



## Evolving assessments of molecular response in CML:

### An overview of the GLEEVEC and 2nd-generation TKI pivotal trials

*The information herein is not presented to compare the efficacy or safety profile among the discussed 2nd-generation TKIs. No implication of superiority or inferiority is intended or should be inferred.*

TKI, tyrosine kinase inhibitor.

#### **GLEEVEC® (imatinib mesylate) tablets are indicated for:**

- Newly diagnosed adult and pediatric patients with Philadelphia chromosome–positive chronic myeloid leukemia (Ph+ CML) in the chronic phase
- Patients with Ph+ CML in blast crisis (BC), accelerated phase (AP), or in chronic phase (CP) after failure of interferon-alpha therapy

#### **IMPORTANT SAFETY INFORMATION**

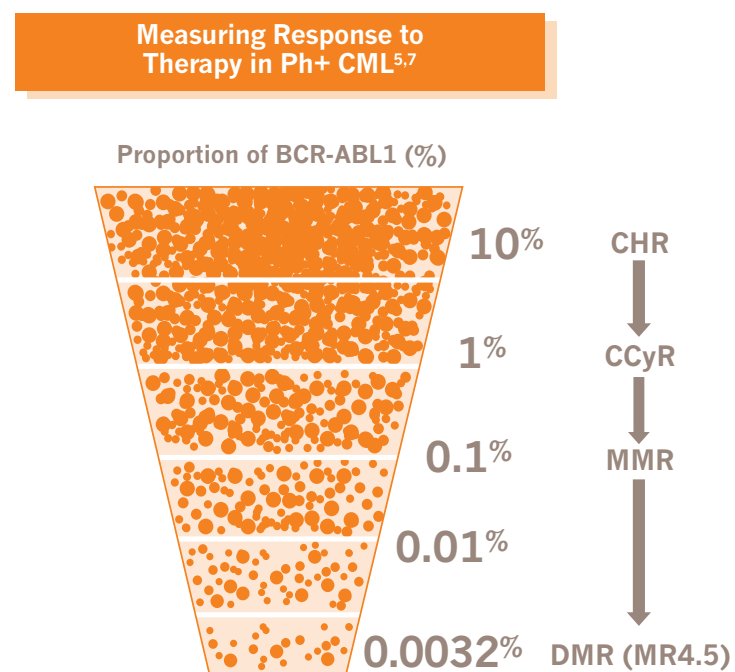
- GLEEVEC is often associated with edema and, occasionally, serious fluid retention. Severe fluid retention was reported in 9% to 13.1% and 2.5% to 11% of patients taking GLEEVEC for GIST and CML, respectively. Patients should be weighed and monitored regularly for signs and symptoms of fluid retention, which can be serious or life threatening, and be advised to report any rapid, unexpected weight gain. The probability of edema tended to be increased among older patients (>65 years) or those taking higher doses of GLEEVEC. Severe edema and superficial edema were observed in 182 (11.1%) GIST patients and 1.5% to 6% in CML patients, respectively. If severe fluid retention occurs, manage with diuretic therapy and withhold GLEEVEC until the event has resolved, and then resume, depending on the initial severity of the event. In a study of patients with newly diagnosed Ph+ CML in chronic phase comparing GLEEVEC and nilotinib, severe (grade 3 or 4) fluid retention occurred in 2.5% of patients receiving GLEEVEC and in 3.9% of patients receiving nilotinib. Effusions or pulmonary edema were observed in 2.1% (none were grade 3 or 4) of patients in the GLEEVEC arm and 2.2% (0.7% grade 3 or 4) of patients in the nilotinib arm

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## Clinical trial end points and molecular milestones have evolved since the approval of GLEEVEC in 2001<sup>1-4</sup>

Molecular response measures have deepened in clinical trials and community practice, establishing new treatment milestones<sup>1-4</sup>

- GLEEVEC® (imatinib mesylate) tablets approval in 2001 shifted the CML treatment paradigm and, with subsequent trials, established TKIs as standard of care<sup>5,6</sup>
- The GLEEVEC pivotal trial measured CHR and MCyR (complete or partial) as secondary end points<sup>1</sup>
- More recent clinical trials use CCyR and MMR as primary end points to assess response<sup>2-4</sup>
- With advancements in the assay sensitivity, milestones for molecular response have also evolved and response measurement continues to deepen<sup>5,7</sup>



CHR, complete hematologic response; MCyR, major cytogenetic response; CCyR, complete cytogenetic response; MMR, major molecular response; DMR, deep molecular response; EMR, early molecular response; IRIS, International Randomized Study of Interferon and ST1571; PCR, polymerase chain reaction; MR, molecular response.

### IMPORTANT SAFETY INFORMATION (cont)

- Cytopenias have been reported. Complete blood counts should be performed weekly for the first month, biweekly for the second month, and periodically thereafter as clinically indicated (eg, every 2-3 months). Dose reduction, treatment interruption, or in rare cases discontinuation of treatment may be required for severe neutropenia or thrombocytopenia (see full Prescribing Information for dose adjustment recommendations)

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Ongoing research with TKI therapy has confirmed the prognostic importance of earlier molecular responses and established EMR as a standard milestone<sup>8,9</sup>

- IRIS was the first randomized trial to demonstrate that monitoring BCR-ABL1 transcript levels throughout therapy with real-time PCR had prognostic value<sup>8</sup>

In an independent retrospective analysis by Marin et al of 282 patients with CML-CP treated with frontline GLEEVEC, followed by either nilotinib or dasatinib upon treatment failure, results demonstrated<sup>10</sup>:

- Patients with BCR-ABL1 transcript levels <9.84% at 3 months had significantly better 8-year OS compared with those who did not achieve an early response (93.3% of 211 patients versus 56.9% of 68 patients)
- While BCR-ABL1 transcript levels at 3, 6, and 12 months all strongly predicted relevant clinical outcomes, such as likelihood of achieving MMR, EMR at 3 months was the only independent predictor for improved overall survival in CML

Measuring response at 3 months is the most accurate method to assess long-term prognosis and allows for earlier clinical intervention<sup>10</sup>

## Current CML treatment goals focus on preventing disease progression to AP/BC with sustained molecular responses<sup>11,12</sup>

Guidelines reflect the importance of both preventing disease progression and attaining deep molecular responses, based on the results of more recent clinical trials.

<b>NCCN</b>	The goal of TKI therapy is to <b>achieve a CCyR</b> ( $\leq 1\%$ BCR-ABL1 IS) within 12 months of initiation of therapy and to <b>prevent disease progression to AP/BC</b> <sup>11</sup>
<b>ESMO</b>	TKI selection should be based on treatment goals and comorbidities; chance to <b>achieve DMR (MR4 or MR4.5)</b> <sup>12</sup>

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NCCN, National Comprehensive Cancer Network; IS, International Scale; ESMO, European Society of Medical Oncology; ENESTnd, Evaluating Nilotinib Efficacy and Safety in Clinical Trials-newly diagnosed patients.

### IMPORTANT SAFETY INFORMATION (cont)

- Congestive heart failure and left ventricular dysfunction (LVD) have been reported. Most patients with reported cardiac events have had other comorbidities and risk factors, including advanced age and previous medical history of cardiac disease. In a phase 3 study of patients with newly diagnosed Ph+ CML in chronic phase, severe cardiac failure and LVD occurred in 0.7% of GLEEVEC patients vs 0.9% of IFN+Ara-C patients. In a study of newly diagnosed Ph+ CML patients in chronic phase comparing GLEEVEC and nilotinib, cardiac failure was observed in 1.1% and 2.2% of patients, respectively, and severe (grade 3 or 4) cardiac failure occurred in 0.7% of patients in each group. Patients with cardiac disease, risk factors for cardiac disease, or history of renal failure should be monitored carefully, and any patient with signs or symptoms consistent with cardiac or renal failure should be evaluated and treated

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## Second-generation TKIs have been built on the foundation of GLEEVEC

GLEEVEC® (imatinib mesylate) tablets has served as the standard comparator for agents in development, and the study designs of the TKI pivotal trials below reflect the evolving goals and expectations of molecular response.

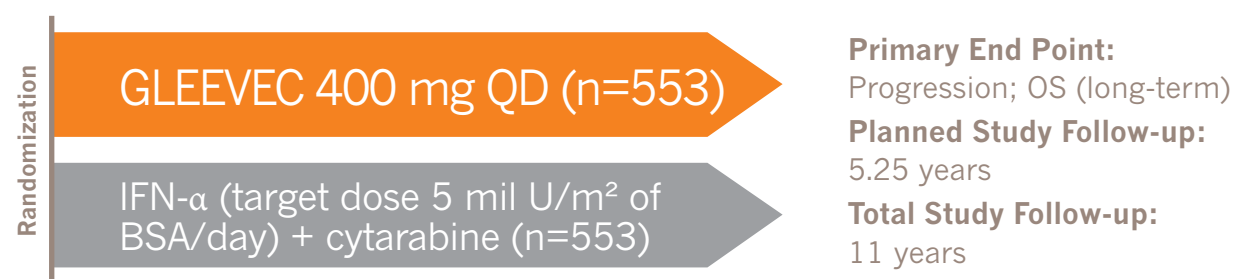
The following pivotal clinical trials in the newly diagnosed setting are included in this piece:

<b>IRIS</b>	International Randomized Study of Interferon and Imatinib
<b>ENESTnd</b>	A Phase 3 Multi-center, Open-label, Study of Imatinib vs Nilotinib in Adult Patients With Newly Diagnosed Ph+ CML in Chronic Phase
<b>DASISION</b>	An Open-Label, Randomized, Multicenter Phase 3 Trial of Dasatinib vs Imatinib in the Treatment of Subjects With Newly Diagnosed Chronic Phase Ph+ CML
<b>BFORE</b>	A Multicenter Phase 3, Open-Label Study of Bosutinib vs Imatinib in Adult Patients With Newly Diagnosed Chronic Phase Chronic Myelogenous Leukemia

