Asciminib (SCEMBLIX)
National Drug Monograph
October 2023

VA Pharmacy Benefits Management Services, Medical Advisory Panel, and VISN Pharmacist Executives

The purpose of VA PBM Services drug monographs is to provide a focused drug review for making formulary decisions. Updates will be made if new clinical data warrant additional formulary discussion. The Product Information or other resources should be consulted for detailed and most current drug information.

FDA Approval Information

Description/Mechanism of Action

- Asciminib is a tyrosine kinase inhibitor.
- It is first-in-class as a Specifically Targeting the ABL Myristoyl Pocket (STAMP) inhibitor; a potent inhibitor of ABL1 kinase of the BCR-ABL1 fusion protein that works by binding allosterically to the ABL myristoyl pocket.
- It has activity against wild-type BCR-ABL1 and multiple mutant forms, including the T315I mutation.

Indication(s) Under Review in This Document

- Treatment of adult patients with Philadelphia chromosome-positive (Ph+) chronic myeloid leukemia in chronic phase (CML-CP) who have received prior treatment with 2 or more tyrosine kinase inhibitors (TKIs).
- Treatment of adult patients with Ph+ CML-CP who have the T315I mutation of BCR-ABL1.

Dosage Form(s) Under Review

- Tablets: 20mg, 40 mg.
- Dose is 80 mg orally once daily or 40 mg orally twice daily for Ph+ CML after previous treatment of 2 or more TKIs.
- Dose is 200 mg orally twice daily for Ph+ CML with the T315I mutation.
- To be taken without food, avoid food at least 2 hours before or 1 hour after.

Clinical Evidence Summary

Efficacy Considerations

- The ASCEMBL trial[1-3] evaluated the efficacy of asciminib for use in Ph+ CML-CP patients following prior treatment with 2 or more TKIs. The phase III, multi-center, randomized, open-label study utilized an active control with the TKI, bosutinib. Of the 233 patients randomized in a 2:1 ratio, 157 were administered asciminib 40 mg twice daily and 76 were administered bosutinib 500 mg once daily. The primary endpoint studied was the major molecular response rate (MMR), defined as BCR-ABL1 IS ≤ 0.1%, at 24 weeks. The secondary efficacy endpoints

were MMR at 96 weeks and complete cytogenetic response (CCyR, defined as 0% Ph+ metaphases in the bone marrow) rates at 24 and 96 weeks.

- The CABL001X2101 (X2101) trial[4-5] investigated the maximum tolerated and recommended dosing for asciminib in the treatment of CML. The study also expanded to include a subgroup analysis of CML patients with the T315I gatekeeper mutation. Of the total study population, 52 participants with the mutation were treated with asciminib 200 mg twice daily; 28 patients were previously treated with third generation TKI, ponatinib, and 21 patients were naïve to ponatinib. The efficacy endpoints analyzed in the cohort expansion were MMR rates in 24-week intervals, through 96 weeks.

Table 1: Efficacy results from clinical trials

<table>
<tr><th>Study</th><th>Design</th><th>Results</th></tr>
<tr><td>Rea, et al.
ASCEMBL
(NCT03106779)[1-3]
Phase III, multi-center, randomized, open-label, active-controlled

Funded by Novartis Pharmaceuticals</td><td>Inclusion
• Male or female ≥ 18 years old
• Active diagnosis of CML-CP
• Baseline labs, must meet all of the following:
o PB and BM blasts < 15%
o PB and BM blasts plus promyelocytes < 30%
o PB basophils < 20%
o Platelets ≥ 50 x 10^9 (≥ 50,000/mm^3)
▪ Except transient prior therapy-related thrombocytopenia
o No extramedullary leukemic involvement (except hepatosplenomegaly)
• BCR-ABL1 ratio > 0.1 IS
• Prior treatment of ≥ 2 ATP-binding site TKIs
• Failure or intolerance to most recent TKI, defined by 2013 ELN Guidelines[5]
Exclusion
• Known T315I or V299L mutation
• Second occurrence of chronic phase of CML after progression to accelerated or blast phase
• Cardiac disorders or abnormalities
o History (within 6 months) of MI, angina pectoris, or CABG
o Clinically significant arrhythmias or AV block
o QTc interval: ≥450 ms (male), ≥460 ms (female), or long QT syndrome
o Torsades de Pointes risk factors (hypokalemia, hypomagnesemia, cardiac failure, significant/ symptomatic bradycardia)
o Uncontrolled cardiovascular disorders</td><td>Baseline Characteristics
• Median age = 59 years old
• Female = 51.5%
• White = 74.7%
• ECOG PS
o 0 = 80.7%
o 1 = 18%
• Previous lines of TKI therapy
o 2 = 48.1%
o 3 = 31.3%
o 4 = 14.6%
o ≥ 5 = 6%

