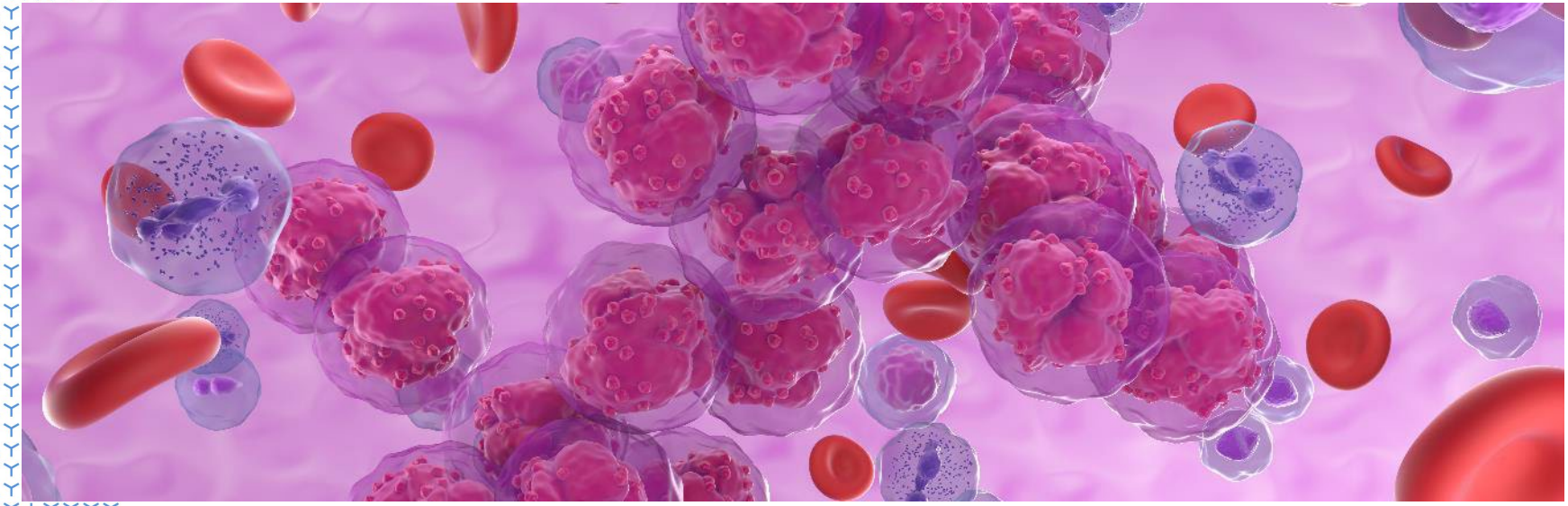

Asciminib Therapeutic Guide

Therapeutic management in adult patients with Philadelphia chromosome-positive chronic myeloid leukemia in chronic phase (Ph+ CML-CP), previously treated with two or more tyrosine kinase inhibitors

Disclaimer

This guideline for the therapeutic management of asciminib in adult patients with Philadelphia chromosome-positive chronic myeloid leukemia in chronic phase (Ph+ CML-CP), previously treated with two or more tyrosine kinase inhibitors was developed together with three hematology experts based on the ASCEMBL trials as well as experience from application in everyday practice.

Notice:

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About this guide

Dear colleagues,

Since June 2022, asciminib, the oral allosteric inhibitor of ABL/BCR::ABL1 tyrosine kinase specifically targeting the ABL myristoyl pocket (STAMP) has been approved in Canada for the treatment of adult patients with Philadelphia chromosome-positive chronic myeloid leukemia (Ph+ CML) in chronic phase (CP) previously treated with two or more tyrosine kinase inhibitors.

This Therapeutic Guide is intended to provide an overview of CML and its management for hematologists who treat CML and for hematology-oncology pharmacists and nurses who help to manage these patients. This document will serve as a reference tool for CML care teams managing this disease in Canada.

The content also includes commentary from an expert scientific steering committee that addresses CML practice tips and practical clinical use of asciminib.

The information is arranged to include:

- Summary points
- Clinical tips for application to practice
- Quotes from steering committee members

Drs. Assouline, Kim, and Savoie

Abbreviations

CML: chronic myeloid leukemia
CP: chronic phase
Ph: Philadelphia chromosome
STAMP: specifically targeting the ABL myristoyl pocket
TKI: tyrosine kinase inhibitor
ABL: Abelson murine leukemia
BCR: breakpoint cluster region
ATP: adenosine triphosphate
PCR: polymerase chain reaction
MMR: major molecular response
TFR: treatment-free remission
CHR: complete hematologic response
MCyR: major cytogenetic response
CCyR: complete cytogenetic response
AEs: adverse events
QoL: quality of life
NCCN: National Comprehensive Cancer Network
ELN: European Leukemia Network
MOA: mechanism of action
CVD: cardiovascular disease
RWE: real-world evidence
HRQoL: health-related quality of life
SOHO: Society of Hematologic Oncology
CV: cardiovascular
ECG: electrocardiogram
CBC: complete blood count
HBV: hepatitis B virus
BID: bis in die – twice a day
QD: quaque die – once a day
CYP: cytochrome P450
OTC: over-the-counter
ANC: absolute neutrophil count
PLT: platelet count
ULN: upper limit of normal
PPIs: proton pump inhibitors
ASH: American Society of Hematology
ALT: alanine transaminase
AST: aspartate aminotransferase
FAQs: frequently asked questions
IS: international scale

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Chronic myeloid leukemia (CML) and the evolving treatment landscape

In this section

Introduction to CML

Although CML was considered as a deadly disease in the past, the availability of *BCR::ABL* tyrosine kinase inhibitors (TKI) has remarkably changed the outlook of this disease. [1,2]

Currently, CML is considered as a disease that is well manageable with oral TKI giving excellent long-term results and the option for stopping treatment in some patients. [1,2]

Prognostic systems are used to estimate the survival risk at baseline. Risk assessment is essential to guide treatment selection. The Sokal score is widely used in Canada. [2]

Score	Calculation	Definition of risk groups
Sokal	Exp 0.0116 × (age — 43.4) +0.0345 × (spleen — 7.51) +0.188 × [(platelet count/ 700)^2 0.563] +0.0887 x (blood blasts — 2.10)	Low risk: <0.8 Intermediate risk: 0.8-1.2 High risk: >1.2

In this chapter

CML mechanism of disease

Historical perspective on TKI treatment

ATP-competitive TKI mechanism of action

Goals of therapy

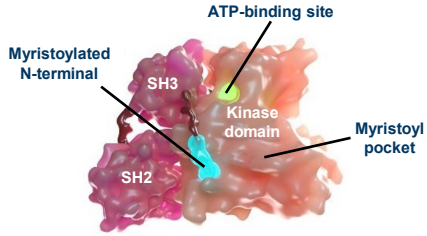
CML mechanism of disease

CML is a myeloproliferative neoplasm that arises from a translocation between the *ABL1* gene on chromosome 9 and the *BCR* gene on chromosome 22, forming the Ph chromosome.[3]

This chromosome contains a *BCR::ABL1* fusion gene that encodes the oncoprotein *BCR::ABL1,* a constitutively active tyrosine kinase that activates various downstream signaling pathways involved in promoting the proliferation and survival of myeloid progenitor cells.[3]

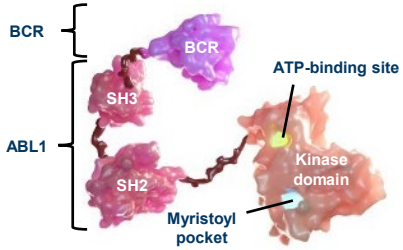
CML is diagnosed by the presence of the Ph chromosome and/or *BCR::ABL1* transcripts in bone marrow or peripheral blood cells.[3]

Most patients are in the chronic phase of CML at diagnosis, although the genetic instability of *BCR::ABL1*–positive cells can result in progression to an accelerated phase and blast phase.[3]



Normal Conditions: Inactive *ABL1*

- ABL1, a tyrosine kinase, regulates a host of cellular processes through the phosphorylation of other proteins[4]
- Normally, ABL1 activity is autoregulated when its myristoylated N-terminus engages with the myristoyl pocket of the kinase domain[4]



CML: Constitutively Active BCR::ABL1

- The oncogenic *BCR::ABL1* lacks the N-terminus and cannot be myristoylated[4]
- As a result, *BCR::ABL1* is in a constitutively open/active conformation[4]

Historical perspective on TKI treatment

TKIs that inhibit the activity of *BCR::ABL1* by preventing it from interacting with ATP are the mainstay treatment options for patients with CML.[4]

Patients diagnosed with CML in chronic phase can now have a life expectancy comparable to that of the general population thanks to the use of TKI therapies.[4,5]

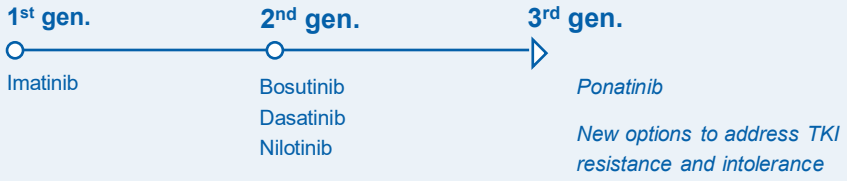
However, drug resistance or intolerance often contribute to the discontinuation of first or subsequent lines of TKI treatment.[4]

Treatment failures may result from various toxicities associated with TKIs, or inadequate reduction in *BCR::ABL1* transcript levels.[4]

Second-generation TKIs have higher response rates compared to first generation, imatinib.[5] They can achieve faster and deeper molecular responses, which are associated with improved long-term outcomes, including survival and progression-free survival.[5]

Challenges remain in the later lines of treatment

Despite the successes of 1st and 2nd generation TKIs, there is still an unmet clinical need for effective therapeutic options for patients with chronic phase CML who have been treated with ≥2 TKIs.[4]

