

A Phase II Study of Alisertib in Children with Recurrent/Refractory Solid Tumors or Leukemia: Children's Oncology Group Phase I and Pilot Consortium (ADVLO921)

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Abstract

Purpose: Aurora A kinase (AAK) plays an integral role in mitotic entry, DNA damage checkpoint recovery, and centrosome and spindle maturation. Alisertib (MLN8237) is a potent and selective AAK inhibitor. In pediatric preclinical models, antitumor activity was observed in neuroblastoma, acute lymphoblastic leukemia, and sarcoma xenografts. We conducted a phase 2 trial of alisertib in pediatric patients with refractory or recurrent solid tumors or acute leukemias (NCT01154816).

Patients and Methods: Alisertib (80 mg/m²/dose) was administered orally, daily for 7 days every 21 days. Pharmacogenomic (PG) evaluation for polymorphisms in the AURK gene and drug metabolizing enzymes (UGT1A1*28), and plasma pharmacokinetic studies (PK) were performed. Using a 2-stage design, patients were enrolled to 12 disease strata

(10 solid tumor and 2 acute leukemia). Response was assessed after cycle 1, then every other cycle.

Results: A total of 139 children and adolescents (median age, 10 years) were enrolled, 137 were evaluable for response. Five objective responses were observed (2 complete responses and 3 partial responses). The most frequent toxicity was myelosuppression. The median alisertib trough concentration on day 4 was 1.3 μmol/L, exceeding the 1 μmol/L target trough concentration in 67% of patients. No correlations between PG or PK and toxicity were observed.

Conclusions: Despite alisertib activity in pediatric xenograft models and cogent pharmacokinetic-pharmacodynamic relationships in preclinical models and adults, the objective response rate in children and adolescents receiving single-agent alisertib was less than 5%.

Introduction

The Aurora kinase family is essential in the regulation of chromosome segregation and cytokinesis during mitosis (1).

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Aurora A kinase (AAK) plays an integral role in mitotic entry, DNA damage checkpoint recovery, and centrosome and spindle maturation (1). Aurora A is overexpressed in many adult tumors including bladder, breast, lung, and head and neck cancers (1-4); as well as pediatric malignancies (5-8). The Aurora A kinase gene (AURK) has 2 common polymorphisms; the phe31Ile polymorphism, which alters the kinase function and is associated with tumorigenesis or advanced cancers (9, 10); and the Va571Ile polymorphism, which in combination with phe31Ile may be associated with an increased risk of cancer- or treatment-related adverse events (11-14).

Alisertib (MLN8237) is a potent and selective AAK inhibitor previously investigated alone and in combination with chemotherapy as a potential treatment for patients with relapsed/refractory peripheral T-cell lymphoma as well as advanced solid tumors (15-18). In preclinical models, antitumor activity and maximum pharmacodynamic effect were associated with alisertib concentrations exceeding 1 μmol/L (18, 19). In adults, the recommended dose of alisertib is 50 mg twice daily for 7 days with associated dose-limiting toxicities (DLT) of neutropenia and stomatitis (20). The maximum concentration (C_{max}) and area under concentration time curve (AUC) following administration of 50-mg enteric coated tablets were 2.9 μmol/L and 20.9 μmol/L·h, respectively; and the steady state trough concentration (C_{min}) exceeded 1 μmol/L (21).

Translational Relevance

The Aurora kinases are a family of serine-threonine kinases that play an essential role in regulating chromosome assembly and segregation during mitosis and are critical for cell proliferation. Aurora A dysregulation has been implicated in cancer, and as such, is a rational therapeutic target. This phase 2 study of alisertib (MLN2837), an oral small molecular inhibitor of Aurora A kinase, was evaluated in 137 pediatric patients with relapsed/refractory solid tumors or acute leukemia. The lack of robust objective responses suggests that alisertib, as a single agent, has limited anti-tumor activity and alternative strategies, including novel combinations simultaneously targeting other oncogenic signaling pathways, should be explored to harness this pathway and simultaneously minimize toxicity. The continuous treatment schedule of alisertib, which was shown to be more effective in preclinical models than the 1-week administration schedule, was not feasible in the clinical setting, providing a potential explanation for the differential observed between preclinical and clinical anti-tumor activity.

