

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 2 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.**

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Takeda | ONCOLOGY

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NCCN, National Comprehensive Cancer Network; Ph+ ALL, Philadelphia chromosome–positive acute lymphoblastic leukemia.

ICLUSIG® (ponatinib) MONOGRAPH OVERVIEW

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INTRODUCTION

This product monograph reviews disease state information and ICLUSIG® (ponatinib) clinical data for Philadelphia Chromosome-Positive Acute Lymphoblastic Leukemia (Ph+ ALL).

This document focuses on ICLUSIG in combination with chemotherapy as a treatment option for adult patients with newly diagnosed Ph+ ALL.

ICLUSIG is also an established monotherapy treatment option for adult patients with Ph+ ALL for whom no other kinase inhibitors are indicated, or for those with T315I-positive Ph+ ALL.

Additional details regarding ICLUSIG are provided in the Product Characteristics section of this document.

The information contained within this monograph is intended for formulary decision makers within payer organizations and healthcare 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 is challenging to treat in newly diagnosed adult patients.[1-5] Ph+ ALL occurs more frequently in adults than in children.[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]

In 2026, it is estimated that 6250 patients in the US will be newly diagnosed with ALL, and of those, approximately 1000 will be newly diagnosed adult patients with Ph+ ALL.[1,2,8,9]

6250 Estimated new cases of **ALL**, US 2026[1,2]

1000 Estimated new cases of **adult Ph+ ALL**, US 2026[8,9]

~25% of adults with ALL are Ph+[8]

Among adults with Ph+ ALL, the estimated 5-year overall survival between 2010 and 2017 was 50%[10*]

***OS estimates are derived from real-world evidence, which is subject to limitations. These include a relatively small number of patients with Ph+ ALL and the absence of treatment-specific data; therefore, the analysis includes patients who may not have received antileukemic therapy and may not reflect outcomes with novel treatments. Results should be interpreted with caution.[10]**

ALL, acute lymphoblastic leukemia; BCR::ABL1, breakpoint cluster region-Abelson; Ph+ ALL, Philadelphia Chromosome-Positive Acute Lymphoblastic Leukemia.

DEEP MOLECULAR RESPONSE RATES & 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[11]*

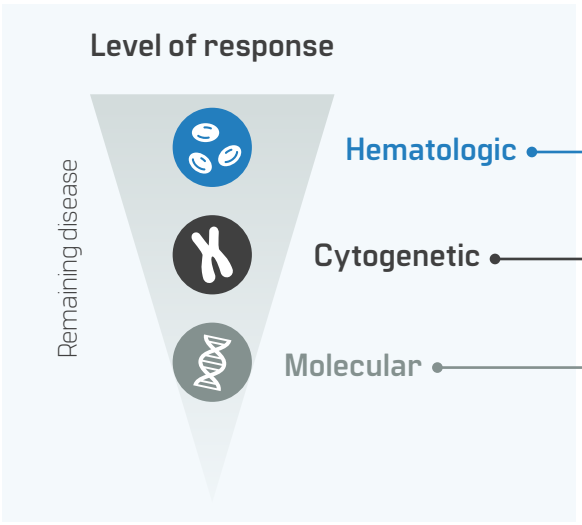
Failure to achieve a CMR[11,12]



- Over **2/3 of patients** failed to achieve a complete molecular response (CMR) with 1G or 2G TKIs + chemotherapy
- Outcomes with 1G and 2G TKIs vary by choice of agent and chemotherapy regimen

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)[12,13]

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. CMR was defined as the absence of detectable BCR::ABL transcripts with a sensitivity of 0.01%.[11]



1G, first-generation; 2G, second-generation; CI, confidence interval; CML, chronic myeloid leukemia; OS, overall survival; TKI, tyrosine kinase inhibitor.

