Phase 1 Trial of Selinexor in Pediatric Recurrent/Refractory Solid and CNS Tumors

Adam L. Green,[1,2] Charles G. Minard,[3] Xiaowei Liu,[4] Stephanie L. Safgren,[5] Kerice Pinkney,[6] **Lauren Harris**,[1] Gabrielle Link,[1] John DeSisto,[1] Stephan Voss,[7] Marvin D. Nelson,[8] Joel M. Reid,[6] Elizabeth Fox,[9] Brenda J. Weigel, [10] Julia Glade Bender[11]

1. Morgan Adams Foundation Pediatric Brain Tumor Research Program, Department of Pediatrics, University of Colorado School of Medicine, Aurora, CO 2. Center for Cancer and Blood Disorders, Children's Hospital Colorado, Aurora, CO 3. Baylor College of Medicine, Houston, TX 4. Children's Oncology Group, Monrovia, CA 5. Mayo Clinic, Rochester, MN 6. Joe DiMaggio Children's Hospital, Hollywood, FL 7. Boston Children's Hospital, Boston, MA 8. Children's Hospital Los Angeles, Los Angeles, CA 9. St. Jude Children's Research Hospital, Memphis, TN 10. University of Minnesota, Minneapolis, MN 11. Memorial Sloan Kettering Cancer Center, New York, NY

University of Colorado Anschutz Medical Campus

CHILDREN'S ONCOLOGY GROUP

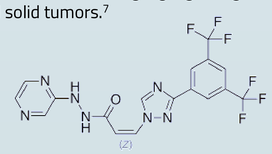
Abstract

- Selinexor is a central nervous system (CNS)-penetrant, oral inhibitor of exportin 1 (XPO1), the main nuclear exporter of many key tumor suppressors.
- We report a phase 1 trial of selinexor in children and adolescents with recurrent CNS and solid tumors (NCT02323880).
- A rolling-six design was used to evaluate the maximum tolerated dose (MTD) and first dose pharmacokinetics (PK) of selinexor administered once (QW, 35-45 mg/m^2) or twice (BIW, 20-35 mg/m^2) weekly during a 28-day cycle (Part A).
- Ten additional patients with high-grade glioma (HGG) were treated at the QW MTD (Part B).
- In Part A, BIW dosing was limited by extended hematologic toxicity. The MTD on a BIW schedule for three weeks on/one-week off (BIW 3/1) was 20 mg/m^2/dose. Dose-limiting toxicities (DLTs) on this schedule included fatigue, acute reversible neurologic changes, neutropenia, thrombocytopenia, and AST/ALT increase. On a QW schedule, the MTD was 35 mg/m^2/dose, DLTs included seizure and thrombocytopenia.
- In Part B (HGG expansion), there were no additional DLTs observed. There were no objective responses.
- Selinexor-related toxicities were primarily hematologic and neurologic requiring dose or dose-frequency reduction.
- The MTD and recommended initial phase 2 dose of selinexor in children and adolescents with recurrent solid and CNS tumors is 35 mg/m^2/dose QW.

1. Background and Objectives

Background

- XPO1 (Exportin 1, CRM1) is the sole nuclear exporter of many key tumor suppressor and growth regulatory proteins (TSP/GRP), including TP53, CDKN1A, CDKN1B, RB1, FOXO, and NFKBIA.[1] XPO1 is overexpressed in many cancer types, and is associated with poor outcomes.[2]
- Active nuclear export of TSP/GRP is a very efficient and rapid means of overcoming normal cell cycle regulation and the genomic stability assessment in cancer cells. Selinexor binds and inactivates XPO1 in a slowly reversible manner, forcing the nuclear retention of key TSP/GRP, and activating cell cycle checkpoints and genomic surveying.[3]
- In malignant cells this leads to apoptosis, whereas normal cells undergo transient cell cycle arrest and subsequent recovery when the export block is released.[4,5]
- Selinexor is orally bioavailable, CNS penetrant, and has shown preclinical efficacy in multiple pediatric cancer models, including high-grade glioma (HGG),[6] other CNS and extracranial solid tumors.[7]



Objectives

- Primary:
  - Estimate maximum tolerated dose (MTD) and/or recommended phase 2 dose (RP2D) of Selinexor
  - Characterize the toxicities and pharmacokinetics (PK) of Selinexor in this population

