# EFFICACY OF OLVEREMBATINIB IN PATIENTS WITH CHRONIC-PHASE CHRONIC MYELOID LEUKEMIA (CP-CML) WITH PRIOR RESISTANCE TO PONATINIB OR ASCIMINIB AND ASXL1 MUTATIONS

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## INTRODUCTION & AIM

- Patients with multi-TKI–resistant CP-CML represent a population with substantial unmet medical needs.
- ASXL1 mutations have emerged as adverse prognostic factors associated with treatment resistance and progression to advanced-phase disease.
- Although olverembatinib has shown potent activity against *BCR::ABL1*-resistant mutations, including T315I and compound mutations, its efficacy in patients with concomitant ASXL1 mutations has not been well established.
- We sought to assess the clinical efficacy of olverembatinib in patients with multi-TKI–resistant CP-CML and to explore treatment outcomes according to ASXL1 mutation status.

## METHODS

- We assessed the baseline mutational landscape and clinical activity of olverembatinib in patients with ponatinib- and/or asciminib-resistant CP-CML enrolled in a phase 1b study.[1]
- The data cutoff was July 23, 2025.

**Table 1. Baseline characteristics**

| | Total (N = 22) |
|---|---|
| Age, yr | |
| Median (range) | 49.0 (21–79) |
| Sex, n (%) | |
| Male | 11 (50.0) |
| Female | 11 (50.0) |
| Race, n (%) | |
| White | 13 (59.1) |
| Black or African American | 6 (27.3) |
| Asian | 3 (13.6) |
| ECOG performance status | |
| 0 | 7 (31.8) |
| 1 | 15 (68.2) |
| T315I mutation, n (%) | |
| T315I mutated | 6 (27.3) |
| T315I unmutated | 16 (72.7) |
| Prior ponatinib treatment | |
| Yes | 16 (72.7) |
| Resistant | 16 (72.7) |
| No | 6 (27.3) |
| Prior asciminib treatment | |
| Yes | 12 (54.5) |
| Resistant | 12 (54.5) |
| No | 10 (45.5) |
| Prior TKIs, n (%) | |
| 2 | 4 (18.2) |
| 3 | 7 (31.8) |
| ≥ 4 | 11 (50.0) |