*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).[11]

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RESISTANCE MUTATIONS

Resistance mutations in BCR::ABL1 occur frequently in Ph+ ALL and drive disease progression

At diagnosis

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

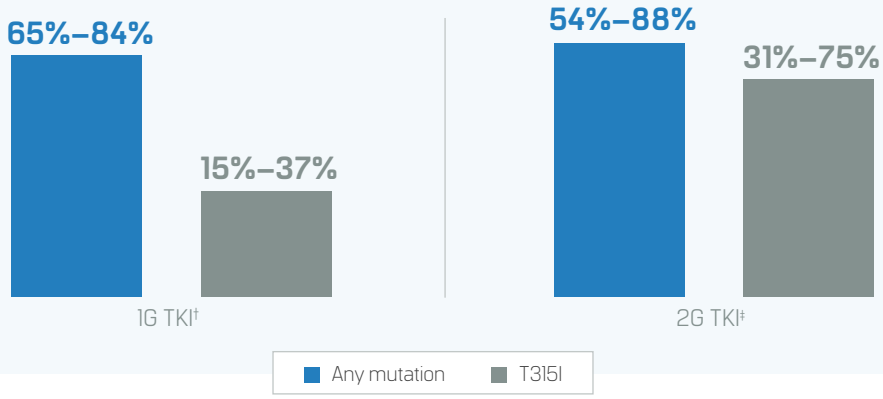
and of those, 17% had a T315I mutation (n=2/12)[15]*

Patients with the **BCR::ABL1 mutation** are

~5x **more likely** to experience disease relapse or death than patients without

In relapsed patients, the mutation was associated with significantly shorter disease-free survival (median, 8 vs 15.6 months, *P*=0.0068; HR=4.5)[16]

Frequency of BCR::ABL1 kinase mutations in relapsed patients following their respective frontline treatment[15-21]



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 heterogeneous patient population.

*This study was a randomized, multicenter, open-label, Phase 2 study to determine the safety and efficacy of induction therapy with imatinib in comparison with standard induction chemotherapy in adult patients older than 55 years with newly diagnosed Ph+ ALL.[15]

†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.[15-17]

‡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.[18-21]

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RESISTANCE MUTATIONS (cont'd)

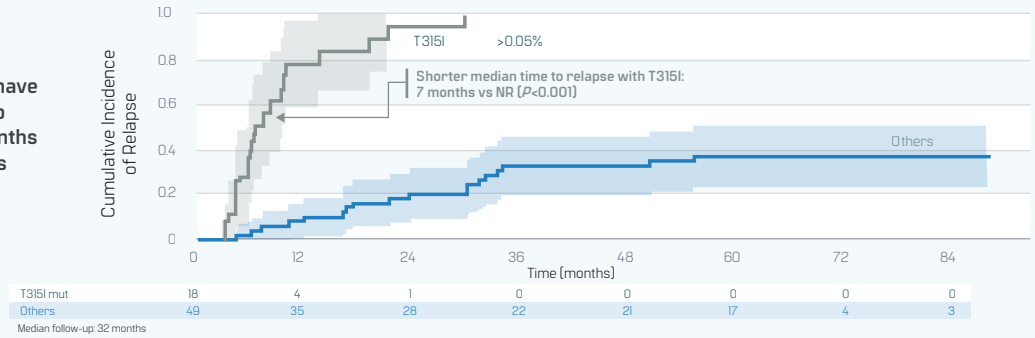
T315I is the most common BCR::ABL1 resistance mutation in Ph+ ALL and is the most difficult to treat

T315I mutations occur in up to 75% of patients with Ph+ ALL.[21] These patients are more likely to relapse faster and have a shorter median survival than patients without the T315I mutation.[15,21,22]

The efficacy and safety of induction and consolidation therapy with a 2G TKI in combination with chemotherapy was evaluated in a Phase 2 study in adult patients aged 55 years or older [N=71] with newly diagnosed Ph+ and/or BCR::ABL1+ ALL.[21]

Time to relapse among patients in CR treated with a 2G TKI + low-intensity chemotherapy with/without T315I[15,21]

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

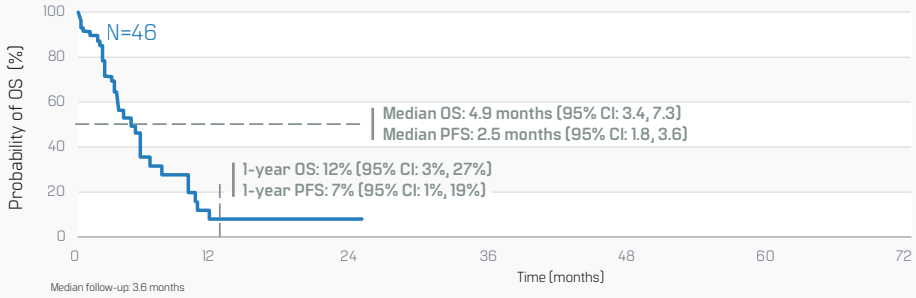


Median follow-up: 32 months

An epidemiologic study evaluated 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 cytogenetic resistance to 1G or 2G TKIs.[22]

OS from first T315I mutation detection[22]*

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



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 heterogeneous patient population.

