Leukemias are cancers involving the bone marrow and blood, and they account for approximately 4% of cancer deaths. The majority of leukemias occur in adults aged >20 years, and the incidence is higher in men than in women. Leukemias are classified by the type of cell involved (ie, lymphocytic or myeloid) and the rate of progression (ie, acute or chronic). Chronic myeloid leukemia (CML) and acute lymphocytic leukemia (ALL) account for approximately 2.5% and 6%, respectively, of deaths resulting from leukemia.

CML arises from the unregulated production of white blood cells in the bone marrow that results from a constitutively active tyrosine kinase that is the fusion product of the Abelson murine leukemia (ABL) gene on chromosome 9 and the breakpoint cluster region (BCR) gene on chromosome 22 after a reciprocal translocation between these chromosomes forms the Philadelphia chromosome (Ph). A related fusion protein occurs in a subset of cases of ALL (ie, Ph-positive [Ph+] ALL).

The Burden and Impact of CML and ALL

The American Cancer Society estimates that almost 6000 new cases each of CML and ALL will be diagnosed in 2013 in the United States, and 610 deaths will result from CML and 1430 deaths from ALL. Leukemia is often associated with bleeding, bruising, weight loss, and infections. In acute leukemia, these symptoms may appear suddenly; in chronic leukemia, there may be few symptoms that progress slowly.

The 5-year survival rate for CML increased from 31% for patients diagnosed during 1990-1992 to 56% for those diagnosed during 2002-2008. The increase in survival for patients with CML is mainly the result of the development of targeted therapies, known as the BCR-ABL-specific tyrosine kinase inhibitors (TKIs). The 5-year relative survival rate for ALL overall has increased from 41% during the 1975-1977 period to 68% in the 2002-2008 period. The prognosis for Ph+ ALL is worse than that for other subtypes of ALL.

The current treatment options for CML include the TKIs imatinib (Gleevec) and nilotinib (Tasigna), which are specific BCR-ABL TKIs, and dasatinib (Sprycel) and bosutinib (Bosulif), which inhibit both ABL and Src kinases. These agents may be used as a part of combination therapy for patients with Ph+ ALL. Although many patients with CML who receive imatinib have a complete cytogenetic response, 25% of patients have disease that either does not respond initially to imatinib (primary resistance) or that progresses after initial response (secondary resistance).

Secondary resistance may be caused by a mutation in the ABL kinase domain known as the T315I (or gatekeeper) mutation, because it prevents imatinib, dasatinib, and bosutinib from entering the ATP-binding pocket and inhibiting the kinase. Resistance to imatinib and other TKIs is associated with many other mutations and other as-yet unidentified causes. However, the presence of a kinase-domain mutation is associated with a high risk for disease progression. Patients may also develop intolerance to approved TKIs. Therefore, there remains a need for new agents that are effective in patients with resistant disease.

Ponatinib Fills an Unmet Need

On December 14, 2012, the US Food and Drug Administration (FDA) granted accelerated approval to ponatinib (Iclusig; ARIAD Pharmaceuticals) based on the results from a phase 2 clinical trial. Ponatinib is indicated for the treatment of adult patients with chronic-phase (CP), accelerated-phase (AP), or blast-phase (BP) CML that is resistant to or is intolerant of previous TKI therapy or for patients with Ph+ ALL that is resistant to or intolerant of previous TKI therapy.

Ponatinib offers a new treatment option for patients with CML, especially those with the T315I mutation, whose disease is not responding to other agents. According to the FDA, these patients have had few therapeutic options. This approval provides patients with earlier access to ponatinib, while the manufacturer conducts additional studies to confirm the clinical benefit and the safe use of this new agent.

The prescribing information for ponatinib states that the indication was based on the response rate to the drug, and that no trials have confirmed an improvement in disease-related symptoms or increased survival with this drug.