## GLEEVEC has served as the comparator across the pivotal trials for second-generation TKIs

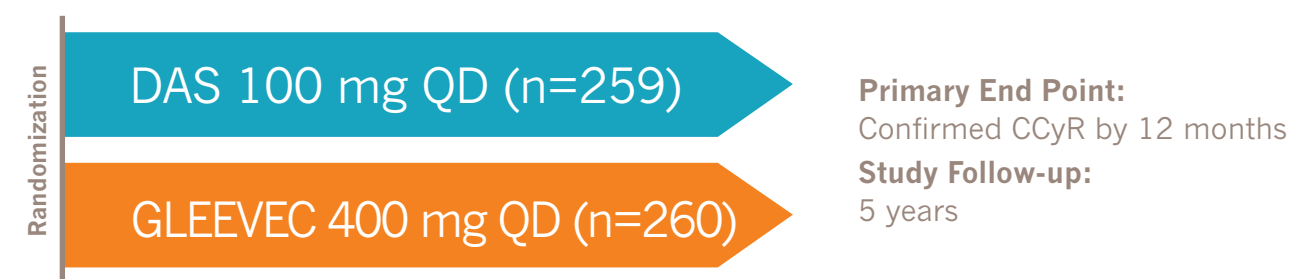
- The EPIC (ponatinib) study was terminated and not included in this review<sup>13</sup>
- The differences in the primary end points reflect evolution of treatment goals and levels of response measures over the last two decades<sup>5,7</sup>

### IRIS: GLEEVEC® (imatinib mesylate) tablets vs IFN<sup>1,14</sup>



Prospective, multicenter, open-label, Phase 3 trial conducted in outpatient setting. Interferon alfa was gradually dosed until maximal tolerated dose was achieved, then low-dose cytarabine was added. Patients in both arms were permitted to receive hydroxyurea for the first 6 months.<sup>1</sup>

### DASISION: Dasatinib vs GLEEVEC<sup>3,16</sup>



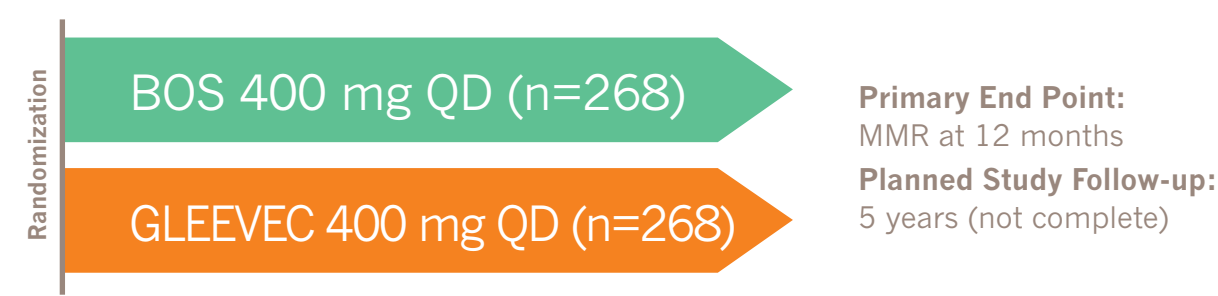
Multinational, open-label, Phase 3 trial. Patients were stratified according to Hasford risk score. Treatment interruptions or dose reductions or escalations were allowed in each arm.<sup>3</sup>

### ENESTnd: Nilotinib vs GLEEVEC<sup>2,15</sup>



Multicenter, open-label, Phase 3 trial. Daily dose of GLEEVEC could be escalated to 800 mg (400 mg BID), but no dose escalation of nilotinib was permitted.<sup>2</sup>

### BFORE: Bosutinib vs GLEEVEC<sup>4</sup>



Ongoing, multinational, Phase 3 trial. Patients were stratified according to Sokal risk score and geographic region. Up to two sequential dose escalations were permitted for suboptimal response.<sup>4</sup>

IFN, interferon; BSA, body surface area.

#### IMPORTANT SAFETY INFORMATION (cont)

- Hepatotoxicity, occasionally severe, may occur. Cases of fatal liver failure and severe liver injury requiring liver transplants have been reported with both short-term and long-term use of GLEEVEC. Assess liver function before initiation of treatment and monthly thereafter, or as clinically indicated. A 25% decrease in the recommended dose should be used for patients with severe hepatic impairment. If severe hepatotoxicity occurs, GLEEVEC should be withheld until the event has resolved and then resumed, depending on the initial severity of the event
- When GLEEVEC is combined with chemotherapy, liver toxicity in the form of transaminase elevation and hyperbilirubinemia has been observed. Additionally, there have been reports of acute liver failure. Monitoring of hepatic function is recommended

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# Overview of patient demographics in TKI pivotal trials

## Select Patient Characteristics

### IRIS<sup>1</sup>

Characteristics		GLEEVEC® (imatinib mesylate) tablets (n=553)	Interferon (n=553)
Median Age (years)		50	51
Sex % (n)	Male	61.7% (341)	56.1% (310)
	Female	38.3% (212)	43.9% (243)
Sokal Risk Assessment % (n)	Low Risk	52.5% (201)	48.2% (190)
	Inter. Risk	29.0% (111)	29.7% (117)
	High Risk	18.5% (71)	22.1% (87)

### DASISION<sup>3</sup>

Characteristics		Dasatinib (n=259)	GLEEVEC (n=260)
Median Age (years)		46	49
Sex % (n)	Male	56% (144)	63% (163)
	Female	44% (115)	37% (97)
Hasford Risk Assessment % (n)	Low Risk	33% (86)	33% (87)
	Inter. Risk	48% (124)	47% (123)
	High Risk	19% (49)	19% (50)

### ENESTnd<sup>2</sup>

Characteristics		Nilotinib (n=282)	GLEEVEC (n=283)
Median Age (years)		47	46
Sex % (n)	Male	56% (158)	56% (158)
	Female	44% (124)	44% (125)
Sokal Risk Assessment % (n)	Low Risk	37% (103)	37% (104)
	Inter. Risk	36% (101)	36% (101)
	High Risk	28% (78)	28% (78)

### BFORE<sup>4</sup>

Characteristics		Bosutinib (n=246)	GLEEVEC (n=241)
Median Age (years)		52	53
Sex % (n)	Male	57.7% (142)	56.0% (135)
	Female	42.3% (104)	44% (106)
Sokal Risk Assessment % (n)	Low Risk	38.2% (94)	39.4% (95)
	Inter. Risk	41.1% (101)	39.4% (95)
	High Risk	20.7% (51)	21.2% (51)

#### IMPORTANT SAFETY INFORMATION (cont)

- In the newly diagnosed CML trial of GLEEVEC vs IFN+Ara-C, 1.8% of patients had grade 3/4 hemorrhage. In a study with newly diagnosed Ph+ CML patients in the chronic phase comparing GLEEVEC and nilotinib, GI hemorrhage occurred in 1.4% and 2.9% of patients, respectively. None of these events were grade 3 or 4 in the GLEEVEC arm; 0.7% were grade 3 or 4 in the nilotinib arm
- GLEEVEC is sometimes associated with GI irritation. There have been rare reports, including fatalities, of GI perforation

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#### IMPORTANT SAFETY INFORMATION (cont)

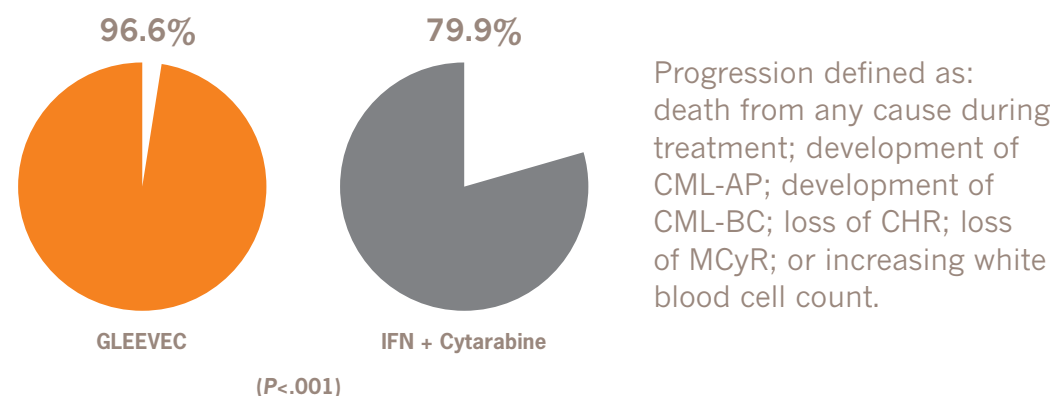
- Bullous dermatologic reactions (eg, erythema multiforme and Stevens-Johnson syndrome) have also been reported. In some cases, the reaction recurred upon rechallenge. Several postmarketing reports describe patients able to tolerate the reintroduction of GLEEVEC at a lower dose, with or without concomitant corticosteroids or antihistamines following resolution or improvement of the bullous reaction