HSCT, hematopoietic stem cell transplantation; NR, not reached; 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.[22]

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PRECISION MEDICINE & NGS TESTING[23]

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

NCCN Guidelines® Treatment Options Based on BCR::ABL1 Mutation Profile

Therapy	Contraindicated Mutations
Imatinib	Too numerous to include
Asciminib*	*A337T, P465S, M244V, or F359V/I/C*
Bosutinib	*T315I, V299L, G250E,* or *F317L*†
Dasatinib	*T315I/A, F317L/V/I/C, or V299L*
Nilotinib	*T315I, Y253H, E255K/V, F359V/C/I,* or *G250E*
Ponatinib*	None‡

NCCN Guidelines recommend:

- Molecular characterization of ALL at diagnosis includes
  - Multigene panel testing (MGPT) for gene fusions and pathogenic variants is recommended
- Tailoring treatment to specific patient and disease characteristics
  - Use of a specific TKI should account for anticipated/prior TKI intolerance, dose used, BCR::ABL1 mutations, and disease-related features

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NGS, next generation sequencing.

*Ponatinib and high-dose asciminib have activity against *T315I* mutations and are effective in treating patients with resistant or progressive disease (PD) on multiple TKIs.

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

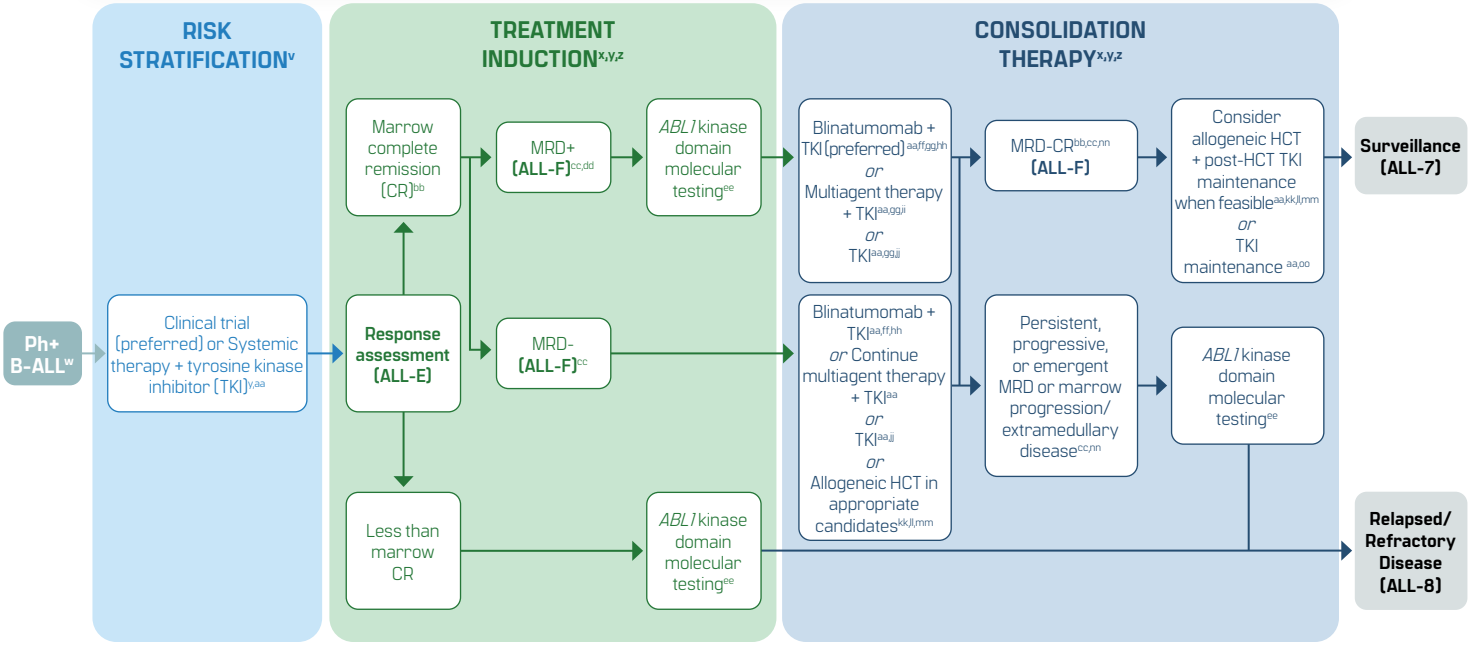
‡There are compound mutations (defined as harboring ≥2 mutations in the same BCR::ABL1 allele, such as *E255V*/*T315I*) that can cause resistance to ponatinib, but those are uncommon following treatment with bosutinib, dasatinib, or nilotinib (Zabriskie MS, et al. *Cancer Cell* 2014;26:428-442).

