Combined asciminib and olverembatinib in blast-phase chronic myeloid leukemia

Chronic myeloid leukemia (CML) is a clonal myeloproliferative disorder typically managed with BCR::ABL1 tyrosine kinase inhibitors (TKI). However, it can progress from chronic phase (CML-CP) to blast phase (CML-BP), during which BCR::ABL1 kinase domain (KD) genetic variants (e.g., T315I, Y253H) and aberrant activation of cellular bypass signaling pathways contribute to multidrug resistance, complicating treatment and potentially causing death. Allogeneic hematopoietic stem cell transplantation (allo-HSCT) remains the only potentially curative option, but patients with advanced disease that cannot revert to a second chronic phase (CP2) have a heightened risk of relapse after transplantation.[1,2] Combining TKI with chemotherapy can improve efficacy, but increases treatment-related toxicity.[3] Therefore, it is essential to facilitate an efficient and rapid reversal from CML-BP to CML-CP.

Asciminib, an allosteric STAMP inhibitor, can overcome ATP-competitive TKI resistance by specifically targeting and binding to the ABL myristoyl. Olverembatinib, a third-generation (3G) TKI developed and approved in China, is indicated for patients with CML-CP and accelerated-phase CML (CML-AP) harboring the *T315I* genetic variant, and for adults with CML-CP who are resistant or intolerant to other TKI.[4-6] Co-administration of 3G TKI and asciminib may elicit synergistic anticancer effects.[7,8] This report introduces clinical data on the efficacy and safety of asciminib plus olverembatinib in patients with CML-BP. The study was performed according to the ethical rules of China.

Case 1

Case 1 is a 51-year-old male who was diagnosed with CML-CP in January 2025 at a primary hospital. He presented with extramedullary infiltration of lymph nodes (LN) and was, therefore, diagnosed as extramedullary blastic. He initially received imatinib (400 mg daily [qd]) and achieved hematologic remission. However, on March 2, 2025, a *T315I* genetic variant was identified, and the LN metastases exhibited a mixed phenotype of lymphoid (T-cell) and myeloid blasts. Treatment was, therefore, switched to olverembatinib (40 mg, every other day [qod]). Follow-up bone marrow (BM) aspiration on March 10 revealed the following: blast cells comprising 28% of the sample, compound mutations (*T315I, E255V,* and *E255K*) with *BCR*::*ABL1* fusion gene positivity of 68.32% (measured by quantitative real-time polymerase chain reaction), and no changes observed in LN, indicating treatment failure. After extensive discussions, the patient declined chemotherapy.

On March 16, 2025, we began closely monitoring peripheral blood (PB) smears daily for blast cell counts and variations in LN size, while administering olverembatinib (40 mg, qod) plus asciminib (80 mg, twice daily [bid]). The plan was to transition to chemotherapy if this treatment regimen failed. During treatment, PB smear tests demonstrated a gradual decrease in blast cell counts. A follow-up BM aspiration on March 27, 2025, revealed that blast cells had decreased to 3%, indicating a return to CML-CP. In addition, no LN enlargement was observed and the positron emission tomography (PET) scans were negative. On April 4, 2025, we documented that the patient had achieved complete cytogenetic response (CCyR) with a *BCR*::*ABL1* International Scale (^{IS}) of 3.029%. By June 9, 2025, the disease had remained under control in CML-CP, and the patient had achieved a *BCR*::*ABL1*^{IS} of 0.019%.

On June 19, 2025, the patient underwent transplantation. The treatment timeline is outlined in Figure 1. During treatment, the patient experienced grade 3 thrombocytopenia and neutropenia, which were managed with supportive transfusions and therapies, resulting in normalization of neutrophil and platelet counts after seven days.