## Primary end points differ, reflecting the evolution of treatment goals and depth of response measures

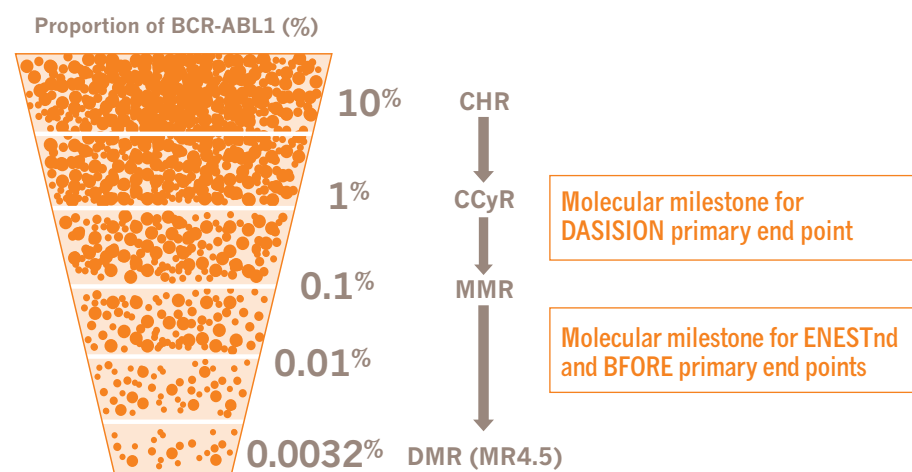
IRIS established GLEEVEC® (imatinib mesylate) tablets as standard of care in CML, as well as the standard comparator against which 2nd-generation TKIs are measured.<sup>2-5</sup>

ENESTnd was the first TKI pivotal trial to assess MMR as the primary end point, establishing evolved standards for molecular response.<sup>7,12,17</sup>

### IRIS: Progression-free survival at 12 months<sup>1</sup>



#### Measuring Response to Therapy in Ph+ CML<sup>5,7</sup>

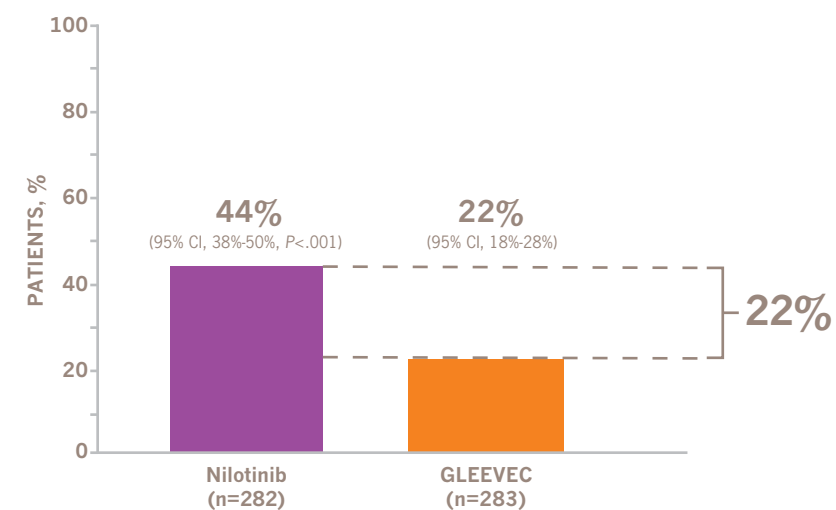


#### IMPORTANT SAFETY INFORMATION (cont)

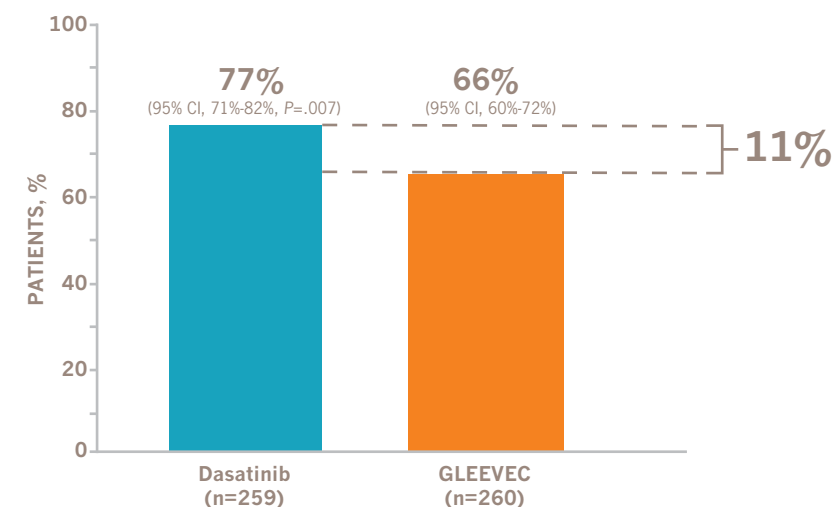
- Clinical cases of hypothyroidism have been reported in thyroidectomy patients undergoing levothyroxine replacement during treatment with GLEEVEC. TSH levels should be closely monitored in such patients
- Fetal harm can occur when administered to a pregnant woman. Test pregnancy status in females of reproductive potential prior to GLEEVEC initiation. Advise sexually active females of reproductive potential to avoid pregnancy and use effective contraception (methods that result in <1% pregnancy rates) when taking GLEEVEC and for 14 days after stopping GLEEVEC. Advise women to avoid breastfeeding during treatment and for 1 month after the last dose because of the potential for serious adverse reactions in breastfed infants. If pregnancy occurs while taking GLEEVEC, apprise the patient of the potential hazard to the fetus

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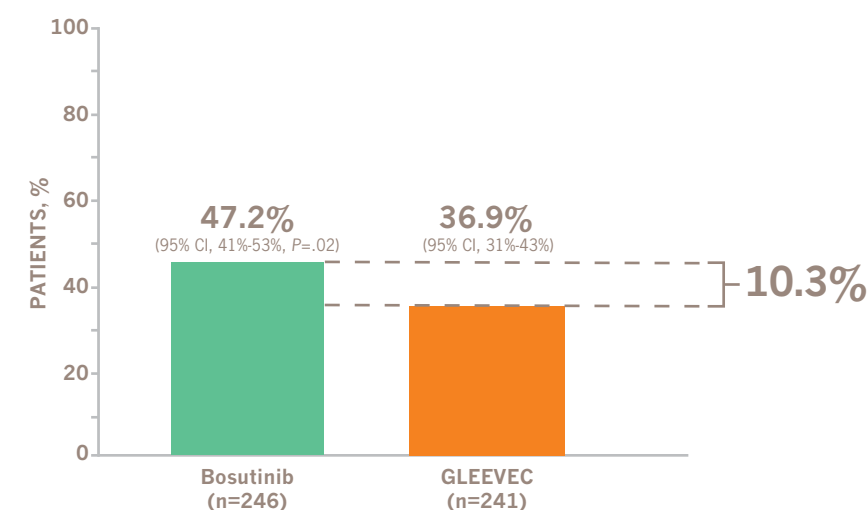
### ENESTnd: MMR at 12 months<sup>2,18</sup>



### DASISION: CCyR by 12 months<sup>3</sup>



### BFORE: MMR at 12 months<sup>4</sup>

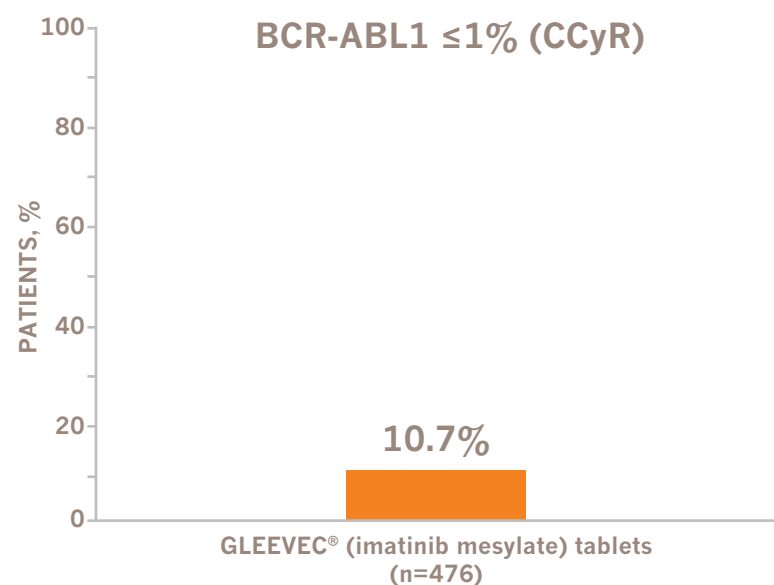


## EMR is an important prognostic indicator of long-term outcomes in patients with CML

Measuring EMR is recognized as an important strategy to assess current patient progress, as well as likelihood of achieving a deeper molecular response and, ultimately, improving survival.<sup>9,11</sup>

The IRIS study did not proactively assess response at 3 months; however, BCR-ABL1 levels were assessed retrospectively at 3-month, 6-month, and 12-month timepoints in the subset of patients from the ITT population with available PCR samples.<sup>8</sup>

### IRIS: CCyR at 3 months<sup>8</sup>



EMR was analyzed in the complete molecular monitoring dataset to demonstrate the long-term prognostic values of the levels of molecular response at specific time points. Patients enrolled in the imatinib arm of the IRIS trial with at least 1 BCR-ABL1 transcript measurement were included.

RQ, real-time quantitative.

