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Results from patient-derived xenograft models support co-administration of allopurinol and 6-mercaptopurine to reduce hepatotoxicity and improve event-free survival in pediatric acute lymphoblastic leukemia

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Author contributions

SHS and XXC designed research. YXM, QZ, MW and ZW collected the data. YXM, QZ, JJW and CCC conducted the animal experiments. YXM, JHC, XXC and SHS analyzed the data. YXM, MW, JHC, YJT and SHS wrote the manuscript. All authors approved the final typescript, take responsibility for the content, and agree to submit for publication. YXM, QZ, MW, and JHC contributed equally as first authors. The order of co–first authors was based on contribution.

Competing Interests

The authors declare no competing financial interests.

The prognosis of pediatric acute lymphoblastic leukemia (ALL) has significantly improved over the past decades. Maintenance therapy, with 6-mercaptopurine (6-MP) and methotrexate (MTX) as its cornerstone drugs, is crucial for achieving long-term remission. However, the clinical use of 6-MP is often compromised by hepatotoxicity related treatment interruptions or dose reductions, which potentially increase the risk of relapse. These challenges are closely linked to the complex and variable metabolism of purines among individuals.[1] To address this challenge, allopurinol, a xanthine oxidase inhibitor, has been proposed as an adjunct therapy to optimize 6-MP metabolism and mitigate hepatotoxicity. Previous studies have shown that allopurinol effectively reduces liver toxicity and modulates thiopurine metabolism,[2-5] but its impact on long-term outcomes remains insufficiently explored. Understanding whether allopurinol can improve tolerability while maintaining the therapeutic efficacy of 6-MP is critical for refining ALL maintenance therapy strategies. To address this gap, we utilized Patient-derived xenografts (PDX) models to evaluate the impact of adding allopurinol on survival in mice, and conducted a large retrospective study to assess whether addition of allopurinol in maintenance therapy influences the prognosis of children with ALL and to evaluate the safety of allopurinol in this setting.

Using preclinical PDX models established from four different ALL patient samples, we compared the survival outcomes between mice receiving combination therapy (halved 6-MP with allopurinol) and those receiving full-dose 6-MP monotherapy. Our results demonstrated the life span in combination group were comparable to those in the monotherapy group (Figure 1A). Importantly, we observed a significant shift in thiopurine metabolism, with higher DNA-incorporated thioguanine (DNA-TG) levels (associated with antileukemic effects)[6] and reduced 6-methylmercaptopurine (6-MMP) levels (associated with hepatotoxicity)[7] in combination group (Figure 1B). In the AL5611 PDX, the spleen size and weight in the combination group were smaller than in the monotherapy group, and the leukemia burden in the spleen and bone marrow was also lower (Figure 1C). These results highlight the potential of allopurinol to modulate 6-MP metabolism effectively, supporting its clinical evaluation in ALL patients to optimize therapy without compromising survival outcomes.

We conducted a retrospective cohort study at the Shanghai Children's Medical Center (SCMC) affiliated to Shanghai Jiao Tong University School of Medicine between December 2014 and June 2023. All patients were in the cohort of Chinese Children’s Cancer Group (CCCG)-ALL-2015 trial (clinical trial number: ChiCTR-IPR-14005706).[8] Inclusion criteria encompassed pediatric ALL patients who underwent continuation therapy as defined in the protocol. High-risk patients and those who did not proceed to continuation therapy were excluded. The study was approved by the Institutional Review Board of SCMC, (No. SCMCIRB-K2024169-1).

A total of 752 pediatric ALL patients were included in the analysis, among whom 459 experienced hepatotoxicity, defined as ALT > 2× ULN or elevated bilirubin levels. Allopurinol co-treatment was initiated in 149 patients according to their liver function and hematology parameter: (1) repeated ALT levels exceeding 10× ULN after resuming 6-MP therapy following temporary discontinuation, or (2) persistent ALT elevation between 2× and 10× ULN for more than 8 weeks despite 6-MP dose adjustments, accompanied by WBC counts remaining above the target range. The median time to allopurinol initiation from the initial detection of liver function abnormalities was 15.6 weeks (approximately 4 months). The demographics and clinical characteristics are summarized in Supplemental Table 1.