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NCCN GUIDELINES

NCCN Guidelines recommend a TKI in combination with multiagent therapy for newly diagnosed adult Ph+ ALL[23]



Note: All recommendations are NCCN Category 2A unless otherwise indicated.

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B-ALL, B-cell acute lymphoblastic leukemia; HCT, hematopoietic cell transplantation; MRD, minimal residual disease.

[v]Cytogenetic and Molecular Prognostic Risk Stratification for B-ALL (ALL-2) [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]TKI options include (in alphabetical order): bosutinib, dasatinib, imatinib, nilotinib, or ponatinib. Asciminib +/- another TKI is a category 2B, useful in certain circumstances option for patients with intolerance or contraindication to multiple other TKIs. 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 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. JAMA 2024;331:1814-1823. For mutations associated with resistance, see Mutation Profile Principles (ALL-D 2 of 29). [y]ALL treatment regimens include CNS prophylaxis. See Evaluation and Treatment of Extramedullary Involvement (ALL-B). [z]Principles of Supportive Care (ALL-C). [aa]Principles of Systemic Therapy (ALL-D). [bb]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. [cc]The preferred method of MRD quantification is an FDA-approved NGS-based assay to detect fusion genes or clonal rearrangements in immunoglobulin (Ig) and T-cell receptor (TCR) loci (does not require patient-specific primers), if available. Given the complexity of MRD management, referral to or consultation with a center with expertise is recommended for any patient with ALL with MRD positivity. [dd]BCR::ABL1 quantitative RT-PCR (qPCR) positivity may reflect persistence in the myeloid compartment. Where feasible, flow sorting to isolate myeloid versus lymphoid cells for FISH/qPCR studies and/or NGS MRD may help to resolve. Of note, the presence of the Ph chromosome in the myeloid compartment does not necessarily imply a diagnosis of CML with lymphoid blast transformation. [ee]ABL1 kinase domain molecular testing may be less sensitive in the setting of minimal disease burden. See Mutation Profile Principles (ALL-D 2 of 29) for treatment options based on BCR::ABL1 mutation profile. [ff]Principles of Supportive Care: Toxicity Management (ALL-C 2 of 6). [gg]Consider using an alternative and more broadly acting TKI. See Mutation Profile Principles (ALL-D 2 of 29). [hh]Blinatumomab + TKI is preferred in consolidation for those who have not achieved an MRD-negative remission and should be considered for those who have achieved MRD negativity. [ii]In the setting of MRD positivity after induction therapy, multiagent therapy + TKI can be a continuation of the initial induction therapy if ongoing decline in MRD is seen with subsequent cycles. Changes in therapy are generally not considered unless MRD positivity persists after 3 months of therapy, depending on the regimen used. [jj]TKI monotherapy is seldom effective as induction; however, it may be considered as consolidation/maintenance in those unfit for additional therapies. [kk]Data suggest that for patients aged ≤21 years, particularly for those who achieve MRD negativity, allogenic 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. [ll]Favored for poor risk B-ALL (ALL-2) and/or slow/incomplete MRD clearance. [mm]Principles of Allogeneic Hematopoietic Cell Transplant (ALL-G). [nn]Consider sequential MRD monitoring for patients with complete molecular remission (undetectable levels). Increased frequency may be indicated for detectable levels or for those discontinuing TKI. [oo]May include other elements of maintenance therapy, such as vincristine, corticosteroids, and IT therapy.

