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Olverembatinib: real progress in BCR::ABL1 leukemia?

Running title: Olverembatinib in leukemia

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ABSTRACT

Olverembatinib (HQP1351) is a potent third-generation (3G) tyrosine kinase inhibitor (TKI) that binds to both the active and inactive conformations of native ABL1 and mutant BCR::ABL1. It was developed as a potent inhibitor with activity against wild-type and mutated BCR::ABL1 for chronic myeloid leukemia (CML) patients. It is effective against the T315I mutation, which confers resistance to first and second generation TKIs. The results of clinical trials in China have led to olverembatinib approval by China's regulatory authority, National Medical Products Administration (NMPA), for adult patients with TKI-resistant chronic phase (CP) or accelerated phase (AP) CML harboring the T315I mutation and for adult CP CML patients with resistance or intolerance to imatinib or 2G TKIs. Olverembatinib has also received breakthrough therapy designation by the NMPA in combination with low intensity chemotherapy for the first-line treatment of Philadelphia chromosome-positive acute lymphoblastic leukemia (Ph+ ALL). Global studies of olverembatinib are underway in CML and Ph +ALL, with the results of the US phase 1b study published in 2025. This review will summarize the safety, tolerability, and efficacy of olverembatinib in CML and Ph+ ALL in China and globally and discuss the role of olverembatinib among existing therapeutics and its future development.

A rationale for additional potent therapeutics in chronic myeloid leukemia (CML) and Philadelphia chromosome-positive acute lymphoblastic leukemia (Ph+ ALL)

BCR::ABL1 targeted therapies have profoundly altered outcomes for CML patients. For many chronic phase (CP) and select *de novo* accelerated phase (AP) patients, near normal life expectancy on single agent targeted therapy is observed.[1, 2] These outcomes are not shared by patients with disease transformation to AP or blast phase (BP), the acute leukemic form of CML.[3] For imatinib, the first orthosteric, adenosine triphosphate (ATP) competitive tyrosine kinase inhibitor (TKI), primary cytogenetic and molecular resistance was reported in ~20-30% of CP patients with higher rates in AP.[4] Current outcomes have been made possible by successive generations of TKIs with increased potency and designed to overcome resistance conferred by the acquisition of point mutations in the BCR::ABL1 kinase domain.[5, 6] Resistance to 2nd generation (2G) TKIs [e.g., bosutinib, dasatinib, nilotinib, flumatinib (China), radotinib (South Korea)] received first-line is seen in ~10-20% and response after failure of 2 prior TKIs is associated with poorer survival and higher resistance rates.[7-11] Access to additional therapeutics has also been important, as highlighted by observational data outside of clinical trials, because the most common reasons for therapy switch are treatment-emergent adverse events (TEAEs).[12]

An important driving force in BCR::ABL1 inhibitor drug development was the need for a treatment that would overcome resistance due to the T315I "gatekeeper" mutation.[5, 6] This mutation substitutes threonine with isoleucine and contributes to resistance via steric hindrance and disrupted interactions.[6] The T315I mutation confers resistance to imatinib and all 2G TKIs. Ponatinib, a third generation (3G) TKI was the first TKI to overcome resistance due to T315I. Ponatinib was approved for CML and Ph+ ALL resistant or intolerant of prior TKI therapy or with T315I by the FDA in December 2012 and EMA in July 2013 based on efficacy demonstrated in the Phase 1 study and Phase 2 PACE trial.[13, 14] Ponatinib was granted accelerated first-line approval by the FDA for newly diagnosed Ph+ ALL in combination with chemotherapy in March 2024 and by the EMA in January 2026 based on superior rates of measurable-residual disease (MRD) negativity as defined as ≤0.01% *BCR::ABL1*^{IS} assessed by real-time quantitative polymerase chain reaction (qPCR, International Scale (IS)).[15] Ponatinib has been an important therapeutic advance. However, toxicities such as increased risk for cardiovascular, cerebrovascular or peripheral arterial events, often termed arterial occlusive events AOEs, are due to its lack of selectivity and have limited ponatinib use in earlier lines of therapy for CML.[16]

In parallel with the development of 3G TKIs, a redesign of BCR::ABL1 targeted therapy was underway. The myristoyl pocket of ABL1 plays an important role in autoregulation.[17] Signaling activity downstream of the kinase is inhibited by the binding of the N-terminal myristoylated glycine residue of ABL1 to this pocket, thereby inducing a closed, inactive state. This inhibition is lost in the fusion protein BCR::ABL1. Asciminib is the first approved allosteric inhibitor targeting the myristoyl pocket of BCR::ABL1.[18] It is potent, highly specific, and, in contrast to TKIs, has minimal off-target kinase activity.[18] Asciminib is active against T315I, although higher doses are required, and it is approved for all lines of therapy for CP CML by the FDA and EMA. Clinical trials have reported lower rates of non-hematologic TEAEs for asciminib vs imatinib and 2G TKIs.[19, 20] Our understanding of resistance to asciminib continues to evolve. To date asciminib resistance is conferred by mutations in the myristoyl pocket and specific kinase domain mutations such as M244V and F359V/I/C; it is also ineffective in CML with rare variants lacking exon 2 of ABL1 (e.g., e13a3 and e14a3 transcript variants).[21, 22]

Olverembatinib: preclinical development, clinical trials, and regulatory approval

Olverembatinib (HQP1351) is a potent 3G TKI developed over 18 years ago by Ascentage Pharma in China. It binds to both the active (phosphorylated activation loop, capable of binding ATP) and inactive (non-phosphorylated) conformations of native and mutant BCR::ABL1 (**Figure 1**).[23, 24] In contrast, ponatinib binds to the inactive conformation only. Like ponatinib, olverembatinib, is a multi-kinase inhibitor with potent activity against other oncogenic kinases, including KIT, PDGFR, SRC, FLT3, FGFR, b-RAF, LCK, LYN, DDR1, RET, TIE1 and TIE2.[23, 24] China's regulatory authority, National Medical Products Administration (NMPA), granted olverembatinib approval in 2021 for the treatment of adult patients with TKI-resistant CP or AP CML harboring the T315I mutation. In 2023 approval was extended to adult CP CML patients with resistance or intolerance to imatinib or 2G TKIs. Olverembatinib received breakthrough therapy designation by the NMPA in combination with low intensity chemotherapy for the first-line treatment of Ph+ ALL in 2025.[25] Olverembatinib is effective against BCR::ABL1 mutations, including T315I and efficacy against rare compound mutations, which are mutations within the same BCR::ABL1 molecule, was demonstrated in pre-clinical studies, although *in vivo* efficacy against compound mutations is still being defined.[26]