Patients in the allopurinol group began treatment with a median allopurinol dose of 35.7 (IQR: 32.8, 39.9) mg/m^2/day and a median duration of use of 47 (IQR: 28, 63) weeks. To minimize the risk of excessive myelosuppression, the 6-MP dose was reduced upon initiation of allopurinol, from a median dose of 49.3 (IQR: 40.3, 58.2) mg/m^2/day to 25.0 (IQR: 18.7, 32.5) mg/m^2/day, approximately half the dose before allopurinol. MTX dosing was also reduced concurrently by one-third. Subsequent dose adjustments of 6-MP were made based on regular blood count monitoring.

The impact of allopurinol co-treatment on event-free survival (EFS) was evaluated using time-dependent multivariate Cox regression analyses, treating allopurinol initiation as a time-dependent variable. The analysis revealed a significant improvement of EFS among allopurinol co-treated patients compared to those didn't receive allopurinol (adjusted hazard ratio [aHR] = 0.29, 95% CI: 0.10–0.80, P = 0.017, Table 1 and Figure 2B). To address potential confounding factors, propensity score matching (PSM) was also conducted to minimize selection bias and ensure comparability between the allopurinol and non-allopurinol groups. After PSM, allopurinol co-treatment remained significantly associated with improved EFS (aHR = 0.25, 95% CI: 0.09–0.69, P = 0.008, Supplemental Table 2, Supplemental Figure 1). These findings, consistent with multivariable Cox regression analyses, confirm that allopurinol co-treatment is an independent prognostic factor for EFS.

To explore the metabolic effects of allopurinol co-treatment, DNA-TG levels in bone marrow were analyzed using available stored leftover frozen bone marrow samples. Allopurinol co-treatment led to significant changes in thiopurine metabolism. DNA-TG levels in bone marrow increased by 3.4-fold (from 131 to 444 fmol/µg DNA, $P < 0.001$, Figure 2E). Liver function also improved markedly after allopurinol initiation. Prior to treatment, ALT levels in the allopurinol group averaged ~500 U/L. Following allopurinol co-treatment, ALT levels decreased significantly in the first month and stabilized at a lower level after the second month and remained consistent thereafter, indicating sustained liver function improvement (Figure 2F, 2G).

In our study, allopurinol co-treatment significantly improved WBC control, with the proportion of patients maintaining WBC within the target range increasing from 34.2% to 68.5% ($P < 0.001$, Figure 2C). Although leukopenia (WBC $<2\times10^9$/L) increased from 37.6% to 53.7% ($P = 0.005$), this did not result in a higher incidence of infections. This observation underscores the safety of allopurinol co-treatment when combined with close monitoring and dose adjustments.

Our study is the first to evaluate the impact of allopurinol co-treatment on EFS in pediatric ALL patients, integrating clinical and preclinical data to highlight its dual benefits in mitigating hepatotoxicity and improving prognosis. While the addition of allopurinol has been studied to improve patient tolerance to 6-MP in both inflammatory bowel disease (IBD)[9, 10] and pediatric ALL[2-5] by balancing thiopurine metabolism, previous studies primarily focused on biochemical markers, such as ALT and 6-MP metabolites. Most of these findings have been based on case reports or small retrospective studies, leaving its impact on long-term outcomes, including EFS, largely unexplored. Although Källström's phase II study demonstrated a significant increase in erythrocyte 6-TGN levels after allopurinol addition,[11] direct evidence linking allopurinol co-treatment to prognosis in ALL patients has been lacking. To address this gap, our study employed a large, retrospective cohort and PDX models to provide evidence supporting the use of low-dose allopurinol in pediatric ALL patients. Our findings confirm that, as previously reported, allopurinol co-treatment effectively improves liver function in patients with hepatotoxicity, enhancing tolerance to 6-MP. More importantly, we found that patients in the allopurinol group had the best prognosis, outperforming both hepatotoxicity without allopurinol group and no hepatotoxicity group.

Previous studies have commonly used allopurinol doses of 50 mg/m^2,[3, 4, 11] finding this dose effective for modifying thiopurine metabolism and well tolerated in ALL patients, with some studies even exploring higher or fixed doses.[12-14] However, in our results from PDXs, we found that a small dose of 3 mg/kg allopurinol was sufficient to achieve desired outcomes in mice. Additionally, given the increased sensitivity to allopurinol observed in the Chinese population,[15] we are inclined to use lower doses in clinical practice. In our study, most patients received a 30-40 mg/m^2 dose of allopurinol and achieved favorable outcomes.