Case 2

Case 2 is a 37-year-old male who had presented with leukocytosis and was diagnosed with CML CP in 2023. Initial treatment was with imatinib (400 mg, qd); however, this treatment failed after six months, with a *BCR*::*ABL1*^{IS} of 97.82%. Treatment was switched to flumatinib (600 mg, qd), but severe hematologic toxicity (G3 anemia, G4 thrombocytopenia) prompted transition to dasatinib 50 mg qd in February 2024. In March, 2024, a follow-up BM aspiration revealed 21.5% blast cells. The treatment regimen was then changed to a generic version of ponatinib plus DCHG regimen (decitabine, cytarabine, homoharringtonine, granulocyte colony-stimulating factor [GCSF]) from March 5 to 11, 2024.

In September 2024, *BCR*::*ABL1* KD mutation testing identified a *T315I* genetic variant, with a *BCR*::*ABL1*^{IS} of 65.45% (karyotype:50, XY, +Y, +9, t(9, 22)(q34 q11.2)x2,+21,+22[18]/46, XY[2]), indicating treatment failure. The same month, the patient was enrolled in a clinical trial examining the safety and efficacy of TGRX-678 (an investigational STAMP inhibitor[9]) in CML intolerant or resistant to prior TKI treatment (clinicaltrials.gov NCT05434312). He received an initial daily dose of 240 mg, which was decreased to 120 mg because of treatment-related thrombocytopenia. After platelet recovery, he resumed treatment at daily doses of 240 mg. On December 5, 2024, a follow-up BM aspiration revealed 45% BM blast cells (karyotype: XY, +Y, +9, t(9 22)(q34;q11.2) x2, +21, +22[20]). In addition, testicular infiltration and the

presence of a *T315I* genetic variant indicated disease progression to CML-BP with acute myeloid features,[10] leading to the patient's withdrawal from the trial.

On December 14, 2024, treatment was changed to olverembatinib (30 mg, qod) plus BCL-2 inhibitor venetoclax and hypomethylating agent azacitidine. However, due to hematologic adverse events and financial constraints (he only received venetoclax for 20 days), treatment was shifted to olverembatinib monotherapy. In March 2025, a BM sample revealed 35% blast cells. Given the failure of all existing TKI treatments, coupled with the patient's concurrent severe pneumonia and myelosuppression, the use of high-dose chemotherapy was deemed unfeasible. Due to concerns regarding treatment tolerance (previous grade 4 hematologic AE), a combination regimen of olverembatinib (20 mg, qod) and asciminib (40 mg, qd) was initiated on March 12, 2025. Grade 4 neutropenia recurred during this treatment; however, the patient's condition improved after GCSF therapy.

On March 20, 2025, flow cytometry analysis of a BM aspirate detected approximately 4.5% of abnormal cells were detected. A follow-up BM aspiration on April 10, 2025, indicated 8.5% blast cells with a *BCR::ABL*^{IS} of 96.24% (karyotype: 47, XY, +8, t(9;22)(q34;q11.2)[20]); the disease returned to CML-CP and remained stable, with 2% blast cells noted on May 8, 2025. Because of economic difficulties, the patient declined allo-HSCT and died on July 18, 2025. The treatment timeline is outlined in Figure 2.

European LeukemiaNet guidelines recommend that patients in CML BP undergo allo-HSCT as early as possible, ideally once they attain CP2.[10] Consequently, consensus guidelines advocate for intensive chemotherapy, with or without TKI, as a bridge to transplantation, often tailored according to mutation analysis. However, some patients cannot tolerate intensive chemotherapy.

This study demonstrates for the first time the potential utility of combining asciminib and olverembatinib in patients with CML-BP. The findings indicate a rapid return to CML-CP with tolerable AE, thus facilitating early allo-HSCT. In Case 1, a patient with newly diagnosed CML-BP responded positively to combination therapy. In Case 2, the patient had multidrug-resistant CML-BP with resistance to both olverembatinib and TGRX-678 monotherapy, yet rapidly reverted to CP2 after the addition of asciminib to olver-