Olverembatinib in CML (Table 1)

CML studies in China

In China access to asciminib and ponatinib in resistant CML and ALL was limited until ~2025. Pivotal studies in China led to olverembatinib NMPA approval and supported further study outside of China. The first-in-human study SJ-002 and Phase 1/2 studies established PK and early efficacy in CP (CC201, NCT03883087) and AP (CC202 (NCT03883100)) CML patients with T315I mutations.[26] Olverembatinib demonstrated linear PK, dose proportional increases in AUC and maximum concentration across the dose range of 1-60 mg on alternate days (QOD). The mean terminal elimination half-life values were 17.5–36.5 hours supporting QOD dosing and, like the approved TKIs, it is predominantly metabolized by CYP3A4. Dose expansion cohorts included 30 mg, 40 mg, and 50 mg QOD.[26] Overall, 127 CP and 38 AP patients were enrolled with a median age of 42 (range 20-74) and 81.8% had received 2 or more lines of prior TKI therapy. Grade 3/4 hematologic treatment-related adverse events (TRAEs) were reported in 51.5%, 11.5%, and 23% for thrombocytopenia, neutropenia, and anemia, respectively. The most common all grade non-hematologic TRAEs were skin pigmentation (84.2%), hypertriglyceridemia (57.6%), proteinuria (50.9%), hyperbilirubinemia (41.8%), hypocalcemia (38.8%), and increased AST and ALT (35.8%). TRAEs were predominantly grade 1 or 2 and most, except for skin pigmentation and proteinuria, decreased over time on therapy. Cardiovascular events (CVE) remain an area of special interest with 3G TKI; with a median follow-up of almost 3 years, olverembatinib-related CVE were reported in 32%.[26] Specifically, hypertension was seen in 13% and arterial or venous events were reported in 5% of patients. For CP patients at 3 years the cumulative incidence of complete cytogenetic (CCyR, comparable to *BCR::ABL1* transcripts < 1%), major molecular (MMR, *BCR::ABL1* $\leq$ 0.1%), MR4 (*BCR::ABL1* $\leq$ 0.01%) and MR4.5 (*BCR::ABL1* $\leq$ 0.003%) responses were 69.0%, 55.9%, 43.5%, and 38.9%, respectively. For AP patients these values were 47.4%, 44.7, 39.3%, and 32.1%, respectively. The probabilities of overall survival (OS) and progression-free survival (PFS) at 3 years were, respectively, 94% and 92% for CP patients and 71% and 60% for AP patients.

The registrational study CC2013 (NCT04126681), reported results for 144 CP CML patients resistant and/or intolerant to imatinib and 2G TKIs (abstract format).[27, 28] For this study patients were randomized 2:1 to either olverembatinib at 40 mg QOD or investigator's choice (imatinib, dasatinib, nilotinib, interferon, hydroxyurea and/or homoharringtonine). Event-free survival (EFS) from the time of randomization through cycle 24 was the primary endpoint. EFS was defined as all-cause mortality, treatment failure (no complete remission within 3 cycles), loss of complete hematologic response and treatment intolerances as per investigator and sponsor. Median EFS was significantly longer in the olverembatinib vs investigators' choice cohort: 21.22 (95% confidence interval (CI), 10.15-not reached (NR)) months vs. 2.86 (95% CI, 2.53-4.73) months (P < .0001; HR, 0.355; 95% CI, 0.230-0.549).

Given the need for long term therapy use in CML patients, increasing attention has focused on the best dosing that limits TEAEs and serious toxicities but preserves efficacy. For example, for dasatinib lower dosing at 50 mg daily preserves efficacy in many patients and reduces rates of pleural effusion.[29] The OPTIC study of ponatinib in CP CML patients led to an important label change. This study demonstrated that a dose reduction strategy once a good response, i.e. *BCR::ABL1* transcripts < 1%, is achieved reduces the risk for AOEs by an estimated 60% vs continued higher ponatinib dosing.[14, 30, 31] Two recently published retrospective studies of olverembatinib in CP and AP CML patients (N=282 and N=130, respectively) including patients with T315I compared 40 mg QOD with 30 mg QOD dosing of olverembatinib across 36 Chinese centers.[32, 33] No differences in therapy response were identified between the two CP cohorts using propensity score matching analyses.[33] In the 30 mg CP cohort, 6-year cumulative incidences of major cytogenetic response (MCyR), CCyR, MMR and MR4 were 84% (95% CI: 75-93%), 84% (95% CI: 73-95%), 57% (95% CI: 45-69%) and 36% (95% CI: 18-54%), respectively. The 6-year probabilities of PFS and OS in the 30 mg QOD cohort were 78% (95% CI: 64-92%) and 82% (95% CI: 67-97%), respectively. Overall, more patients in the 30 mg QOD cohort continued therapy, 67% vs 47% in the 40 mg QOD cohort, and fewer patients in the 30 mg QOD cohort reduced dose permanently or discontinued therapy due to TRAEs.[33]

