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Addressing Unmet Needs in Chronic Phase CML With Third-Generation TKI

BRIEF OVERVIEW OF CML

Chronic myeloid leukemia (CML) is an uncommon type of malignancy that is characterized by the presence of the Philadelphia (Ph) chromosome, which generates a *BCR-ABL1* fusion gene mutation in the blood-forming cells of the bone marrow (early or immature myeloid cells).¹ *BCR-ABL1*, the oncogenic tyrosine kinase protein that initiates the primary event, causes cells to proliferate uncontrollably, leading to the development of CML.¹ An estimated 8860 new cases of CML will be diagnosed in 2022 in the United States. CML is most frequently diagnosed among adults aged 65 to 74 years.^{2,3}

INDICATIONS AND USAGE

ICLUSIG® (ponatinib) is a kinase inhibitor indicated for the treatment of adult patients with:

- Chronic phase (CP) chronic myeloid leukemia (CML) with resistance or intolerance to at least two prior kinase inhibitors.
- Accelerated phase (AP) or blast phase (BP) CML or Philadelphia chromosome positive acute lymphoblastic leukemia (Ph+ ALL) for whom no other kinase inhibitors are indicated.
- T315I-positive CML (chronic phase, accelerated phase, or blast phase) or T315I-positive Ph+ ALL.

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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Classification

CML is a progressive disease that is classified into 3 phases of severity as determined by the percentage of blasts (ie, immature white blood cells) in the blood or bone marrow samples.⁴ Most patients are diagnosed in the chronic phase (CP). CP-CML is defined as the presence of less than 15% blasts, less than 20% basophils, and less than 30% blasts plus promyelocytes in peripheral blood or bone marrow and a platelet count of at least 100,000/mm³, with no extramedullary involvement.⁵ Blast phase (BP)-CML is defined as at least 30% blasts. Accelerated phase (AP)-CML is defined as CML that does not fulfill criteria for CP or BP disease, but meets criteria for the presence of at least 15%, but less than 30%, blasts in peripheral blood or bone marrow, at least 20% basophils, and at least 30% blasts plus promyelocytes. CP-CML may progress to AP-CML or BP-CML.^{4,5}

Standard of Care

First- and second-generation tyrosine kinase inhibitors (TKIs) are the standard first-line treatment strategy for patients with newly diagnosed CP-CML.⁶ TKIs inhibit the aberrant tyrosine kinase activity of the BCR-ABL1 oncoprotein and block the dysregulated signal cascade that maintains the leukemia phenotype of CML.⁶⁻⁹ The primary goal of TKI therapy is to prevent progression of CP-CML to AP- or BP-CML.⁶ Several first- and second-generation TKIs are available to treat patients with CML (**Table 1**).⁷⁻¹³ However, about 40% to 60% of patients with

CP-CML experience resistance to first- or second-line treatment and progress to later lines of therapy.^{6,7,14-17} In a 1-million-member plan, an estimated 19 patients each year will be diagnosed with CML. About 11% of these patients will progress to third-line therapy (2 new patients each year).^{3,14}

Although it is a common practice in the management of progressive disease or treatment resistance and/or intolerance to prior TKI therapies, sequential use (or cycling) of second-generation TKIs in the third line setting is associated with poor response rates and poor treatment outcomes in patients with CP-CML. There is an unmet need for available TKIs that can be used in the third-line setting (and beyond) to overcome treatment resistance and potentially improve patient outcomes in later lines.^{7-9,14-17,19,20}

TKI TREATMENT CONSIDERATIONS

TKI Resistance

TKI resistance is an important consideration in the treatment of CP-CML. Appropriate selection and sequencing of TKIs are needed to optimize clinical outcomes and to address the economic burdens of the total costs of CP-CML care (eg, treatment costs and resource utilization).^{6,14}

There are 2 types of resistance to TKIs: primary and secondary, which may be associated with poor response and outcomes.^{6,14} Primary TKI resistance is the lack of response to initial TKI therapy. As shown in

Table 1. FDA-Approved TKIs in CP-CML⁷⁻¹³

TKIs indicated first-line or after ≥ 1 prior TKI				TKIs indicated after ≥ 2 prior TKIs	
2001 ^{7,10}	2006 ^{8,10}	2007 ^{9,10}	2012 ^{10,11}	2012 ^{10,12}	2021 ^{10,13}
Gleevec® (imatinib)	Sprycel® (dasatinib)	Tasigna® (nilotinib)	Bosulif® (bosutinib)	ICLUSIG® (ponatinib) ^{a,b}	Scemblix® (asciminib) ^a
1G TKI	2G TKI	2G TKI	2G TKI	3G TKI	STAMP inhibitor
Indicated in CP-CML, AP-CML, BP-CML, Ph+ ALL	Indicated in CP-CML, AP-CML, BP-CML, Ph+ ALL	Indicated in CP-CML, AP-CML	Indicated in CP-CML, AP-CML, BP-CML	Indicated in CP-CML, AP-CML, BP-CML, Ph+ ALL	Indicated in CP-CML

1G, first generation; 2G, second generation; 3G, third generation; AP-CML, accelerated-phase chronic myeloid leukemia; BP-CML, blast-phase chronic myeloid leukemia; CP-CML, chronic-phase chronic myeloid leukemia; Ph+ ALL, Philadelphia chromosome–positive acute lymphocytic leukemia; STAMP, specifically targeting the ABL myristoyl pocket; TKIs, tyrosine kinase inhibitors.

^aIndicated for patients with T315I mutations.^{12,13}

^bIndicated for patients with AP-CML, BP-CML, and Ph+ ALL, for whom no other kinase inhibitors are indicated.¹²

IMPORTANT SAFETY INFORMATION (Continued) WARNINGS AND PRECAUTIONS

Arterial Occlusive Events (AOEs): AOEs, including fatalities, have occurred in patients who received ICLUSIG in OPTIC and PACE. These included cardiovascular, cerebrovascular, and peripheral vascular events. 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 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 OPTIC and PACE, AOEs were more frequent with increasing age.

