Why test: There is an inherent need for consistent monitoring of patients with CML

Resistance can be primary or secondary and may be due to mutations within the BCR::ABL1 domain[1,2]

Rates of BCR::ABL1 mutations and treatment resistance both increase with each subsequent line of TKI treatment*

	Frequency of BCR::ABL1 mutations	Rates of treatment resistance (with or without BCR::ABL1 mutation)
1L	5%-18%[3-5]	16%-40%[1,10]
2L	**21%-33%[6,7]**	**32%-50%[11-13]**
3L[a]	**23%-43%[8,9,b]**	**60%[9]**

- BCR::ABL1 point mutations are a common cause of secondary resistance to TKI therapy and are associated with poor prognosis and a higher risk of disease progression[14]
- T315I is the most problematic BCR::ABL1 mutation and confers in vitro resistance to all 1st- and 2nd-generation TKIs[15]

[a]Results are primarily from a 3L study with 2G TKI therapy, but also included 3 patients taking 4L 2G TKI therapy.
[b]Approximately two-thirds of patients have not yet mutated.
***Based on nonrandomized, observational, retrospective studies that may have unobserved confounding and treatment selection biases as well as other limitations that should be considered when comparing results with clinical trials. Outcomes should be interpreted with caution due to small sample size.**
1L=first line; 2G=second generation; 2L=second line; 3L=third line; 4L=fourth line; TKI=tyrosine kinase inhibitor.

There is an inherent need for consistent monitoring of patients with CP-CML[16,c]:



of patients with CP-CML who received TKI therapy did not receive cytogenetic monitoring by 12 months

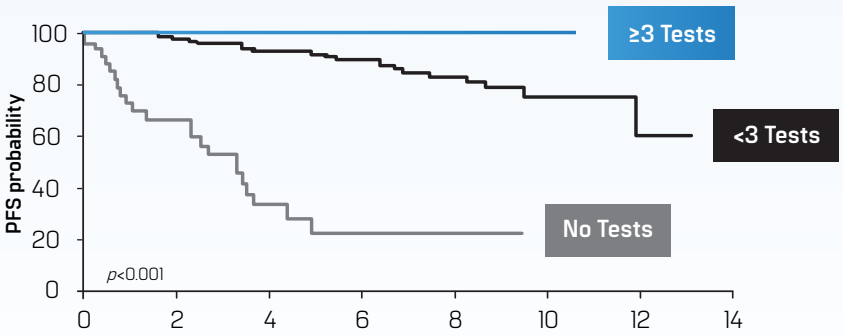


of patients with CP-CML who received TKI therapy did not receive any molecular monitoring by 18 months

[c]Findings from a retrospective study of 410 patients with CP-CML initiating TKI therapy between January 2008 and December 2010.[16]

PCR monitoring is associated with a lower risk of progression or mortality[17]

Survival probability for mortality or progression to AP- or BP-CML in all patients, stratified by the number of PCR tests[17]



No. at risk							
No tests	35	22	10	4	4		
<3 tests	143	130	102	79	42	19	6
≥3 tests	67	59	33	13	5	2	

AP-CML=accelerated phase chronic myeloid leukemia; BCR::ABL1=breakpoint cluster region-Abelson 1; BP-CML=blast phase chronic myeloid leukemia; CP-CML=chronic phase chronic myeloid leukemia; PCR=polymerase chain reaction; PFS=progression-free survival; TKI=tyrosine kinase inhibitor.

When to test: NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) select recommendations for monitoring response to TKI therapy

Monitoring early treatment response milestones for resistance[14]

BCR::ABL1^{IS}	3 months	6 months	12 months[a]
>10%[b]	●	●	●
>1%-10%[c]			●

Monitoring Response to TKI Therapy[14]

Concern	Clinical Considerations[d]
● **TKI-resistant disease**[e]	• Evaluate patient adherence and drug interactions • Consider BCR::ABL1 kinase domain mutational analysis[f] • Consider bone marrow cytogenetic analysis to assess ACAs
● **Possible TKI resistance**[e]	• Evaluate patient adherence and drug interactions • Consider BCR::ABL1 kinase domain mutational analysis[f]
● **Possible TKI resistance**[e]	• Evaluate patient adherence and drug interactions • Consider BCR::ABL1 kinase domain mutational status[f] • Consider bone marrow cytogenetic analysis to assess for CCyR at 12 months

