciminib. MMR was achieved by 24

weeks and 96 weeks in 42% (95% CI: 28 – 58) and 49% (95% CI: 34 – 64) of patients, respectively.[1]

The most frequent (≥10%) all grade adverse reactions reported were[1]:

- Musculoskeletal pain (42%)
- Fatigue (31%)
- Nausea (27%)
- Rash (27%)
- Diarrhea (21%)
- Headache (19%)
- Vomiting (19%)
- Abdominal pain (17%)
- Arthralgia (17%)
- Cough (15%)
- Hemorrhage (15%)
- Hypertension (13%)
- Pruritus (13%)
- Upper respiratory tract infection (13%)
- Edema (10%)

Serious adverse reactions occurred in 23% of patients who received asciminib. Serious adverse reactions in > 1% included abdominal pain (4.2%), vomiting (4.2%), pneumonia (4.2%), musculoskeletal pain (2.1%), headache (2.1%), hemorrhage (2.1%), constipation (2.1%), arrhythmia (2.1%), and pleural effusion (2.1%). Permanent discontinuation of asciminib due to an adverse reaction occurred in 10% of patients. Adverse reactions which resulted in permanent discontinuation of asciminib in > 2% of patients included pancreatic enzymes increased (2.1%).[1] 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.[4]

Literature support

1. Scemblix [Prescribing Information]. East Hanover, NJ: Novartis Pharmaceuticals Corp; 2021.
2. Réa, 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.
3. Hughes, et al. Asciminib in chronic myeloid leukemia after ABL kinase inhibitor failure. *N Engl J Med*. 2019;381(24):2315-2326. doi:10.1056/NEJMoa1902328.
4. 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.

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
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Enclosures: Prescribing Information and referenced primary literature; author disclosures included within references.