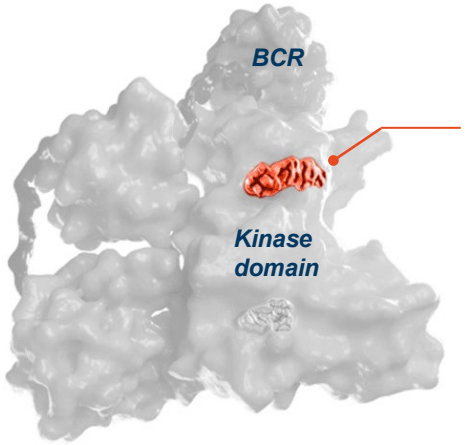


ATP-competitive TKI mechanism of action

ATP-competitive TKIs target the ATP-binding site of ABL1, preventing ATP from accessing and activating the enzyme and catalyzing phosphorylation.[6]

Without tyrosine kinase activation, phosphoryl groups cannot be transferred to tyrosine residues on target proteins.[6]

Selective inhibition of specific tyrosine kinases helps suppress their downstream signalling cascades which are involved in tumorigenesis and malignant progression and metastasis.[6]



Target of:[7]

- Bosutinib
- Dasatinib
- Imatinib
- Nilotinib
- Ponatinib*

These TKIs all work through an ATP-competitive mechanism[7]

Ponatinib is only available in Canada through a controlled distribution program

Goals of therapy

According to international guidelines and faculty experts alike, the short-term goal is the same for any line of treatment: to obtain a response of either MMR or *BCR::ABL1* ≤1%.[2]

Response criteria[2]	Clinical definition[2]
Response 2 log reduction (= MR2, also called CCyR)	*BCR::ABL1*^{IS} ≤1%
MMR (= MR3)	*BCR::ABL1*^{IS} ≤0.1%
MR4 (= deep molecular response)	*BCR::ABL1*^{IS} ≤0.01%
MR4.5	*BCR::ABL1*^{IS} ≤0.0032%
MR5	*BCR::ABL1*^{IS} ≤0.001%

In general, the goals of therapy for patients with CML are:

- To achieve clinical, cytogenetic, and molecular remission
- To maintain long-term disease control
- To avoid progression to advanced disease (i.e., accelerated phase or blast phase).[3]

At the same time, treatments should optimize quality of life by limiting treatment-related toxicity.[3]

Faculty insights +

Faculty insights +

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Unmet needs in CML

Despite the improvements ushered in by first, second, and third generation TKIs, additional therapeutic options are needed for therapy intolerance and disease resistance or sub-optimal response.[1]

"Before asciminib, the third line setting was not a fun place to be. If you're giving a **2nd generation TKI in third line, the responses are quite limited** in terms of quality of response. You often had to consider ponatinib, which is a drug that has a lot of challenges. But **now with asciminib, that's been greatly improved**."

Dr. Sarit Assouline
McGill University, Montreal, QC

"**Treatment switches** more commonly happen due to **intolerance** rather than lack of efficacy if the patient has been compliant with therapy."

Dr. Lynn Savoie
University of Calgary, Calgary, AB

In this chapter

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Resistance and intolerance to TKIs

Beyond second-line therapy, there is a need for drugs with greater efficacy and an improved understanding of how to manage treatment.[2]

Resistance

Defined by European Leukemia Net 2020 as *BCR::ABL1* >10% at 3 mos or 6 mos and >1% at 12 mos[3]

Intolerance

When manifestation of an adverse event results in a dose reduction or interruption[3]

Faculty insights +

Half of all patients with chronic phase CML treated with imatinib eventually develop resistance, loss of response, or intolerance to therapy.[2]

Efficacy decreases with each subsequent line of therapy and new mutations often develop.[2]

After 5 years, a 4.5 log molecular response (*BCR::ABL1* ≤0.0032%) is achieved by only **30% of patients** treated with **imatinib** and **30–55%** treated with **second generation TKIs**.[2]

TKIs and quality of life

Along with survival, QoL has become a significant factor in TKI treatment decision-making.[4]

Impact of low-grade AEs on QoL over the long term

- Intolerance of TKIs can **affect quality of life** adversely and can result in inadequate response and **increased risk of treatment failure**.[4]
- The ELN guidelines recommend that **patient comorbidities** and possible **TKI-related toxicities** be considered during the drug selection.[4]
- Data from the Québec registry created in 2009 demonstrated:

i. Switching of TKI is frequent and mainly driven by **intolerance** in all lines of treatment

ii. Serial intolerance is **6.6 times more frequent** than serial resistance suggesting a class effect for intolerance in some patients

iii. All TKIs have a **similar retention level** in all lines of treatment

iv. Patients necessitating **3 or more lines** of treatment have a survival disadvantage.

Analysis of treatment patterns in CML:

Aside from intolerance, there is a **significant difference in survival** in favour of patients needing only one or two lines of treatment compared to those that reach third or more lines.[5]

The CML-SUN survey found that many patients report **treatment affects QoL**, including physical or emotional fatigue, difficulty in exercising, and constant stress about treatment effectiveness.[6]

These results suggest that one of the most important unmet medical needs in CML management is availability of better tolerated drugs[5]

TKI treatment decision-making

There is a need for amplified patient voice during treatment discussions that balance QoL, efficacy, and tolerability goals across all lines of therapy.[6]

Patients focus on stopping or slowing disease progression, maintain/improving QoL, and minimizing/managing side effects

19-26% of **patients** state that treatment decisions are discussed and decided together with their physician

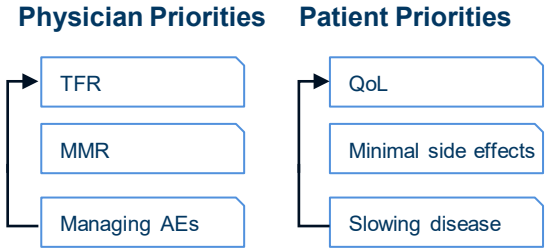
Physicians place greater emphasis on treatment efficacy.[6]

44-48% of **physicians** report making treatment decisions with little to no input from the patient across lines of therapy.[6]

48% to 66% of physicians report presenting only one treatment option to patients, while 39% to 43% of patients report only receiving information about one treatment from their physician

A global patient and physician survey disrupts the notion that CML is a solved disease[6]

The CML-SUN data revealed a necessity for **greater communication and shared decision-making** between patients and physicians.[6]



The decision to switch TKIs

According to faculty experts, when considering treatment switch, think about: patient response, tolerability, QoL, patient age, and adherence.

Intolerances

Many patients who received ≥2 TKIs are at a higher risk of experiencing TKI intolerance.[2]

AEs that may lead to a switch:

- Myelosuppression, pancreatic toxicity, hypertension and/or cardiovascular toxicity[2,7]

Resistance

Point mutations in the *BCR::ABL1* kinase domain are a common mechanism of resistance to TKI therapy and are related to higher risk of disease progression.[7]

- The ELN recommends switching therapy to another 2G-TKI after resistance to two TKIs.[7]

Faculty insights

"If a patient is compliant, then there are more patients with intolerance in my practice than true resistance."

Dr. Lynn Savoie
University of Calgary, Calgary, AB

"There are many ways to get to third line therapy. Intolerance is most common, and sometimes intolerance leads to suboptimal molecular responses because patients are not able to remain compliant"

Dr. Sarit Assouline
McGill University, Montreal, QC

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When to switch for resistance

ELN milestones:

Faculty insights +

- Switching to a 2G-TKI is common after intolerance or resistance to the first-line TKI.[7]
- The NCCN and ELN state that in cases of failure/resistance, the change is mandatory.[3]
- *BCR::ABL1* KD mutation analysis, evaluation of drug interactions and adherence to therapy are recommended before the initiation of second line TKI therapy.[7]
- All agree that the decision to change TKI in case of intolerance is partially subjective, depending on patient's comorbidities, physician's clinical judgment, supportive care options, and response to date.[7]
- NCCN experts highlight that asciminib was recently approved for patients with CP-CML harbouring the T315I mutation and/or CP-CML with resistance or intolerance to at least two prior TKIs.[7]

IN CONVERSATION **WITH EXPERTS**

Here's how CML experts approach switching treatment in practice.

What are the main triggers that cause you to switch therapy?

Therapy will be switched in the case of treatment resistance or loss of response.

However, reasons for switching are often the drug-specific AEs like:

- Pancreatitis
- Pulmonary hypertension
- Recurrent pleural effusions (or any effusions)
- Lymphoid hyperplasia
- Diarrhea

CLINICAL SPOTLIGHT

Have you faced a scenario like this patient experienced?

63-year-old diagnosed with chronic phase CML.

March 2019, started on imatinib, but discontinued 1 month later (before PCR was done) after significant leg pain and periorbital edema.

April 2019, started dasatinib 100 mg daily. Discontinued March 2020, due to pleural effusion.

She was then placed on nilotinib in March 2020, but discontinued in May 2020 as she did not tolerate it and had difficulty with the schedule.

"She has been struggling since we last spoke. She could not get on a schedule with the nilotinib twice a day without food. She also felt like she was "on drugs."
She felt unsteady. She really did not like how she felt on it.
She feels back to normal after stopping it."

Clinical scenario provided by Dr. Savoie

CLINICAL SPOTLIGHT

Have you faced a scenario like this patient experienced?

63-year-old diagnosed with chronic phase CML

Dasatinib resumed at 50 mg daily in May 2020, and discontinued in March 2021, though she had achieved an MMR of 4.5 in October 2020

"She continues to be unwell since our last follow-up. She reports poor quality of life with ongoing shortness of breath on exertion and generalized aches and pains throughout her body. She struggles to go from the chair to her bathroom because of shortness of breath. She also has pains in her hips, bilateral feet, and her arms. She has also noticed increasing fatigue and generalized unwell ness. She wonders whether these symptoms are related the dasatinib."

Bosutinib was started with the intention to ramp up the dose. However, the dose was never increased to more than 200 mg a day and was discontinued in July 2021 due to diarrhea

Asciminib was started July 2021. Her q. PCR once again showed a good MMR of at least 4.0.

This is reassuring that she has responsive disease as long as she takes a TKI on a regular basis.

Clinical scenario provided by Dr. Savoie

CLINICAL SPOTLIGHT

Have you faced a scenario like this patient experienced?

Tips and tricks on how to engage patients as partners in their care to improve adherence with treatment:

- Ask them to bring their pills with them to clinic appointment
- Encourage them to write down their symptoms and timing to their medication
- Ask specific questions about known side effects in case they forget to bring things up and to make them feel free to talk about side effects

IN CONVERSATION **WITH EXPERTS**

Here's how CML experts approach suboptimal response.

