T315I is the most common mutation in TKI-resistant CML[1-3]

Among patients with a BCR::ABL1 mutation, the frequency of the T315I mutation was 10-27%.[2,4-6,a]

Reviews of the clinical literature showed that:

- Development of the T315I mutation leads to resistance with first- or second-generation TKIs[1,7]
- BCR::ABL1 mutation testing helps inform TKI treatment choice[7,8]

Prior to the approval of therapies in T315I+ CML, the overall survival of T315I+ CML patients at 5 years was 0-30%[1,9,b]

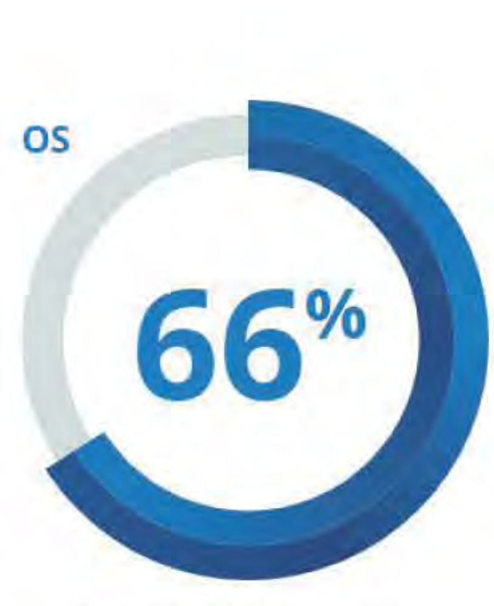
[a] The frequency of the T315I mutation was 10% in the Qin et al (n=7/74), 27% in the Lewandowski et al (n=3/11), and 12% in the Soverini et al (n=15/127) publications.[4-6]

[b] Data from two studies. Nicolini, 2013 (n=64) measured 5-year OS from the time of imatinib resistance and Nicolini, 2009 (n=82) measured 5-year OS from the time of T315I mutation detection.[1,9]

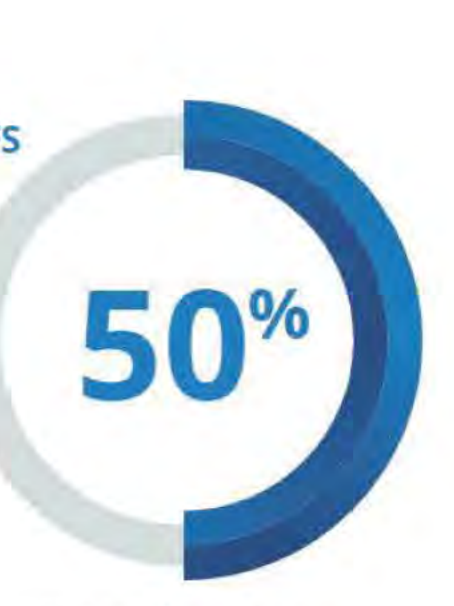
ICLUSIG is the only third-generation pan-mutational TKI that delivers proven long-term efficacy for patients with a T315I mutation[10-12]

NCCN CATEGORY 2A PREFERRED RECOMMENDATION

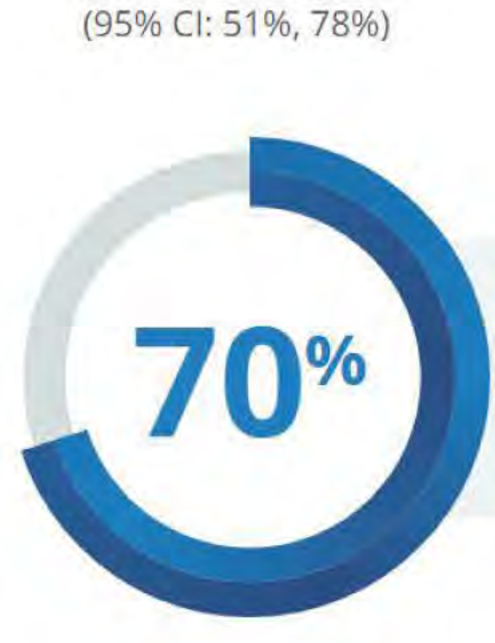
Ponatinib is the preferred treatment option for patients with a T315I mutation in any phase. It is also a treatment option for CP-CML with resistance or intolerance to at least two prior TKIs, or for patients with AP-CML or BP-CML for whom no other TKI is indicated.[7]



estimated at 5 years
(95% CI: 51%, 78%)



estimated at 5 years
(95% CI: 32%, 65%)



of CP-CML patients with a T315I mutation in the PACE trial (n=64) achieved MCyR, and responses were deep and durable[12]

PACE trial design

PACE was a single-arm, open-label, international, multicenter, phase 2 trial in adult CML or Ph+ ALL patients whose disease was considered to be resistant or intolerant to a prior kinase inhibitor or who had T315I mutation (N=449; n=64 T315I-positive CML). At study completion, the mediation duration of follow-up for the trial (all cohorts) was 40.5 months (range 0.1 months to 79.5 months). The major efficacy outcome measure (primary endpoint) for patients with CP-CML was MCyR by 12 months, which included CCyR and PCyR.[11,12]

ICLUSIG 5-year safety data in CP-CML

Discover CP-CML PACE data

ICLUSIG simple once-daily oral dosing

Learn about ICLUSIG dosing

CCyR=complete cytogenetic response; CML=chronic myeloid leukemia; CP-CML=chronic phase chronic myeloid leukemia; MCyR=major cytogenetic response; NCCN=National Comprehensive Cancer Network® (NCCN®); OS=overall survival; PCyR= partial cytogenetic response; Ph+ ALL= Philadelphia chromosome-positive acute lymphoblastic leukemia; TKI=tyrosine kinase inhibitor.

INDICATIONS AND USAGE

ICLUSIG is indicated for the treatment of adult patients with:

Philadelphia Chromosome-Positive Acute Lymphoblastic Leukemia (Ph+ ALL)

- Newly diagnosed Ph+ ALL in combination with chemotherapy.
  This indication is approved under accelerated approval based on minimal residual disease (MRD)-negative complete remission (CR) at the end of induction. Continued approval for this indication may be contingent upon verification of clinical benefit in a confirmatory trial(s).
- As monotherapy in Ph+ ALL for whom no other kinase inhibitors are indicated or T315I-positive Ph+ ALL.

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.**

WARNINGS AND PRECAUTIONS

Arterial Occlusive Events (AOEs): AOEs, including fatalities, have occurred in patients who received ICLUSIG in PhALLCON, OPTIC and PACE. These included cardiovascular, cerebrovascular, and peripheral vascular events. In PhALLCON, 6% of 163 patients experienced AOEs; 3.7% experienced Grade 3 or 4. The incidence of AOEs in OPTIC (45 mg → 15 mg) was 14% of 94 patients; 6% experienced Grade 3 or 4. In PACE, the incidence of AOEs was 26% of 449 patients; 14% experienced Grade 3 or 4. Fatal AOEs occurred in 0.6% of patients in PhALLCON, 2.1% of patients in OPTIC, and in 2% of patients in PACE. Some patients in PACE experienced recurrent or multisite vascular occlusion. Patients with and without cardiovascular risk factors, including patients age 50 years or younger, experienced these events. The most common risk factors observed with these events in PACE were history of hypertension, hypercholesterolemia, and non-ischemic cardiac disease. In PhALLCON, OPTIC and PACE, AOEs were more frequent with increasing age.

In PhALLCON, patients with uncontrolled hypertension, hypertriglyceridemia, or diabetes were excluded. Patients with clinically significant, uncontrolled, or active cardiovascular disease, including any history of myocardial infarction, peripheral vascular infarction, revascularization procedure, venous thromboembolism, clinically significant atrial/ventricular tachyarrhythmias, unstable angina, or congestive heart failure within the 6 months prior to the first dose of ICLUSIG, were also excluded.

In OPTIC, patients with uncontrolled hypertension or diabetes and patients with clinically significant, uncontrolled, or active cardiovascular disease were excluded.

In PACE, patients with uncontrolled hypertriglyceridemia and patients with clinically significant or active cardiovascular disease within the 3 months prior to the first dose of ICLUSIG were excluded.

Consider whether the benefits of ICLUSIG are expected to exceed the risks. Monitor for evidence of AOEs. Interrupt, then resume at the same or decreased dose or discontinue ICLUSIG based on recurrence/severity. Consider benefit-risk to guide a decision to restart ICLUSIG.

