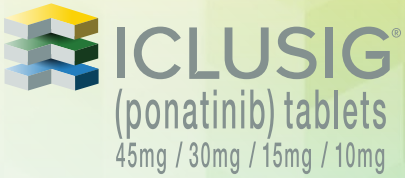


ICLUSIG® (ponatinib) PRODUCT MONOGRAPH

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.**

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

Takeda | ONCOLOGY

Table of Contents

FDA, US Food and Drug Administration; NCCN, National Comprehensive Cancer Network; NGS, next-generation sequencing; Ph+ ALL, Philadelphia chromosome–positive acute lymphoblastic leukemia.

ICLUSIG® (ponatinib) MONOGRAPH OVERVIEW

INTRODUCTION

This product monograph reviews disease state information and ICLUSIG® (ponatinib) clinical data for Ph+ ALL.

Given that ICLUSIG is an established treatment option as monotherapy for adult patients with Ph+ ALL for whom no other kinase inhibitors are indicated or T315I-positive Ph+ ALL, this product monograph focuses on ICLUSIG in combination with chemotherapy for the treatment of newly diagnosed adult patients with Ph+ ALL. Additional ICLUSIG information is included in the Product Characteristics section of this monograph.

The information contained within this monograph is intended for formulary decision makers at payers or institutions, including, but not limited to, pharmacy, medical, and quality directors, clinical pharmacists, and case managers.

Ph+ ALL OVERVIEW

EPIDEMIOLOGY

Ph+ ALL is a rare and aggressive hematologic cancer that occurs more frequently in adults than in children.[1-5] The Philadelphia chromosome (BCR::ABL1 oncogene) is formed by a translocation between parts of chromosomes 9 and 22. This gene alteration produces a unique tyrosine kinase that drives the pathogenesis of Ph+ ALL.[2,6,7]

Estimated new cases of ALL, US 2024[1]

6550

~25% of adults with ALL are Ph+[2]

Estimated new cases of Ph+ ALL, US 2024[1,2]

1638

In 2024, an estimated 6550 adults in the US will be diagnosed with ALL, of which about 1638 cases will be Ph+ ALL.[1,2] Since 2010, the 5-year overall survival (OS) rate of adults with Ph+ ALL is 50%.[8]

OS rate is based on real-world evidence. All real-world evidence has limitations. The limitations of this analysis include: relatively small number of patients with Ph+ ALL and no data on treatment, so the analysis includes patients who did not receive any antileukemic treatment and may not reflect novel treatments. Results should be interpreted with caution.

ALL, acute lymphoblastic leukemia; BCR::ABL1, breakpoint cluster region-Abelson.

DEEP MOLECULAR RESPONSE RATES and CLINICAL OUTCOMES

In a meta-analysis, low deep molecular response rates contribute to suboptimal survival with 1G and 2G TKIs in adults with newly diagnosed Ph+ ALL*

Low rates of deep molecular responses[9]

- 32% of patients (95% CI: 25%, 40%) achieved a complete molecular response (CMR)† with a 1G or 2G TKI (n=526/1644)

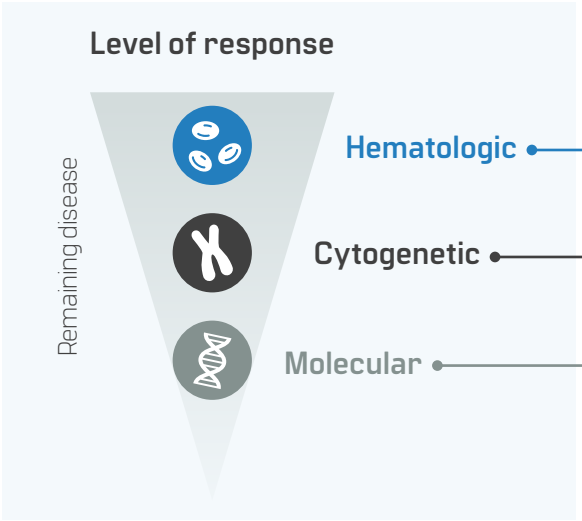
Suboptimal survival[9]

- Patients who received a 1G or 2G TKI had a
  - 2-year OS of 58% (95% CI: 53%, 63%)
  - 3-year OS of 50% (95% CI: 42%, 58%)

CMR (also known as minimal residual disease [MRD] negativity) may be an important determinant of clinical outcomes across genetic subtypes and may be the next major clinical goal after achieving a hematologic complete remission (CR)[10,11]

This meta-analysis (25 studies; N=1644) had several limitations: it relied on study-level data with heterogeneous treatment regimens; it included studies based on targeted rather than systemic literature search; results may be limited due to changes in treatment patterns and clinical practice since data were reported; and data for analysis were limited to studies available at the time of analysis. Data should be interpreted with caution.

*Based on a 2018 targeted literature review of 25 clinical studies comparing the effectiveness of BCR::ABL1 TKIs as frontline therapy in 1644 patients with newly diagnosed Ph+ ALL (median age: 46 years; age range: 8–85 years).[9]



1G, first-generation; 2G, second-generation; CI, confidence interval; CML, chronic myeloid leukemia; TKI, tyrosine kinase inhibitor.
†CMR was defined as the absence of detectable BCR::ABL1 transcripts with a sensitivity of 0.01%.[9]

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RESISTANT MUTATIONS

Resistant mutations in BCR::ABL1 occur frequently in Ph+ ALL and drive disease progression[13]

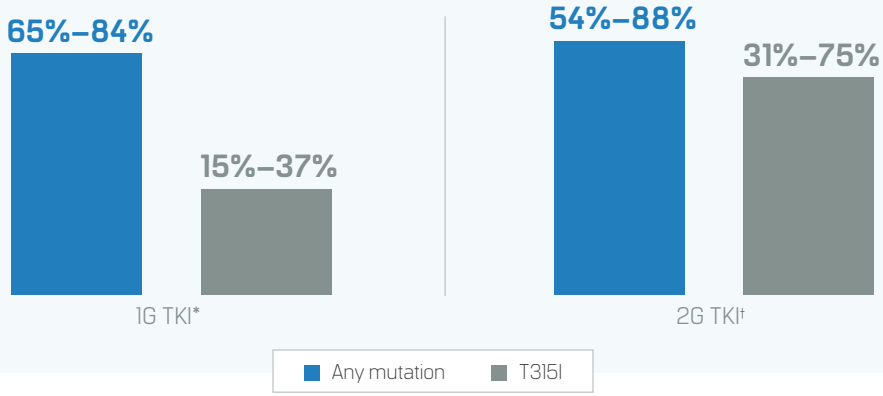
At diagnosis

38% of all patients with Ph+ ALL (n=12/32) had a BCR::ABL1 resistance mutation; of those **17%** had a T315I mutation (n=2/12)

At diagnosis, about 38% (37.5%) of patients with Ph+ ALL will have a BCR::ABL1 mutation.[13] In relapsed patients following their respective frontline treatments, 65%–84% of patients treated with a 1G TKI had a BCR::ABL1 mutation, and 54%–88% of patients treated with a 2G TKI had a BCR::ABL1 mutation.[13-19] These patients are approximately 5x more likely to experience disease relapse or death compared with other patients with ALL.[15]

At relapse[13-19]

Frequency of BCR::ABL1 kinase mutations in relapsed patients following their respective frontline treatment



Unadjusted, indirect comparison for descriptive purposes only; clinical significance is not implied. Cross-trial comparisons are potentially confounded by differences in trial design and study population. Studies may have unobserved, confounding, and treatment selection biases as well as other limitations that should be considered when comparing results with clinical trials. Outcomes should be interpreted with caution because of small sample size, limited follow-up, and heterogenous patient population.