Mechanism of Action

Ponatinib is a TKI that was designed to inhibit the
BCR-ABL genetic mutations, including drug-resistant mutations that arise during treatment. Ponatinib is the only TKI that is active against the T315I mutation of BCR-ABL, which is the most frequent mutation, occurring in up to 20% of patients with TKI resistance. In vitro, ponatinib inhibited the tyrosine kinase activity of ABL and T315I-mutant ABL, as well as that of additional kinases, including members of the vascular endothelial growth factor receptors, platelet-derived growth factor receptors, fibroblast growth factor receptors, and ephrin receptors; the Src families of kinases; and KIT, RET, TIE2, and FLT3.

Dosing and Administration

Ponatinib is administered orally once daily at a recommended dose of 45 mg. Dose modifications are suggested if patients experience neutropenia or thrombocytopenia that is unrelated to their leukemia. The dose of ponatinib should be modified or the treatment should be interrupted if serious nonhematologic reactions occur. Treatment may be resumed once the event has resolved, or if the benefit of resuming therapy outweighs the risk; in patients with serious ischemic reactions, in addition to considering the risk-benefit ratio, ponatinib should be resumed only if the patient has no other treatment options.

Use with CYP3A inhibitors. The recommended dose should be reduced to 30 mg once daily when administering ponatinib with strong cytochrome (CY) P3A inhibitors.

Phase 2 Pivotal Clinical Trial

Ponatinib was approved on the basis of the pivotal phase 2 Ponatinib Ph+ ALL and CML Evaluation (PACE) trial in patients with CML or Ph+ ALL whose disease was resistant to or intolerant of previous TKI therapy, or whose leukemia had the T315I mutation of BCR-ABL.

The phase 2 PACE trial was a single-arm, open-label, international, multicenter trial. The starting dose for all patients was 45 mg of ponatinib once daily. A total of 449 patients were enrolled, of whom 444 were evaluable for efficacy. Patients were assigned to 1 of 6 cohorts based on disease phase, resistance or intolerance to previous TKI therapy (ie, dasatinib or nilotinib), and the presence of the T315I mutation. Disease phases included CP-CML, AP-CML, and BP-CML/Ph+ ALL. The primary efficacy end point in CP-CML was major cytogenetic response, which included complete and partial cytogenetic responses. The primary efficacy end point in patients with AP-CML, BP-CML, and Ph+ ALL was major hematologic response, defined as a complete hematologic response or no evidence of leukemia.

Patient Population

The study included 267 patients with CP-CML (resistant or intolerant cohort, N = 203; T315I mutation cohort, N = 64), 83 patients with AP-CML, 62 patients with BP-CML, and 32 patients with Ph+ ALL. Key baseline demographic and disease characteristics of the evaluable patients are listed in Table 1.

Safety Profile

At the time of the safety analysis, the median duration of treatment with ponatinib was 337 days in patients with CP-CML, 362 days in patients with AP-CML, 89 days in patients with BP-CML, and 81 days in patients with Ph+ ALL. The median dose intensity was 37 mg, or 83% of the expected 45-mg dose. Overall, the most frequent nonhematologic adverse reactions (≥20%) were hypertension, rash, abdominal pain, fatigue, headache, dry skin, constipation, arthralgia, nausea, and pyrexia. Hematologic adverse reactions included thrombocytopenia, anemia, neutropenia, lymphopenia, and leukopenia.

The rates of treatment-emergent adverse events (AEs) resulting in discontinuation were 13% in the patients with CP-CML, 11% in AP-CML, 15% in BP-CML, and 9% in the patients with Ph+ ALL. The most frequent AEs that led to treatment discontinuation were thrombocytopenia (4%) and infections (1%).
Dose modifications (delays or reduction) resulting from adverse reactions occurred in 74% of the patients. The most common adverse reactions (≥5%) that led to dose modifications include thrombocytopenia (30%), neutropenia (13%), increases in lipase (12%), rash (11%), abdominal pain (11%), pancreatitis (6%), and alanine aminotransferase, aspartate aminotransferase, or an increase in gamma-glutamyl transferase (6%). Myelo suppression occurred in all patient populations.

