

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

The only 3rd-generation pan-mutational TKI in CML[1-5]

INDICATION

ICLUSIG 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.

TKI=tyrosine kinase inhibitor; CML=chronic myeloid leukemia.

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

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.

TKI resistance is a critical event in the treatment of CP-CML

CCyR rates with back-to-back 2G TKIs are low, particularly for patients with resistance to their last prior therapy[6,7]

≤18% rate of CCyR with a 3L 2G TKI after failure of a prior 2G TKI due to resistance[7-9,a,b]

≥40% of patients with with CP-CML receiving a 2G TKI in 2L experience resistance or intolerance over the course of treatment[10-13,c]

Cycling through 2G TKIs after patients develop resistance to prior therapies is associated with low rates of response[6,7]

Resistance may be due to mutations within the BCR::ABL1 domain[14,15]

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

	Frequency of BCR::ABL1 mutations	Rates of treatment resistance (with or without BCR::ABL1 mutation)
1L	5%-18%[16-18]	16%-40%[15,19]
2L	21%-33%[20-21]	32%-50%[22-24]
3L[d]	23%-43%[25,26,e]	60%[26]

Early identification of resistant mutations is crucial to informing your patient's next line of treatment[27]

- **T315I** is one of the mutations most commonly associated with relapse, the most frequently identified mutation in TKI-resistant patients, and confers complete resistance to first-generation and second-generation TKIs[28,29]

Treatment-resistant patients need a therapy with a high rate of response and durability as their disease progresses[27]

[a]Data are from the Ibrahim et al (N=26), Garg et al (N=48), and García-Gutiérrez et al (N=105) publications. Ibrahim et al analyzed a cohort of patients with CP-CML who failed dasatinib (n=20) or nilotinib (n=6) after imatinib in various phase 2 studies; none of the 7 patients with prior hematologic resistance to TKI therapy achieved CCyR. Garg et al analyzed CML patients (AP, BP, and CP) sequentially treated with 3 different TKIs at MD Anderson Cancer Center; 34 received dasatinib after imatinib and nilotinib failure, and 14 received nilotinib after imatinib and dasatinib failure. Among 25 patients with CP-CML receiving 3L therapy, only 2 of 17 who had failed 2L due to resistance achieved CCyR in 3L. García-Gutiérrez et al identified 105 patients treated with a 2G TKI in 2L after imatinib failure in a Spanish national registry; 17 of 31 patients who started 3L therapy with another TKI did so due to resistance, and the cumulative incidence of CCyR among these patients was 18%.[7-9]

[b]**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.**

[c]Data are from clinical trials of 2L bosutinib (N=46; N=288), nilotinib (N=321), and dasatinib (N=150) in patients with CP-CML who were resistant or intolerant to prior TKI therapy.

[d]Results are primarily from a 3L study with 2G TKI therapy but also included 3 patients taking 4L 2G TKI therapy.

[e]**Approximately two-thirds of patients have not yet mutated.**

1L=first line; 2G=second generation; 2L=second line; 3L=third line; 4L=fourth line; AP=accelerated phase; BP=blast phase; CCyR=complete cytogenetic response; CML=chronic myeloid leukemia; CP=chronic phase; CP-CML=chronic phase chronic myeloid leukemia; TKI=tyrosine kinase inhibitor.

IMPORTANT SAFETY INFORMATION (cont'd)