Pharmacokinetic parameters derived from a population pharmacokinetic (PK) model based on data from 363 adults enrolled on 7 alisertib single-agent trials showed a terminal half-life of 19.3 hours and an apparent clearance (CL/F) of 4.25 L/h (22). Although the major metabolic pathway of alisertib is glucuronidation via the UDP-glucuronosyltransferase, UGT1A1, alisertib CL/F was not altered in adult subjects with UGT1A1*28 polymorphisms. Single-agent phase II trials of alisertib demonstrated modest activity in adults with ovarian cancer (23), acute myeloid leukemia (AML; ref. 24), and T- or B-cell lymphoma (17).

In the Pediatric Preclinical Testing Program (PPIP) alisertib was active in neuroblastoma (NBL) and acute lymphoblastic leukemia (ALL) xenografts with maintained complete responses observed in 3 of 7 NBL xenografts and 6 of 6 ALL xenografts; sustained concentrations $\geq 1 \mu\text{mol/L}$ were associated with response (25). Statistically significant improvement in event-free survival (EVS) in Wilms tumor (WT), rhabdomyosarcoma (RMS), and osteosarcoma (OS) xenograft models was also observed (26). In these preclinical studies, alisertib was administered 5 days per week for 3 and 6 consecutive weeks for ALL and solid tumor models, respectively. In addition, alisertib was active in p53-wild-type, therapy-refractory NBL cell lines (27), as a result of disruption of the Aurora-A/N-Myc complex resulting in inhibition of N-Myc dependent transcription (28). Alisertib has also been shown to induce cell death and augment radiation sensitivity in atypical teratoid rhabdoid (ATRT) cell lines that overexpress AAK and have mutations in SMARCB1 (SNF5/INI1), a tumor suppressor and component of chromatin remodeling (7).

Based on the preclinical antitumor activity in pediatric cell lines and xenograft models and the clinical antitumor activity in adult trials, a Children's Oncology Group phase I trial of alisertib in children and adolescents with relapsed or refractory solid tumors evaluated both once daily and twice daily schedules (29). The recommended phase II dose and schedule was 80 mg/m² orally, once daily for 7 days. DLTs included myelosuppression,

mood alterations, somnolence, mucositis, fatigue, alopecia, elevated hepatic transaminases, agitation, and euphoria. In contrast to adults, the twice daily schedule in children resulted in a higher frequency of neutropenia and palmar-plantar erythrodysesthesia. There was marked inter-patient variability in the alisertib PK parameters in children. At the recommended dose, the C_{max} and AUC were $7.5 \pm 0.1 \mu\text{mol/L}$ and $75 \pm 13.5 \mu\text{mol/L}\cdot\text{h}$, respectively. The alisertib trough 24 hours after the first dose at the 80 mg/m² dose level was 1.1 $\mu\text{mol/L}$. Of 33 response evaluable children in the phase I trial, 1 with hepatoblastoma (HBL) had a PR and 8 [NBL ($n = 4$) and sarcoma ($n = 4$)] had stable disease for 5 to 35 cycles (29).

Based on the mechanism of action and preclinical activity of alisertib, a phase II trial was conducted to evaluate the objective response rate of alisertib in children and adolescents with relapsed/refractory solid tumors or acute leukemia. In parallel, and subsequent to the establishment of a dose and schedule for alisertib in a pediatric population, we selected 2 ALL xenografts against which we have previously reported single-agent alisertib efficacy at a dose resulting in drug plasma levels that are achievable in humans for additional testing to compare dosing schedules.

Patients and Methods

Patient population

Patients with relapsed or refractory cancer were enrolled in 1 of 12 strata based on histology, including 2 strata for NBL; one for those with measurable disease by CT or MRI and another for those with disease evaluable by MIBG scintigraphy, but no measurable disease. Patients with NBL limited to the bone marrow were not eligible. Patients with other solid tumors were required to have measurable disease as defined by RECIST 1.1 (30). Strata for patients with sarcoma included rhabdomyosarcoma (RMS), non-RMS soft tissue sarcoma (NR-STS), OS, or Ewing sarcoma (EWS)/peripheral PNET. Additional solid tumor strata included enrollment of patients with WT, hepatoblastoma (HBL), malignant germ cell tumors (GCT), and rhabdoid tumors (central nervous system atypical teratoid rhabdoid or other malignant rhabdoid tumors) with loss of INI1 by IHC or molecular analysis. Patients with hematologic malignancies without CNS involvement who were refractory or recurrent after at least 2 prior induction chemotherapy regimens, including those with AML and at least 5% myeloblasts in the bone marrow or those with ALL and greater than 25% blasts (M3) in bone marrow, were also eligible. Subjects enrolled on the COG phase I trial (ADV0812) who received alisertib at the recommended phase II dose and who met criteria for inclusion in 1 of the 12 disease stratum defined in this trial were included in this study population by prospective design (29).