If a patient has suboptimal response in the second-line setting, are you likely to switch therapy?

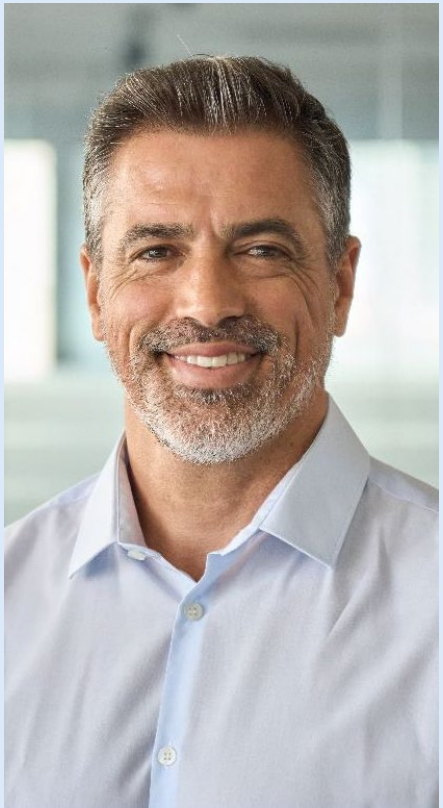
It depends on the patient in front of you. A 2-log reduction in *BCR::ABL1* is suboptimal. But in a patient with many comorbidities who is 75 years old, that may be a completely acceptable response.

However, if the goal is to reach MMR and potentially stop medication for TFR, then therapy should be switched.

Questions about when to switch based on toxicities and the quality of the molecular response often go together. A patient's suboptimal response may be because of poor compliance following toxicity.

CLINICAL SPOTLIGHT

Have you faced a scenario like the one this this patient experienced?



40-year-old man, diagnosed with chronic phase CML with a Sokal score indicating high risk.

Patient was informed of his choices of first-line therapy, including imatinib, dasatinib and nilotinib. But was advised to consider a second generation TKI due to the high Sokal score.

The patient chose to start with dasatinib because of tolerability profile.

Dasatinib 50 mg daily was started. The patient experienced mild fatigue but was able to conduct his usual activities.

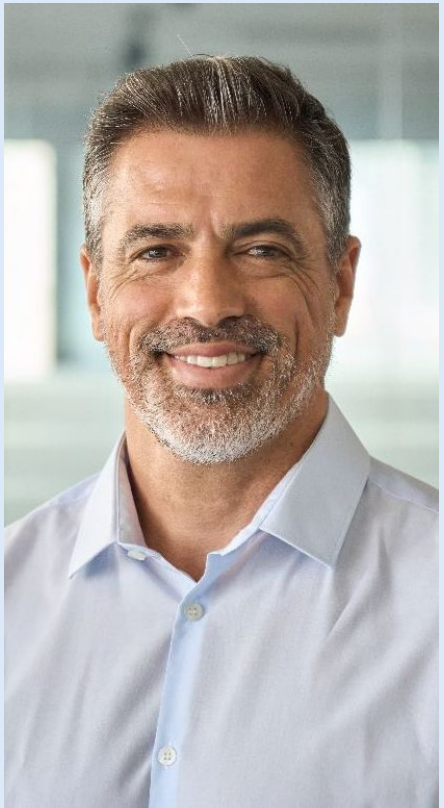
After 3 months, PCR for *BCR::ABL1* was 9%. At 6 months, the PCR was 1%. By 9 months the PCR was 0.19%. But at one year the PCR was 1%. He was considered to have resistant disease. No mutations were found, and the patient was switched to nilotinib.

On nilotinib, the PCR fluctuated between 8-15% for 6 months.

The patient was then switched to asciminib. By 3 months he had achieved MMR.

CLINICAL SPOTLIGHT

Have you faced a scenario like this patient has experienced?



Tips and tricks: Questions to engage patients in their treatment

- “In the last week, how many doses were you unable to take?”
- “What barriers prevented you from taking your medication?”
- “Describe to me how you take your medication for CML.”

IN CONVERSATION **WITH EXPERTS**

Here's how CML experts approach suboptimal response.

If a patient has suboptimal response in the second-line setting, are you likely to switch therapy?

For a young patient, achievement of MMR with first-line therapy is the primary goal. This patient did not achieve MMR and in fact had a PCR that was greater than MR2, which is concerning for disease progression and long-term survival.

Since he had received a second generation TKI in the frontline, there was little hope that a second generation TKI could be effective in the second line setting, though it had to be tried.

After an inadequate response to second-line therapy, the patient was switched to asciminib and had an excellent molecular response.

In an older patient, this kind of response would also not be acceptable though we would accept an MR2 especially if there are significant comorbidities.

It is important to discuss treatment goals with the patient.

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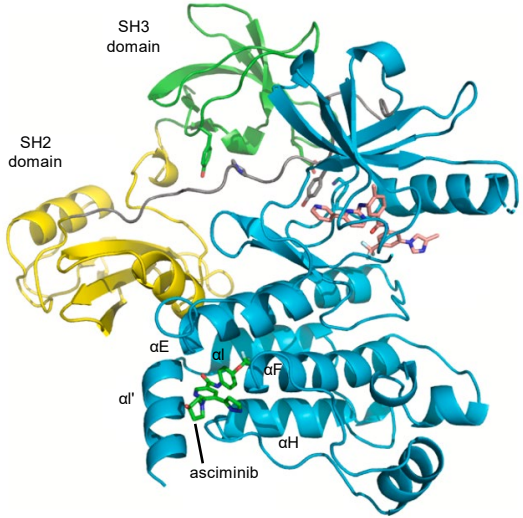
Introduction to asciminib

Indication: for the treatment of adult patients with Philadelphia chromosome-positive chronic myeloid leukemia (Ph+ CML) in chronic phase (CP) previously treated with two or more tyrosine kinase inhibitors.[1]



Asciminib is an orally administered, small molecule, selective allosteric inhibitor targeting the myristoyl pocket of BCR-ABL1

In this chapter

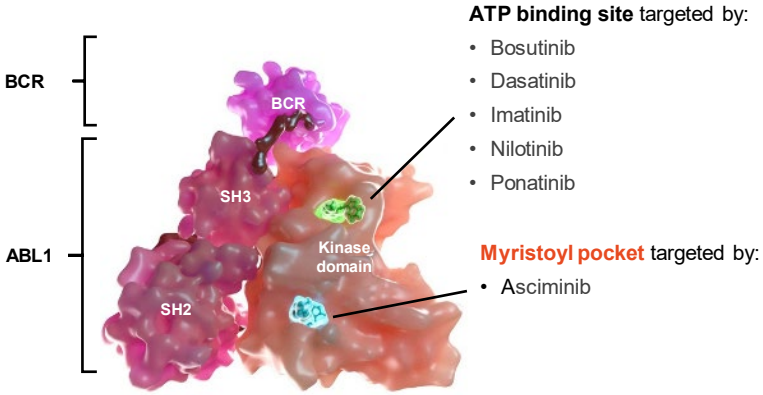
Asciminib mechanism of action vs other TKIs

Asciminib characteristics:

- Effect of specificity on tolerability
- Potential for use in combination therapy
- Efficacy in specific mutations for 1st and 2nd generation TKIs vs asciminib

Asciminib addressing unmet needs

Asciminib mechanism of action



ATP binding site targeted by:

- Bosutinib
- Dasatinib
- Imatinib
- Nilotinib
- Ponatinib

Myristoyl pocket targeted by:

- Asciminib

Asciminib acts by selectively binding to the myristoyl pocket of ABL1 (rather than its catalytic ATP-binding site), inducing and stabilizing an inactive conformation of the kinase.[2] Upon binding, asciminib restores inhibition of ABL1 kinase activity.[2]

STAMP inhibitor:

- **S**pecifically
- **T**argeting the
- **A**BL1
- **M**yristoyl
- **P**ocket

Asciminib characteristics

Asciminib's distinct mechanism of action and current data suggest that it may provide a novel option for patients who experience treatment failure or intolerance with second-line therapy.[3]

Effect of specificity on tolerability profile

- Unlike other BCR::ABL1 inhibitors, asciminib is independent of the ATP-binding pocket and may be a preferred option in patients with previously documented toxicities related to ATP-competitive TKIs.[3]

Potential for use in combination therapy

- Combination treatments with ATP-pocket binding TKI may potentially make it less likely that a single mutation will cause treatment failure.[3]

Efficacy in specific mutations for 1st and 2nd generation TKIs vs. asciminib

- Asciminib use may be acceptable in the T315I mutation, which confers resistance to all 1st and 2nd generation TKIs.[3]

What are the implications of asciminib's specific MOA relative to other TKIs?

Asciminib has shown specificity and potency against wild-type *BCR::ABL1* and several mutant forms of the kinase.[1] The potency of inhibition potentially overcomes point mutations that have been observed with TKIs.[3]

Faculty insights

Blocking myristoyl binding site likely contributes to **superior tolerability profile.**

Fewer AEs could be related **to not blocking ABL** in the same way.

Asciminib addressing unmet needs

Available therapies for patients with resistance to or intolerance of ≥ 2 TKIs are often limited by modest efficacy, safety concerns, or both.[4] One of the most important unmet medical needs in CML management is availability of better tolerated drugs.[5]

30 to 40%

Patients started on any TKI **switch to an alternative TKI** because of side effects or inadequate response.[6]

- Asciminib demonstrates tolerability in patients with lack of efficacy on prior TKIs[4]
- Compared to that of bosutinib, asciminib has shown superior efficacy, deeper molecular response rates, and a favourable safety profile.[4]

An increase in thrombotic cardiovascular events has been seen with other TKIs.[6]

- Asciminib may be preferred in patients with significant vascular risk factors, or a history of CVD, or in patients previously documented toxicities that are expected to be related to other TKIs.[3]

20 to 30%

Patients with CML experience **therapeutic failure** with TKI therapies.[3]

- Current therapies aside from asciminib bind to the kinase domain at the BCR::ABL1 protein where more than 50-point mutations are observed and is a cause of TKI resistance.[3]
- Asciminib can be of value to some patients whose CML is resistant to standard TKI therapies.[6]

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Who are the right patients for asciminib?

