UPDATED RESULTS OF POLARIS-1 (PART 1), A GLOBAL REGISTRATIONAL PHASE 3 STUDY: OLVEREMBATINIB COMBINED WITH LOW-INTENSITY CHEMOTHERAPY IN NEWLY DIAGNOSED PH+ ALL

Suning Chen,[1] Yu Wu,[2] Jianyu Weng,[3] Cheng Zhang,[4] Hongsheng Zhou,[5] Vadim Doronin,[6] Mei Hong,[7] Ying Wang,[8] Xudong Wei,[9] Yurii Osipov,[10] Yulia Alexeeva,[10] Bo Huang,[11] Wei Chu,[11] Lichuang Men,[11] Hengbang Wang,[11] Lixin Jiang,[12] Dengkun Xiong,[11] Weili Zhao,[13] and Yifan Zhai,[11,12,14*]

[1]The First Affiliated Hospital of Soochow University, Suzhou, China; [2]West China Hospital Sichuan University, Chengdu, China; [3]Guangdong Provincial People's Hospital, Guangzhou, China; [4]Xinqiao Hospital Army Medical University, Chongqing, China; [5]Nanfang Hospital, Guangzhou, China; [6]Moscow SBHI City Clinical Hospital Named After S.P. Botkin of the Moscow Healthcare Department, Moscow, Russia; [7]Union Hospital Tongji Medical College Huazhong University of Science & Technology, Wuhan, China; [8]Institute of Hematology & Blood Diseases Hospital, Chinese Academy of Medical Sciences, Tianjin, China; [9]Henan Cancer Hospital, Zhengzhou, China; [10]National Medical Research Center Named After V.A. Almazov, Saint Petersburg, Russia; [11]Ascentage Pharma (Suzhou) Co., Ltd., Suzhou, China; [12]Ascentage Pharma Group Inc., Rockville, MD, United States; [13]Shanghai Institute of Hematology, State Key Laboratory of Medical Genomics, National Research Center for Translational Medicine at Shanghai, Ruijin Hospital Affiliated to Shanghai Jiao Tong University School of Medicine, Shanghai, China; [14]Guangzhou Healthquest Pharma Co., Ltd., Guangzhou, China. *Address correspondence to: yzhai@ascentage.com

INTRODUCTION

- Philadelphia chromosome–positive acute lymphoblastic leukemia (Ph+ ALL) is the most common molecular subtype of adult ALL and is associated with a high risk of relapse and poor clinical outcomes. Targeted therapies have become an integral component of treatment strategies for this disease.
- Olverembatinib is a third-generation BCR::ABL1 tyrosine kinase inhibitor that exhibits potent activity against both wild-type and mutant *BCR::ABL1*, supporting its potential role in the management of Ph+ ALL.
- The global phase 3 POLARIS-1 study (NCT06051409) was designed to evaluate the efficacy and safety of olverembatinib combined with reduced-intensity chemotherapy in patients with newly diagnosed Philadelphia chromosome–positive acute lymphoblastic leukemia (ND Ph+ ALL).

METHODS

- Part A of this multicenter, phase 3 study enrolled patients with ND Ph+ ALL with *BCR::ABL1* rearrangements, ECOG performance status ≤2, and adequate organ function. Patients received olverembatinib (30 or 40 mg) orally every other day in 28-day cycles.
- Induction therapy consisted of three cycles of vincristine + dexamethasone (VD) or VD + daunorubicin (VDP), followed by consolidation with alternating cycles of high-dose methotrexate and cytarabine, and subsequent maintenance therapy with mercaptopurine plus methotrexate alternating with VP.
- The primary endpoint was MRD negativity (BCR::ABL1/ABL1 ≤0.01% by qPCR) at the end of induction. Correlative analyses were conducted to assess the impact of baseline genomic alterations on treatment response.

RESULTS

- As of January 10, 2026, 55 patients with ND Ph⁺ ALL were enrolled in Part 1.
- Fifteen patients received olverembatinib 40 mg QOD, and 40 received 30 mg QOD.
- 49 received olverembatinib + VD and 6 received olverembatinib + VDP
- The mean treatment duration of all patients in Part 1 was 11.6 months.

