

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

# Start Strong With ICLUSIG[1]

## In Newly Diagnosed Adult Patients With Ph+ ALL

*Hypothetical patients.

MRD=minimal residual disease; Ph+ ALL=Philadelphia chromosome-positive acute lymphoblastic leukemia.

## Offer the Chance of a Strong Start and Meaningful Response[1]

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### INDICATIONS AND USAGE

ICLUSIG is a kinase inhibitor indicated for the treatment of adult patients with newly diagnosed Philadelphia chromosome-positive acute lymphoblastic leukemia (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).

### IMPORTANT SAFETY INFORMATION

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

*See full prescribing information for complete boxed warning.*

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

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

# JOHN

## A Newly Diagnosed Patient With Ph+ ALL, Otherwise Healthy



Hypothetical patient.

### John presents with high bone marrow blasts, but no contraindicated comorbidities

John is 48, an active father and working professional with a full calendar — school drop-offs, kids' activities, and the hobbies that keep him feeling like himself. With so much depending on him, he wants a treatment option that has a meaningful response.

## John's Treatment Journey

### At Presentation

**John, an otherwise healthy adult, was diagnosed with Ph+ ALL**

**Laboratory results**

- Bone marrow blasts 78%
- BCR::ABL1/ABL1 (p190) 78%
- Blood pressure considered in normal range, no medication
- A1c 5.5%, no medication

### Treatment Choice

**Began first-line regimen with ICLUSIG 30 mg + chemotherapy**

- Targeting early molecular clearance

### Early Response

**John achieved his early response milestones**

- MRD negative CR after induction (3 months)*
- BCR::ABL1/ABL1 <0.01% by PCR after Cycle 2 (~8 weeks)
- Therapy was generally well-tolerated and abdominal pain was actively monitored and managed and did not result in discontinuation of ICLUSIG

*Dose was reduced to 15 mg upon achievement of MRD-negative CR after Cycle 2.

## Why John's Physician Recommends ICLUSIG

John and his physician are focused on maximizing his chance of long-term survival by achieving a durable remission. Their priority is rapid first-line disease control, shown by early, deep MRD reduction, and a fast, deep response while reducing the risk of relapse-driving mutations and the need for a stem cell transplant.

**After sharing decision-making with his oncologist, they chose ICLUSIG in combination with chemotherapy for the chance of a fast, deep response and its pan-mutational activity.[1]**

## ? What are your treatment strategies for maintaining remission?

AR=adverse reaction; BCR::ABL1IS=BCR::ABL1 International Scale; CR=complete remission/response; MRD=minimal residual disease; Ph+ ALL=Philadelphia chromosome-positive acute lymphoblastic leukemia.

## IMPORTANT SAFETY INFORMATION (cont'd)

### WARNINGS AND PRECAUTIONS

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

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# SARAH

## A Newly Diagnosed Patient With Ph+ ALL With Comorbidities*


Hypothetical patient.

### Sarah presents with hypertension and diabetes, both managed by medication

Sarah is 63 years old, a retired teacher in a rural community who stays active through local events and social groups. Despite managing type 2 diabetes and hypertension, she is generally fit, engaged, and proud of maintaining her independence and role in the community. With her new Ph+ ALL diagnosis, she worries about how treatment may affect her ability to stay involved and live the life she values.

## Sarah's Treatment Journey

### At Presentation

**Sarah was managing type 2 diabetes and hypertension when she was newly diagnosed with Ph+ ALL**

**Comorbidities**
- Type 2 diabetes (controlled, metformin)
- Hypertension (controlled, ACE inhibitor)

**Laboratory results**
- Bone marrow blasts 62%
- BCR::ABL1/ABL1 (p190) 64%
- WBC 21x10

### Treatment Choice

**Began first-line regimen with ICLUSIG + chemotherapy**
- Targeting MRD-negative CR by the end of the induction period (~3 months)

### Early Response

**Sarah achieved her early response milestones**
- MRD negative by CR at end of induction (3 months)
- Increased blood pressure was managed with medication dose adjustment and did not result in discontinuation of ICLUSIG

## Why Sarah's Physician Recommends ICLUSIG

Given her comorbidities, Sarah and her oncologist are prioritizing a tolerable regimen with manageable safety that still offers a chance at long-term remission. Given the disease's agressive nature, they need an option that can be delived in a community setting and provides rapid first-line disease control with early, deep MRD reduction, a fast, deep response, and pan-mutational activity.