- 2 **Please see Important Safety Information for ICLUSIG® (ponatinib) throughout.**
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Table 2.^{19,21} TKI response is measured clinically by major cytogenetic response (MCyR), which includes complete cytogenetic response (CCyR) and partial cytogenetic response (PCyR).¹² An acceptable response to TKI therapy is a CCyR.²² Secondary TKI resistance is the loss of response and disease progression (either due to the development of mutations in the *BCR-ABL1* kinase domain or other mechanisms of resistance).^{6,14} Some patients with CP-CML develop TKI resistance without known resistance mutations (*BCR-ABL1* kinase domain mutations).¹⁴

TKI resistance is associated with substantial economic burden with increasing costs of care for patients after first-, second-, and third-line TKI therapy. For patients who fail first-line TKI treatment, the average cost of care per year is \$78,677 (2012 US\$), inclusive of the costs of emergency department visits, inpatient services, ambulatory care, and laboratory tests. Costs increase to \$99,624 with failure of second-line treatment and \$181,029 with failure of third-line treatment.²³

T315I Mutation

Development of the T315I mutation, a point mutation in the *BCR-ABL1* kinase domain, confers secondary resistance to all first- and second-generation TKIs.⁶ It is the most common *BCR-ABL1* mutation in CML and is considered to be the most difficult-to-treat *BCR-ABL1* mutation.^{6,18,24-27} Approximately 17% of newly diagnosed patients with CML will develop a T315I mutation each year.¹⁸ This mutation contributes to disease progression, loss of response, and poor survival outcomes.²⁸ Patients with the T315I mutation have a 5-year overall survival (OS) ranging from 0% to 25% when treated with a second-generation TKI.²⁵ Because patients with T315I mutations

can experience resistance to all first- and second-generation TKIs, *BCR-ABL1* mutation testing to detect the T315I mutation can help inform TKI treatment selection.^{6,21,29,30}

TKI Treatment Sequencing in the Third-line Setting

In the first-line setting, patients typically experience high rates of CCyR ($\geq 77\%$), defined as less than or equal to 1% of cells in the bone marrow that contain the Ph chromosome, and OS ($\geq 92\%$).⁶ However, response rates and OS decrease with each progressive line of therapy.^{7-9,31-37}

The sequential use of second-generation TKIs (cycling) in the third-line setting results in low overall CCyR response rates and poor survival outcomes. Among patients who receive a second-generation TKI in the third-line setting, just 22% to 26% achieve a CCyR, and 64% of patients are still alive at 4 years.^{31,32} Patients with treatment resistance have worse outcomes with second-generation TKI cycling in the third-line setting. The overall CCyR rate is $\leq 18\%$, and OS is 26% (data from Ibrahim et al [n = 7] García-Gutiérrez et al [n = 17], and Garg et al [n = 12] publications).³¹⁻³⁵ This highlights the unmet need, as at least 82% of patients with CP-CML resistant to a second-generation TKI do not achieve CCyR when using a second-generation TKI in the third-line setting.³³⁻³⁵

TKI Options After Second-Generation TKI Treatment

There are opportunities to improve patient outcomes and address unmet treatment needs with the availability of a third-generation TKI. Expanding access to a third-generation TKI is an important consideration to overcome the limitations of TKI treatment resistance.¹²

To overcome treatment resistance in CP-CML, access to TKIs that can be used in the third-line setting and for patients with the T315I mutation must be improved. For patients with treatment resistance to a second-generation TKI, the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines[®]) recommend consideration of *BCR-ABL1* mutation status, including T315I.⁶

ICLUSIG[®] (ponatinib) has a distinct binding site on *BCR-ABL1*.^{12,13} ICLUSIG is the only third-generation, pan-mutational TKI that was purposefully engineered to inhibit *BCR-ABL1*, with or without kinase domain mutations.¹² It binds to the adenosine triphosphate binding site of *BCR-ABL1* and inhibits the activity of *BCR-ABL1*, leading to cell death.^{12,30} ICLUSIG shows activity against all known single-point

Table 2. Definitions for TKI Response Assessment Measures^{19,21}

	Response definition
MCyR ¹⁹	Ph+ chromosome detectable in 0%-35% of 20 metaphases; equivalent to <i>BCR-ABL1</i> $\leq 10\%$
CCyR ¹⁹	Ph+ chromosome undetectable; equivalent to <i>BCR-ABL1</i> $\leq 1\%$
PCyR ¹⁹	1% to 35% have Ph+ chromosome
MMR ²¹	<i>BCR-ABL1</i> $\leq 0.1\%$

CCyR, complete cytogenetic response; CP-CML, chronic-phase chronic myeloid leukemia; MCyR, major cytogenetic response; MMR, major molecular response; PCR, polymerase chain reaction; PCyR, partial cytogenetic response; Ph+, Philadelphia chromosome-positive.

IMPORTANT SAFETY INFORMATION (Continued) WARNINGS AND PRECAUTIONS (Continued)

Arterial Occlusive Events (AOEs) (continued): 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.

resistance mutations, including T315I.^{38,39} ICLUSIG® (ponatinib) is indicated for the treatment of adult patients with CP-CML with resistance or intolerance to at least 2 prior kinase inhibitors, AP-CML, BP-CML, or Ph+ ALL for whom no other kinase inhibitors are indicated, and T315I-positive CML (CP, AP, or BP) or T315I-positive Ph+ ALL. ICLUSIG is not indicated and is not recommended for the treatment of patients with newly diagnosed CP-CML.¹²

Scemblix (asciminib) is a kinase inhibitor indicated for the treatment of adult patients with Ph+ CML in CP that was previously treated with 2 or more TKIs and Ph+ CML in CP with the T315I mutation.¹³ Asciminib is a first-in-class STAMP inhibitor (specifically targeting the ABL myristoyl pocket). It binds to the myristoyl pocket in the kinase domain of *BCR-ABL1* to inhibit kinase activity. Asciminib shows activity against certain mutations (mutant forms of the *BCR::ABL1* kinase including T315I mutation).¹³

The NCCN Guidelines® for CML recommend ponatinib (ICLUSIG) as the preferred treatment option for patients with a T315I mutation.⁶ It is also a treatment option for CP-CML with resistance or intolerance to at least 2 prior TKIs, or for patients with AP-CML or BP-CML for whom no other TKI is indicated.⁶ There are compound mutations that can cause resistance to ICLUSIG, but those are uncommon following treatment with bosutinib, dasatinib, or nilotinib.^{12,28,34,35}

ICLUSIG® (PONATINIB) IN DIFFICULT-TO-TREAT CML

ICLUSIG is the only third-generation TKI and it is indicated for the treatment of adult patients with CP-CML with resistance or intolerance to at least 2 prior kinase inhibitors and T315I-positive CML (CP, AP, or BP).¹² ICLUSIG is not indicated, and is not recommended, for the treatment of patients with newly diagnosed CP-CML.¹² ICLUSIG has a Boxed Warning for arterial occlusive events (AOEs), venous thromboembolic events, heart failure, and hepatotoxicity.¹²

See additional Indications and Important Safety Information, including Boxed Warning, throughout this article.