WARNINGS AND PRECAUTIONS

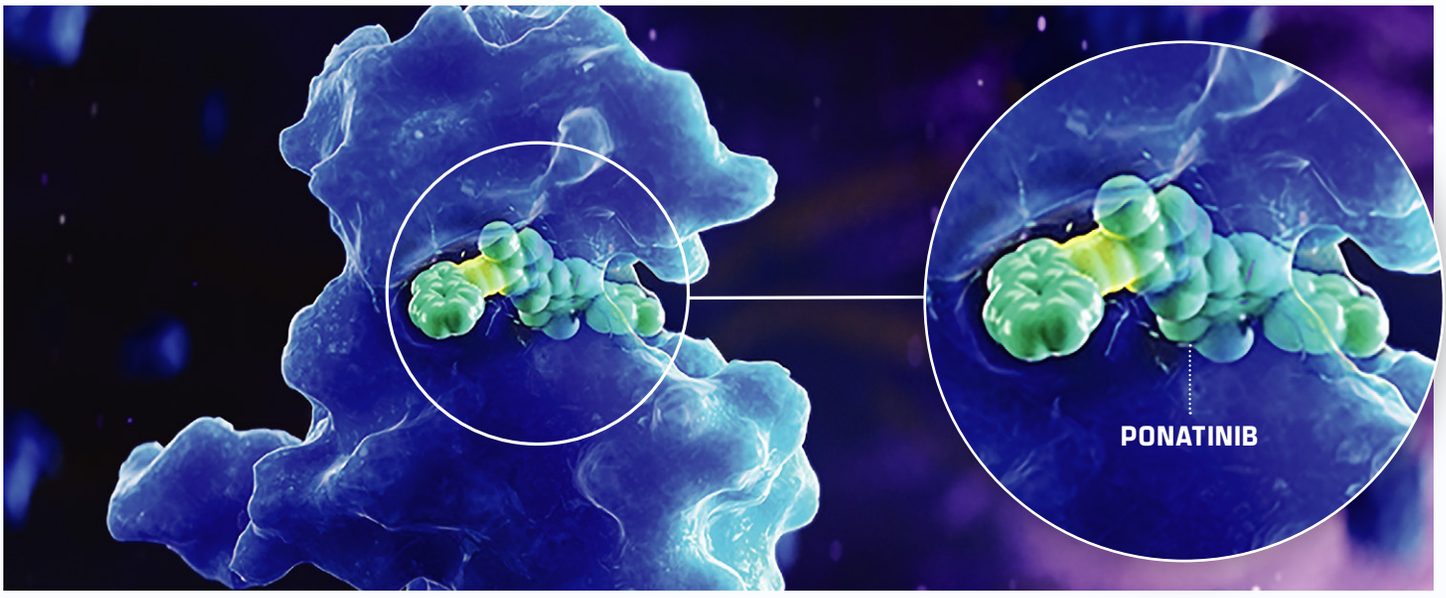
Arterial Occlusive Events (AOEs): AOEs, including fatalities, have occurred in patients who received ICLUSIG. These included cardiovascular, cerebrovascular, and peripheral vascular events, and occurred in patients with and without cardiovascular risk factors. Monitor for evidence of AOEs. Interrupt,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

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.

Consider ICLUSIG, the only pan-mutational inhibitor of BCR::ABL[1,3-6]

3rd-generation TKI

ICLUSIG (ponatinib) is the only 3rd-generation TKI in CML and is purposefully engineered to inhibit BCR::ABL regardless of mutation status[14-16]



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.

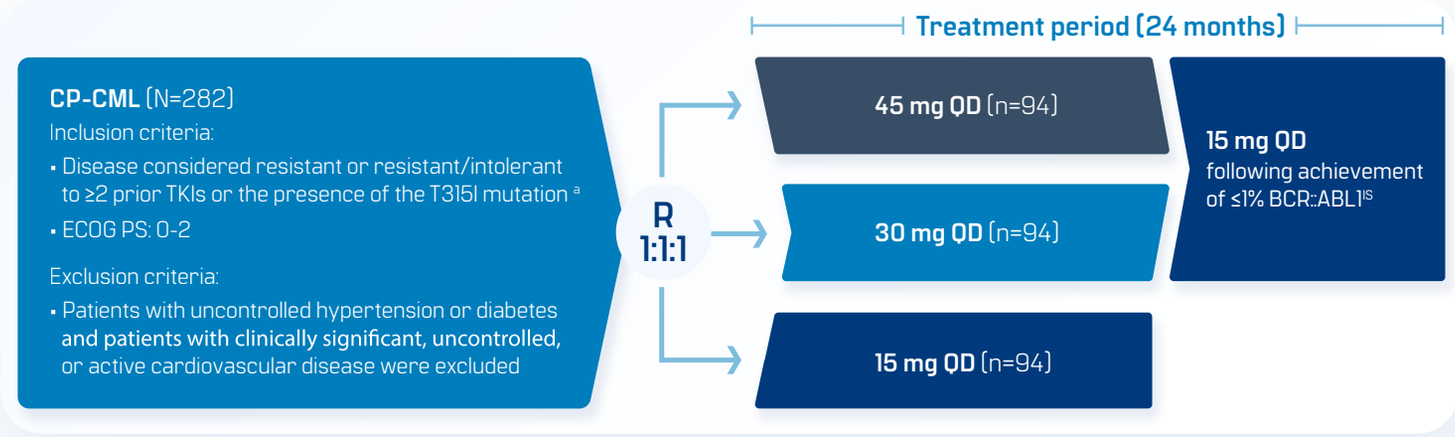
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OPTIC: A trial built with a response-based dosing strategy to manage tolerability without compromising efficacy[1]