In this section

Asciminib clinical development data

For patients with CML-CP who are intolerant of or resistant to ≥2 prior TKIs, therapeutic options become more limited due to emerging mutations, existing comorbidities, or toxicities associated with previous treatments.

In this chapter

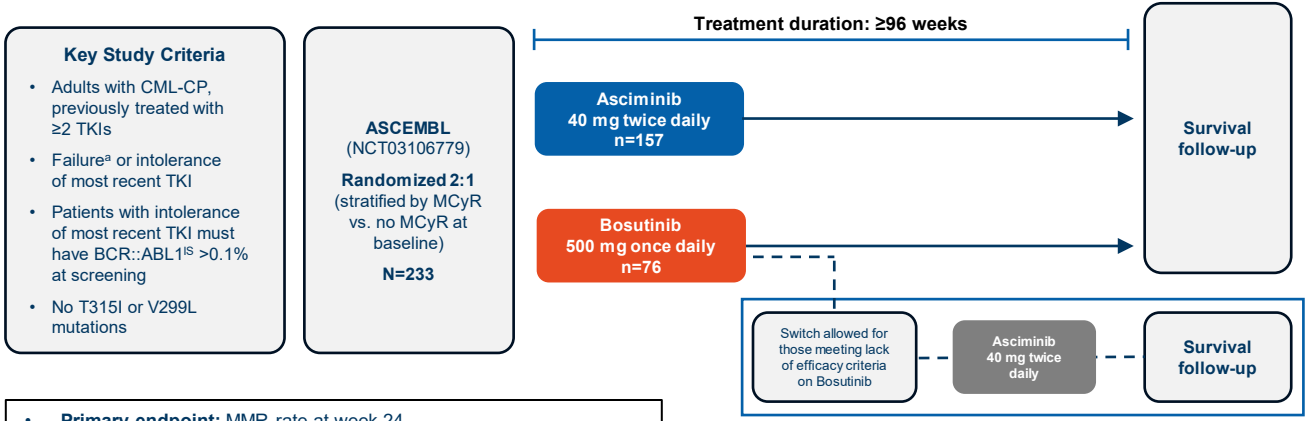
ASCEMBL study protocol[1]

Asciminib monotherapy in patients resistant/intolerant to ≥2 TKIs

Phase III ASCEMBL Asciminib Monotherapy in Patients Resistant/Intolerant to ≥2 TKIs

Study Design:

Patients continued treatment until unacceptable toxicity or treatment failure occurred. The median duration of exposure was **23.7 months (range, 0.0-46.2 months)** for patients receiving **Asciminib** and **7.0 months (range, 0.2-43.4 months)** for patients receiving **Bosutinib**



- **Primary endpoint:** MMR rate at week 24
- **Key secondary endpoint:** MMR rate at week 96
- Efficacy outcomes can be found on pages 4 and 5 of this section
- Safety outcomes can be found on pages 8 and 9 of this section

ASCEMBL population demographics[2]

INCLUSION CRITERIA

- Aged ≥ 18 years previously treated with ≥ 2 TKIs
- Previous treatment failure (lack of efficacy according to ELN 2013 criteria for second-line TKI or intolerance)
- *BCR-ABL1* transcript levels ≥ 1% on the international scale; protocol amended to ≥ 0.1% for patients with previous intolerance

EXCLUSIONS

- Bosutinib-resistant *BCR-ABL1* mutations of T315I or V299L detected at any time prior to study entry

STUDY DISCONTINUATION

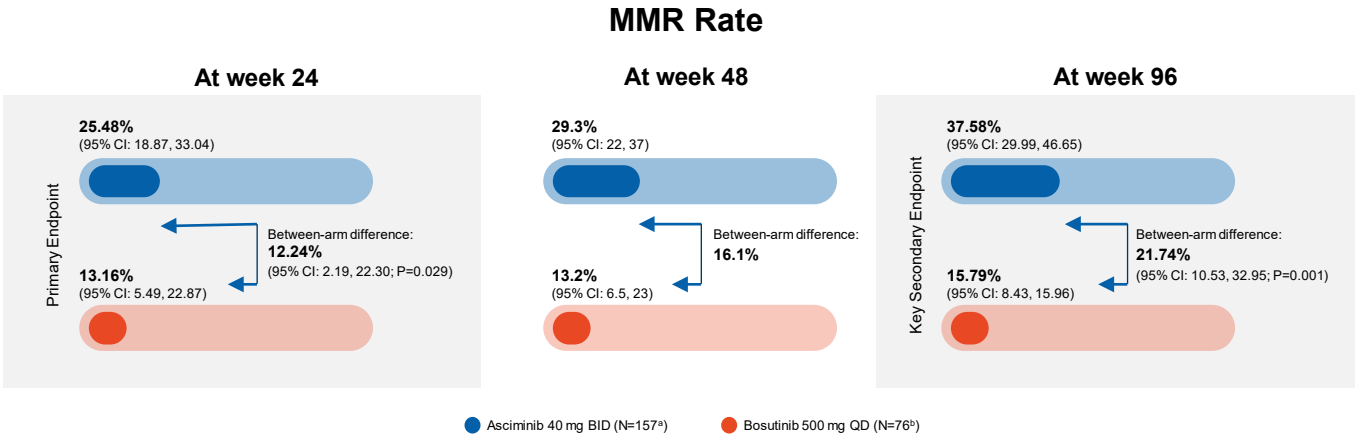
- Protocol-mandated study discontinuation if lack of efficacy as per the 2013 ELN second-line TKI therapy criteria
- Protocol amendment (December 14, 2018), allowing the option to switch to asciminib if treatment failure with bosutinib secondary to lack of efficacy (efficacy data for patients switched to asciminib not included in primary analysis)

KEY CHARACTERISTICS

- Female: 48% asciminib, 59% bosutinib
- White: 75% asciminib, 74% bosutinib
- Lack of efficacy as reason for discontinuation of last TKI: 61% asciminib, 71% bosutinib
- Baseline *BCR-ABL*^{IS} > 10%: 62% asciminib, 65% bosutinib

Efficacy of asciminib vs bosutinib in patients with Ph+ CML-CP[3]

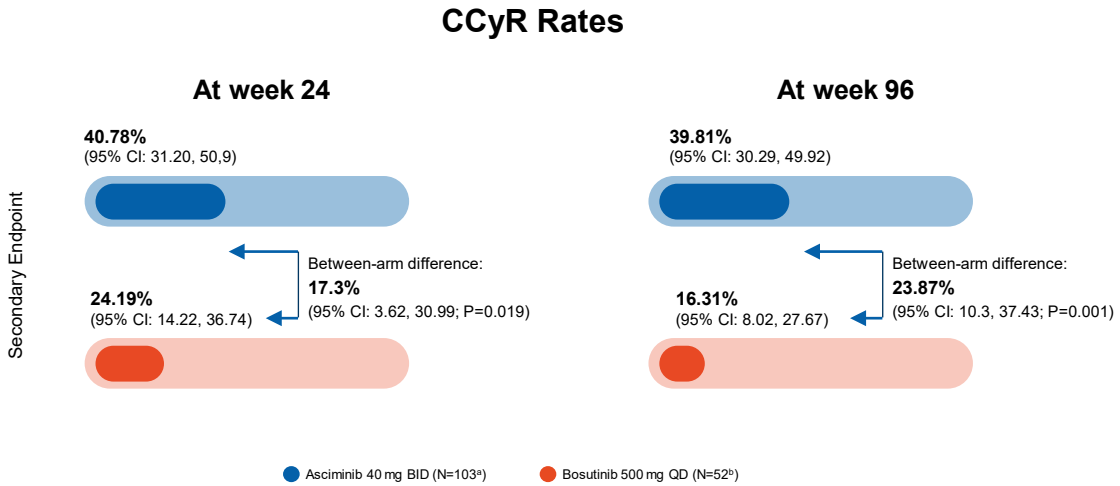
MMR at 24, 48, and 96 weeks (i.e., MMR is reduction in amount of *BCR::ABL1* transcript to ≤0.1% of baseline at 24, 48 and 96 weeks)



The MMR rate at week 96 showed a consistent trend in favour of asciminib over bosutinib across all analyzed subgroups for demographic and prognostic factors of response, including baseline MCyR status, reason for discontinuation of the last prior TKI, number of prior lines of TKI therapy, and *BCR::ABL1* mutation status at baseline.

Efficacy of asciminib vs bosutinib in patients with Ph+ CML-CP[3]

CCyR rates at 24 and 96 weeks



The complete cytogenetic response rate at week 96 in patients who were not in CCyR at baseline was 39.8% with asciminib and 16.1% with bosutinib. The CCyR rate difference between the two arms, after adjusting for baseline MCyR status, was 23.9% (95% CI, 10.3–37.4)

Durability of response[2]

MMR is associated with improved long-term survival outcomes and lower risks of treatment failure

- **ELN 2020 recommends *BCR-ABL1*^{IS} ≤ 1% at 24 weeks, ≤ 0.1% (i.e., MMR) at 12 months[4]**

Week 24 *BCR-ABL1*^{IS} ≤ 1%:

- **Asciminib 49.0%**
- **Bosutinib 23.7%**

The cumulative incidence of MMR by Week 24:

- **Asciminib 25.0%**
- **Bosutinib 12.0%**
- **The probability of achieving MMR over time remained consistently superior for asciminib compared to bosutinib, through Week 96**

Week 24 MR^4 (*BCR-ABL1*^{IS} ≤ 0.01%):

- **Asciminib 10.8%**
- **Bosutinib 5.3%**

"Sustained deep molecular response following TKI therapy of at least 2 years or longer is a mandatory requirement to qualify for treatment-free remission. By enhancing the depth of molecular response, the chance of being eligible for treatment-free remission will increase."

Dr. Dennis Kim
Princess Margaret Cancer Centre, Toronto, ON

Subgroup analyses

Asciminib was consistently favoured over bosutinib across various subgroup analyses

Subgroups of interest:

- **Asciminib was favoured regardless of the number of previous TKI therapies**
- **Asciminib was favoured if lack of efficacy was the reason for discontinuation of previous TKI**

Asciminib may be preferred in patients with significant vascular risk factors, or a history of cardiovascular disease, or in patients with previously documented toxicities that are expected to be related to the class of ATP-competitive TKIs. Asciminib may also be the preferred choice in patients who have failed to achieve time-dependent molecular targets but appear to be TKI responsive.