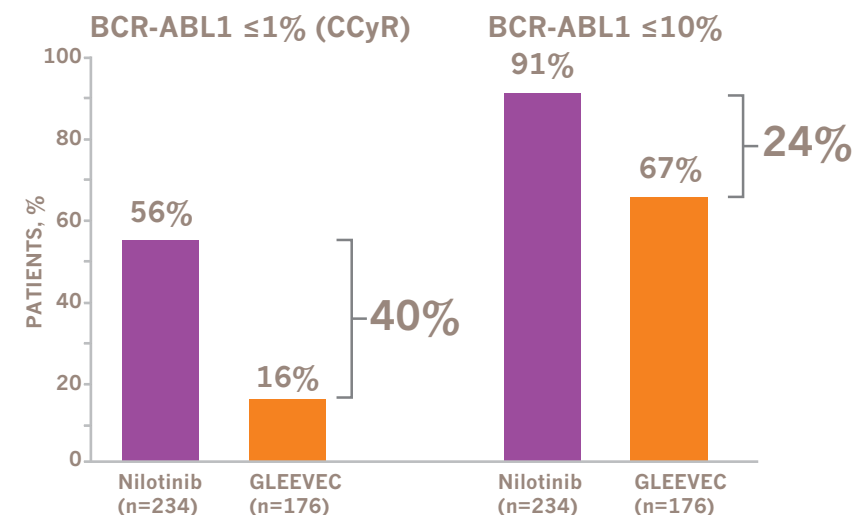
### IMPORTANT SAFETY INFORMATION (cont)

- Growth retardation has been reported in children and preadolescents receiving GLEEVEC. The long-term effects of prolonged treatment with GLEEVEC on growth in children are unknown; therefore, monitoring of growth in children taking GLEEVEC is recommended
- Cases of tumor lysis syndrome (TLS), including fatal cases, have been reported. The patients at risk for TLS are those with tumors having a high proliferative rate or high tumor burden prior to treatment. These patients should be monitored closely and appropriate precautions taken. Correction of clinically significant dehydration and treatment of high uric acid levels are recommended prior to initiation of GLEEVEC

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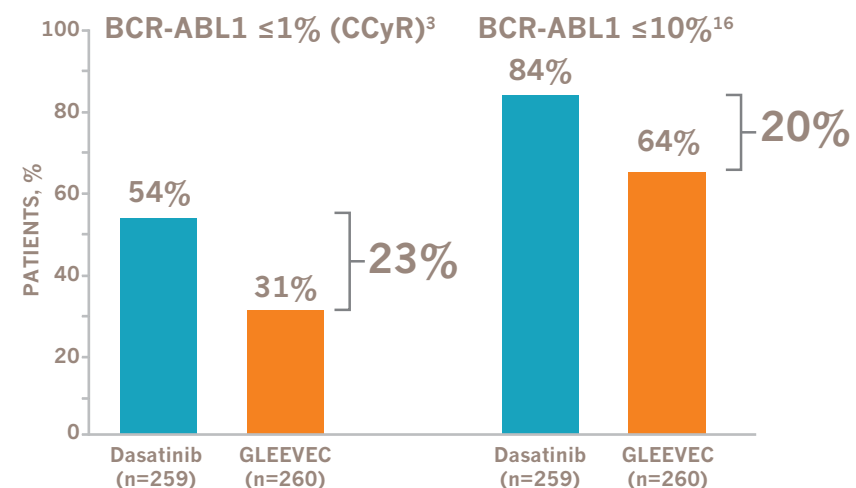
## Early Response

### ENESTnd: EMR 3-month analysis<sup>9</sup>



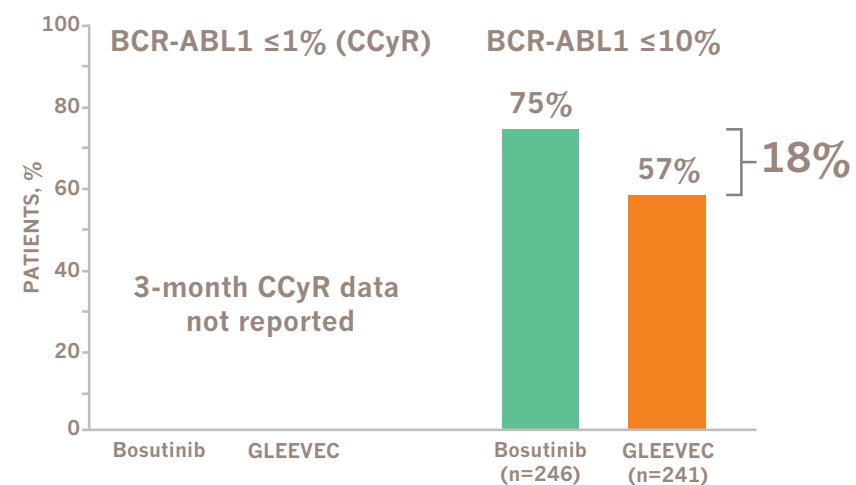
Descriptive analysis in patients with typical b2a2 and/or b3a2 BCR-ABL transcripts and evaluable RQ-PCR samples at 3 months.<sup>9</sup>

### DASISION: EMR 3-month analysis



The predictive value of early responses for the outcomes of patients treated with a minimum follow-up of 3 years was assessed in a retrospective landmark analysis. All patients registered and enrolled were assessed for responses.<sup>19</sup>

### BFORE: EMR 3-month analysis<sup>4</sup>

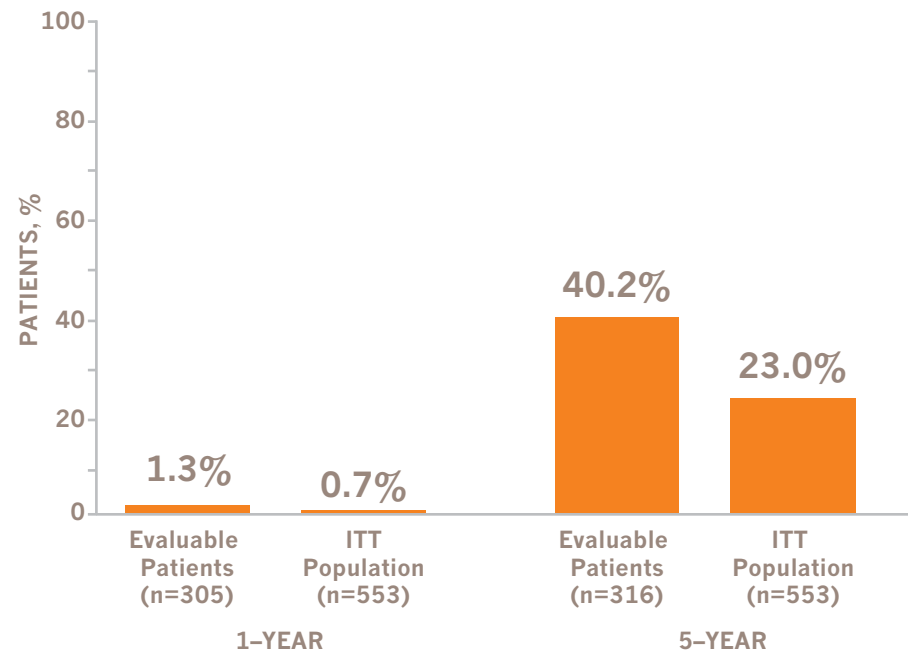


# Deep molecular response is a critical treatment milestone in the current CML landscape

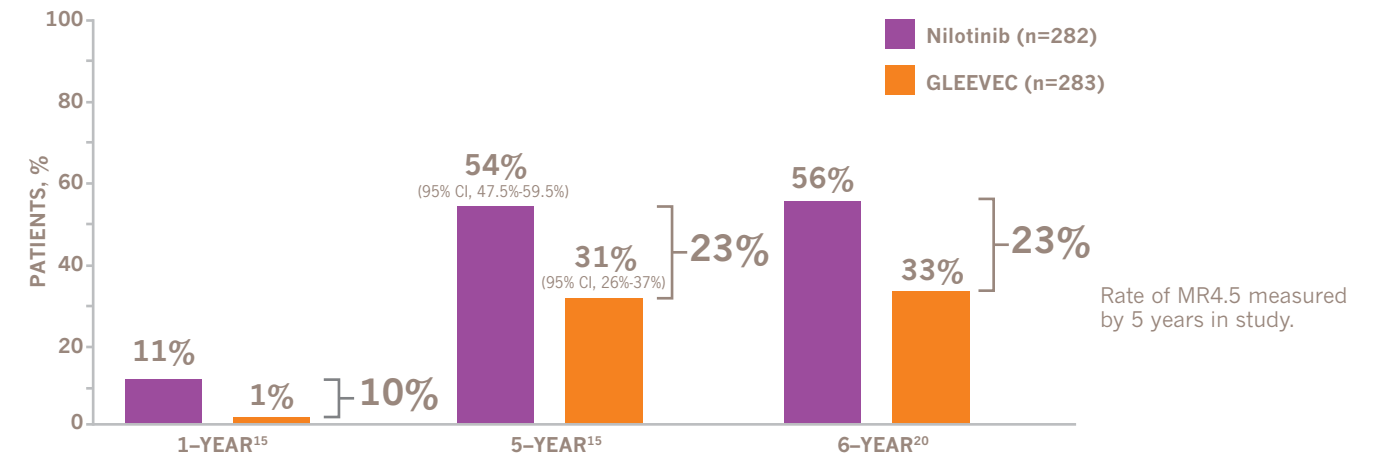
MR4.5

## IRIS: MR4.5 analysis<sup>14</sup>

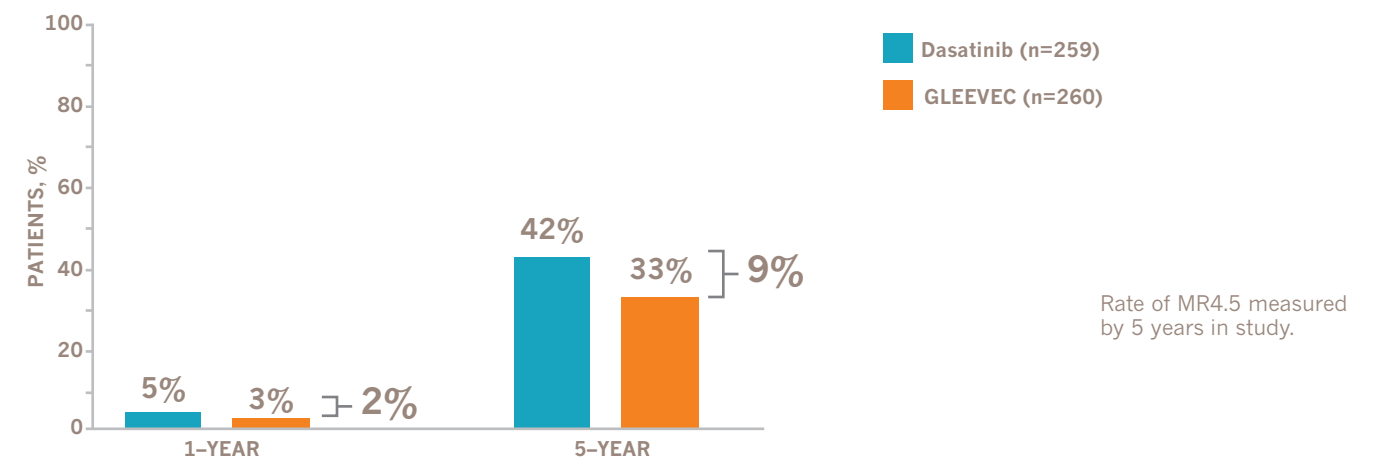
Assessment of MR4.5 was an exploratory analysis and was calculated at each time point for the ITT population and by those who could be evaluated