[a]BCR::ABL1 ^{IS} ≤0.1% at 12 months is associated with a very low probability of subsequent loss of response and a high likelihood of achieving a subsequent deep molecular response (DMR MR4.0; BCR::ABL1 ^{IS} ≤0.01%), which is a prerequisite for a trial of treatment-free remission (TFR).
[b]Achievement of response milestones must be interpreted within the clinical context. Patients with BCR::ABL1 only slightly >10% at 3 months and/or with a steep decline from baseline may achieve <10% at 6 months and have generally favorable outcomes. Therefore, it is important to interpret the value at 3 months in this context before making drastic changes to the treatment strategy. The same dose of TKI can be continued for another 3 months, but imatinib is associated with slower molecular responses.
[c]Achievement of response milestones must be interpreted within the clinical context. Patients achieving MCyR (BCR::ABL1 ^{IS} ≤10%) at 12 months have good long-term survival. Patients with more than 50% reduction compared to baseline or minimally above the 10% cutoff can continue the same dose of TKI for another 3 months. Consider switching to an alternative 2G TKI or 3G TKI or allosteric TKI in the absence of a continuing decline in BCR::ABL1 transcript levels.
[d]Switching to an alternate TKI for intolerance is appropriate for patients with disease responding to TKI therapy.
[e]Consider referral to a specialized CML center and/or enrollment in a clinical trial.
[f]Consider myeloid mutation panel to identify BCR::ABL1-independent resistance mutations in patients with no BCR::ABL1 kinase domain mutations.

The detection of mutations following first-line treatment resistance is crucial to ensure appropriate second- or third-line drug selection[18]

NCCN Guidelines®: Types of tests and when to use each

Mutational analysis should be considered when patients experience any of the following[14,18]:

1 Failure to achieve response milestones

2 Progression to a more advanced phase

3 Display any sign of loss of response (hematologic or cytogenetic relapse)

A

Bone marrow cytogenetics[g]
- At diagnosis
- Response milestones not reached
- Any sign of loss of hematologic response
- Any sign of loss of CCyR or its molecular response correlate (MR2.0: BCR::ABL1 ^{IS} ≤1%)—defined as an increase in BCR::ABL1 transcript to >1%

B

qPCR using IS
- At diagnosis
- Every 3 months after initiating treatment. After BCR::ABL1 ^{IS} ≤1% (MR2.0)[h] has been achieved, every 3 months for 2 years and every 3-6 months thereafter
- If there is a 1-log increase in BCR::ABL1 transcript levels with MMR, qPCR should be repeated in 1-3 months

C

BCR::ABL1 kinase domain mutation analysis[i]
- Chronic phase
  - Response milestones not reached
    - Any sign of loss of hematologic response
    - Any sign of loss of CCyR or its molecular response correlate (MR2.0: BCR::ABL1 ^{IS} ≤1%)— defined as an increase in BCR::ABL1 transcript to >1%
    - 1-log increase in BCR::ABL1 transcript levels and loss of MMR
- Disease progression to accelerated or blast phase[i]

[g]FISH has been inadequately studied for monitoring response to treatment.
[h]CCyR correlates with BCR::ABL1 ^{IS} ≤1% (MR2.0).
[i]Consider myeloid mutation panel to identify BCR::ABL1-independent resistance mutations in patients with no BCR::ABL1 kinase domain mutations.
2G=second generation; 3G=third generation; ACA=additional chromosomal abnormalities; CCyR=complete cytogenetic response; FISH=fluorescence in situ hybridization; IS=International Scale; MMR=major molecular response; qPCR=quantitative polymerase chain reaction; TKI=tyrosine kinase inhibitor.

Kinase domain testing results and TKI sensitivity[19,20]

IC_{50} (nM) of ATP-competitive BCR::ABL1 TKIs against single mutants[a]

(corrected for protein binding and drug bioavailability)

■ IC_{50} <75% C_{ave} ■ IC_{50} 75%-150% C_{ave} ■ IC_{50} 150%-300% C_{ave} ■ IC_{50} >300% C_{ave}

