LETTER TO THE EDITOR

Frontline ponatinib plus hyper-CVAD over imatinib in adults with Ph-positive acute lymphoblastic leukemia: real-world efficacy and risks of early ponatinib dose reduction

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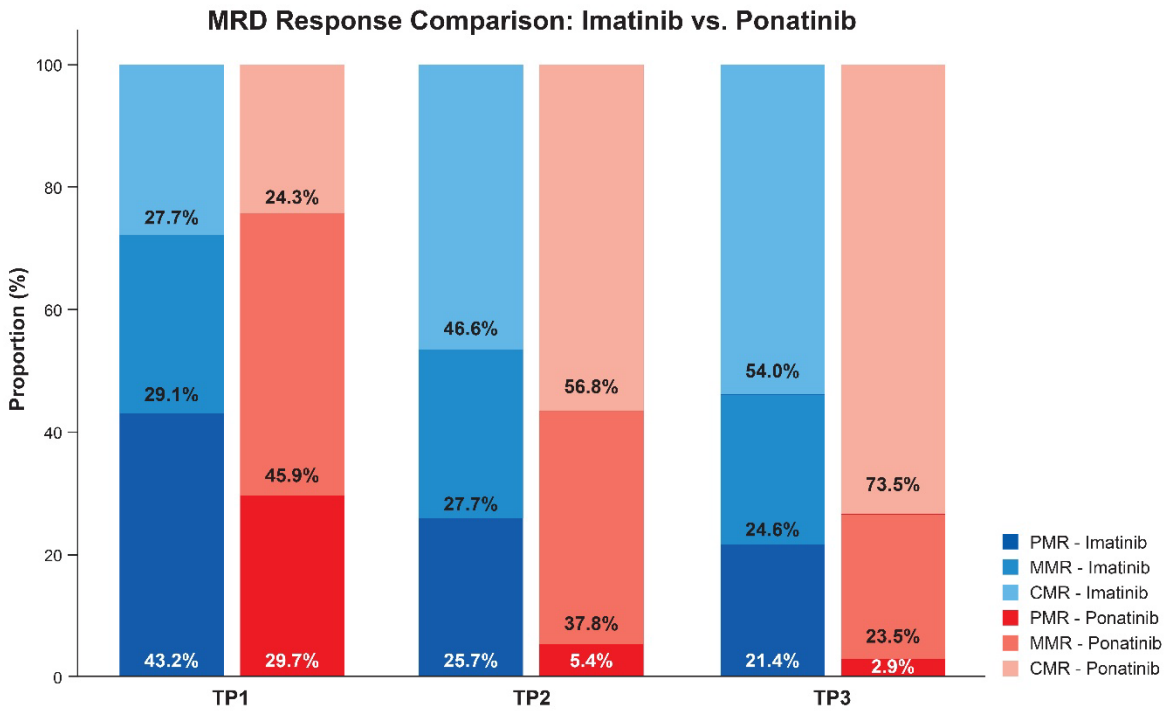
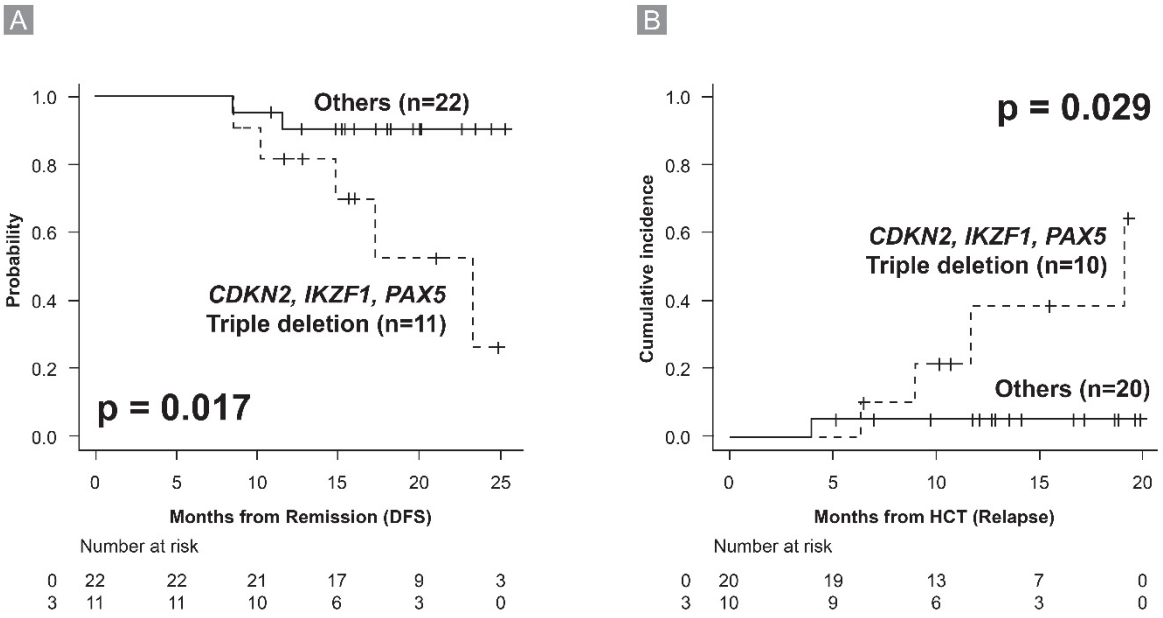