Treatment Groups
• Asciminib 40 mg twice daily (n = 157)
• Bosutinib 500 mg once daily (n = 76)

Median treatment duration: 67 weeks (0.1 – 162)

Primary and Secondary Endpoints
<table><tr><th></th><th>Asciminib</th><th>Bosutinib</th><th>Difference (95% CI)</th></tr><tr><td>MMR (24 weeks)</td><td>25.5%</td><td>13.2%</td><td>12 (2.19 – 22.3)
p = 0.029</td></tr><tr><td>CCyR (24 weeks)</td><td>40.8%</td><td>24.2%</td><td>17 (3.62 – 30.99)</td></tr><tr><td>MMR (96 weeks)</td><td>37.6%</td><td>15.8%</td><td>21.7 (10.50 – 33.00)
p = 0.001</td></tr><tr><td>CCyR (96 weeks)</td><td>40%</td><td>16%</td><td>24 (10.00 – 37.00)</td></tr></table></td></tr>
<tr><td>Hughes, et al.
CABL001X2101
(NCT02081378)[4-5]</td><td>Inclusion
• Male or female ≥ 18 years old</td><td>Baseline Characteristics
• Median age = 54 years old
• Male = 75%</td></tr>
</table>

<table>
<tr>
<td>Phase I, multi-center, open-label, active-controlled

Funded by Novartis Pharmaceuticals</td>
<td>
• Active diagnosis of CML in chronic or accelerated phase with:
o Prior treatment of ≥ 2 TKIs and either relapsed or were intolerant
OR
o Relapsed disease due to presence of T315I gatekeeper mutation after ≥ 1 TKI
• ECOG PS 0 to 2
<u>Exclusion</u>
• Systemic antineoplastic or immunologic therapy within 14 days
• Radiation therapy within 4 weeks (if wide field) or 1 week (if limited field)
• Major surgery within 2 weeks
• Lab abnormalities, defined as:
o Total bilirubin > 1.5 times ULN
o AST or ALT > 3 times ULN
o Alkaline phosphatase > 2.5 times ULN
o Serum creatinine > 1.5 times ULN
o Amylase or lipase above institutional ULN
o If CML in chronic or accelerated phase:
▪ ANC ≤ 0.5 x 10^9/L
▪ Hgb ≤ 9 g/dL
▪ Platelets ≤ 50 x 10^9/L
o If CML-BP or ALL:
▪ PB Blasts > 50,000/mm^3
• Treatment with any QT-prolonging medications or QTc interval > 480 ms
• Active infection or severe infection within 2 weeks
• Pregnancy
</td>
<td>
• ECOG PS
o 0 = 75%
o 1 = 25%
• Treatment status (at data cutoff)
o Ongoing: 67.3%
o Ended: 32.7%
• BCR-ABL IS (baseline)
o > 0.1% to ≤ 1%: 15.4%
o > 1% to ≤ 10%: 25%
o > 10%: 53.8%
o Unknown: 5.8%
<u>Treatment Groups</u>
• Asciminib 200 mg twice daily (n = 52)
o Ponatinib-naïve (n = 21)
o Ponatinib-pretreated (n = 28)

Median treatment duration: 68.4 weeks (2 - 175)

<u>Efficacy Endpoints</u>

* 3 patients did not undergo efficacy analyses due to unknown BCR-ABL1 IS at baseline
<table>
<tr><th>MMR at time points (in weeks)</th><th>Ponatinib Naïve (n=21)</th><th>Ponatinib Pretreated (n=28)</th><th>Total (n=49)</th></tr>
<tr><td>24</td><td>57.1%</td><td>28.6%</td><td>40.8%</td></tr>
<tr><td>48</td><td>57.1%</td><td>32.1%</td><td>42.9%</td></tr>
<tr><td>72</td><td>61.9%</td><td>32.1%</td><td>44.9%</td></tr>
<tr><td>96</td><td>66.7%</td><td>32.1%</td><td>46.9%</td></tr>
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</tr>
</table>