<u>Global CML studies</u>

The results of the US phase 1b study of olverembatinib in CML and Ph+ ALL with a median follow-up of 48 (range, 0-166) weeks were recently published.[34] The primary study endpoint was to establish the PK profile of olverembatinib and dosing for a Phase 3 study. Eighty (62 CP CML and 18 advanced phase CML or Ph+ ALL) patients resistant or intolerant to at least 2 TKIs were enrolled. The median age was 54 (range 21-80) years, 57.5% were male, and 81.3% had received 3 or more prior lines of therapy. CP patients were randomized to 30 mg QOD (N=28), 40 mg QOD (N=26) and 50 mg QOD (N=8). Among CP patients 67.7% were resistant to prior ponatinib and 73.7% resistant to prior asciminib. At study entry among CP patients 69.4% (43 of 62) had *BCR::ABL1* transcripts > 10% and 90.0% > 1% . As compared to studies in China, no differences in PK profile were identified. Among evaluable CP CML patients in all dosing cohorts, CCyR and MMR rates were 60.8% (31/51) and 42.4% (25/59) in all patients, 63.6% (21/33) and 41.5% (17/41) in patients without T315I, and 55.6% (10/18) and 44.4% (8/18) in patients with T315I, respectively. Similar response rates were seen in patients who had received prior ponatinib and/or asciminib. Fifteen of 26 (57.7%) patients with prior ponatinib treatment (13 of 15 with T315I) achieved CCyR, and 11 of 30 (36.7%) achieved MMR. In patients with prior asciminib treatment, 60% (6/10) had CCyR and 29.4% (5/17) MMR. Among advanced leukemia cases 3/17 (18%) achieved MMR and 3 of 14 (21%) CCyR.

Grade 3/4 hematologic toxicity was seen in 17.5% (thrombocytopenia), 12.5% (neutropenia) and 6.3% (anemia). The most common all grade TEAEs were increased CPK (38.8%), nausea (26.3%), fatigue (25%), ALT increase (23.8%), and AST increase (21%). The most common grade 3/4 TEAEs were increased CPK (12.5%) and isolated lipase increase (7.5%). Although skin hyperpigmentation was seen, the rates were substantially lower in the US study vs studies in China, 13.8% all grade and 1.3% grade 3/4. Among all patients enrolled, 9 (11.3%) experienced treatment-emergent AOEs across all doses examined; 2 were reported as treatment-related and all were grade 1 or 2. However, follow-up time is short. Overall, clinical efficacy was similar between 30 and 40 mg QOD. Fewer dose interruptions, discontinuations, and serious AEs were observed in patients receiving 30 mg QOD. The Phase 3 global, multicenter open label registrational study, POLARIS-2, is underway in CP CML patients. Similar to the ASCEMBL study which led to FDA approval of asciminib, Part A randomizes patients who have received 2 or more lines of therapy, but without T315I mutations, 2:1 to olverembatinib 30 mg QOD vs bosutinib 500 mg daily. Part B is a single arm study of CP CML patients with T315I mutations who receive olverembatinib 40 mg QOD.

Olverembatinib in Ph+ ALL (Table 2)

BCR::ABL1 targeted therapies have substantially improved outcomes for Ph+ ALL patients receiving both higher intensity chemotherapy regimens and lower intensity treatments.[35, 36] With the approval of the bispecific monoclonal antibody blinatumomab effective chemotherapy-free regimens are available for older patients or patients with comorbidities.[37] The optimal integration of blinatumomab into frontline therapies is under study. Based on the efficacy of these new therapeutics, for patients with no evidence of MRD by *BCR*::*ABL1* qPCR and/or immunoglobulin/T-cell receptor (*IG/TR*) gene rearrangement (clonoSEQ), allogeneic hematopoietic cell transplantation (HCT) may be deferred in eligible patients.[38] For relapsed Ph+ ALL patients chimeric antigen receptor (CAR) T cell therapy and the antibody-drug conjugate (ADC) inotuzumab are available. The emergence of *BCR::ABL1* kinase domain mutations, most often T315I, is a common mechanism of variant-acquired resistance in Ph+ ALL following treatment with imatinib or dasatinib. Based on the results of several pivotal studies, ponatinib, which has the least vulnerability to this mechanism of resistance, is favored.[15, 35] The PhALLCON phase 3 randomized clinical trial compared frontline reduced-intensity chemotherapy combined with either imatinib or ponatinib.[15] The primary endpoint was MRD-negative complete remission (≤0.01% *BCR::ABL1*^{IS}) at the end of cycle 3, which was significantly higher with ponatinib (34.4% [53/154]) vs imatinib (16.7% [13/78]); $P = .002$). Median event-free survival was 29 months in imatinib-treated patients vs not reached in patients receiving ponatinib. AOEs were reported in 2.5% of patients receiving ponatinib and 1.2% of patients receiving imatinib.

Olverembatinib received breakthrough therapy designation by the NMPA in combination with low intensity chemotherapy for the first-line treatment of Ph+ ALL (POLARIS-1) in 2025.[25] Ongoing studies in China and globally are outlined in **Table 2.** Updates to part A of the global Phase 3 POLARIS-1 study have been published in abstract format.[25] Patients received olverembatinib at 40 mg or 30 mg QOD together with induction chemotherapy with vincristine and dexamethasone or vincristine, dexamethasone, and daunorubicin followed by consolidation with high-dose methotrexate and cytarabine. The primary endpoint was MRD negative complete remission by the end of cycle 3 and MRD-negative CR rates by qPCR were 35.8% after C1, 50.9% after C2, and 52.8% after C3.[25] This study is now opening globally. One possible limitation to enrollment is the increasing use of blinatumomab in the front-line setting in some countries. The ongoing US phase 1b study of CML and Ph+ ALL will also provide additional data in relapsed/refractory Ph+ ALL and is examining olverembatinib in combination with blinatumomab in Arm D and in combination with chemotherapy in Arm E. In China, for relapsed Ph+ ALL, studies are examining lower intensity combination approaches with olverembatinib in the setting of MRD or as a bridge to allogeneic HCT or CAR-T therapy and in the front-line setting in combination with venetoclax and reduced intensity chemotherapy for newly diagnosed Ph+ ALL.[39-42]