Based on the positive results, we recommend that for patients experiencing hepatotoxicity during maintenance therapy, a low dose of allopurinol (25-50 mg/m^2) may be considered. Simultaneously, the 6-MP dose should be halved from the pre-allopurinol dose. During the initial adjustment phase, a complete blood count should be monitored twice weekly, and the doses of 6-MP and MTX should be adjusted according to the blood counts, following the same principles. Generally, there is no need to adjust the allopurinol dosage.

Despite its retrospective nature, our study has several strengths, including a large sample size, and the incorporation of PDX models. Limitations include potential selection biases, clinician discretion in initiating allopurinol, and variability in 6-MP and MTX dose adjustments.

Furthermore, the observed increase in EFS with the allopurinol and 6-MP combination may be protocol-specific, which should be considered when applying the findings to other protocols

In conclusion, allopurinol co-treatment effectively reduces 6-MP-induced hepatotoxicity, improves WBC control, and enhances event-free survival in pediatric ALL patients. Our findings provide important evidence supporting the co-administration of allopurinol during maintenance therapy for pediatric ALL patients with hepatotoxicity. A larger randomized trial is needed to evaluate allopurinol's impact on outcomes and toxicity in pediatric ALL.

References

1. Lafolie P, Bjork O, Hayder S, Ahstrom L, Peterson C. Variability of 6-mercaptopurine pharmacokinetics during oral maintenance therapy of children with acute leukemia. Med Oncol Tumor Pharmacother. 1989;6(4):259-265.

2. Mosher N, Torkildson J, Golden C, et al. Utilization of Thiopurine Metabolites and Allopurinol in Pediatric Acute Lymphoblastic Leukemia: Consideration for an Algorithmic Approach. J Pediatr Hematol Oncol. 2022;44(2):e521-e525.

3. Lines M, Kemper RM, Wallace J, et al. Use of allopurinol to manage skewed 6-mercaptopurine metabolism in pediatric maintenance acute lymphoblastic leukemia treatment. Eur J Haematol. 2024;113(5):584-592.

4. Brackett J, Schafer ES, Leung DH, Bernhardt MB. Use of allopurinol in children with acute lymphoblastic leukemia to reduce skewed thiopurine metabolism. Pediatr Blood Cancer. 2014;61(6):1114-1117.

5. Kamojjala R, Bostrom B. Allopurinol to Prevent Mercaptopurine Adverse Effects in Children and Young Adults With Acute Lymphoblastic Leukemia. J Pediatr Hematol Oncol. 2021;43(3):95-100.

6. Nielsen SN, Grell K, Nersting J, et al. DNA-thioguanine nucleotide concentration and relapse-free survival during maintenance therapy of childhood acute lymphoblastic leukaemia (NOPHO ALL2008): a prospective substudy of a phase 3 trial. Lancet Oncol. 2017;18(4):515-524.

7. Adam de Beaumais T, Fakhoury M, Medard Y, et al. Determinants of mercaptopurine toxicity in paediatric acute lymphoblastic leukemia maintenance therapy. Br J Clin Pharmacol.

2011;71(4):575-584.

8. Yang W, Cai J, Shen S, et al. Pulse therapy with vincristine and dexamethasone for childhood acute lymphoblastic leukaemia (CCCG-ALL-2015): an open-label, multicentre, randomised, phase 3, non-inferiority trial. Lancet Oncol. 2021;22(9):1322-1332.

9. Hoentjen F, Seinen ML, Hanauer SB, et al. Safety and effectiveness of long-term allopurinol-thiopurine maintenance treatment in inflammatory bowel disease. Inflamm Bowel Dis. 2013;19(2):363-369.

10. Vasudevan A, Con D, De Cruz P, et al. Clinical trial: Combination allopurinol-thiopurine versus standard thiopurine in patients with IBD escalating to immunomodulators (the DECIDER study). Aliment Pharmacol Ther. 2024;59(4):504-514.

11. Kallstrom J, Niinimaki R, Fredlund J, et al. Effects of allopurinol on 6-mercaptopurine metabolism in unselected patients with pediatric acute lymphoblastic leukemia: a prospective phase II study. Haematologica. 2024;109(9):2846-2853.