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; CI=confidence interval; CP-CML=chronic phase chronic myeloid leukemia; ECOG PS=Eastern Cooperative Oncology Group performance status; ITT=intent-to-treat; QD=once daily; 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.

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.

Primary analysis

ICLUSIG achieved and maintained a clinically meaningful depth of response[1]

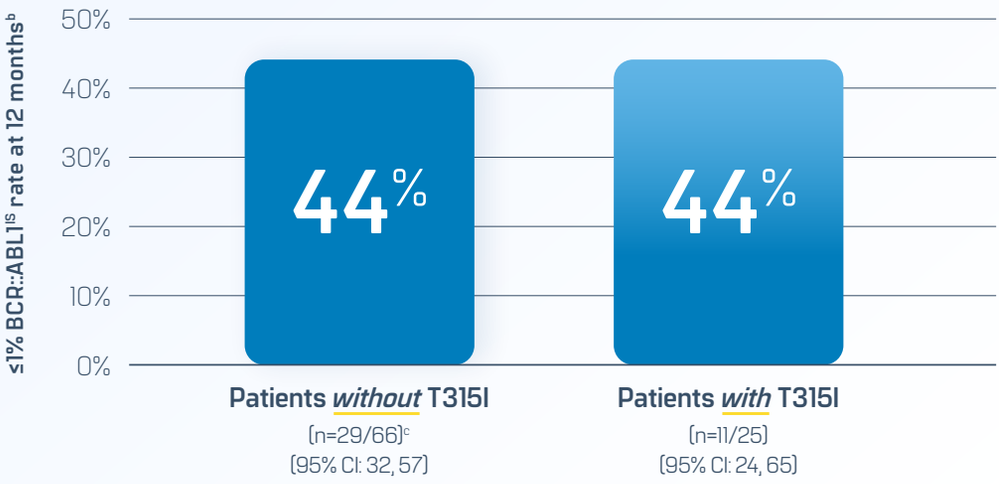
TKI-resistant population

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[1]
- Only **2%** of patients achieved ≤1% BCR::ABL1^{IS} or better on their last prior therapy[3,3]

Efficacy regardless of mutation status

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



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

Response maintained



of patients (n=25/45)[d] maintained their response at the reduced dose for at least 1 year[1]

Of the 25 patients who maintained their response at the reduced dose of 15 mg for at least 1 year, 64% (16/25) maintained response for greater than 60 months[1]

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.

IMPORTANT SAFETY INFORMATION (cont'd)

WARNINGS AND PRECAUTIONS (cont'd)

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.