Conclusions and new directions in leukemia

The future of olverembatinib in CML and Ph+ ALL will depend on the results of ongoing Phase 3 studies. With the approval of asciminib and clinical trials of new allosteric inhibitors such as TERN-701 and TGRX-678, the therapeutic landscape for CML continues to expand quickly. For the rarer resistant CML patient, all these options including more information on how to sequence these therapies is needed. To date there are no studies directly comparing potent 3G TKIs like ponatinib or olverembatinib to asciminib. A recent matching-adjusted indirect comparison analysis retrospectively compared patients using data from the phase 1 study and the ASCEMBL study for asciminib and PACE and OPTIC for ponatinib.[43] Patients receiving ponatinib with or without T315I mutations had higher molecular response rates (*BCR::ABL1* ≤1% and ≤0.1%) by 6 and 12 months. Although not statistically significant, ponatinib was also favored when comparing CP CML patients without baseline response.[43] Recognizing the limitations of such analyses, these observations highlight the need for 3G TKIs in resistant CML patients and in patients with AP and BP. In contrast to asciminib, potent 3G TKIs address non-kinase domain mediated resistance mechanisms, which contribute to resistance despite BCR::ABL1 inhibition.[5] Approximately 40% of TKI resistance is characterized by sustained BCR::ABL1 inhibition without mutations in BCR::ABL1.[6] Multi-kinase inhibitors such as ponatinib and olverembatinib may not only prevent reactivation of signaling pathways downstream of BCR::ABL1, but also prevent survival by alternative pathways. For example, FGFR3 targeting by ponatinib (and potentially olverembatinib) has been shown to impair survival of unmutated resistant CML cells due to diminished FGF2 production in the bone marrow microenvironment.[44] Additionally, although rare, overcoming resistance due to highly resistant compound mutations, as demonstrated in pre-clinical studies of olverembatinib, is also important.[26] The use of olverembatinib in earlier lines of therapy in CML will depend on the balance of efficacy and safety. More potent BCR::ABL1 inhibitors are associated with higher rates of deep molecular responses, which are needed to become eligible to stop therapy. Very high rates of deep molecular response were seen on the terminated first-line study of ponatinib (EPIC); however, the risk of AOEs with ponatinib has limited its use to later lines.[16] As a multi-kinase inhibitor, olverembatinib may share a similar risk profile. Treatment-emergent AOEs were reported in 11.3% of patients enrolled on the US Phase 1b study.[34] Global development of olverembatinib can benefit from the lessons learned with ponatinib. In the OPTIC study, using a response based dose reduction approach the exposure adjusted AOE rates per 100 patient-years were 4.1, 3.8, and 2.0 for 45-mg, 30-mg, and 15-mg cohorts at 5 years, respectively.[45] Selecting an effective olverembatinib dose that minimizes toxicities will be critical. Emerging data support that 30 mg QOD is an effective dose for many patients; however, the impact of olverembatinib dose on AOE risk remains unclear. Longer follow-up is needed to establish more clearly AOE risk, the impact of dose selection on risk, and the continued need for cardiovascular risk-factor management or monitoring. In Ph+ ALL because of superior MRD rates, ponatinib is becoming a preferred choice. Asciminib is also under study, including in combination with dasatinib as a strategy to prevent emergence of resistant subclones harboring mutations, although our understanding of the mutation vulnerabilities of asciminib is evolving. The availability of olverembatinib as an additional potent alternative in Ph+ ALL could be highly clinically relevant, especially if AOE rates are low. Lastly, as a multi-kinase inhibitor, case reports of olverembatinib activity in myeloid/lymphoid neoplasm with FGFR1 rearrangements, acute myeloid leukemia, Ph-negative ALL and T-ALL, as well as in solid tumors such as gastrointestinal stromal tumors are emerging. In summary, despite the rapid expansion of BCR::ABL1 therapeutics, there is still a clear need for potent, tolerable TKIs that have the potential to limit resistance due to BCR::ABL1 kinase domain mutations and non-kinase domain mediated resistance.

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Table 1. Summary of Data: Olverembatinib for Chronic Myeloid Leukemia.

Clinical Trial	Interventions	Patients	Median Follow-up	CCyR	MMR	MR4	EFS[e]	PFS	OS
Jabbour et al. (2025)[1] **R/R** *Phase 1b, published*	Olverembatinib 30 mg every other day	62[a] (51 evaluable)	48 weeks	47.8%	35.7%	-	-	-	-
	Olverembatinib 40 mg every other day			75%	52.2%				
	Olverembatinib 50 mg every other day			62.5%	37.5%				
Yuan et al. (2025)[2] **Frontline** *Retrospective published*	Olverembatinib 20 mg every other day	130 (de novo AP-CML: 29; transformed AP-CML: 101)	28 months	47%[b] (at median 4 months) 53% (6-year cumulative)	43%[b] 52% (6-year cumulative)	31%[b] 42% (6-year cumulative)	-	• 81% (6-year probability transformation) • 76% (6-year probability CML-related)	71% (6-year probability)
	Olverembatinib 30 mg every other day								
	Olverembatinib 40 mg every other day								
	Olverembatinib 50 mg every other day								
Zhang et al. (2025)[3] **R/R** *Retrospective published*	Olverembatinib 30 mg every other day	66 (62 evaluable)	28 months	67%[b] (at median 3 months) 84% (6-year cumulative)	44%[b] 57% (6-year cumulative)	28%[b] 36% (6-year cumulative)	-	78% (6-year probability)	82% (6-year probability)
	Olverembatinib 40 mg every other day	216 (200 evaluable)	25 months	60%[b] (at median 3 months) 71% (4-year cumulative)	45%[b] 59% (4-year cumulative)	34%[b] 51% (4-year cumulative)		82% (4-year probability)	84% (4-year probability)
Jiang et al. (2022)[4] **R/R** *Phase 1/2 published*	Olverembatinib 40 mg every other day[c,d]	CP-CML:127 (126 evaluable)	34.3 months	69.4%[b] (at median 3 months) 69.0% (3-year cumulative)	55.6%[b] 55.9% (3-year cumulative)	44.4%[b] 43.5% (3-year cumulative)	-	92% (3-year probability)	94% (3-year probability)
		AP-CML: 38		47.7%[b] (at median 4 months) 47.4% (3-year cumulative)	44.7%[b] 44.7% (3-year cumulative)	36.8%[b] 39.3% (3-year cumulative)		60% (3-year probability)	71% (3-year probability)
Jiang et al. (2023 and 2025)[5,6] *Phase 2 abstract*	Olverembatinib 40 mg every other day	96	21.4 months	-	-	-	Median: 21.22 months • 73% (6 months) • 58.7% (12 months) • 46.9% (24 months)	-	Not reached
	Best available therapy	48	2.9 months				Median: 2.86 months • 32.6% (6 months) • 26.1% (12 months) • 16.9% (24 months)	-	
Bao et al. (2025)[7] **R/R** *Prospective published*	Ponatinib or Olverembatinib + Azacitidine[f]	37, myeloid blast phase	30 months	24%[g]	16%[g]	-	-	• Median: 5 months • 19% (3-year probability)	• Median: 9 months • 23% (3-year probability)