*Based on 3 studies of adult patients with relapsed Ph+ ALL (n=26, n=20, n=54) given imatinib + chemotherapy according to protocol in respective studies.[13-15]

†Based on 4 studies of adult patients with relapsed Ph+ ALL (n=13, n=13, n=17, n=24) given dasatinib + chemotherapy according to protocol in respective studies.[16-19]

RESISTANT MUTATIONS (cont'd)

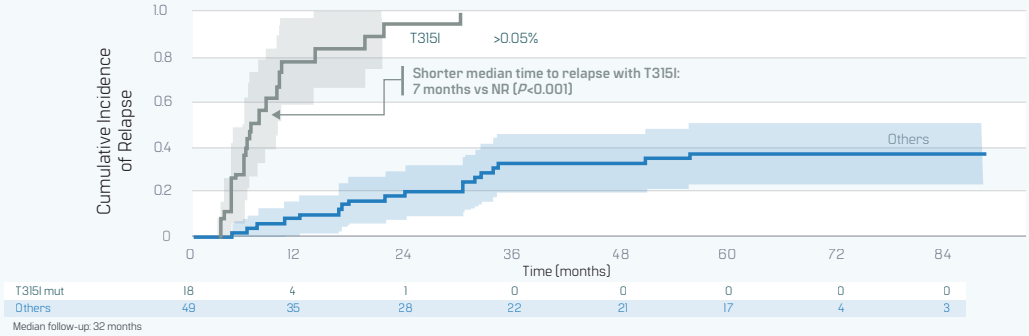
T315I is the most common BCR::ABL1 resistant mutation in Ph+ ALL and is the most difficult to treat

T315I mutations occur in up to 75% of patients with Ph+ ALL.[19] These patients are more likely to relapse faster and have a shorter median survival than patients without the T315I mutation.[13,19,20]

The below study was a Phase 2 study done in adult patients aged 55 years or older (N=71) with newly diagnosed Ph+ and/or BCR::ABL1+ ALL to evaluate the efficacy and safety of induction and consolidation therapy with a 2G TKI in combination with chemotherapy.[19]

Patients with a T315I mutation have a median time to relapse of 7 months vs NR in patients without T315I (*P*<0.001)[13,19]

Time to relapse among patients in CR treated with a 2G TKI + low-intensity chemotherapy with/without T315I

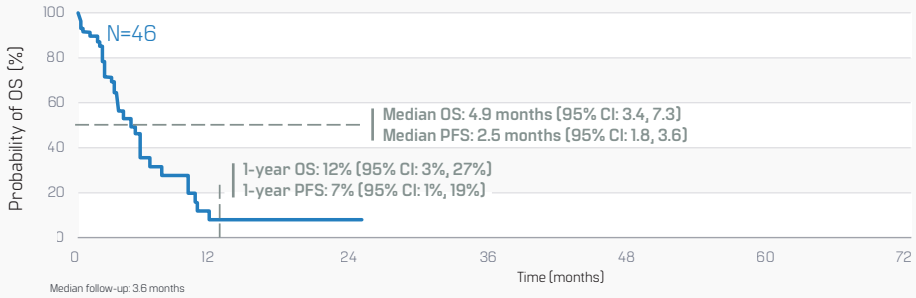


Median follow-up: 32 months

The below study was an epidemiologic study on survival of adult patients aged 18 years or older (N=222) with CML or Ph+ ALL possessing the T315I mutation with a documented hematologic or cytogenic resistance to 1G or 2G TKIs.[20]

Patients with a T315I mutation have a 1-year OS of only 12%[20]

OS from first T315I mutation detection*



Median follow-up: 3.6 months

Real-world analyses are often nonrandomized, observational, retrospective studies that may have unobserved confounding and treatment selection biases as well as other limitations that should be considered when comparing results with clinical trials. Outcomes should be interpreted with caution because of small sample size, limited follow-up, and heterogenous patient population.

HSCT, hematopoietic stem cell transplantation; NR, not reached; OS, overall survival; PFS, progression-free survival.

*Treatments after detection of T315I were reported in 216 patients (CML and Ph+ ALL grouped). Treatments included ≥1 of the following: 2G BCR::ABL1 TKI, hydroxyurea, imatinib, cytarabine, HSCT, MK-0457, other investigational drug, or interferon-α.[20]

PRECISION MEDICINE and NGS TESTING[21]

Ponatinib is the only BCR::ABL1 TKI with no contraindicated mutations

NCCN Guidelines–Recommended Treatment Options Based on BCR::ABL1 Mutation Profile

Therapy	Contraindicated Mutations*
Imatinib	Too numerous to include
Dasatinib	*T315I/A, F317L/V/I/C,* or *V299L*
Nilotinib	*T315I, Y253H, E255K/V, F359V/C/I,* or *G250E*
Bosutinib	*T315I, V299L, G250E,* or *F317L*†
Ponatinib	None‡

The NCCN Guidelines recommend:

- Molecular characterization of ALL at diagnosis
  - Comprehensive testing by NGS for gene fusions and pathogenic mutations
- Tailoring treatment to specific patient and disease characteristics
  - Use of a specific TKI should account for anticipated/prior TKI intolerance, BCR::ABL1 mutations, and disease-related features