ATP-binding site mutations	1st-generation	2nd-generation			3rd-generation
	Imatinib	Nilotinib	Dasatinib	Bosutinib	Ponatinib
WT	201	15	2	71	3
M244V	287	12	2	147	3
L248R	10,000	549	6	874	8
G250E	1087	41	4	85	5
Y253H	4908	179[b]	3	40	5
E255K	2487	127[b]	9	181	6
E255V	8322	784[b]	11	214	16
V299L	295	24	16[b]	1228[b]	4
T315A	476	50	59[b]	122	4
T315I	9773	8091[b]	10,000[b]	4338[b]	6
F317C	324	16	45[b]	165	3
F317I	266	25	40[b]	232	7
F317L[c]	675	21	10[b]	82[b]	4
F317V	1023	26	104[b]	1280	10
F359C[c]	728	47[b]	2	70	6
F359I[c]	324	64[b]	3	76	11
F359V[c]	346	41[b]	2	59	4
H396R	395	23	2	60	4
E459K	612	38	4	127	5

[a]Mean IC_{50} from 3 separate experiments in engineered Ba/F3 cells (corrected for protein binding and drug availability in the serum).[19]
[b]Mutations conferring clinical resistance to 2nd-generation *BCR::ABL1* TKIs: T315I, V299L, G250E, and F317L for bosutinib; T315I/A, F317L/V/I/C, and V299L for dasatinib; and T315I, Y253H, E255K/V, and F359V/C/I for nilotinib.[13,21-26]

Asciminib (non-ATP competitive TKI)

[c]NCCN Guidelines state that **A337T, P465S, M244V, F359V/I/C, b2(e13)a3,** and **b3(e14)a3** are contraindicated mutations/variants for asciminib.[14]

Preclinical data do not translate into clinical efficacy. The clinical effect of these data is not known as they are from in vitro studies. Clinical efficacy can only be proven through randomized controlled trials.

How to test: Ordering BCR::ABL1 kinase domain mutational testing

Select national laboratory centers that perform kinase domain mutational analysis[a]

	Test Name	Specimen Requirements[b]	Contact
Labcorp	BCR-ABL1 Kinase Domain Mutation Analysis	Whole blood or bone marrow	labcorp.com | **T:** 800-710-1800
Mayo Clinic Laboratories	BCR/ABL1, Tyrosine Kinase Inhibitor Resistance, Kinase Domain Mutation Screen, Sanger Sequencing, Varies	Whole blood (preferred) or bone marrow	mayocliniclabs.com **T:** 800-533-1710 | **E:** mcl@mayo.edu
NeoGenomics	ABL1 Kinase Domain Mutation Analysis	Whole blood or bone marrow	neogenomics.com | **T:** 866-776-5907 **E:** client.services@neogenomics.com
ARUP Laboratories	BCR-ABL1 Mutation Analysis for Tyrosine Kinase Inhibitor Resistance by Next Generation Sequencing	Whole blood or bone marrow	aruplab.com | **T:** 800-522-2787 **E:** clientservices@aruplab.com
Quest Diagnostics	ABL Kinase Domain Mutation CML, Cell-based	Whole blood or bone marrow	questdiagnostics.com | Online chat center **T:** 866-MYQUEST
Knight Diagnostic Laboratories	BCR-ABL Kinase Domain Mutations/ ABL Sequencing (Qualitative)	Whole blood or bone marrow	knightdxlabs.ohsu.edu | **T:** 855-535-1522 **E:** KDLClientServices@ohsu.edu

[a]This is not an all-inclusive list of labs that perform testing, and Takeda does not provide preference for any lab over another.
[b]Frozen within 1 hour of collection.

Patients treated with sequential TKIs have a higher risk of developing resistance and novel mutations[27]

ATP=adenosine triphosphate; C_{ave}=average plasma concentration; IC_{50}=half maximal inhibitory concentration; NR=not reported.

INDICATIONS AND USAGE

ICLUSIG® (ponatinib) is indicated for the treatment of adult patients with:

- Chronic phase (CP) chronic myeloid leukemia (CML) with resistance or intolerance to at least two prior kinase inhibitors.
- Accelerated phase (AP) or blast phase (BP) CML for whom no other kinase inhibitors are indicated.
- T315I-positive CML (chronic phase, accelerated phase, or blast phase).

Limitations of Use: ICLUSIG is not indicated and is not recommended for the treatment of patients with newly diagnosed CP-CML.

IMPORTANT SAFETY INFORMATION

WARNING: ARTERIAL OCCLUSIVE EVENTS, VENOUS THROMBOEMBOLIC EVENTS, HEART FAILURE, and HEPATOTOXICITY

See full prescribing information for complete boxed warning.