Patients were required to swallow alisertib tablets intact. Other inclusion criteria included age >12 months and <22 years; performance status of ≥ 50 by the Karnofsky scale for patients >16 years or by the Lansky scale if ≤ 16 years; adequate renal function (normal serum creatinine for age and gender); and hepatic function (total bilirubin ≤ 1.5 -fold greater than the upper limit of normal, alanine aminotransferase (ALT) less than 225 U/L, and serum albumin of at least 2 g/dL) was required. In patients with solid tumors, bone marrow function for patients without known tumor infiltration of bone marrow included an absolute neutrophil count (ANC) $\geq 1,000/\mu\text{L}$, platelet count

$\geq 100,000/\mu\text{L}$, and hemoglobin ≥ 8 g/dL; for patients with solid tumors and known bone marrow metastatic disease an ANC $\geq 750/\mu\text{L}$, platelet count $\geq 50,000/\mu\text{L}$, and hemoglobin ≥ 8 g/dL were required. Patients with leukemia could enroll if they were not refractory to red blood cell or platelet transfusions.

Patients were required to have recovered from the acute toxic effects of all prior treatment. Requirements for the interval of time from prior therapy were standard (29). Exclusion criteria included uncontrolled infection; pregnancy; lactation; concurrent administration of selected P-glycoprotein substrates (digoxin, cyclosporine, tacrolimus or sirolimus); or use of daily benzodiazepines, because of the potential benzodiazepine-like effects of alisertib.

This study was conducted in compliance with the Declaration of Helsinki, the International Conference on Harmonization, Guideline for Good Clinical Practice, and applicable national and local regulatory requirements. Institutional Review Boards at participating institutions approved the study. Informed consent was obtained from patients, ages 18 years or older, or from parents/legal guardians of children aged less than 18 years, with child assent when appropriate, according to institutional policies.

Treatment program

Alisertib (Millennium Pharmaceuticals, Inc.) was distributed by the NCI Cancer Therapy Evaluation Program as 10-mg enteric-coated tablets. Alisertib ($80\text{ mg}/\text{m}^2$) was administered orally once daily for 7 consecutive days. Cycle duration was 21 days. The dose was reduced to $60\text{ mg}/\text{m}^2$ for reversible toxicity as outlined in the protocol. The maximum daily dose of alisertib was 160 mg. Adherence was monitored using daily dosing diaries completed by the patient or parent/guardian. In the absence of progressive disease or unacceptable toxicity, the maximum total duration of protocol therapy was 35 cycles, approximately 2 years.

Toxicity monitoring and dose modifications

The Common Terminology and Adverse Events (CTCAE v 4.0) criteria were used to grade toxicity. Prior to each cycle, physical examination, complete blood count (CBC), serum electrolytes, creatinine, and liver function tests were performed. During cycle 1, physical examinations and serum chemistries were performed weekly; CBCs were performed twice weekly. In subsequent cycles, CBCs were performed weekly or more frequently if hematologic toxicity occurred.

Response

Disease evaluations were performed at baseline, the end of cycle 1 and after completion of every other cycle of protocol therapy. In patients with non-CNS solid tumors, response was assessed using RECIST version 1.1 criteria (30). Response in NBL subjects with nonmeasurable but MIBG evaluable disease was assessed using the Curie Score criteria (31). Response for subjects with AML was assessed using the International Working Group Criteria (32) and for those with ALL response was defined by morphology. Response in patients with central nervous system ATRT was assessed based on the sum of the products of the longest diameter \times perpendicular diameter. All objective responses were confirmed by central review.

Any eligible patient who received at least 1 dose of alisertib was considered evaluable for response provided: (i) the patient was observed on protocol therapy for at least 1 cycle and the tumor was not removed surgically prior to the time an objective response was confirmed; or (ii) the patient demonstrated a

complete or partial response as confirmed by central review; or (iii) the patient demonstrated progressive disease or died while on protocol therapy. All other evaluable patients with solid tumors were considered to be nonresponders. The maximum evaluation period for determination of the overall best response was 6 treatment cycles for ADVL0921; the evaluation period for determination of overall best response for ADVL0812 was the time from enrollment to termination of protocol therapy.