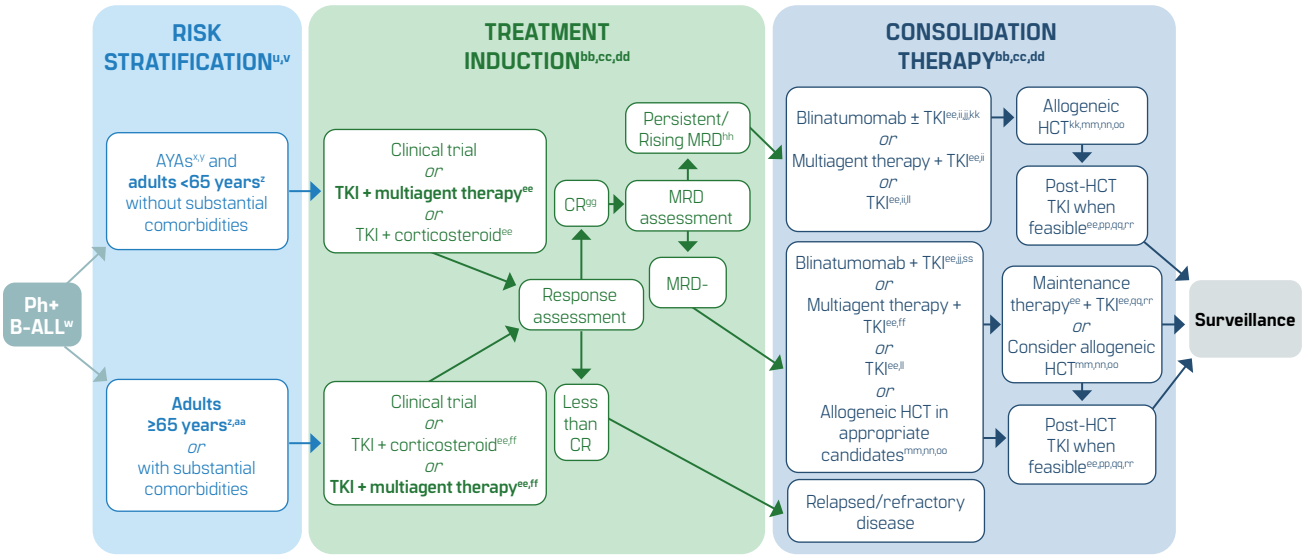
*There are compound mutations that can cause resistance to ponatinib, but those are uncommon following treatment with bosutinib, dasatinib, or nilotinib.

†Nilotinib may be preferred over bosutinib in patients with F317L mutation.

‡Ponatinib has activity against T315I mutations and is effective in treating patients with resistant or progressive disease on multiple TKIs. However, it is associated with a high frequency of serious vascular events (eg, strokes, heart attacks, tissue ischemia). For details, see https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/203469s037lbl.pdf

NCCN GUIDELINES

The NCCN Guidelines recommend a TKI in combination with multiagent therapy for newly diagnosed adult Ph+ ALL[21]



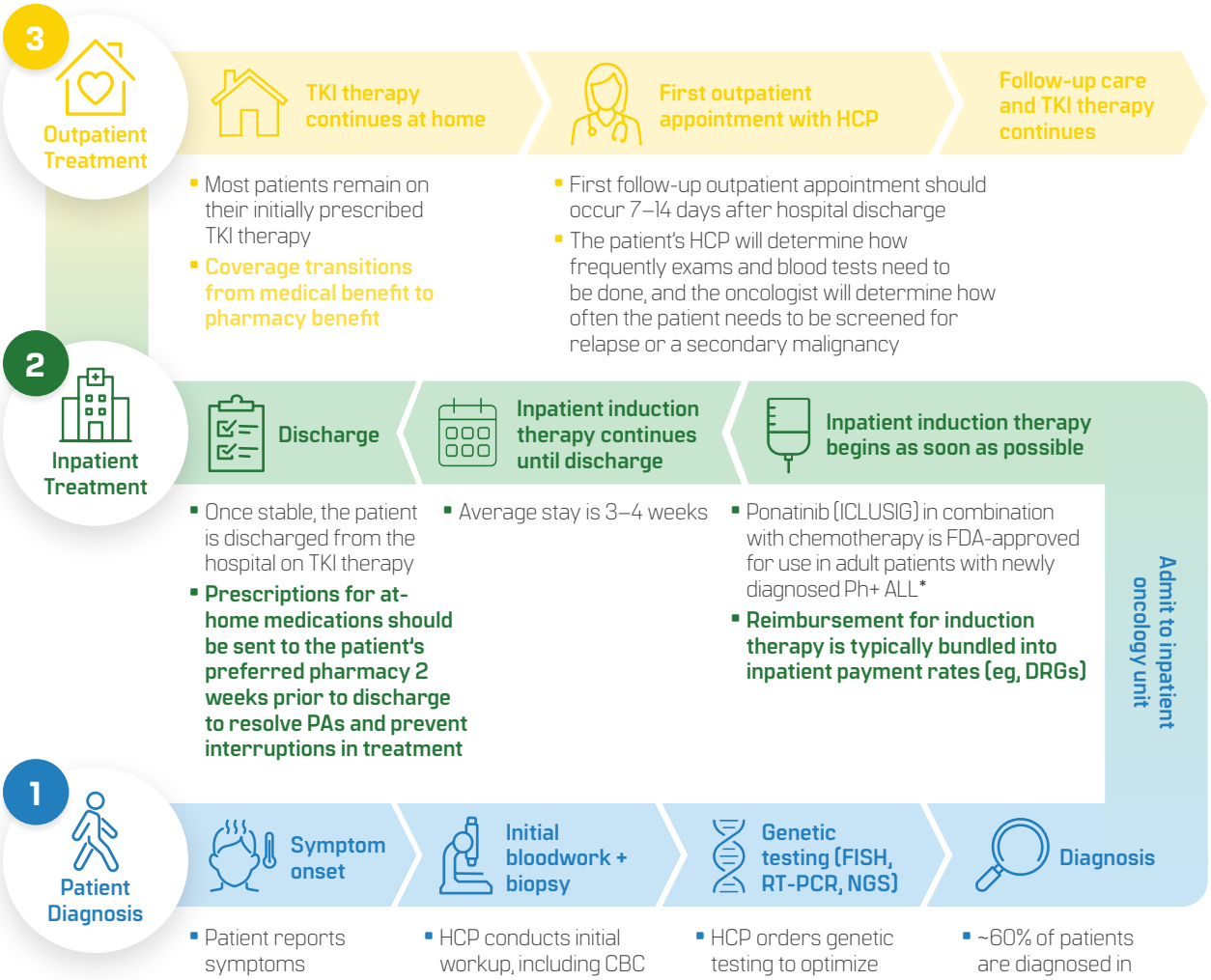
AYA, adolescent and young adult; B-ALL, B-cell acute lymphoblastic leukemia; HCT, hematopoietic cell transplantation; MRD, minimal residual disease.

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.

