

ICLUSIG®
(ponatinib) tablets
45mg / 30mg / 15mg / 10mg

The Only TKI With No Contraindicated Mutations (including T315I)[1,2]

for Adult Patients with CP-CML

*Hypothetical patients.

Offer the Chance of a Meaningful Response[2]

VISIT **ICLUSIG.COM/HCP** FOR MORE INFORMATION

INDICATIONS AND USAGE

ICLUSIG (ponatinib) is indicated for the treatment of adult patients with:
Chronic Myeloid Leukemia (CML)
- Chronic phase (CP) 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

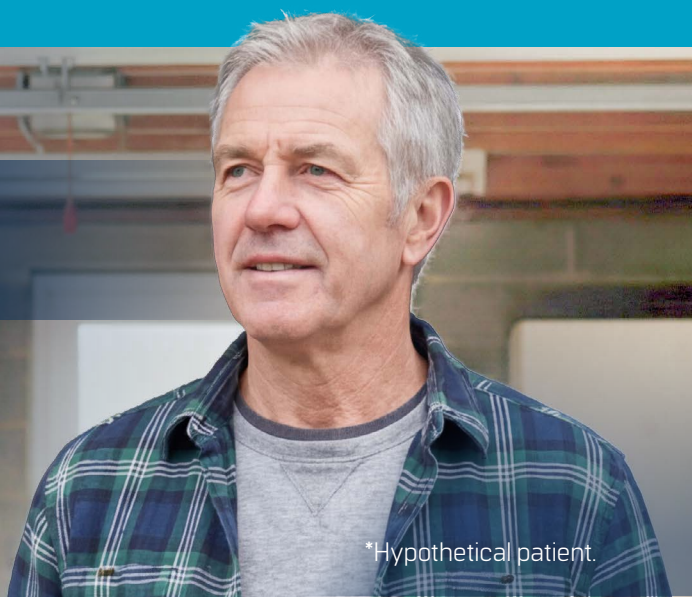
WARNING: ARTERIAL OCCLUSIVE EVENTS, VENOUS THROMBOEMBOLIC EVENTS, HEART FAILURE, and HEPATOTOXICITY
See full prescribing information for complete boxed warning.

- 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.

Please see additional Important Safety Information throughout and accompanying full Prescribing Information, including Boxed Warning.

ROBERT

Experiencing Resistance in CP-CML with a T315I Mutation



*Hypothetical patient.

Robert Presents With Rising BCR::ABL1^{IS} Levels After His First TKI Therapy

Robert is a 55-year-old engineer who wants to regain control of his disease to maintain his career and family life. After losing response to a 2nd generation TKI, recent labs show the development of a T315I mutation, prompting him to consider a treatment option that addresses resistance.

Robert's Treatment Journey

At Presentation

Loss of response to 2nd generation TKI after originally being in remission

- PCR testing showed rising BCR::ABL1^{IS}
- Mutation testing revealed Robert was T315I mutation positive BCR::ABL1^{IS}

Treatment history

- 1L 2nd generation TKI
  - Originally under control and in remission
  - Rising BCR::ABL1^{IS} indicates a loss of molecular response

Laboratory results

- BCR::ABL1^{IS} is rising and is now 6.4%, despite adherence to 2nd generation TKI
- T315I mutation detected

Treatment Choice

Began 2L treatment with ICLUSIG 45 mg

- Looking to regain durable and deep disease control[3]

Early Response

Robert achieved his early response milestones

- BCR::ABL1^{IS} down to 0.8% by **MONTH 3**
- Used a response-based dose-reduction approach consistent with the OPTIC* trial design (dose reduced to 15 mg after achieving ≤1% BCR::ABL1^{IS})[2]
- Slight rise in blood pressure was managed medically with no new arterial events

Why Robert's Physician Recommends ICLUSIG

After developing resistance to a 2nd generation TKI, Robert underwent BCR::ABL1 mutation testing and was found to be T315I-positive. Robert and his oncologists selected ponatinib (ICLUSIG) because it is recommended as a treatment option by the National Comprehensive Cancer Network® (NCCN®) treatment guidelines for certain patients with T315I mutation, and it's the only TKI with no known contraindicated BCR::ABL1 mutations[1-4]