**Sarah's physician recommended ICLUSIG + chemotherapy after careful discussion with Sarah about managing treatment with her comorbidities.[1,3]**

**When comorbidities are a factor in newly diagnosed Ph+ ALL,**
**What's your approach to achieving long-term MRD-negative remission while managing tolerability?**

BCR::ABL1IS=BCR::ABL1 International Scale; MRD=minimal residual disease; Ph+ ALL=Philadelphia chromosome-positive acute lymphoblastic leukemia; WBC=white blood cell.

## IMPORTANT SAFETY INFORMATION (cont'd)

**WARNINGS AND PRECAUTIONS** (cont'd)

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

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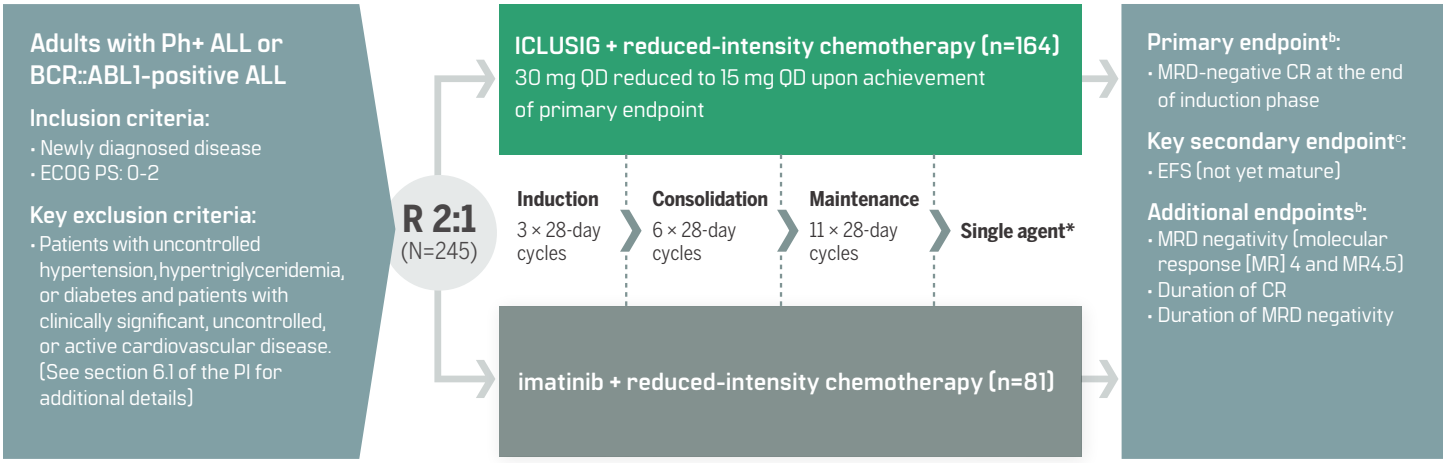
# Redefine Ph+ ALL treatment for newly diagnosed patients

## The FIRST and ONLY FDA-APPROVED TKI for adults with NEWLY DIAGNOSED Ph+ ALL, in combination with chemotherapy[1]

*Study design*

## PhALLCON was the first head-to-head phase 3 clinical trial vs another TKI in adults with newly diagnosed Ph+ ALL

**245 global participants were randomized 2:1 to receive ICLUSIG + chemotherapy or imatinib + chemotherapy in a study with a composite primary endpoint of MRD-negative CR[b] at the end of induction**




**Only patients who achieved the primary endpoint of MRD-negative CR or CRi at the end of induction could continue study treatment at the investigator's discretion.[1]**

- Single-agent therapy after chemotherapy for newly diagnosed Ph+ ALL is not an approved regimen

[a]Following combination therapy, patients continued to receive ICLUSIG or imatinib as single-agent therapy until relapse from CR, progressive disease (PD), hematopoietic stem cell transplantation (HSCT), start of alternative therapy, or unacceptable toxicity.[1]
[b]MRD negativity was defined as ≤0.01% BCR::ABL1/ABL1 or undetectable BCR::ABL1 transcripts in cDNA with ≥10,000 ABL1 transcripts BCR::ABL1/ABL1 levels were reported as an absolute (raw) ratio for the p190 variant test and on the International Scale (BCR::ABL1[IS]) for the p210 variant test. Patients were considered to achieve CR if they maintained/had no circulating blasts and <5% blasts and normal maturation of all cellular components in the bone marrow, no extramedullary disease, ANC ≥1000/mcL, and platelets ≥100,000/mcL for at least 4 weeks. Patients who met both criteria were considered to have achieved MRD-negative CR.[1]
[c]EFS defined as dates of randomization until death due to any cause, failure to achieve CR by the end of induction, or relapse from CR.[35]
[d]Every 12 hours.[1]