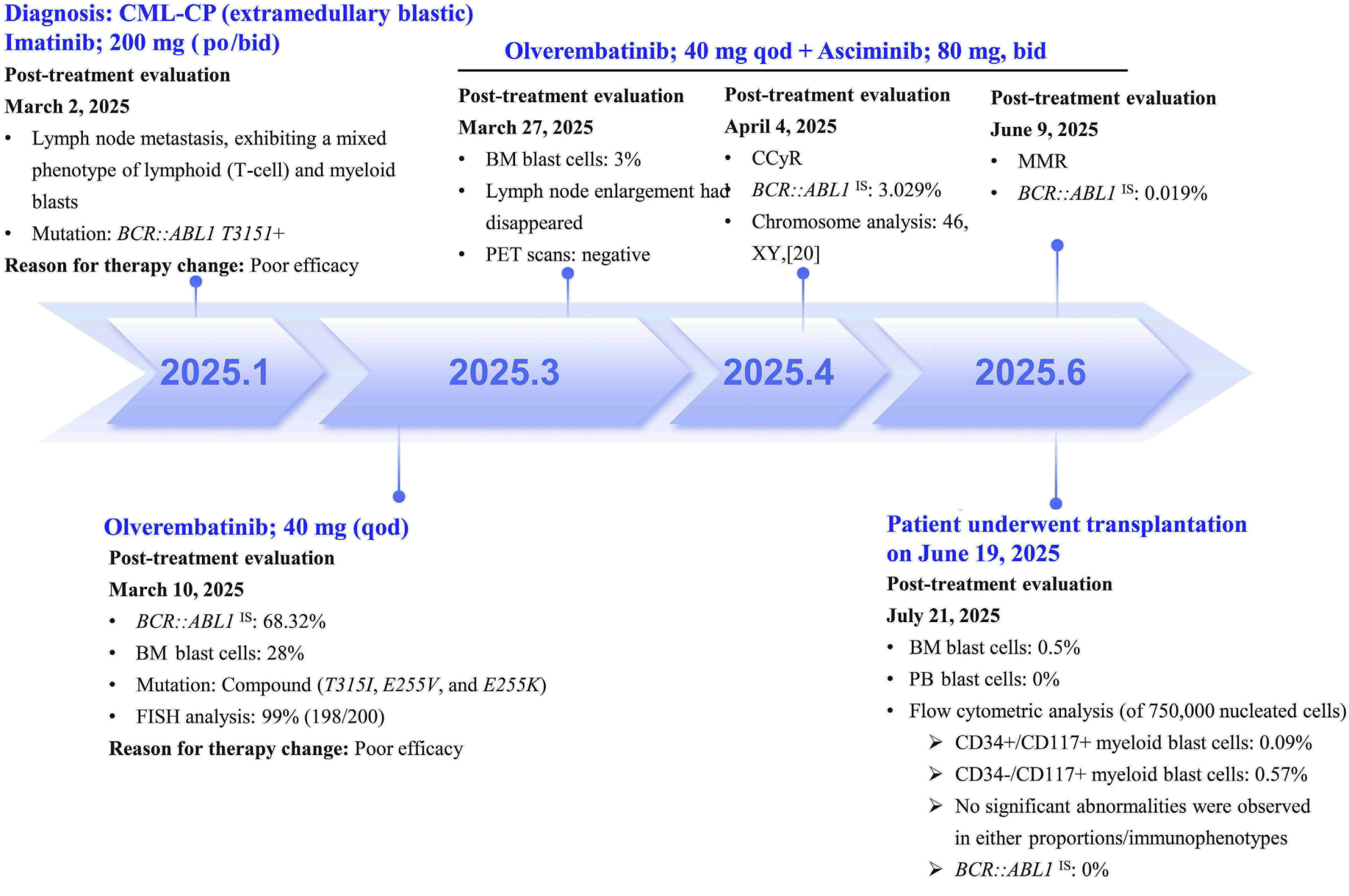

Figure 1. Outline of treatment schedule for Case 1. bid: twice daily; BM: bone marrow; CCyR: complete cytogenetic response; CML-CP: chronic myeloid leukemia-chronic phase; FISH: fluorescence *in situ* hybridization; IS: International Scale; MMR: major molecular response; PB: peripheral blood; PET: positron emission tomography; po: oral administration; qod: every other day.