12. Stuckert AJ, Schafer ES, Bernhardt MB, Baxter P, Brackett J. Use of allopurinol to reduce hepatotoxicity from 6-mercaptopurine (6-MP) in patients with acute lymphoblastic leukemia (ALL). Leuk Lymphoma. 2020;61(5):1246-1249.

13. Cohen G, Cooper S, Sison EA, Annesley C, Bhuiyan M, Brown P. Allopurinol use during pediatric acute lymphoblastic leukemia maintenance therapy safely corrects skewed 6-mercaptopurine metabolism, improving inadequate myelosuppression and reducing gastrointestinal toxicity. Pediatr Blood Cancer. 2020;67(11):e28360.

14. Giamanco NM, Cunningham BS, Klein LS, Parekh DS, Warwick AB, Lieuw K. Allopurinol Use During Maintenance Therapy for Acute Lymphoblastic Leukemia Avoids

Mercaptopurine-related Hepatotoxicity. J Pediatr Hematol Oncol. 2016;38(2):147-151.

15. Stamp LK, Barclay ML. How to prevent allopurinol hypersensitivity reactions? Rheumatology (Oxford). 2018;57(suppl_1):i35-i41.

Tables

Table 1. Multivariate Cox regression analysis for event-free survival

Category	No. (%) of patients (n = 752)	HR (95%CI)	P value
Combination with ALLO[a]			
No	603 (80.2)	1 [Reference]	**0.017**
Yes	149 (19.8)	0.29 (0.10-0.80)	
Age, year			
<10	652 (86.7)	1 [Reference]	0.25
≥10	100 (13.3)	0.70 (0.38-1.29)	
Sex			
Male	489 (65.0)	1 [Reference]	0.48
Female	263 (35.0)	0.70 (0.38-1.29)	
Final risk			
Low	415 (55.2)	1 [Reference]	**0.004**
Intermediate	337 (44.8)	2.15 (1.28-3.60)	
Immunophenotype			
B	670 (89.1)	1 [Reference]	0.55
T	82 (10.9)	0.80 (0.37-1.69)	
Day 19 MRD level			
<0.01%	365 (48.5)	1 [Reference]	**0.002**
≥0.01%	370 (49.2)	2.27 (1.35-3.82)	

Hepatotoxicity[b]			
Yes	459 (61.0)	1 [Reference]	0.20
No	293 (39.0)	1.33 (0.86-2.07)	

[a]Combination with allopurinol was treated as a time-dependent variable.

[b]Alanine aminotransferase > 2 times the upper limit of normal or elevated bilirubin at least once during maintenance therapy.