Yeung et al Blood 2022

Subgroup (MMR rate difference)	**Asciminib, n/N (%)**	**Bosutinib, n/N (%)**	**Favours Bosutinib**	**Favours Asciminib**	**Risk difference, % (95% CI)**
Line of therapy of randomized treatment					
3	34/82 (41.5)	9/30 (30.0)			11.5 (-8.1 to 31.0)
4	16/44 (36.4)	3/29 (10.3)			26.0 (8.0 to 44.0)
≥5	9/31 (29.0)	0/17 (0.0)			29.0 (13.1 to 45.0)

Safety[2]

Asciminib demonstrated an improved safety profile as compared with bosutinib in patients after receiving ≥ 2 prior TKIs

AEs leading to treatment discontinuation:

- **Asciminib 5.8% (thrombocytopenia, 3.2%)**
- **Bosutinib 21.1% (increased ALT, 5.3%)**

≥ 1 dose reduction leading to treatment discontinuation:

- **Asciminib 21.2%**
- **Bosutinib 42.1%**

Arterial-occlusive events:

- **Asciminib 3.2% (n = 5); 1 arterial embolism, 1 ischemic stroke, 2 myocardial ischemia, 1 coronary artery disease**
- **Bosutinib 1.3% (n = 1); acute coronary syndrome**

Faculty insights +

"Tolerability to asciminib and quality of life with asciminib is not comparable to that from other 2G-TKIs or imatinib. Patients love to take this medication because it does not increase side effects but shows excellent response."

Dr. Dennis Kim
Princess Margaret Cancer Centre, Toronto, ON

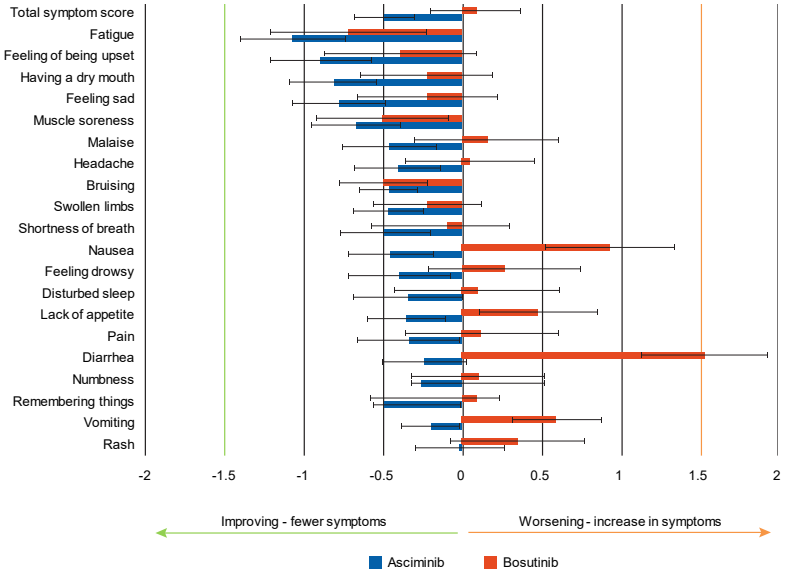
HRQoL[3,6]

Society of Hematologic Oncology (SOHO) 2021

Most patients with CML-CP on 3+ line of treatment do not achieve an adequate response, and many experience poor tolerability and deteriorated HRQoL.

Patients treated with asciminib showed improvement in treatment-related symptoms and HRQoL compared with baseline and relative to bosutinib, within the first 24 weeks of treatment

- **Fatigue and feeling upset** were the most common baseline symptoms. Mean baseline scores were **higher for distress items**, with impact on work, mood, and general activity contributing to **overall symptom distress**.
- **Symptoms improved** after treatment with **asciminib** (up to 24 weeks of treatment), particularly fatigue, feeling upset, and mood.
- Some **symptoms worsened with bosutinib**, with the greatest deterioration seen in nausea and diarrhea.



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2. Réa et al. Blood. 2021;138:2031-2041
3. Hochhaus et al. Leukemia 2023; 37:617-626
4. Hochhaus A et al. Leukemia 2020;34:966-984
5. Yeung DT, et al. *Blood*. 2022;139(24):3474-3479
6. Mauro MJ et al. Presented at: SOHO 2021; September 8-11, 2021. Presentation 155888

Real-world effectiveness

Real-world evidence studies provide unique and complementary information on treatment patterns, efficacy, side effects and may help identify unmet medical needs in patients with CML.

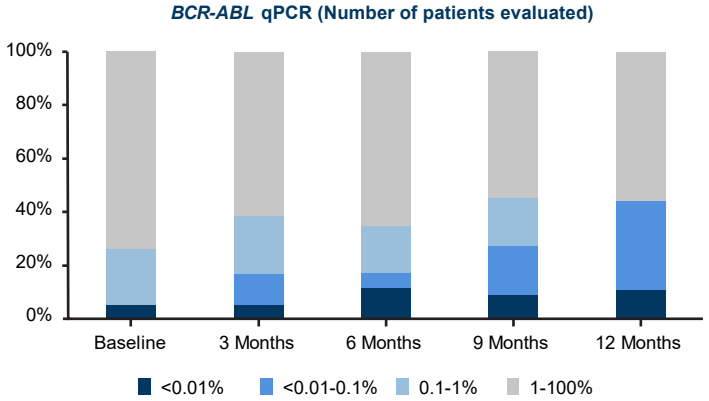
In this chapter

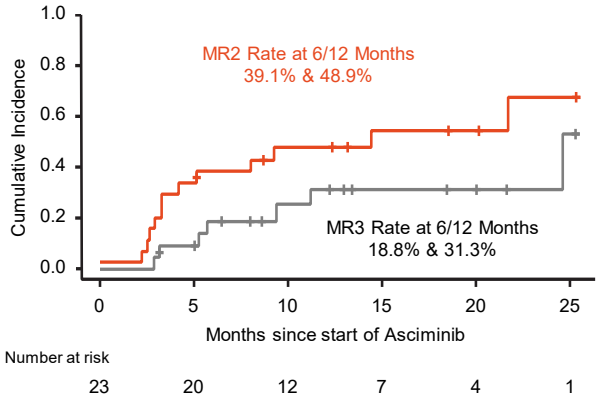
Canadian RWE (MAP)

The first North American real-world experience of asciminib use in heavily pre-treated patients (N=23) with CML with limited treatment options and significant CV burden

Real world asciminib dosing:

Non-T315I mutation CML	T315I mutation CML
40 mg PO BID	80 or 120 mg PO BID with gradual escalation to 200 mg PO BID





Canadian RWE (MAP)

The first North American real-world experience of asciminib use in heavily pre-treated patients (N=23) with CML with limited treatment options and significant CV burden

Adverse events: Clinically relevant adverse events included muscle cramps (n=4), elevated lipase (n=2), and pleural/pericardial effusions (n=2). No CV events were noted in any of the patients after a median of 15 months on asciminib.

- Patients discontinued treatment with asciminib (N=4) due to resistance (N=3) or due to Grade 4 thrombocytopenia (N=1).

No patient developed disease progression on asciminib or acquired a new mutation

Achievement of MR2 and MR3 was assessed at 6 and 12 months:

- MR2 rate at 6/12 months: 39.1% and 48.9%
- MR3 rate at 6/12 months: 18.8% and 31.3%

MR3 and MR2 rates were comparable to that in the published literature

No cardiovascular events were noted including in the 17 patients with a history of CV disease.

References

1. Busque L, et al. Oral session S159. HemaSphere 6:p 60-61, June 2022
2. Khadadah F et al. Canadian asciminib real world data. Presented at American Society of Hematology 2021, Poster 3610.

Practical guide to asciminib use

In this section

Treatment initiation

Treatment with asciminib should be initiated by a physician experienced in the use of anticancer therapies.

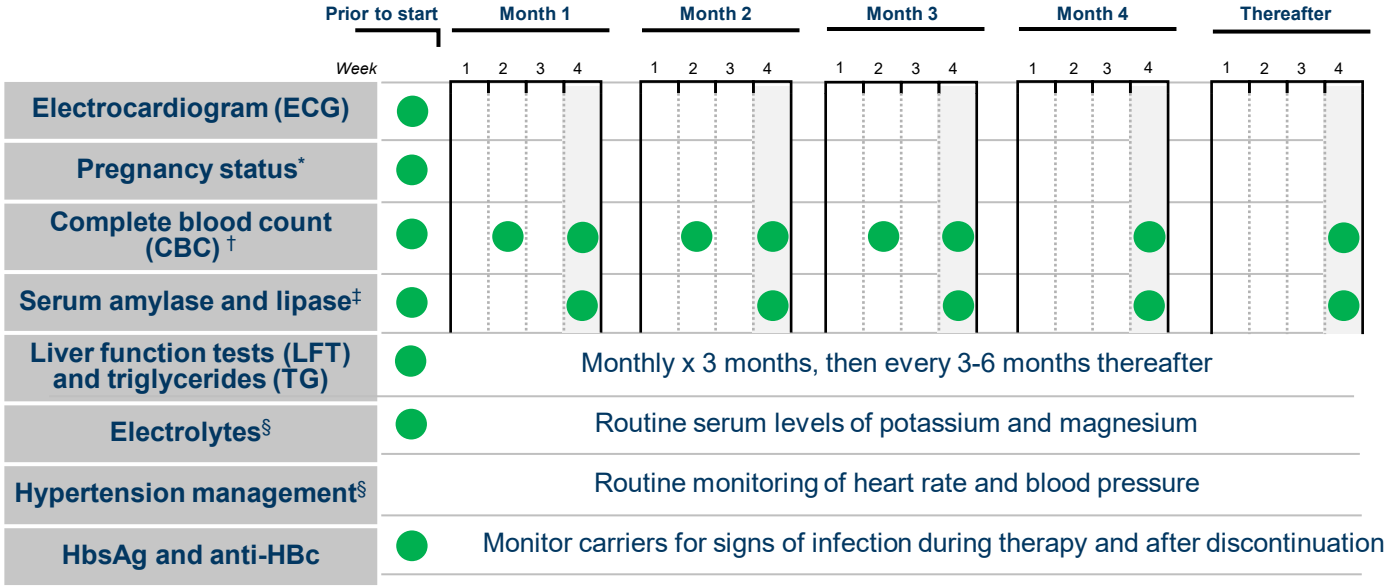
The pregnancy status of females of reproductive potential should be verified prior to starting treatment

In this chapter

Monitoring requirements

Monitoring and laboratory tests should be performed at the start of treatment and during treatment as clinically indicated.