[u]Clinical Risk Stratification (ALL-2). [v]Cytogenetic and Molecular Prognostic Risk Stratification for B-ALL (ALL-3). [w]It is reasonable to approach the initial treatment of BP-CML with similar strategies to Ph+ ALL, with a goal of proceeding to HCT. [x]The ALL Panel considers AYA to be within the age range of 15 to 39 years. However, this age range is not a firm reference point because some of the recommended regimens have not been comprehensively tested across all ages. [y]For additional considerations in the care of AYA patients with ALL, see the NCCN Guidelines for Adolescent and Young Adult (AYA) Oncology. [z]Chronological age is a poor surrogate for fitness for therapy. Patients should be evaluated on an individual basis, including for the following factors: end-organ reserve, end-organ dysfunction, and performance status. [aa]For additional considerations in the care of adult patients ≥65 years with ALL, see the NCCN Guidelines for Older Adult Oncology. [bb]TKI options include (in alphabetical order): bosutinib, dasatinib, imatinib, nilotinib, or ponatinib. Not all TKIs have been directly studied within the context of each specific regimen and the panel notes that there are limited data for bosutinib in Ph+ ALL. Use of a specific TKI should account for anticipated/prior TKI intolerance, dose used, BCR::ABL1 mutations, and disease-related features. Imatinib use in first line should be restricted to patients who cannot tolerate broader acting TKIs. Jabbour E, et al. *J Clin Oncol* 2023;41, no. 36_suppl. 398868. For contraindicated mutations, see ALL-D 4 of 9. [cc]ALL treatment regimens include CNS prophylaxis. See Evaluation and Treatment of Extramedullary Involvement (ALL-B). [dd]Principles of Supportive Care (ALL-C). [ee]Principles of Systemic Therapy (ALL-D). [ff]Consider dose modifications appropriate for patient age and performance status. Principles of Systemic Therapy - Treatment of Adults ≥65 years or Adults with Substantial Comorbidities (ALL-D 7 of 9). [gg]Adequate count recovery per protocol is recommended before transitioning to post-remission therapy, even in the presence of MRD negativity. If count recovery is not achieved, additional follow-up for MRD may be warranted. Assess for myelosuppression secondary to TKI and consider dose reduction. [hh]The prognostic significance of MRD positivity may be regimen-, ALL subtype-, and/or ALL risk-dependent. MRD timepoints and levels prompting allogeneic HCT should be guided by the specific treatment protocol being used. For patients with negative MRD by flow cytometry but positive MRD by an FDA-approved NGS assay, consider repeat testing before consolidation is started to confirm MRD status. In general, MRD positivity at the end of induction predicts high relapse rates and should prompt evaluation for allogeneic HCT. Therapy aimed at eliminating MRD prior to allogeneic HCT is preferred when possible (Discussion). [ii]Consider using an alternative and more broadly acting TKI. Treatment options are based on BCR::ABL1 mutation profile (ALL-D 4 of 9). [jj]Supportive Care: Toxicity Management (ALL-C 2 of 4). [kk]Although long-term remission after blinatumomab monotherapy is possible, allogeneic HCT should be considered as consolidative therapy. [ll]TKI monotherapy is seldom effective as induction; however, it may be considered as consolidation/maintenance in those unfit for additional therapies. [mm]Optimal timing of HCT is not clear. For fit patients, additional therapy is recommended to eliminate MRD prior to transplant. Proceeding to allogeneic HCT with MRD is not optimal. [nn]Data suggest that for patients aged ≤21 years, particularly for those who achieve MRD negativity, allogeneic HCT may not offer an advantage over chemotherapy + TKI. Schultz KR, et al. *J Clin Oncol* 2009;27:5175-5181; Schultz KR, et al. *Leukemia* 2014;28:1467-1471. [oo]Many variables determine eligibility for allogeneic HCT including donor availability, depth of remission, comorbidities, and social support. [pp]See Discussion for use of different TKIs in this setting. [qq]TKI should be continued for at least 2 years post-HCT. The recommended duration of TKI during maintenance chemotherapy is at least until completion of maintenance chemotherapy. The optimal duration of TKI is unknown in both settings. [rr]Consider periodic MRD monitoring (no more than every 3 months) for patients with complete molecular remission (undetectable levels). Increased frequency may be indicated for detectable levels. [ss]For patients who are not candidates for multiagent therapy.

PATIENT TREATMENT JOURNEY

The Ph+ ALL patient treatment journey often begins immediately at diagnosis with inpatient induction treatment transitioning to outpatient treatment[19,21-26]



*This indication is approved under accelerated approval based on MRD-negative CR at the end of induction. Continued approval for this indication may be contingent upon verification of clinical benefit in a confirmatory trial(s).

CBC, complete blood count; DRG, diagnosis-related group; FISH, fluorescence in situ hybridization; HCP, health care provider; PA, prior authorization; RT-PCR, reverse transcriptase polymerase chain reaction.

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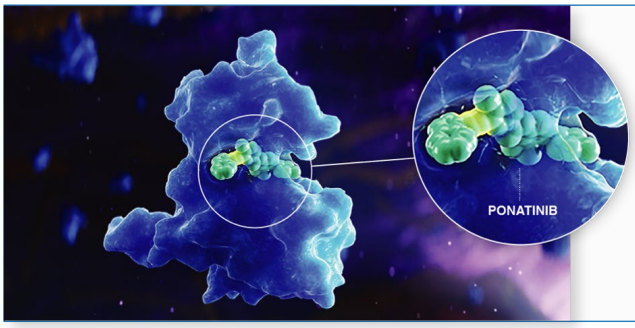
MECHANISM OF ACTION

Ponatinib is the only pan-mutational BCR::ABL1 inhibitor and the only 3G TKI in Ph+ ALL.[25]

Ponatinib is a kinase inhibitor. Ponatinib inhibited the in vitro tyrosine kinase activity of ABL and T315I-mutant ABL with IC_{50} concentrations of 0.4 nM and 2.0 nM, respectively. Ponatinib inhibited the in vitro activity of additional kinases with IC_{50} concentrations between 0.1 nM and 20 nM, including members of the VEGFR, PDGFR, FGFR, EPH receptors and SRC families of kinases, and KIT, RET, TIE2, and FLT3. Ponatinib inhibited the in vitro viability of cells expressing native or mutant BCR::ABL, including T315I. In mice, treatment with ponatinib reduced the size of tumors expressing native or T315I-mutant BCR::ABL when compared to controls.



- Ponatinib inhibits BCR::ABL1 with and without kinase domain mutations[25,27,28]
- Ponatinib shows activity against all known single-point resistance mutations, including T315I[25,27,28]

Preclinical activity does not necessarily correlate with clinical outcomes.

EPH, erythropoietin-producing hepatoma; FGFR, fibroblast growth factor receptor; FLT3, fms-like tyrosine kinase 3; IC_{50}, half-maximal inhibitory concentration; KIT, receptor protein-tyrosine kinase; PDGFR, platelet-derived growth factor receptor; RET, rearranged during transfection; SRC, sarcoma; TIE2, epidermal growth factor homology domains-2; VEGFR, vascular endothelial growth factor receptor.