Table 1. Baseline characteristics and disposition

	Overall (n = 55)
Age, yr	
Median (range)	43.0 (18-70)
Sex, n (%)	
Female	35 (63.6)
Male	20 (36.4)
Race, n (%)	
Asian	50 (90.9)
White	5 (9.1)
BCR::ABL1 type, n (%)	
P190	36 (65.5)
P210	16 (29.1)
P190+P210	2 (3.6)
P230	1 (1.8)
Treatment discontinuation, n (%)	
No	29 (52.7)
Yes	26 (47.3)
Reasons for treatment discontinuation, n (%)	
Adverse events	6 (10.9)
Consent withdrawal	6 (10.9)
Hematopoietic stem cell transplantation	5 (9.1)
Death	2 (3.6)
Investigator decision	1 (1.8)
Lost to follow-up	1 (1.8)
Lack of efficacy	1 (1.8)
Progressive disease	4 (7.3)

EFFICACY

Figure 4. Key efficacy highlights (54 efficacy-evaluable patients).

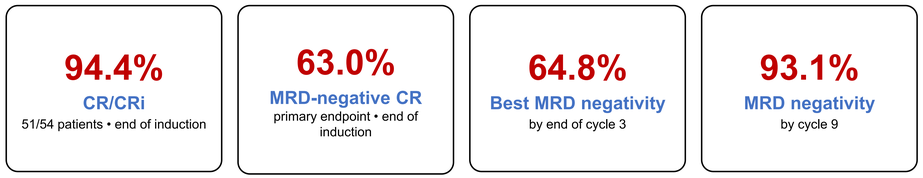
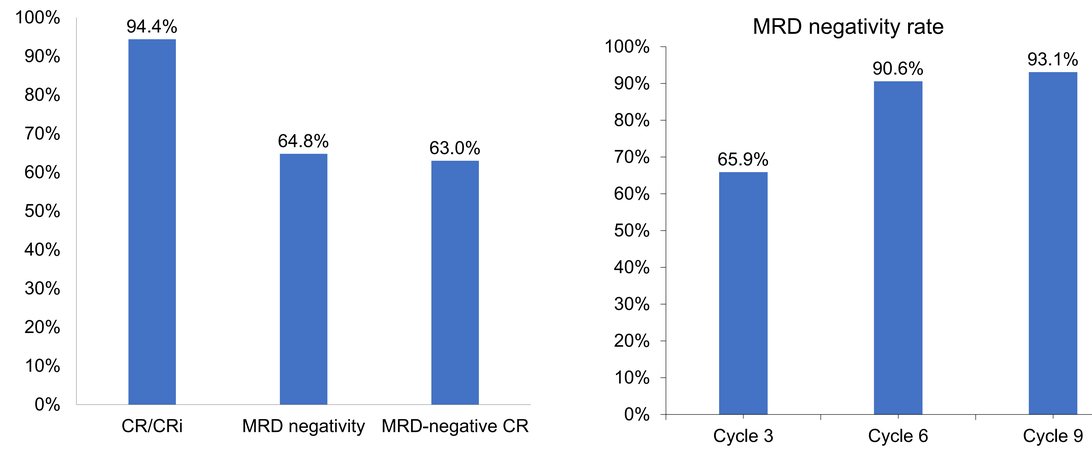


Figure 1. Response rates by treatment cycle



Efficacy takeaways:

Among 54 efficacy-evaluable patients:

- CR or CR with incomplete hematologic recovery (CRi) was achieved in 51 patients (94.4%) by the end of induction.
- The rate of minimal residual disease (MRD) negativity increased over time (Figure 1).
- After three cycles, the best MRD-negativity rate was 64.8%, and the MRD-negative CR rate was 63.0%.

SAFETY

Figure 2. TEAEs with incidence ≥ 30%.