Robert and his oncologist selected ICLUSIG because it is the only TKI with no known contraindicated BCAR::ABL1 mutations and is recommended as a treatment option by the NCCN treatment guidelines for certain patients with T315I mutation.[1-4]

*OPTIC is an open-label, multicenter, randomized study designed to evaluate ICLUSIG across multiple response-based dosing regimens for patients with CP-CML.[1,2] A total of 282 patient received ICLUSIG and were divided into 3 cohorts: The first cohort (n=94) received a starting dose of 45 mg, the second (n=94) received a starting dose of 30 mg, and the third (n=94) received a starting dose of 15 mg. Patient in cohorts 1 and 2 were reduced to 15 mg daily upon achievement of ≤1% BCR::ABL^{IS}. The primary endpoint for OPTIC was ≤1% BCR::ABL^{IS} at 12 months.[2,5]

BCR::ABL1^{IS}=BCR::ABL1 International Scale; CP-CML=chronic phase chronic myeloid leukemia; TKI=tyrosine kinase inhibitor.

When T315I is detected after first-line TKI therapy, how do you pivot treatment?

IMPORTANT SAFETY INFORMATION (cont'd)

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.

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FACES OF ICLUSIG®*

NAOMI

CP-CML with a Suboptimal Molecular Response Due to Her Intolerance With a 2nd TKI



Naomi's BCR::ABL1 Remains Above Target Despite TKI Cycling

Naomi is 62 years old, retired, and an active member of the community. She cycled through two 2nd generation TKIs. Despite continuing treatment with a 2L TKI, she is experiencing interruptions in her treatment.

Naomi's Treatment Journey

At Presentation

Naomi was treated with 1L 2nd generation TKI but lost response by 12 months

- Initially reached ≤1% BCR::ABL1^{IS}
- At 12 months, her BCR::ABL1^{IS} was 5.6%

Treatment history

- Prior failure on 1L first generation TKI
- Intolerance to 2L 2nd generation TKI
  - Interruptions in treatment
  - Discontinued 2nd generation TKI due to pleural effusions
- Disease was not under optimal control

Laboratory results

- BCR::ABL1^{IS} was 2.1% 6 months after starting 2nd generation TKI

Treatment Choice

Began treatment with 2L 2nd generation TKI

- Experienced pleural effusions and treatment interruptions
- Discontinued at 6 months, having never reached ≤1% BCR::ABL1^{IS}
- BCR::ABL1^{IS} at 6 months was 2.1%

Began treatment with 3L ICLUSIG

Early Response

Naomi achieved her early response milestones

- BCR::ABL1^{IS} down to 0.7% by **MONTH 6**
- Used a response-based dose-reduction approach consistent with the OPTIC* trial design (dose reduced to 15 mg after achieving ≤1% BCR::ABL1^{IS})[2]
- Treatment is generally well-tolerated with no new safety events

Why Naomi's Physician Recommends ICLUSIG

Because Naomi was intolerant to her 2nd TKI, she and her physician agreed that she now needs a therapy capable of delivering deep, durable responses with manageable tolerability to help her achieve optimal disease control.[2,3]

Due to her intolerance and prior loss of response to a 2nd generation TKI, her physician recommended ICLUSIG, a 3rd-generation TKI, for the potential of a deeper response and achieving disease control.[2,6]

*OPTIC is an open-label, multicenter, randomized study designed to evaluate ICLUSIG across multiple response-based dosing regimens for patients with CP-CML.[1,2] A total of 282 patient received ICLUSIG and were divided into 3 cohorts: The first cohort (n=94) received a starting dose of 45 mg, the second (n=94) received a starting dose of 30 mg, and the third (n=94) received a starting dose of 15 mg. Patient in cohorts 1 and 2 were reduced to 15 mg daily upon achievement of ≤1% BCR::ABL^{IS}. The primary endpoint for OPTIC was ≤1% BCR::ABL1^{IS} at 12 months. Overall, 44% of patients achieved ≤1% BCR::ABL^{IS} at 12 months. 56% of patients maintained their response at the reduced dose for at least 1 year.[2,5]

BCR::ABL1^{IS}=BCR::ABL1 International Scale; CP-CML=chronic phase chronic myeloid leukemia; TKI=tyrosine kinase inhibitor.