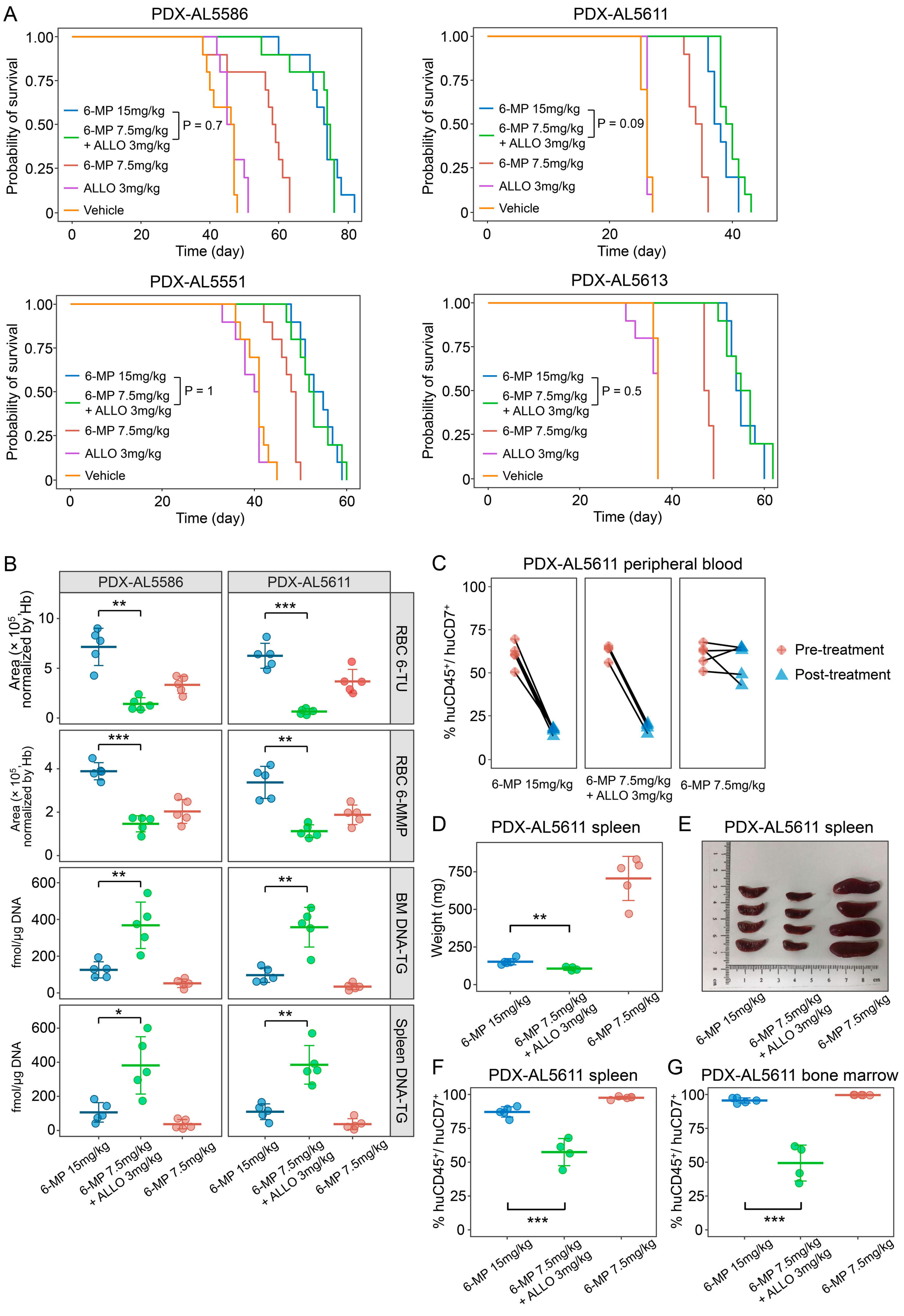
Abbreviations: HR, hazard ratio; CI, confidence interval; ALLO, allopurinol; MRD, Minimal residual disease.