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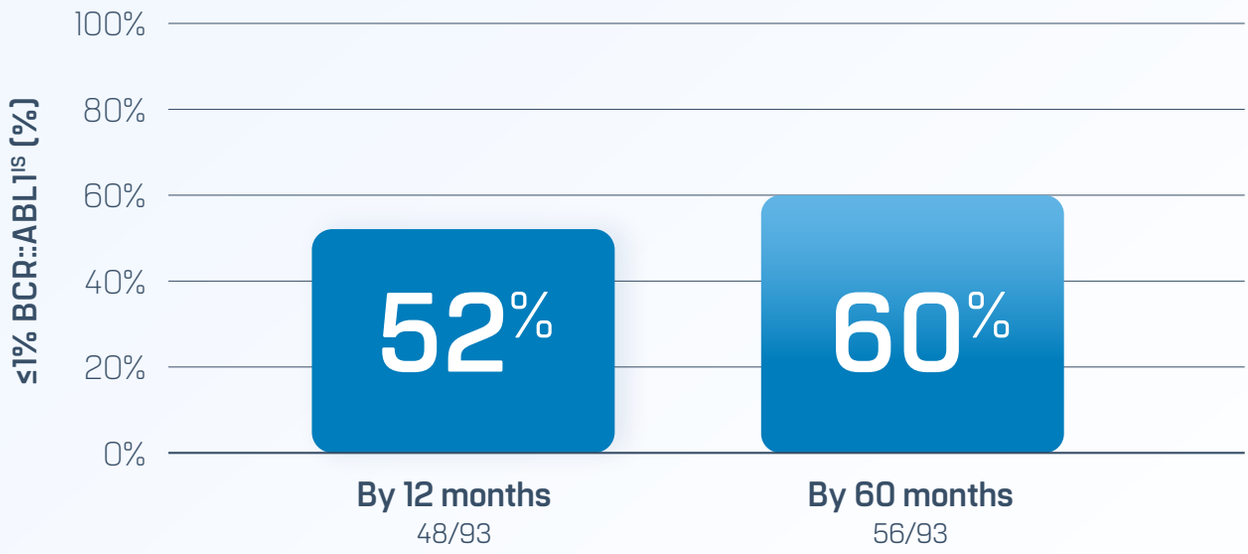
5-year follow-up analysis

Long-term efficacy data: More than half of patients had a response by 5 years in the 45 mg→15 mg cohort[2]

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)

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[33]

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.

[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; CML=chronic myeloid leukemia; MMR=major molecular response; MR=molecular response; TKI=tyrosine kinase inhibitor.

IMPORTANT SAFETY INFORMATION (cont'd)

WARNINGS AND PRECAUTIONS (cont'd)

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.

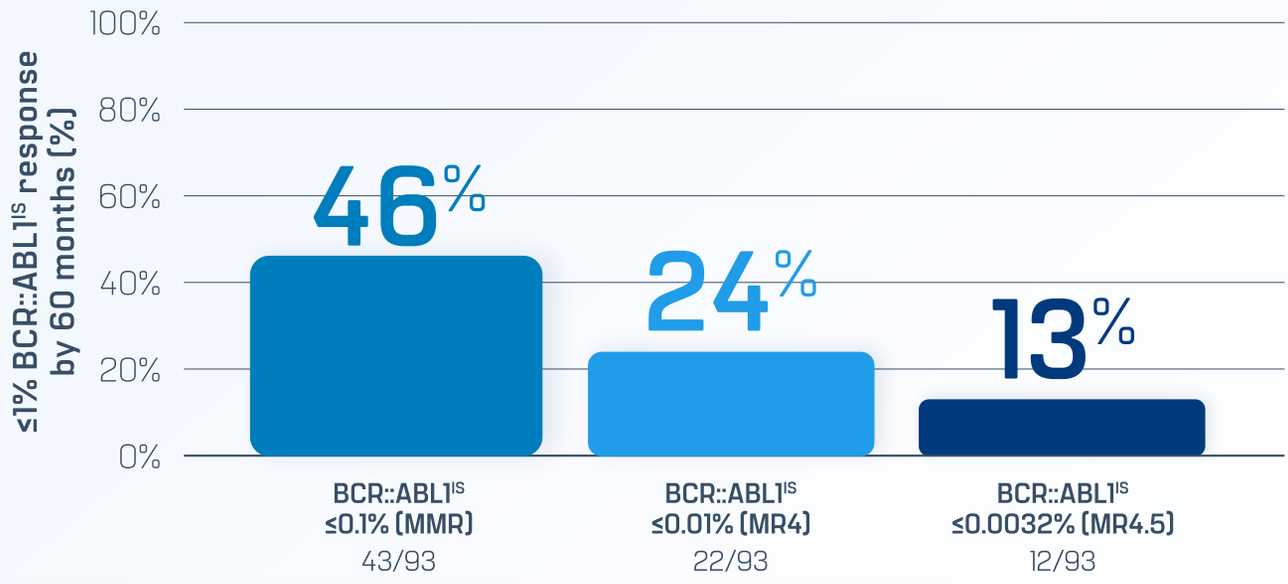
5-year follow-up analysis

Deep, durable efficacy achieved with ICLUSIG[2]