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ICLUSIG® (ponatinib) in Combination With Chemotherapy: CLINICAL EFFICACY DATA and SAFETY PROFILE in ADULT PATIENTS WITH NEWLY DIAGNOSED Ph+ ALL

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FDA-Approved Indications for Adults With Ph+ ALL

Ponatinib (ICLUSIG) is the first and only FDA-approved TKI for patients with newly diagnosed Ph+ ALL, in combination with chemotherapy

BCR::ABL1 TREATMENT	Contraindicated mutations[21]	Newly diagnosed Ph+ ALL	T315I+ Ph+ ALL	Other indications in Ph+ ALL
Imatinib[29]	Yes	✖	✖	✔ Relapsed/refractory
Dasatinib[30]	Yes	✖	✖	✔ Resistance/intolerance to prior therapy
Nilotinib[31]	Yes	✖	✖	✖
Bosutinib[32]	Yes	✖	✖	✖
Ponatinib (ICLUSIG)[25]	No	✔*	✔	✔ When no other kinase inhibitors are indicated

*ICLUSIG in combination with chemotherapy. This indication is approved under accelerated approval based on MRD-negative CR at the end of induction. Continued approval for this indication may be contingent upon verification of clinical benefit in a confirmatory trial(s).

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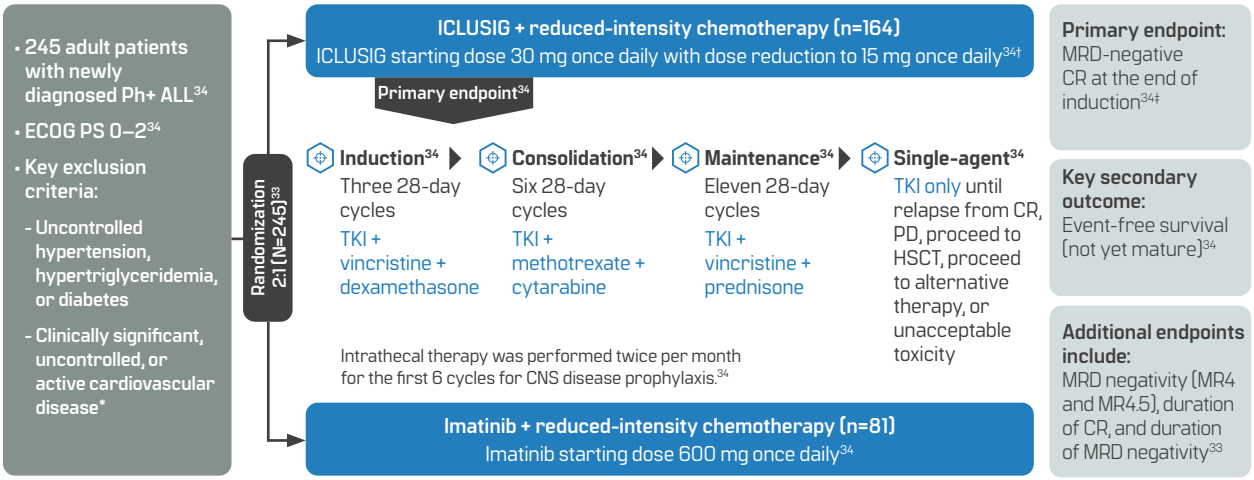
PhALLCON TRIAL DESIGN

PhALLCON was the first head-to-head phase 3 clinical trial in adult patients with newly diagnosed Ph+ ALL[33]

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 at the end of induction[25]



- 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[25]
- Single-agent therapy after chemotherapy for newly diagnosed Ph+ ALL is not an approved regimen[25]

AP, accelerated phase; BP, blast phase; cDNA, complementary deoxyribonucleic acid; CNS, central nervous system; CRi, incomplete remission; ECOG PS, Eastern Cooperative Oncology Group performance status; HSCT, hematopoietic stem cell transplant; PD, progressive disease.

*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 excluded.[25]

†The ICLUSIG dose was reduced to 15 mg once daily after completion of the induction phase and achievement of MRD-negative CR.[25]

‡MRD-negative was defined as ≤0.01% BCR::ABL1/ABL1 or undetectable BCR::ABL1 transcripts in cDNA with ≥10,000 ABL1 transcripts, and meeting criteria for CR.[25]

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BASELINE CHARACTERISTICS[25]

Patient Characteristics at Entry	ICLUSIG 30 mg → 15 mg With Chemotherapy (n=164)	Imatinib 600 mg With Chemotherapy (n=81)
Median age, years (range)	54 (19–82)	52 (19–75)
Age category, n (%)		
18 to <45 years	58 (35)	29 (36)
45 to <60 years	45 (27)	22 (27)
≥60 years	61 (37)	30 (37)
Sex, n (%)		
Female	90 (55)	43 (53)
Race, n (%)		
White	104 (63)	62 (77)
Not reported	28 (17)	2 (3)
Asian	20 (12)	11 (14)
Black or African American	9 (5)	4 (5)
ECOG performance status, n (%)		
0	72 (44)	33 (41)
1	85 (52)	43 (53)
2	7 (4)	5 (6)
Baseline BCR::ABL1 Dominant Variant, n (%)		
p190	114 (70)	53 (65)
p210	40 (24)	25 (31)
Undetermined/not tested	10 (6)	3 (4)
Prephase Therapy*	74 (45)	41 (51)
Comorbidities, n (%)		
Hypertension	58 (35)	30 (37)
Diabetes	39 (24)	24 (30)
Dyslipidemia	29 (18)	23 (28)

*Per protocol, patients were allowed to receive one cycle of optional prephase therapy, excluding TKI prior to randomization.

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CLINICAL EFFICACY DATA

Efficacy was based on the MRD-negative CR rate at the end of induction[21,25,33]

Term	Definition
MRD-Negative	≤0.01% BCR::ABL1/ABL1 or undetectable BCR::ABL1 transcripts in cDNA with ≥10,000 ABL1 transcripts
CR	Met the following criteria for at least 4 weeks: • No circulating blasts and <5% blasts in the bone marrow • Normal maturation of all cellular components in the bone marrow • No extramedullary disease • ANC >1000/mcL • Platelets >100,000/mcL

If a patient achieves MRD negativity alone, they may not be in CR based on platelet recovery and ANC.

Efficacy results in patients with Ph+ ALL with baseline BCR::ABL1 dominant variant of p190 or p210[25]

ICLUSIG in combination with chemotherapy demonstrated a statistically significant higher MRD-negative CR rate at the end of induction compared with imatinib in combination with chemotherapy.