How do you manage CP-CML after two TKIs when intolerance is limiting response?

IMPORTANT SAFETY INFORMATION (cont'd)

WARNINGS AND PRECAUTIONS (cont'd)

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.

Please see additional Important Safety Information throughout and accompanying full Prescribing Information, including Boxed Warning.

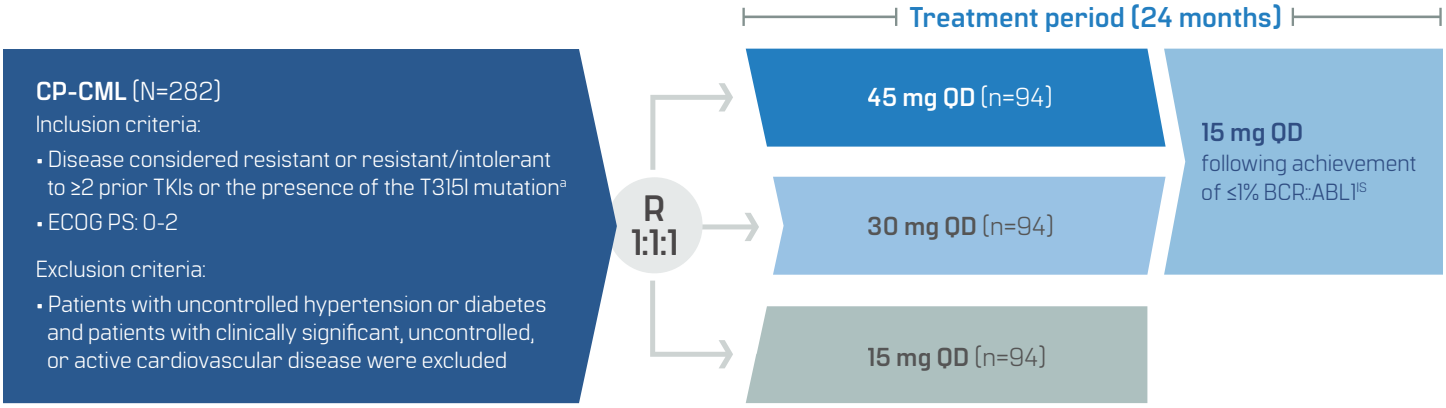
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Study design

OPTIC: A trial built with an optimized dosing strategy to manage tolerability without compromising efficacy[2]

OPTIC is an open-label, multicenter, randomized study that employs a dose-reduction strategy aiming to maximize the benefit of ICLUSIG while helping to mitigate risk in patients with CP-CML who are resistant to at least 2 prior TKIs or have the T315I mutation.

The primary endpoint for OPTIC is ≤1% BCR::ABL1[IS] at 12 months.



The 5-year data provide an update on the long-term efficacy and safety profile of ICLUSIG in this setting and aim to provide more robust data on the best approaches for managing these patients over an extended period of time.

Dose reductions (45 mg QD → 30 mg QD, 30 mg QD → 15 mg QD, and 15 mg QD → 10 mg QD) were permitted in patients who experienced adverse reactions.
[a]Resistance in CP-CML while on a prior TKI therapy was defined as failure to achieve either a CHR (by 3 months), a minor cytogenetic response (by 6 months), a major cytogenetic response (by 12 months), or development of a new BCR::ABL1[IS] kinase domain mutation or new clonal evolution.

BCR::ABL1[IS]=BCR::ABL1 International Scale; CHR=complete hematologic response; CP-CML=chronic phase chronic myeloid leukemia; ECOG PS=Eastern Cooperative Oncology Group performance status; QD=once daily; TKI=tyrosine kinase inhibitor.

IMPORTANT SAFETY INFORMATION (cont'd)

WARNINGS AND PRECAUTIONS (cont'd)

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.