CML-CP = chronic myeloid leukemia in chronic phase; PB = peripheral blood; BM = bone marrow; IS = international scale; TKIs = tyrosine kinase inhibitors; MI = myocardial infarction; CABG = coronary artery bypass graft; ECOG PS = Eastern Cooperative Oncology Group performance status; MMR = major molecular response; CCyR = complete cytogenetic response; CML-BP = chronic myeloid leukemia in blast phase (≥ 30% blasts in peripheral blood or bone marrow -or- extramedullary involvement other than hepatosplenomegaly); ALL = acute lymphoid leukemia; ULN = upper limit of normal; ANC = absolute neutrophil count; Hgb = hemoglobin

- For the ASCEMBL trial, the median duration of exposure was 103.1 weeks for asciminib and 30.5 weeks for bosutinib; median duration of follow-up was 28 months. In patients with CML-CP following at least 2 prior treatments with TKIs, asciminib demonstrated superiority over bosutinib. Major molecular response rates were significantly improved at 24 and 96 weeks for those treated with asciminib, compared to bosutinib. Subgroup analyses supported the findings of asciminib benefits in all major demographics regardless of number of previous TKI therapies. Ponatinib was not considered to serve as an active comparator as the optimal dose was being reassessed in the OPTIC trial.

- For the X2101 trial expansion, the median duration of treatment was about 68 weeks and the data cutoff was set for April 2, 2020. In patients with CML in either chronic or accelerated phase and the T315I mutation, asciminib displayed clinical improvement based on MMR rates at each time point. There was a notable difference between ponatinib naïve and pretreated patients; asciminib may provide better efficacy when started without prior ponatinib treatment. Since this was an expansion, there was a lack in focused analysis that would provide more certain clinical application.

Safety Considerations

Safety Results from Clinical Trials:

- The ASCEMBL trial exhibited a favorable safety profile for asciminib when compared to another third line TKI, bosutinib. The improved safety profile led to longer treatment duration and adverse effect follow-up for the asciminib group, however the new drug still displayed better safety outcomes and tolerability. Overall, there were less all grade and serious adverse events in the asciminib group compared to the bosutinib group. The most common adverse effects were thrombocytopenia (28.8%) and neutropenia (21.8%).
- The X2101 expansion displayed a relatively similar side effect profile to other clinical trials. Participants were exposed to a higher overall dose (200 mg twice daily) compared to other studies (mostly 80 mg total daily). The increased dose may explain slightly higher percentages of certain toxicities and presence of new toxicities (gastrointestinal AEs- 48.1%; hypersensitivity- 26.9%; pancreatic toxicity- 25.0%; hepatotoxicity- 23.1%; hemorrhage- 17.3%).

Table 2: Safety results from clinical trials

<table>
<tr><th>Study</th><th>Results</th><th>Comments</th></tr>
<tr>
<td>Rea, et al. ASCEMBL (NCT03106779)[1-3]</td>
<td>
<u>Asciminib vs. Bosutinib (%)</u>

Median follow-up 2.3 years
All-grade AEs: 91.0 vs. 97.4
Grade 3-4: 56.4 vs. 68.4

<u>Common (> 10%)</u>
<table>
<tr><th></th><th colspan="2">Asciminib</th><th colspan="2">Bosutinib</th></tr>
<tr><th>Severity</th><th>All Grades</th><th>Grade 3-4</th><th>All Grades</th><th>Grade 3-4</th></tr>
<tr><td>Thrombocytopenia</td><td>29.5</td><td>22.4</td><td>19.7</td><td>9.2</td></tr>
<tr><td>Neutropenia</td><td>23.1</td><td>18.6</td><td>21.1</td><td>14.5</td></tr>
<tr><td>Headache</td><td>19.9</td><td>1.9</td><td>15.8</td><td>0</td></tr>
<tr><td>Fatigue</td><td>14.7</td><td>0.6</td><td>9.2</td><td>1.3</td></tr>
<tr><td>Hypertension</td><td>13.5</td><td>6.4</td><td>5.3</td><td>3.9</td></tr>
<tr><td>Arthralgia</td><td>12.8</td><td>0.6</td><td>3.9</td><td>0</td></tr>
<tr><td>Diarrhea</td><td>12.8</td><td>0</td><td>72.4</td><td>10.5</td></tr>
<tr><td>Nausea</td><td>11.5</td><td>0.6</td><td>46.1</td><td>0</td></tr>
<tr><td>Nasopharyngitis</td><td>10.9</td><td>0</td><td>3.9</td><td>0</td></tr>
<tr><td>Anemia</td><td>10.3</td><td>1.3</td><td>7.9</td><td>3.9</td></tr>
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<td>