Supplementary Figure 1. Comparison of molecular response dynamics between imatinib and ponatinib groups across three timepoints (TP1, TP2, TP3). Stacked bar graphs display the proportion of patients achieving complete molecular response (CMR), major molecular response (MMR), and partial molecular response (PMR) at each timepoint. Ponatinib group showed a significantly higher rate of CMR and a marked reduction in PMR by TP3.



Supplementary Figure 2. Impact of *IKZF1, CDKN2A/B,* and *PAX5* triple deletion on DFS and relapse incidence. A. Patients with triple deletion exhibited significantly poor DFS. B. Relapse incidence was also markedly higher in the triple deletion group (38.6%, 95% CI: 5.7–72.9%) compared to 5.0% (95% CI: 0.3–21.1%).

Supplementary Table 1. Baseline characteristics between shorter and longer application of ponatinib 30mg according to MRD response.

	Shorter ponatinib 30mg <3mo Early dose reduction (n=17)	Longer ponatinib 30mg > 3mo Dose maintained (n=20)	p
Age			
Median (range)	42 (20-64)	41 (26-72)	0.714
> 40 years old	10 (58.8%)	11 (55.0%)	1.000
Gender, Male	10 (58.8%)	9 (45.0%)	0.515
Leucocyte count ($\times 10^9$/L)	49.0 (1.3-221.0)	33.1 (1.3-494.0)	0.916
> 30.0 ($\times 10^9$/L)	11 (64.7%)	11 (55.0%)	0.792
BCR::ABL1 transcript			
Minor	16 (94.1%)	15 (75.0%)	
Major	1 (5.9%)	5 (25.0%)	
Gene deletions, available	15 (88.2%)	18 (90.0%)	
IKZF1	12 (80.0%)	14 (77.8%)	1.000
CDKN2	9 (60.0%)	7 (38.9%)	0.391
PAX5	8 (53.3%)	6 (33.3%)	0.421
Triple deletions	6 (40.0%)	5 (27.8%)	0.711
MRD, qPCR			
TP1			
CMR, not detected	9 (52.9%)	0 (0.0%)	< 0.001
MMR, any to < 0.1%	7 (41.2%)	10 (50.0%)	
PMR ≥ 0.1%	1 (5.9%)	10 (50.0%)	
TP2			
CMR, not detected	16 (94.1%)	5 (25.0%)	< 0.001
MMR, any to < 0.1%	1 (5.9%)	13 (65.0%)	
PMR ≥ 0.1%	0 (0.0%)	2 (10.0%)	
TP3 (Pre-HCT)			
CMR, not detected	14 (82.4%)	11 (64.7%)	0.438
MMR, any to < 0.1%	3 (17.6%)	5 (29.4%)	
PMR ≥ 0.1%	0 (0.0%)	1 (5.9%)	
Time to transplantation	5.5 months (5.2-6.1)	5.5 months (5.0-7.1)	0.796
Allo-HCT in CR1	17 (100%)	17 (85.0%)	0.420
Donor			
Matched sibling donor	4 (23.5%)	4 (23.5%)	1.000
Unrelated donor	8 (47.1%)	8 (47.1%)	
Haploidentical donor	5 (29.4%)	5 (29.4%)	
Intensity			
Myeloablative	0 (0.0%)	2 (11.8%)	0.485
Reduced toxicity	17 (100%)	15 (88.2%)	