Figure legends

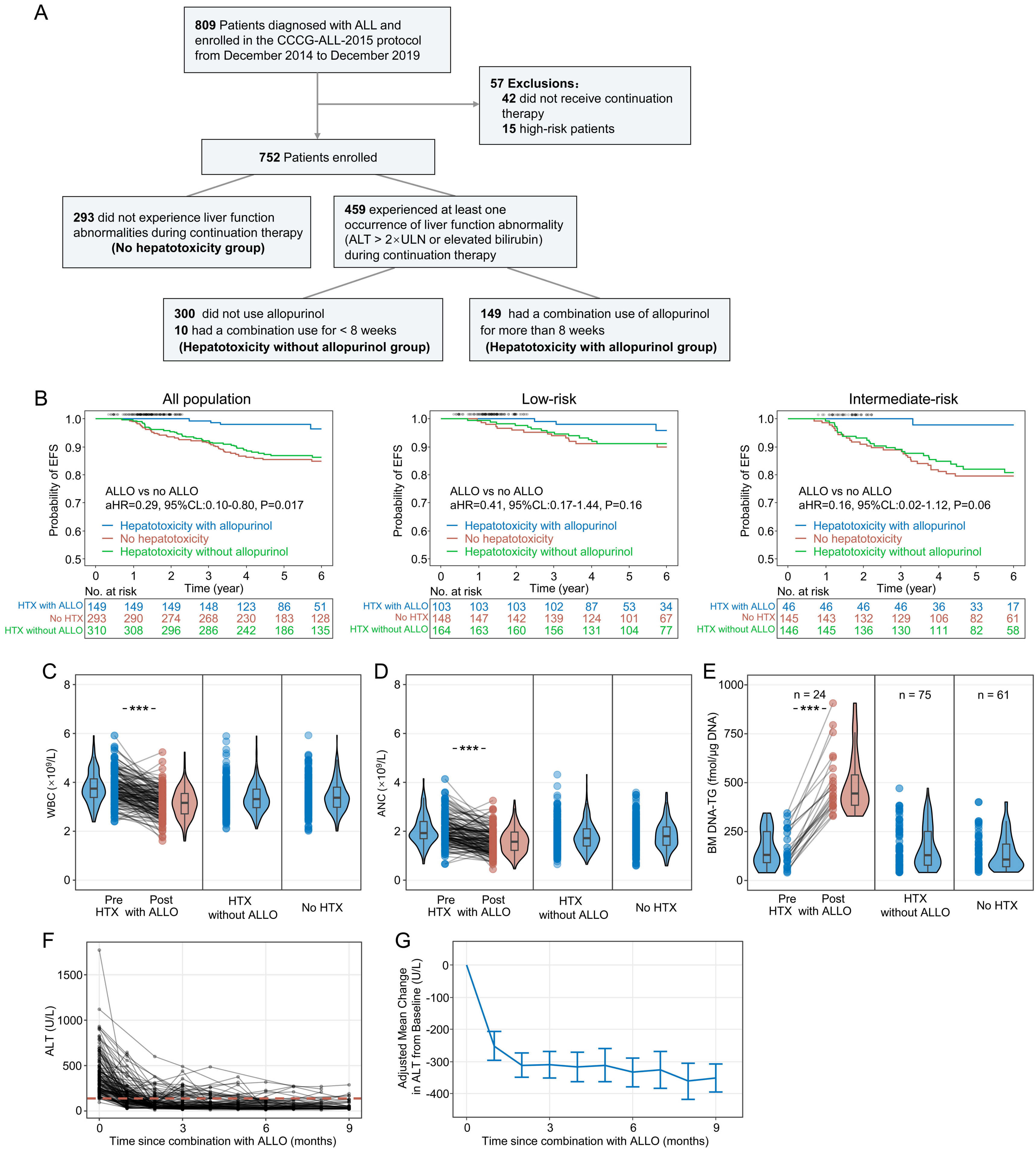
Figure 1. Preclinical evaluation of the effects of allopurinol (ALLO) on 6-mercaptopurine (6-MP) efficacy and metabolism in patient-derived xenograft (PDX) models of acute lymphoblastic leukemia. (A) Survival analysis in four ALL PDX models comparing 6-MP and ALLO combination therapy with 6-MP monotherapy. (B) 6-MP metabolite and DNA-TG levels in PDXs following ALLO co-treatment. The levels of 6-TU and 6-MMP in red blood cells (RBC) were normalized by hemoglobin (Hb) level, and the DNA-TG levels in bone marrow (BM) and spleen were normalized by DNA content. (C) Proportion of leukemia cells (huCD45^{+}/huCD7^{+}) in peripheral blood before and after treatment in PDX-5611. (D, E) Images and weights of the spleens after treatment in PDX-5611. (F, G) Proportion of leukemia cells in the spleen and bone marrow after treatment. * indicates $P<0.05$, ** indicates $P<0.01$, *** indicates $P<0.001$, Student's t-test.

Figure 2. Clinical evaluation of allopurinol (ALLO) co-treatment during maintenance therapy in pediatric acute lymphoblastic leukemia patients, including its impact on event-free survival (EFS) and laboratory parameters. (A) Patient enrollment and group classification. (B) Kaplan-Meier curves for EFS in the hepatotoxicity (HTX) with ALLO group, no HTX group, and HTX without ALLO group in the entire population, low-risk patients, and intermediate-risk patients. Black dots represent the time points when allopurinol treatment started. Adjusted hazard ratio (aHR) with 95% confidence intervals (CI) and P values were estimated using the time-dependent Cox regression analysis, adjusted for age, sex, final risk, immunophenotype, day 19 MRD level, and liver function

abnormality. Changes in laboratory parameters following ALLO co-treatment, including white blood cell (WBC) (C), absolute neutrophil count (ANC) in peripheral blood (D), DNA-incorporated thioguanine (DNA-TG) in bone marrow (BM) (E), alanine aminotransferase (ALT) (F), and mean change in ALT from baseline (adjusted MMRM analysis) (G). *** indicates $P<0.001$, Wilcoxon signed-rank test.