Most common adverse effect was thrombocytopenia
AEs leading to discontinuation (7.7%) were thrombocytopenia, neutropenia, increased amylase, decreased ejection fraction, and ischemic stroke
Deaths occurred in five asciminib-treated patients (3.2%)

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Hughes, et al. CABL001X2101 (NCT02081378)[4-5]	Treatment-related AEs (%) • All-grades: 86.5 • Grade 3-4: 32.7 • Serious: 3.8 • Deaths: 0 Common > 10% (All-grade, %) • Gastrointestinal toxicity: 48.1 • Hypersensitivity: 26.9 • Myelosuppression: 25.0 • Pancreatic toxicity: 25.0 • Hepatotoxicity: 23.1 • Thrombocytopenia: 21.2 • Hemorrhage: 17.3 • Leukopenia: 15.4 • Edema: 13.5	• Most common adverse effect was gastrointestinal toxicity • AEs leading to discontinuation (5.8%) were thrombocytosis, elevated lipase, and pancytopenia. • No deaths occurred in the 52 patients on asciminib therapy • Serious AEs included ischemic stroke and peripheral arterial occlusion in 1 patient each

AEs = adverse effects; URTI = upper respiratory tract infection

- **Boxed warnings:** None
- **Contraindications:** Known A337T, P465S, or F359V/I/C mutations[7]
- **Other warnings / precautions**:
    - Myelosuppression: thrombocytopenia occurred in 28% of patients, neutropenia occurred in 19% of patients, and anemia occurred in 13% of patients based on pooled safety data.[1-5] Recommended to perform complete blood count labs every two weeks for three months, followed by monthly labs. May need to hold or adjust dose based on severity and occurrence.
    - Pancreatic toxicity: pancreatitis and elevated pancreatic enzymes (amylase and lipase) occurred in 2.5% and 21% of patients based on pooled safety data.[1-5] Recommended to check serum amylase and lipase levels monthly. May need to hold, adjust dose, or discontinue based on severity.
    - Hypertension: occurred in 19% of patients based on pooled safety data.[1-5] Recommended to monitor and manage blood pressure throughout treatment. May need to hold, adjust dose, or discontinue based on severity.
    - Hypersensitivity: occurred in 32% of patients based on pooled safety data.[1-5] Recommended to monitor for and manage any signs of hypersensitivity. May need to hold, adjust dose, or discontinue based on severity.
    - Cardiovascular toxicity: occurred in 13% of patients, arrhythmias occurred in 7% of patients, and cardiac failure occurred in 2.5% of patients based on pooled safety data.[1-5] Recommended to assess risk factors and manage accordingly throughout treatment. May need to hold, adjust dose, or discontinue based on severity.
    - Embryo-fetal toxicity: potential to cause fetal harm in pregnant women found in animal studies. Recommended to avoid in pregnancy and implement effective contraception during and one week following treatment for women of child-bearing potential.
- **Adverse reactions**
    - **Common (≥20%)**: thrombocytopenia, hypertriglyceridemia, neutropenia, anemia, elevated creatine kinase, increased amylase and lipase, increased AST/ALT, upper respiratory tract infections, musculoskeletal pain, headache, fatigue, nausea, rash, lymphocytopenia, diarrhea