a. Chronic phase CML cohort only; see Table 2 for data on Acute Leukemia cohorts
b. Among evaluable patients, reported at median follow-up and as cumulative incidence
c. All data shown are based on results from phase 2 of the study
d. Percentages for rates are based on different denominators (CP-CML cohort - CCyR: 121 patients; MMR: 126 patients; MR4: 126 patients; AP-CML cohort – CCyR: 38; MMR: 38; MR4: 38)
e. EFS was defined as: time from randomization to CML progression; all-cause mortality; relapse; treatment failure; loss of complete hematologic response; and treatment intolerance as per investigator and study sponsor
f. Ponatinib 45 mg once daily; olverembatinib 30 mg every other day; azacitidine (75 mg/m2 daily for 7 days) in 28-day cycles. The choice of 3G-TKI was based on availability. Eligible patients who returned to chronic phase underwent allogeneic HCT.
g. Response rate during study treatment

Abbreviations: CML = chronic myeloid leukemia; AP = accelerated phase; CCyR = complete cytogenetic response; MMR = major molecular response, *BCR::ABL1* transcripts < 0.1%; MR4 = molecular response 4.0, *BCR::ABL1* transcripts < 0.01%; PFS = progression-free survival; OS = overall survival; EFS = event-free survival; R/R = relapsed/refractory; HCT = hematopoietic cell transplant.

[1]Jabbour E, Oehler VG, Koller PB, et al. JAMA Oncol. 2025;11(1):28-35. [2]Yuan M, Zhou L, Li W, et al. Haematologica. 2026;111(3):906-917. [3]Zhang X, Yang Y, Liu B, et al. Haematologica. 2025;110(12):2986-2996. [4]Jiang Q, Li Z, Qin Y, et al. J Hematol Oncol. 2022;15(1):113. [5]Jiang Q, Li Z, Zhang G, et al. Blood 2023; 142 (Supplement 1): 869. [6]Jiang Q, Li A, Zhang Y, et al. Blood 2025; 146 (Supplement 1): 3788. [7]Bao M, Zhang XS, Li ZR, et al. Cancer. 2025;131(22):e70166.

Table 2. Summary of Data: Olverembatinib for Ph+ Acute Lymphoblastic Leukemia and Lymphoid Blast Phase CML.

Clinical Trial	Interventions	Patients	Median Follow-up	CCyR	MMR	CR	CMR[l]	MRD Negative[m]	EFS[n]	RFS	OS
Zhu Y. et al. (2024)[1] **Frontline** *Retrospective published*	Olverembatinib 40 mg every other day + physician's choice for induction and consolidation[a]	20	17.2 months	-	-	100% (after induction)	35% (C1) 70% (C2)	-	100% (1 year)	-	100% (1 year)
Jabbour et al. (2025)[2] **R/R** *Phase 1b published*	Olverembatinib 30 mg every other day Olverembatinib 40 mg every other day Olverembatinib 50 mg every other day	18[b] (17 evaluable)	48 weeks	21%[k]	18%[k]	-	-	-	-	-	-
Chen et al. POLARIS-1 (2025)[3] **Frontline** *Phase 3 abstract*	Olverembatinib 40 or 30 mg was administered orally every other day in combination with reduced-intensity chemotherapy[c]	55 (53 evaluable)	As of July 2025	-	-	94.3% (after induction)	-	35.8% (C1) 50.9% (C2) 52.8% (C3)	-	-	-
Gong et al. (2025)[4] **Frontline** *Phase 2 published*	Olverembatinib 40 mg every other day in combination with venetoclax, vincristine, prednisone[d]	80 (79 evaluable)	12 months	-	16.5% (C3)	100%[e] (induction, CR + CRi)	62% (C3)	100% (C3)	89.1% (estimated 1 year)	-	93.1% (estimated 1 year)
Zhang X. et al. (2025)[5] **R/R** *Retrospective published*	Olverembatinib 40 mg every other day in combination with venetoclax, vincristine, prednisone as induction followed by HCT	17 (persistent MRD+: 15; R/R: 2)	28.5 months	-	-	-	70.6%	-	-	79.4% (2 years)	88.2% (2 years)
Tang et al. (2024)[6] **Frontline** *Phase 1/2 interim*	Olverembatinib 40 mg every other day in combination with dexamethasone, venetoclax as induction followed by HCT (only if MRD-neg CMR not achieved after 3 cycles induction therapy)	10	7.4 months	-	80% (C1D14)	-	90% (after cycle 2)	100% (persisted through last follow-up)	-	-	100% (7.4 months; range 1.8-16 months)
Zhang X. et al. (2025)[7] **R/R** *Retrospective published*	Olverembatinib 40 mg every other day in combination with inotuzumab followed by HCT and post-transplant[f] maintenance with olverembatinib	14 (persistent MRD+: 9; R/R: 5)	18.8 months	100%	-	100%	78.6%	-	-	62.9% (2 years)	83.3% (2 years)
Jiang et al. (2025)[8] **R/R** *Retrospective published*	Olverembatinib in combination with chemotherapy[g] followed by HSCT	22 (persistent MRD+: 10; R/R: 12)	Unknown	-	• 50% (after C1) • 87.5 % (after C2; 8 evaluable)	• 75% (after C1) • 87.5 % (after C2; 8 evaluable)	-	• 75% (after C1) • 87.5 % (after C2; 8 evaluable)	-	-	23 months
Xu et al. (2023)[9] **Frontline** *Phase 2 abstract*	Olverembatinib 40 mg every other day in combination with vincristine, prednisone	29 (25 evaluable)	8.03 months	-	-	96%	84%[h]	-	-	-	-