	ICLUSIG 30 mg → 15 mg With Chemotherapy (n=154)	Imatinib 600 mg With Chemotherapy (n=78)
MRD-negative CR* at end of induction		
Achieved at the end of induction % (n/N)	30 (46/154)	12 (9/78)
Risk difference (95% CI)†	0.18 (0.08, 0.28)	
P-value†	0.0004	
CR‡ at end of induction % (n/N)	79 (122/154)	63 (49/78)

The analysis population for MRD-negative CR included 232 randomized patients who had a baseline BCR::ABL1 dominant variant of p190 or p210 as determined by central laboratory tests (154 patients in the ICLUSIG arm and 78 in the imatinib arm).

ANC, absolute neutrophil count; cDNA, complementary deoxyribonucleic acid; COVID-19, coronavirus disease of 2019.

*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.

†Difference, 95% CI and two-sided *P*-value are based on Cochran-Mantel-Haenszel method stratified by the randomization stratification factor.

‡CR is defined as no circulating blasts and <5% blasts in the bone marrow with normal maturation of all cellular components; no evidence of extramedullary disease (ie, CNS involvement, lymphadenopathy, splenomegaly, skin/gum infiltration, testicular mass); and hematologic recovery of ANC >1.0 x 10^9/L and platelets >100 x 10^9/L for at least 4 weeks.

CLINICAL SAFETY PROFILE[25]

Serious adverse reactions occurred in 63% of patients receiving ICLUSIG in combination with chemotherapy

Serious adverse reactions in >2% of patients (N=244)	
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%
Acute kidney injury	2.5%
Fatal adverse reactions occurred in 6% of patients who received ICLUSIG in combination with chemotherapy	
Sepsis	3.7%
Sudden death	0.6%
Pneumonitis	0.6%
Respiratory failure	0.6%

Dose modifications and discontinuations with ICLUSIG

Permanent discontinuation of ICLUSIG due to adverse reactions

- Occurred in 13% of patients

Adverse reactions resulting in permanent discontinuation of ICLUSIG in >2% of patients

- Arterial occlusive events
- Sepsis

Dose modifications (interruption or reduction) of ICLUSIG due to adverse reactions

- Occurred in 71% of patients

Adverse reactions leading to dose modifications of ICLUSIG in >5% of patients

- Increased ALT
- Neutropenia
- Increased lipase
- Thrombocytopenia
- Increased AST
- Febrile neutropenia
- Abdominal pain

ALT, alanine transaminase; AST, aspartate transaminase.

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

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

CLINICAL SAFETY PROFILE[25] (cont'd)

Adverse reactions (>10%) in patients with newly diagnosed Ph+ ALL

Adverse Reaction	ICLUSIG 30 mg → 15 mg With Chemotherapy (n=163)		Imatinib 600 mg With Chemotherapy (n=81)	
	All grades (%)	Grade 3 or 4 (%)	All grades (%)	Grade 3 or 4 (%)
Hepatobiliary disorders				
Hepatotoxicity	66	30	57	14
Musculoskeletal and connective tissue disorders				
Arthralgia*	47	4.3	35	1.2
Myalgia	13	1.2	10	1.2
Nervous system disorders				
Headache	45	1.8	43	1.2
Neuropathy peripheral	33	1.2	24	1.2
Paresthesia	22	0	10	0
Peripheral sensory neuropathy	12	0	12	0
Skin and subcutaneous tissue disorders				
Rash and related conditions	47	1.2	33	1.2
Gastrointestinal disorders				
Abdominal pain†	43	4.9	28	0
Constipation	41	0.6	21	1.2
Nausea	37	3.1	52	7
Oral mucositis	35	4.9	30	10
Pancreatitis/lipase elevation	34	15	37	20
Vomiting	24	1.2	40	2.5
Diarrhea	20	0	35	2.5

CTCAE, Common Terminology Criteria for Adverse Events.
Graded using CTCAE v5.0.

*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.

†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.

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

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

CLINICAL SAFETY PROFILE[25] (cont'd)

Adverse reactions (>10%) in patients with newly diagnosed Ph+ ALL (cont'd)

Adverse Reaction	ICLUSIG 30 mg → 15 mg With Chemotherapy (n=163)		Imatinib 600 mg With Chemotherapy (n=81)	
	All grades (%)	Grade 3 or 4 (%)	All grades (%)	Grade 3 or 4 (%)
General disorders				
Pyrexia	44	4.3	26	2.5
Fatigue or asthenia	40	2.5	38	3.7
Fluid retention and edema	24	0.6	48	3.7
Vascular disorders				
Hypertension	34	14	15	7
Hemorrhage	31	1.8	30	7
Venous thromboembolic events	12	3.1	10	2.5
Blood and lymphatic system disorders				
Febrile neutropenia	28	25	22	20
Metabolism and nutrition disorders				
Impaired glucose tolerance	20	4.9	20	9
Hyperlipidemia	16	1.2	15	1.2
Decreased appetite	10	0	19	3.7
Cardiac disorders				
Cardiac arrhythmias	22	2.5	17	6
Infections				
Sepsis*	17	12	15	11
Pneumonia	11	7	11	6
Respiratory, thoracic, and mediastinal disorders				
Cough	17	0	6	0
Dyspnea	13	1.2	4.9	2.5

Clinically relevant adverse reactions in ≤10% of patients receiving ICLUSIG in combination with chemotherapy: urinary tract infections (10%), arterial occlusive events (6%), cardiac failure (6%), and acute kidney injury (4.3%).

The most common Grade 3 or 4 laboratory abnormalities (>20%) included decreased white blood cell count, decreased neutrophil cell count, decreased platelet count, decreased lymphocyte cell count, decreased hemoglobin, increased lipase and increased ALT.

Graded using CTCAE v5.0.

*Includes abdominal sepsis, bacteremia, bacterial sepsis, device-related sepsis, escherichia bacteremia, fungemia, klebsiella bacteremia, klebsiella sepsis, neutropenic sepsis, pseudomonal sepsis, sepsis, septic shock, staphylococcal bacteremia, staphylococcal sepsis, streptococcal bacteremia, and urosepsis.

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

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

VALUE SUMMARY

1. Ponatinib is the **only pan-mutational BCR::ABL1 inhibitor** and the **only third-generation TKI** in Ph+ ALL[21,35]

2. ICLUSIG in combination with chemotherapy is the **first and only FDA-approved frontline TKI for adults with newly diagnosed Ph+ ALL**[25]

3. **The PhALLCON study is a Phase 3, randomized, international, open-label, multicenter trial evaluating the efficacy and safety of ICLUSIG** versus imatinib in combination with reduced-intensity chemotherapy as a frontline therapy for adult patients with **newly diagnosed Ph+ ALL**

4. **Efficacy results in patients with Ph+ ALL with baseline BCR::ABL1 dominant variant of p190 or p210:** PhALLCON demonstrated a **statistically significant higher MRD-negative CR rate** at the end of induction for patients randomized to the ICLUSIG arm (30%) compared with the imatinib arm (12%) (P=0.0004)[25]

5. **Serious adverse reactions** occurred in 63% of patients, including febrile neutropenia in 18% of patients receiving ICLUSIG in combination with chemotherapy[25]

6. **Permanent discontinuation** of ICLUSIG due to adverse reactions occurred in 13% of patients[25]

PRODUCT CHARACTERISTICS

DOSING and ADMINISTRATION[25]

Recommended starting dose

Newly Diagnosed Ph+ ALL

The recommended starting dosage of ICLUSIG in combination with chemotherapy is 30 mg orally once daily with a reduction to 15 mg orally once daily upon achievement of MRD-negative (≤0.01% BCR::ABL1/ABL1) CR at the end of induction. Continue ICLUSIG in combination with chemotherapy for up to 20 cycles until loss of response or unacceptable toxicity.