- **Serious Adverse events / Deaths / Discontinuation:** cardiac dysfunction, fever, urinary tract infection, headache, and thrombocytopenia
  - Death: 1.3% (ASCEMBL), 0% (X2101)
  - Discontinuation: 7.7% (ASCEMBL), 5.8% (X2101)
  - Dose reduction: 21.2% (ASCEMBL), 25% (X2101)
  - Dose interruption: 51.9% (ASCEMBL), 34.6% (X2101)
- Drug-drug interactions
  - Strong CYP3A4 inhibitors: Coadministration increases asciminib AUC and C_{max}, leading to more adverse effects. Monitor closely if using strong CYP3A4 inhibitors with the 200 mg twice daily dosing.
  - Itraconazole (solution containing hydroxypropyl-β-cyclodextrin): Coadministration decreases asciminib AUC and C_{max}, leading to less efficacy. Avoid concomitant use at all recommended doses.
  - CYP3A4 substrates: Coadministration could increase other the AUC and C_{max} of other substrates. Monitor closely if using strong CYP3A4 inhibitors with the 80 mg once daily dosing and avoid concomitant use with the 200 mg twice daily.
  - CYP2C9 substrates: Coadministration could increase other the AUC and C_{max} of other substrates. Avoid concomitant use at all recommended doses.
  - P-gp substrates: Coadministration could increase other the AUC and C_{max} of other substrates. Monitor concomitant use at all recommended doses.

Other Considerations

- Pregnancy: No available human studies. Based on animal studies, asciminib demonstrated embryo-fetal toxicity in both rats and rabbits.[8] Adverse events included fetal mortality, cardiac abnormalities, increased birth weight, edema, and cleft palate. Advise pregnant women and those of reproductive potential of the potential risks to a fetus.
- Lactation: No available evidence of presence in breastmilk. Advise women to avoid breastfeeding during and one week after end of treatment with asciminib.
- Dose adjustments
  - Renal: None required for estimated glomerular filtration rate (eGFR) of 15-89 mL/min/1.73 m^2 without dialysis.
  - Hepatic: None required
- Absorption: AUC and C_{max} decreased when taken with food: 62% and 68% with high fate meal; 30 and 35% with low fat meal, respectively. Median T_{max} = 2.5 hours.
- Distribution: 97% protein-bound (*in vitro*), $V_{d\ ss}$ = 151 L
- Metabolism: Primarily metabolized by CYP3A4, UGT2B7, and UGT2B17. Also, an inhibitor of CYP2C9 and P-gp.
- Excretion: 57% unchanged drug found in feces and 2.5% found in urine unchanged.
- Elimination: $t_{1/2}$ = 5.5 hours (80 mg once daily) and 9 hours (200 mg twice daily)

Risk-Benefit Assessment (for Oncology NMEs only)

- **Outcome in clinically significant area**
  - After ≥2 prior TKIs: MMR (at 96 weeks) = 37.6% vs. 15.8%; asciminib vs. bosutinib, respectively[1-3]
  - T315I mutation: MMR (at 96 weeks) = 46.9%[4-5]
- **Effect Size**
  - After ≥2 prior TKIs: Difference = 21.7% (95% CI, 10.5 – 33.0); p = 0.001 for MMR[1-3]
  - T315I mutation: Estimated rate of first durable MMR (at 96 weeks) = 87% (95% CI, 68.4 – 100.0)[4-5]
- **Potential Harms:** Moderate[4-5]
  - ≥20%: Myelosuppression, hypertriglyceridemia, elevated creatine kinase, increased amylase and lipase, increased AST/ALT, upper respiratory tract infections, musculoskeletal pain, headache, fatigue, nausea, rash, diarrhea
- **Net Clinical Benefit:** Moderate[1-5]

Other Therapeutic Options

Alternative treatments for chronic myeloid leukemia in chronic phase are listed in table 3 and 4 below.

Table 3: Treatment Alternatives

Drug	Formulary status	Clinical Guidance[9]	Other Considerations
Asciminib	TBD	• **FDA Indications (2021)**: Ph+ CML-CP in patients previously treated with at least 2 TKIs or presence of T315I mutation	• 80 mg once daily or 40 mg twice daily (treatment failure from previous TKIs); 200 mg twice daily (T315I mutation) • Take without food • No renal or hepatic dose adjustments required • Monitor with concomitant use of strong CYP3A4 inhibitors and P-gp substrates • Avoid concomitant use with itraconazole, certain CYP3A4 substrates, and certain CYP2C9 substrates.
Ponatinib (3rd generation)	NF	• Reserved for CML-CP patients with T315I mutation; not a candidate for other 2nd generation TKIs as 2nd or 3rd line therapy	• 45 mg once daily; may consider lower starting dose of 15 or 30 mg and titrating up for tolerability • Take with or without food • Hepatic dose adjustment required • Adjust dose with concomitant use of strong CYP3A4 inhibitors • Black box warning: arterial thrombosis and hepatotoxicity • Remains effective at lower doses and with less toxicities • Demonstrated OS benefit across all 3 doses • Less expensive (compared to asciminib, especially for use in T315I mutation patients)
Bosutinib (2nd generation)	NF	• Available for newly diagnosed CML-CP patients as first-line therapy; subsequent therapy after failure or intolerance to imatinib or another 2nd generation TKI	• Dose escalation of 100 mg once daily; usual dose of 500 mg once daily • Take with food • Renal and hepatic dose adjustments required • Avoid concomitant use with