ALL=acute lymphoblastic leukemia; ANC=absolute neutrophil count; cDNA=complementary DNA; CNS=central nervous system; CR=complete remission/response; CRi=incomplete hematologic response; ECOG PS=Eastern Cooperative Oncology Group performance status; EFS=event-free survival; MRD=minimal residual disease; Ph+ ALL=Philadelphia chromosome-positive acute lymphoblastic leukemia; PI=Prescribing Information; PO=*per os*; QD=once daily; SCT=stem cell transplantation; TKI=tyrosine kinase inhibitor.

## IMPORTANT SAFETY INFORMATION (cont'd)

### WARNINGS AND PRECAUTIONS (cont'd)

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

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

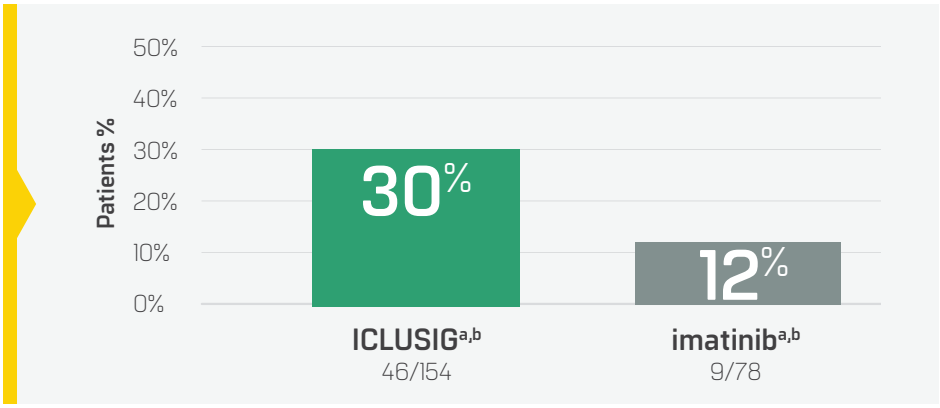
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*Primary endpoint: MRD-negative CR*

## Significantly superior rate of MRD-negative CR with ICLUSIG vs imatinib at the end of induction[1]

**In PhALLCON, ICLUSIG delivered more than double the rate of MRD-negative CR at the end of the 3-month induction phase[1]**




**>2X rate of MRD-negative CR**

was achieved with ICLUSIG vs imatinib at the end of induction[1]

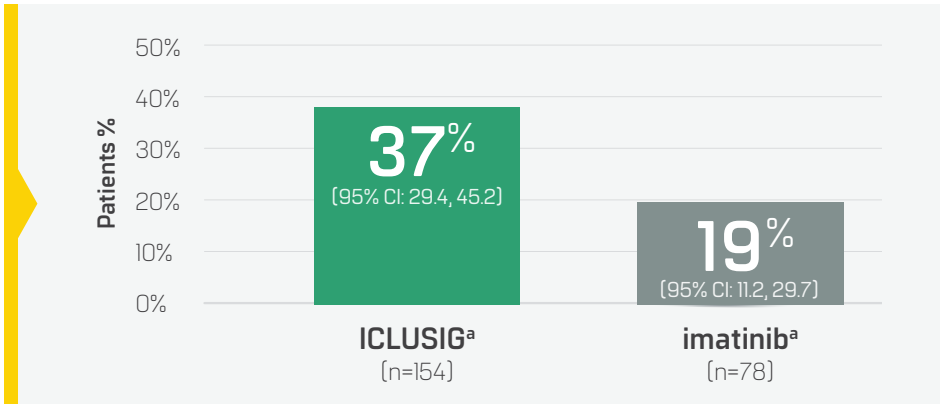
Risk difference 0.18 (95% CI: 0.08, 0.28)
*P*=0.0004

- MRD-negative CR is defined as ≤0.01% BCR::ABL1/ABL1 or undetectable BCR::ABL1 transcripts in cDNA with ≥10,000 ABL1 transcripts, and meeting criteria for CR.*