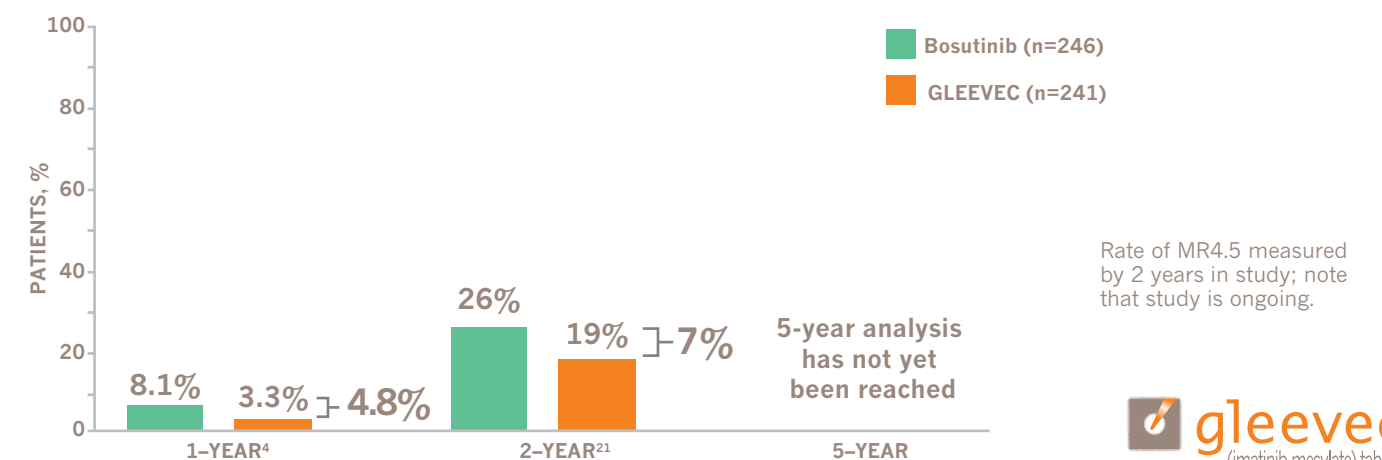
## ENESTnd: MR4.5 analysis<sup>15,20</sup>



## DASISION: MR4.5 analysis<sup>16</sup>



## BFORE: MR4.5 analysis<sup>4,21</sup>



### IMPORTANT SAFETY INFORMATION (cont)

- Motor vehicle accidents involving patients receiving GLEEVEC® (imatinib mesylate) tablets have been reported. Advise patients that they may experience side effects such as dizziness, blurred vision, or somnolence during treatment with GLEEVEC. Caution is recommended when driving a car or operating machinery
- A decline in renal function may occur in patients receiving GLEEVEC. Evaluate renal function at baseline and during therapy, with attention to risk factors for renal dysfunction such as preexisting renal impairment, diabetes mellitus, hypertension, and congestive heart failure

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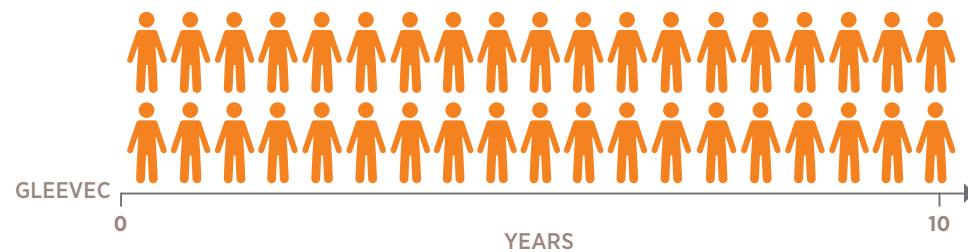


# Preventing progression to advanced stages of CML is an important treatment goal according to NCCN Clinical Practice Guidelines In Oncology (NCCN Guidelines®)<sup>11</sup>

- Patients with CML who progress to AP or BC are at risk for lower survival and have fewer options to regain disease control<sup>5,11</sup>
- Disease progression was assessed in all of the pivotal TKI trials, though the measures vary: PFS versus progression to advanced disease stage

Pivotal Trial	Progression Assessment
<b>IRIS</b>	Progression to AP/BC was the primary end point and assessed throughout follow-up <sup>1</sup>
<b>ENESTnd</b>	Progression to AP/BC or CML-related death was a key secondary end point and was assessed throughout follow-up <sup>2</sup>
<b>DASISION</b>	Transformation to AP/BC was an exploratory end point <sup>3</sup>
<b>BFORE</b>	Transformation to AP/BC was included in the criteria for EFS, which was a key secondary end point <sup>4,22</sup>

## IRIS: 10-year analysis of progression to AP/BC<sup>14</sup>



38 patients of 553 progressed to AP/BC in 10 years on GLEEVEC® (imatinib mesylate) tablets

EFS, event-free survival.

### IMPORTANT SAFETY INFORMATION (cont)

- In Ph+ CML trials,\* severe (grades 3/4) lab abnormalities included neutropenia (3.6%-48%), anemia (1%-42%), thrombocytopenia (<1%-33%), and hepatotoxicity (~5%). Severe (grades 3/4) adverse reactions experienced by Ph+ CML patients who received GLEEVEC in clinical studies included hemorrhage (1.8%-19%), fluid retention (eg, pleural effusion, pulmonary edema, and ascites) (2.5%-11%), superficial edema (1.5%-6%), and musculoskeletal pain (2%-9%).<sup>†</sup> Severe fluid retention appears to be dose related, was more common in the advanced phase studies (where the dosage was 600 mg/day), and is more common in the elderly. In an additional study of patients with Ph+ CML in chronic phase comparing GLEEVEC and nilotinib, severe (grades 3/4) adverse reactions and those with rates greater than 1% were diarrhea (4%), nausea (2%), and rash (2%)

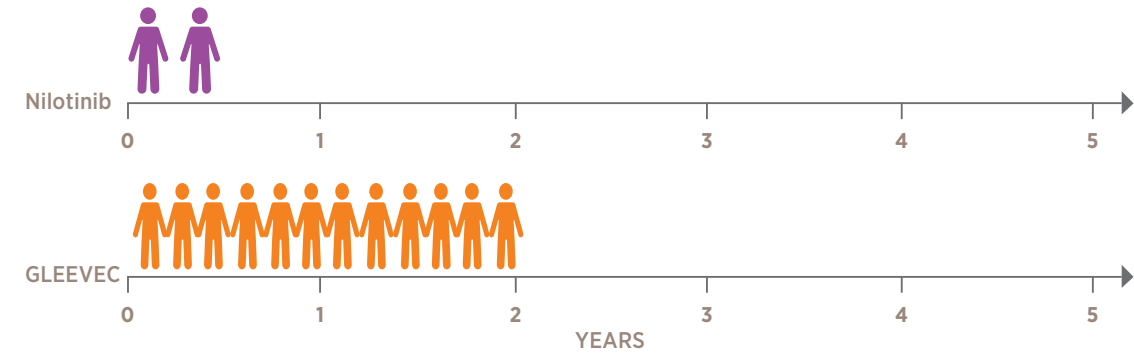
\*For more detailed study information, please see accompanying full Prescribing Information.

<sup>†</sup>Numbers indicate the range of percentages in 4 studies among patients with newly diagnosed Ph+ CML, patients in blast crisis, in accelerated phase, and in the chronic phase after failure of interferon-alpha therapy.