			strong CYP3A4 inhibitors and inducers or proton pump inhibitors • Unique toxicities: significant diarrhea and hepatotoxicity
Dasatinib (2nd generation)	NF	• Available for newly diagnosed CML-CP patients as first-line therapy; subsequent therapy after failure or intolerance to imatinib or another 2nd generation TKI	• 100 mg once daily • Take with or without food • No renal or hepatic dose adjustments required • Avoid concomitant use with strong CYP3A4 inhibitors and proton pump inhibitors • Monitor with concomitant use of CYP3A4 inducers and substrates • Unique toxicities: fluid retention, pleural effusions, platelet inhibition, pulmonary arterial hypertension
Nilotinib (2nd generation)	NF	• Available for newly diagnosed CML-CP patients as first-line therapy; subsequent therapy after failure or intolerance to imatinib or another 2nd generation TKI	• 400 mg twice daily • Take without food • Hepatic dose adjustments required • Monitor with concomitant use of CYP3A4 inhibitors and inducers • Black box warning: QT prolongation • Unique toxicities: metabolic syndrome, pancreatitis, peripheral arterial occlusive disease
Imatinib (1st generation)	PA-F	• Preferred for newly diagnosed CML-CP patients as first-line therapy with low to intermediate risk score • Available for newly diagnosed CML-CP patients as first-line therapy with high risk score	• 400 mg once daily (chronic phase); 600 mg once daily (accelerated or blast phase) • Take with food • Renal and hepatic dose adjustments required • Monitor with concomitant use of CYP3A4 inhibitors and inducers
Omacetaxine (Protein	NF	• Considered for CML-CP patients with progressive	• Induction: 1.25 mg/m^2 twice daily for 14 days of 28-day cycle

synthesis inhibitor)		disease after ≥2 prior TKIs; with T315I mutation and progressive disease on ponatinib	• Maintenance: 1.25 mg/m^2 twice daily for 7 days of 28-day cycle • Subcutaneous dosing • No renal or hepatic dose adjustments required

TBD = to be determined; Ph+ = Philadelphia chromosome positive; CML = chronic myeloid leukemia; CP = chronic phase; TKI = tyrosine kinase inhibitors; NF = non-formulary; ALL = acute lymphoblastic leukemia; AP = accelerated phase

Table 4: Alternative Treatment Response Rates

Drug (Dose)	Trial	Interventions	Time Cut Off	CCyR (%)	MMR (%)	PFS (%)	OS (%)
Asciminib 40mg twice daily	ASCEMBL[1-3]	40mg twice daily (n=157) Bosutinib 500mg once daily (n=76)	2 yrs	40 16	38 16	94[a] 91[a]	97[a] 99[a]
Asciminib 200mg twice daily	X2101[4-5]	T315I mutation (n=52)	96 wks	-	47	-	-
Dasatinib 100mg once daily	CA180-034[10]	Imatinib-R (n=124) Imatinib-I (n=43)	7 yrs	-	43 55	39 51	63 70
Nilotinib 400mg twice daily	Giles, et al[11]	Imatinib-R or I (n=321)	4 yrs	45	-	57	78
Bosutinib 500mg once daily	Cortes, et al[12]	Imatinib and Dasatinib-R (n=38) Imatinib and Dasatinib-I (n=50) Imatinib and Nilotinib-I (n=26)	4 yrs	22 40 31	-	-	67 80 87
Ponatinib 45mg once daily	PACE[13]	Dasatinib or Nilotinib-R or I (n=203)	57 mos	49	35	52[b]	76[b]