## RESULTS

**Figure 1.** Response in patients with prior pontanib/asciminib[1]

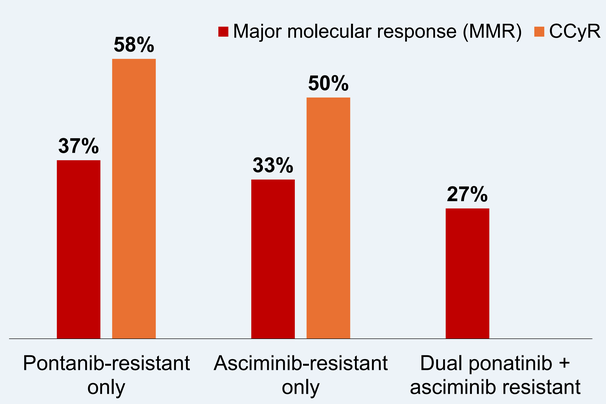



**Figure 2.** Response in the ASXL1-mutated subgroup (n = 9)

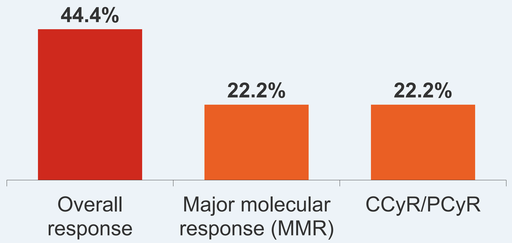
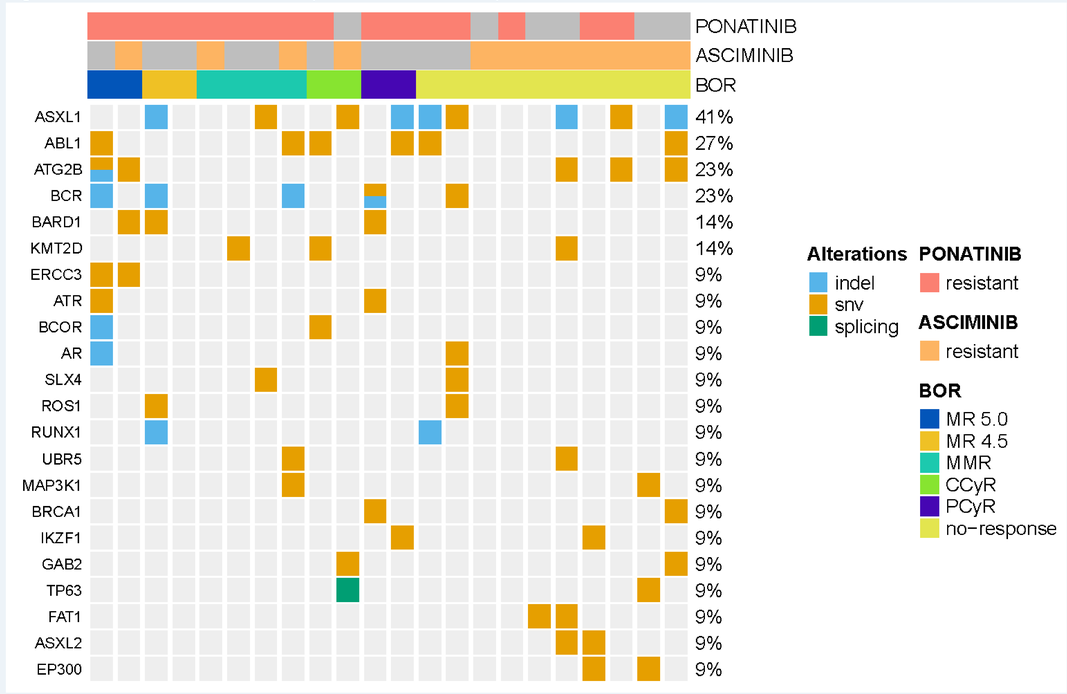



**Figure 3.** Baseline mutational landscape in the 22 evaluable patients




- In an earlier report, we found that a total of 15 of 26 patients with prior ponatinib treatment (58%; 95%CI, 36.9-76.6) achieved CCyR, and 11 of 30 (37%; 95%CI, 19.9-56.1) achieved MMR. A total of 4 of 8 patients with asciminib resistance (50%; 95%CI, 15.7-84.3) had CCyR, and 4 of 12 (33%; 95%CI, 9.9-65.1) had MMR. A total of 3 of 11 patients with treatment failure with both ponatinib and asciminib (27%; 95%CI, 6.0-60.9) achieved MMR with olverembatinib **(Figure 1)**[1]
- In this report, among 22 evaluable patients, 16 had ponatinib-resistant disease (ponatinib only, n=10; dual-resistant, n=6) and 12 had asciminib-resistant disease (asciminib only, n=6; dual-resistant, n=6).
- Baseline peripheral blood samples were analyzed using a next-generation sequencing panel, including assessment of ASXL1 mutations.
- Among 22 patients with mutational analysis results, 10 and 8 experienced lack of efficacy on ponatinib and asciminib, respectively, as their immediate prior TKI.
- Baseline BCR::ABL1 transcript levels ranged between 0.4% and 417%.
- Seven of 22 (31.8%) patients had *ABL1* kinase domain mutations, including T315I (in 5), F359I, and E255V/F317L multiple mutations (both in 1 each).

**ASXL1-mutated subgroup: 40.9% (9/22)**

- Apart from *ABL1* and ASXL1, mutations detected in at least two samples included ATG2B, BCR, BARD1, KMT2D, ERCC3, ATR, BCOR, AR, ROS1, RUNX1, SLX4, UBR5, MAP3K1, GAB2, TP63, BRCA1, IKZF1, FAT1, ASXL2, and EP300 (Figure 3)
- A total of five, three, and one patient had ponatinib-, asciminib-, and dual-TKI–resistant disease, respectively

**Response rate: 44.4% (4/9) (Figure 2)**

- Major molecular response (MMR): 22.2% (1 MR4.5)
- Complete/partial cytogenetic response (CCyR/PCyR): two patients

**Duration of response:**

- Complete/partial cytogenetic response: 0.03–19.6 months
- MMR: 2.8–22.1 months, including one patient with early withdrawal for transplantation
- Responses were observed in patients with ASXL1 and T315I (MMR) and ASXL1 with concomitant *ABL1* mutations (PCyR)

## CONCLUSIONS

- Olverembatinib demonstrated clinically meaningful activity in patients with heavily pretreated CP-CML, including those with prior ponatinib/asciminib resistance.
- Responses were observed across high-risk genomic subgroups, including ASXL1 and compound *ABL1* mutations.

## REFERENCES

1. Jabbour E et al. *JAMA Oncol* 2025;11:28-35.

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