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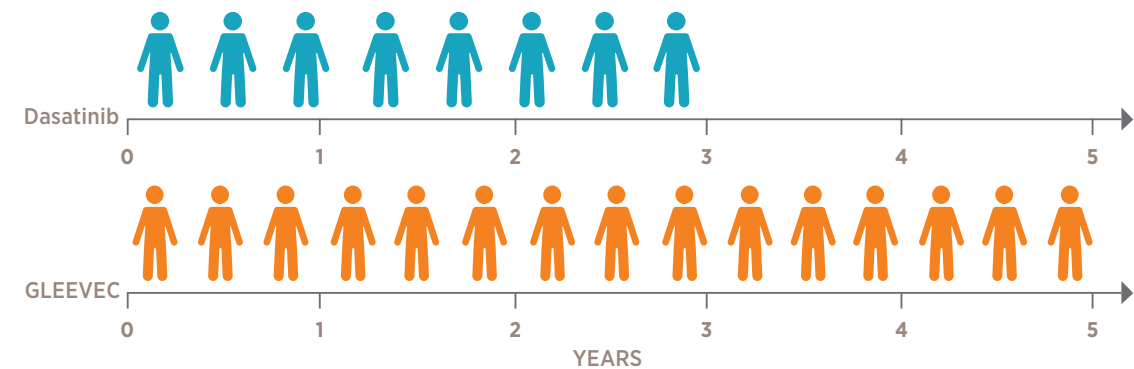
## Progression to AP/BC

### ENESTnd: 5-year analysis of progression to AP/BC<sup>15</sup>



2 patients of 282 progressed to AP/BC in 6 months vs 12 patients of 283 in 2 years on GLEEVEC

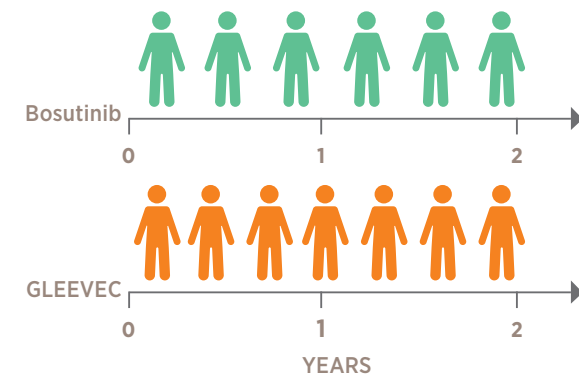
### DASISION: 5-year analysis of transformation to AP/BC<sup>23</sup>



8 patients of 259 transformed to AP/BC in 3 years vs 15 patients of 260 in 5 years on GLEEVEC

### BFORE: 2-year analysis of transformation to AP/BC<sup>21</sup>

(5-year not yet reached)



6 patients of 246 transformed to AP/BC in 2 years vs 7 patients of 241 in 2 years on GLEEVEC

## Extending survival is an important treatment goal

Overall Survival

Overall survival was assessed in all of the pivotal TKI trials. Median overall survival was not yet reached in these trials.

Pivotal Trial	Overall Survival Assessment
IRIS	Overall survival was a long-term primary end point and was assessed throughout follow-up <sup>14</sup>
ENESTnd	Overall survival was a key secondary end point and was assessed throughout follow-up <sup>24</sup>
DASISION	Overall survival was a secondary end point <sup>3</sup>
BFORE	Overall survival was a key secondary end point <sup>4</sup>

### IRIS: 10-year estimated survival<sup>14</sup>

<b>GLEEVEC® (imatinib mesylate) tablets</b>	<b>83.3% of 553</b> (95% CI, 80.1%-86.6%) (A range of 64.4%-84.4% reflects 111 patients with unknown survival status at time of final analysis, assuming either all patients were alive or all patients had died at time of analysis)
<b>IFN + Cytarabine</b>	<b>78% of 553</b> (95% CI, 75.0%-82.5%)

After 7 years, the trial was extended for imatinib only. Patients in the group that received interferon alfa plus cytarabine were eligible to continue in the trial if they crossed over to imatinib.

#### IMPORTANT SAFETY INFORMATION (cont)

- CYP3A4 is the major enzyme responsible for the metabolism of GLEEVEC. Concomitant administration of GLEEVEC and strong CYP3A4 inducers may reduce total exposure of GLEEVEC; consider alternative agents. Concomitant administration of GLEEVEC and strong CYP3A4 inhibitors may result in a significant GLEEVEC exposure increase. Grapefruit juice should be avoided because it may increase plasma concentrations of GLEEVEC. GLEEVEC will also increase plasma concentrations of other CYP3A4 metabolized drugs (eg, triazolo-benzodiazepines, dihydropyridine calcium channel blockers, certain HMG-CoA reductase inhibitors, etc). Use caution when administering GLEEVEC with CYP3A4 and CYP2D6 substrates that have a narrow therapeutic window. Because warfarin is metabolized by CYP2C9 and CYP3A4, use low-molecular weight or standard heparin instead of warfarin.

Please see additional GLEEVEC Important Safety Information on pages 24-26, and [click here](#) for full Prescribing Information.

### ENESTnd: 5-year estimated survival<sup>15</sup>

<b>Nilotinib</b>	<b>93.7% of 282</b> (95% CI, 90.8%-96.6%)
<b>GLEEVEC</b>	<b>91.7% of 283</b> (95% CI, 88.3%-95.0%)

Overall survival (all deaths) was defined as the time between randomization and death due to any cause at any time during the study, including the follow-up period after treatment discontinuation.

### DASISION: 5-year estimated survival<sup>16,23</sup>

<b>Dasatinib</b>	<b>91% of 259</b> (95% CI, 86.6%-93.8%)
<b>GLEEVEC</b>	<b>90% of 260</b> (95% CI, 85.2%-92.8%)

### BFORE: 2-year estimated survival<sup>21</sup>

<b>Bosutinib</b>	<b>99% of 268</b> (95% CI NR)
<b>GLEEVEC</b>	<b>97% of 268</b> (95% CI NR)

NR, not reported.

## Overview of frequently reported adverse events in TKI pivotal trials

### IRIS: 10-year safety analysis<sup>14</sup>

Treatment discontinuation due to adverse events	
GLEEVEC® (imatinib mesylate) tablets	6.9%

#### Most common adverse reactions (≥10%)<sup>25</sup>

Fluid retention (superficial edema), nausea, muscle cramps, musculoskeletal pain, diarrhea, rash, fatigue, headache, joint pain, abdominal pain, nasopharyngitis, hemorrhage, myalgia, vomiting, dyspepsia, cough, pharyngolaryngeal pain, upper respiratory tract infection, dizziness, pyrexia, weight increased, insomnia, depression, influenza, bone pain, constipation, sinusitis

### ENESTnd: 5-year safety analysis<sup>26</sup>

Treatment discontinuation due to adverse events	
Nilotinib	12.1%
GLEEVEC	13.4%

Treatment discontinuation rate reported for nilotinib 300 mg BID study arm.

#### Most common adverse reactions (≥10%)<sup>18</sup>

Nilotinib 300 mg BID: rash, pruritus, alopecia, dry skin, nausea, constipation, diarrhea, vomiting, abdominal pain, dyspepsia, headache, dizziness, fatigue, pyrexia, asthenia, myalgia, arthralgia, muscle spasms, pain in extremity, back pain, cough, oropharyngeal pain, dyspnea, nasopharyngitis, upper respiratory tract infection, influenza, insomnia, hypertension, myelosuppression (thrombocytopenia, neutropenia)

GLEEVEC: rash, nausea, diarrhea, vomiting, abdominal pain, dyspepsia, headache, dizziness, fatigue, pyrexia, asthenia, peripheral edema, face edema, myalgia, arthralgia, muscle spasms, pain in extremity, back pain, cough, nasopharyngitis, upper respiratory tract infection, gastroenteritis, eyelid edema, periorbital edema, neutropenia

### DASISION: 5-year safety analysis<sup>16</sup>

Treatment discontinuation due to intolerance*	
Dasatinib	16%
GLEEVEC	7%

\*As decided by investigator. Intolerance is defined as recurrent grade ≥3 hematologic toxicity or grade ≥2 nonhematologic toxicity requiring discontinuation despite dose reduction.

#### Most common adverse reactions (≥10%)<sup>23</sup>

Dasatinib 100 mg QD: fluid retention (pleural effusion, superficial localized edema), diarrhea, musculoskeletal pain, rash, headache, abdominal pain, fatigue, nausea, neutropenia, thrombocytopenia, anemia

GLEEVEC: fluid retention (superficial localized edema), diarrhea, musculoskeletal pain, rash, headache, fatigue, nausea, myalgia, arthralgia, vomiting, muscle spasms

### BFORE: 1-year safety analysis<sup>4</sup>

Treatment discontinuation due to adverse events	
Bosutinib	12.7%
GLEEVEC	8.7%

#### Most common adverse reactions (≥10%)<sup>27</sup>

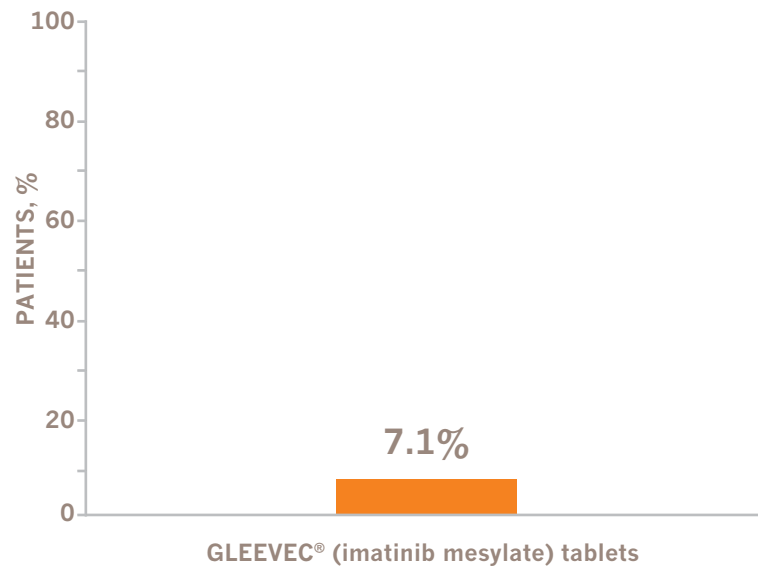
Bosutinib 400 mg QD: diarrhea, nausea, thrombocytopenia, rash, ALT increased, AST increased, abdominal pain, anemia, headache, fatigue, vomiting, lipase increased, pyrexia, respiratory tract infection, neutropenia, arthralgia, asthenia, appetite decreased

GLEEVEC: diarrhea, nausea, thrombocytopenia, rash, abdominal pain, anemia, headache, fatigue, vomiting, respiratory tract infection, neutropenia, arthralgia

## Overview of CV events observed in TKI pivotal trials

The definitions and reporting of CV events differed in the pivotal TKI trials, as is reflected in the observed rates of adverse events. The time points of the follow-up analysis also vary, based on individual study protocol and timing.

