ARIAD

January 09, 2013

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Date of Request:	January 09, 2013
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 consideration of ponatinib (Iclusig®) in the NCCN guidelines and compendium.

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

Ponatinib is a kinase inhibitor indicated for the treatment of adult patients with chronic myeloid leukemia (CML) (chronic phase [CP-], accelerated phase [AP-], or blast phase [BP-]) who are T315I-positive or for whom no other tyrosine kinase inhibitor (TKI) is indicated.

Specific Changes Recommended within the Guidelines and Compendium

For adult patients with CP-, AP-, or BP-CML who are T315I-positive or for whom no other TKI is indicated, we request that 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

Ponatinib was approved by the FDA for this indication on December 20, 2013.

Rationale for Recommended Change

Ponatinib is a treatment option that will fulfill an unmet need for CML patients who are T315I-positive or for whom no other TKI is indicated.

Data Summary

Ponatinib Revised Labeling

On December 14, 2012, ponatinib received accelerated approval by the FDA 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. Based on this approval, ponatinib was included in the NCCN CML guidelines.

The initial US Prescribing Information (USPI) for ponatinib contained a boxed warning for arterial thrombotic events. In October 2013, ARIAD and the FDA announced that continuing analyses of clinical trial data with longer follow-up showed the cumulative incidence of vascular occlusive events (which includes cardiovascular, cerebrovascular, peripheral vascular and venous thromboembolic events) was higher than the initial report that supported the accelerated approval. As a result, ARIAD suspended marketing and commercial distribution of ponatinib in the US as requested by the FDA, and ponatinib was removed from the NCCN CML guidelines. A revised USPI was approved by the FDA on December 20, 2013, along with a Risk Evaluation and Mitigation Strategy (REMS). Marketing and commercial distribution of ponatinib in the US has resumed.

The updated USPI for ponatinib has 3 main changes: a revised indication, updated safety information on the risk of vascular occlusion, and new dosing considerations.

- **Indication:** ponatinib was previously indicated for CML patients resistant or intolerant to prior TKI therapy; the indication has been revised to T315I-positive CML patients or those for whom no other TKI is indicated.
- **Risk of vascular occlusion:** the revised USPI for ponatinib contains a boxed warning for vascular occlusion, which has occurred in at least 27% of ponatinib-treated patients. This incidence combines events from the phase 1 and phase 2 trials of ponatinib, and includes serious and non-serious arterial and venous thromboembolic events. The boxed warning on the initial USPI (dated December 14, 2012) reports the incidence from the phase 2 trial only, and is limited to arterial thrombotic events (not including venous).
- **New dosing considerations:** the starting dose for ponatinib remains 45 mg taken orally once daily, with a new recommendation to consider dose reduction for CP- and AP-CML patients who achieve a major cytogenetic response, and discontinuation if response is not achieved by 3 months.

Ponatinib Data Update

Ponatinib received initial approval based on data from the ongoing pivotal phase 2 international PACE (**P**onatinib Ph+ **A**LL and **C**ML **E**valuation) trial evaluating 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. The PACE trial results at a median of 15 months follow-up were published in November 2013 in NEJM. In addition, there were a number of PACE presentations at the annual meeting of the American Society of Hematology (ASH) in New Orleans, LA, December 7-10, 2013, with a median follow-up of 2 years.

- ***Efficacy: Robust Response Rates at 2-year Follow-up***

In the heavily pretreated PACE population (58% ≥3 prior TKIs), robust responses were observed with a median of 2 years follow-up (CP-CML: 60%, 54%, and 38% MCyR, CCyR and MMR at any time, respectively; AP-CML: 61% MaHR; BP-CML: 31% MaHR). Response in CP-CML is durable with 89% estimated to maintain MCyR for at least 2 years (only 13 patients lost MCyR at the time of analysis; no T315I patient lost response). In a subgroup of CP-CML patients who received 2 prior TKIs, responses achieved by 12 months were high: 73% MCyR in 33 patients who had prior imatinib and nilotinib; 60% MCyR in 52 patients who had prior imatinib and dasatinib. At 2 years, overall survival in CP-CML is 86% (median not yet reached), 72% in AP-CML (median not yet reached), and 18% in BP-CML (median 7 months).

- ***Safety: Increased Cumulative Incidence of Vascular Events, Otherwise Consistent with Previous Reports***

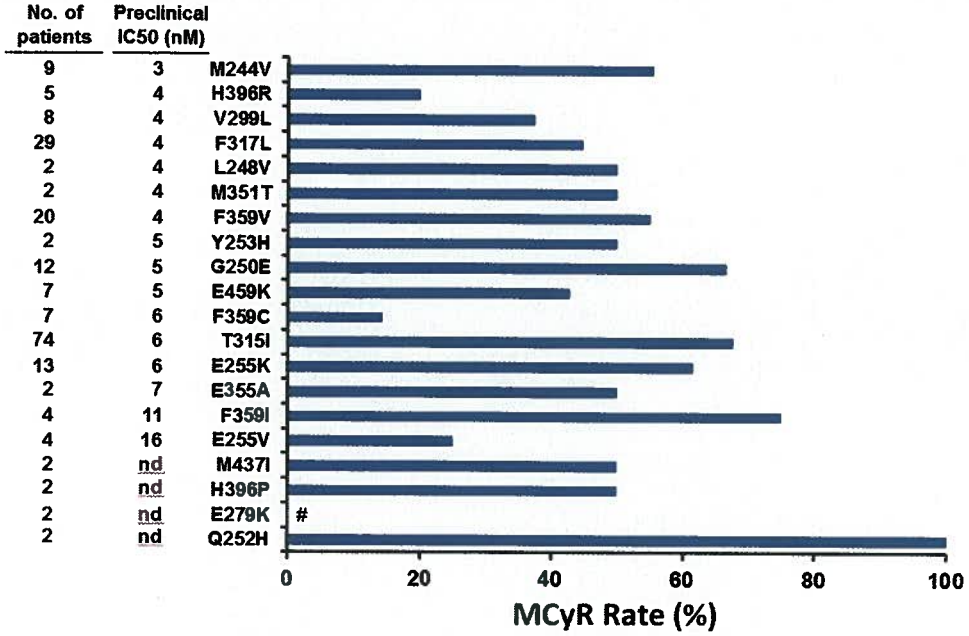
With the exception of vascular occlusive events, the safety profile of ponatinib remains consistent with the initial report. Longer follow-up has shown that the cumulative incidence of vascular occlusive events has increased; the median time to first onset of an arterial thrombotic event is approximately 7 months. Patients with and without cardiovascular risk factors have experienced these events. A multivariate analysis has shown that these events increase with increasing dose intensity. Dosing considerations have been included in the USPI to mitigate the risk of vascular occlusion. A risk-benefit analysis should guide decisions to prescribe ponatinib. Patients with risk factors should be actively managed.