Review of ICLUSIG Clinical Evidence

ICLUSIG has demonstrated long-term efficacy and safety in patients with difficult-to-treat CP-CML regardless of mutation status. These results are presented next.

PACE Trial

PACE was a 5-year, single-arm, open-label, international, multicenter, phase 2 trial that evaluated the safety and efficacy of ICLUSIG in difficult-to-treat CML and Ph-positive ALL. Of the enrolled study population (N = 449), 267 patients had CP-CML that was resistant or intolerant to a prior TKI or had a T315I mutation. Of patients representative of the difficult-to-treat CP-CML population (N = 270), 93% (n = 251) had received 2 or more TKI therapies, and 80% demonstrated resistance to prior TKI therapy. A proportion of patients in the CP-CML population of the trial had *BCR-ABL1* mutations: 49% (n = 132) had 1 or more kinase domain mutations in *BCR-ABL1*, and 24% had the T315I mutation.³⁸

Prior to receiving ICLUSIG, patients with CP-CML in the trial had high rates of resistance and poor responses to their prior TKI therapy.³⁸ Response rates to prior first- and second-line TKIs (dasatinib or nilotinib) were low; just 26% (n = 66/256) had achieved MCyR or better, including 13% who achieved CCyR and 3% (n = 8/256) had achieved major molecular response (MMR) or better.^{38,40}

Results

In the 5-year PACE trial, ICLUSIG delivered deep and durable efficacy in difficult-to-treat CP-CML regardless of mutation status. The median duration of follow-up for patients with CP-CML was 56.8 months (range, 0.1-73.1). The median duration of follow-up for the trial (all cohorts) was 37.3 months (range, 0.1-73.1).³⁸

At the primary end point, 70% of patients (n = 64) with T315I-positive CP-CML achieved MCyR by 12 months (**Figure 1A**); responses were deep and durable, with 82% of responders estimated to remain in MCyR at 5 years.^{12,38} Of patients with CP-CML (N = 267), 46% (n = 123) achieved CCyR by 12 months; of those, 40% of patients without the T315I mutation and 66% with the T315I mutation achieved CCyR by 12 months (**Figure 1B**).¹² Overall, 40% of patients with CP-CML (n = 107) achieved MMR at any time; 35% of patients without the T315I mutation and 58% with the T315I mutation achieved MMR at any time (**Figure 1C**).¹² In terms of long-term survival in patients with difficult-to-treat CML (with and without the T315I mutation), the estimated 5-year OS was 73%, and the estimated 5-year progression-free survival (PFS) was 53%.³⁸

Serious adverse reactions (ARs) occurred in 69% of patients who received ICLUSIG. Serious ARs in >2% of patients included AOEs (20%), pneumonia (10%), cardiac arrhythmias (8%), pancreatitis/lipase elevation (7%), abdominal pain (6%), cardiac failure (6%),

IMPORTANT SAFETY INFORMATION (Continued) WARNINGS AND PRECAUTIONS (Continued)

Venous Thromboembolic Events (VTEs): Serious or severe VTEs have occurred in patients who received ICLUSIG. In PACE, VTEs occurred in 6% of 449 patients including serious or severe (Grade 3 or 4) VTEs in 5.8% of patients. VTEs included deep venous thrombosis, pulmonary embolism, superficial thrombophlebitis, retinal vein occlusion, and retinal vein thrombosis with vision loss. The incidence was higher in patients with Ph+ ALL (9% of 32 patients) and BP-CML (10% of 62 patients). One of 94 patients in OPTIC experienced a VTE (Grade 1 retinal vein occlusion). Monitor for evidence of VTEs. Interrupt, then resume at the same or decreased dose or discontinue ICLUSIG based on recurrence/severity.

hemorrhage (6%), sepsis (5%), VTEs (5%), fluid retention and edema (4.5%), pyrexia (4.5%), secondary malignancies (5%), anemia (3.3%), hypertension (3.1%), thrombocytopenia (3.1%), febrile neutropenia (2.9%), cellulitis (2.7%), and arthralgia (2.2%). Fatal ARs occurred in 9% of patients who received ICLUSIG® (ponatinib); the most frequent fatal ARs were AOEes (2%), sepsis (1.6%), and hemorrhage (1.3%).¹² The most common (>20%) non-hematologic ARs were rash and related conditions, arthralgia, abdominal pain, fatigue, constipation, headache, dry skin, fluid retention and edema, hepatic dysfunction, hypertension, pyrexia, nausea, hemorrhage, pancreatitis/lipase elevation, AOEes, diarrhea, vomiting, and myalgia.¹²

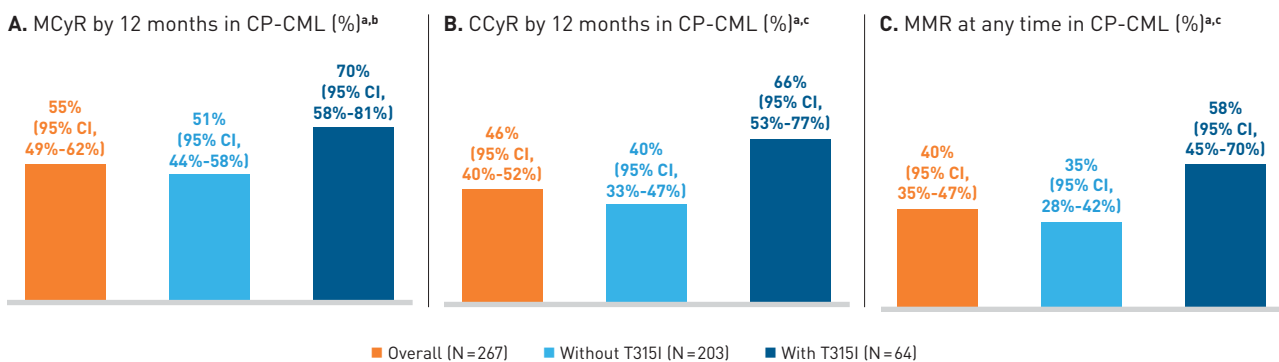
OPTIC Trial

OPTIC is an ongoing, open-label, multicenter, randomized phase 2 trial designed to evaluate ICLUSIG across 3 response-based dosing regimens for patients with CP-CML whose disease was considered resistant or resistant or intolerant to at least 2 prior TKIs or who have

the T315I mutation. The OPTIC trial established a response-based dosing strategy in CP-CML as a path to maximize benefit and mitigate risk.