Wen et al. (2025)[10] **R/R** *Retrospective published*	Olverembatinib 40 mg every other day monotherapy OR in combination with chemotherapy[i] (regimen based on leukemia type) followed by allogeneic HCT (only if response achieved and eligible)	BP-CML: 19[j]	5.6 months	26.3%	10.5%	63.2% (day 28)	-	-	23% (1-year probability)	DFS: 52% (1-year probability)	75.6% (1-year probability)
		Ph+ ALL: 40	8.3 months	-	-	92.5% (day 28)	55%	75%	80.2% (1-year probability)	80.3% (1-year probability)	93.3% (1-year probability)
Bao et al. (2026)[11] **R/R** *Retrospective published*	Olverembatinib 30 mg or 40 mg every other day monotherapy or in combination with chemotherapy[o]	75 (LBP-CML: 26; Ph+ ALL: 49)[p]	18 months	69%	49%	78% (day 28)	49%	-	• Median: 8 months • 28% (2-year probability)	-	• Median: 18 months • 43% (2-year probability)
Liu et al. (2024)[12] **R/R** *Retrospective published*	Olverembatinib 40 mg every other day in combination with chemotherapy[q]	31 (MRD+: 17; R/R: 14)	16.3 months	-	-	RR cohort (71.4% at median time of 1.1 month)	41.9%	51.7%	Median: 6.5 months	-	Median: 11.5 months
Li et al. (2023)[13] **R/R** *Retrospective abstract*	Olverembatinib 30 or 40 mg every other day in combination with chemotherapy[r]	31 (15 R/R and 16 with molecular resistance	R/R cohort (8 months) Molecular resistance cohort (9 months)	-	-	R/R cohort (86% after induction)	Molecular resistance cohort (50%))	-	-	R/R cohort (52% at 1 year) Molecular resistance (67% at 1 year)	R/R cohort (68% at 1 year) Molecular resistance (93% at 1 year)
Zhu K. et al. (2023)[14] **Frontline** *Retrospective abstract*	Olverembatinib 40 mg every other day in combination with chemotherapy[s]	13	8.97 months	-	-	100%	• Day 14: 15.4% • Day 30: 38.5% • Day 60: 61.3% • Day 90: 84.6%	-	-	-	Median: not reached
Lou et al. (2022)[15] **Frontline** *Retrospective abstract*	Olverembatinib 40 mg every other day in combination with chemotherapy[t]	12	5 months	-	-	-	60% (4 weeks) 100% (8 weeks)	-	-	-	-
Zhang J. et al. (2024)[16] **R/R** *Retrospective abstract*	Olverembatinib + lisaftoclax + dexamethasone[u]	9 (age < 18 years)	-	-	-	33.3% (at end of olverembatinib monotherapy phase) 83.3% (at end of olverembatinib + lisaftoclax combination course)	-	71.4% (5 of 7 evaluable pts)	-	-	-
Zhao et al. (2023)[17] **Frontline and R/R** *Retrospective abstract*	Olverembatinib in combination with chemotherapy[v]	33	-	-	-	100% (after course 1)	-	66.67% (after course 1)	-	-	-

a. Combined regimens included intensive chemotherapy, blinatumomab, allogeneic hematopoietic cell transplant (HCT), chimeric antigen T cell (CAR-T)
b. Acute leukemia cohort only; see Table 1 for data on CP-CML cohort; the acute leukemia cohort contains: AP-CML: 9; BP-CML: 6, Ph+ ALL: 3
c. Induction therapy comprised 3 cycles of VD or VDP: vincristine, dexamethasone, and daunorubicin; consolidation alternated high-dose methotrexate with cytarabine; maintenance therapy of mercaptopurine plus methotrexate and VP was alternated for 12 cycles at standard dosages
d. Before starting induction therapy, patients may receive prephase treatment with prednisone at a dose of 1mg/kg/day for 3 to 5 days to reduce tumor burden; by the cut-off date, 20 patients (25.3%) had undergone autologous HCT, 24 patients (30.4%) had undergone allogeneic HCT, 28 patients (35.4%) received chemotherapy, and 7 patients (8.9%) received blinatumomab as consolidation.
e. One patient excluded due to cerebral infarction on day 13
f. Patients underwent either autologous HCT or allogeneic HCT; if no HCT, olverembatinib-based maintenance therapy was initiated
g. Chemotherapy included blinatumomab; MA (methotrexate + cytarabine); inotuzumab ozogamicin; VIP (vincristine + idarubicin + prednisone); DECM (decitabine +

cyclophosphamide + etoposide + mitoxantrone); CVAD (cyclophosphamide + vincristine + doxorubicin + prednisone); VCP (vincristine + cyclophosphamide + prednisone); of note, some regimens were not listed in the publication

h. Overall CMR at any time

i. Patients diagnosed with myeloid blast phase received olverembatinib either as monotherapy or in combination with systemic chemotherapy or blinatumomab. Chemotherapy regimens included the HA regimen (homoharringtonine and cytarabine) and hypomethylating agents such as azacitidine or decitabine. Patients with lymphoid blast phase were treated with either monotherapy or a combination therapy involving the vincristine, daunorubicin, and prednisone (VDP) regimen or blinatumomab. Patients with Ph+ ALL received olverembatinib in combination with blinatumomab, systemic chemotherapy, or radiotherapy (for extramedullary leukemia only). Chemotherapy regimens included the VDP regimen and the hyper-fractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone (hyper-CVAD) regimen

j. BP-CML cohort included 11 MBP, 7 LBP and 1 MPAL

k. Among evaluable patients, the rates were achieved at any time point during follow-up