Monitoring during treatment with asciminib



* Verification of baseline pregnancy status due to risk of teratogenicity and fertility impairment
† Should be performed every 2 weeks for the first 3 months of treatment and monthly thereafter (monitoring for myelosuppression)
‡Monthly monitoring for pancreatic toxicity
§ Regular tests including blood tests during treatment

Dosage

Asciminib, a first-in-class *BCR-ABL1* inhibitor Specifically Targeting the ABL Myristoyl Pocket (STAMP), has the potential to overcome resistance/intolerance to approved TKIs.

Recommended daily dose: 80 mg

Taken once daily or as 40 mg twice daily at 12-hour intervals

- Recommended dosage in Ph+ CML in CP: 80 mg orally once daily or 40 mg twice daily.
- Recommended dosage in Ph+ CML in CP with the T315I Mutation: 200 mg orally twice daily.

"Once a day is almost always better than twice a day for compliance reasons. I usually start at the full dose of a drug unless there is a specific comorbidity that I am worried the drug will make worse."

Dr. Lynn Savoie
University of Calgary, Calgary, AB

"It's really hard for a fasting patient to take a pill twice daily. In practice, we would suggest to take it once a day as long as it's tolerated.."

Marianne Boyer
Integrated Cancer Centre CHUM Montreal, QC

"A starting dose pf 40 mg PO BID maybe used for patients with ++ diarrhea with previous TKI treatment."

Tina Crosbie
The Ottawa Hospital Ottawa, ON

Dosage

Asciminib, a first-in-class *BCR-ABL1* inhibitor Specifically Targeting the ABL Myristoyl Pocket (STAMP), has the potential to overcome resistance/intolerance to approved TKIs.

Administration

Asciminib should be taken orally without food.

- Bioavailability is decreased by 62.3% when taken with a high-fat meal and 30% with a low-fat meal compared to fasted state
- Food consumption should be avoided for at least 2 hours before and 1 hour after taking asciminib. Peak blood concentrations occur 2-3 hours after a dose is taken.

Asciminib film-coated tablets should be swallowed whole and should not be broken, crushed, or chewed.

> "Some patients may need to eat something because of nausea. A low-fat food selection is better than high-fat."

Tina Crosbie
The Ottawa Hospital Ottawa, ON

80 mg daily is comparable to 40 mg PO bid

632.CHRONIC MYELOID LEUKEMIA: CLINICAL AND EPIDEMIOLOGICAL | NOVEMBER 15, 2022

Justification for Asciminib Dosing in Patients with Philadelphia Chromosome-Positive Chronic Myeloid Leukemia (Ph+ CML-CP) with and without the T315I Mutation

Francois Pierre Combes, Ying Fei Li, Sherwin K.B. Sy, Sebastien Lorenzo, Kohinoor Dasgupta, Shruti Kapoor, Matthias Hoch, Yu-Yun Ho

Population pharmacokinetics has previously shown that total systemic exposure of asciminib over 24 h was comparable between 80 mg QD and 40 mg BID (AUC0-24h 12,646 vs. 12,638 ng*h/mL)

This analysis demonstrated:

- Similar efficacy was predicted for asciminib 80 mg daily vs 40 mg BID in patients without the T315I mutation (predicted MMR rate [mean ± SE] at wk 24: 24.8 ± 4.2% vs. 27.6 ± 4.5%; wk 48: 30.6 ± 4.7% vs. 32.3 ± 4.8%, respectively); rates were similar to those observed in ASCEMBL. Predicted efficacy did not differ significantly between the two regimens regardless of the different asciminib minimum and maximum plasma concentrations.
- The ER-safety analysis showed that increasing asciminib exposure was not associated with increased probability of experiencing fatigue/asthenia or hypertension

The authors concluded: *"The 80 mg QD dose regimen is likely to support better treatment adherence, potentially improving benefit from therapy. "*

Drug-drug interactions

Asciminib is …

- A weak base and exhibits pH-dependent solubility, which is high at acidic pH and decreases with increasing pH. Thus, acid reducing agents may theoretically affect bioavailability of asciminib.[4]
- Eliminated through direct glucuronidation (by UGT2B7) and oxidation (by CYP3A4) with the CYP3A4 pathway being responsible for ~36% of clearance. Thus, CYP3A4 inhibitors or inducers can potentially affect metabolism of asciminib.[4,5]
- A substrate of P-gp meaning that inhibitors of P-gp may increase asciminib concentration.[5]

Drug-drug interactions

Asciminib can **affect** the metabolism of other medications and **be affected by** other medications and foods. Caution should be taken with concomitant administration of asciminib and drugs with potential interactions.

Drugs that may alter asciminib plasma concentrations

CYP3A4 inhibitors

Asciminib 200 mg twice daily with a strong CYP3A4 inhibitor may increase the risk of adverse reactions

Examples of strong CYP3A4 inhibitors:
Clarithromycin, itraconazole, ketoconazole, voriconazole, or ritonavir

CYP3A4 inducers

Concomitant use with strong inducers reduces asciminib plasma concentrations, which may affect efficacy[1]

Examples of CYP3A4 inducers:[1]
Carbamazepine, phenobarbital, rifampicin, phenytoin, or St. John's wort

Itraconazole Oral Solution[1,4]
Avoid use of itraconazole oral solution containing cyclodextrin as the cyclodextrin can sequester asciminib in the gut and lead to reduced absorption, decreased AUCinf by 40% and Cmax by 50%

Some evidence has shown that CYP3A4 and P-gp interactions may not be clinically significant due to the large therapeutic window of asciminib.[4]

Drug-drug interactions

Asciminib can **affect** the metabolism of other medications and **be affected by** other medications and foods. Caution should be taken with concomitant administration of asciminib and drugs with potential interactions.

Drugs that may have their plasma concentrations altered by asciminib

CYP3A4 substrates

Asciminib is a CYP3A4 substrate. Other CYP3A4 substrates with an NTI may have their plasma concentrations altered if given with asciminib at all recommended doses.[1] Closely monitor for adverse reactions during concomitant use.

Examples of CYP3A4 substrates:[1]
Fentanyl, midazolam

Co-administration of asciminib with midazolam increased midazolam AUCinf and Cmax by 28% and 11%, respectively, in healthy subjects receiving asciminib 40 mg twice daily[1,5]

CYP2C9 substrates

Asciminib 200 mg twice daily with CYP2C9 sensitive substrates and those known to have an NTI should be avoided, and alternative medications should be considered. Consider reducing the CYP2C9 substrate dose if coadministration with asciminib 80 mg total daily dose is unavoidable.

Examples of CYP2C9 substrates:[1]
Phenytoin or warfarin

Co-administration of asciminib with warfarin increases S-warfarin AUCinf and Cmax by 41% and 8%, respectively.[1] Follow INR more closely when adding or removing asciminib to someone already stable on warfarin

P-gp inhibitors

Caution should be exercised during concomitant administration of asciminib with P-gp substrates known to have an NTI[1]

Examples of P-gp inhibitors: Quinidine, digoxin, dabigatran

Some evidence has shown that CYP3A4 and P-gp interactions may not be clinically significant due to the large therapeutic window of asciminib.[4]

Drug-drug interactions

Asciminib can **affect** the metabolism of other medications and **be affected by** other medications and foods. Caution should be taken with concomitant administration of asciminib and drugs with potential interactions.

Drugs that may have a pharmacodynamic interaction with asciminib

Acid reducing agents

Administration of asciminib with rabeprazole reduced Cmax of asciminib by 9% but did not meaningfully change AUC or Tmax[4]

Examples:
PPI (rabeprazole) and H2-blockers

QT prolonging agents

Arrhythmia and QTc prolongation have been observed when combined with asciminib[1]

Consider QT* monitoring

Examples of agents that prolong QT intervals:[1]
Clarithromycin, chloroquine, methadone, moxifloxacin or haloperidol

NTI, narrow therapeutic index.
* Make sure that QTcF is the one generated, not QTcB

Management of special populations

Pregnant women and male patients

Establish pregnancy status of females of reproductive potential prior to starting asciminib

If the patient becomes pregnant, or thinks they may be pregnant, during treatment, discontinue therapy and complete pharmacovigilance process

Males taking asciminib are to use barrier method of contraception and female sex partners are to use another method of contraception during treatment and for a week after the last dose

Breast-feeding women

Breastfeeding is not recommended during treatment with asciminib and for at least 7 days after the last dose

Geriatrics

No overall differences in the safety or efficacy of asciminib were observed between patients ≥65 years of age and younger patients

There is an insufficient number of patients ≥75 years of age to assess whether there are differences in safety or efficacy

Management of special populations

Evidence for asciminib in patients with kidney or liver impairment

Kidney Impairment

- Compared to subjects with normal renal function (eGFR ≥90 mL/min/1.73m^2), subjects with severe renal impairment not requiring dialysis (eGFR 15 to <30 mL/min/1.73m^2) had ascinimib AUCinf increased by 56% and Cmax increased by 8%
- No clinically significant effect has been observed in mild to moderate renal impairment (eGFR 30 to <90 mL/min/1.73m^2)

Liver Impairment

- Compared to subjects with normal hepatic function, following oral administration of a single dose of 40 mg asciminib AUCinf was increased:

Mild hepatic impairment (Child-Pugh A)	**22%**
Moderate hepatic impairment (Child-Pugh B)	**3%**
Severe hepatic impairment (Child-Pugh C)	**66%**

Patient counselling

For safe and effective use of medication

- Inquire about history of severe upper stomach pain (inflamed pancreas, pancreatitis)
- Inquire about hepatitis B infection
- Inquire about heart problems
- Inquire about all prescribed medications, OTC medication, and herbal therapies
- Ensure women are not pregnant prior to treatment and counsel about avoiding pregnancy and adequate birth control
- Inform patients about possible side effects
- Educate patients on the need for medication adherence

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Management of adverse events

A higher proportion of patients on asciminib than bosutinib remained on treatment and continued to derive benefit over time, supporting asciminib as a standard of care for patients with CML-CP previously treated with ≤2 TKIs.