The enrolled study population includes adults who were resistant or intolerant to 2 prior TKIs or with presence of a T315I mutation (N = 282).^{12,41} Among patients enrolled, there was a high rate of prior TKI resistance. The majority (98%) of patients had developed resistance to their prior line of therapy before receiving ICLUSIG, and 44% of participants had mutations in 1 or more *BCR-ABL1* kinase domain mutations. Only 2% of patients achieved $\leq 1\%$ *BCR::ABL1* transcript levels on their last prior therapy.⁴¹ Patients were randomized (1:1:1) to either of the 3 response-based dosing regimens: 45 mg orally once daily (n = 94), 30 mg orally once daily (n = 94), or 15 mg orally once daily (n = 94).^{12,41} The major efficacy outcome measure (primary end point) was $\leq 1\%$ *BCR-ABL1*^{IS} at 12 months.^{12,41} Patients who received a starting dose of ICLUSIG 45 mg or 30 mg orally once daily had a mandatory dose reduction to 15 mg once daily upon achievement of $\leq 1\%$ *BCR-ABL1*^{IS}.¹²

Figure 1. PACE Trial Depth of Response Efficacy Outcomes¹²



BCR-ABL1, the *BCR-ABL1* fusion gene; CCyR, complete cytogenetic response; CP-CML, chronic-phase chronic myeloid leukemia; MCyR, major cytogenetic response; MMR, major molecular response; Ph+, Philadelphia chromosome-positive; qRT-PCR, quantitative reverse transcriptase-polymerase chain reaction; T315I, a point mutation in the *BCR-ABL1* kinase domain.

^aMedian duration of ICLUSIG treatment was 35 months for patients with CP-CML.

^bPrimary end point for CP-CML cohorts was MCyR by 12 months, which combines both complete (no detectable Ph+ cells) and partial (1%-35% Ph+ cells in at least 20 metaphases) cytogenetic responses.

^cCCyR: no detectable Ph+ cells. MMR: proportion of patients who met the criteria for MMR at least once after the initiation of study treatment measured in peripheral blood. Defined as a $\leq 0.1\%$ ratio of *BCR-ABL1* to *ABL1* transcripts on the International Scale (IS) (ie, $\leq 0.1\%$ *BCR-ABL1*^{IS}); patients must have had the b2a2/b3a2 (p210) transcript in peripheral blood measured by qRT-PCR.

IMPORTANT SAFETY INFORMATION (Continued) WARNINGS AND PRECAUTIONS (Continued)

Heart Failure: Fatal, serious or severe heart failure events have occurred in patients who received ICLUSIG. In PACE, heart failure occurred in 9% of 449 patients; 7% experienced serious or severe (Grade 3 or higher). Heart failure occurred in 13% of 94 patients in OPTIC; 1.1% experienced serious or severe (Grade 3 or 4). In PACE, the most frequently reported heart failure events ($\geq 2\%$) were congestive cardiac failure (3.1%), decreased ejection fraction (2.9%), and cardiac failure (2%). In OPTIC, the most frequently reported heart failure events (>1 patient each) were left ventricular hypertrophy (3.2%) and BNP increased (3.2%). 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.

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Results

Patients with difficult-to-treat CP-CML who received ICLUSIG® (ponatinib) 45 mg followed by a dose reduction to 15 mg (45 mg→15 mg) achieved a clinically meaningful depth of response in difficult-to-treat CP-CML. The median duration of follow-up in the 45 mg cohort in the OPTIC trial was 27 months.¹²

Overall, 44% (n = 41) of patients achieved $\leq 1\%$ BCR-ABL1¹⁵ at 12 months. ICLUSIG was effective in patients with (n = 11; 44%) and without (n = 29; 44%) the T315I mutation.¹² Of patients with T315I mutations, 60% achieved $\leq 1\%$ BCR-ABL1¹⁵ response rates by 36 months in 45 mg cohort (n=94) (without T315I mutations, 54.5%).⁴³ Of the 45 patients given a dose reduction after achieving $\leq 1\%$ BCR-ABL1¹⁵, 62% (n = 28) maintained the response at the reduced dose for at least 90 days. Of these 28 patients, 64% (n = 18) maintained their response for at least 1 year. Median duration of response was not reached.¹²

Serious ARs occurred in 34% of patients who received ICLUSIG at a starting dose of 45 mg. Serious ARs in > 2% of patients included AOE (9%; of which 2.1% were sudden death), cardiac arrhythmias (6%), thrombocytopenia (5%), pyrexia (4.3%), anemia (3.2%), abdominal pain (3.2%), atrial fibrillation (2.1%), pancreatitis/lipase elevation (2.1%), neutropenia (2.1%), and hypertension (2.1%). Fatal ARs occurred in 2 patients (2.1%), both of which were sudden death. The most common (> 20%) ARs were rash and related conditions, hypertension, arthralgia, hyperlipidemia, hepatic dysfunction, pancreatitis/lipase elevation, and abdominal pain. The most common (> 20%) Grade 3 or 4 laboratory abnormalities were platelet count decreased and neutrophil cell count decreased.¹²

Overall, results from OPTIC demonstrate a benefit in a highly-resistant CP-CML population across dosing cohorts. Based on results from the OPTIC trial, the recommended response-based dosing strategy for patients with CP-CML is an initial dose of ICLUSIG 45 mg once daily followed by a dose reduction to 15 mg upon achievement of $\leq 1\%$ BCR::ABL1¹⁵. Patients with loss of response can re-escalate the dose of ICLUSIG to a previously tolerated dose of 30 mg or 45 mg orally once daily.¹²

ECONOMIC CONSIDERATIONS FOR ICLUSIG® (PONATINIB) AND ASCIMINIB

Overall, ICLUSIG is a cost-effective option for difficult-to-treat CP-CML in patients whose disease was resistant or intolerant to 2 prior TKIs and in patients with the T315I mutation.