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PATIENT TREATMENT JOURNEY

The Ph+ ALL patient treatment journey often begins immediately at diagnosis, with inpatient induction treatment transitioning to outpatient treatment[21,23-28]

1 Patient Diagnosis

Symptom onset

- Patient reports symptoms indicative of low blood counts

Initial bloodwork + biopsy

- HCP conducts initial workup, including CBC and bone marrow aspiration and biopsy
- An ALL diagnosis generally requires ≥20% lymphoblasts in the blood or bone marrow

Genetic testing (FISH, RT-PCR, NGS)

- HCP orders genetic testing to optimize risk stratification and treatment planning
- The most common mutation is T315I, which occurs in up to 75% of patients with Ph+ ALL

Diagnosis

- ~60% of patients are diagnosed in the inpatient setting

Admit to inpatient oncology unit

2 Inpatient Treatment

Inpatient induction therapy begins as soon as possible

- Ponatinib (ICLUSIG) in combination with chemotherapy is FDA-approved for use in adult patients with newly diagnosed Ph+ ALL*
- **Reimbursement for induction therapy is typically bundled into inpatient payment rates (e.g., DRGs)**

Inpatient induction therapy continues until discharge

- Average stay is 3–4 weeks

Discharge

- Once stable, the patient is discharged from the hospital on TKI therapy
- **Prescriptions for at-home medications should be sent to the patient's preferred pharmacy 2 weeks prior to discharge to resolve PAs and prevent interruptions in treatment**

3 Outpatient Treatment

TKI therapy continues at home

- Most patients remain on their initially prescribed TKI therapy
- **Coverage transitions from medical benefit to pharmacy benefit**

First outpatient appointment with HCP

- First follow-up outpatient appointment should occur 7–14 days after hospital discharge
- The patient's HCP will determine how frequently exams and blood tests need to be done, and the oncologist will determine how often the patient needs to be screened for relapse or a secondary malignancy

Follow-up care and TKI therapy continues

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.

*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).

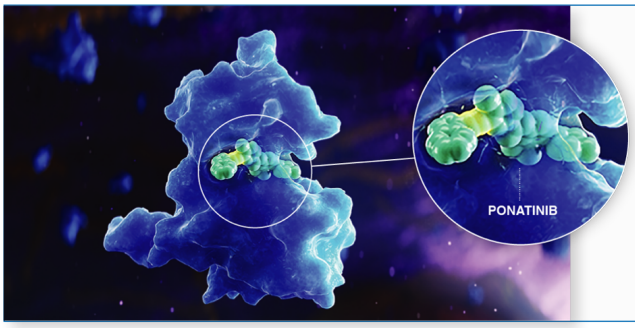
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MECHANISM OF ACTION

Ponatinib is the only pan-mutational BCR::ABL1 inhibitor, the only 3G TKI available in Ph+ ALL, and the only TKI FDA approved for newly diagnosed Ph+ ALL patients[27]

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[27,29,30]
- Ponatinib shows activity against all known single-point resistance mutations, including T315I[27,29,30]

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 & SAFETY DATA IN ADULT PATIENTS WITH NEWLY DIAGNOSED Ph+ ALL

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OVERVIEW OF TREATMENT OPTIONS IN ADULTS WITH Ph+ ALL

Ponatinib (ICLUSIG) is the first and only FDA-approved TKI indicated for the treatment of adult patients with newly diagnosed Ph+ ALL, in combination with chemotherapy[27]

BCR::ABL1 TKI TREATMENT	Contraindicated mutations[23]	Adults with newly diagnosed Ph+ ALL	T315I+ Ph+ ALL	Other adult indications in Ph+ ALL
Imatinib[31]	Yes	✖	✖	✔ Relapsed/ refractory
Dasatinib[32]	Yes	✖	✖	✔ Resistance/ intolerance to prior therapy
Nilotinib[33]	Yes	✖	✖	✖
Bosutinib[34]	Yes	✖	✖	✖
Asciminib[35]	Yes	✖	✖	✖
Ponatinib (ICLUSIG)[27]	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).

