



Ruth du Moulin, PhD
VP, Medical Affairs Operations
ARIAD Pharmaceuticals Inc
125 Binney Street, Cambridge, MA 02142
Phone: +1-617-621-2265
Email: ruth.dumoulin@ariad.com
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NCCN Guidelines Panel: ALL

Re: Request for review of clinical data and recommendation for ponatinib in the NCCN Clinical Practice Guidelines in Oncology® - Acute Lymphoblastic Leukemia (ALL)

On behalf of Ariad Pharmaceuticals, Inc., I respectfully request the NCCN ALL Panel to review the enclosed phase 2 study results^{1,2} and meta-analysis³ in support of ponatinib in combination with hyper-CVAD as frontline therapy for Philadelphia chromosome-positive (Ph+) ALL.

Suggested Changes: We respectfully ask the NCCN Panel to consider the following:

- **“Principles of Systemic Therapy” ALL-D, 1 of 4:**
 - **“Adult patients aged ≥40 years”, bullet 1 “TKIs + hyper-CVAD”:**
revise to “ponatinib (preferred)¹⁻³ or imatinib or dasatinib”
 - **“Protocols for AYA patients aged 15-39 years”, bullet 3 “TKIs + hyper-CVAD”:**
revise to “ponatinib (preferred)¹⁻³ or imatinib or dasatinib”
 - **“Maintenance regimens”, bullet 1:**
revise to “ponatinib (preferred)¹⁻³ or imatinib or dasatinib”
 - For the above entries, consider “preferred” status for ponatinib based on meta-analysis³ demonstrating significantly better odds of complete molecular response (CMR) and 3-year overall survival (OS) compared with other tyrosine kinase inhibitors (TKIs)

- **ALL-D, new footnote** (beside ponatinib entries above): “In the phase 2 study, after initial increased incidence of vascular events with ponatinib was recognized, patients were offered the option to reduce the dose of ponatinib or switch TKI. The protocol was later amended to reduce the dose of ponatinib from 45 mg to 30 mg after induction, then further reduced to 15 mg once CMR was achieved. No further vascular events or any other serious adverse events were reported after dose optimization.^{1,2}”

FDA Clearance: Ponatinib (Iclusig®) is approved by the FDA for the treatment of adult patients with chronic phase, accelerated phase, or blast phase chronic myeloid leukemia (CML) or Ph+ ALL for whom no other TKI therapy is indicated. It is also approved for the treatment of adult patients with T315I-positive CML (chronic phase, accelerated phase, or blast phase) or T315I-positive Ph+ ALL.⁴

Rationale:

Phase 2 study: The efficacy of ponatinib in combination with hyper-CVAD in the frontline setting was studied in a single-center (The University of Texas MD Anderson Cancer Center), phase 2, single-arm trial in patients with previously untreated Ph+ ALL.^{1,2} Patients received 8 cycles of hyper-CVAD alternating with high-dose methotrexate and cytarabine every 21 days. Ponatinib 45 mg was given daily for the first 14 days of cycle 1 then continuously for the subsequent cycles. Patients in complete remission received

maintenance with ponatinib 45 mg daily with vincristine and prednisone monthly for 2 years followed by ponatinib indefinitely. The primary endpoint for this study was event-free survival. In an updated report, 50 patients with untreated Ph+ ALL and 8 previously treated patients have received a median of 6 cycles.² All patients were in complete remission after cycle 1. To date, 97% have achieved a major molecular response, 79% have achieved a CMR at a median of 10 weeks from initiation. Minimally residual disease status by flow cytometry is negative in 96% of patients at a median of 3 weeks. Ten patients underwent allogeneic transplantation after a median of 4 cycles. Two patients had grade 5 vascular events with no underlying risk factors. After protocol modification and ponatinib dose optimization, no further VE were reported (see suggested footnote). The 3-year complete response duration and OS rates were 78% and 75%, respectively.²

Meta-analysis: The effectiveness of frontline treatment combinations with ponatinib was compared with other TKIs (imatinib, dasatinib, nilotinib) in Ph+ ALL in a meta-analysis of 25 phase 2 to 4 clinical studies and 1 retrospective analysis.³ Study arms where patients received chemotherapy or corticosteroids only, a single TKI agent, or autologous stem cell transplant exclusively were excluded. Compared with other TKIs, ponatinib was associated with a statistically significant increase in the odds of achieving CMR (79% vs. 34%; odds ratio, 6.09; 95% CI, 1.16-31.90; $P=0.034$). Ponatinib was also associated with a statistically significant increase in the odds of 3-year OS (79% vs. 50%; odds ratio, 4.49; 95% CI, 1.00-20.13, $P=0.050$) compared with earlier generation TKIs.

Results of the ongoing phase 2 study^{1,2} showed that ponatinib in combination with hyper-CVAD is effective in achieving early sustained remissions with newly diagnosed Ph+ ALL. No further vascular events were observed after dose optimization. Based on the meta-analysis, frontline treatment with ponatinib in combination with chemotherapy or corticosteroids was associated with significantly better odds of CMR and 3-year OS in patients newly diagnosed with Ph+ ALL than combination therapy with earlier generations of TKIs.³

Sincerely,



Ruth du Moulin, PhD
VP, Medical Affairs Operations
ARIAD Pharmaceuticals, Inc.

References (enclosed):

1. Jabbour EJ, et al. Combination of hyper-CVAD with ponatinib as first-line therapy for patients with Philadelphia chromosome-positive acute lymphoblastic leukaemia: a single-centre, phase 2 study. *Lancet Oncol.* 2015;16(15):1547-55.
2. Sasaki K, et al. Phase II Study of the Frontline Hyper-CVAD in Combination with Ponatinib for Patients with Philadelphia Chromosome Positive Acute Lymphoblastic Leukemia [abstract]. *Blood.* 2016;128(22): Abstract 757.
3. Jabbour EJ, et al. Meta-Analysis and Meta-Regression of the Efficacy of Front-Line Treatment Combinations with Ponatinib Versus 1st- and 2nd-Generation Tyrosine Kinase Inhibitors for Ph+ Acute Lymphoblastic Leukemia [abstract]. *Blood.* 2016;128(22): Abstract 5189.
4. ICLUSIG® (ponatinib) prescribing information. ARIAD Pharmaceuticals Inc. 11/2016.