Long-term molecular response by 60 months in the 45 mg →15 mg cohort[2]

- 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[2,a,b]



If your patients with CML also have a T315I mutation:

- 64% of patients with T315I mutation achieved ≤1 BCR::ABL1^{IS} by 60 months[1]
- Ponatinib (ICLUSIG) is recommended as a treatment option by the National Comprehensive Cancer Network® (NCCN®) treatment guidelines for certain patients with T315I mutation[28]

[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; TKI=tyrosine kinase inhibitor.

IMPORTANT SAFETY INFORMATION (cont'd)

WARNINGS AND PRECAUTIONS (cont'd)

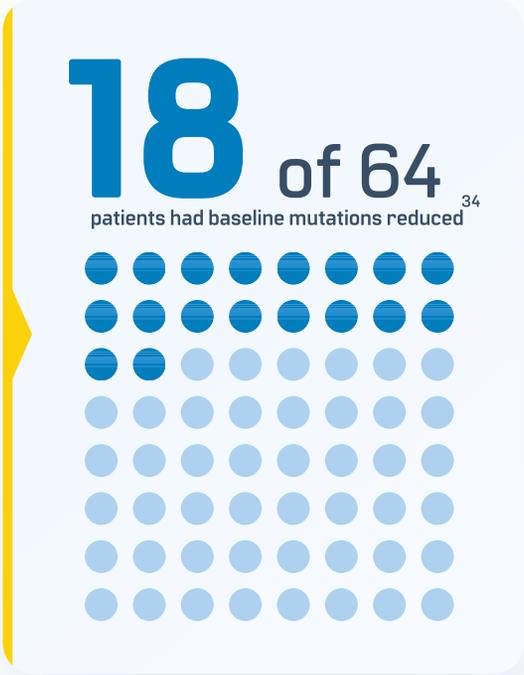
Fluid Retention: Fatal and serious events, including one instance of fatal brain edema and serious events of pleural effusion, pericardial effusion, and angioedema have occurred. The most frequent occurrences of fluid retention in patients who received ICLUSIG were peripheral edema, pleural effusion, 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.

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5-year follow-up analysis

ICLUSIG may reduce detectable pre-existing mutations and inhibit the emergence of new mutations[34]



ICLUSIG may reduce detectable pre-existing mutations[34]

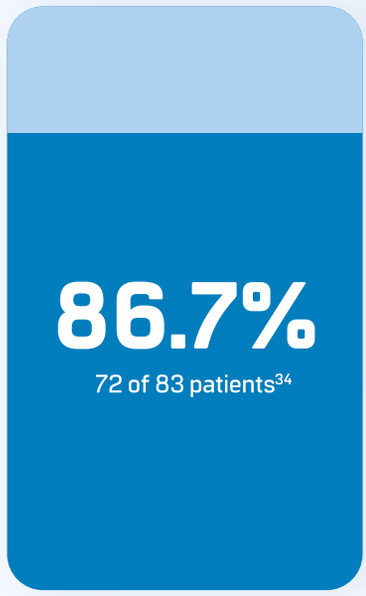
Based on exploratory post-hoc mutation analyses of 144 patients with baseline and end-of-treatment mutation data available from the OPTIC trial. Among 64 patients with ≥1 baseline BCR::ABL1 mutation, 18 patients had baseline mutations reduced below the level of detection and 14 distinct mutations were no longer detectable following ponatinib treatment.[34]

Clinical significance has not been established. No formal statistical testing was conducted for this analysis. Results are presented descriptively.