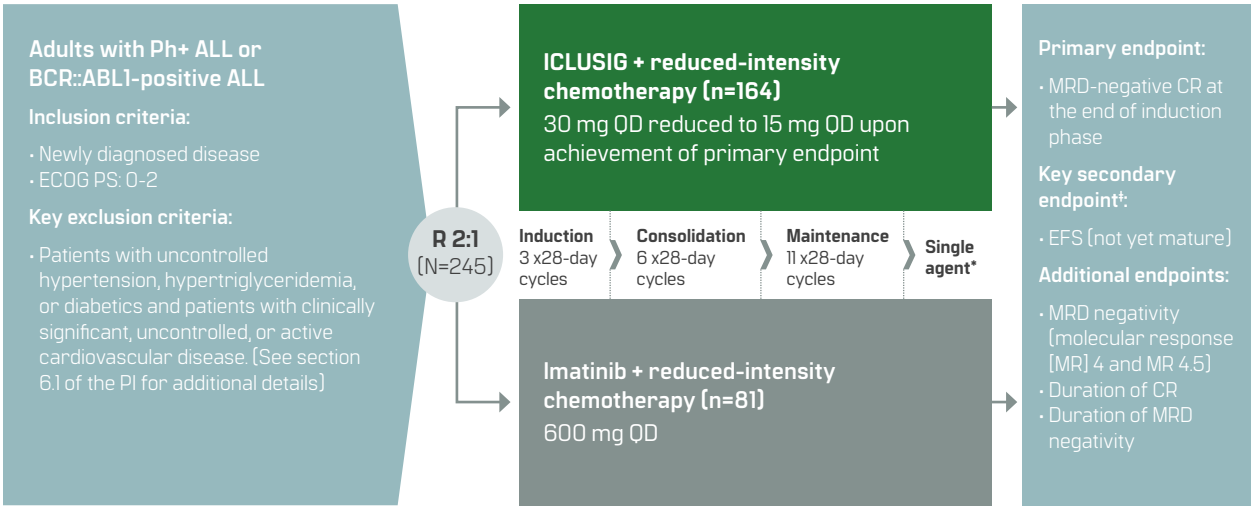
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PhALLCON TRIAL DESIGN

PhALLCON was the first head-to-head Phase 3 clinical trial comparing 2 TKIs in adult patients with newly diagnosed Ph+ ALL[27]

245 global participants were randomized 2:1 to receive ICLUSIG + chemotherapy* (n=164) or imatinib + chemotherapy* (n=81) in a study with a composite primary endpoint of MRD-negative CR† at the end of induction[27,37]



- 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[27]
- Single-agent therapy after chemotherapy for newly diagnosed Ph+ ALL is not an approved regimen[27]

ANC, absolute neutrophil count; cDNA, complementary deoxyribonucleic acid; CRi, incomplete remission; ECOG PS, Eastern Cooperative Oncology Group performance status; EFS, event-free survival.

*Patients received either ICLUSIG 30 mg or imatinib 600 mg once daily in combination with vincristine and dexamethasone for Cycles 1-3 (induction), alternating methotrexate and cytarabine for Cycles 4-9 (consolidation), and vincristine and prednisone for Cycles 10-20 (maintenance). ICLUSIG dose was reduced to 15 mg once daily after completion of the induction phase and achievement of MRD-negative CR. Following combination therapy, patients continued to receive ICLUSIG or imatinib as single-agent therapy until relapse from CR, progressive disease, hematopoietic stem cell transplantation, start of alternative therapy, or unacceptable toxicity.[27]

†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.[36] 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, and 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.[27,37]

‡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.[27,37]

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BASELINE CHARACTERISTICS[27]

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

EFFICACY DATA

Efficacy was based on the MRD-negative CR rate at the end of induction[27,37]

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[27]*

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.