A
PDX-AL5586
PDX-AL5611
PDX-AL5551
PDX-AL5613
Probability of survival
Time (day)
6-MP 15mg/kg
6-MP 7.5mg/kg + ALLO 3mg/kg
6-MP 7.5mg/kg
ALLO 3mg/kg
Vehicle
P = 0.7
P = 0.09
P = 1
P = 0.5
B
PDX-AL5586
PDX-AL5611
RBC 6-TU
RBC 6-MMP
BM DNA-TG
Spleen DNA-TG
Area (× 10^5, normalized by Hb)
fmol/µg DNA
C
PDX-AL5611 peripheral blood
% huCD45+/ huCD7+
Pre-treatment
Post-treatment
D
PDX-AL5611 spleen
Weight (mg)
E
PDX-AL5611 spleen
F
PDX-AL5611 spleen
G
PDX-AL5611 bone marrow



A
809 Patients diagnosed with ALL and enrolled in the CCCG-ALL-2015 protocol from December 2014 to December 2019
57 Exclusions：
42 did not receive continuation therapy
15 high-risk patients
752 Patients enrolled
293 did not experience liver function abnormalities during continuation therapy (No hepatotoxicity group)
459 experienced at least one occurrence of liver function abnormality (ALT > 2×ULN or elevated bilirubin) during continuation therapy
300 did not use allopurinol
10 had a combination use for < 8 weeks
(Hepatotoxicity without allopurinol group)
149 had a combination use of allopurinol for more than 8 weeks
(Hepatotoxicity with allopurinol group)
B
All population
ALLO vs no ALLO
aHR=0.29, 95%CL:0.10-0.80, P=0.017
Low-risk
ALLO vs no ALLO
aHR=0.41, 95%CL:0.17-1.44, P=0.16
Intermediate-risk
ALLO vs no ALLO
aHR=0.16, 95%CL:0.02-1.12, P=0.06
Hepatotoxicity with allopurinol
No hepatotoxicity
Hepatotoxicity without allopurinol
Probability of EFS
Time (year)
No. at risk
HTX with ALLO 149 149 149 148 123 86 51
No HTX 293 290 274 268 230 183 128
HTX without ALLO 310 308 296 286 242 186 135
HTX with ALLO 103 103 103 102 87 53 34
No HTX 148 147 142 139 124 101 67
HTX without ALLO 164 163 160 156 131 104 77
HTX with ALLO 46 46 46 46 36 33 17
No HTX 145 143 132 129 106 82 61
HTX without ALLO 146 145 136 130 111 82 58
C
WBC (×10⁹/L)
***
Pre HTX with ALLO Post
HTX without ALLO
No HTX
D
ANC (×10⁹/L)
***
E
BM DNA-TG (fmol/μg DNA)
n = 24
n = 75
n = 61
***
F
ALT (U/L)
Time since combination with ALLO (months)
G
Adjusted Mean Change in ALT from Baseline (U/L)
Time since combination with ALLO (months)

Supplemental Table 1. Characteristics of enrolled patients

Characteristic	Total n = 752	No ALLO Combination n = 603	ALLO combination n = 149	P value
Male sex, n (%)	489 (65.0)	392 (65.0)	97 (65.1)	1
Age[a], n (%)				0.03
<1	21 (2.8)	17 (2.8)	4 (2.7)	
1 to <5	404 (53.7)	313 (51.9)	91 (61.1)	
5 to <10	227 (30.2)	182 (30.2)	45 (30.2)	
≥10	100 (13.3)	91 (15.1)	9 (6.0)	
Risk stratification, n (%)				<0.001
Low risk	415 (55.2)	312 (51.7)	103 (69.1)	
Intermediate risk	337 (44.8)	291 (48.3)	46 (30.9)	
Immunophenotype, n (%)				0.006
B	670 (89.1)	528 (87.6)	142 (95.3)	
T	82 (10.9)	75 (12.4)	7 (4.7)	
Cytogenetic subtypes, n (%)				0.32
Hyperdiploidy	254 (33.8)	195 (32.3)	59 (39.6)	
TEL::AML1	137 (18.2)	106 (17.6)	31 (20.8)	
MLL-rearranged	29 (3.9)	22 (3.6)	7 (4.7)	
TCF3::PBX1	37 (4.9)	31 (5.1)	6 (4.0)	
BCR::ABL1	28 (3.7)	26 (4.3)	2 (1.3)	
MRD D19, n (%)				0.08
<0.01%	365 (48.5)	282 (46.8)	83 (55.7)	
0.01% to <0.1%	130 (17.3)	103 (17.1)	27 (18.1)	
0.1% to <1%	128 (17.0)	103 (17.1)	25 (16.7)	
≥1%	112 (14.9)	99 (16.4)	13 (8.7)	
MRD D46, n (%)				0.07
<0.01%	649 (86.3)	511 (84.7)	138 (92.6)	
0.01% to <0.1%	48 (6.4)	43 (7.1)	5 (3.4)	
≥0.1%	24 (3.2)	22 (3.6)	2 (1.3)	