- ***Mutations: Effective against Clinically Relevant Mutations***

Ponatinib was designed to optimize binding to the BCR-ABL kinase domain, resulting in a potent TKI with activity against mutated and unmutated forms of the protein. In vitro experiments demonstrated that ponatinib has potent activity against 21 clinically relevant mutations, including those that confer resistance to dasatinib (T315I, V299L, T315A, F317L/V/I/C), nilotinib (T315I, Y253H, E255K/V, F359V/C/I) and bosutinib (T315I, V299L). In clinical trials, patients with and without BCR-ABL mutations responded to

ponatinib, including patients with low level mutations and compound mutations. Responses have been observed for all individual mutations detected in ≥2 CP-CML patients (see Figure 1). In vitro experiments have also shown that ponatinib has the ability to suppress the emergence of mutations. In PACE, no single mutation has been identified that consistently confers primary and/or secondary resistance to ponatinib.

Figure 1: Response to Ponatinib for All Individual Mutations Detected by Next Generation Sequencing in ≥2 CP-CML Patients in the PACE Trial



Source: Deininger MW et al. Oral Presentation ASH 2013. Abstract 652
#MMR detected in 1 patient at 9 months, CCyR assessed only at 3 months; nd=not determined

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 phase 2 trial of ponatinib in Philadelphia chromosome-positive leukemias. N Engl J Med 2013; 369(19):1783-1796.
- Khoury HJ, Cortes JE, Kim DW, et al. Analysis of the cardiovascular risk profile of Ph+ leukemia patients treated with ponatinib. J Clin Oncol. 2013;31(Suppl):Abstract 7048.
- Cortes JE, Kim DW, Pinilla-Ibarz J, et al. Ponatinib in patients (pts) 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: 2-year follow-up of the PACE trial. Blood. 2013; 122(21):Abstract 650.
- Deininger MW, Shah NP, Cortes JE, et al. Impact of baseline (BL) mutations, including low-level and compound mutations, on ponatinib response and end of treatment (EOT) mutation analysis in patients (pts) with chronic phase chronic myeloid leukemia (CP-CML). Blood. 2013; 122(21);Abstract 652.
- Le Coutre PD, Kim DW, Pinilla-Ibarz J, et al. Ponatinib in heavily pretreated patients with chronic phase chronic myeloid leukemia (CP-CML): management of adverse events (AEs). Blood. 2013; 122(21):Abstract 1496.
- Hochhaus A, Cortes JE, Kim DW, et al. Efficacy and safety of ponatinib following failure of dasatinib in patients (pts) with chronic phase chronic myeloid leukemia (CP-CML) in the PACE trial. Blood. 2013; 122(21):Abstract 1498.
- Kantarjian HM, Cortes JE, Kim DW, et al. Efficacy and safety of ponatinib following failure of nilotinib in patients with chronic phase chronic myeloid leukemia (CP-CML) in the PACE trial. Blood. 2013; 122(21):Abstract 2738.
- Gozgit JM, Schrock AB, Chen T-H, et al. Comprehensive analysis of the in vitro potency of ponatinib and all other approved BCR-ABL TKIs against a panel of clinically-relevant single and compound BCR-ABL mutants. Blood. 2013; 122(21):Abstract 3992.

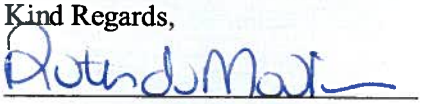
- Pinilla-Ibarz J, Cortes JE, Kim DW, et al. Clinical impact of dose modification on response to ponatinib in patients with chronic phase chronic myeloid leukemia (CP-CML). Blood. 2013; 122(21):Abstract 4007.
- Lipton JH, Bryden P, Sidhu MK, et al. Comparative efficacy among chronic phase-chronic myeloid leukemia (CP-CML) patients after failure of 2nd generation tyrosine kinase inhibitors (2G TKIs). Blood. 2013; 122(21):Abstract 4010.

Additional Data Enclosures

- Iclusig US Prescribing Information, 2012.
- Iclusig US Prescribing Information, 2013.
- ASCO 2013 Poster Presentation for abstract number 7048
- ASH 2013 Oral Presentations for abstract numbers 650 and 652.
- ASH 2013 Poster Presentations for abstract numbers 1496, 1498, 2738, 3992, 4007 and 4010.

We appreciate the Panel's consideration of ARIAD's submission for inclusion of ponatinib on the NCCN CML guidelines.

Kind Regards,



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