Monotherapy for Ph+ ALL for Whom No Other Kinase Inhibitors Are Indicated or T315I-positive Ph+ ALL

The optimal dose of ICLUSIG has not been identified.

The recommended starting dosage of ICLUSIG is 45 mg orally once daily. Continue ICLUSIG until loss of response or unacceptable toxicity.

Consider discontinuing ICLUSIG if response has not occurred by 3 months.

CP-CML

The recommended starting dosage of ICLUSIG 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 dosage of 30 mg or 45 mg orally once daily. Continue ICLUSIG until loss of response at the re-escalated dose or unacceptable toxicity.

Consider discontinuing ICLUSIG if hematologic response has not occurred by 3 months.

AP-CML and BP-CML

The optimal dose of ICLUSIG has not been identified.

The recommended starting dosage of ICLUSIG is 45 mg orally once daily. Consider reducing the dose of ICLUSIG for patients with AP-CML who have achieved a major cytogenetic response (MCyR). Continue ICLUSIG until loss of response or unacceptable toxicity.

Consider discontinuing ICLUSIG if response has not occurred by 3 months.

Recommended dose modifications

Permanently discontinue ICLUSIG for any of the following adverse events:

- Grade 3 or 4 cardiovascular or cerebrovascular AOE
- Grade 4 peripheral vascular and other AOE or VTE
- Grade 4 heart failure
- AST or ALT ≥3 times ULN with bilirubin >2 times ULN and alkaline phosphatase <2 times ULN
- Symptomatic pancreatitis and serum lipase greater than 5 times ULN

AOE, arterial occlusive event; ULN, upper limit of normal; VTE, venous thromboembolism.

DOSING and ADMINISTRATION[25] (cont'd)

Recommended dose reductions

Dose reduction	Dosage for patients with CP-CML	Dosage for patients with AP-CML, BP-CML, and Ph+ ALL monotherapy	Dosage for patients with newly diagnosed Ph+ ALL
First	30 mg orally once daily	30 mg orally once daily	15 mg orally once daily
Second	15 mg orally once daily	15 mg orally once daily	10 mg orally once daily
Third	10 mg orally once daily	Permanently discontinue ICLUSIG in patients unable to tolerate 15 mg orally once daily	Permanently discontinue ICLUSIG in patients unable to tolerate 10 mg orally once daily
Subsequent reduction	Permanently discontinue ICLUSIG in patients unable to tolerate 10 mg orally once daily		

Recommended dose modifications for coadministration of strong CYP3A inhibitors

Avoid coadministration of ICLUSIG with strong CYP3A inhibitors. If coadministration of a strong CYP3A inhibitor cannot be avoided, reduce the dosage of ICLUSIG as recommended in the table below.

After the strong CYP3A inhibitor has been discontinued for 3 to 5 elimination half-lives, resume the ICLUSIG dosage that was tolerated prior to initiating the strong CYP3A inhibitor.

Current ICLUSIG dosage	Recommended ICLUSIG dosage with a strong CYP3A inhibitor
45 mg orally once daily	30 mg orally once daily
30 mg orally once daily	15 mg orally once daily
15 mg orally once daily	10 mg orally once daily
10 mg orally once daily	Avoid coadministration of ICLUSIG with a strong CYP3A inhibitor

Administration

ICLUSIG may be taken with or without food

Swallow tablets whole. Do not crush, break, cut, or chew tablets

If a dose is missed, take the next dose at the regularly scheduled time the next day

AP, acute phase chronic myeloid leukemia; BP, blast phase chronic myeloid leukemia; CYP, cytochrome p450.
Based on CTCAE v5.0: Grade 1 mild, Grade 2 moderate, Grade 3 severe, Grade 4 life-threatening.

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

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

HOW SUPPLIED/STORAGE and HANDLING[25]

ICLUSIG is available as 10-mg, 15-mg, 30-mg, and 45-mg tablets

Strength	NDC
10 mg	63020-536-30
15 mg	63020-535-30
30 mg	63020-533-30
45 mg	63020-534-30

Store ICLUSIG tablets at 20°C to 25°C (68°F to 77°F); excursions permitted to 15°C to 30°C (59°F to 86°F)

NDC, National Drug Code; USP, United States Pharmacopeia.

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

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

PHARMACODYNAMICS[25]

The efficacy of ICLUSIG was evaluated in PACE, a single-arm, open-label, international, multicenter trial. Eligible patients had CML and Ph+ ALL whose disease was considered to be resistant or intolerant to a prior kinase inhibitor. Patients were assigned to one of six cohorts based on disease phase (CP-CML, AP-CML, or BP-CML/Ph+ ALL), resistance or intolerance (R/I) to prior kinase inhibitors, and the presence of the T315I mutation. Patients were administered a starting dose of ICLUSIG 45 mg orally once daily. The major efficacy outcome measure for patients with CP-CML was MCyR, which included complete and partial cytogenetic responses (CCyR and PCyR). The major efficacy outcome measure for patients with AP-CML, BP-CML, and Ph+ ALL was major hematologic response (MaHR), defined as either a complete hematologic response (CHR) or no evidence of leukemia (NEL). In PACE, the dose intensity-safety relationship indicated that there are significant increases in Grade ≥3 adverse reactions (hypertension, thrombocytopenia, pancreatitis, neutropenia, rash, ALT increase, AST increase, lipase increase, myelosuppression) over the dose range of 15 mg to 45 mg. In addition to dose, increased age and history of ischemia, hypertension, diabetes, or hypercholesterolemia were also contributory factors to a higher incidence of AOEs.

The efficacy of ICLUSIG was evaluated in OPTIC, a dose-optimization trial. Eligible patients had CP-CML whose disease was considered to be resistant or resistant/intolerant to at least 2 prior kinase inhibitors or who had the T315I mutation. Patients received one of three starting dosages: 45 mg orally once daily, 30 mg orally once daily, or 15 mg orally once daily. Patients who received a starting dose of 45 mg or 30 mg had a dose reduction to 15 mg once daily upon achieving ≤1% BCR-ABL1[IS]. The major efficacy outcome measure was ≤1% BCR-ABL1[IS] at 12 months. In OPTIC, an exposure-response relationship between ponatinib exposure and molecular response rate at 12 months was observed. A relationship between higher ponatinib exposures and higher incidence of adverse reactions, including thrombocytopenia (Grade ≥3) and AOEs, was observed. In vitro, there was no significant inhibition of platelet aggregation with ponatinib at concentrations seen clinically and up to 0.7 mcg/mL (1.23 μM).

