SAFETY AND PRELIMINARY EFFICACY OF OLVEREMBATINIB (HQP1351) COMBINED WITH LISAFTOCLAX (APG-2575) IN CHILDREN AND ADOLESCENTS WITH RELAPSED/REFRACTORY PHILADELPHIA-POSITIVE ACUTE LYMPHOBLASTIC LEUKEMIA (R/R PH+ ALL): RESULTS OF A PHASE 1B STUDY

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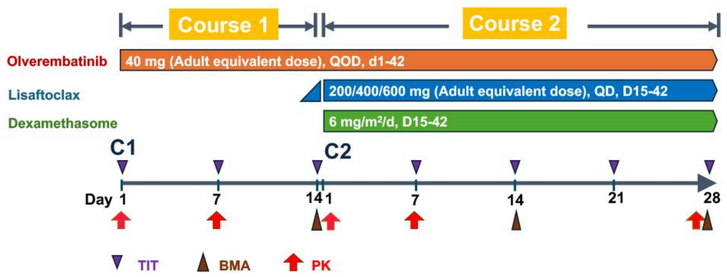
INTRODUCTION

- Pediatric Philadelphia chromosome–positive acute lymphoblastic leukemia (Ph+ ALL) is associated with poor outcomes after tyrosine kinase inhibitor (TKI) failure.
- Olverembatinib is a third-generation BCR::ABL1 inhibitor that is active against resistant mutations including T315I.
- Lisaftoclax is a novel selective BCL-2 inhibitor with promising antileukemic activity.
- We evaluated the safety and preliminary efficacy of olverembatinib plus lisaftoclax in pediatric patients with relapsed/refractory (R/R) Ph+ ALL.

METHODS

- This ongoing open-label, phase 1b dose-escalation and expansion study (NCT05495035) enrolled pediatric patients (<18 years) with R/R Ph+ ALL resistant or intolerant to ≥1 prior TKI.
- A standard "3+3" design governed dose escalation. Patients initially received olverembatinib monotherapy (40 mg adult-equivalent dose [AED], every other day [QOD]) on days 1–14, followed by combination treatment with lisaftoclax (200, 400, or 600 mg AED once daily after a 3-day ramp-up) and dexamethasone (6 mg/m²/day on days 15–42) (Figure 1).

Figure 1. Schematic workflow



Baseline characteristics (N = 17)

	Lisaftoclax 200 mg	Lisaftoclax 400 mg	Lisaftoclax 600 mg	Overall
Population	**4**	**4**	**9**	**17**
Age, yr				
Median (range)	12.5 (11; 13)	14.5 (9; 15)	13.0 (9; 14)	13.0 (9; 15)
Sex, n (%)				
Female	3 (75.0)	0	5 (55.6)	8 (47.1)
Male	1 (25.0)	4 (100.0)	4 (44.4)	9 (52.9)
Karnofsy/Lansky performance scale, n (%)				
100	4 (100.0)	4 (100.0)	7 (77.8)	15 (88.2)
90	0	0	1 (11.1)	1 (5.9)
80	0	0	1(11.1)	1 (5.9)
Baseline status, n (%)				
Relapsed/refractory	3 (75.0)	4 (100.0)	7 (77.8)	14 (82.4)
Intolerant of prior TKI	3 (75.0)	0	3 (33.3)	6 (29.4)
Prior TKI, n (%)				
Imatinib	1 (25.0)	3 (75.0)	2 (22.2)	5 (29.4)
Dasatinib	4 (100.0)	3 (75.0)	8 (88.9)	16 (94.1)
Prior therapy lines, n (%)				
1	2 (50.0)	2 (50.0)	7 (77.8)	12 (70.6)
2	2 (50.0)	2 (50.0)	2 (22.2)	5 (29.4)
Extramedullary involvement, n (%)				
CNS	2 (50.0)	1 (25.0)	2 (22.2)	5 (29.4)
Other sites		1 (25.0)		1 (5.9)
BCR::ABL1 mutation, n (%)				
p.F317L	1 (25.0)	0	0	1 (5.9)
p.T315I	0	2 (50.0)	2 (22.2)	4 (23.5)
p.L248N	0	0	1 (11.1)	1 (5.9)

EFFICACY

Olverembatinib monotherapy (days 1–14)

55.6%
ORR (CR + CRi)
5/9 patients • EOM

Olverembatinib + lisaftoclax combination therapy (day 15 onward)