2. Methodology

Eligibility Criteria:

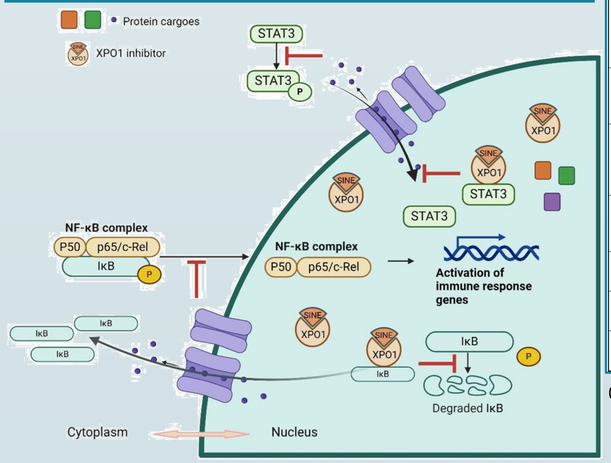
- Between 1-21 years
- Recurrent/refractory solid tumor, including lymphoma and CNS tumors (Part A), or recurrent/refractory HGG not requiring surgical resection (Part B)
- Karnofsky/Lansky performance score ≥ 50%
- If currently required, a stable or decreasing corticosteroid dose
- BMI ≥ third percentile
- None of the following: Grade ≥ 3 ataxia or Grade ≥ 2 extrapyramidal movement disorder, macular degeneration, uncontrolled glaucoma, or cataracts
- There was no limit on prior treatment regimens
- Hematologic criteria: ANC ≥ 1,000 cells/uL, transfusion-independent platelet count ≥ 100,000 × 109 /L, and baseline hemoglobin ≥ 8 g/dL.
- Standard organ function

Table 1: Most Common Diagnoses

Diagnosis	Total Number of Patients (%)
High Grade Glioma	30 (50.9)
Osteosarcoma	6 (10.2)
Ependymoma	5 (8.5)

Study Design and Participants

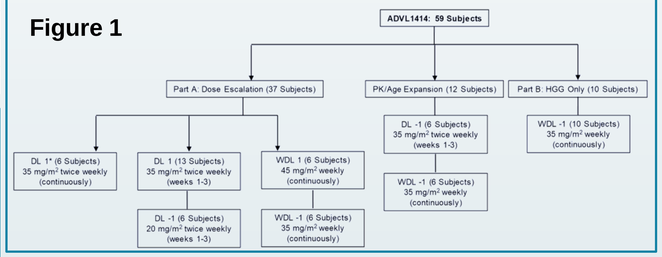
- 59 total patients enrolled (see top 3 diagnoses in **table 1**)
- For Part A, the starting dose of selinexor was 35/mg/m2 twice weekly, continuously
- Dose escalations to 45 mg/m2 and 65 mg/m2 were planned with a possible dose de-escalation to 20 mg/m2
- Rolling-six design was used for dose escalation
- MTD was defined as the maximum dose at which fewer than one-third of patients experienced DLT during cycle 1 of therapy
- Once the MTD or RP2D were defined, 12 additional patients were included in a PK expansion cohort to acquire additional PK data in subjects under 12 years of age
- Part B was designed to enroll patients with recurrent /progressive HGG not requiring surgical resection to be treated at the MTD on the schedule with the highest mean Cmax as determined in Part A
- See **figure 1** for breakdown of patients in each group
- Toxicities graded according to CTCAE version 5.0



Response and PK/PD Studies

- Radiographic Response Assessment
  - Solid Tumors: Response Evaluation Criteria in Solid Tumors (RECIST, version 1.1)
  - CNS Tumors: Modified Response Assessment in NeuroOncology (RANO)
  - Performed at end of cycles 1, 3 and 5, and every 3 cycles thereafter
  - Objective responses required two consecutive 2D measurements on standard imaging done 4 weeks apart.
  - Partial or complete responses and prolonged stable disease (≥ 6 cycles) required central review.
- PK Studies
  - Blood samples were drawn prior to and at 0.5, 1, 2, 3, 4, 6, 8, and 24 hours following the first dose
- PD Studies
  - Blood samples were drawn prior to and 4 hours after the first dose