[a]Of the 245 randomized patients, 244 were treated. Efficacy population included patients with baseline BCR::ABL1 dominant variant p190 and p210; 13/245 patients had atypical, missing, or unevaluable BCR::ABL1 assessment and were not included in the efficacy analysis.[1,2]
[b]Treatments were used in combination with chemotherapy.[1]
*BCR::ABL1/ABL1 levels were reported as an absolute (raw) ratio for the p190 variant test and on the International Scale (BCR::ABL1[IS]) for the p210 variant test. Patients were considered to achieve CR if they maintained/had no circulating blasts and <5% blasts and normal maturation of all cellular components in the bone marrow, no extramedullary disease, ANC ≥1000/mcL, and platelets ≥100,000/mcL for at least 4 weeks. Patients who met both criteria were considered to have achieved MRD-negative CR.[2]
ANC=absolute neutrophil count; cDNA=complementary DNA; CI=confidence interval; CR=complete remission/response; EFS=event-free survival; MRD=minimal residual disease.

*Additional endpoint*

## ICLUSIG delivered a higher rate of MRD negativity* vs imatinib at the end of induction[1,2]




**~18%**

more ICLUSIG patients achieved MRD negativity vs imatinib patients at the end of induction[3,4]

Risk difference 0.18 (95% CI: 0.06, 0.29)

- **Limitations:** PhALLCON was designed to show a statistically significant difference between arms for MRD-negative CR,* the trial was not designed to show a statistically significant difference between arms for MRD negativity alone[2]

[a]Treatments were used in combination with chemotherapy.[1]
*MRD negativity was defined as ≤0.01% BCR::ABL1/ABL1 or undetectable BCR::ABL1 transcripts in cDNA with ≥10,000 ABL1 transcripts. BCR::ABL1/ABL1 levels were reported as an absolute (raw) ratio for the p190 variant test and on the International Scale (BCR::ABL1[IS]) for the p210 variant test.[3,5]
CI=confidence interval; CR=complete remission/response; MR=molecular response; MRD=minimal residual disease.

## IMPORTANT SAFETY INFORMATION (cont'd)

**WARNINGS AND PRECAUTIONS** (cont'd)

**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.

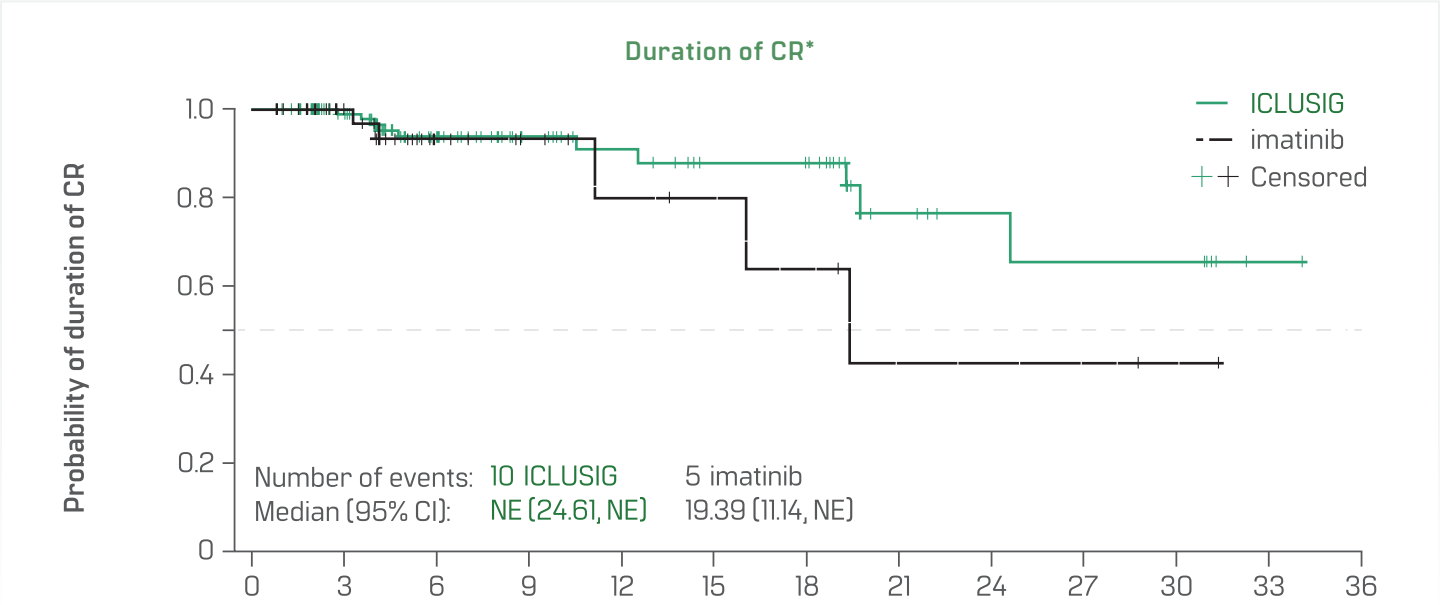
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*Additional endpoint*

