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 consideration of ponatinib (Iclusig®) for treatment for adult CML patients after failure of two prior TKIs, regardless of mutation status.

Specific Changes Recommended: Update to CML-2 to CML-8 to include ponatinib as a treatment option for adult patients with CP-, AP- or BP-CML after failure of two prior TKIs, regardless of mutation status, or for patients with the T315I mutation, along with reinstatement of CML-K (version 1.2014) to provide more specific guidance on TKI use by mutation.

FDA Approval: Ponatinib is currently approved by the FDA for patients with CP-, AP-, and BP-CML who are T315I-postive or for whom no other TKI is indicated.

Rationale: In the largest study, to date, in resistant or intolerant CML, the pivotal phase 2 PACE (**P**onatinib Ph+ **A**LL and **C**ML **E**valuation) trial demonstrated ponatinib effectively induced rapid and durable responses in patients who experienced failure of a second generation TKI, regardless of mutation status, who otherwise had a poor prognosis.

Data Summary: The PACE trial included 449 patients with resistant or intolerant CP-, AP-, BP-CML and Ph+ALL, 93% of whom received at least two prior TKIs.

Benefit-Risk Considerations for Patients Resistant or Intolerant to Two Prior TKIs

Prognosis in 3rd-line CML: Patients who are resistant to prior TKI therapy or who have progressed to advanced disease face a poor prognosis and high likelihood of CML-related death. The median failure-free survival in 3rd-line CP-CML is 20 months; five months in AP-CML, three months in BP-CML. In two 3rd-line CP-CML studies where investigator-reported cause of death details were provided, CML accounted for 10 of 14 deaths (71%) after two to three years of follow-up. Only one death was deemed treatment-related, with the other three attributed to unrelated/unspecified causes. Similarly, in advanced CML, available data suggest the risk of death from disease (59% of deaths [19/32]) is nearly ten times the risk from treatment-related causes (6% [2/32]) after three years' follow-up. Therefore, the potential benefit of an effective treatment for resistant or intolerant CML is likely to be the paramount consideration, and may outweigh the potential risk of treatment induced adverse events (AEs).

- In PACE, 40% (107/270) of CP-CML patients were 3rd-line. At a median follow-up of 15 months, responses in CP-CML were high: 64%, 54%, and 35% MCyR, CCyR and MMR, respectively. Prior to PACE, only 36% of CP-CML patients achieved MCyR or better (4% MMR or better) with their most recent TKI. Responses with ponatinib were significantly higher in 3rd-line than 4th-line, yet substantial responses were still achieved in 4th-line: MCyR, 64% vs 47%, p=0.007; CCyR, 54% vs 38%, p=0.01.
- Responses were durable in CP-CML patients, a majority of whom had experienced failure of ≥2 TKIs: 89% estimated to maintain MCyR at two years.
- In 3rd-line CP-CML patients who received ponatinib following different ordering of prior TKIs, responses by 12 months were high: ponatinib after imatinib followed by nilotinib (n=33): 73% MCyR, 67% CCyR, 46% MMR; ponatinib after imatinib followed by dasatinib (n=52): 60% MCyR, 46% CCyR, 37% MMR. In both subgroups, median time to response with ponatinib was rapid: <3

months and <6 months for MCyR and MMR, respectively. Responses were durable: 95% and 86% estimated to maintain MCyR at one year for those who received ponatinib after imatinib followed by nilotinib, and after imatinib followed by dasatinib, respectively.

Discontinuation rate and duration of therapy: Both of these factors may be important to the benefit-risk consideration when initiating 3rd-line TKI therapy. In a study of CP-CML patients treated with a TKI primarily in 3rd-line, only 33/114 (29%) 3rd-line patients continued therapy after 28.5 months; median duration of treatment was approximately 8 months.

- With a median of 15 months follow-up, 55% CP-CML patients remain on the PACE trial; median duration of ponatinib treatment is 22 months.

Safety: Ponatinib is associated with increased risk for vascular occlusive events. Risk mitigation strategies (eg, dose reduction, managing underlying conditions) may decrease the risk of AEs while maintaining the efficacy benefit observed with ponatinib.

- In a multivariate analysis of PACE, dose intensity of ponatinib was the most significant predictor of AEs: each 15 mg dose reduction resulted in ~40% risk reduction. While the multivariate analysis also predicts that MCyR increases with increasing dose intensity, the PACE data show that 97% of CP-CML responders who had dose reductions maintained MCyR.
- Overall, the incidence of AEs in 3rd-line patients in the PACE trial is comparable with the overall population, though some AEs may occur less frequently in patients treated with fewer prior TKIs: abdominal pain, arthralgia, thrombocytopenia, increased lipase.

Ponatinib is Likely to be Effective after Failure of a Second Generation TKI

In a systematic literature review to assess the efficacy of ponatinib compared with another TKI after failure of a second generation TKI, findings confirm sequential use of second generation TKIs is of limited value for most patients (probability of achieving CCyR ranged from 22% - 26%); with ponatinib, the probability of achieving CCyR was nearly twice as high (60%). Based on available data, ponatinib is estimated to have >90% likelihood of providing a better treatment response in this setting than any of the second generation TKIs.

Ponatinib is Effective against Clinically Relevant Mutations

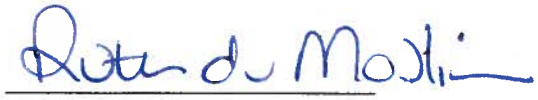
In patients who develop the T315I mutation, median overall survival is <2 years post detection of the mutation in CP-CML; <5 months post detection in BP-CML and Ph+ALL patients.

- 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.
- 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.

As mutation testing techniques evolve, physicians will be tasked with selecting TKI therapy based on kinase domain mutation status more frequently, and earlier in therapy. Data with next generation sequencing (NGS) suggests mutations may be underestimated with traditional Sanger sequencing, and NGS may allow for identification of emerging TKI-resistant mutants earlier in therapy. In a retrospective longitudinal cohort study of CP-CML patients treated with TKIs in community clinical practices, only 22% of eligible patients were tested for kinase domain mutations. Clear guidance on use of TKIs in patients with evidence of a mutation will benefit academic and community physicians, alike.

We appreciate the Panel's consideration of ARIAD's submission.

Kind Regards,



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Citation of Literature Support and Complete Articles Supporting Recommended Change

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- Kim D-W, 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 leuemia in chronic phase (CP-CML): results from the PACE trial. Blood. 2012; 120(21); Abstract 3749.
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Additional Data Enclosures: ASH 2013 Oral Presentations for abstract numbers 650 and 652; ASH 2013 Poster Presentations for abstract numbers 1498, 2738, 3749, 3992, 4007 and 4010.