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NCCN Guidelines Panel: Chronic Myeloid Leukemia (CML)

Ponatinib response-based dosing regimen in patients with chronic phase (CP)-CML who are resistant or intolerant to prior tyrosine kinase inhibitor (TKI) therapy

On behalf of Takeda Oncology, I respectfully request the NCCN CML Panel to consider data from the Phase 2 OPTIC trial in which a response-based dosing regimen for ponatinib was used to optimize the benefit:risk of ponatinib treatment in CP-CML.[1,2] The trial data at the interim analysis (IA), with a median follow-up of 21 months, showed that response-based dosing of ponatinib achieved and maintained meaningful responses in a highly resistant CP-CML patient population who had failed ≥2 prior TKIs, while also lowering the rate of arterial occlusive events (AOE) compared with the Phase 2 PACE study.[2,3]

Please consider the following suggested changes:

- **CML-G (6 of 8) – "Management of Ponatinib Toxicity"**
  Under "Dosing", revise the existing bullet to reflect: The current recommended initial dose of ponatinib is 45 mg once daily. However, a dose reduction to 15 mg upon achievement of clinically meaningful response (e.g., ≤1% BCR-ABL1^{IS}) may be safer and effective in CP-CML patients.
- **Modification of the discussion section and associated references to include the OPTIC clinical trial data[1,2] (MS-13).**

Rationale Summary: Ponatinib is an orally active third-generation TKI designed to optimally inhibit all BCR-ABL1 single mutants. Patients with resistant and intolerant CP-CML with substantial prior treatment demonstrated deep, lasting responses to ponatinib in the pivotal Ponatinib Ph+ ALL and CML Evaluation (PACE) trial.[4] However, AOEs were observed as a serious adverse event (AE) in the Phase 2 PACE trial that led to mandatory dose reductions. A post hoc analysis of pooled data from ponatinib clinical trials, including PACE, suggested a dose dependency of both AEs and response rates.[5,6] The OPTIC trial was conducted to prospectively determine the optimal dosing of ponatinib that can maximize the benefit:risk of treating CP-CML pateints.[1,2]

Summary of OPTIC trial: The ongoing, prospective Phase 2 OPTIC randomized clinical trial enrolled 283 adult patients with CP-CML who were resistant or intolerant to two or more prior TKIs or were BCR-ABL1 *T315I* mutation-positive.[1,2] Patients were randomized into three cohorts with ponatinib starting doses of 45, 30, or 15 mg/day; patients who initially received 45 or 30 mg/day underwent a dose reduction to 15 mg/day when they achieved ≤1% BCR-ABL1^{IS}. Key efficacy and safety results of this IA are summarized below:[1,2]

- With a median follow-up of 21 months, the OPTIC IA demonstrated that the maximum rate of ≤1% BCR-ABL1^{IS} at 12 months (38.7%) was achieved and maintained with the regimen that started at 45 mg/day, followed by dose reduction to 15 mg/day on achievement of ≤1% BCR-ABL1^{IS} in a highly resistant patient population – where majority of patients (>60%) failed to achieve a response greater than complete hematologic response (CHR) on immediate prior therapy.
- Benefit of ponatinib treatment with all three dosing regimens was demonstrated in this highly resistant population.
- In order to provide a more accurate characterization of AOE incidence, blinded adjudication of AOEs observed in OPTIC was performed by an independent committee using standard definitions developed by the American College of Cardiology (ACC)/American Heart Association (AHA), and the FDA; for the dosing regimen with the highest starting dose (45 mg/day), the adjudicated AOE rate was 5.3%, which was considerably lower than the reported adjudicated AOE rate of 17.4% in the PACE trial.[1,2]
- In the 15 mg/day starting dose cohort, a substantially lower proportion of patients with the *T315I* mutation achieved ≤1% BCR-ABL1^{IS} at 12 months, compared with the other cohorts.

Key Efficacy and Safety Results in the OPTIC Study.

Outcome	**Initial 45 → 15 mg/day (optimal benefit:risk)**	**30 → 15 mg/day**	**15 mg/day**
≤1% BCR-ABL1^{IS} at 12 mo	38.7%	27.4%	26.5%
≤1% BCR-ABL1^{IS} at 12 mo in pts with T315I at baseline	42%	24%	8%
24-mo PFS	80.6%	79.8%	84.0%
24-mo OS	92.7%	95.1%	94.0%
Adjudicated AOE*	5.3%	4.3%	1.1%
AOE deaths	0	0	0
Grade ≥3 TEAE**	66.0%	56.4%	57.4%

*Independent adjudication committee reviewed AOEs using the ACC/AHA definitions.
**The most common grade 3 or higher TEAEs were thrombocytopenia (31.9%), neutropenia (17.0%), anemia (6.7%), hypertension (6.7%), and increased lipase (6.0%).

FDA Label[7]: Ponatinib (ICLUSIG®) is a kinase inhibitor indicated for the treatment of adult patients with chronic phase, accelerated phase, or blast phase chronic myeloid leukemia (CML) or Philadelphia chromosome positive acute lymphoblastic leukemia (Ph+ ALL) for whom no other tyrosine kinase inhibitor (TKI) therapy is indicated and for the treatment of adult patients with T315I-positive chronic myeloid leukemia (chronic phase, accelerated phase, or blast phase) or T315I-positive Ph+ ALL. ICLUSIG is not indicated and is not recommended for the treatment of patients with newly diagnosed chronic phase CML.

Respectfully submitted,

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Vice President, Head of US Medical Affairs Oncology

References:

1. Cortes J, et al. Interim analysis from the OPTIC trial: A dose-ranging study of 3 starting doses of ponatinib. Presented at ASCO Annual Meeting 2020. Abstract 7502.
2. Cortes J, et al. Interim analysis from the OPTIC trial: A dose-ranging study of 3 starting doses of ponatinib [encore]. Presented at EHA Annual Meeting 2020. Abstract S172.
3. Januzzi JL, et al. An independent review of arterial occlusive events in the ponatinib phase 2 PACE trial in patients with Ph+ leukemia. Presented at ASCO Annual Meeting 2020. Poster 323.
4. Cortes JE, et al. Ponatinib efficacy and safety in Philadelphia chromosome–positive leukemia: final 5-year results of the phase 2 PACE trial. Blood 2018;132:393-404.
5. Dorer DJ, et al. Impact of dose intensity of ponatinib on selected adverse events: Multivariate analyses from a pooled population of clinical trial patients. Leuk Res 2016;48:84–91.
6. Pinilla-Ibarz J, et al. Clinical impact of ponatinib dose modification in patients with Philadelphia chromosome-positive leukemias. Presented at ASH Annual Meeting 2013. December 7–10, New Orleans, LA. Poster 4007.
7. ICLUSIG® (ponatinib) prescribing information, 2020. Takeda Oncology, Inc.