WAC Pricing and Dosing of ICLUSIG in CP-CML (Including BCR-ABL1 T315I Mutation)

ICLUSIG has a 30-day wholesale acquisition cost (WAC) price of \$18,809 for treatment in CP-CML, with or without the T315I mutation (Tables 3 and 4).^{7-9,11-13,44} In comparison, asciminib has a 30-day WAC price of \$18,616 for CP-CML patients without the T315I mutation and of \$93,080 for patients with the T315I mutation. The reason for the higher asciminib WAC price in patients with the T315I mutation is the higher dose requirement to achieve an optimal response.^{12,44}

Number Needed to Treat and Cost per Response Study for ICLUSIG and Asciminib

To estimate the anticipated costs for payers, a cost-effectiveness analysis evaluated the number needed to treat (NNT) and cost per response (CpR) to obtain 1 CCyR achieved with asciminib and ICLUSIG in patients with resistant or intolerant CP-CML in the third-line setting after failure of at least 1 second-generation TKI or who had T315I mutation.⁴⁵ This study was sponsored by Takeda Development Center Americas, Inc. and funded by Takeda Pharmaceuticals, USA, Inc. The results were presented at AMCP Nexus 2022.⁴⁵

A systematic literature review of published clinical trial data and other published studies available between 2006 and 2021 was conducted to identify studies reporting CCyR for patients with CP-CML treated with ICLUSIG or asciminib whose disease was resistant or intolerant to at least 1 second-generation TKI or who had T315I mutation.⁴⁵ Given the heterogeneity in later-line patient populations, the analysis targeted patients with TKI resistance and/or intolerance who did not have baseline CCyR response or who had the T315I mutation at time of treatment initiation. Of the 3680 publications identified for all TKIs in CP-CML, 6 studies (including OPTIC) were eligible for ICLUSIG, and 3 studies (including ASCSEMBL) were eligible for asciminib.⁴⁵ All costs were based on 2022 WAC pricing and were used to estimate the cost per additional response based on daily dose over 12 months. Unadjusted pooled probabilities of CCyR were estimated with a Bayesian meta-analysis and used to calculate noncomparative estimates with a 95% credible interval (CrI) of the NNT to observe an additional response.⁴⁵

NNT to achieve 1 additional CCyR in the third-line setting among patients who were refractory or intolerant to TKI without baseline response with ICLUSIG was 2.1 patients (95% CrI, 1.9-2.3) compared

IMPORTANT SAFETY INFORMATION (Continued) WARNINGS AND PRECAUTIONS (Continued)

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. Hepatotoxicity occurred in 28% of 94 patients in OPTIC and 32% of 449 patients in PACE. Grade 3 or 4 hepatotoxicity occurred in OPTIC (6% of 94 patients) and 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.

Table 3. 2022 WAC Pricing of TKIs in CP-CML^{7-9,11-13,44}

Drug	WAC pricing	Dosing	Monthly cost (30 days)
ICLUSIG® (ponatinib) ^{12,44}	45 mg (30 tablets): \$18,809.00	Resistant or intolerant to 2 TKIs CP-CML: 45 mg once daily with a reduction to 15 mg once daily upon achievement of $\leq 1\%$ <i>BCR-ABL</i> ¹⁵	CP-CML: \$18,809.00 Hepatic impairment: \$18,809.00
	30 mg (30 tablets): \$18,809.00		
	15 mg (30 tablets): \$18,809.00		
	10 mg (30 tablets): \$18,809.00		
Scemblix® (asciminib) ^{13,44}	40 mg (60 tablets): \$18,616.00	Previously treated CP-CML: 80 mg once daily or 40 mg twice daily	\$18,616.00
	20 mg (60 tablets): \$18,616.00		
Gleevec® (imatinib mesylate) ^{7,44}	400 mg (30 tablets): \$10,122.43	Resistant CP-CML: 400 mg once daily	CP-CML: \$10,122.43
Generic (imatinib) ^{7,44}	400 mg (30 tablets): \$1000.00	Resistant CP-CML: 400 mg once daily	CP-CML: \$1000.00
Sprycel® (dasatinib) ^{8,44}	100 mg (30 tablets): \$15,843.10	Resistant or intolerant CP-CML: 100 mg once daily	CP-CML: \$15,843.10
	140 mg (30 tablets): \$15,843.10		
Tasigna® (nilotinib) ^{9,44}	200 mg (112 tablets): \$17,024.73	Resistant or intolerant Ph+ CML-CP: 400 mg twice daily	\$18,240.78
Bosulif® (bosutinib) ^{11,44}	500 mg (30 tablets): \$17,361.70	Ph+ CP-CML with resistance or intolerance to prior therapy: 500 mg once daily	\$17,361.70

CP-CML, chronic phase-chronic myeloid leukemia; Ph+, Philadelphia chromosome-positive; WAC, wholesale acquisition cost.

Table 4. WAC Pricing and Dosing of TKIs in Patients With T315I CP-CML^{12,13,44}

Drug	WAC pricing	Dosing in T315I CP-CML	Number of tablets per day and special instructions	Monthly cost (30 days) in T315I CP-CML
ICLUSIG® (ponatinib) ^{12,44}	45 mg (30 tablets): \$18,809.00	45 mg once daily with a reduction to 15 mg once daily upon achievement of $\leq 1\%$ <i>BCR-ABL</i> ¹⁵	One tablet per day May be taken with or without food	\$18,809.00
	30 mg (30 tablets): \$18,809.00			
	15 mg (30 tablets): \$18,809.00			
	10 mg (30 tablets): \$18,809.00			
Scemblix® (asciminib) ^{13,44}	40 mg (60 tablets): \$18,616.00	200 mg twice daily	Ten 40 mg tablets per day Avoid food for at least 2 hours before and 1 hour after taking asciminib	\$93,080.00
	20 mg (60 tablets): \$18,616.00			

CP-CML, chronic phase-chronic myeloid leukemia; WAC, wholesale acquisition cost.