- **Arterial occlusive events (AOEs), including fatalities, have occurred in ICLUSIG-treated patients. AOEs included fatal myocardial infarction, stroke, stenosis of large arterial vessels of the brain, severe peripheral vascular disease, and the need for urgent revascularization procedures. Patients with and without cardiovascular risk factors, including patients age 50 years or younger, experienced these events. Monitor for evidence of AOEs. Interrupt or discontinue ICLUSIG based on severity. Consider benefit-risk to guide a decision to restart ICLUSIG.**
- **Venous thromboembolic events (VTEs) have occurred in ICLUSIG-treated patients. Monitor for evidence of VTEs. Interrupt or discontinue ICLUSIG based on severity.**
- **Heart failure, including fatalities, occurred in ICLUSIG-treated patients. Monitor for heart failure and manage patients as clinically indicated. Interrupt or discontinue ICLUSIG for new or worsening heart failure.**
- **Hepatotoxicity, liver failure and death have occurred in ICLUSIG-treated patients. Monitor liver function tests. Interrupt or discontinue ICLUSIG based on severity.**

WARNINGS AND PRECAUTIONS

Arterial Occlusive Events (AOEs): AOEs, including fatalities, have occurred in patients who received ICLUSIG. These included cardiovascular, cerebrovascular, and peripheral vascular events, and occurred in patients with and without cardiovascular risk factors. Monitor for evidence of AOEs. Interrupt, then resume at the same or decreased dose, or discontinue ICLUSIG based on recurrence/severity. Consider benefit-risk before restarting ICLUSIG.

Venous Thromboembolic Events (VTEs): Serious or severe VTEs have occurred in patients who received ICLUSIG, including events such as deep vein thrombosis, embolism, pulmonary embolism, superficial vein thrombosis, thrombosis, jugular vein thrombosis, superficial thrombophlebitis, retinal vein occlusion, and retinal vein thrombosis with vision loss. Monitor for evidence of VTEs. Interrupt, then resume at the same or decreased dose, or discontinue ICLUSIG based on recurrence/severity.

Heart Failure: Fatal, serious, or severe heart failure events have occurred, including increased brain natriuretic peptide (BNP), left ventricular hypertrophy, left ventricular dysfunction, congestive cardiac failure, cardiac failure, left atrial dilatation, and decreased ejection fraction. Monitor for signs or symptoms of heart failure and manage as clinically indicated. Interrupt, then resume at reduced dose, or discontinue ICLUSIG for new or worsening heart failure.

Hepatotoxicity: ICLUSIG can cause hepatotoxicity, including liver failure and death. Fulminant hepatic failure leading to death has occurred. The most frequent hepatotoxic events were elevations of ALT, AST, GGT, bilirubin, and alkaline phosphatase, and decreased albumin and blood fibrinogen. Monitor liver function tests at baseline, then at least monthly or as clinically indicated. Interrupt, then resume at a reduced dose, or discontinue ICLUSIG based on recurrence/severity.

Hypertension: Serious or severe hypertension, including hypertensive crisis, has occurred. Patients may require urgent intervention for hypertension with confusion, headache, chest pain, or shortness of breath. Monitor blood pressure at baseline and as clinically indicated and manage as clinically indicated. Interrupt, dose reduce, or discontinue ICLUSIG if hypertension is not medically controlled. For significant worsening, labile or treatment-resistant hypertension, interrupt ICLUSIG and consider evaluating for renal artery stenosis.