Venous Thromboembolic Events (VTEs): Serious or severe VTEs have occurred in patients who received ICLUSIG. In PhALLCON, VTEs occurred in 12% of 163 patients, including serious or severe (Grade 3 or 4) in 3.1% of patients. One of 94 patients in OPTIC experienced a VTE (Grade 1 retinal vein occlusion). In PACE, VTEs occurred in 6% of 449 patients including serious or severe (Grade 3 or 4) VTEs in 5.8% of patients. In PhALLCON and PACE VTEs included deep venous thrombosis, embolism, pulmonary embolism, superficial vein thrombosis, thrombosis, jugular vein thrombosis, superficial thrombophlebitis, retinal vein occlusion, and retinal vein thrombosis with vision loss. The incidence of VTEs in PACE was higher in patients with Ph+ ALL (9% of 32 patients) and BP-CML (10% of 62 patients). 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 in patients who received ICLUSIG. In PhALLCON, heart failure occurred in 6% of 163 patients; 1.2% experienced serious or severe (Grade 3 or 4) heart failure. Heart failure occurred in 13% of 94 patients in OPTIC; 1.1% experienced serious or severe (Grade 3 or 4). In PACE, heart failure occurred in 9% of 449 patients; 7% experienced serious or severe (Grade 3 or higher). In PhALLCON the most frequently reported heart failure event (>1 patient) was increased brain natriuretic peptide (BNP) (2.5%). In OPTIC, the most frequently reported heart failure events (>1 patient each) were left ventricular hypertrophy (3.2%) and BNP increased (3.2%). In PACE, the most frequently reported heart failure events (≥2%) were congestive cardiac failure (3.1%), decreased ejection fraction (2.9%), and cardiac failure (2%). Monitor patients for signs or symptoms consistent with heart failure and manage heart failure 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 occurred in 3 patients, with hepatic failure occurring within 1 week of starting ICLUSIG in one of these patients. These fatal cases occurred in patients with BP-CML or Ph+ ALL treated with monotherapy. Hepatotoxicity occurred in 66% of 163 patients in PhALLCON, in 28% of 94 patients in OPTIC and in 32% of 449 patients in PACE. Grade 3 or 4 hepatotoxicity occurred in PhALLCON (30% of 163 patients), in OPTIC (6% of 94 patients), and in PACE (13% of 449 patients). The most frequent hepatotoxic events were elevations of ALT, AST, GGT, bilirubin, and alkaline phosphatase. 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 in patients who received ICLUSIG. Patients may require urgent clinical intervention for hypertension associated with confusion, headache, chest pain, or shortness of breath. Monitor blood pressure at baseline and as clinically indicated and manage hypertension as clinically indicated. Interrupt, dose reduce, or stop 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 in patients who received ICLUSIG. 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 thereafter 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 45 mg once daily increased the risk of serious adverse reactions 2-fold compared to single agent imatinib 400 mg once daily. The median exposure to treatment was less than 6 months. The trial was halted for safety. Arterial and venous thrombosis and occlusions occurred at least twice as frequently in the ICLUSIG arm compared to the imatinib arm. Compared to imatinib-treated patients, ICLUSIG-treated patients exhibited a greater incidence of myelosuppression, pancreatitis, hepatotoxicity, cardiac failure, hypertension, and skin and subcutaneous tissue disorders. 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 patients in PhALLCON, OPTIC and PACE. Some of these events in PhALLCON and PACE were Grade 3 or 4. Monitor patients for symptoms of neuropathy, 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 toxicity leading to blindness or blurred vision have occurred in ICLUSIG-treated patients. The most frequent ocular toxicities occurring in PhALLCON, OPTIC and PACE were dry eye, blurred vision, and eye pain. Retinal toxicities included age-related macular degeneration, macular edema, retinal vein occlusion, retinal hemorrhage, and vitreous floaters. Conduct comprehensive eye exams at baseline and periodically during treatment.

Hemorrhage: Fatal and serious hemorrhage events have occurred in patients who received ICLUSIG. Fatal hemorrhages occurred in PACE and serious hemorrhages occurred in PhALLCON, OPTIC and PACE. In PACE, the incidence of serious bleeding events was higher in patients with AP-CML, BP-CML, and Ph+ ALL. Intracranial hemorrhage, gastrointestinal hemorrhage and subdural hematoma were the most frequently reported serious hemorrhages. Events often occurred in patients with Grade 4 thrombocytopenia. Monitor for hemorrhage and manage patients as clinically indicated. Interrupt, then resume at the same or reduced dose or discontinue ICLUSIG based on recurrence/severity.

Fluid Retention: Fatal and serious fluid retention events have occurred in patients who received ICLUSIG. In PACE, one instance of brain edema was fatal and serious events included pleural effusion, pericardial effusion, and angioedema. In PhALLCON serious fluid retention included pericardial effusion. The most frequent occurrences of fluid retention in patients who received ICLUSIG were peripheral edema and pleural effusion. Monitor for fluid retention and manage patients 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, atrial arrhythmias, tachycardia, syncope, atrial fibrillation and supraventricular tachycardia occurred in patients in PhALLCON, OPTIC, and PACE. For some patients, events were serious or severe (Grade 3 or 4) and led 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 events of neutropenia, thrombocytopenia, and anemia occurred in patients in PhALLCON, OPTIC and PACE. In PACE, the incidence of myelosuppression was greater in patients with AP-CML, BP-CML, and Ph+ ALL treated with monotherapy than in patients with CP-CML. Obtain complete blood counts every 2 weeks for the first 3 months and then monthly or as clinically indicated. If ANC less than 1 x 10⁹/L or platelets less than 50 x 10⁹/L, interrupt ICLUSIG until ANC at least 1.5 x 10⁹/L and platelets at least 75 x 10⁹/L, then resume at same or reduced dose.

Tumor Lysis Syndrome (TLS): Serious TLS was reported in ICLUSIG-treated patients in PhALLCON, OPTIC and PACE. Ensure adequate hydration and treat high uric acid levels prior to initiating ICLUSIG.

Reversible Posterior Leukoencephalopathy Syndrome (RPLS): RPLS (also known as Posterior Reversible Encephalopathy Syndrome) has been reported in patients who received ICLUSIG. Patients may present with neurological signs and symptoms, visual disturbances, and hypertension. Diagnosis is made with supportive findings on magnetic resonance imaging (MRI) of the brain. Interrupt ICLUSIG until resolution. The safety of resumption of ICLUSIG in patients 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 prior to elective surgery. Do not administer for at least 2 weeks following major surgery and until adequate wound healing. The safety of resumption of ICLUSIG after resolution of wound healing complications has not been established. Gastrointestinal perforation or fistula occurred in patients receiving ICLUSIG. Permanently discontinue in patients with gastrointestinal perforation.

Embryo-Fetal Toxicity: Based on its mechanism of action and findings from animal studies, ICLUSIG can cause fetal harm when administered to a pregnant woman. Advise pregnant women of the potential risk to the fetus. Advise females of reproductive potential to 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, headache, constipation, dry skin, hypertension, fatigue, fluid retention and edema, pyrexia, nausea, pancreatitis/lipase elevation, hemorrhage, anemia, hepatic dysfunction and AOEs. 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: hepatic dysfunction, 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 1-844-217-6468 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 30mg orally once daily for patients with pre-existing hepatic impairment as these patients are more likely to experience adverse reactions compared to patients with normal hepatic function. For patients with newly diagnosed Ph+ ALL, no dosage adjustment is recommended.

Please see full Prescribing Information, including Boxed Warning.

SHOW REFERENCES

References: **1.** Nicolini FE, Ibrahim AR, Soverini S, et al. *Haematologica.* 2013;98(10):1510-1516. **2.** Soverini S, Branford S, Nicolini FE, et al. *Leuk Res.* 2014;38(1):10-20. **3.** Ursan ID, Jiang R, Pickard EM, Lee TA, Ng D, Pickard AS. *J Manag Care Spec Pharm.* **4.** Qin Y, Chen S, Jiang B, et al. *Ann Hematol.* 2011;90:47–52. **5.** Lewandowski K, Warzocha K, Hellmann A, et al. *Pol Arch Med Wewn.* 2009;119:789–794. **6.** Soverini S, Colarossi S, Gnani A, Rosti G, et al. *Clin Cancer Res.* 2006;12:7374–7379. **7.** Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Chronic Myeloid Leukemia V.2.2024. © National Comprehensive Cancer Network, Inc. 2024. All rights reserved. Accessed March 7, 2024. To view the most recent and complete version of the guideline, go online to NCCN.org. NCCN makes no warranties of any kind whatsoever regarding their content, use or application and disclaims any responsibility for their application or use in any way. **8.** Soverini S, De Benedittis C, Mancini M, Martinelli G. *Oncologist.* 2016;21(5):626-633. **9.** Nicolini FE, Mauro MJ, Martinelli G, et al. *Blood.* 2009;114(26):5271-5278. **10.** Deininger MW, Hodgson JG, Shah NP, et al. *Blood.* 2016;127(6):703-712. **11.** Cortes JE, Kim D-W, Pinilla-Ibarz J, et al. *Blood.* 2018;132(4):393-404. **12.** ICLUSIG. Prescribing information. Takeda Pharmaceuticals U.S.A. Inc. 03/2024.

09/24 USO-ICL-0558

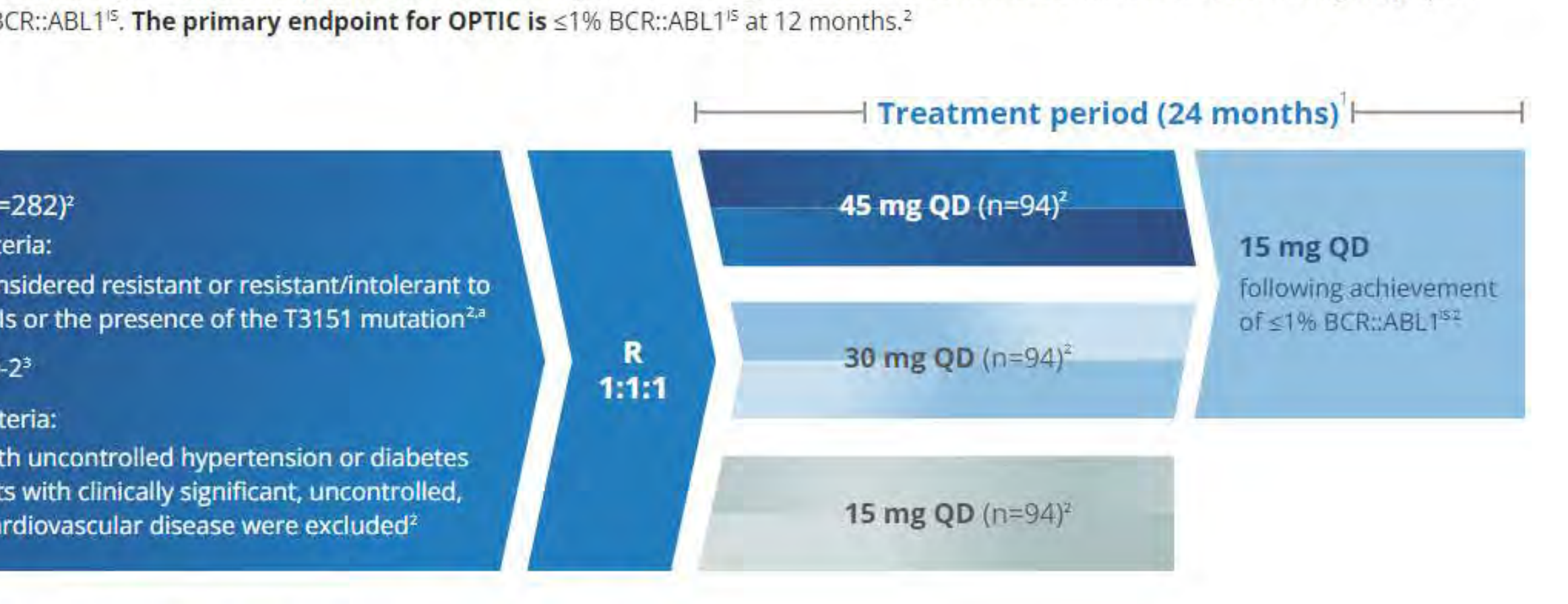
OPTIC trial: Optimize ICLUSIG (ponatinib) efficacy with a response-based dosing strategy[1]