Diagnosis: CML-CP
Imatinib; 200 mg (po/bid)

Post-treatment evaluation

June 20, 2023

- *BCR::ABL1* ^{IS}: 97.83%
- Chromosome analysis: 46, XY, t(9;22)(q34;q11.2)[20]
- PB blast cells: 2%
- BM blast cells: 4.5%
- No mutations observed

Reason for therapy change: Poor efficacy

Flumatinib; 600/400/200 mg (qd, po, alternate use

Post-treatment evaluation

October 10, 2023

- *BCR::ABL1* ^{IS}: 61.96%
- Chromosome analysis: 46, XY, t(9;22)(q34;q11.2)[[20]
- PB blast cells: 0%
- BM blast cells: 4.5%

Reason for therapy change: Adverse events (grade 3 anemia, grade 4 thrombocytopenia) and poor efficacy

Dasatinib; 50 mg qd, po

Post-treatment evaluation

March 5, 2024

- BM blast cells: 21.5%

March 13, 2024

- Chromosome analysis: 46, XY, t(9;22)(q34;q11.2)[12]/47~50,idem,+Y, +9,t(9;22)(q34;q11.2),+21[cp8]

Reason for therapy change: Poor efficacy.

Ponatinib; 45/15 mg qd; alternate use plus DCHG:

- **Decitabine; 10 mg, D1-5**
- **Cytarabine; 25 mg, every 12 hours, D1-7**
- **Homoharringtonine; 2 mg, D1-7**
- **Granulocyte colony-stimulating factor**

Post-treatment evaluation

March 13, 2024

- BM blast cells: 0%

August 27, 2024

- *BCR::ABL1* ^{IS}: 65.45%
- Mutation: *BCR::ABL1 T3151+*
- Chromosome analysis: 50, XY, +Y,+9,t(9 22)(q34 q11.2)x2,+21,+22[18]/46,XY[2]
- BM blast cells: 2.5%

Reason for therapy change: Severe hematological AEs and poor efficacy

TGRX-678; 240/120 mg, alternate use

Post-treatment evaluation[a]

December 5, 2024

- *BCR::ABL1* ^{IS}: 122.44%
- Mutation: *BCR::ABL1 T3151+*
- Chromosome analysis: XY, +Y, +9, t(9 22)(q34;q11.2)x2, +21+22[20]
- PB blast cells: 48%
- BM blast cells: 45% (with testicular infiltration)

December 10, 2024

- PB blast cells: 61%

Reason for therapy change: Adverse events (grade 3 anemia, grade 4 thrombocytopenia) and poor efficacy

Olverembatinib; 30 mg (qod) + Venetoclax; 100-400 mg ramp up, 400 mg qd + Azacitidine; 75 mg/m² qd, D1-7

Post-treatment evaluation[b]

January 1, 2025

- *BCR::ABL1* ^{IS}: 12.93%

February 29, 2025

- BM blast cells: 35%

Reason for therapy change: Olverembatinib dose reduced because of intolerance

Olverembatinib; 20 mg qod + Asciminib; 40 mg, qd

Post-treatment evaluation

March 20, 2025

- PB blast cells: 15%[c]

April 10, 2025

- *BCR::ABL1* ^{IS}: 96.24%
- Mutation: *BCR::ABL1 T3151+*
- Chromosome analysis: 47, XY,+8, t(9;22)(q34;q11.2)[20]
- PB blast cells: 7%
- BM blast cells: 8.5%
- Emergent adverse event: pleural effusion