IMPORTANT SAFETY INFORMATION (Continued) WARNINGS AND PRECAUTIONS (Continued)

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.

with 2.4 patients with asciminib (95% CrI, 2.0-2.9). The estimated 12-month CpR achieved was \$476,784 (\$431,499-\$533,171) for ICLUSIG® (ponatinib) versus \$518,896 (\$441,230-\$631,620) for asciminib.⁴⁵ Despite a higher percentage of TKI-resistant patients in the ponatinib group (76%-100%) compared with the asciminib group (35%-61%), patients with CP-CML who were treated with ICLUSIG showed an improved NNT and CpR compared with those treated with asciminib in the third-line setting and beyond.⁴⁵

The cost difference between the 2 drugs was much greater in the T315I mutation group due to lower response rate and higher dose requirement related to asciminib therapy. Among patients with a T315I mutation, the NNT was 1.5 patients (95% CrI, 1.3-1.8) for ICLUSIG and 2.3 patients (95% CrI, 1.6-4.0) for asciminib. The estimated 12-month CpR achieved was \$351,517 (\$308,452-\$408,942) for ICLUSIG and \$2,485,315 (\$1,706,030-\$4,411,298) for asciminib.⁴⁵

There were limitations to this study. Given the recent approval of asciminib by the US Food and Drug Administration (29 October 2021), this analysis relied heavily on conference abstracts for post-approval data. Naive comparisons from studies with patients with heterogeneous baseline disease characteristics, such as resistance and intolerance, limit the ability to draw estimates of relative effect between interventions. Further population-adjusted analysis with patient-level data may help to balance the background difference between the studies.⁴⁵

Given the heterogeneity in later-line patient populations with CP-CML, this analysis assessed patients with TKI resistance or intolerance without baseline CCyR response or those who had the T315I mutation at time of treatment initiation.⁴⁵ Overall, despite a higher percentage of TKI-resistant patients with CP-CML in the ICLUSIG group compared with the asciminib group, the results from this analysis showed that patients who were treated with ICLUSIG had a trend toward favorable CCyR and NNT, leading to lower CpRs compared with those treated with asciminib. The CpR over 1 year could be 7-fold higher for asciminib compared with ICLUSIG (\$2,485,315 vs \$351,517) for patients with T315I mutations. Notably, the CpR for asciminib increased with higher T315I mutation incidence because a higher dose of asciminib is required to treat patients with CP-CML with T315I mutations, whereas the CpR for ICLUSIG was not dependent on T315I mutation status. The results of this analysis may inform decision-making among formulary and value assessment committees.⁴⁵

CONCLUSIONS

CML is a rare form of leukemia in which an abnormal gene, the *BCR-ABL1* oncogene, transforms the cell and instigates cancer. Patients with CP-CML and the T315I mutation typically have high treatment resistance to first- and second-generation TKIs and poor survival outcomes. As a third-generation TKI, ICLUSIG has demonstrated deep and durable responses in patients with CP-CML.^{6,12,13,18,25,31-35,46-48}

There are currently only 2 TKIs (ICLUSIG and asciminib) available for the treatment of adult patients with CP-CML with resistance or intolerance to at least 2 prior kinase inhibitors and T315I-positive CML (CP, AP, or BP). ICLUSIG is the only third-generation *BCR-ABL1* inhibitor that demonstrates activity regardless of mutation status. Results from the PACE and OPTIC trials have provided efficacy and safety data of ICLUSIG, with durable responses and survival outcomes noted among patients with CP-CML for the treatment of adult patients with CP-CML with resistance or intolerance to at least 2 prior kinase inhibitors and T315I-positive CML (CP, AP, or BP).^{12,38}

The availability of additional TKIs that can be used in the third-line setting to improve patient outcomes can address unmet needs for these patients to overcome treatment resistance in CP-CML. ICLUSIG is a cost-effective option for patients with difficult-to-treat CP-CML with resistance or intolerance to at least 2 prior kinase inhibitors and in patients with the T315I mutation. The ICLUSIG 30-day WAC price supports its use in this population. Further, a cost-effectiveness analysis exhibited a trend towards a favorable NNT and CpR to obtain 1 CCyR with ICLUSIG in patients with CP-CML in the third-line setting after failure of at least 1 second-generation TKI.^{31,45} ●

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IMPORTANT SAFETY INFORMATION (Continued) WARNINGS AND PRECAUTIONS (Continued)

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 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.

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IMPORTANT SAFETY INFORMATION (Continued) WARNINGS AND PRECAUTIONS (Continued)

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.

Please see Important Safety Information for ICLUSIG® (ponatinib) throughout.
Please see full Prescribing Information, including Boxed Warning.

Payer Perspectives in the Management of CP-CML: Q&A With Roy Beveridge, MD

AJMC®: How does your organization manage chronic phase-chronic myeloid leukemia (CP-CML) currently, and what factors or considerations are taken into account when managing CP-CML?

ROY BEVERIDGE, MD: This can be broken down in multiple ways. Insurance can be seen from a commercial perspective, a Medicare Advantage perspective, or a perspective of an entity that's taking full risk that would have to be segmented if it's being looked at it from a payer perspective.

From a commercial standpoint, the formulary is determined by a pharmacy and therapeutics committee; it is largely dictated by what is FDA-approved and what key opinion leaders (KOLs) say and, particularly, the clinical pathways they write about and espouse. In a commercial plan, it's quite broad, but lines of therapy become very important. They will usually follow NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®), but they may want to look at another pathway entity, as well.

From a managed care perspective, it is a bit more restrictive. Providers use the same NCCN Guidelines®, but because they're taking full risk, they are going to be looking at what is less expensive for the choices on a clinical pathway. Generic products or lower cost specialty drugs will certainly always be preferred, and there is much more of a strict tiering mechanism that occurs.

AJMC®: Regarding your formulary management, is it required to try 1 agent from each line of therapy that is available on your formulary?

BEVERIDGE: If a patient has intolerance to imatinib or another drug, providers may want to push to a more expensive product and change or progress down that line of therapy. In a commercial plan, it is usually easy to say the patient was intolerant, but, if it's a significantly more costly event, the plan or the entity at risk will

usually ask for documentation to demonstrate that the patient had diarrhea or another form of intolerance.

AJMC®: What payer considerations are at the forefront in the CP-CML landscape?

BEVERIDGE: From a pharmacy benefit manager's or a payer's perspective, they will frequently be looking at associated rebates for a class of drugs. If there is the assumption by a pathway committee that there's interchangeability of products, then the responsible entity, either on the commercial side or the Medicare Advantage side, will be looking at rebates from the manufacturer. That will help heavily when considering the placement of 1 product ahead of another if they are clinically interchangeable.

AJMC®: How have payers recognized advancements in the current CP-CML treatment landscape with the availability of tyrosine kinase inhibitors (TKI)?

BEVERIDGE: With TKIs, there is a wide variety of options for patients with CP-CML. I am old enough to remember the time before we had these drugs—patients uniformly died or went on to allogeneic stem cell transplant. There are several of us who are old enough to remember and recognize just how impactful this whole class of drugs are to the CP-CML population. There's wide acceptance by payers that these are a necessary drug for this patient population. No one is trying to restrict the use of TKIs. If a patient can tolerate a first-generation TKI, and it's less expensive, payers are trying to make sure that guidelines are being followed and that this is the agent that should be used first.