ICLUSIG achieved and maintained a clinically meaningful depth of response with a 45 mg → 15 mg dose reduction upon achievement of ≤1% BCR::ABL1^{IS} in patients with CP-CML[1]

Trial design | Response-based dosing strategy | Response rates | Estimated OS/PFS

OPTIC TRIAL DESIGN: Utilizing a response-based dosing strategy with ICLUSIG

OPTIC is an ongoing, 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 patients 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. Patients in cohorts 1 and 2 were reduced to 15 mg daily upon achievement of ≤1% BCR::ABL1^{IS}. **The primary endpoint for OPTIC is** ≤1% BCR::ABL1^{IS} at 12 months.[2]


Treatment period (24 months)[1]

CP-CML (N=282)[2]

Inclusion criteria:
- Disease considered resistant or resistant/intolerant to ≥2 prior TKIs or the presence of the T315I mutation[2,a]
- ECOG PS: 0-2[3]

Exclusion criteria:
- Patients with uncontrolled hypertension or diabetes and patients with clinically significant, uncontrolled, or active cardiovascular disease were excluded[2]

Dose reductions were utilized in response to adverse reactions.[1]
Patients receiving 15 mg had their dose reduced to 10 mg QD.[2]

[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), or a major cytogenetic response (by 12 months), or development of a new BCR::ABL1 kinase domain mutation or new clonal evolution.

PATIENT CHARACTERISTICS REVEAL HIGH TKI RESISTANCE AND MUTATIONS

Demographic and disease characteristics in OPTIC[1,2]

Patient Characteristics at Entry	ICLUSIG 45 mg→15 mg (n=94)
Age	
Median years (range)	46 (19–81)
Sex, n (%)	
Male	50 (53%)
Race, n (%)	
White	73 (78%)
Asian	16 (17%)
Black or African American	1 (1%)
Other/Unknown	4 (4%)
ECOG performance status, n (%)	
ECOG 0 or 1	93 (99%)
Disease history	
Median time from diagnosis to first dose, years (range)	5.5 (1 to 21)
Resistant to prior kinase inhibitors, n (%)	92 (98%)
Presence of one or more BCR-ABL kinase domain mutations, n (%)	41 (44%)
Number of prior kinase inhibitors, n (%)	
1	1 (1%)
2	43 (46%)
≥3	50 (53%)
T315I mutation at baseline	25 (27%)
Comorbidities	
Hypertension	29 (31%)
Diabetes	5 (5%)
Hypercholesterolemia	3 (3%)
History of ischemic heart disease	3 (3%)
Best response to last prior therapy, n (%)	
≤1% BCR::ABL1^{IS} or better[c]	2 (2%)

98% of participants were resistant to their prior therapy[2]

99% were heavily pretreated with TKIs[2]

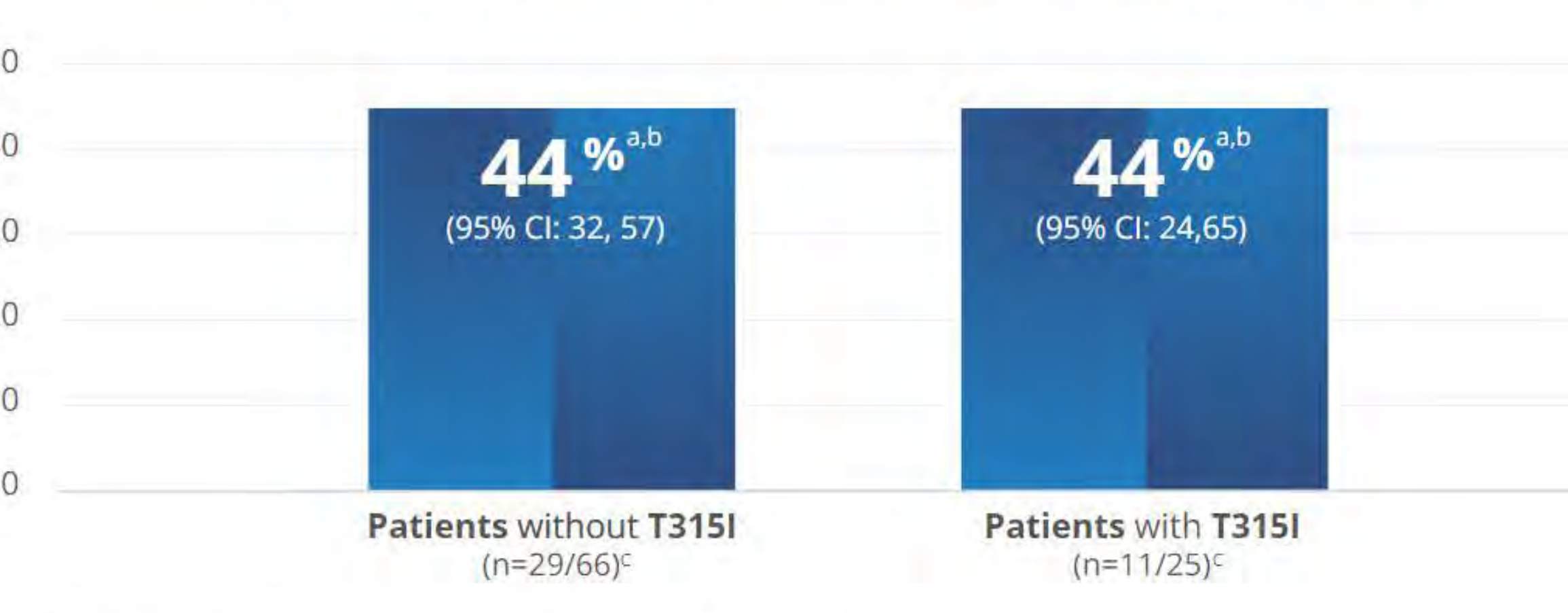
44% of participants had mutations in BCR::ABL[2]

ICLUSIG 45 mg → 15 mg: The path to maximizing benefit and mitigating risk[1]

ICLUSIG demonstrated response rates (≤1% BCR::ABL1^{IS}) at 12 months, irrespective of mutation status[2]

Results from OPTIC demonstrate a benefit in a highly-resistant CP-CML population across dosing cohorts. However, optimal benefit:risk outcomes occurred in the cohort with a 45 mg starting dose that reduced to 15 mg upon achievement of ≤1% BCR::ABL1^{IS}.[1] The recommended starting dose is 45 mg orally once daily with a reduction to 15 mg orally once daily upon achievement of ≤1% BCR::ABL1^{IS}. Patients with loss of response can re-escalate the dose of ICLUSIG to a previously tolerated dose of 30 mg or 45 mg orally once daily.[2]

Patients with ≤1% BCR::ABL1^{IS} at 12 months[2] (primary endpoint)



[a] ITT population (N=93) defined as patients who had b2a2/b3a2 BCR::ABL1 transcripts.[2]
[b] The primary endpoint was ≤1% BCR::ABL1^{IS} rate at 12 months. Defined as a ≤1% ratio of BCR::ABL1 to ABL transcripts on the International Scale (ie, ≤1% BCR::ABL1^{IS}); patients must have the b2a2/b3a2 (p210) transcript), in peripheral blood measured by qRT PCR.[2]
[c] Of the 93 patients, 2 did not have a baseline mutation assessment and were excluded from the response by mutation analysis.[2]

Discover response-based dosing in CP-CML ›

DURABLE RESPONSE WAS OBSERVED AT A REDUCED DOSE OF 15 mg[2]

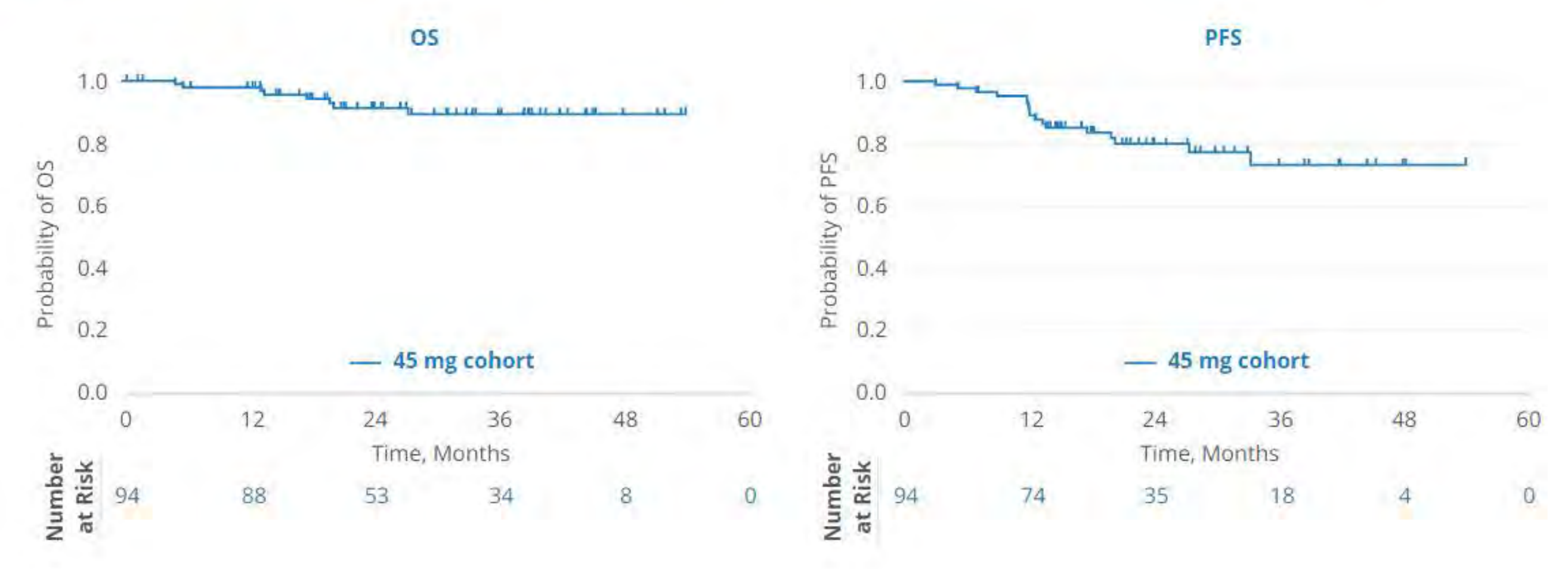
Median duration of follow-up in the 45 mg→15 mg arm was 27.0 months[2]

of patients (n=28/45)[a] maintained response at a reduced dose of 15 mg[2]