*13 patients had atypical, missing, or unevaluable BCR::ABL1 assessment and were not included in the efficacy analysis.[24]

†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.[27]

‡Difference, 95% CI and two-sided P-value are based on Cochran-Mantel-Haenszel method stratified by the randomization stratification factor (age at the time of induction therapy: 18 to <45 years; ≥45 to <60 years; and ≥60 years).[27]

§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 (i.e., 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.[27]

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SAFETY DATA[27]

In adults with newly diagnosed Ph+ ALL:

ICLUSIG + chemotherapy had a comparable safety profile to imatinib + chemotherapy by utilizing optimized dosing[27]

Most common ARs* ≥20% in the PhALLCON study[27]

	ICLUSIG (n=163)		Imatinib (n=81)	
Adverse Reaction	**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	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‡	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	2.5	17	6

AR, adverse reaction; 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.

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SAFETY DATA[27] (cont'd)

ICLUSIG + chemotherapy safety profile in the PhALLCON study[24,27]

Serious and fatal adverse reactions

- Serious adverse reactions occurred in 63% of ICLUSIG patients and 57% of imatinib patients[24,27]
- 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%)[27]
- 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 (2.4%) 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)[24,27]

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[27]

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[27]

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%)[27]

In PhALLCON, ICLUSIG demonstrated comparable safety outcomes with imatinib, including rates and severity of AOEs and VTE[38]

- 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

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

VALUE SUMMARY

1. Ponatinib is the **only pan-mutational BCR::ABL1 inhibitor** and the **only third-generation TKI** in Ph+ ALL[23,39]

2. ICLUSIG in combination with chemotherapy is the **first and only FDA-approved frontline TKI for adults with newly diagnosed Ph+ ALL**[24,27]*

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**[27]

4. **Efficacy results in patients with Ph+ ALL:** 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)[27]

5. **Serious adverse reactions** occurred in 63% of ICLUSIG patients and 57% of imatinib patients[27]

6. **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[27]

*Approved under accelerated approval. Please see full Indications and Usage.

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

PRODUCT CHARACTERISTICS

DOSING & ADMINISTRATION[27]

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 concurrent with bilirubin >2 times ULN and alkaline phosphatase <2 times ULN
- Symptomatic pancreatitis and serum lipase >5 times ULN

AOE, arterial occlusive event; AP-CML, acute phase chronic myeloid leukemia; BP-CML, blast phase chronic myeloid leukemia; CP-CML, Chronic phase chronic myeloid leukemia; ULN, upper limit of normal; VTE, venous thromboembolism.

DOSING & ADMINISTRATION[27] (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

CYP, cytochrome p450.
Based on CTCAE v5.0: Grade 1 mild, Grade 2 moderate, Grade 3 severe, Grade 4 life-threatening.

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HOW SUPPLIED/STORAGE & HANDLING[27]

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

Strength	National Drug Codes (NDCs)
10 mg	63020-536-30
15 mg	63020-535-30
	63020-535-60
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)

PHARMACODYNAMICS[27]

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[27]

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 (e.g., 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.

DRUG INTERACTIONS[27]

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-glycoprotein (P-gp) and breast cancer resistance protein (BCRP). Ponatinib is not a substrate for organic anion transporting polypeptides (OATP1B1, OATP1B3) and organic cation transporter 1 (OCT1).

Ponatinib inhibits P-gp, BCRP, and bile salt export pump (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.

IMPORTANT SAFETY INFORMATION (CONT'D)

WARNINGS AND PRECAUTIONS

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

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

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

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

Hypertension: Serious or severe hypertension, including hypertensive crisis, has occurred. Patients may require urgent intervention for hypertension with confusion, headache, chest pain, or shortness of breath. Monitor blood pressure at baseline and as clinically indicated and manage as clinically indicated. Interrupt, dose reduce, or discontinue ICLUSIG if hypertension is not medically controlled. For significant worsening, labile or treatment-resistant hypertension, interrupt ICLUSIG and consider evaluating for renal artery stenosis.

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

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.

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.

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 $<1 \times 10^9$/L or platelets $<50 \times 10^9$/L, and resume when ANC $\geq 1.5 \times 10^9$/L and platelets $\geq 75 \times 10^9$/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.

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.

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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 30 mg orally once daily for patients with pre-existing hepatic impairment. For patients with newly diagnosed Ph+ ALL, no dosage adjustment is recommended when administering ICLUSIG to patients with mild hepatic impairment.

Please see full Prescribing Information, including Boxed Warning.

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

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