l. CMR was defined as follows: Zhu et al. (*BCR::ABL1* transcripts ≤ 0.01%); Gong et al. (undetectable *BCR::ABL1* transcripts with sensitivity of up to 0.001%); Zhang et al. (reference 5; not defined); Tang et al. (*BCR::ABL1* transcripts ≤ 0.01%); Zhang et al. (reference 7; *BCR::ABL1* transcripts by RT-PCR (< 0.01% and flow cytometry (FACS) < 0.1 %); Xu et al. (*BCR::ABL1* transcripts ≤ 0.01%); Wen et al. (*BCR::ABL1* transcripts ≤ 0.01%); Bao et al. (*BCR::ABL1* transcripts ≤ 0.01%); Liu et al. (real-time quantitative PCR (RT-qPCR) at a sensitivity of 0.001%); Li et al. (*BCR::ABL1* transcripts ≤ 0.01%); Zhu, K. et al. (undetectable *BCR::ABL1* transcripts by PCR analysis at a sensitivity of 0.01%, and continuously monitored on day 14, day 30, day 60 and day 90 after receiving olverembatinib); Lou et al. (*BCR::ABL1* transcripts ≤ 0.01%)

m. MRD analysis completed using the following methods: Chen et al., POLARIS-1 (*BCR::ABL/ABL1* ≤ 0.01% by qPCR); Gong et al. (real-time quantitative PCR, eight-color flow cytometry (FCM), and next-generation sequencing (NGS) based immunosequencing assays for immunoglobulin (IG) or T-cell receptor (TR) rearrangements with sensitivities of up to 0.001% , 10^{-5}, and 10^{-6}, respectively); Tang et al. (ten-color FCM, sensitivity of $<1 \times 10^{-4}$): Jiang et al (qPCR ≤0.01%); Wen et al. (eight-color FCM with sensitivity of up to 0.01%); Liu et al. (multiparameter flow cytometry at a sensitivity of at least 0.01% and quantitative PCR at a sensitivity of up to 0.001%); Zhao et al. (not reported)

n. EFS was defined as follows: Zhu et al. (time from diagnosis until relapse or death from any other cause); Gong et al. (time from diagnosis to induction failure, relapse, death from any cause, or the last follow-up, whichever comes earliest); Wen et al. (time from initiation of olverembatinib to earliest occurrence of any of the following events: failure at day 28, relapse, treatment discontinuation, or death); Bao et al. 2026. (interval from the start of olverembatinib-based therapy to no response by 28 days, relapse, death from any cause or censored at the last follow-up); Liu et al. (time from the start of treatment with olverembatinib to relapse, no response, death from any cause, or last follow-up)

o. Chemotherapy regimens included vincristine and prednisone (VP) or vincristine, daunorubicin and prednisone (VDP), hyperfractionated cyclophosphamide, vincristine, doxorubicin and dexamethasone (hyper-CVAD), immunotherapies such as blinatumomab, inotuzumab and chimeric antigen receptor T-cells.

p. Olverembatinib monotherapy (n = 8); olverembatinib + chemotherapy (n = 67); total 74 evaluable patients

q. Chemotherapy consisted of VP-based regimens; allogeneic HCT was recommended for all eligible patients

r. Chemotherapy consisted of VP or hyper-CVAD; 2 patients in molecular resistance cohort received olverembatinib monotherapy; eligible patients received allogeneic HCT

s. Chemotherapy according to PDT-ALL-2016 protocol, a GRAALL-backbone pediatric-inspired regimen

t. Chemotherapy consisted of vindesine and dexamethasone/prednisone followed by consolidation with allogeneic HCT, or blinatumomab, or intensive chemotherapy at discretion of investigator and patient preference

u. Olverembatinib was administered orally at 40 mg every other day for 2 weeks (Days 1-14), followed by same dose of olverembatinib in combination with lisaftoclax at an assigned dose of 200/400/600 mg daily on D13-42 (a 3-day dose ramp-up from D13-15 was needed). Dexamethasone 6 mg/m^2/day was administered orally QD from D15-42

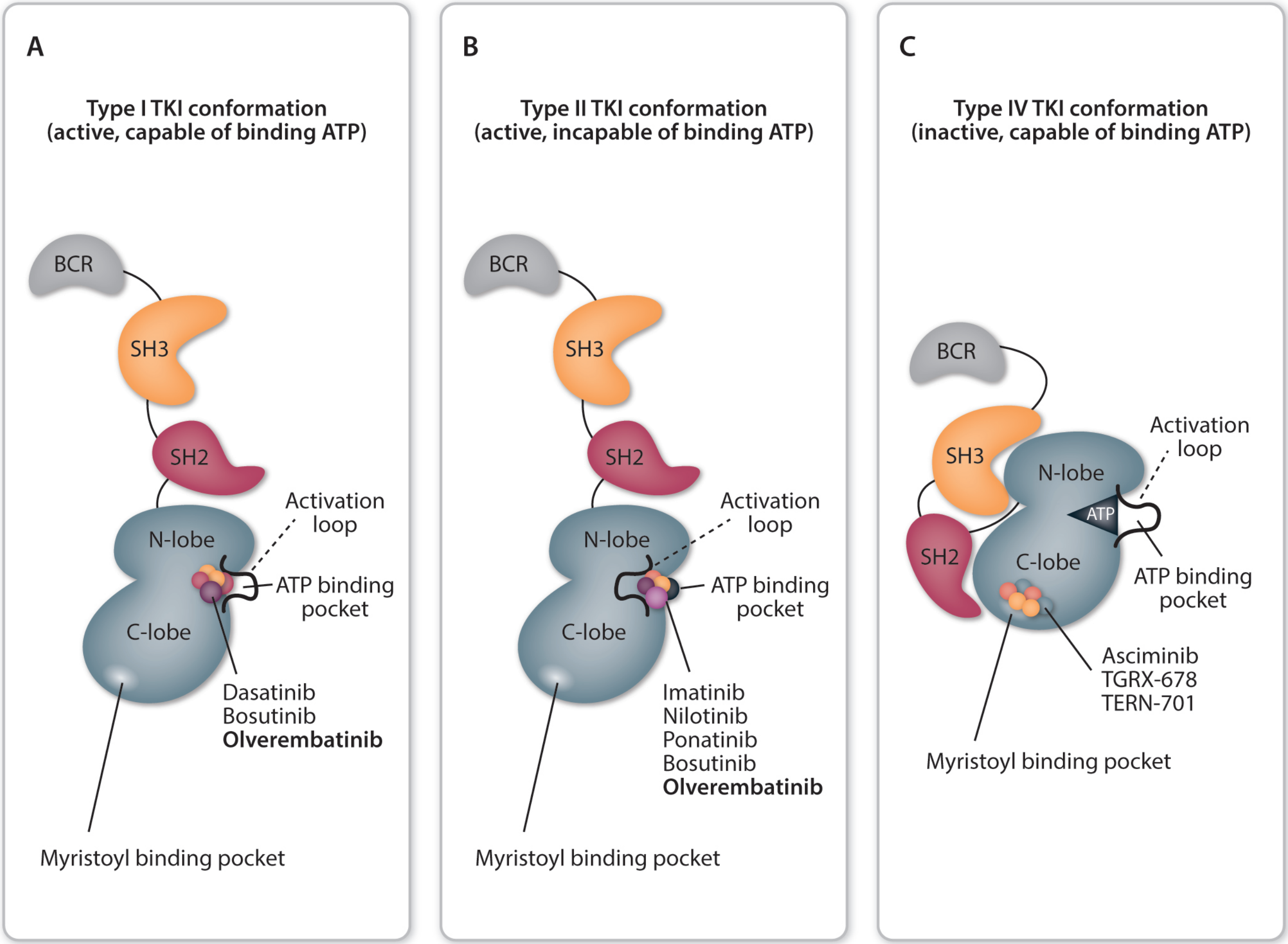
v. Chemotherapy consisted of blinatumomab, inotuzumab, VD (vincristine, dexamethasone), VDCP (vincristine, daunorubicin, cyclophosphamide, prednisone), or CAM(cyclophosphamide, cytarabine, 6-mercaptopurine)