Abbreviations: MRD, measurable residual disease; qPCR, real-time quantitative polymerase chain reaction; TP, MRD time point; CMR, complete molecular response; MMR major molecular response; PMR, poor molecular response; Allo-HCT, allogeneic hematopoietic cell transplantation; CR, complete remission.

Supplementary Table 2. Adverse events of ponatinib plus hyper-CVAD.

		CTCAE grade				
Toxicity	Total	1	2	3	4	5
Infection						
Neutropenia fever	22 (59.4%)	8 (21.6%)	11 (29.7%)	3 (8.1%)	0 (0.0)	0 (0.0)
Pneumonia	5 (13.5%)	3 (8.1%)	2 (5.4%)	0 (0.0)	0 (0.0)	0 (0.0)
Sepsis	4 (10.8%)	0 (0.0)	2 (5.4%)	1 (2.7%)	0 (0.0)	1 (2.7%)
Viral infection	4 (10.8%)	2 (5.4%)	2 (5.4%)	0 (0.0)	0 (0.0)	0 (0.0)
Fungal infection	3 (8.1%)	0 (0.0)	1 (2.7%)	1 (2.7%)	0 (0.0)	1 (2.7%)
Necrotizing fasciitis	3 (8.1%)	0 (0.0)	0 (0.0)	0 (0.0)	3 (8.1%)	0 (0.0)
Hepatobiliary						
Pancreatitis	3 (8.1%)	1 (2.7%)	2 (5.4%)	0 (0.0)	0 (0.0)	0 (0.0)
Hyperbilirubinemia	4 (10.8%)	2 (5.4%)	2 (5.4%)	0 (0.0)	0 (0.0)	0 (0.0)
Transaminitis	6 (16.2%)	1 (2.7%)	2 (5.4%)	3 (8.1%)	0 (0.0)	0 (0.0)
Cardiovascular						
Hypertension	4 (10.8%)	3 (8.1%)	1 (2.7%)	0 (0.0)	0 (0.0)	0 (0.0)
Thromboembolism	1 (2.7%)	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.7%)	0 (0.0)
Gastrointestinal						
Nausea	3 (8.1%)	2 (5.4%)	1 (2.7%)	0 (0.0)	0 (0.0)	0 (0.0)
Dyspepsia	3 (8.1%)	3	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Constipation	2 (5.4%)	2 (5.4%)	1 (2.7%)	0 (0.0)	0 (0.0)	0 (0.0)
Neurological						
Headache	4 (10.8%)	3 (8.1%)	1 (2.7%)	0 (0.0)	0 (0.0)	0 (0.0)
Blurred vision	4 (10.8%)	2 (5.4%)	1 (2.7%)	1 (2.7%)	0 (0.0)	0 (0.0)
Tinnitus	3 (8.1%)	1 (2.7%)	2 (5.4%)	0 (0.0)	0 (0.0)	0 (0.0)
Others						
Skin rash	5 (13.5%)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Arthralgia	3 (8.1%)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)