100% of patients (n=28/28) who maintained ≤1% BCR-ABL1 at 15 mg did so for ≥90 days[2]

[a] Patients who achieved ≤1% BCR::ABL1 at any time.

ESTIMATED OS AND PFS DATA FOR OPTIC WITH A RESPONSE-BASED DOSING STRATEGY[1]



In PACE, ICLUSIG demonstrated durable efficacy in CML

Explore the data ›

ICLUSIG safety profile in the OPTIC Trial

ICLUSIG safety profile: OPTIC Trial ›

Learn to identify patients with CP-CML who are appropriate for ICLUSIG

Explore patient profiles ›

BCR::ABL1^{IS}=BCR::ABL1 international scale; CP-CML=chronic-phase chronic myeloid leukemia; ECOG PS=Eastern Cooperative Oncology Group performance status; ITT=intent-to-treat; OS=overall survival; PFS=progression-free survival; TKI=tyrosine kinase inhibitor; QD=once a day; qRT PCR=quantitative reverse transcriptase polymerase chain reaction.

INDICATIONS AND USAGE

ICLUSIG is indicated for the treatment of adult patients with:

Philadelphia Chromosome-Positive Acute Lymphoblastic Leukemia (Ph+ ALL)

- Newly diagnosed Ph+ ALL in combination with chemotherapy.
  This indication is approved under accelerated approval based on minimal residual disease (MRD)-negative complete remission (CR) at the end of induction. Continued approval for this indication may be contingent upon verification of clinical benefit in a confirmatory trial(s).
- As monotherapy in Ph+ ALL for whom no other kinase inhibitors are indicated or T315I-positive Ph+ ALL.

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.

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See full prescribing information for complete boxed warning.

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WARNINGS AND PRECAUTIONS

Arterial Occlusive Events (AOEs): AOEs, including fatalities, have occurred in patients who received ICLUSIG in PhALLCON, OPTIC and PACE. These included cardiovascular, cerebrovascular, and peripheral vascular events. In PhALLCON, 6% of 163 patients experienced AOEs; 3.7% experienced Grade 3 or 4. The incidence of AOEs in OPTIC (45 mg → 15 mg) was 14% of 94 patients; 6% experienced Grade 3 or 4. In PACE, the incidence of AOEs was 26% of 449 patients; 14% experienced Grade 3 or 4. Fatal AOEs occurred in 0.6% of patients in PhALLCON, 2.1% of patients in OPTIC, and in 2% of patients in PACE. Some patients in PACE experienced recurrent or multisite vascular occlusion. Patients with and without cardiovascular risk factors, including patients age 50 years or younger, experienced these events. The most common risk factors observed with these events in PACE were history of hypertension, hypercholesterolemia, and non-ischemic cardiac disease. In PhALLCON, OPTIC and PACE, AOEs were more frequent with increasing age.

In PhALLCON, patients with uncontrolled hypertension, hypertriglyceridemia, or diabetes were excluded. Patients with clinically significant, uncontrolled, or active cardiovascular disease, including any history of myocardial infarction, peripheral vascular infarction, revascularization procedure, venous thromboembolism, clinically significant atrial/ventricular tachyarrhythmias, unstable angina, or congestive heart failure within the 6 months prior to the first dose of ICLUSIG, were also excluded.

In OPTIC, patients with uncontrolled hypertension or diabetes and patients with clinically significant, uncontrolled, or active cardiovascular disease were excluded.

In PACE, patients with uncontrolled hypertriglyceridemia and patients with clinically significant or active cardiovascular disease within the 3 months prior to the first dose of ICLUSIG were excluded.

Consider whether the benefits of ICLUSIG are expected to exceed the risks. Monitor for evidence of AOEs. Interrupt, then resume at the same or decreased dose or discontinue ICLUSIG based on recurrence/severity. Consider benefit-risk to guide a decision to restart ICLUSIG.

Venous Thromboembolic Events (VTEs): Serious or severe VTEs have occurred in patients who received ICLUSIG. In PhALLCON, VTEs occurred in 12% of 163 patients, including serious or severe (Grade 3 or 4) in 3.1% of patients. One of 94 patients in OPTIC experienced a VTE (Grade 1 retinal vein occlusion). In PACE, VTEs occurred in 6% of 449 patients including serious or severe (Grade 3 or 4) VTEs in 5.8% of patients. In PhALLCON and PACE VTEs included deep venous thrombosis, embolism, pulmonary embolism, superficial vein thrombosis, thrombosis, jugular vein thrombosis, superficial thrombophlebitis, retinal vein occlusion, and retinal vein thrombosis with vision loss. The incidence of VTEs in PACE was higher in patients with Ph+ ALL (9% of 32 patients) and BP-CML (10% of 62 patients). 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 in patients who received ICLUSIG. In PhALLCON, heart failure occurred in 6% of 163 patients; 1.2% experienced serious or severe (Grade 3 or 4) heart failure. Heart failure occurred in 13% of 94 patients in OPTIC; 1.1% experienced serious or severe (Grade 3 or 4). In PACE, heart failure occurred in 9% of 449 patients; 7% experienced serious or severe (Grade 3 or higher). In PhALLCON the most frequently reported heart failure event (>1 patient) was increased brain natriuretic peptide (BNP) (2.5%). In OPTIC, the most frequently reported heart failure events (>1 patient each) were left ventricular hypertrophy (3.2%) and BNP increased (3.2%). In PACE, the most frequently reported heart failure events (≥2%) were congestive cardiac failure (3.1%), decreased ejection fraction (2.9%), and cardiac failure (2%). Monitor patients for signs or symptoms consistent with heart failure and manage heart failure 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 occurred in 3 patients, with hepatic failure occurring within 1 week of starting ICLUSIG in one of these patients. These fatal cases occurred in patients with BP-CML or Ph+ ALL treated with monotherapy. Hepatotoxicity occurred in 66% of 163 patients in PhALLCON, in 28% of 94 patients in OPTIC and in 32% of 449 patients in PACE. Grade 3 or 4 hepatotoxicity occurred in PhALLCON (30% of 163 patients), in OPTIC (6% of 94 patients), and in PACE (13% of 449 patients). The most frequent hepatotoxic events were elevations of ALT, AST, GGT, bilirubin, and alkaline phosphatase. 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 in patients who received ICLUSIG. Patients may require urgent clinical intervention for hypertension associated with confusion, headache, chest pain, or shortness of breath. Monitor blood pressure at baseline and as clinically indicated and manage hypertension as clinically indicated. Interrupt, dose reduce, or stop 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 in patients who received ICLUSIG. 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 thereafter 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 45 mg once daily increased the risk of serious adverse reactions 2-fold compared to single agent imatinib 400 mg once daily. The median exposure to treatment was less than 6 months. The trial was halted for safety. Arterial and venous thrombosis and occlusions occurred at least twice as frequently in the ICLUSIG arm compared to the imatinib arm. Compared to imatinib-treated patients, ICLUSIG-treated patients exhibited a greater incidence of myelosuppression, pancreatitis, hepatotoxicity, cardiac failure, hypertension, and skin and subcutaneous tissue disorders. 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 patients in PhALLCON, OPTIC and PACE. Some of these events in PhALLCON and PACE were Grade 3 or 4. Monitor patients for symptoms of neuropathy, 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 toxicity leading to blindness or blurred vision have occurred in ICLUSIG-treated patients. The most frequent ocular toxicities occurring in PhALLCON, OPTIC and PACE were dry eye, blurred vision, and eye pain. Retinal toxicities included age-related macular degeneration, macular edema, retinal vein occlusion, retinal hemorrhage, and vitreous floaters. Conduct comprehensive eye exams at baseline and periodically during treatment.

Hemorrhage: Fatal and serious hemorrhage events have occurred in patients who received ICLUSIG. Fatal hemorrhages occurred in PACE and serious hemorrhages occurred in PhALLCON, OPTIC and PACE. In PACE, the incidence of serious bleeding events was higher in patients with AP-CML, BP-CML, and Ph+ ALL. Intracranial hemorrhage, gastrointestinal hemorrhage and subdural hematoma were the most frequently reported serious hemorrhages. Events often occurred in patients with Grade 4 thrombocytopenia. Monitor for hemorrhage and manage patients as clinically indicated. Interrupt, then resume at the same or reduced dose or discontinue ICLUSIG based on recurrence/severity.