Pharmacokinetics and pharmacogenomics

To characterize the PKs of alisertib in children and adolescents, blood samples (3 mL, EDTA) were required in all participants during cycle 1 prior to alisertib administration on days 1, 4 ± 1 , and 7 ± 1 . If consent was provided, optional sampling was performed at 1 to 2, 3 to 4, and 6 to 8 hours after the first dose. Plasma was stored at -80°C until analysis. Alisertib concentrations were measured as previously described and PK parameters were calculated using noncompartmental analyses (29, 33).

Consenting patients provided whole blood in EDTA tubes prior to day 7 of the first cycle for genotyping of patients for germline polymorphisms in UGT1A1 or aurora AAK gene (AURK, Phe31Ile, and Val57Ile). DNA was extracted by QIAamp DNA Blood Mini Kit as per manufacturer's instructions. Methods were validated with a panel of 60 Caucasian DNA samples from the Coriell Institute. Positive and negative controls were included for each analysis. For UGT1A1 *28 (rs1875347), the number of TA repeats in the promoter region were detected and quantified by a modification of the method described by Akaba and colleagues (34). UGT1A1 polymorphisms rs4124874 and rs10929302 were evaluated with PCR amplification and dye-terminator sequencing. Specific primers were designed and validated to amplify the region for both SNPs. Forward and reverse primers are AGTTCTCTTCACCTCCTCCT and AATAA CCCCACCTCACCAC, respectively. For AURKA, genotyping for the G>A polymorphism (rs1047972 in codon 57) and T>A polymorphism (rs2273535 in codon 31) was performed by amplification and detected on a Bio-Rad CFX384 Real-Time PCR detection system. The real-time PCR methods were validated against a standard PCR reaction with sequence detection of the polymorphisms. Primer and probe sequences were provided by Millennium Pharmaceuticals, Inc. The forward and reverse primer sequences for rs227353 were CTGGCCACTATTACAGG-TAATGGA and TGGAGGTCCAAACGTGTTCTC, respectively with probe/reporter 1 (VIC-labeled) sequence ACTCAGCAA-TTTCCTT and probe/reporter 2 (FAM-labeled) sequence CTCAGCAAATTCCCTT. The forward and reverse primer sequences for rs1047972 were CCGCTTGACTGGAGACA and GGGTC-TTGTGTCCTTCAAATTCCTC, respectively with probe/reporter 1 (VIC-labeled) sequence CAGCGGTTCCCTT and probe/reporter 2 (FAM-labeled) sequence CAGCGCATTCCCTT. The AURKA haplotypes were determined using the Phe31Ile and val57Ile SNPs as described by Ishikawa and colleagues (14).

Statistical analysis plan

A 2-stage design was used to evaluate alisertib antitumor activity in 7 primary strata: NBL with RECIST measurable disease, NBL with MIBG only evaluable disease, OS, EWS, RMS, ALL, and AML. For each of the 2 NBL strata, 14 patients were enrolled at the first stage. If no patients experienced a complete or partial response, alisertib was considered inactive in that stratum, and further enrollment to that stratum was terminated. If 1 or

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more patients achieved an objective response, 10 additional patients were enrolled to the stratum. Alisertib was active if ≥ 4 of 24 patients in an expanded stratum experienced an objective response. With this design, alisertib was identified as inactive with probability 0.96 if the true response rate was 5% and as active with probability 0.91 if the true response rate was 25%. For the other 5 secondary strata (NRSTS, HBL, GCT, WT, and rhabdoid tumors), at the first stage for each stratum, 10 patients were enrolled. If no patients experienced an objective response, alisertib was considered inactive in that stratum and enrollment was terminated. If 1 or more patients experienced an objective response, 10 additional patients were enrolled to that stratum. Alisertib was considered active if ≥ 3 of 20 patients in an expanded stratum experienced an objective response. With this design, alisertib would be identified as inactive with probability 0.93 if the true response rate was 5%, and was identified as active with probability 0.88 if the true response rate was 25%. Because of the rarity of tumors in the secondary strata, enrollment to the study was designed to be closed, irrespective of enrollment numbers, when the evaluation of the 7 primary strata was completed. If sufficient enrollment was obtained, the 2-stage design used for the non-NBL stratum was applied to the secondary stratum.