Abbreviations: C= cycle; D= day; CMR = complete molecular response, depending on study this includes undetectable transcripts with assay sensitivity of 0.01%, 0.0032% or 0.001% as defined by each study; AP = accelerated phase; BP = blast phase; Ph+ ALL = Philadelphia-chromosome positive acute lymphoblastic leukemia; CR = complete remission; CRi = complete remission with incomplete hematologic recovery; MRD = minimal/measurable residual disease; EFS = event-free survival, RFS = relapse-free survival, OS = overall survival; HCT=hematopoietic cell transplant; R/R = relapsed/refractory; MBP = myeloid blast phase; LBP = lymphoid blast phase; MPAL = mixed phenotype acute leukemia; DFS = disease-free survival; C = cycle; PCR = polymerase chain reaction; FCM = flow cytometry; NGS = next-generation sequencing; CCyR = complete cytogenetic response; MMR = major molecular response, *BCR::ABL1* transcripts ≤ 0.1%.

[1]Zhu Y, Huang J, Wang Y, et al. Ann Hematol. 2024;103(11):4643-4648. [2]Jabbour E, Oehler VG, Koller PB, et al. JAMA Oncol. 2025;11(1):28-35. [3]Chen S, WU Y, Weng J, et al. Blood 2025; 146 (Supplement 1): 1574. [4]Gong X, Liu W, Liu Y, et al. Leukemia. 2025;39(8):1838-1847. [5]Zhang X, Zhao Y, Zhai W, et al. Ann Hematol. 2025;104(12):6463-6466. [6]Tang H, Jia W, Jia S, et al. Am J Hematol. 2024;99(6):1177-1179. [7]Zhang X, Cao Y, Wei J, et al. Am J Hematol. 2025;100(10):1924-1928. [8]Jiang X, Zhou M, Ma J, et al. Front Med (Lausanne). 2025;12:1662512. [9]Xu G, Lou Y, Wang H, et al. Blood 2023; 142 (Supplement 1): 4205. [10]Wen Z, Liu Z, Ye X, et al. Front Immunol. 2025;16:1546371. [11]Bao M, Huang J, Li Z, et al. Clin Lymphoma Myeloma Leuk. Published online February 16, 2026. doi:10.1016/j.clml.2026.02.005; [12]Liu W, Wang C, Ouyang W, et al. Br J Haematol. 2024;205(6):2228-2233. [13]Li Z, Ting Z, Hu L, Duan W, Jiang Q. Blood. 2023; 142 (Supplement 1): 5895. [14]Zhu K, Zhang T, Wang Z, et al. HemaSphere. 2023;7(S3):e68180f9. [15]Lou Y, Xu G, Wang H, et al. Blood. 2022;140(Supplement 1):11683–4. [16]Zhang J, Wang J, Guo H, et al. Blood. 2024; 144 (Supplement 1): 1443. [17]Zhao Y, Zhai W, Pang A, et al. Blood. 2023;142(Supplement 1):5893.

Figure Legends

Figure 1. Structural conformation of BCR::ABL1 as it binds to various TKIs or allosteric inhibitors. Aspartate-Phenylalanine-Glycine (Asp-Phe-Gly), called DFG, is a highly conserved motif at the start of the activation loop, which regulates kinase activity by switching between an “in" conformation capable of binding ATP and an “out" conformation that is incapable of binding ATP. (a) Dasatinib binds to BCR::ABL1 in the “DFG in” conformation (Type I TKI). (b) Imatinib, nilotinib, and ponatinib bind to BCR::ABL1 in the “DFG out” conformation (Type II TKI). Bosutinib and olverembatinib can bind to both conformations. (c) Allosteric inhibitors such as asciminib bind to the myristoyl pocket in BCR::ABL1 and induce an inactive conformation with the SH2-SH3 clamp complex that is capable of binding ATP.


A
Type I TKI conformation
(active, capable of binding ATP)
BCR
SH3
SH2
N-lobe
C-lobe
Activation loop
ATP binding pocket
Dasatinib
Bosutinib
Olverembatinib
Myristoyl binding pocket
B
Type II TKI conformation
(active, incapable of binding ATP)
BCR
SH3
SH2
N-lobe
C-lobe
Activation loop
ATP binding pocket
Imatinib
Nilotinib
Ponatinib
Bosutinib
Olverembatinib
Myristoyl binding pocket
C
Type IV TKI conformation
(inactive, capable of binding ATP)
BCR
SH3
SH2
N-lobe
C-lobe
ATP
Activation loop
ATP binding pocket
Asciminib
TGRX-678
TERN-701
Myristoyl binding pocket