ARIAD

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NCCN® Guidelines Panel:	Chronic Myelogenous Leukemia

Dear Ms McClure,

On behalf of ARIAD Pharmaceuticals, Inc., I respectfully request the NCCN® Chronic Myelogenous Leukemia Guideline Panel to review the enclosed submission for the inclusion of Iclusig™ (ponatinib) in the NCCN guidelines and compendium.

Request for NCCN Guidelines Panel to Consider Review of Data for a Specific Indication

Iclusig (ponatinib) is a kinase inhibitor indicated for the treatment of adult patients with chronic phase (CP), accelerated phase (AP), or blast phase (BP) chronic myeloid leukemia (CML) resistant or intolerant to prior tyrosine kinase inhibitor (TKI) therapy.

Specific Changes Recommended within the Guidelines and Compendium

For adult patients with CP-, AP-, or BP-CML resistant or intolerant to prior TKI therapy, we request that Iclusig (ponatinib) be recommended as a treatment option in CML-2 to CML-6, and CML-J.

Statement of Whether the Submitted Use is or is not FDA Approved for that Indication

Iclusig (ponatinib) was approved by the FDA for this indication on December 14, 2012.

Rationale for Recommended Change

Iclusig (ponatinib) is a new treatment option that will fulfill an unmet need for CML patients who develop resistance or intolerance to prior TKIs.

Data Summary

On December 14, 2012, the FDA approved Iclusig (ponatinib) for the treatment of adult patients with CP-, AP-, or BP-CML, as well as Philadelphia chromosome-positive acute lymphoblastic leukemia (Ph+ ALL), resistant or intolerant to prior TKI therapy. The basis for approval was the single arm, open-label, pivotal phase 2 international PACE (**P**onatinib Ph+ **A**LL and **C**ML **E**valuation) trial conducted to evaluate the efficacy and safety of ponatinib in CP-, AP-, or BP-CML and Ph+ ALL patients who were resistant or intolerant to prior dasatinib or nilotinib or who had the T315I mutation. This FDA-approved indication was based on response rate.

In the PACE trial, 449 patients were enrolled and analyzed for safety, with 444 included in the analysis of efficacy. Patients were assigned to one of six cohorts based on disease phase (CP-, AP-, or BP-CML or Ph+ ALL), resistance or intolerance to prior dasatinib or nilotinib, and the presence

of the T315I mutation. All patients were administered a starting dose of 45 mg ponatinib orally once daily—the recommended dose determined in the phase 1 dose escalation trial.

The median age of the patient population was 59 (18-94) years, and the median time from diagnosis to ponatinib was 6 (0.3-28) years. Patients were heavily pretreated: 96% received prior imatinib, 84% dasatinib, 65% nilotinib; the median number of prior TKIs was 3. In patients previously treated with dasatinib or nilotinib (n=427), 88% had a history of resistance and 12% were intolerant. The best prior response to most recent dasatinib or nilotinib was 26% major cytogenetic response (MCyR) or better in CP-CML, and 23% major hematologic response (MaHR) or better in advanced disease. Frequent BCR-ABL mutations confirmed at entry were: 29% T315I, 8% F317L, 4% E255K, 4% F359V, and 3% G250E. No mutations were detected in 44% of patients.

At the time of the analysis included in the FDA-approved US prescribing information for ponatinib, the median follow-up was 10 months (minimum 6 months for all ongoing patients). Ponatinib demonstrated robust anti-leukemic activity, with 54% of CP-CML patients achieving MCyR - the primary endpoint in CP-CML. The median time to MCyR was 84 (49-334) days, and the median duration of response was not yet reached. In patients with advanced disease, 52% of AP-CML patients and 31% of BP-CML patients achieved MaHR - the primary endpoint in advanced disease. The median time to MaHR in AP-CML and BP-CML was 21 (12-176) days and 29 (12-113) days, respectively. The median duration of MaHR was 9.5 (1.1-17.7) months and 4.7 (1.8-14.1+) months, respectively.

Updated PACE data were presented at the Annual American Society of Hematology Meeting held in Atlanta, GA, December 2012, with 12 months minimum follow-up for all ongoing patients. The updated response rates were: 56% MCyR in CP-CML, 57% MaHR in AP-CML, and 31% MaHR in BP-CML. In CP-CML, responses were deep with 46% of patients achieving complete cytogenetic response (CCyR), 34% major molecular response (MMR) and 15% MR4.5. In addition, 59% had BCR-ABL $\leq$10% at 3 months—an important milestone becoming widely accepted as indicative of prognosis. Updated data from the ponatinib phase 1 study were also presented: with a median of 30 months follow-up in CP-CML (N=43), the MCyR rate was 72%, response duration ranged from 1.9 to 41+ months (median not yet reached), and 84% of responders are estimated (Kaplan-Meier) to remain in response at 2 years.

In PACE, there was a trend for higher response rates in patients with fewer prior TKI treatments. In CP-CML, patients who received only 1 prior TKI (imatinib, dasatinib, or nilotinib) achieved a MCyR rate of 84%. Patients who received 2 prior TKIs had a MCyR rate of 64%, and those who received 3 prior TKIs had a rate of 47%. There was a similar trend for improved response rates with less prior treatment in patients with advanced disease, and in the phase 1 study.

