Palbociclib in Combination with Chemotherapy in Pediatric and Young Adult Patients with Relapsed/Refractory Acute Lymphoblastic Leukemia and Lymphoma: A Children's Oncology Group Study (AINV18P1)

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Abstract

Background Cyclin D has been shown to play an essential role in acute lymphoblastic leukemia (ALL) initiation and progression, providing rationale for targeting the CDK4/6-cyclin D complex that regulates cell cycle progression. **Procedure** The Children's Oncology Group AINV18P1 phase 1 trial evaluated the CDK4/6 inhibitor, palbociclib, in combination with standard four-drug reinduction chemotherapy in children and young adults with relapsed/refractory B- and T-cell lymphoblastic leukemia (ALL) and lymphoma. Palbociclib (50 mg/m ^{2}/dose) was administered orally once daily for 21 consecutive days, first as a single agent (days 1-3) and subsequently combined with reinduction chemotherapy. This two-part study was designed to determine the maximum tolerated dose (MTD) or recommended phase 2 dose (RP2D) followed by an expansion pharmacokinetic (PK) cohort. **Results** Twelve heavily pretreated patients enrolled, all of whom were evaluable for toxicity. One dose-limiting hematologic toxicity (DLT) occurred at the starting dose of 50 mg/m ^{2}/dose orally for 21 days. No additional DLTs were observed in the dose determination or PK expansion cohorts and overall rates of grade 3/4 non-hematologic toxicities were comparable to those observed with the chemotherapy platform alone. Five complete responses were observed, two among four patients with T-ALL and three among seven patients with B-ALL. Pharmacokinetic studies showed similar profiles with both liquid and capsule formulations of palbociclib. **Conclusions** Palbociclib in combination with reinduction chemotherapy was well tolerated with a RP2D of 50 mg/m ^{2}/day for 21 days. Complete responses were observed among heavily pretreated patients.

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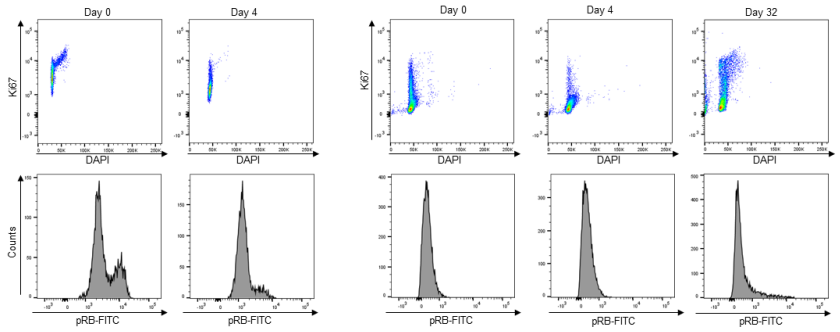
Figure 1

A **Secondary Outcome Measures for Patient Samples**

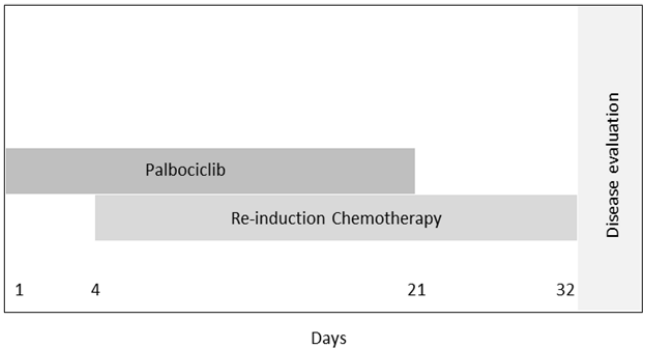
	Disease Status	Response	Ki67 (% of cells +)			pRB (% of cells +)			Cyclin D3 MFI/Unstained MFI			CDK4 MFI/Unstained MFI			CDK6 MFI/Unstained MFI		
Patient ID			**Day 0**	**Day 4**	**Day 32**	**Day 0**	**Day 4**	**Day 32**	**Day 0**	**Day 4**	**Day 32**	**Day 0**	**Day 4**	**Day 32**	**Day 0**	**Day 4**	**Day 32**
#11	B-ALL (R3)	PD		22.80%			25.80%			5.21			1.65			5.22	
#6	B-ALL (R2)	CRi	13.30%	0.90%		37%	8.38%		3.01	5.14		1.80	1.50		1.97	4.26	
#12	T-ALL (R1)	SD	17%	3.27%	25.3%	3.35%	4.87%	15.90%	15.08	13.95	45.65	6.18	10.04	10.88	31.55	22.71	142.00
#2	T-ALL (R2)	SD		0.60%	0.14%		19.10%	1.47%		20.66	29.19		10.67	5.72		11.99	21.24
#5	T-ALL (R5)	CR		0.73%			13%			26.59			10.99			15.57	

B **B-ALL (R2) #6**

C **T-ALL (R1) #12**



Supplemental Figure 1



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