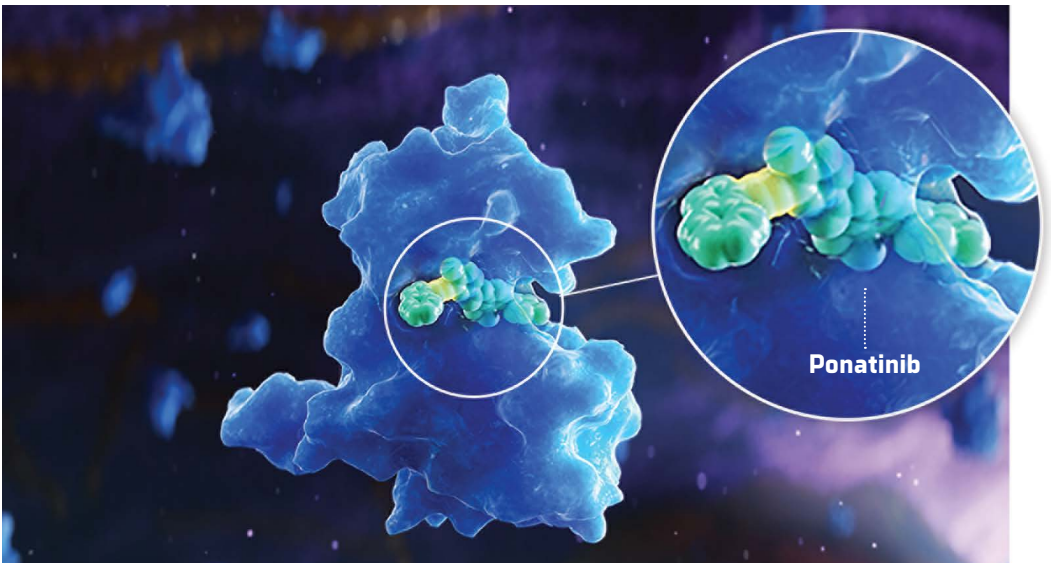
Pancreatitis: Serious or severe pancreatitis has occurred. Elevations of lipase and amylase also occurred. In the majority of cases that led to dose modification or treatment discontinuation, pancreatitis resolved within 2-3 weeks. Monitor serum lipase every 2 weeks for the first 2 months and then monthly or as clinically indicated. Consider additional serum lipase monitoring in patients with a history of pancreatitis or alcohol abuse. Interrupt, then resume at the same or reduced dose, or discontinue ICLUSIG based on severity. Evaluate for pancreatitis when lipase elevation is accompanied by abdominal symptoms.

Increased Toxicity in Newly Diagnosed Chronic Phase CML: In a prospective randomized clinical trial in the first-line treatment of newly diagnosed patients with CP-CML, single agent ICLUSIG increased the risk of serious adverse reactions. The trial was halted for safety. ICLUSIG is not indicated and is not recommended for the treatment of patients with newly diagnosed CP-CML.

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ICLUSIG is the only 3rd-generation TKI that shows activity against all single point mutations in CML[28,29]



ICLUSIG was designed to overcome limitations of earlier-generation TKIs that have reduced activity with specific BCR::ABL1 mutations[28-31]

Preclinical activity does not necessarily correlate with clinical outcomes.

There are no contraindicated mutations for ICLUSIG[28]

For more resources, go to
iclusig.com/hcp

IMPORTANT SAFETY INFORMATION (continued)

WARNINGS AND PRECAUTIONS (continued)

Neuropathy: Peripheral and cranial neuropathy occurred in ICLUSIG-treated patients, including Grade 3 or 4 events. Monitor for symptoms such as hypoesthesia, hyperesthesia, paresthesia, discomfort, a burning sensation, neuropathic pain, or weakness. Interrupt, then resume at the same or reduced dose, or discontinue ICLUSIG based on recurrence/severity.

Ocular Toxicity: Serious or severe ocular toxicities leading to blindness and blurred vision have occurred. The most frequent ocular toxicities were dry eye, blurred vision, and eye pain. Retinal toxicities included retinal vein occlusion, retinal hemorrhage, age-related macular degeneration, arteriosclerotic retinopathy, retinal vascular disorder, macular edema, and vitreous floaters. Conduct comprehensive eye exams at baseline and periodically during treatment.

Hemorrhage: Fatal and serious hemorrhages have occurred. Intracranial hemorrhage, gastrointestinal hemorrhage, and subdural hematoma were the most frequently reported serious hemorrhages. Most hemorrhages occurred in patients with Grade 4 thrombocytopenia. Monitor for hemorrhage and manage as clinically indicated. Interrupt, then resume at the same or reduced dose, or discontinue ICLUSIG based on recurrence/severity.

Fluid Retention: Fatal and serious events, including one instance of fatal brain edema and serious events of pleural effusion, pericardial effusion, and angioedema have occurred. The most frequent occurrences of fluid retention in patients who received ICLUSIG were peripheral edema, pleural effusion, hydrothorax, pericardial effusion, and peripheral swelling. Monitor for fluid retention and manage as clinically indicated. Interrupt, then resume at the same or reduced dose, or discontinue ICLUSIG based on recurrence/severity.