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Primary analysis

ICLUSIG achieved and maintained a clinically meaningful depth of response[2]

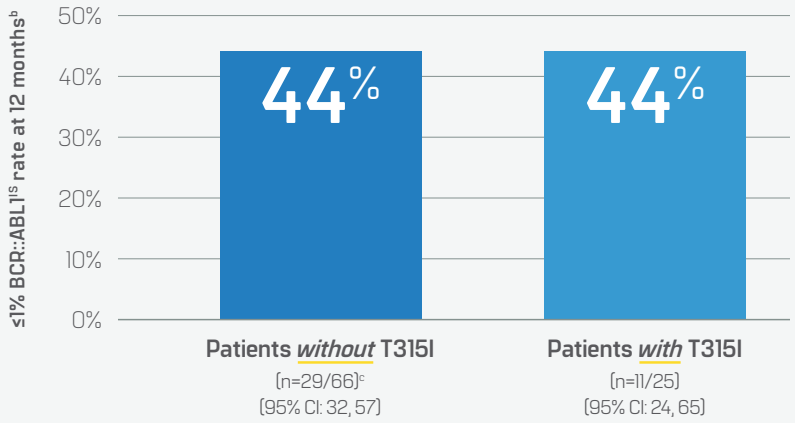
TKI-resistant population

High rate of prior TKI resistance among patients in the 45 mg→15 mg cohort

- **98%** of patients had developed resistance to their prior line of therapy before receiving ICLUSIG[2]
- Only **2%** of patients achieved ≤1% BCR::ABL1^{IS} or better on their last prior therapy[4]

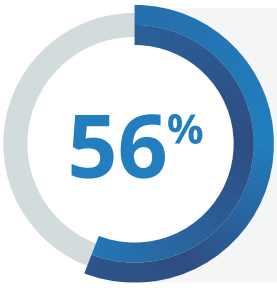
Efficacy regardless of mutation status

Overall, 44% of patients achieved ≤1% BCR::ABL1^{IS} at 12 months (n=41/93)[2,a,b]



- Median duration of follow-up in the 45 mg→15 mg cohort was 27.0 months[2]

Response maintained



25 of the 45[a] patients maintained their response at the reduced dose of 15 mg for at least 1 year, and **64% (16/25) maintained response for greater than 60 months.**[2]

Please see Table 13 in Full Prescribing Information for full demographics including age, disease history, and comorbidities.

[a]ITT population (N=93) defined as patients who had b2a2/b3a2 BCR::ABL1^{IS} (p210) transcripts.
[b]Primary endpoint was ≤1% BCR::ABL1^{IS} rate at 12 months. Defined as a ≤1% ratio of BCR::ABL1^{IS} to ABL transcripts on the International Scale (IS) (ie, ≤1% BCR::ABL1^{IS}; patients must have the b2a2/b3a2 (p210) transcript), in peripheral blood measured by quantitative reverse transcriptase polymerase chain reaction (qRT PCR).
[c]Of the 93 patients, 2 did not have a baseline mutation assessment and were excluded from the response by mutation analysis.
[d]Patients who achieved ≤1% BCR::ABL1^{IS} at any time.
BCR::ABL1^{IS}=BCR::ABL1 International Scale; CI=confidence interval; ITT=intent-to-treat; TKI=tyrosine kinase inhibitor.

IMPORTANT SAFETY INFORMATION (cont'd)

WARNINGS AND PRECAUTIONS (cont'd)

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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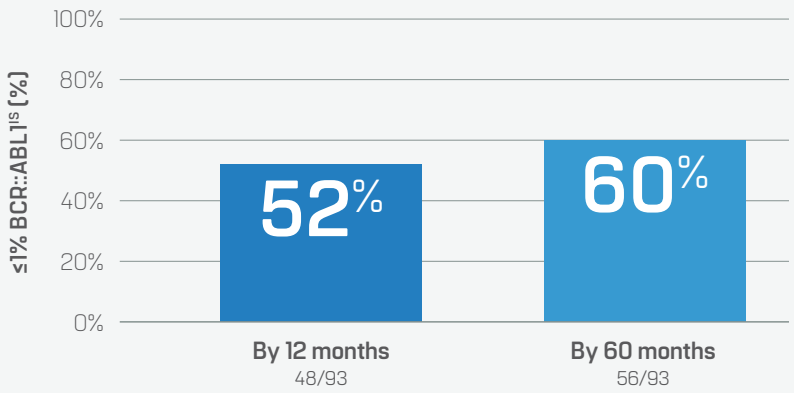
5-year follow-up analysis