## ICLUSIG extended the duration of complete remission vs imatinib[2]

**Median duration of CR was not reached with ICLUSIG vs 19.4 months with imatinib**




**Study features**[1,2]

- The median duration of follow-up was 20.4 months (95% CI: 18.4, 23.9) with ICLUSIG and 18.1 months (95% CI: 13.9, 24.3) with imatinib[1]
- **Relapse from CR:** 8.2% (n=10) of ICLUSIG patients vs 10.2% (n=5) of imatinib patients at the time of data cutoff (August 12, 2022)
- **Limitations:** PhALLCON was designed to show a statistically significant difference between arms for MRD-negative CR,‡ the trial was not designed to show statistically significant difference between arms for duration of CR

*CR was defined as meeting all of the following for ≥4 weeks: <5% lymphoblasts in bone marrow, no lymphoblasts in blood, blood cell counts have normalized, and all signs and symptoms of ALL are gone.[35]
†Complete remission is also known as complete response.[1]
‡MRD negativity was defined as ≤0.01% BCR::ABL1/ABL1 or undetectable BCR::ABL1 transcripts in cDNA with ≥10,000 ABL1 transcripts. BCR::ABL1/ABL1 levels were reported as an absolute (raw) ratio for the p190 variant test and on the International Scale (BCR::ABL1[IS]) for the p210 variant test.[35]

ALL=acute lymphoblastic leukemia; CI=confidence interval; CR=complete remission/response; MRD=minimal residual disease; NE=not evaluable.

## IMPORTANT SAFETY INFORMATION (cont'd)

**WARNINGS AND PRECAUTIONS** (cont'd)

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

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

**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.

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*In adults with newly diagnosed Ph+ ALL*

## ICLUSIG + chemotherapy had a comparable safety profile to imatinib + chemotherapy by utilizing optimized dosing[1]

### Most common ARs[a] ≥20% in the PhALLCON study[1]

| Adverse reaction | ICLUSIG (n=163) | | imatinib (n=81) | |
|---|---|---|---|---|
| | All Grades (%) | Grades 3 or 4 (%) | All Grades[a] (%) | Grades 3 or 4 (%) |
| **Hepatobiliary disorders** | | | | |
| Hepatotoxicity | 66 | 30 | 57 | 14 |
| **Musculoskeletal and connective tissue disorders** | | | | |
| Arthralgia[b] | 47 | 4 | 35 | 1 |
| **Nervous system disorders** | | | | |
| Headache | 45 | 2 | 43 | 1 |
| Neuropathy peripheral | 33 | 1 | 24 | 1 |
| Paresthesia | 22 | 0 | 10 | 0 |
| **Skin and subcutaneous tissue disorders** | | | | |
| Rash and related conditions | 47 | 1 | 33 | 1 |
| **Gastrointestinal disorders** | | | | |
| Abdominal pain[c] | 43 | 5 | 28 | 0 |
| Constipation | 41 | 1 | 21 | 1 |
| Nausea | 37 | 3 | 52 | 7 |
| Oral mucositis | 35 | 5 | 30 | 10 |
| Pancreatitis/lipase elevation | 34 | 15 | 37 | 20 |
| Vomiting | 24 | 1 | 40 | 3 |
| Diarrhea | 20 | 0 | 35 | 3 |
| **General disorders** | | | | |
| Pyrexia | 44 | 4 | 26 | 3 |
| Fatigue or asthenia | 40 | 3 | 38 | 4 |
| Fluid retention and edema | 24 | 1 | 48 | 4 |
| **Vascular disorders** | | | | |
| Hypertension | 34 | 14 | 15 | 7 |
| Hemorrhage | 31 | 2 | 30 | 7 |
| **Blood and lymphatic system disorders** | | | | |
| Febrile neutropenia | 28 | 25 | 22 | 20 |
| **Metabolism and nutrition disorders** | | | | |
| Impaired glucose tolerance | 20 | 5 | 20 | 9 |
| **Cardiac disorders** | | | | |
| Cardiac arrhythmias | 22 | 3 | 17 | 6 |