Cardiac Electrophysiology

The QT interval prolongation potential of ICLUSIG was assessed in 39 patients with cancer who received ICLUSIG 30 mg, 45 mg, or 60 mg (0.67 to 1.33 times the approved maximum recommended starting dose) orally once daily. No large mean increase (i.e., >20 msec) in QTc interval was detected.

QTc, corrected QT.

PHARMACOKINETICS[25]

Ponatinib administered to patients with cancer exhibited approximately dose proportional increases in both steady-state C_{max} and AUC over the dose range of 2 mg to 60 mg (0.04 to 1.33 times the approved maximum recommended starting dose). The mean (CV%) C_{max} and $AUC_{(0-24)}$ of ICLUSIG 45 mg orally once daily at presumed steady-state in patients with advanced hematologic malignancies were 73 ng/mL (74%) and 1253 ng•hr/mL (73%), respectively. The mean (CV%) C_{max} and $AUC_{(0-24)}$ of ICLUSIG 30 mg orally once daily at presumed steady-state in patients with advanced hematologic malignancies were 65 ng/mL (28%) and 1080 ng•hr/mL (29%), respectively. Exposure increased by approximately 90% (median; range: 20%–440%) between the first dose and presumed steady-state.

Absorption

The absolute bioavailability of ponatinib is unknown. Peak concentrations of ponatinib are observed within 6 hours after ICLUSIG oral administration.

Effect of Food

Following ingestion of either a high-fat (approximately 900 to 1000 calories with approximately 150, 250, and 500 to 600 calories derived from protein, carbohydrate, and fat, respectively) or low-fat meal (approximately 547 calories with approximately 56, 428, and 63 calories derived from protein, carbohydrate, and fat, respectively) by 22 healthy volunteers, plasma ponatinib exposures (AUC and C_{max}) were not different when compared to fasting conditions.

Distribution

Ponatinib is greater than 99% bound to plasma proteins in vitro. There was no plasma protein binding displacement of ponatinib (145 nM) in vitro by other highly protein bound medications (ibuprofen, nifedipine, propranolol, salicylic acid, and warfarin). The mean (CV%) apparent steady-state volume of distribution is 1223 liters (102%) following oral administration of ICLUSIG 45 mg orally once daily for 28 days in patients with cancer.

Elimination

The mean (range) terminal elimination half-life of ponatinib was approximately 24 (12–66) hours following ICLUSIG 45 mg orally once daily for 28 days in patients with cancer.

Metabolism

At least 64% of a dose undergoes Phase I and Phase II metabolism. CYP3A4 and to a lesser extent CYP2C8, CYP2D6, and CYP3A5 are involved in the Phase I metabolism of ponatinib in vitro. Ponatinib is also metabolized by esterases and/or amidases.

Excretion

Following a single oral dose of radiolabeled ponatinib, approximately 87% of the radioactive dose was recovered in the feces and approximately 5% in the urine.

Specific Populations

No clinically significant differences in the pharmacokinetics of ponatinib were observed based on age (19–85 years), body weight (41–152 kg), and mild-to-moderate renal impairment (creatinine clearance 30–89 mL/min, estimated by the Cockcroft-Gault equation).

Patients with Renal Impairment

ICLUSIG has not been studied in patients with severe renal impairment. Although renal excretion is not a major route of ponatinib elimination, the potential for severe renal impairment to affect hepatic elimination has not been determined.

Patients with Hepatic Impairment

A single, 30 mg oral dose of ICLUSIG was administered to subjects with normal hepatic function and to subjects with mild (Child-Pugh A), moderate (Child-Pugh B), and severe (Child-Pugh C) hepatic impairment. Compared to subjects with normal hepatic function, there was no trend of increased ponatinib exposure in subjects with hepatic impairment. There was an increased incidence of adverse reactions (eg, gastrointestinal disorders, including a case of severe pancreatitis) in subjects with hepatic impairment compared with subjects with normal hepatic function.

AUC, area under the curve; $AUC_{(0-24)}$, area under the curve from time zero to 24 hours; C_{max}, maximum concentration; CV, coefficient of variant.

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

DRUG INTERACTIONS[25]

Strong CYP3A Inhibitors

Coadministration of ponatinib with multiple doses of ketoconazole (strong CYP3A inhibitor) increased the ponatinib $AUC_{0\text{-}INF}$ by 78% and C_{max} by 47%.

Strong CYP3A Inducers

Coadministration of ponatinib with multiple doses of rifampin (strong CYP3A inducer) decreased the ponatinib $AUC_{0\text{-}INF}$ by 62% and C_{max} by 42%.

Gastric Acid Reducing Agents

Coadministration of ponatinib with multiple doses of lansoprazole (proton pump inhibitor) decreased the ponatinib $AUC_{0\text{-}INF}$ by 6% and C_{max} by 25%.

In Vitro Studies

CYP Enzymes: Ponatinib does not inhibit CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP3A, or CYP2D6 and does not induce CYP1A2, CYP2B6, or CYP3A.

Transporter Systems: Ponatinib is a weak substrate for both P-gp and BCRP. Ponatinib is not a substrate for OATP1B1, OATP1B3, and OCT1.

Ponatinib inhibits P-gp, BCRP, and BSEP. Ponatinib does not inhibit OATP1B1, OATP1B3, OCT1, OCT2, or the organic anion transporters OAT1 and OAT3.

$AUC_{0\text{-}INF}$, area under the curve from zero to time infinity; BCRP, breast cancer resistance protein; BSEP, bile salt export pump; OATP, organic anion transporting polypeptides; OCT1, organic cation transporter; P-gp, P-glycoprotein.

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

IMPORTANT SAFETY INFORMATION (CONT'D)

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.

IMPORTANT SAFETY INFORMATION (CONT'D)

WARNINGS AND PRECAUTIONS (CONT'D)

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.

IMPORTANT SAFETY INFORMATION (CONT'D)

WARNINGS AND PRECAUTIONS (CONT'D)

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 1×10^9/L or platelets less than 50×10^9/L, interrupt ICLUSIG until ANC at least 1.5×10^9/L and platelets at least 75×10^9/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 1-844-817-6468 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

IMPORTANT SAFETY INFORMATION (CONT'D)

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 accompanying full Prescribing Information, including Boxed Warning.

To learn more about ICLUSIG, please visit www.iclusig.com/hcp.

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