Patient died

2023.2 → 2023.7 → 2024.2 → 2024.3 → 2024.9 → 2024.12 → 2025.3 → 2025.7.18

Figure 2. Outline of treatment schedule for Case 2. [a]Prior to assessment on December 5, 2024, the patient appeared to have initially responded to treatment. On October 10, 2024, we observed a BCR::ABL International Scale (IS) of 60.39%, peripheral blood (PB) blasts at 1%, bone marrow (BM) blasts at 0.5%, no mutation, and the following chromosome profile: 50, XY, +Y,+9,t(9 22)(q34 q11 .2)x2,+21,+22[19]/46,XY,(9;22)(q34; q11.2)[1]. Subsequent assessments on October 23, 2024, November 6, 2024, and November 20, 2024, showed PB blasts cells at 0%, 0%, and 0.5%, respectively. [b]The specific treatment regimen was administered at an external hospital, and information is incomplete since follow-up evaluations of efficacy were undocumented. During this period, the patient developed pancytopenia (reduction in all three blood cell lineages), with the lowest recorded white blood cell count at $0.34x10^9$/L. Intermittent discontinuation of therapy and dose reduction of medications occurred throughout the treatment course. [c]Flow cytometric analysis (via CD45/side scatter [SSC] dot plot) gating analysis revealed that blast/precursor region cells accounted for approximately 4.5% of nucleated cells. Within the detection range, these cells positively expressed HLA-DR, CD13, CD33, CD34, CD117, and CD123, suggesting the presence of immunophenotypically abnormal cells. bid: twice daily; CML-CP: chronic myeloid leukemia-chronic phase; po: oral administration; qd: daily; qod: every other day.

embatinib. These observations suggest that dual inhibition targeting distinct BCR::ABL1 sites may overcome the resistance encountered with traditional ATP-competitive TKI. In addition, allosteric ligands may synergistically enhance the antileukemic activity of TKI.

Preclinical studies suggest that asciminib exhibits synergistic effects when combined with traditional TKI.[7] Synergy mechanisms may include: 1) conformational locking, in that asciminib stabilizes the inactive state of BCR::ABL1, enhancing ponatinib binding to resistant mutants; 2) overcoming compound mutations: asciminib + ponatinib eradicated T315I-containing IMP-R clones (e.g., T315I+H396R Y253H) in murine models; and 3) the combination inhibited expansion of resistant subpopulations. Eide *et al.*[11] first reported the effectiveness of combining ponatinib and asciminib in patients with CML-CP harboring the *BCR*::*ABL1 T315I/E355G* variant. Ponatinib and asciminib exhibit a three-tiered synergistic mechanism (conformation-occupancy-signaling pathway) against *BCR*::*ABL1* compound mutations. Critically, the binding pockets for ponatinib and asciminib do not overlap, allowing simultaneous saturation at clinically achievable concentrations. Concurrent targeting of two distinct sites elevated the mutation barrier and reduced the emergence of *in vitro* resistant clones by >100-fold. Furthermore, due to their divergent pharmacokinetic pathways, synergistic efficacy could be maintained at lower individual doses, potentially reducing toxicities.

Similarly, Hall and colleagues[12] documented clinical efficacy of the asciminib-bosutinib combination in overcoming TKI resistance in patients with CML CP. Clinical trials (e.g., clinicaltrials.gov NCT03578367 and NCT02081378) are evaluating effects of asciminib plus TKI among newly diagnosed patients, previously treated with at least one other TKI, and relapsed CML-AP or CML-CP.[13,14] The study demonstrated that asciminib combined with TKI provided rapid efficacy in CML-CP/AP patients, but was less well-tolerated than asciminib monotherapy. In the subset of patients who may respond to this proposed combination therapy, one potential benefit is that it offers greater efficacy (*vs*. monotherapy); this may prevent TKI switching that might result in the development of treatment-resistant mutations.

These case reports present the first empirical evidence supporting the feasibility of this combination treatment strategy in patients with CML-BP, providing a rationale for its prospective evaluation in a clinical trial. Future larger studies are warranted to validate these findings and define potential mechanisms.

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Contributions

WL is responsible for study concept and design. Both authors wrote, reviewed, and approved the final version of the manuscript for publication.

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Data-sharing statement

The data generated in this study are not publicly available due to information that could compromise patient privacy or consent.

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