### IRIS: 10-year analysis of serious cardiac adverse events<sup>28</sup>



Definitions:  
Serious cardiovascular disorders included: myocardial infarction; angina pectoris; coronary artery disease; acute myocardial infarction; unstable angina; arteriosclerosis coronary artery; ischemic cardiomyopathy; atrial fibrillation; cardiac arrest; congestive cardiac failure; arrhythmia; left ventricular dysfunction; cardiac failure; bradycardia; pericardial effusion; cardio-respiratory arrest; ventricular fibrillation; ventricular tachycardia; sick sinus syndrome; supraventricular tachycardia; torsades de pointes; ventricular extrasystoles; nodal arrhythmia; cardiomyopathy; cardiac tamponade; aortic valve stenosis; cardiovascular disorder; palpitations; pericarditis

### IMPORTANT SAFETY INFORMATION (cont)

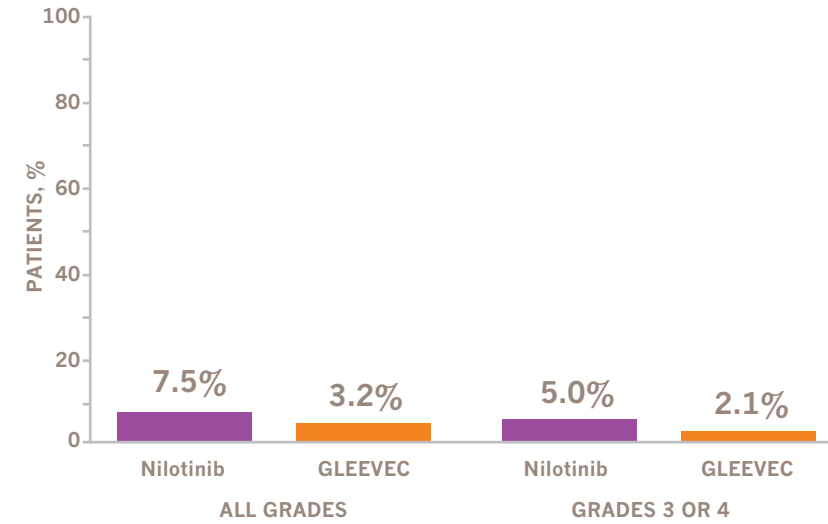
- Patients with moderate renal impairment (CrCL=20-39 mL/min) should receive a 50% decrease in the recommended starting dose; future doses can be increased as tolerated. Doses greater than 600 mg are not recommended in patients with mild renal impairment (CrCL=40-59 mL/min). For patients with moderate renal impairment, doses greater than 400 mg are not recommended. GLEEVEC should be used with caution in patients with severe renal impairment

\*Numbers indicate the range of percentages in 4 studies among patients with newly diagnosed Ph+ CML, patients in blast crisis, in accelerated phase, and in the chronic phase after failure of interferon-alpha therapy.

Please see additional GLEEVEC Important Safety Information on pages 24-26, and [click here](#) for full Prescribing Information.

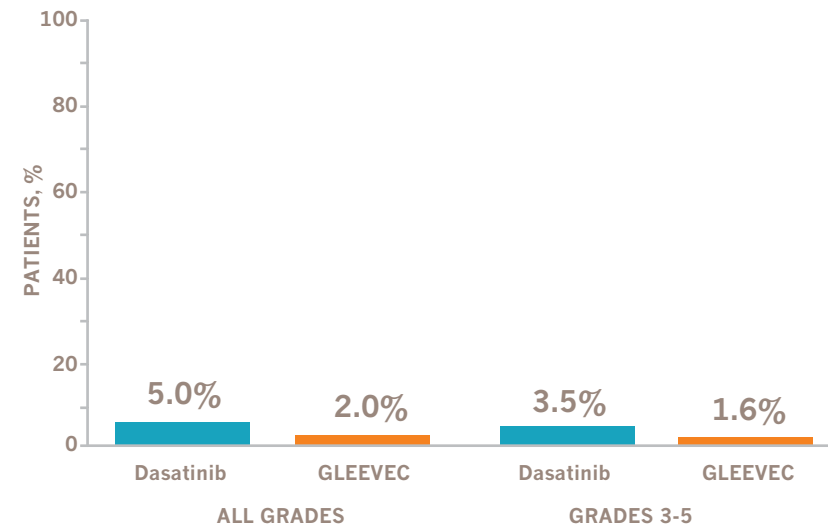
## CV Events

### ENESTnd: 5-year analysis of cardiovascular disease<sup>29</sup>



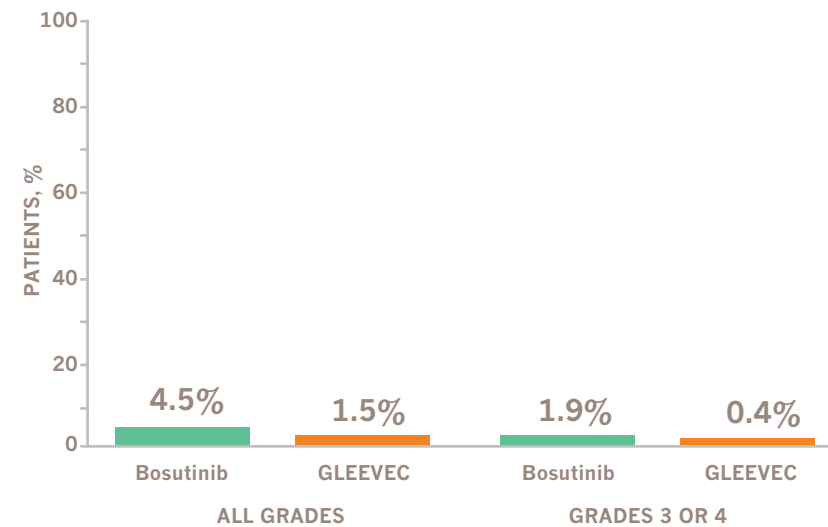
Definitions:  
Cardiovascular diseases include: angina pectoris; coronary artery disease; myocardial infarction; coronary artery occlusion; acute myocardial infarction; angina unstable; coronary artery stenosis; blood creatine phosphokinase MB increased; Troponin I increased; troponin increased; troponin T increased; transient ischemic attack; subdural hemorrhage; subdural hematoma; paralysis; cerebrovascular disorder; basilar artery stenosis; amaurosis fugax; monoparesis; hemiparesis; cerebral ischemia; cerebral infarction; carotid artery stenosis; aphasia; ischemic stroke; cerebral hemorrhage; cerebrovascular accident; peripheral arterial occlusive disease; peripheral artery stenosis; intermittent claudication; peripheral ischemia; arterial occlusive disease

### DASISION: 5-year analysis of any-cause arterial ischemic events<sup>16</sup>



Definitions:  
Arterial ischemic events: myocardial infarction; angina pectoris; coronary artery disease; acute coronary syndrome; transient ischemic attack; peripheral arterial disease

### BFORE: 1-year analysis of any vascular events<sup>22</sup>



Definitions:  
Vascular events: coronary artery disorders; angina pectoris; coronary artery disease; myocardial ischemia; coronary artery occlusion; acute coronary syndrome; central nervous system hemorrhages; cerebrovascular accidents; central nervous system vascular disorders NEC; transient cerebrovascular events; vascular imaging procedures NEC; vascular therapeutic procedures NEC; arteriosclerosis; stenosis; vascular insufficiency; necrosis; embolism; thrombosis; arterial therapeutic procedures (excluding aortic); non-site specific vascular disorders NEC; peripheral vascular disorders NEC (excluding flushing and hot flash)



## IMPORTANT SAFETY INFORMATION

- GLEEVEC is often associated with edema and, occasionally, serious fluid retention. Severe fluid retention was reported in 9% to 13.1% and 2.5% to 11% of patients taking GLEEVEC for GIST and CML, respectively. Patients should be weighed and monitored regularly for signs and symptoms of fluid retention, which can be serious or life threatening, and be advised to report any rapid, unexpected weight gain. The probability of edema tended to be increased among older patients (>65 years) or those taking higher doses of GLEEVEC. Severe edema and superficial edema were observed in 182 (11.1%) GIST patients and 1.5% to 6% in CML patients, respectively. If severe fluid retention occurs, manage with diuretic therapy and withhold GLEEVEC until the event has resolved, and then resume, depending on the initial severity of the event. In a study of patients with newly diagnosed Ph+ CML in chronic phase comparing GLEEVEC and nilotinib, severe (grade 3 or 4) fluid retention occurred in 2.5% of patients receiving GLEEVEC and in 3.9% of patients receiving nilotinib. Effusions or pulmonary edema were observed in 2.1% (none were grade 3 or 4) of patients in the GLEEVEC arm and 2.2% (0.7% grade 3 or 4) of patients in the nilotinib arm
- Cytopenias have been reported. Complete blood counts should be performed weekly for the first month, biweekly for the second month, and periodically thereafter as clinically indicated (eg, every 2-3 months). Dose reduction, treatment interruption, or in rare cases discontinuation of treatment may be required for severe neutropenia or thrombocytopenia (see full Prescribing Information for dose adjustment recommendations)
- Congestive heart failure and left ventricular dysfunction (LVD) have been reported. Most patients with reported cardiac events have had other comorbidities and risk factors, including advanced age and previous medical history of cardiac disease. In a phase 3 study of patients with newly diagnosed Ph+ CML in chronic phase, severe cardiac failure and LVD occurred in 0.7% of GLEEVEC patients vs 0.9% of IFN+Ara-C patients. In a study of newly diagnosed Ph+ CML patients in chronic phase comparing GLEEVEC and nilotinib, cardiac failure was observed in 1.1% and 2.2% of patients, respectively, and severe (grade 3 or 4) cardiac failure occurred in 0.7% of patients in each group. Patients with cardiac disease, risk factors for cardiac disease, or history of renal failure should be monitored carefully, and any patient with signs or symptoms consistent with cardiac or renal failure should be evaluated and treated
- Hepatotoxicity, occasionally severe, may occur. Cases of fatal liver failure and severe liver injury requiring liver transplants have been reported with both short-term and long-term use of GLEEVEC. Assess liver function before initiation of treatment and monthly thereafter, or as clinically indicated. A 25% decrease in the recommended dose should be used for patients with severe hepatic impairment. If severe hepatotoxicity occurs, GLEEVEC should be withheld until the event has resolved and then resumed, depending on the initial severity of the event
- When GLEEVEC is combined with chemotherapy, liver toxicity in the form of transaminase elevation and hyperbilirubinemia has been observed. Additionally, there have been reports of acute liver failure. Monitoring of hepatic function is recommended
- In the newly diagnosed CML trial of GLEEVEC vs IFN+Ara-C, 1.8% of patients had grade 3/4 hemorrhage. In a study with newly diagnosed Ph+ CML patients in the chronic phase comparing GLEEVEC and nilotinib, GI hemorrhage occurred in 1.4% and 2.9% of patients, respectively. None of these events were grade 3 or 4 in the GLEEVEC arm; 0.7% were grade 3 or 4 in the nilotinib arm
- GLEEVEC is sometimes associated with GI irritation. There have been rare reports, including fatalities, of GI perforation
- Bullous dermatologic reactions (eg, erythema multiforme and Stevens-Johnson syndrome) have also been reported. In some cases, the reaction recurred upon rechallenge. Several postmarketing reports describe patients able to tolerate the reintroduction of GLEEVEC at a lower dose, with or without concomitant corticosteroids or antihistamines following resolution or improvement of the bullous reaction