Long-term efficacy data: More than half of patients had a response by 5 years in the 45 mg→15 mg cohort[3]

In the 45 mg→15 mg cohort, patients had their dose reduced from 45 mg to 15 mg once response was achieved regardless of amount of time on treatment

Response of patients by 12 months and 60 months in the 45 mg→15 mg cohort receiving ICLUSIG following ≥2 prior TKIs

Percentage of patients who achieved BCR::ABL1^{IS} ≤1%[a-e]



- Median duration of follow-up for the 45 mg cohort was 72.9 months (range: 0.5-106.3 months)

Study Limitations: The OPTIC 5-year follow-up analysis was a planned, exploratory, post hoc analysis. It was not powered to detect differences across subgroups. Results are presented descriptively.

60% (56/93) of patients achieved ≤1% BCR::ABL1^{IS} by 60 months[3]

- In the 45 mg→15 mg cohort, 52% (48/93) of patients achieved ≤1% BCR::ABL1^{IS} by 12 months[6]

[a]Response by each time point means the best outcome up to each time point after randomization.
[b]Analysis conducted in the intent-to-treat population.
[c]Data cutoff date: May 15, 2024.
[d]29% of patients in the 45 mg→15 mg cohort remained on therapy, with a median follow-up of 78 months.
[e]The number of patients with ≤1% BCR::ABL1^{IS} was counted on a cumulative basis by each time point, and a patient with response was counted only once. Percentages are based on the number of patients in each cohort as the denominator.

BCR::ABL1^{IS}=BCR::ABL1 International Scale; TKI=tyrosine kinase inhibitor.

IMPORTANT SAFETY INFORMATION (cont'd)

WARNINGS AND PRECAUTIONS (cont'd)

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.

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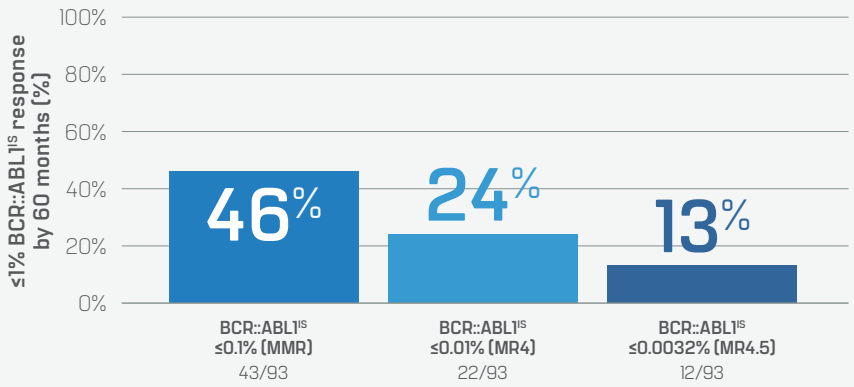
5-year follow-up analysis

Deep, durable efficacy achieved with ICLUSIG[3]

Long-term molecular response by 60 months in the 45 mg⟶15 mg cohort[3]

- As of the 5-year follow-up data cutoff, the median duration of ≤1% BCR::ABL1^{IS} had not been reached
- In the 45 mg⟶15 mg cohort (n=93), 56 patients achieved ≤1% BCR::ABL1^{IS}
  - 45 of the 56 patients had a dose reduction to 15 mg after achieving response
  - 68.9% (n=31) of these patients maintained their response at the time of the 5-year data follow-up cutoff

Depth of response: MMR, MR4, and MR4.5 by 60 months[a,b]



If your patients with CML also have a T315I mutation:

- 64% of patients with T315I mutation achieved BCR::ABL1^{IS} ≤1 by 60 months[2]
- Ponatinib (ICLUSIG) is recommended as a treatment option by the NCCN treatment guidelines for certain patients with T315I mutation[1]

[a]Response by each time point means the best outcome up to each time point after randomization.
[b]Analysis conducted in the intent-to-treat population.

BCR::ABL1^{IS}=BCR::ABL1 International Scale; CML=chronic myeloid leukemia; MMR=major molecular response; MR=molecular response.