Fluid Retention: Fatal and serious fluid retention events have occurred in patients who received ICLUSIG. In PACE, one instance of brain edema was fatal and serious events included pleural effusion, pericardial effusion, and angioedema. In PhALLCON serious fluid retention included pericardial effusion. The most frequent occurrences of fluid retention in patients who received ICLUSIG were peripheral edema and pleural effusion. Monitor for fluid retention and manage patients 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, atrial arrhythmias, tachycardia, syncope, atrial fibrillation and supraventricular tachycardia occurred in patients in PhALLCON, OPTIC, and PACE. For some patients, events were serious or severe (Grade 3 or 4) and led 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 events of neutropenia, thrombocytopenia, and anemia occurred in patients in PhALLCON, OPTIC and PACE. In PACE, the incidence of myelosuppression was greater in patients with AP-CML, BP-CML, and Ph+ ALL treated with monotherapy than in patients with CP-CML. Obtain complete blood counts every 2 weeks for the first 3 months and then monthly or as clinically indicated. If ANC less than 1 x 10^9/L or platelets less than 50 x 10^9/L, interrupt ICLUSIG until ANC at least 1.5 x 10^9/L and platelets at least 75 x 10^9/L, then resume at same or reduced dose.

Tumor Lysis Syndrome (TLS): Serious TLS was reported in ICLUSIG-treated patients in PhALLCON, OPTIC and PACE. Ensure adequate hydration and treat high uric acid levels prior to initiating ICLUSIG.

Reversible Posterior Leukoencephalopathy Syndrome (RPLS): RPLS (also known as Posterior Reversible Encephalopathy Syndrome) has been reported in patients who received ICLUSIG. Patients may present with neurological signs and symptoms, visual disturbances, and hypertension. Diagnosis is made with supportive findings on magnetic resonance imaging (MRI) of the brain. Interrupt ICLUSIG until resolution. The safety of resumption of ICLUSIG in patients 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 prior to elective surgery. Do not administer for at least 2 weeks following major surgery and until adequate wound healing. The safety of resumption of ICLUSIG after resolution of wound healing complications has not been established. Gastrointestinal perforation or fistula occurred in patients receiving ICLUSIG. Permanently discontinue in patients with gastrointestinal perforation.

Embryo-Fetal Toxicity: Based on its mechanism of action and findings from animal studies, ICLUSIG can cause fetal harm when administered to a pregnant woman. Advise pregnant women of the potential risk to the fetus. Advise females of reproductive potential to 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, headache, constipation, dry skin, hypertension, fatigue, fluid retention and edema, pyrexia, nausea, pancreatitis/lipase elevation, hemorrhage, anemia, hepatic dysfunction and AOEs. 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: hepatic dysfunction, 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 1-844-217-6468 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 30mg orally once daily for patients with pre-existing hepatic impairment as these patients are more likely to experience adverse reactions compared to patients with normal hepatic function. For patients with newly diagnosed Ph+ ALL, no dosage adjustment is recommended.

Please see full Prescribing Information, including Boxed Warning.

SHOW REFERENCES

References: 1. Cortes J, Apperley J, Lomaia E, et al. *Blood*. 2021;138(21):2042-2050. **2.** ICLUSIG (ponatinib) [prescribing information]. Cambridge, MA: Takeda Pharmaceuticals U.S.A., Inc. 03/2024. **3.** Data on file. Takeda Pharmaceutical Company Limited, Inc. 2024.

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09/24 USO-ICL-0558

PACE 5-year data in CML:

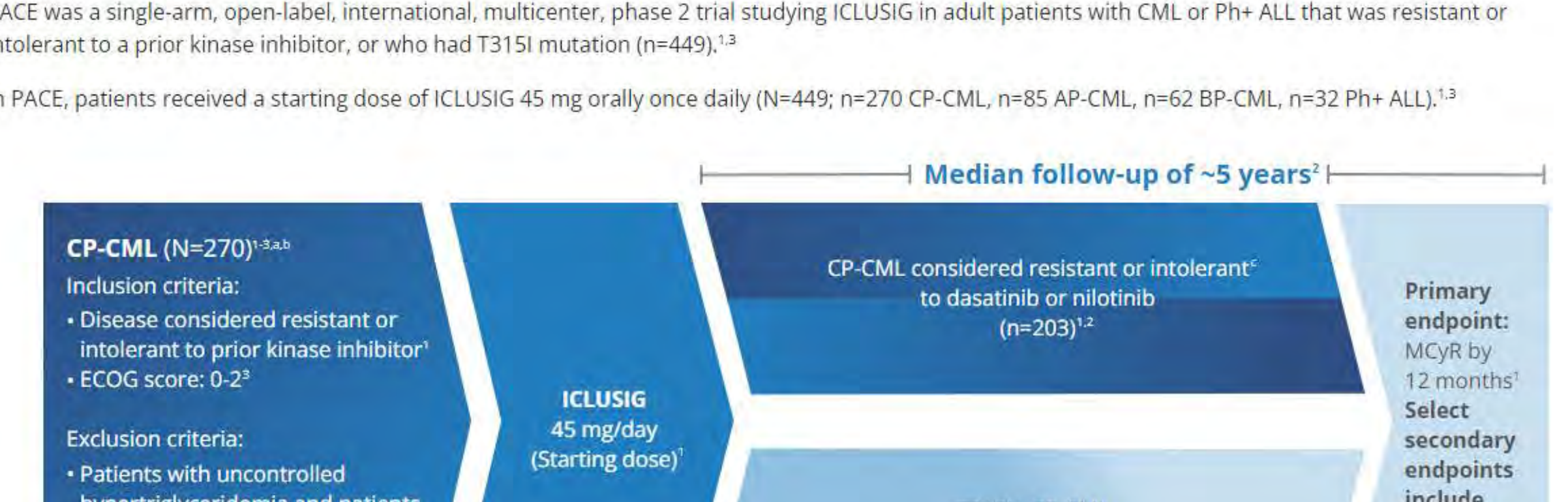
ICLUSIG (ponatinib) delivered deep and durable efficacy[1,2]

Trial design | Response Rates | Estimated OS/PFS

PACE TRIAL DESIGN

PACE was a single-arm, open-label, international, multicenter, phase 2 trial studying ICLUSIG in adult patients with CML or Ph+ ALL that was resistant or intolerant to a prior kinase inhibitor, or who had T315I mutation (n=449).[1,3]

In PACE, patients received a starting dose of ICLUSIG 45 mg orally once daily (N=449; n=270 CP-CML, n=85 AP-CML, n=62 BP-CML, n=32 Ph+ ALL).[1,3]



Median follow-up of ~5 years[2]

CP-CML (N=270)[1-3,a,b]
Inclusion criteria:
- Disease considered resistant or intolerant to prior kinase inhibitor[1]
- ECOG score: 0-2[3]

Exclusion criteria:
- Patients with uncontrolled hypertriglyceridemia and patients with clinically significant or active cardiovascular disease were excluded

ICLUSIG
45 mg/day
(Starting dose)[1]

CP-CML considered resistant or intolerant[c] to dasatinib or nilotinib (n=203)[1,2]

T315I+ CP-CML, regardless of prior TKI use (n=64)[1,2]

Primary endpoint: MCyR by 12 months[1]
Select secondary endpoints include MMR, OS and PFS[3]

[a] Three patients who had not received prior dasatinib or nilotinib did not have T315I confirmed at baseline and were not evaluable for efficacy.[1]
[b] Dose reductions to 15 mg once daily or 30 mg once daily were applied to patients with and without MCyR, respectively, and were applied to manage AEs, or implemented proactively following an accumulation of AOEs.[1,2]
[c] Resistance in CP-CML while on prior TKI therapy was defined as failure to achieve either a CHR (by 3 months), a minor cytogenetic response (by 6 months), or a MCyR (by 12 months). Patients with CP-CML who experienced a loss of response or development of a kinase domain mutation in the absence of a CCyR or progression to AP-CML or BP-CML at any time on prior TKI therapy were also considered resistant. Intolerance was defined as the discontinuation of prior TKI therapy due to toxicities despite optimal management in the absence of a CCyR in patients with CP-CML or MaHR for patients with AP-CML, BP-CML, or Ph+ ALL.[1]

- At study completion, the median duration of follow-up for the trial (all cohorts) was 40.5 months (range: 0.1 months to 79.5 months)[1]
- The major efficacy outcome measure (primary endpoint) for patients with CP-CML was MCyR by 12 months, which included CCyR and PCyR[1,a]
- Dose reductions to 30 mg or 15 mg once daily were applied to manage adverse reactions, per protocol, or implemented proactively in 2013[2,b]

[a] Primary endpoint was MCyR by 12 months for CP-CML and MaHR by 6 months for AP-CML, BP-CML, or Ph+ ALL. Secondary endpoints included major molecular response (MMR), time to and duration of response, progression-free survival (PFS), overall survival (OS), and safety.[2]

[b] 15 mg once daily for CP-CML patients with MCyR, and 30 mg once daily for CP-CML patients without MCyR, AP-CML, and BP-CML patients.[2]

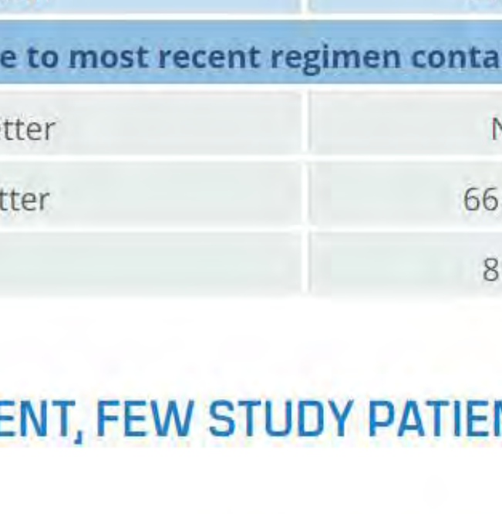
PATIENT CHARACTERISTICS

CP-CML patients in the PACE trial had highly-resistant disease—80% of patients were resistant* to prior TKI therapy and 24% had at least one BCR::ABL1 mutation[1,2]