In vitro, ponatinib demonstrated potent activity against native BCR-ABL, against all tested mutant forms of BCR-ABL (including T315I), and was found to suppress the emergence of any individual BCR-ABL mutation. In PACE, patients responded to ponatinib regardless of mutation status. Similar response rates were observed in patients with and without BCR-ABL mutations in all disease groups. In CP-CML, response rates appeared to be higher in patients with the T315I mutation: 70% MCyR in T315I vs. 51% in non-T315I patients. However, a post hoc multivariate analysis found that presence of T315I was not a significant predictor of response. The difference in response rate is explained by the higher median dose of ponatinib received by T315I patients, along with the baseline characteristics of this group: T315I patients were younger, previously treated with fewer TKIs, and more recently diagnosed. Although follow-up in the PACE trial is still relatively short, responses in CP-CML have been observed for all mutations in BCR-ABL that were detected in at least two patients at study entry.

Ponatinib was generally well tolerated with a manageable safety profile. Overall, the most common (incidence ≥20%) non-hematologic treatment-emergent (regardless of relationship to ponatinib) adverse reactions were hypertension, rash, abdominal pain, fatigue, headache, dry skin, constipation, arthralgia, nausea, and pyrexia. The most common (incidence ≥20%) grade 3 or 4 treatment-emergent hematologic abnormalities were thrombocytopenia, neutropenia, leukopenia, and anemia. Treatment-emergent serious adverse reactions reported with an incidence ≥3% included pancreatitis, pneumonia, myocardial infarction or worsening of coronary artery disease, cardiac failure, abdominal pain, pyrexia, effusions (pericardial, pleural, and ascites), febrile neutropenia, and thrombocytopenia.

Citation of Literature Support and Complete Articles Supporting Recommended Change

Citations

- O'Hare T, Shakespeare WC, Zhu X, et al. AP24534, a pan-BCR-ABL inhibitor for chronic myeloid leukemia, potently inhibits the T315I mutant and overcomes mutation-based resistance. Cancer Cell. 2009 Nov 6;16(5):401-12.
- Cortes JE, Kantarjian H, Shah NP, et al. Ponatinib in refractory Philadelphia chromosome-positive leukemias. N Engl J Med. 2012;367(22):2075-88.
- Cortes JE, Kim DW, Pinilla-Ibarz J, et al. A pivotal phase 2 trial of ponatinib in patients with chronic myeloid leukemia (CML) and Philadelphia chromosome-positive acute lymphoblastic leukemia (Ph+ALL) resistant or intolerant to dasatinib or nilotinib, or with the T315I BCR-ABL mutation: 12-month follow-up of the PACE trial. Blood. 2012;120 (21):Abstract 163.
- Kantarjian HM, Kim DW, Pinilla-Ibarz J, et al. Efficacy and safety of ponatinib in patients with accelerated phase or blast phase chronic myeloid leukemia (AP-CML or BP-CML) or Philadelphia chromosome-positive acute lymphoblastic leukemia (Ph+ ALL): 12-month follow-up of the PACE trial. Blood. 2012; 120 (21):Abstract 915.
- Mauro MJ, Cortes JE, Kim DW, et al. Multivariate analyses of the clinical and molecular parameters associated with efficacy and safety in patients with chronic myeloid leukemia (CML) and Philadelphia chromosome-positive acute lymphoblastic leukemia (Ph+ ALL) treated with ponatinib in the PACE trial. Blood. 2012; 120 (21):Abstract 3747.
- Kim DW, Cortes JE, Pinilla-Ibarz J, et al. Efficacy and safety of ponatinib according to prior approved tyrosine kinase inhibitor (TKI) therapy in patients with chronic myeloid leukemia in chronic phase (CP-CML): results from the PACE trial. Blood. 2012; 120 (21):Abstract 3749.
- Hochhaus A, Kim DW, Pinilla-Ibarz J, et al. Molecular responses with ponatinib in patients with Philadelphia chromosome-positive (Ph+) leukemia: results from the PACE trial. Blood. 2012; 120 (21):Abstract 3763.
- Deininger, MW, Cortes JE, Kantarjian HM et al, Long-term anti-leukemic activity of ponatinib in patients with Philadelphia chromosome-positive leukemia: updated results from an ongoing phase 1 study. Blood. 2012; 120 (21):Abstract 3743.

Additional Data Enclosures

- Iclusig US Prescribing Information, 2012.
- ASH 2012 Oral Presentations for abstract numbers 163 and 915.
- ASH 2012 Poster Presentations for abstract numbers 3743, 3747, 3749 and 3763.

We appreciate the Panel's consideration of ARIAD's submission of Iclusig (ponatinib) for the treatment of adult patients with CP-, AP-, or BP-CML that is resistant or intolerant to prior TKI therapy.

Kind Regards,

Ruth du Moulin

Ruth du Moulin, PhD

Director, Medical Communications

ARIAD Pharmaceuticals, Inc.