AJMC®: From the payer perspective, what are benefits of early mutation testing in CP-CML? How can the detection of

IMPORTANT SAFETY INFORMATION (Continued) WARNINGS AND PRECAUTIONS (Continued)

Neuropathy: Peripheral and cranial neuropathy occurred in patients in OPTIC and PACE. Some of these events in 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 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.

resistance mutations with testing be utilized for appropriate treatment decision making?

BEVERIDGE: One of the biggest concerns that payers have is the underutilization of testing. Clear recommendations are provided in pathways, and this testing is a best practice. When looking at claims data, there is a need for medical oncologists to do more testing on these patients. That is an established problem on the commercial side, the risk side, and the Medicare Advantage side.

There's a big push for providers to do more mutation testing in patients with CP-CML. From the payer's perspective, a patient is a candidate for mutation testing if they are not responding or may be intolerant to a first-generation TKI. As a patient's illness progresses despite treatment, they could be admitted to the hospital in need of blood transfusions or they could have additional treatment-emergent events. That is not a good financial output, and, moreover, it is a terrible clinical output. The payer's primary focus is to follow evidence-based medicine.

AJMC®: What clinical and economic evidence is reviewed by payers to inform formulary decision-making and pathways development in CP-CML?

BEVERIDGE: Payers look at NCCN Guidelines, other pathways; if the pathways are not clear, they bring KOLs together for discussion. Most of the data that payers use to back decision-making are claims-based. When looking at claims data for patients with CP-CML, it is possible that payers see if a patient had testing at some point, but there isn't enough deep clinical information to know whether the testing was done correctly or if the results were interpreted correctly. There is potential to figure out whether the testing was done correctly from a time standpoint by seeing if the patient had testing every 3 or 6 months; however, using claims

data can be very hard. For this level of information, a payer or health care provider would need to access the electronic health record, and that data is even more complex to analyze. It is also possible to pull data from a LabCorp request; however, so many of these tests are not done just by LabCorp, and they are done either by specialty or hospital laboratories. In terms of interpretation, those testing data from the laboratories are very hard to pull out and codify. Payers are looking at evidence regarding clinical costs, hospital costs, emergency room costs, patient tolerability, treatment of adverse reactions, and effectiveness of the treatment. Payers won't consider evidence from studies like an economic analysis of how CP-CML relates to work or lost time away from home, because they're not responsible for that outcome.

Payers fundamentally look at the FDA-approved treatments, and they are glad that they are efficacious at this level of review. Payers will then seek evidence on how their patient population will tolerate these treatments. For a Medicare Advantage plan like United Healthcare, the randomized clinical trials and studies used for FDA approval will enroll participants who are in wonderful health, don't have kidney problems, and tend to be much healthier than the patients who get the drug in the real-world setting. Patients who receive treatment with the drug are typically older, and they have many more comorbidities.

Payers are looking at data regarding the real-world experience and toxicity in the patient group that they're responsible for when making formulary decisions. Payers are internally looking at their own data from health economics and outcomes research (HEOR), their own claims data, and data they can pull from certain clinicians. That internal data is a big source of determinants as payers are piecing together the evidence and reviewing recommendations from KOLs and the NCCN Guidelines. In general, payers are looking at their own HEOR data, because they trust in the data that they generate internally. •

IMPORTANT SAFETY INFORMATION (Continued) WARNINGS AND PRECAUTIONS (Continued)

Hemorrhage: Fatal and serious hemorrhage events have occurred in patients who received ICLUSIG. Fatal hemorrhages occurred in PACE and serious hemorrhages occurred in OPTIC and PACE. In PACE, the incidence of serious bleeding events was higher in patients with AP-CML, BP-CML, and Ph+ ALL. 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.

Clinical Perspectives in the Management of CP-CML: Q&A With Dr Koller

AJMC®: What is the current standard of care management approach for chronic phase–chronic myeloid leukemia (CP-CML)?

PAUL B. KOLLER, MD: The current standard of care after diagnosis is to evaluate treatment goals, comorbidities, and potential drug interactions. Some form of risk stratification score like the Sokal Index for CML, the Hasford, or EUTOS (European Treatment and Outcome Study) scoring system should be calculated. For patients with intermediate or high-risk CP-CML the standard of care is to start treatment with a second-generation tyrosine kinase inhibitor (TKI) upfront. For those with low-risk disease, we can start with imatinib or a second-generation TKI, however at our institution the consensus is to start with a second generation TKI unless not allowed by insurance.

AJMC®: What are the unmet needs to address in the treatment of CP-CML?

KOLLER: There is a need to increase treatment-free remission rates and improve compliance with TKI treatment. Additionally, there is a need to address TKI treatment resistance, because the rates of TKI resistance and intolerance substantially affect the treatment options available for this population.

AJMC®: How is TKI resistance identified in patients with CP-CML?

KOLLER: TKI resistance is identified by recognizing *BCR-ABL1* kinase domain mutations, reviewing drug interactions, ensuring compliance, and other methods. Resistance without mutations does occur and it is important to identify both kinds of resistance. Each clinical case is different, which reinforces the need to not only evaluate mutations as a cause of resistance but other things

like compliance, cost, drug interactions, etc to make sure the right TKI is selected for each patient.

AJMC®: What are the challenges in treatment of resistant CP-CML?

KOLLER: There are high resistance rates observed with second-generation TKIs. Second-generation TKIs have similar mechanisms of action; therefore, if we see that patients are resistant to 1 of these TKIs, we find that they are frequently resistant to all of them. The long-term outcomes of second-generation TKI cycling can be a challenge in the treatment of CP-CML resistant to 2 or more prior TKIs. Among such patients who receive a second-generation TKI in the third-line setting, only 22% to 26% achieve a CCyR and just 64% of patients are still alive at 4 years.^{1,2}

AJMC®: At what stage of treatment is it recommended that patients with CP-CML undergo mutation testing?

KOLLER: Patients with CP-CML undergo mutation testing if they fail to reach predefined response milestones; have any sign of loss of hematologic response; have any sign of loss of CCyR or its major molecular response (MMR) correlate, defined as an increase in *BCR-ABL1* transcript to > 1%; have a 1-log increase in *BCR-ABL1* transcript levels and loss of MMR; or have a disease progression to accelerated-phase or blast-phase CML.

AJMC®: How might this information be used to inform clinical decision-making when discovered early in the treatment of CP-CML?