The frequencies of grade 3 or 4 thrombocytopenia, neutropenia, and anemia were higher in patients with AP-CML, BP-CML, and Ph+ ALL (47%, 57%, and 47%, respectively) than in patients with CP-CML (36%). Patients with Ph+ ALL had the highest rates of grades 3 and 4 neutropenia and leukopenia (63%); patients with BP-CML had the highest rates of grades 3 and 4 anemia (55%) and lymphopenia (37%).

Response

At the time of the analysis for response, the median follow-up was 10 months (with a minimum of 6 months of follow-up for all ongoing patients). The median duration of ponatinib treatment was 281 days in patients with CP-CML, 286 days in patients with AP-CML, 89 days in patients with BP-CML, and 81 days in patients with Ph+ ALL. The efficacy results for patients with CP-CML are summarized in Table 2.

The efficacy results for patients with AP-CML, BP-CML, and Ph+ ALL are summarized in Table 3.

Warnings and Precautions

The ponatinib prescribing information contains a Boxed Warning about arterial thrombosis and hepatotoxicity, advising clinicians about the potential for the following serious events:

- **Arterial thrombosis.** Cardiovascular, cerebrovascular, and peripheral vascular thrombosis, including fatal myocardial infarction and stroke, have occurred in patients receiving ponatinib. In clinical trials, serious arterial thrombosis occurred in 8% of patients receiving ponatinib. In patients receiving ponatinib who develop arterial thrombotic events, ponatinib should be interrupted and discontinuation should be considered.

- **Hepatotoxicity.** Hepatotoxicity, liver failure, and death have occurred in patients receiving ponatinib. Hepatic liver failure and death have occurred in patients receiving ponatinib. Hepatic liver failure and death have occurred in patients receiving ponatinib.

### Table 2 Efficacy of Ponatinib in Patients with Resistant or Intolerant Chronic-Phase CML

<table>
<thead>
<tr>
<th>Cytogenetic response</th>
<th>Total patients (N = 267)</th>
<th>Patients with resistant/intolerant disease (N = 203)</th>
<th>Patients with T315I mutation (N = 64)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MCyR, % (95% CI)</td>
<td>54 (48-60)</td>
<td>49 (42-56)</td>
<td>70 (58-81)</td>
</tr>
<tr>
<td>CCyR, % (95% CI)</td>
<td>44 (38-50)</td>
<td>37 (31-44)</td>
<td>66 (53-77)</td>
</tr>
<tr>
<td>Median time to MCyR, days (range)</td>
<td>84 (49-334)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median duration of MCyR</td>
<td>Not reached</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Table 3 Efficacy of Ponatinib in Patients with Resistant or Intolerant Advanced Disease (Including Resistant/Intolerant and T315I Mutation Cohorts)

<table>
<thead>
<tr>
<th>Hematologic response</th>
<th>AP-CML (N = 83)</th>
<th>BP-CML (N = 62)</th>
<th>Ph+ ALL (N = 32)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major response, % (95% CI)</td>
<td>52 (41-63)</td>
<td>31 (20-44)</td>
<td>41 (24-59)</td>
</tr>
<tr>
<td>Complete response, % (95% CI)</td>
<td>47 (33-55)</td>
<td>21 (12-33)</td>
<td>34 (19-53)</td>
</tr>
<tr>
<td>Median time to major response, days (range)</td>
<td>21 (12-176)</td>
<td>29 (12-113)</td>
<td>20 (11-168)</td>
</tr>
<tr>
<td>Median time of major response, months (range)</td>
<td>9.5 (1.1-17.7)</td>
<td>4.7</td>
<td>3.2 (1.8-8.8+)</td>
</tr>
</tbody>
</table>

**The primary end point for chronic-phase CML cohorts was MCyR, which combines complete and partial cytogenetic responses.**

**CCyR indicates complete cytogenetic response; CI, confidence interval; CML, chronic myeloid leukemia; MCyR, major cytogenetic response; Ph+, Philadelphia chromosome-positive.**