ICLUSIG may inhibit the emergence of new mutations[34]

Based on an exploratory post-hoc analysis of patients who discontinued treatment due to lack of efficacy or progressive disease and had mutation data available, 72 of 83 patients (86.7%) did not acquire new detectable BCR::ABL1 mutations during ponatinib therapy.[34]

Clinical significance has not been established. No formal statistical testing was conducted for this analysis. Results are presented descriptively.



IMPORTANT SAFETY INFORMATION (cont'd)

WARNINGS AND PRECAUTIONS (cont'd)

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.

5-year follow-up analysis

Safety profile with an optimized dosing strategy[1]

Adverse reactions (≥10%) among patients who received ICLUSIG 45 mg→15 mg in OPTIC (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 or 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

Graded using CTCAE v5.0.

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)

Of the 94 patients who received a starting dose of 45 mg, 2 patients experienced a VTE (Grade 1 retinal vein occlusion and grade 2 phlebitis).

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.

[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; AP-CML=accelerated phase chronic myeloid leukemia; BCR::ABL1^{IS}=BCR::ABL1 International Scale; BP-CML=blast phase chronic myeloid leukemia; CP-CML=chronic phase chronic myeloid leukemia; CTCAE=Common Terminology Criteria for Adverse Events. VTE= Venous Thromboembolic Events

IMPORTANT SAFETY INFORMATION (cont'd)

WARNINGS AND PRECAUTIONS (cont'd)

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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ICLUSIG response-based dosing: The path to maximize efficacy and manage tolerability[1,33]

45 mg→15 mg for patients who achieve ≤1% BCR::ABL1[IS]

The OPTIC trial established an optimized dosing strategy in CP-CML.

START with 45 mg

Start at 45 mg to establish efficacy

- Start at 30 mg orally once daily in patients taking strong CYP3A inhibitors and in patients with pre-existing hepatic impairment (Child-Pugh A, B, or C)

REDUCE to 15 mg to manage tolerability

Reduce the dose to 15 mg orally once daily after ≤1% BCR::ABL1[IS] is achieved

- In the OPTIC trial, of the 93 patients who received ICLUSIG 45 mg→15 mg, 52 achieved ≤1% BCR::ABL1/ABL1[IS] at any time
- Consider discontinuing ICLUSIG if hematologic response has not occurred by 3 months

MAINTAIN on 15 mg for as long as response is maintained

Patients can continue with the 15-mg, once-daily dose of ICLUSIG for as long as they maintain response

- Patients who lose response can have their dose re-escalated to a previously tolerated dosage of 30 mg or 45 mg orally once daily
- Of the 52 patients who achieved ≤1% BCR::ABL1[IS] at any time, 13 patients lost response and had their dose re-escalated
  - 62% of these patients (n=8/13) regained response following dose re-escalation
- Patients taking 15 mg orally once daily who experience an adverse reaction can have their dose reduced to 10 mg orally once daily once the adverse reaction resolves

ICLUSIG **One pill | Once a day | With or without food**

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Coverage, Access, and Support Resources Are Available for Your Patient with CML

Takeda Oncology Here2Assist®

We're here to help your patients with their coverage, financial, and educational resource needs.

Access support

Our Case Managers can work with your patients' insurance companies to conduct benefits verifications* and create a summary of coverage options for each enrolled patient.**

Financial assistance

Takeda Oncology Here2Assist® can help identify financial assistance programs that may be able to help your patients with the cost of their Takeda Oncology treatment.

Helpful resources

Takeda Oncology Here2Assist® Case Managers are here to address your patients' day-to-day treatment questions and provide resources and information about additional support.

*Verification of benefits is not a guarantee of payment and does not take the place of written policy information. Healthcare providers should carry out their own benefits investigation, as necessary.
**Please view the Here2Assist Terms and Conditions below.

Enrolling your patients with CML is simple

Takeda Oncology Here2Assist® enrollment can be completed online or by downloading and printing the Enrollment Form to fill out with your patient.