88.9%
ORR (CR + CRi)
8/9 patients • C2D15

25.0% → 66.7%
MRD negativity
EOM → C2D15

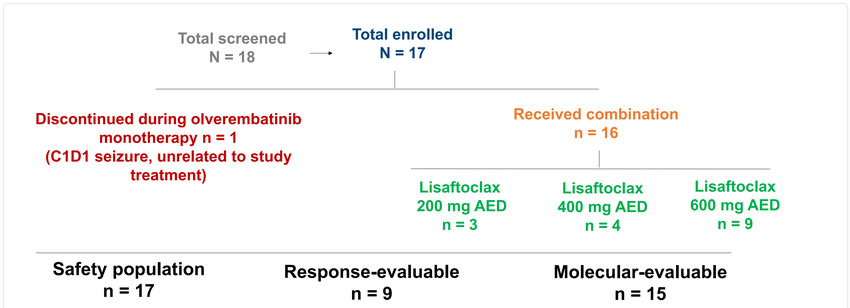
56.3%
MMR or deeper
9/16 evaluable patients • After combination therapy

CCyR increased from 40.0% at EOM to 88.9% at C2D15. Complete molecular response was achieved in approximately 20% of patients. CR, complete remission; CRi, CR with incomplete count recovery; ORR, overall response rate; CCyR, complete cytogenetic response; MRD, measurable residual disease; MMR, major molecular response; EOM, end of monotherapy; C2D15, cycle 2 day 15.

Efficacy takeaways:

- Robust antileukemic activity was observed. Following olverembatinib monotherapy, the overall response rate (ORR; CR + CRi) was 55.6% (5/9).
- After combination treatment with lisaftoclax, ORR was 88.9% (8/9); all 8 responders achieved CR by C2D15. Response depth also improved substantially, with the complete cytogenetic response rate (CCyR) increasing from 40.0% at the end of monotherapy (EOM) to 88.9% at C2D15 and MRD negativity increasing from 25.0% to 66.7%.
- After combination therapy, MMR or deeper responses were achieved in 56.3% (9/16) of evaluable patients, including patients with baseline ABL1 KD mutations.

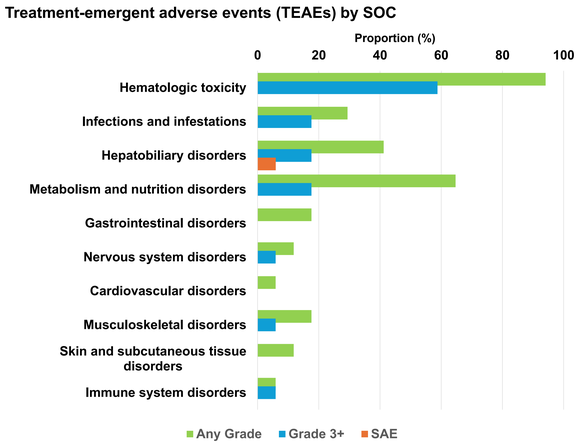
PATIENT DISPOSITION

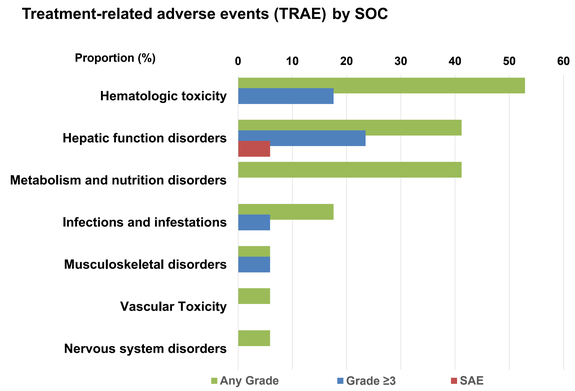


- Between September 2022 and February 2026, 18 pediatric patients with Ph+ ALL were screened, of whom 17 were enrolled and received study treatment (lisaftoclax AED 200 mg, n = 4; 400 mg, n = 4; 600 mg, n = 9).
- The median age was 13.0 years (range, 9–15).
- Baseline *BCR::ABL1* kinase domain mutations were identified in 6 of 15 evaluable patients (40%), including T315I (n = 4), L248N (n = 1), and F317L (n = 1).
- One patient discontinued treatment on cycle 1 day 1 because of a seizure deemed unrelated to study treatment.
- Sixteen eligible patients received lisaftoclax at AEDs of 200 mg (n = 3), 400 mg (n = 4), or 600 mg (n = 9); 14 had R/R disease, and 6 were intolerant to prior TKI therapy (Table 1).

SAFETY

Figure 2. Summary of adverse events by system organ class (SOC).





Safety takeaways:

- The safety profile was manageable. Grade ≥ 3 TEAEs and TRAEs occurred in 70.6% and 64.7% of patients, respectively.
- Two patients discontinued treatment because of adverse events, including one unrelated seizure and one lisaftoclax-related hepatotoxicity. Hepatic adverse events were generally manageable, and no treatment-related deaths occurred (Figure 2).

CONCLUSIONS

- Olverembatinib plus lisaftoclax demonstrated rapid, deep, and durable responses with a manageable safety profile in pediatric patients with R/R Ph+ ALL.
- The chemotherapy-free combination showed promising antileukemic activity across *BCR::ABL1* kinase domain mutations, including evidence of CNS penetration.
- These findings support the potential of this oral dual-targeted regimen as an effective treatment strategy for this high-risk population.

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