Source: Iclusig (ponatinib) tablets for oral use [prescribing information]. Cambridge, MA: ARIAD Pharmaceuticals, Inc; December 2012.
Ponatinib is now being further investigated in a phase 3 randomized clinical trial that is comparing ponatinib with imatinib in patients with newly diagnosed CP-CML.\textsuperscript{13} As the second-generation BCR-ABL inhibitors are replacing imatinib in the treatment of newly diagnosed CML, the aim of this trial is to determine if ponatinib is effective in this patient population, and if it has the ability to prevent the emergence of resistant mutations that occur with other TKIs.\textsuperscript{10,13} A recent commentary by J.M. Goldman regarding the multikinase activity of ponatinib, as well as the preliminary results in patients with CML that is resistant to imatinib and second-generation TKIs, suggest that ponatinib may be “another step forward in the march toward real success with molecularly targeted therapy for cancer.”\textsuperscript{6} ■

**Table 4** Summary of Ponatinib Warnings and Precautions

<table>
<thead>
<tr>
<th>Potential adverse reactions</th>
<th>Description/events reported$^a$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thrombosis/thromboembolism</td>
<td>CV, cerebrovascular, and peripheral vascular thrombosis; serious arterial thrombosis, 8%; MI, 5%; VTE, 3%; serious cerebral vascular or peripheral arterial events, 2% each</td>
</tr>
<tr>
<td>Other CV events</td>
<td>Congestive heart failure; any grade, 7%; serious, 4% Cardiac arrhythmias: includes bradyarrhythmias (1% required pacemaker implantation; tachyarrhythmias) Hypertension: overall, 67%; serious requiring urgent intervention, 2% Fluid retention: overall, 23%; serious, 3%; 1 fatal brain edema</td>
</tr>
<tr>
<td>Hepatotoxicity</td>
<td>Fatal in 3 patients; OR, ALT elevation, 56% (8% grades 3 or 4)</td>
</tr>
<tr>
<td>Pancreatitis</td>
<td>Clinical, 6%; grade 3, 5%; lipase elevation, 41%</td>
</tr>
<tr>
<td>Hemorrhage</td>
<td>Overall, 24%; serious events including fatal events, 5%; most common with grade 4 thrombocytopenia</td>
</tr>
<tr>
<td>Myelosuppression</td>
<td>Severe, 48%</td>
</tr>
<tr>
<td>Tumor lysis syndrome</td>
<td>Serious in 2 patients (&lt;1%); serious hyperuricemia, 7%</td>
</tr>
<tr>
<td>Compromised wound healing</td>
<td>No formal studies, but could occur</td>
</tr>
<tr>
<td>Gastrointestinal perforation</td>
<td>1 patient with fistula 38 days postcholecystectomy</td>
</tr>
<tr>
<td>Embryo-fetal toxicity</td>
<td>Can cause fetal harm based on method of operation and animal studies</td>
</tr>
</tbody>
</table>

$^a$Percentage refers to proportion of patients in the pivotal trial (N = 444).

ALT indicates alanine aminotransferase; AST, aspartate aminotransferase; CV, cardiovascular; MI, myocardial infarction; VTE, venous thromboembolism.

Source: Iclusig (ponatinib) tablets for oral use [prescribing information]. Cambridge, MA: ARIAD Pharmaceuticals, Inc; December 2012.

Conclusion

Ponatinib is now being further investigated in a phase 3 randomized clinical trial that is comparing ponatinib with imatinib in patients with newly diagnosed CP-CML.\textsuperscript{13} As the second-generation BCR-ABL inhibitors are replacing imatinib in the treatment of newly diagnosed CML, the aim of this trial is to determine if ponatinib is effective in this patient population, and if it has the ability to prevent the emergence of resistant mutations that occur with other TKIs.\textsuperscript{10,13} A recent commentary by J.M. Goldman regarding the multikinase activity of ponatinib, as well as the preliminary results in patients with CML that is resistant to imatinib and second-generation TKIs, suggest that ponatinib may be “another step forward in the march toward real success with molecularly targeted therapy for cancer.”\textsuperscript{6}

**References**


