A Phase 1 Study of Ruxolitinib in Children with Relapsed/Refractory Solid Tumors, Leukemias, or Myeloproliferative Neoplasms: a Children's Oncology Group Phase 1 Consortium Study (ADVL1011)

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CHILDREN'S ONCOLOGY GROUP

The world's childhood cancer experts

Background

- Activation of receptor and non-receptor tyrosine kinases and associated signaling pathways occurs commonly in cancer.
- Ruxolitinib, an orally bioavailable JAK1 and JAK2 inhibitor, may play a role in the treatment of childhood cancers with *JAK1*, *JAK2*, *CRLF2,* or other *BCR-ABL1*-like (Ph-like) alterations.
- We performed a Phase 1 study of ruxolitinib in children with relapsed or refractory solid tumors or hematologic malignancies.

Hypothesis

Ruxolitinib can be administered safely to children with relapsed/refractory cancer and will inhibit oncogenic JAK/STAT signaling.

Methods

- Ruxolitinib was administered orally twice daily (BID) continuously in 28 day cycles.
- The starting dose (dose level 1) was equivalent to the recommended adult dose of 25 mg/dose BID.
- Dose escalation was performed using the rolling six trial design:

Dose Level (DL)	Ruxolitinib
0	12 mg/m^2/dose BID
1	15 mg/m^2/dose BID
2	21 mg/m^2/dose BID
3	29 mg/m^2/dose BID
4	39 mg/m^2/dose BID
5	50mg/m^2/dose BID

- Patients with leukemia and myeloproliferative neoplasms (MPN) (Part B) were enrolled at one dose level below patients with solid tumors (Part A).
- Pharmacokinetic sampling was performed in all patients during Cycle 1.
- JAK mutation and pharmacodynamic analyses were performed during Cycle 1 in consenting patients enrolled in Part B.

Results: Pharmacokinetic Analyses

- Pharmacokinetics of ruxolitinib in children were similar to those in adults.
- Peak plasma concentrations were achieved 1 hour (range 1 – 4) after the first dose and decreased in a monoexponential fashion with a mean ± standard deviation half-life of 2.3 ± 0.9 hours.
- Mean plasma clearance (Cl/F) and volume of distribution (V/F) among all patients were 14.8 ± 5.9 L/h and 59.4 ± 29.1 L, respectively, and were independent of dose level.

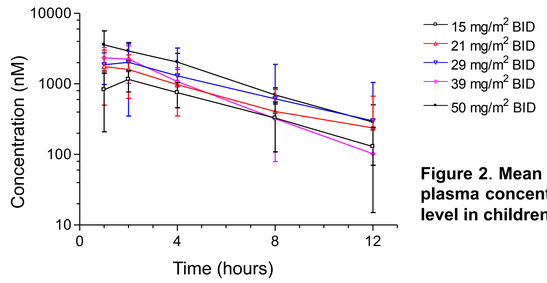

Figure 2. Mean (± standard error) ruxolitinib plasma concentrations versus time by dose level in children treated on ADVL1011.

Table 3. Summary of ruxolitinib pharmacokinetics.

Dose Level	Dose (mg/m^2)	N	C_{max} (μM)	T_{max} (h)	Half-life (h)	$AUC_{0-\infty}$ (h x μM)	CL/F (L/h)	V/F (L)
1	15	N	9	9	8	8	8	8
		Mean ± SD	1.26 ± 0.40	1.9 ± 0.9	2.8 ± 0.8	6.72 ± 3.43	11.5 ± 5.4	44.9 ± 20.0
2	21	N	8	8	6	6	6	6
		Mean ± SD	1.76 ±1.05	1.9 ± 1.4	2.3 ± 0.7	8.00 ± 4.94	14.8 ± 7.5	43.5 ± 20.7
3	29	N	10	10	10	10	10	10
		Mean ± SD	1.90 ± 756	1.3 ± 0.5	2.2 ± 0.9	7.16 ± 3.25	15.9 ± 5.5	52.3 ± 35.4
4	39	N	9	9	8	8	8	8
		Mean ± SD	2.88 ±1.12	1.4 ± 0.5	2.1 ± 0.8	10.6 ± 4.8	15.9 ± 5.5	48.8 ± 25.3
5	50	N	6	6	5	5	5	5
		Mean ± SD	3.82 ± 1.77	1.5 ± 1.2	3.3 ± 0.9	18.8 ± 4.94	15.9 ± 6.5	74.2 ± 40.1

Results: Genetic and Pharmacodynamic Analyses

- No *JAK1* or *JAK2* mutations were identified in patients with leukemia. A *JAK2* V617F mutation was identified in a patient with polycythemia vera.
- Median peak plasma inhibitory activity of phosphorylated (p) JAK2 (44.8%), STAT5 (58.9%), and S6 (62.3%) was generally dose-independent with exception of greater pSTAT5 inhibition at DL5.