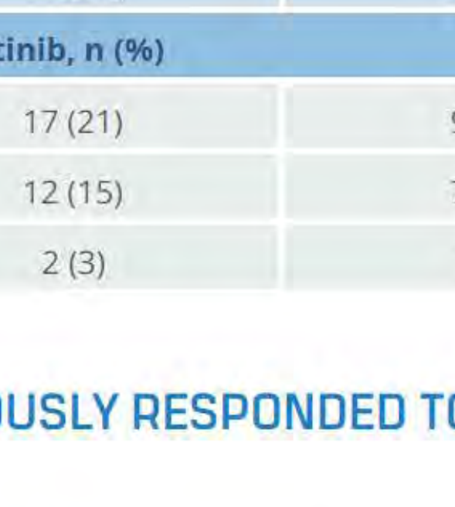
Baseline Characteristics	CP-CML (n=270)	AP-CML (n=85)	BP-CML (n=62)
Age			
Median years (range)	60 (18 to 94)	60 (23-82)	53 (18–74)
Sex, n (%)			
Female	126 (47)	48 (56)	25 (40)
Previous use of approved TKIs, n (%)			
≥2 drugs	251 (93)	80 (94)	60 (97)
≥3 drugs	154 (57)	47 (55)	37 (60)
Duration of previous treatment, years (range)			
Median duration of previous treatment with approved TKIs	5.4 (0.4–13.3)	5.1 (0.3–12.1)	2.0 (0.1–11.6)
Resistant or intolerant to dasatinib or nilotinib, n (%)			
Resistant	215 (80)	74 (87)	59 (95)
Intolerant only	39 (14)	6 (7)	2 (3)
Both resistant and intolerant	52 (19)	11 (13)	13 (21)
Mutation status, n (%)			
No mutation detected	138 (51)	40 (47)	17 (27)
T315I mutation	64 (24)	18 (21)	24 (39)
Best response to most recent regimen containing dasatinib or nilotinib, n (%)			
MaHR or better	ND	17 (21)	9 (15)
MCyR or better	66 (26)	12 (15)	7 (11)
MMR	8 (3)	2 (3)	1 (2)

AT ENROLLMENT, FEW STUDY PATIENTS HAD PREVIOUSLY RESPONDED TO A PRIOR TKI[3]

Best response to any treatment prior to ICLUSIG[2,a]



of patients achieved MCyR or better



of patients achieved MMR

[a] Most recent regimen containing dasatinib or nilotinib.[1,3]

IN PACE, TKI-RESISTANT PATIENTS ACHIEVED DEEP, CLINICALLY SIGNIFICANT RESPONSES AND HIGH RATES OF MMR[1]

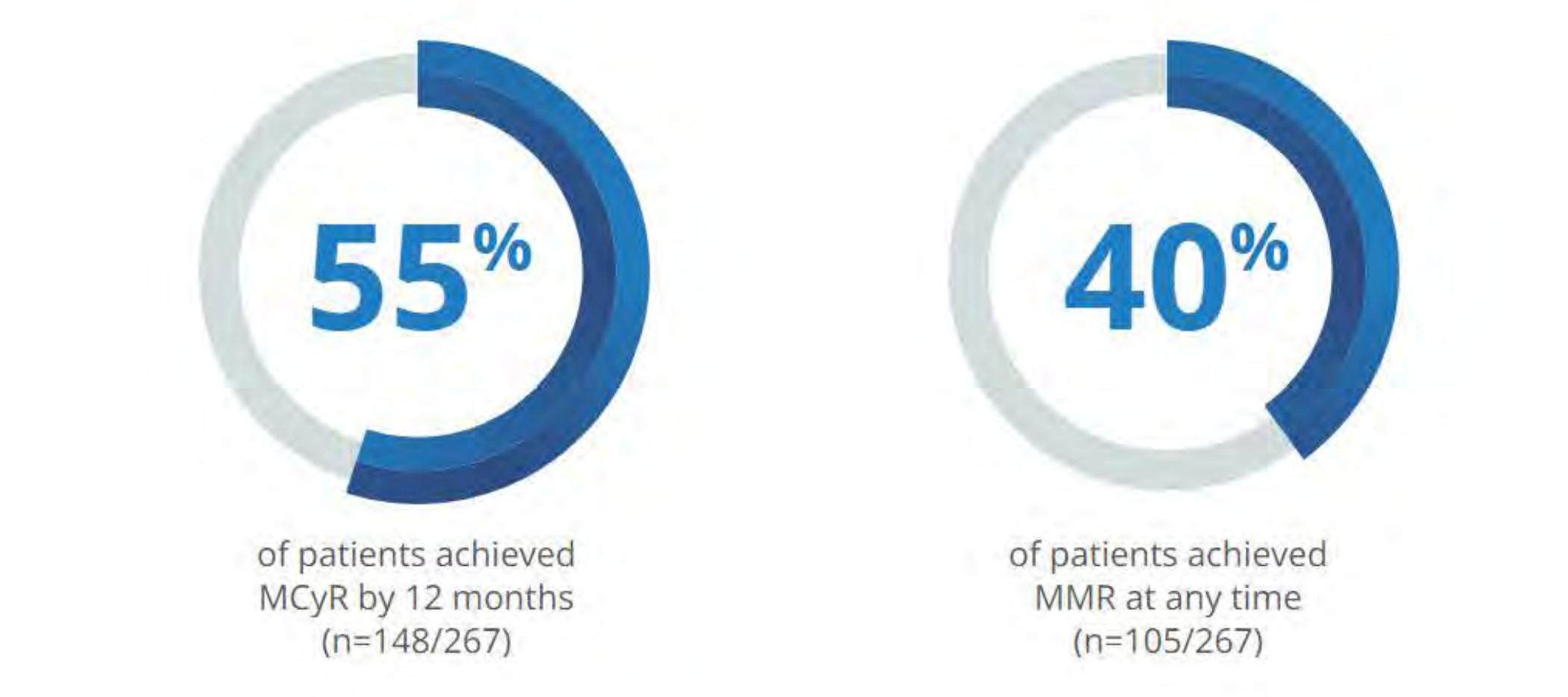
Proven long-term benefit in patients with TKI-resistant CP-CML (n=267)[1]

of patients achieved MCyR by 12 months (n=148/267)

of patients achieved MMR at any time (n=105/267)

ICLUSIG ACHIEVED A DEEP AND DURABLE RESPONSE OVER 5 YEARS IN CP-CML, TKI-RESISTANT, AND T315I PATIENTS[1]

Achieved MCyR by 12 months%^[1]

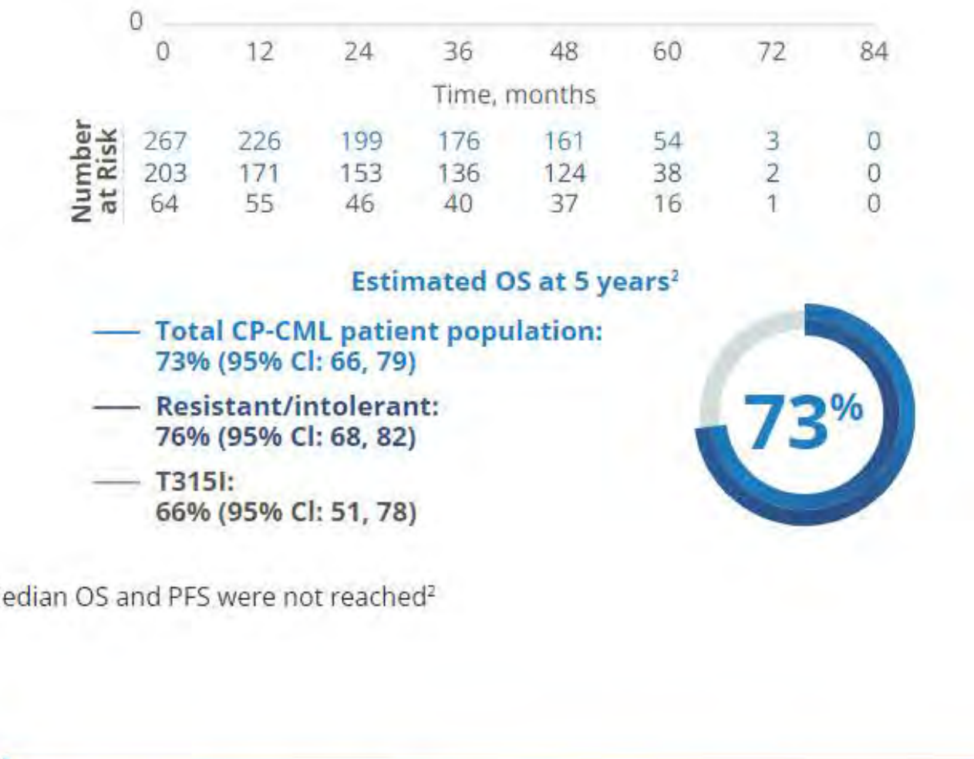


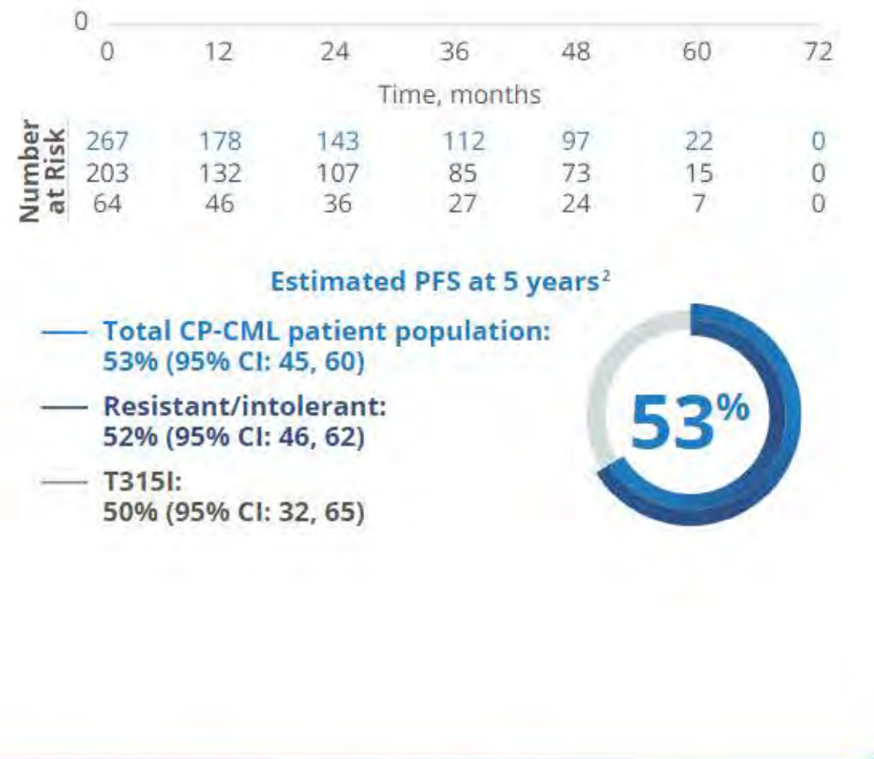
- Median duration of treatment for CP-CML patients was 35 months[1]