[a]Graded using CTCAE v5.0.
[b]Includes arthralgia, arthritis, back pain, flank pain, intervertebral disc degeneration, joint swelling, osteoarthritis, neck pain, pain, pain in extremity, pain of skin, sciatica, spinal pain, tendonitis, and tenosynovitis.
[c]Includes abdominal discomfort, abdominal distension, abdominal pain, abdominal pain lower, abdominal pain upper, chronic gastritis, colitis, enteritis, enterocolitis, gastric ulcer, gastritis, gastroenteritis, gastrointestinal pain, gastroesophageal reflux disease, and helicobacter gastritis.

AR=adverse reaction; CTCAE=Common Terminology Criteria for Adverse Events; Ph+ ALL=Philadelphia chromosome-positive acute lymphoblastic leukemia.

## 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.

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

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# ICLUSIG + chemotherapy safety profile in the PhALLCON study[1,2]

### Serious and fatal adverse reactions

- Serious adverse reactions occurred in 63% of ICLUSIG patients and 57% of imatinib patients[1,2]
- Serious adverse reactions (>2%) in ICLUSIG patients included febrile neutropenia (18%), pyrexia (6%), thrombocytopenia (4.3%), sepsis (3.7%), septic shock (3.7%), anemia (2.5%), hemorrhage (2.5%), neutropenia (2.5%), pancreatitis (2.5%), peripheral neuropathy (2.5%), pneumonia (2.5%), and acute kidney injury (2.5%)[1]
- Fatal adverse reactions occurred in 6% of patients in both arms (ICLUSIG: 9 patients; imatinib: 5 patients). These events included sepsis in 6 (3.7%) ICLUSIG patients and 2 (2.5%) imatinib patients, sudden death, pneumonitis, and respiratory failure in 1 (0.6%) ICLUSIG patient each, and pulmonary sepsis, depressed level of consciousness, and pseudomembranous colitis in 1 (1.2%) imatinib patient each. One fatal TEAE was considered treatment-related in the imatinib arm (depressed level of consciousness)[1,2]

### Discontinuations

- Permanent discontinuation due to adverse reactions occurred in 13% of ICLUSIG patients. Adverse reactions resulting in permanent discontinuation in >2% of ICLUSIG patients included arterial occlusive events and sepsis[1]

### Laboratory abnormalities

- The most common Grade 3 or 4 laboratory abnormalities (≥20%) in ICLUSIG patients are decreased white blood cell count, decreased neutrophil cell count, decreased platelet count, decreased lymphocyte cell count, decreased hemoglobin, increased lipase, and increased ALT[1]

### Clinically relevant

- Clinically relevant adverse reactions in ≤10% of ICLUSIG patients included urinary tract infection (10%), arterial occlusive events (6%), cardiac failure (6%), and acute kidney injury (4.3%)[1]

### In PhALLCON, ICLUSIG demonstrated comparable safety outcomes with imatinib, including rates and severity of AOEs and VTE[3,4]

- The rate of TE-VTEs was 11.7% in ICLUSIG patients vs 12.3% in imatinib patients
- The rate of TE-AOEs was 2.5% in ICLUSIG patients vs 1.2% in imatinib patients

AOEs=arterial occlusive events; ALT=alanine aminotransferase; TE-AOEs=treatment-emergent arterial occlusive events; TE-VTEs=treatment-emergent venous thromboembolic events; TEAE=treatment-emergent adverse event; VTEs=venous thromboembolic events.

## IMPORTANT SAFETY INFORMATION (cont'd)

**WARNINGS AND PRECAUTIONS** (cont'd)

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

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

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

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

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

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# Important Safety Information (cont'd.)

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

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

## ADVERSE REACTIONS

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

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

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

## DRUG INTERACTIONS

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

**Strong CYP3A Inducers:** Avoid coadministration.

## USE IN SPECIFIC POPULATIONS

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

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

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

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

**References: 1.** ICLUSIG. Prescribing information. Takeda Pharmaceuticals U.S.A. Inc. 10/2025. **2.** Sasaki K, Kantarjian HM, Short NJ, et al. *Cancer*. 2021;127(15):2648-2656. **3.** Jabbour E, Kantarjian HM, Aldoss I, et al. Supplement 2. eTbale1. *JAMA*. 2024;331(21):1814 1823.

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