ASCEMBL authors

In this chapter

AE recommendations

Most common adverse reactions (≥20%) were musculoskeletal pain, upper respiratory tract infections, thrombocytopenia, fatigue, headache, increased pancreatic enzymes, arthralgia, and nausea

AEs of any grade (incidence ≥20%)

AE	Incidence
Musculoskeletal pain	37.9%
Upper respiratory tract infections	28.1%
Thrombocytopenia	27.5%
Fatigue	25.8%
Headache	23.6%
Increased pancreatic enzymes	21.3%
Arthralgia	21.3%
Nausea	20.2%

"Let the patient know ahead of time that musculoskeletal pain can happen. Monitor by asking questions at follow-up visits. Check magnitude, duration, and location of the pain, and refer to grading scale.

May require dose reduction if severe or persistent and not responsive to supportive measures."

Tina Crosbie
The Ottawa Hospital Ottawa, ON

"Supportive measures: Begin mild stretching and strengthening routines. Apply hot and/or cold compresses to affected areas.

Increase hydration and drink tonic water in the evening to help reduce if have muscle cramping at night."

Tina Crosbie
The Ottawa Hospital Ottawa, ON

Grade 3/4 Adverse Events

The most common adverse reactions of ≥ grade 3 (incidence ≥5%) in patients receiving asciminib:

- Thrombocytopenia (18.5%)
- Neutropenia (15.7%)
- Increased pancreatic enzymes (12.4%)
- Hypertension (8.4%)
- Anemia (5.3%)

Clinical Tips

- Regular monitoring of bloodwork is important
- Ensure primary care is monitoring blood pressure

Dosage adjustments for adverse events

If adverse drug reactions are effectively managed, asciminib may be resumed as described.

Cytopenia's: ANC1 <1 x 10^9/L and/or PLT2 <50 x 10^9/L
- Withhold until resolved to ANC ≥1 x 10^9/L and/or PLT ≥50 x 10^9/L
- If resolved:
  - Within 2 weeks: resume at starting dose
  - After more than 2 weeks: resume at reduced dose
- For severe recurrent thrombocytopenia and/or neutropenia:
  - Withhold until resolved to ANC ≥1 x 10^9/L and PLT ≥50 x 10^9/L, then resume at reduced dose

Asymptomatic amylase and/or lipase elevation: Elevation >2 x ULN3
- Withhold until resolved to <1.5 x ULN
  - If resolved: resume at reduced dose → If events reoccur at reduced dose, permanently discontinue
  - If not resolved: permanently discontinue and perform diagnostic tests to exclude pancreatitis

Non-hematologic adverse reactions including QTc prolongation, hypertension, and immune toxicity : Grade 3 or higher
- Withhold until resolved to grade 1 or lower
  - If resolved: resume at a reduced dose
  - If not resolved: permanently discontinue

Asciminib dose adjustment

Starting dose	Reduced dose	Resumed dose
80 mg once daily	40 mg once daily	80 mg once daily
40 mg once daily	20 mg twice daily	40 mg twice daily

When to discontinue

Asciminib should be permanently discontinued in patients unable to tolerate a total daily dose of 40 mg.[1,2]

	Dose[2,6]	
Starting dose	40 mg twice daily (or 80 mg once daily)	200 mg twice daily
First dose reduction	20 mg twice daily (or 40 mg once daily)	160 mg twice daily
Subsequent dose reduction	Discontinue if unable to tolerate first dose reduction	

CLINICAL SPOTLIGHT

Insights on triggers for treatment switching from the faculty

Patient with comorbid pancreatitis

Ms. EI, 63 years old, has a diagnosis of CML.

She was initially treated with imatinib, then dasatinib, but experienced recurrent episodes of pancreatitis to both imatinib and dasatinib.

She has comorbidities of diabetes and inflammatory bowel disease.

Ms. EI can no longer stay on dasatinib therapy due to recurrent pancreatitis. What would you do next to control her CML?

CLINICAL SPOTLIGHT

Insights on triggers for treatment switching from the faculty

Tips and tricks

- If a patient had an optimal response on an ATP binding inhibitor but had a history of pancreatitis, then suggest to start asciminib at 20 mg daily. If the patient tolerates, then gradually escalate to 40 mg daily, then 40 mg BID.
- However, if the response to other TKIs was suboptimal and transcript levels have gone up to diagnostic levels, then there is not time. Suggest to either start with 40 mg BID (full dose) or 40 mg QD and escalate quickly to BID.

"Prior pancreatitis does not reliably predict future pancreatitis, even if rechallenging with the same TKI that caused pancreatitis in the first place. Elevation of amylase and lipase is generally transient; for true pancreatitis there is always some additional co-occurring factor like alcohol, gallstones, other drugs. Address these issues and then another TKI can be tried without worrying about pancreatitis recurrence."

Dr. Dennis Kim
Princess Margaret Cancer Centre, Toronto, ON

Is dosage adjustment needed in special populations (renal, hepatic impairment, etc.)?

- **No dose adjustment** is required in patients with **mild, moderate or severe renal impairment** not requiring dialysis (absolute Glomerular Filtration Rate (**aGFR) ≥15 mL/min**) receiving asciminib.
- Asciminib has **not been studied** in subjects with **end-stage renal disease requiring dialysis**.
- **No dose adjustment** is required in patients with **mild** (Child-Pugh A), **moderate** (Child-Pugh B), or **severe** (Child-Pugh C) **hepatic impairment** receiving asciminib.
- **No dose adjustment** is required in patients **65 years of age or above**.
- For the management of **adverse reactions**, the **dose of asciminib can be reduced** based on individual safety and tolerability:
  - A starting dose of **80 mg once daily** can be reduced to **40 mg once daily**, then the 80 mg once daily dose can be resumed if and once adverse reactions are effectively managed.
  - A starting dose of **40 mg once daily** can be reduced to **20 mg once daily**, then the 40 mg once daily dose can be resumed if and once adverse reactions are effectively managed.
  - Asciminib should be **permanently discontinued** in patients **unable to tolerate a total daily dose of 40 mg**.

Is it possible to stop asciminib (treatment-free remission (TFR))?

- Most guidelines only suggest **TFR** where an **undetectable MMR was easily achieved**, which becomes less likely in the third line setting
- **Discontinuation of TKI therapy** appears to be **safe** in select chronic CML patients, with **more frequent monitoring** than typically recommended for patients on TKI therapy.*
- It is reasonable to assume that the likelihood of **TFR following discontinuation** would be **similar** irrespective of TKI in patients who have achieved and maintained **deep molecular response** for **≥2 years**.†,‡
- Some patients have experienced **significant adverse events** that are believed to be due to **TKI discontinuation**.
- **Discontinuation of TKI therapy** should only be performed in consenting patients after a **thorough discussion** of the potential **risks and benefits**.

* Monthly molecular monitoring for one year, then every 6 weeks for the second year, and every 12 weeks thereafter (indefinitely) is recommended for patients who remain in MMR (MR3; BCR-ABL1 0.1% IS) after discontinuation of TKI therapy. † Deep molecular response: MR4.0; ≤0.01% BCR-ABL1 IS. ‡ Based on the extrapolation of findings from the studies that have evaluated TFR following discontinuation of imatinib, dasatinib, or nilotinib.

How do we manage women of childbearing potential?

- The **pregnancy status** of women of reproductive potential should be **verified** prior to starting treatment with asciminib.
- Pregnant women and women of reproductive potential should be advised of the **potential risk to a fetus** if asciminib is used during pregnancy or if the patient becomes pregnant while taking asciminib.
- Sexually active females and males of reproductive potential should **use effective contraception** (in addition to a barrier method) during treatment with asciminib and for at least **7 days after the last dose**.
- **Breastfeeding is not recommended** due to the potential secretion into breast milk. Breastfeeding should be avoided during treatment and for at least **1 week after the last dose**.
- Would treat like other TKI and **stop for a desired pregnancy** or if a **woman becomes pregnant.**

What are specific recommendations for patients with comorbidities?

- Patients reporting **pancreatitis** with a previous tyrosine kinase inhibitor (TKI) may be at **increased risk of experiencing pancreatitis** with asciminib. If serum lipase and amylase elevation are accompanied by abdominal symptoms, treatment should be temporarily with held and appropriate diagnostic tests should be considered to exclude pancreatitis.
- Reactivation of **Hepatitis B virus** (HBV) has occurred in chronic carriers of HBV after receiving TKIs; **screen for HBV infection** prior to treatment.
- **QTc prolongation and arrhythmia** have been reported; **monitor ECG and electrolytes** in patients with known risk factors and correct electrolyte abnormalities prior to treatment. Caution should be exercised when administering asciminib concomitantly with medicinal **products with known risk of torsades de pointes**.
- **Fatal arterial thromboembolism and ischemic stroke** have occurred in patients with **pre-existing cardiovascular conditions** and prior exposure to tyrosine kinase inhibitors (TKIs).

Can asciminib be used concomitantly with PPIs?

- Co-administration of a **proton pump inhibitor**, rabeprazole, had **no effect on the AUC and C_{max}** of asciminib.
- Asciminib is a **substrate of CYP 3A4**. At asciminib doses of **80 mg daily**, the effect of concurrent administration with CYP 3A4 inhibitors is **not expected to be clinically significant**.

How to switch from QD to BID and vice versa?

- Patients changing from **40 mg twice daily** to **80 mg once daily** should start taking asciminib once daily approximately **12 hours after the last twice-daily dose**, and then continue at 80 mg once daily.[1]
- Patients changing from **80 mg once daily** to **40 mg twice daily** should start taking asciminib twice daily approximately **24 hours after the last once-daily dose** and then continue at 40 mg twice daily at approximately 12-hour intervals.[1]
- Any change in the dosage regimen is at the prescriber's discretion, as necessary for the management of the patient.[1]

Is there any difference between QD and BID? What is the data to support?

- In two exposure-response (ER)-efficacy analyses, assessing the association between asciminib exposure and efficacy endpoint (based on longitudinal *BCR::ABL1* and summarized as major molecular response (MMR) rates at weeks (wks) 24 and 48), both the **80 mg QD** and **40 mg BID** asciminib regimens demonstrated **substantial efficacy** in patients with Ph+ CML-CP, regardless of baseline *BCR::ABL1 l*evels or number of prior TKIs received.[3]
- However, **the 80 mg QD** dose regimen is likely to support **better treatment adherence**, potentially improving benefit from therapy.[3]

Are there specific guidance for the use of asciminib in patients with history of certain AEs, like pancreatitis or pleural effusions?