Please see additional GLEEVEC Important Safety Information on pages 24-26, and [click here for full Prescribing Information](#).

- Clinical cases of hypothyroidism have been reported in thyroidectomy patients undergoing levothyroxine replacement during treatment with GLEEVEC. TSH levels should be closely monitored in such patients
- Fetal harm can occur when administered to a pregnant woman. Test pregnancy status in females of reproductive potential prior to GLEEVEC initiation. Advise sexually active females of reproductive potential to avoid pregnancy and use effective contraception (methods that result in <1% pregnancy rates) when taking GLEEVEC and for 14 days after stopping GLEEVEC. Advise women to avoid breastfeeding during treatment and for 1 month after the last dose because of the potential for serious adverse reactions in breastfed infants. If pregnancy occurs while taking GLEEVEC, apprise the patient of the potential hazard to the fetus
- Growth retardation has been reported in children and preadolescents receiving GLEEVEC. The long-term effects of prolonged treatment with GLEEVEC on growth in children are unknown; therefore, monitoring of growth in children taking GLEEVEC is recommended
- Cases of tumor lysis syndrome (TLS), including fatal cases, have been reported. The patients at risk for TLS are those with tumors having a high proliferative rate or high tumor burden prior to treatment. These patients should be monitored closely and appropriate precautions taken. Correction of clinically significant dehydration and treatment of high uric acid levels are recommended prior to initiation of GLEEVEC
- Motor vehicle accidents involving patients receiving GLEEVEC have been reported. Advise patients that they may experience side effects such as dizziness, blurred vision, or somnolence during treatment with GLEEVEC. Caution is recommended when driving a car or operating machinery
- A decline in renal function may occur in patients receiving GLEEVEC. Evaluate renal function at baseline and during therapy, with attention to risk factors for renal dysfunction such as preexisting renal impairment, diabetes mellitus, hypertension, and congestive heart failure
- In Ph+ CML trials,\* severe (grades 3/4) lab abnormalities included neutropenia (3.6%-48%), anemia (1%-42%), thrombocytopenia (<1%-33%), and hepatotoxicity (~5%). Severe (grades 3/4) adverse reactions experienced by Ph+ CML patients who received GLEEVEC in clinical studies included hemorrhage (1.8%-19%), fluid retention (eg, pleural effusion, pulmonary edema, and ascites) (2.5%-11%), superficial edema (1.5%-6%), and musculoskeletal pain (2%-9%).<sup>†</sup> Severe fluid retention appears to be dose related, was more common in the advanced phase studies (where the dosage was 600 mg/day), and is more common in the elderly. In an additional study of patients with Ph+ CML in chronic phase comparing GLEEVEC and nilotinib, severe (grades 3/4) adverse reactions and those with rates greater than 1% were diarrhea (4%), nausea (2%), and rash (2%)
- CYP3A4 is the major enzyme responsible for the metabolism of GLEEVEC. Concomitant administration of GLEEVEC and strong CYP3A4 inducers may reduce total exposure of GLEEVEC; consider alternative agents. Concomitant administration of GLEEVEC and strong CYP3A4 inhibitors may result in a significant GLEEVEC exposure increase. Grapefruit juice should be avoided because it may increase plasma concentrations of GLEEVEC. GLEEVEC will also increase plasma concentrations of other CYP3A4 metabolized drugs (eg, triazolo-benzodiazepines, dihydropyridine calcium channel blockers, certain HMG-CoA reductase inhibitors, etc). Use caution when administering GLEEVEC with CYP3A4 and CYP2D6 substrates that have a narrow therapeutic window. Because warfarin is metabolized by CYP2C9 and CYP3A4, use low-molecular weight or standard heparin instead of warfarin

\*For more detailed study information, please see accompanying full Prescribing Information.

<sup>†</sup>Numbers indicate the range of percentages in 4 studies among patients with newly diagnosed Ph+ CML, patients in blast crisis, in accelerated phase, and in the chronic phase after failure of interferon-alpha therapy.

## IMPORTANT SAFETY INFORMATION (cont)

- Patients with moderate renal impairment (CrCL=20-39 mL/min) should receive a 50% decrease in the recommended starting dose; future doses can be increased as tolerated. Doses greater than 600 mg are not recommended in patients with mild renal impairment (CrCL=40-59 mL/min). For patients with moderate renal impairment, doses greater than 400 mg are not recommended. GLEEVEC should be used with caution in patients with severe renal impairment

### Common Side Effects of GLEEVEC Tablets

- Almost all adult Ph+ CML patients who received GLEEVEC in clinical studies experienced adverse reactions at some time. In 4 Ph+ CML studies, the most frequently reported adverse reactions (all grades) and those with rates greater than 45% were superficial edema (60%-74%), nausea (50%-73%), diarrhea (43%-57%), hemorrhage (29%-57%), musculoskeletal pain (38%-49%), fatigue (39%-48%), rash and related terms (36%-47%), muscle cramps (28%-62%), and vomiting (23%-58%).\* In an additional study of patients with newly diagnosed Ph+ CML in chronic phase comparing GLEEVEC and nilotinib, the most frequently reported adverse reactions (all grades) and those with rates greater than 15% were diarrhea (46%), nausea (41%), muscle spasms (34%), vomiting (27%), headache (23%), nasopharyngitis (21%), fatigue (20%), peripheral edema (20%), rash (19%), myalgia (19%), eyelid edema (19%), arthralgia (17%), back pain (17%), and pain in extremity (16%)
- Supportive care may help reduce the severity of some mild to moderate adverse reactions. However, in some cases, either a dose reduction or interruption of treatment with GLEEVEC may be necessary
- Doses of 400 mg or 600 mg should be administered once daily, whereas a dose of 800 mg should be administered at 400 mg twice a day. For daily dosing of 800 mg and above, dosing should be accomplished using the 400-mg tablet to reduce exposure to iron
- GLEEVEC tablets should be taken with food and a large glass of water to minimize GI irritation
- Patients should be instructed to take GLEEVEC exactly as prescribed and not to change their dose or stop taking GLEEVEC unless they are told to do so by their doctor. If patients miss a dose, they should be advised to take their dose as soon as possible unless it is almost time for their next dose, in which case the missed dose should not be taken. A double dose should not be taken to make up for any missed dose

\*Numbers indicate the range of percentages in 4 studies among patients with newly diagnosed Ph+ CML, patients in blast crisis, in accelerated phase, and in the chronic phase after failure of interferon-alpha therapy.

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### GLEEVEC® (imatinib mesylate) tablets are indicated for:

- Newly diagnosed adult and pediatric patients with Philadelphia chromosome–positive chronic myeloid leukemia (Ph+ CML) in the chronic phase
- Patients with Ph+ CML in blast crisis (BC), accelerated phase (AP), or in the chronic phase (CP) after failure of interferon-alpha therapy

### IMPORTANT SAFETY INFORMATION

- GLEEVEC is often associated with edema and, occasionally, serious fluid retention. Severe fluid retention was reported in 9% to 13.1% and 2.5% to 11% of patients taking GLEEVEC for GIST and CML, respectively. Patients should be weighed and monitored regularly for signs and symptoms of fluid retention, which can be serious or life threatening, and be advised to report any rapid, unexpected weight gain. The probability of edema tended to be increased among older patients (>65 years) or those taking higher doses of GLEEVEC. Severe edema and superficial edema were observed in 182 (11.1%) GIST patients and 1.5% to 6% in CML patients, respectively. If severe fluid retention occurs, manage with diuretic therapy and withhold GLEEVEC until the event has resolved, and then resume, depending on the initial severity of the event. In a study of patients with newly diagnosed Ph+ CML in chronic phase comparing GLEEVEC and nilotinib, severe (grade 3 or 4) fluid retention occurred in 2.5% of patients receiving GLEEVEC and in 3.9% of patients receiving nilotinib. Effusions or pulmonary edema were observed in 2.1% (none were grade 3 or 4) of patients in the GLEEVEC arm and 2.2% (0.7% grade 3 or 4) of patients in the nilotinib arm

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