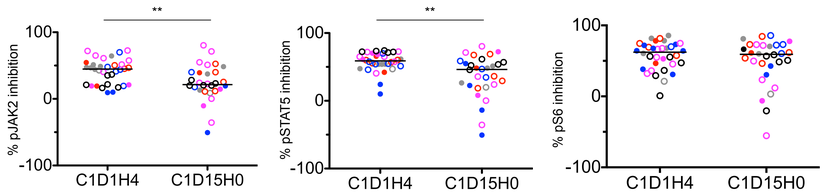

Figure 1. Quantification of *in vivo* signaling inhibition. MUTZ5 (*CRLF2*/*JAK2*-mutant ALL cell line) cells were incubated with plasma obtained at baseline and at subsequent timepoints from patients treated with ruxolitinib, then analyzed by phosphoflow cytometry to quantify inhibition of signal transduction proteins at peak (C1D1H4; n=37 patients) and trough (C1D15H0; n=32 patients) timepoints. Loss of pJAK2 and pSTAT5, but not pS6, inhibition was observed over time. ** $p < 0.005$ via Mann-Whitney two-tailed test

Results: Patients and Toxicity Analyses

- 28 solid tumor and 21 leukemia/MPN patients with a median age of 14.4 years (range 2.1 – 21.4) were enrolled.
- 27 solid tumor and 10 leukemia/MPN patients were evaluable.
- Patients received a median of 1 cycle (range 1 – 18).
- Dose-limiting and non-dose-limiting toxicities of ruxolitinib are shown in the tables below.

Table 1. Dose-limiting toxicity (DLT) summary for Cycle 1 (n=49 patients, 37 evaluable).

Stratum	Dose Level	Number Patients Entered	Number Patients Evaluable	Number Patients with DLT	Toxicity (Grade)
Part A (Solid tumor)	15 mg/m^2	4	3	0	-
	21 mg/m^2	6	6	1	ALT (4), dehydration (3), hypotension (3), multi-organ failure (5), nausea (3), vomiting (3), death (5)
	29 mg/m^2	6	6	1	Neutropenia (4)
	39 mg/m^2	6	6	1	Neutropenia (4)
	50 mg/m^2	6	6	1	CPK increased (4)
Part B (Leukemia and MPN)	15 mg/m^2	6	4	0	-
	21 mg/m^2	3	1	0	-
	29 mg/m^2	6	3	0	-
	39 mg/m^2	6	2	1	Creatinine (3), acute kidney injury (3)

Table 2. Non-dose-limiting hematologic and non-hematologic toxicities observed in evaluable patients (n=37).

Toxicity Type	Maximum grade of toxicity across Cycle 1 (total = 37 cycles)				Maximum grade of toxicity across Cycles 2 to 18 (total = 36 cycles)			
	Grade 1	Grade 2	Grade 3	Grade 4	Grade 1	Grade 2	Grade 3	Grade 4
Hematologic								
Anemia	9	7	8	1	3	5	7	
Lymphopenia	4	7	1	4	3	2	4	4
Lymphocytosis		2						
Leukopenia	10	6	3		3	2	2	2
Neutropenia	3	7	5	4	2	5	1	2
Thrombocytopenia	10	2	2	5	4			4
Abdominal pain	4	1			1			
Non-hematologic								
Alanine aminotransferase	4	3		1	1	1		
Aspartate aminotransferase	8		1		2	1	1	
Bilirubin	3	1				1		
Constipation	4							
Creatinine	3	1	1					
Fatigue	7	3				1		
Headache	3	1			1			
Hypocalcemia	6				1			
Hyponatremia	4				1			
Nausea	8	1	1		2			
Vomiting	3		1					

Note: This table consists of non-dose-limiting toxicities independent of frequency and attribution.

Conclusions & Future Directions

- Ruxolitinib was generally well-tolerated in children and adolescents with relapsed or refractory cancer.
- The recommended Phase 2 dose of ruxolitinib is 50 mg/m^2/dose BID.
- A Phase 2 trial of ruxolitinib and chemotherapy for patients with *de novo* acute lymphoblastic leukemia with JAK pathway alterations is in development.

We thank the Incyte Corporation for providing ruxolitinib for this trial and Dr Xuejun Chen of Incyte for performance of PK analyses. We also acknowledge Mr Daniel Magoon for assistance with PIA assays and Dr Julie Gastier-Foster for JAK mutation analyses. This work was supported by the National Cancer Institute (NCI) grant 5UM1 CA097452-12 and a Cookies for Kids' Cancer award to the Children's Oncology Group Phase 1/Pilot Consortium, the NCI career development award K12CA076931 to the University of Pennsylvania (SKT), a Conquer Cancer Foundation/American Society of Clinical Oncology Young Investigator Award (SKT), an Alex's Lemonade Stand Foundation Young Investigator Award (SKT), a St Baldrick's Foundation Scholar Award (KRR), and a Leukemia & Lymphoma Society Translational Research Program Award (KRR). SKT is an Alex's Lemonade Stand Foundation Scholar in Developmental Therapeutics.