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IMPORTANT SAFETY INFORMATION (continued)

WARNINGS AND PRECAUTIONS (continued)

Cardiac Arrhythmias: Cardiac arrhythmias, including ventricular and atrial arrhythmias, tachycardia, bradycardia, cardio-respiratory arrest, syncope, atrial fibrillation, and supraventricular tachycardia, have occurred, including some patients with serious or severe (Grade 3 or 4) events leading to hospitalization. Monitor for signs and symptoms suggestive of slow heart rate (fainting, dizziness) or rapid heart rate (chest pain, palpitations, or dizziness) and manage patients as clinically indicated. Interrupt, then resume at the same or reduced dose, or discontinue ICLUSIG based on recurrence/severity.

Myelosuppression: Grade 3 or 4 neutropenia, thrombocytopenia, and anemia have occurred. Obtain complete blood counts every 2 weeks for the first 3 months and then monthly or as clinically indicated. Interrupt ICLUSIG if ANC <1 × 10^9/L or platelets <50 × 10^9/L, and resume when ANC ≥1.5 × 10^9/L and platelets ≥75 × 10^9/L, at same or reduced dose.

Tumor Lysis Syndrome (TLS): Serious TLS has occurred. Ensure adequate hydration and treat elevated uric acid prior to initiating ICLUSIG.

Reversible Posterior Leukoencephalopathy Syndrome (RPLS): RPLS has been reported. Patients can present with hypertension, seizure, headache, decreased alertness, altered mental functioning, vision loss, and other visual and neurological disturbances. MRI is necessary to confirm diagnosis. Interrupt ICLUSIG until resolution. The safety of resumption of ICLUSIG upon resolution of RPLS is unknown.

Impaired Wound Healing and Gastrointestinal Perforation: Impaired wound healing occurred in patients receiving ICLUSIG. Withhold ICLUSIG for at least 1 week before elective surgery and for at least 2 weeks after major surgery until adequate wound healing. Gastrointestinal perforation or fistula have occurred. Permanently discontinue ICLUSIG in patients with gastrointestinal perforation.

Embryo-Fetal Toxicity: ICLUSIG can cause fetal harm when administered to pregnant women. Advise pregnant women of the potential risk to the fetus. Females of reproductive potential should use effective contraception during treatment with ICLUSIG and for 3 weeks after the last dose.

ADVERSE REACTIONS

The most common adverse reactions (occurring in >20% of patients) are:

- ICLUSIG as a single agent: rash and related conditions, arthralgia, abdominal pain, fatigue, headache, constipation, hypertension, dry skin, hepatotoxicity, fluid retention and edema, pyrexia, pancreatitis/lipase elevation, nausea, hemorrhage, anemia, AOEs, and cardiac arrhythmias. The most common Grade 3 or 4 laboratory abnormalities (>20%) are platelet count decreased, neutrophil cell count decreased, and white blood cell decreased.
- ICLUSIG in combination with chemotherapy: hepatotoxicity, arthralgia, rash and related conditions, headache, pyrexia, abdominal pain, constipation, fatigue, nausea, oral mucositis, hypertension, pancreatitis/lipase elevation, neuropathy peripheral, hemorrhage, febrile neutropenia, fluid retention and edema, vomiting, paresthesia, and cardiac arrhythmias. The most common Grade 3 or 4 laboratory abnormalities (>20%) are decreased white blood cell count, decreased neutrophil cell count, decreased platelet count, decreased lymphocyte cell count, decreased hemoglobin, increased lipase, and increased alanine aminotransferase.

To report SUSPECTED ADVERSE REACTIONS, contact Takeda Pharmaceuticals at 1-844-817-6468 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

Strong CYP3A Inhibitors: Avoid coadministration or reduce ICLUSIG dose if coadministration cannot be avoided.

Strong CYP3A Inducers: Avoid coadministration.

USE IN SPECIFIC POPULATIONS

Lactation: Advise women not to breastfeed during treatment with ICLUSIG and for 1 week following last dose.

Females and Males of Reproductive Potential: Verify pregnancy status of females of reproductive potential prior to initiating ICLUSIG. Ponatinib may impair fertility in females, and it is not known if these effects are reversible.

Pre-existing Hepatic Impairment: For patients with CP-CML, AP-CML, BP-CML, and Ph+ ALL receiving monotherapy, reduce the starting dose of ICLUSIG to 30 mg orally once daily for patients with pre-existing hepatic impairment. For patients with newly diagnosed Ph+ ALL, no dosage adjustment is recommended when administering ICLUSIG to patients with mild hepatic impairment.

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