Figure 1



3. Results

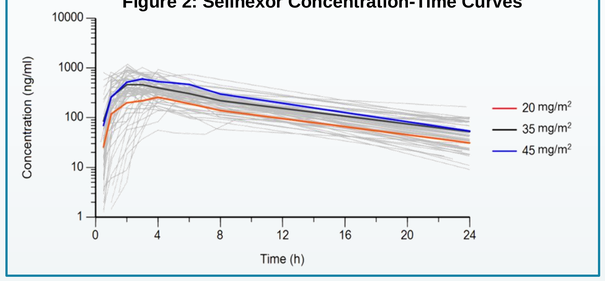
Table 2: Dose Escalation and DLT Summary

Dose Level	Selinexor Dose	Schedule (4 week cycles)	Part	Number of Patients Entered	Number of Patients Evaluable	Number of Patients Inevaluable	Number of Patients with Cycle 1 DLT	Cycle 1 DLTs Observed	Number of Patients with Later-Cycle DLTs
DL 1*	35 mg/m²	Twice weekly continuously	Part A	6	6	0	0		1
DL 1	35 mg/m² (DL 1)	Twice weekly weeks 1-3	Part A	13	12	1	4	Fatigue (2), ALT increase, platelet decrease	1
DL -1	20 mg/m² (DL -1)	Twice weekly weeks 1-3	Part A	6	6	0	1	ALT/AST increase	.
DL -1	20 mg/m² (DL -1)	Twice weekly weeks 1-3	PK	6	6	0	2	Acute neurologic change, neutropenia	1
WDL 1	45 mg/m² (Weekly Dose Level (WDL) 1)	Weekly continuously	Part A	6	6	0	2	Platelet decrease, seizure	.
WDL -1	35 mg/m² (WDL-1)	Weekly continuously	Part A	6	6	0	1	Platelet decrease	.
WDL -1	35 mg/m² (WDL-1)	Weekly continuously	PK	6	6	0	0		.
WDL -1	35 mg/m² (WDL-1)	Weekly continuously	Part B	10	7	3	0		.

Common cycle 1 DLT's included elevated LFTs, thrombocytopenia, and fatigue.

3. Results, continued

Figure 2: Selinexor Concentration-Time Curves



At weekly dose level 1 (WDL1, 45 mg/m2 /dose), 2/6 patients experienced DLT (prolonged grade 2 neutropenia, and grade 3 seizure). The dose was de-escalated to 35 mg/m2 (WDL -1) and only 1/6 patients experienced DLT (grade 3 thrombocytopenia); 35 mg/m2 was thus declared the MTD on the QW schedule and the overall initial RP2D.

Table 3: Selinexor First Dose PK Data

Dose	Schedule[a]	N	T_{max} (hrs)	C_{max} (ng/mL)	Half-life (hrs)	$AUC_{0\text{-}24h}$ (hrs•ng/mL)	CL/F (L/hr/m^2)	V/F (L/m^2)
20 mg/m^2	DL -1	12	3.6±1.5	324±116	7.2±1.2	2774±815	7.0±1.6	73.1±22.9
35 mg/m^2	DL 1*, DL 1 and WDL -1	41	3.4±3.9	599±254	7.5±3.4[c]	4885±1476	6.9±2.1	73.3±39.9
45 mg/m^2	WDL 1	4	3.5±1.7	755±238	6.0±1.7	6195±1593	6.9±1.5	59.2±23.0

[a] Schedule (DL1*: BIW continuously; DL 1 and DL -1: BIW weeks 1-3; WDL 1 and WDL -1: QW continuously)

4. Conclusions

1. Selinexor-related toxicities were primarily hematologic and neurologic requiring dose or dose-frequency reduction.
2. The MTD and recommended initial phase 2 dose of selinexor in children and adolescents with recurrent solid and CNS tumors is 35 mg/m^2/dose QW.
3. Supportive care interventions, such as eltrombopag or romiplostim for thrombocytopenia and filgrastim for neutropenia, were not evaluated in this trial but could be considered in future studies
4. A phase 1/2 study of selinexor in combination with radiation for pediatric patients with newly diagnosed HGG (COG ACNS1821, NCT05099003) has been initiated with a plan to try to further escalate QW dosing in a treatment naïve population.

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