[a]Data at diagnosis.

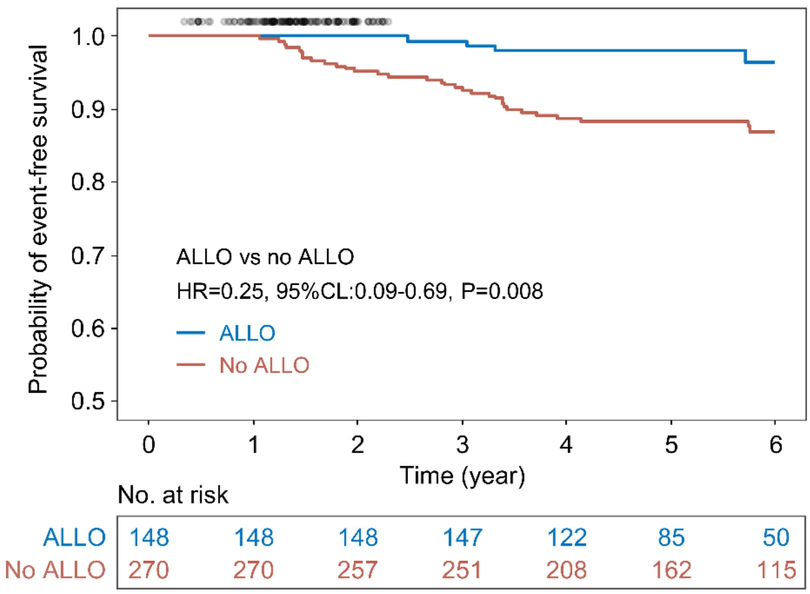
Abbreviations: ALLO, allopurinol; MRD, minimal residual disease.

Supplemental Table 2. Characteristics of enrolled patients after Propensity Score Matching

Characteristic	No ALLO Combination n = 270	ALLO combination n = 148	P value
Male sex, n (%)	176 (65.2)	96 (64.9)	0.95
Age[a], n (%)			0.91
<1	10 (3.7)	4 (2.7)	
1 to <5	156 (57.8)	90 (60.8)	
5 to <10	86 (31.9)	45 (30.2)	
≥10	18 (6.7)	9 (6.0)	
Risk stratification, n (%)			0.88
Low risk	188 (69.6)	102 (68.9)	
Intermediate risk	82 (30.4)	46 (30.9)	
Immunophenotype, n (%)			0.75
B	259 (95.9)	141 (95.3)	
T	11 (4.1)	7 (4.7)	
Cytogenetic subtypes, n (%)			0.86
Hyperdiploidy	96 (35.6)	58 (39.2)	
TEL::AML1	58 (21.5)	31 (20.8)	
MLL-rearranged	12 (4.4)	7 (4.7)	
TCF3::PBX1	14 (5.2)	6 (4.0)	
BCR::ABL1	7 (2.6)	2 (1.3)	
MRD D19, n (%)			0.81
<0.01%	141 (52.2)	83 (55.7)	
0.01% to <0.1%	49 (18.1)	27 (18.1)	
0.1% to <1%	53 (19.6)	24 (16.2)	
≥1%	21 (7.8)	13 (8.7)	

[a]Data at diagnosis.

Abbreviations: ALLO, allopurinol; MRD, minimal residual disease.



Supplemental Figure 1. Kaplan-Meier curves for event-free survival in allopurinol (ALLO) group and no allopurinol group. Propensity score matching was performed to balance baseline characteristics between the two groups. Black dots represent the time points when allopurinol treatment started. Hazard ratio (HR) with 95% confidence intervals (CI) and P values were estimated using the time-dependent Cox regression analysis.