		T315I mutation (n=64)		70	58	50[b]	66[b]
Ponatinib once daily	OPTIC[14]	45mg (n=93) 30mg (n=93) 15mg (n=91)	32 mos	44 29 23	34 25 23	73[c] 66[c] 70[c]	89[c] 89[c] 92[c]

CCyR = complete cytogenetic response; MMR = major molecular response; PFS = progression-free survival; OS = overall survival; yrs = years; wks = weeks; R = resistant; I = intolerant; mos = months

[a] PFS and OS for ASCEMBL evaluated at 2-year follow-up

[b] PFS and OS for PACE evaluated at 5-year follow-up

[C] PFS and OS for OPTIC evaluated at 3-year follow-up

Projected Place in Therapy

- Chronic myeloid leukemia (CML) is the unregulated proliferation of cells originating from the myeloid cell line and is characterized by the Philadelphia chromosome, BCR-ABL1 fusion oncogene. The indolent disease course is separated into three main phases; chronic, accelerated, and blast. Due to the introduction of TKI therapies, the life expectancy has significantly improved with a 5-year estimated survival rate over 70%.
- CML accounted for almost 9,000 new cases and over 1,000 deaths across the United States in 2022. Nearly half of the known CML patient population is over 65 years old with an average age of diagnosis of 64 years.
- Failure to meet major molecular response (MMR) or complete cytogenetic response (CCyR) criteria after 2nd line therapies leads to use 3rd line TKI therapy. Over 60% patients fail to reach MMR and over 50% do not meet CCyR after two-year follow up on 2nd line TKI therapy.[15]
- BCR-ABL1 mutations can manifest in many different forms; one of the most common mutations is T315I. This gatekeeper mutation accounts for 10-27% of those with an active mutation and 3-15% of all patients with CML.[15] There are currently very few available treatment options for patients with this mutation. Prior to asciminib, ponatinib was the only oral therapy on the market along with omacetaxine (subcutaneous) and allogeneic stem cell transplant. Asciminib provides an alternative oral treatment option for these patients.
- Guidelines
    - NCCN: Asciminib is recommended by the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) as a **Category 2A** treatment option for patients with treatment failure to at least 2 previous TKIs or the presence of the T315I mutation. Additionally, NCCN Guidelines® recommends ponatinib as a **Category 2A, Preferred** treatment option for patients with treatment failure to at least 2 previous TKIs or the presence of the T315I mutation.[7]
    - ASCO: Asciminib not mentioned in the most recent recommendations (2015).[16]
- Asciminib has been studied and displayed benefit for use in patients with Ph+ CML in chronic phase after use of at least two other TKIs or presence of the T315I mutation. Due to the lack of head-to-head studies with all available TKI agents (including third generation ponatinib), asciminib is provided as an additional option for patients with prior TKI use.
- Comparisons of available literature, in lieu of head-to-head trials, have shown better response for patients with T315I mutation on ponatinib vs. asciminib. Research is still needed to determine any potential efficacy or safety benefits between the two 3rd line agents.[17]
- In summary, there appears to be a benefit regarding both the efficacy and safety of asciminib among other options in Ph+ CML-CP patients after at least two other TKI treatments or presence of the gatekeeper mutation, T315I. Asciminib may be considered for use in these populations along with clinical judgement in the selection of next-line TKI therapy.

References

1. Rea D, Mauro MJ, Boquimpani C, et al. A phase 3, open-label, randomized study of asciminib, a STAMP inhibitor, vs bosutinib in CML after 2 or more prior TKIs. Blood. 2021;138(21):2031-2041. doi: 10.1182/blood.2020009984
2. Rea D, Mauro MJ, Hochhaus A, et al. efficacy and safety results from ASCEMBL, a phase 3 study of asciminib versus bosutinib (BOS) in patients with chronic myeloid leukemia in chronic phase (CML-CP) after ≥2 prior tyrosine kinase inhibitors (TKIs): week 96 update. J Clin Oncol. 2022;40(16):7004. doi: 10.1200/jco.2022.10.16_suppl.7004
3. Hochhaus A, Rea D, Boquimpani C, et al. Asciminib vs bosutinib in chronic-phase chronic myeloid leukemia previously treated with at least two tyrosine kinase inhibitors: longer-term follow-up of ASCEMBL. Leukemia. 2023;37:617-626. doi: 10.1038/s41375-023-01829-9
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