KOLLER: We can use this information to select an appropriate TKI based on the mutation found. For example, asciminib or ponatinib (ICLUSIG®) are therapeutic options considered for patients with

IMPORTANT SAFETY INFORMATION (Continued) WARNINGS AND PRECAUTIONS (Continued)

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. Monitor for fluid retention and manage patients as clinically indicated. Interrupt, then resume at the same or reduced dose or discontinue ICLUSIG based on recurrence/severity.

Cardiac Arrhythmias: Cardiac arrhythmias, including ventricular and atrial arrhythmias, occurred in patients in 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.

a T315I mutation identified during mutational analysis. For specific mutations in CP-CML, the National Comprehensive Cancer Network® (NCCN®) has a list of expected resistance to various TKIs that can be used to guide treatment considerations and decisions.³

AJMC®: What are your considerations when selecting the next line of treatment after second-generation TKI resistance? How do you identify patients with CP-CML who are appropriate for a third-generation TKI treatment?

KOLLER: In both cases, we consider clinical trials, comorbidities, drug-drug interactions, and prior TKI treatment.

AJMC®: How does the efficacy and safety data from the PACE trial factor into your selection of treatment for patients with CP-CML?

KOLLER: The study data confirms that ICLUSIG® (ponatinib) is a very active agent in CP-CML.³ The initial response rates from the PACE trial demonstrated that 55% of patients with CP-CML achieved MCyR by 12 months with ICLUSIG treatment.^{4,5} Durable responses were demonstrated with 5-year follow-up data from the PACE trial, with estimated progression-free survival (PFS) and OS of 53% and 73%, respectively.⁶ Serious adverse reactions (ARs) occurred in 69% of patients who received ICLUSIG. Serious ARs in >2% of patients included arterial occlusive events (AOEs) (20%), pneumonia (10%), cardiac arrhythmias (8%), pancreatitis/lipase elevation (7%), abdominal pain (6%), cardiac failure (6%), hemorrhage (6%), sepsis (5%), VTEs (5%), fluid retention and edema (4.5%), pyrexia (4.5%), secondary malignancies (5%), anemia (3.3%), hypertension (3.1%), thrombocytopenia (3.1%), febrile neutropenia (2.9%), cellulitis (2.7%), and arthralgia (2.2%). Fatal ARs occurred in 9% of patients who received ICLUSIG; the most frequent fatal ARs were AOEs (2%), sepsis (1.6%), and hemorrhage (1.3%).⁵

The most common (>20%) non-hematologic ARs were rash and related conditions, arthralgia, abdominal pain, fatigue, constipation,

headache, dry skin, fluid retention and edema, hepatic dysfunction, hypertension, pyrexia, nausea, hemorrhage, pancreatitis/lipase elevation, AOE, diarrhea, vomiting, and myalgia. Overall, these data may be used to provide confidence that ICLUSIG treatment is aligned with treatment goals for patients with CP-CML who had resistance and/or intolerance to 2 or more prior TKIs.⁵

AJMC®: What is the optimal ICLUSIG dosing strategy that is recommended for patients with CP-CML?

KOLLER: Results of the OPTIC trial established a response-based dosing strategy with ICLUSIG in CP-CML. Based on results from the OPTIC trial, the recommended response-based dosing strategy for patients with CP-CML is ICLUSIG 45 mg, reduced to 15 mg, taken once daily when $\leq 1\%$ BCR-ABL1 is achieved. The OPTIC trial enrolled a study population with difficult-to-treat CP-CML—patients who were resistant or intolerant to 2 prior TKIs or with presence of a T315I mutation—and there was a high rate of prior TKI resistance among patients enrolled. Patients who received ICLUSIG 45 mg followed by a dose reduction to 15 mg achieved a clinically meaningful depth of response, and it was associated with favorable long-term survival outcomes, with an estimated PFS rate of 73% and an OS rate of 89% at 36 months.⁷

Serious ARs occurred in 34% of patients who received ICLUSIG at a starting dose of 45 mg. Serious ARs in >2% of patients included AOEs (9%; of which 2.1% were sudden death), cardiac arrhythmias (6%), thrombocytopenia (5%), pyrexia (4.3%), anemia (3.2%), abdominal pain (3.2%), atrial fibrillation (2.1%), pancreatitis/lipase elevation (2.1%), neutropenia (2.1%), and hypertension (2.1%). Fatal ARs occurred in 2 patients (2.1%), both of which were sudden death. The most common (>20%) ARs were rash and related conditions, hypertension, arthralgia, hyperlipidemia, hepatic dysfunction, pancreatitis/lipase elevation, and abdominal pain. The most common (>20%) Grade 3 or 4 laboratory abnormalities were platelet count decreased and neutrophil cell count decreased. Dose reductions were utilized in response to ARs. Patients receiving the ICLUSIG 45-mg dose had their dose reduced to 30 mg and followed by 15 mg and 10 mg if ARs persisted.^{5,6}

IMPORTANT SAFETY INFORMATION (Continued) WARNINGS AND PRECAUTIONS (Continued)

Myelosuppression: Grade 3 or 4 events of neutropenia, thrombocytopenia, and anemia occurred in patients in OPTIC and PACE. The incidence of myelosuppression was greater in patients with AP-CML, BP-CML, and Ph+ ALL 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 $1 \times 10^9/L$ or platelets less than $50 \times 10^9/L$, interrupt ICLUSIG until ANC at least $1.5 \times 10^9/L$ and platelets at least $75 \times 10^9/L$, then resume at same or reduced dose.

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

Please see Important Safety Information for ICLUSIG® (ponatinib) throughout.
Please see full Prescribing Information, including Boxed Warning.

Using a response-based dosing strategy can help maximize the benefit-risk profile of ICLUSIG® (ponatinib). Follow the prescribing information for managing ARS, response-based dosing, dose modifications, and other dosing considerations, or call on your friendly CML expert. •

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IMPORTANT SAFETY INFORMATION (Continued) WARNINGS AND PRECAUTIONS (Continued)

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 (>20%) adverse reactions are 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 AOE. The most common Grade 3 or 4 laboratory abnormalities (>20%) are platelet count decreased, neutrophil cell count decreased, and white blood cell decreased.

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

DRUG INTERACTIONS

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

Strong CYP3A Inducers: Avoid coadministration.

USE IN SPECIFIC POPULATIONS

Lactation: Advise women not to breastfeed during treatment with ICLUSIG and for 6 days 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: 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.

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