In PACE, ICLUSIG provided durable, clinically meaningful responses in TKI-resistant CP-CML patients, including those with the T315I mutation.[1]

Additional long-term data >

CONSISTENT ESTIMATED OS/PFS THROUGH YEAR 5, EVEN IN PATIENTS WITH A T315I MUTATION[2]





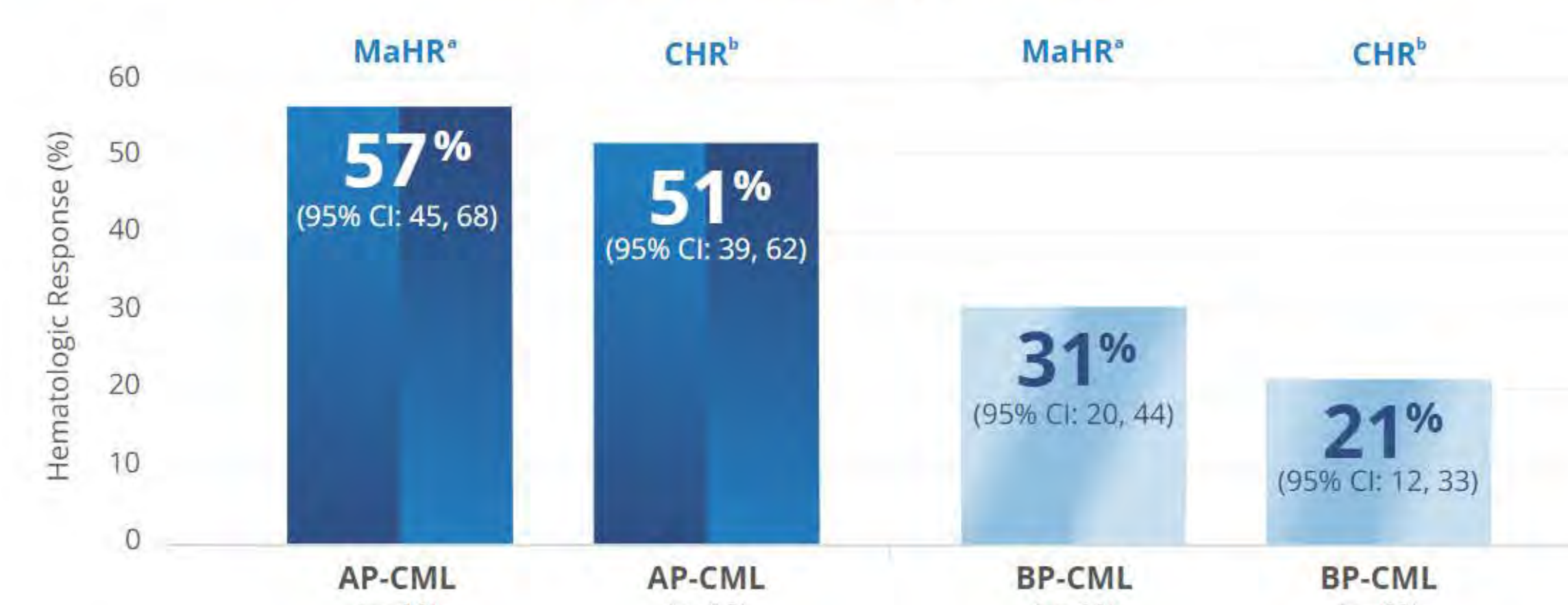
Median OS and PFS were not reached[2]

ICLUSIG demonstrated long-term efficacy in the PACE trial

Discover 5-year data >

ICLUSIG DEMONSTRATED EFFICACY IN AP- AND BP-CML PATIENTS WITH RESISTANT OR INTOLERANT ADVANCED DISEASE[1]

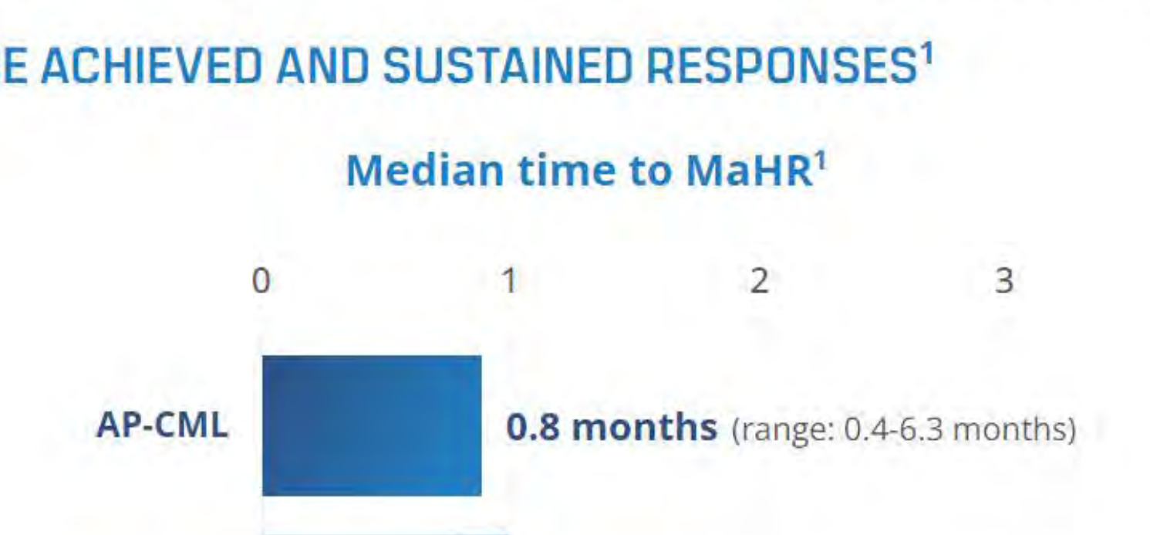
Efficacy of ICLUSIG in patients with resistant or intolerant advanced disease (includes R/I and T315I cohorts) in PACE[1]



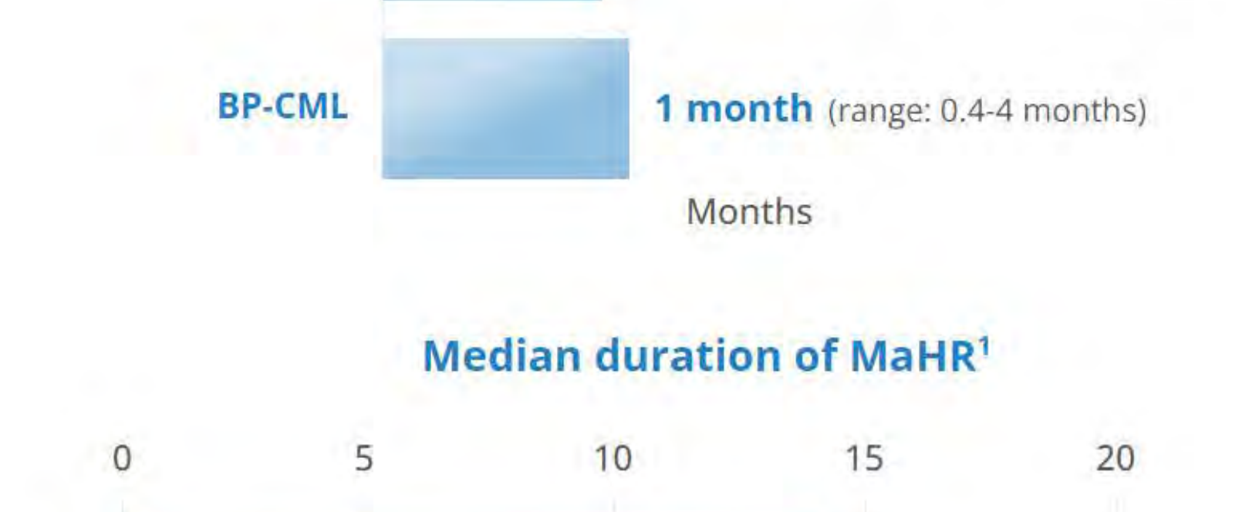
[a] Primary endpoint for patients with AP-CML, BP-CML, and Ph+ ALL was MaHR by 6 months, which combines complete hematologic responses and no evidence of leukemia.[1]
[b] CHR: WBC ≤ institutional ULN, ANC ≥1000/mm³, platelets ≥100,000/mm3, no blasts or promyelocytes in peripheral blood, bone marrow blasts ≤5%, <5% myelocytes plus metamyelocytes in peripheral blood, basophils <5% in peripheral blood, no extramedullary involvement (including no hepatomegaly or splenomegaly).[1]

PATIENTS IN PACE ACHIEVED AND SUSTAINED RESPONSES[1]

Median time to MaHR[1]



Median duration of MaHR[1]



An established safety profile CP-CML

PACE safety data >

ICLUSIG (ponatinib) has a distinct inhibitory mechanism in CP-CML

Delve into ICLUSIG MOA >

AOE=arterial occlusive events; AP-CML=accelerated-phase chronic myeloid leukemia; BP-CML=blast-phase chronic myeloid leukemia; CCyR=complete cytogenetic response; CI=confidence interval; CHR=complete hematologic response; CML=chronic myeloid leukemia; CP CML=chronic-phase chronic myeloid leukemia; ECOG PS=Eastern Cooperative Oncology Group performance status; MaHR=major hematologic response; MCyR=major cytogenetic response; MMR=major molecular response; OS=overall survival; PCyR=partial cytogenetic response; Ph+ ALL=Philadelphia chromosome-positive acute lymphoblastic leukemia; PFS=progression-free survival; QD=once daily; TKI=tyrosine kinase inhibitor.