To enroll online, visit www.Here2Assist.com/hcp/getting-started and click "Enroll Online." Here's what you need to know:

1. **Ensure you have all necessary materials ready before you begin the enrollment process to avoid any inconvenience**
   – To enroll a new patient, you will need patient and/or care partner information, insurance details, and prescription information, including pharmacy preference (ie, specialty pharmacy or in-office dispensing)
2. **Review to ensure the accuracy of all supplied information**
3. **Notify your patient they will need to complete the consent portion on the Takeda Oncology Here2Assist website**
4. **Complete the attestation form**

Or enroll by filling out this form together with your patient using the instructions below:

1. **DOWNLOAD** and print the Takeda Oncology Here2Assist Enrollment Form from www.Here2Assist.com
2. **COMPLETE** and sign the Enrollment Form together with your patient
3. **FAX** the completed Enrollment Form and a copy of your patient's insurance card and prescription to 1-844-269-3038

Alternatively, your patient can now initiate enrollment digitally. If your patient has submitted a digital enrollment, you will be notified and asked to complete the form via fax or email.

****By enrolling in the Takeda Oncology Co-Pay Assistance Program (the "Program"), you acknowledge that you currently meet the eligibility criteria and will comply with the following terms and conditions:** You must be at least 18 years old, a resident of the United States or a US Territory, and have commercial (private) prescription insurance that does not cover the entire cost of the medication. The Program is not valid for patients who are enrolled in any state or federal government program, including, but not limited to, Medicare, Medicare Advantage, Medigap, Medicaid, Department of Defense (DoD), Veterans Affairs (VA), TRICARE, Puerto Rico Government Insurance, or any state patient or pharmaceutical assistance program. Patients who become eligible for or start using government insurance will no longer be eligible for the Program. The Program is not valid if the entire cost of your prescription is reimbursable by a private insurance plan or other private health or pharmacy benefit programs. You are responsible for reporting receipt of Program assistance to any insurer, health plan, or other third party who pays for or reimburses any part of the medication cost, as may be required. You agree that you will not submit the cost of any portion of the product dispensed pursuant to this Program to a federal or state healthcare program (including, but not limited to, Medicare, Medicare Advantage, Medicaid, TRICARE, VA, DOD, etc.), for purposes of counting it toward your out-of-pocket expenses, and to notify Takeda Oncology Here2Assist® if you become eligible for a federal or state healthcare program. This Program is not conditioned on any past, present or future purchase of any Takeda product, including refills. This Program is valid for 12 months, and your co-pay card may be renewed every 12 months, subject to continued eligibility. This offer is not valid with any other program, discount, or offer involving your prescribed Takeda Oncology medication. This offer may be rescinded, revoked, or amended without notice. No reproductions. This offer is void where prohibited by law, taxed, or restricted. Limit one offer per purchase. No income requirements or membership fees. This Program is not health insurance. Cash value of 1/100 of 1¢. For questions about this offer, please contact the Takeda Oncology Co-Pay Assistance Program, a patient support service of Takeda Oncology Here2Assist, at 1-844-817-6468, Option 2, Monday-Friday, 8AM-8PM ET.

Physician Instructions: To use this offer, your patient needs one prescription for a 1-month supply of his or her Takeda Oncology medication. Pharmacy Instructions: By submitting this offer for reimbursement to McKesson, you certify that: (1) you have dispensed the prescribed medication to an eligible patient in accordance with the Eligibility Requirements of this offer and the accompanying prescription; (2) you have not submitted and will not submit a claim for reimbursement for the portion of the drug covered by this coupon to any payer; and (3) your participation in this program is consistent with all applicable laws and any obligations, contractual or otherwise, that you may have as a pharmacy provider. For questions about processing this card, please call the McKesson Customer Service Center at 1-855-902-6725, Monday-Friday, 8AM-8PM ET.

IT'S TIME **TO REIMAGINE** CML TREATMENT **WITH ICLUSIG**

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IMPORTANT SAFETY INFORMATION (cont'd)

WARNINGS AND PRECAUTIONS (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 arrythmias. 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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ICLUSIG® (ponatinib) tablets
45mg / 30mg / 15mg / 10mg