IMPORTANT SAFETY INFORMATION (cont'd)

WARNINGS AND PRECAUTIONS (cont'd)

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.

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.

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5-year follow-up analysis

Safety profile with an optimized dosing strategy[2]

Adverse reactions (≥10%) among patients who received ICLUSIG 45 mg→15 mg (n=94)

	All Grades (%)	Grade 3 or 4 (%)
Skin and Subcutaneous Tissue Disorders		
Rash and related conditions	47	3.2
Dry skin	12	0
Vascular Disorders		
Hypertension	37	14
Arterial occlusive events	18	7
Hemorrhage	13	2.1
Hepatobiliary Disorders		
Hepatotoxicity	34	7
Musculoskeletal and Connective Tissue Disorders		
Arthralgia[a]	33	0
Metabolism and Nutrition Disorders		
Hyperlipidemia[b]	32	4.3
Impaired glucose tolerance	10	2.1
Gastrointestinal Disorders		
Abdominal pain[c]	31	3.2
Pancreatitis/lipase elevation	29	16
Constipation	15	0
Cardiac Disorders		
Cardiac arrhythmias	27	5
Cardiac failure	20	2.1
Nervous System Disorders		
Headache	20	0
Neuropathy	13	0
General Disorders and Administration Site Conditions		
Pyrexia	18	1.1
Fatigue or asthenia	18	1.1
Infections and Infestations		
Upper respiratory tract infection	11	0
Respiratory Thoracic and Mediastinal Disorders		
Cough	10	0

Serious adverse reactions occurred in 40% of patients who received ICLUSIG at a starting dose of 45 mg. Serious adverse reactions in >2% of patients, included AOEs (13%; of which 2.1% were sudden death), cardiac arrhythmias (9%; of which, 2.1% were atrial fibrillation), thrombocytopenia (5%), pyrexia (4.3%), anemia (3.2%), abdominal pain (3.2%), pancreatitis/lipase elevation (2.1%), neutropenia (2.1%), hypertension (2.1%), and hepatotoxicity (2.1%). Fatal adverse reactions occurred in 4 patients (4.3%) including sudden death (2.1%), myocardial infarction (1.1%), and myocardial ischemia (1.1%).

- 18% of patients experienced any grade AOEs, of which 11%, 4.3%, and 3.2% experienced cardiovascular, cerebrovascular or peripheral vascular AOEs, respectively
- Grade 3 or 4 AOEs occurred in 7% of patients; the most frequent Grade 3 or 4 AOEs were myocardial infarction, acute coronary syndrome, arterial thrombosis, ischemic stroke, ischemic cerebral infarction, subclavian artery stenosis, and unstable angina (1.1% each)

Permanent discontinuation of ICLUSIG due to an adverse reaction occurred in 24% of patients who received ICLUSIG at a starting dose of 45 mg. Adverse reactions which resulted in permanent discontinuation in >2% of patients included AOEs, thrombocytopenia, hypertension, and sudden death.

Graded using CTCAE v5.0

[a]Arthralgia includes arthralgia, back pain, osteoarthritis, pain, neck pain, pain in extremity, spinal pain, tendonitis, bone pain, musculoskeletal pain, chondrocalcinosis, enthesopathy, pain in jaw.
[b]Hyperlipidemia includes blood cholesterol increased, blood triglycerides increased, dyslipidemia, hypercholesterolemia, hyperlipidemia, hypertriglyceridemia, low density lipoprotein increased.
[c]Abdominal pain includes abdominal distension, abdominal pain, abdominal pain upper, chronic gastritis, duodenal ulcer, duodenitis, duodenogastric reflux, dyspepsia, gastric ulcer, gastritis, gastroenteritis, gastrointestinal pain, helicobacter gastritis, peptic ulcer.

AOE=arterial occlusive event; CTCAE=Common Terminology Criteria for Adverse Events.

IMPORTANT SAFETY INFORMATION (cont'd)

WARNINGS AND PRECAUTIONS (cont'd)

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.

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Important Safety Information (cont'd.)

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.

Please see additional Important Safety Information throughout and accompanying full Prescribing Information, including Boxed Warning.

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