INDICATIONS AND USAGE

ICLUSIG is indicated for the treatment of adult patients with:

Philadelphia Chromosome-Positive Acute Lymphoblastic Leukemia (Ph+ ALL)

- Newly diagnosed Ph+ ALL in combination with chemotherapy.
  This indication is approved under accelerated approval based on minimal residual disease (MRD)-negative complete remission (CR) at the end of induction. Continued approval for this indication may be contingent upon verification of clinical benefit in a confirmatory trial(s).
- As monotherapy in Ph+ ALL for whom no other kinase inhibitors are indicated or T315I-positive Ph+ ALL.

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.**

WARNINGS AND PRECAUTIONS

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In PhALLCON, patients with uncontrolled hypertension, hypertriglyceridemia, or diabetes were excluded. Patients with clinically significant, uncontrolled, or active cardiovascular disease, including any history of myocardial infarction, peripheral vascular infarction, revascularization procedure, venous thromboembolism, clinically significant atrial/ventricular tachyarrhythmias, unstable angina, or congestive heart failure within the 6 months prior to the first dose of ICLUSIG, were also excluded.

In OPTIC, patients with uncontrolled hypertension or diabetes and patients with clinically significant, uncontrolled, or active cardiovascular disease were excluded.

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Venous Thromboembolic Events (VTEs): Serious or severe VTEs have occurred in patients who received ICLUSIG. In PhALLCON, VTEs occurred in 12% of 163 patients, including serious or severe (Grade 3 or 4) in 3.1% of patients. One of 94 patients in OPTIC experienced a VTE (Grade 1 retinal vein occlusion). In PACE, VTEs occurred in 6% of 449 patients including serious or severe (Grade 3 or 4) VTEs in 5.8% of patients. In PhALLCON and PACE VTEs included deep venous thrombosis, embolism, pulmonary embolism, superficial vein thrombosis, thrombosis, jugular vein thrombosis, superficial thrombophlebitis, retinal vein occlusion, and retinal vein thrombosis with vision loss. The incidence of VTEs in PACE was higher in patients with Ph+ ALL (9% of 32 patients) and BP-CML (10% of 62 patients). 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 in patients who received ICLUSIG. In PhALLCON, heart failure occurred in 6% of 163 patients; 1.2% experienced serious or severe (Grade 3 or 4) heart failure. Heart failure occurred in 13% of 94 patients in OPTIC; 1.1% experienced serious or severe (Grade 3 or 4). In PACE, heart failure occurred in 9% of 449 patients; 7% experienced serious or severe (Grade 3 or higher). In PhALLCON the most frequently reported heart failure event (>1 patient) was increased brain natriuretic peptide (BNP) (2.5%). In OPTIC, the most frequently reported heart failure events (>1 patient each) were left ventricular hypertrophy (3.2%) and BNP increased (3.2%). In PACE, the most frequently reported heart failure events (≥2%) were congestive cardiac failure (3.1%), decreased ejection fraction (2.9%), and cardiac failure (2%). Monitor patients for signs or symptoms consistent with heart failure and manage heart failure 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 occurred in 3 patients, with hepatic failure occurring within 1 week of starting ICLUSIG in one of these patients. These fatal cases occurred in patients with BP-CML or Ph+ ALL treated with monotherapy. Hepatotoxicity occurred in 66% of 163 patients in PhALLCON, in 28% of 94 patients in OPTIC and in 32% of 449 patients in PACE. Grade 3 or 4 hepatotoxicity occurred in PhALLCON (30% of 163 patients), in OPTIC (6% of 94 patients), and in PACE (13% of 449 patients). The most frequent hepatotoxic events were elevations of ALT, AST, GGT, bilirubin, and alkaline phosphatase. 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 in patients who received ICLUSIG. Patients may require urgent clinical intervention for hypertension associated with confusion, headache, chest pain, or shortness of breath. Monitor blood pressure at baseline and as clinically indicated and manage hypertension as clinically indicated. Interrupt, dose reduce, or stop 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 in patients who received ICLUSIG. 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 thereafter 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 45 mg once daily increased the risk of serious adverse reactions 2-fold compared to single agent imatinib 400 mg once daily. The median exposure to treatment was less than 6 months. The trial was halted for safety. Arterial and venous thrombosis and occlusions occurred at least twice as frequently in the ICLUSIG arm compared to the imatinib arm. Compared to imatinib-treated patients, ICLUSIG-treated patients exhibited a greater incidence of myelosuppression, pancreatitis, hepatotoxicity, cardiac failure, hypertension, and skin and subcutaneous tissue disorders. 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 patients in PhALLCON, OPTIC and PACE. Some of these events in PhALLCON and PACE were Grade 3 or 4. Monitor patients for symptoms of neuropathy, 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 toxicity leading to blindness or blurred vision have occurred in ICLUSIG-treated patients. The most frequent ocular toxicities occurring in PhALLCON, OPTIC and PACE were dry eye, blurred vision, and eye pain. Retinal toxicities included age-related macular degeneration, macular edema, retinal vein occlusion, retinal hemorrhage, and vitreous floaters. Conduct comprehensive eye exams at baseline and periodically during treatment.

Hemorrhage: Fatal and serious hemorrhage events have occurred in patients who received ICLUSIG. Fatal hemorrhages occurred in PACE and serious hemorrhages occurred in PhALLCON, OPTIC and PACE. In PACE, the incidence of serious bleeding events was higher in patients with AP-CML, BP-CML, and Ph+ ALL. Intracranial hemorrhage, gastrointestinal hemorrhage and subdural hematoma were the most frequently reported serious hemorrhages. Events often occurred in patients with Grade 4 thrombocytopenia. Monitor for hemorrhage and manage patients as clinically indicated. Interrupt, then resume at the same or reduced dose or discontinue ICLUSIG based on recurrence/severity.

Fluid Retention: Fatal and serious fluid retention events have occurred in patients who received ICLUSIG. In PACE, one instance of brain edema was fatal and serious events included pleural effusion, pericardial effusion, and angioedema. In PhALLCON serious fluid retention included pericardial effusion. The most frequent occurrences of fluid retention in patients who received ICLUSIG were peripheral edema and pleural effusion. Monitor for fluid retention and manage patients 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, atrial arrhythmias, tachycardia, syncope, atrial fibrillation and supraventricular tachycardia occurred in patients in PhALLCON, OPTIC, and PACE. For some patients, events were serious or severe (Grade 3 or 4) and led 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 events of neutropenia, thrombocytopenia, and anemia occurred in patients in PhALLCON, OPTIC and PACE. In PACE, the incidence of myelosuppression was greater in patients with AP-CML, BP-CML, and Ph+ ALL treated with monotherapy than in patients with CP-CML. Obtain complete blood counts every 2 weeks for the first 3 months and then monthly or as clinically indicated. If ANC less than 1 x 10^9/L or platelets less than 50 x 10^9/L, interrupt ICLUSIG until ANC at least 1.5 x 10^9/L and platelets at least 75 x 10^9/L, then resume at same or reduced dose.

Tumor Lysis Syndrome (TLS): Serious TLS was reported in ICLUSIG-treated patients in PhALLCON, OPTIC and PACE. Ensure adequate hydration and treat high uric acid levels prior to initiating ICLUSIG.

Reversible Posterior Leukoencephalopathy Syndrome (RPLS): RPLS (also known as Posterior Reversible Encephalopathy Syndrome) has been reported in patients who received ICLUSIG. Patients may present with neurological signs and symptoms, visual disturbances, and hypertension. Diagnosis is made with supportive findings on magnetic resonance imaging (MRI) of the brain. Interrupt ICLUSIG until resolution. The safety of resumption of ICLUSIG in patients 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 prior to elective surgery. Do not administer for at least 2 weeks following major surgery and until adequate wound healing. The safety of resumption of ICLUSIG after resolution of wound healing complications has not been established. Gastrointestinal perforation or fistula occurred in patients receiving ICLUSIG. Permanently discontinue in patients with gastrointestinal perforation.

Embryo-Fetal Toxicity: Based on its mechanism of action and findings from animal studies, ICLUSIG can cause fetal harm when administered to a pregnant woman. Advise pregnant women of the potential risk to the fetus. Advise females of reproductive potential to 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, headache, constipation, dry skin, hypertension, fatigue, fluid retention and edema, pyrexia, nausea, pancreatitis/lipase elevation, hemorrhage, anemia, hepatic dysfunction and AOEs. 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: hepatic dysfunction, 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 1-844-217-6468 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 30mg orally once daily for patients with pre-existing hepatic impairment as these patients are more likely to experience adverse reactions compared to patients with normal hepatic function. For patients with newly diagnosed Ph+ ALL, no dosage adjustment is recommended.

Please see full Prescribing Information, including Boxed Warning.

SHOW REFERENCES

References: 1. ICLUSIG (ponatinib) [prescribing information]. Cambridge, MA: Takeda Pharmaceuticals; 03/2024. **2.** Cortes JE, Kim DW, Pinilla-Ibarz J, et al. *Blood*. 2018;132(4):393-404. **3.** Cortes JE, Kim DW, Pinilla-Ibarz J, et al. PACE Investigators. *N Engl J Med*. 2013;369(19):1783-1796.

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