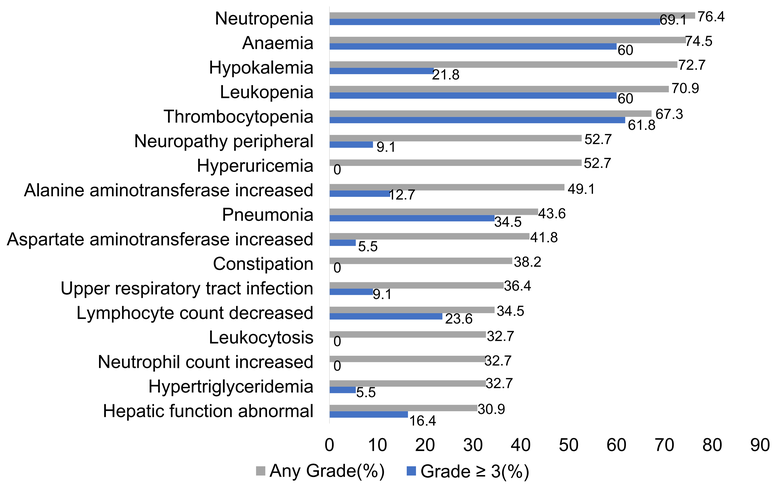


Table 2. Summary of TEAEs

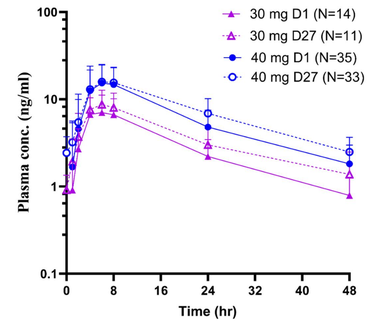
	Overall (n = 55)
Any TEAE, n (%)	55 (100)
Grade ≥ 3	50 (90.9)
Any SAE	36 (65.5)
Any TEAE leading to discontinuation of olverembatinib	8 (14.5)
Any TEAE leading to death	2 (3.6)
Any TRAE, n (%)	46 (83.6)
Grade ≥ 3	24 (43.6)
Any serious adverse reaction	11 (20.0)
Any TRAE leading to discontinuation of olverembatinib	3 (5.5)
Any TRAE leading to death	0

Safety takeaways:

- Most treatment-emergent adverse events (TEAEs) were grade 1/2 (Figure 2).
- Olverembatinib + chemotherapy was generally well tolerated (Table 2).
- Fatal TEAEs (n = 2): 1 pneumonia (unrelated); 1 pulmonary edema with septic shock (unlikely related).
- Grade 2 coronary artery disease in 1 patient (possibly related to olverembatinib).

PHARMACOKINETIC (PK)/BIOMARKER DATA

Figure 3. Mean olverembatinib plasma concentration-time profile.



- The PK profile of olverembatinib in combination with chemotherapy was comparable to that observed with monotherapy (Figure 3).
- Copy number alterations in *IKZF1, CDKN2A/B, PAX5, PAR1, EBF1, ETV6, BTG1*, and *RB1* were assessed at baseline using multiplex ligation-dependent probe amplification (MLPA) and next-generation sequencing (NGS).
- Among 50 evaluable patients, 10 harbored the *IKZF1*^{plus} genotype; of these, 9 achieved MRD-negative status by the end of induction, while 1 was not evaluable for efficacy.
- Notably, all 7 patients with concurrent-*IKZF1* and *BTG1* deletions achieved MRD negativity during the induction period.

CONCLUSIONS

- In patients with ND Ph+ ALL, including those with high-risk genomic features, olverembatinib combined with chemotherapy achieved a 63% MRD-negative complete remission (CR) rate after induction therapy.
- Treatment was associated with a favorable safety profile and permitted an extended therapeutic window.

ACKNOWLEDGMENTS

We thank all patients who participated in this study, their families, and the investigators and study team members. Ashutosh K. Pathak, MD, PhD, MBA, FRCP (Edin.), Stephen W. Gutkin, Ndiya Drew, PhD, and Paul O. Fletcher, PhD, of Ascentage Pharma Group Inc., provided editorial support.