Thrombocytopenia and/or neutropenia – absolute neutrophil count (ANC) <1 x 10^9/L and/or PLT <50 x 10^9/L: Withhold asciminib until resolved to ANC ≥1 x 10^9/L and/or platelets (PLT) ≥50 x 10^9/L.

- If resolved within 2 weeks: resume asciminib at starting dose.
- If resolved after more than 2 weeks: resume asciminib at reduced dose.
- For severe recurrent thrombocytopenia and/or neutropenia, withhold asciminib until resolved to ANC ≥1 x 10^9/L and PLT ≥50 x 10^9/L, then resume at reduced dose.

Asymptomatic amylase and/or lipase elevation – Elevation >2 x upper limit of normal (ULN): Withhold asciminib until resolved to <1.5 x ULN.

- If resolved: resume ascimnib at reduced dose. If events reoccur at reduced dose, permanently discontinue asciminib.
- If not resolved: permanently discontinue asciminib. Perform diagnostic tests to exclude pancreatitis.

Non-hematologic adverse reactions – Grade 3 or higher* adverse reactions: Withhold asciminib until resolved to grade 1 or lower.

- If resolved: resume asciminib at a reduced dose.
- If not resolved: permanently discontinue asciminib.

* Based on National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) v 4.03.

Can asciminib be used in earlier lines of treatment?

- Asciminib is currently indicated for the treatment of adult patients with Philadelphia chromosome-positive chronic myeloid leukemia (Ph+ CML) in chronic phase (CP) previously treated with **two or more TKIs**.[1]
- However, ASC4FIRST (NCT04971226) is an ongoing phase III, multicenter, open-label, randomized study of asciminib versus investigator-selected TKI in patients with **newly diagnosed chronic myeloid leukemia in chronic phase**.[4]
  - The primary end point is **major molecular response at week 48**.
  - Final data for the primary outcome measure (estimated primary completion date) are expected in Q1 2024.

What action should be taken if MMR is not achieved at 6 months? At 1 year?

- Real-world data on **22 Canadian CML patients** treated with asciminib between 2018 and 2021 after failing **multiple TKIs** showed that **MMR** was achieved in **18% and 38%** of patients at **6 and 12 months**, respectively.[5]
- **MR2** was achieved in **41% and 50%** of patients, respectively.
- Results from ASC4MORE, a randomized study of asciminib add-on to **imatinib** (IMA), continued IMA, or switch to nilotinib (NIL) in patients with CML-CP who **did not achieve deep molecular responses** (DMR) after **≥1 year** of IMA therapy, showed that more patients **achieved DMR at Week 48 with asciminib** add-on to IMA vs continued IMA or switch to NIL.[6]
- If the patient is **young** enough and this is **3rd line treatment failure**, consider **transplant**.

Can I use asciminib in patients with X mutation? Should I adjust the dose?

An exposure-efficacy analysis of asciminib therapy in Ph+ CML patients included 303 patients from a phase I trial and from the phase III ASCEMBL trial, with doses ranging from 10 to 200 mg bid or 40 to 200 mg qd, in which a total of 67 patients harboured the T315I mutation.[7]

- The model demonstrated the appropriateness of a total daily dose of asciminib 80 mg in patients without the T315I mutation and 200 mg bid in patients with the T315I mutation.

In the real-world study of 22 Canadian CML patients treated with asciminib between 2018 and 2021 after failing multiple TKIs previously mentioned, patients with the T315I mutation (n=4) started at either 80 mg or 120 mg bid, with gradual dose escalation to 200 mg bid.[5]

- Side effects included myalgias (n=4), elevated lipase (n=2) and pleural/pericardial effusions (n=2). No CV events were noted in the 22 patients.

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Asciminib patient profiles

Patient Profiles

What types of patients might benefit from asciminib in the third-line setting?

“The patient who has cytopenias on two 2nd generation TKIs”

“ The patient who failed at least 2 lines of TKI therapy”

“The patient who has fatigue on imatinib”

“The patient who is experiencing the same type of side effects with each TKI they try”

“The patient who developed resistance to other 2 TKIs but without having any specific mutation known to be resistant to asciminib.”

“The patient for whom intolerance is leading to lack of adherence”

“The patient who requires a lot of dose reductions on previous TKIs”

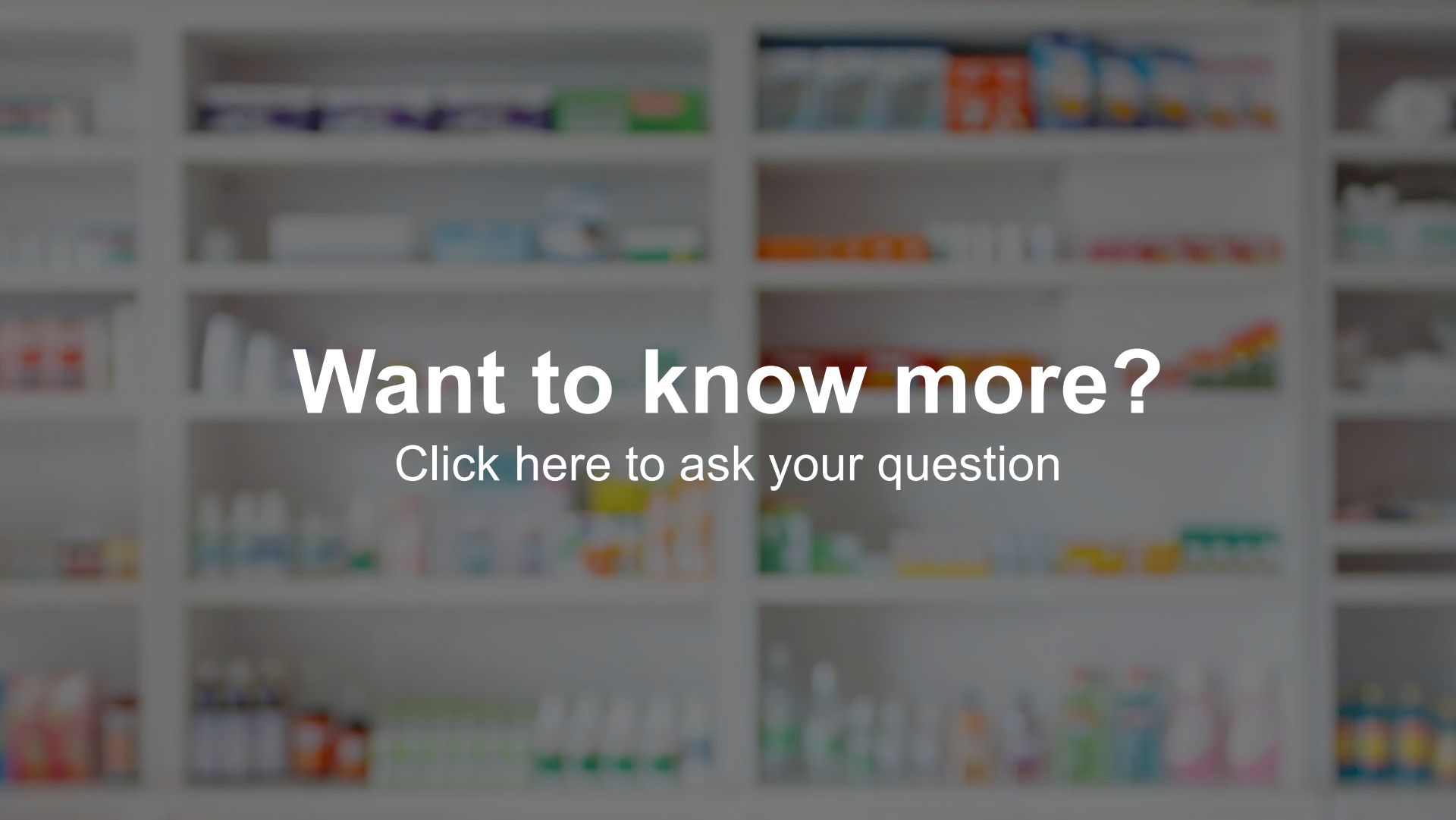
“The patient for whom quality of life is adversely affected on previous TKIs”

“The patient having cardiovascular comorbidity for which nilotinib/ponatinib are contraindicated but failed other 2 lines of TKI therapy already”

In this chapter

Patient Profiles

Characteristic	Patient 1	Patient 2	Patient 3	Patient 4
Scenario	Resistance and Intolerance	Intolerance	Intolerance	Resistance
Age	68	76	63	57
Sex	Female	Male	Male	Female
Comorbidities & concomitant medicines	Anxiety controlled with anxiolytic	Active dyslipidemia managed with a non-statin cholesterol-lowering medication	Diabetes managed with insulin	No comorbidities
Time since CML diagnosis	6 years	1.5 years	1.5 years	2.5 years
Duration of first TKI	~5 years	~6 months	~1 year	~ 2 years
Response to first TKI	• Achieved MMR • Experienced chronic grade 2 fatigue that was not resolved with dose reduction	• Achieved CCyR (*BCR::ABL1*: 0.6%) • Experienced grade 3 peripheral edema that was not resolved with dose reduction, but was resolved with diuretics	• Achieved MMR at 6 months • Lost MMR at 1 year (*BCR::ABL1*: 1.3%) • No resistance mutation	• Slow to reach MMR (*BCR::ABL1*: 11% at 3 months, 5% at 6 months, ≤0.1% at 1 year) • Lost MMR at 2 years (*BCR::ABL1*: 12%) • No resistance mutation
Duration of second TKI	1 year	1 year	3 months	6 months
Response to second TKI	• *BCR::ABL1* at 12 months: 1.5% • Did not achieve CCyR • Worsening grade 3 fatigue not resolved with dose reduction	• Achieved MMR at 12 months and maintained • Developed grade 2 pleural effusion • Pending pulmonary consult to discuss thoracentesis after an unsuccessful dose reduction	• Grade 3 rash • Elevated ALT/AST	• *BCR::ABL1*: 15% at 3 months • *BCR::ABL1*: 10.1% at 6 months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