Xenograft studies

Subsequent to the prior preclinical evaluation in which alisertib was administered on a twice-daily schedule for 5 days and repeated for 3 weeks (25), the maximum tolerated dose in pediatric patients was determined to be once daily for 7 days (29). An experiment was designed to compare the preclinical and clinical schedules. ALL xenografts were generated as described previously (26, 35). ALL-8 and ALL-19 xenograft cells, generated from 2 patients with relapsed ALL, were inoculated into NOD/SCID mice and engraftment monitored by weekly flow cytometric enumeration of the percentage of human CD45 (%huCD45) cells in murine peripheral blood (PB). When the %huCD45 cells reached a median of $>1\%$ for the entire cohort, mice were randomized to receive treatment with alisertib or vehicle control. Alisertib was administered using 2 alternative schedules: schedule A, twice daily for 7 days; or schedule B, twice daily for 5 days repeated for 3 weeks. In both cases, the dose used was 10.4 mg/kg, administered by oral gavage as a suspension in 10% cyclodextrin. Groups of 4 to 6 mice were euthanized at days 0, 7, and 21 posttreatment initiation and at the end of the

evaluation period (day 42) to assess leukemic infiltration of PB, bone marrow, and spleens. An additional experimental endpoint for each mouse was when the %huCD45 cells in PB reached 25% (deemed an event). Mice were euthanized if morbid or if they experienced weight loss $\geq 20\%$. EFS, Treated-Control (T-C), T/C, and overall response measure (ORM) estimations were carried out according to established methodology (35). Individual mice were assigned an ORM depending on the leukemic growth characteristics observed in the 42 days following treatment according to the established criteria used for evaluating single agents, and the median ORM was used to obtain the group score.

Results

Patients

Characteristics for all patients are presented in Table 1. All patients ($n = 139$) were eligible. Two patients, 1 with RECIST-measurable NBL and 1 with AML, were not evaluable for response due to rapid progression of disease prior to the start of protocol therapy. The median number of treatment cycles for 137 response-evaluable patients was 2 (range, 1–35). A total of 500 cycles of alisertib were delivered. Three patients completed 35 cycles (24 months) of protocol therapy.

Toxicity

During cycle 1, 18 patients (13%) experienced dose-limiting toxicity including myelosuppression, mucositis, febrile neutropenia, enterocolitis, diarrhea, depression, hypersomnia, photophobia, tumor lysis syndrome, hyperbilirubinemia, and/or electrolyte abnormalities. The frequency of alisertib-related grade 3 and 4 toxicities is shown in Table 2. Alisertib-related grade 3 or 4 toxicities that occurred in $\geq 10\%$ of delivered cycles ($n = 500$) were anemia (13.6%), lymphopenia (12.2%), neutropenia (51.8%), thrombocytopenia (20.8%), and leukopenia (33%). During cycle 1, 2 patients had fatal adverse events possibly related to alisertib: a patient with pelvic soft tissue sarcoma experienced grade 5 respiratory failure and a patient with hepatoblastoma experienced a fatal hepatic hemorrhage.

Response

Five objective responses were observed. Two patients had complete responses, 1 patient with MIBG-only evaluable NBL (Fig. 1) and 1 patient with WT. Three patients had partial

Table 1. Patient characteristics at enrollment

	Total	NBL measur- able	NBL evaluable	AML	ALL	EWS	RMS	NR-ST5	OS	WT	HBL	GCT	MRT
Eligible (N)	139	25	24	11	10	10	10	10	10	10	8	7	4
Age (years) ^a	10 (2–21)	9 (3–20)	8 (4–19)	10 (3–15)	13 (7–19)	14 (6–20)	12 (4–21)	15 (9–20)	17 (12–21)	10 (3–18)	6 (3–14)	11 (3–19)	5 (2–7)
Female (%)	45%	48%	29%	55%	30%	30%	70%	50%	30%	70%	38%	57%	50%
Race, n (%)													
Caucasian	80 (58%)	19 (76%)	15 (63%)	2 (18%)	5 (50%)	8 (80%)	7 (70%)	4 (40%)	7 (70%)	5 (50%)	4 (50%)	4 (57%)	-
Black	21 (15%)	2 (8%)	4 (17%)	2 (18%)	2 (20%)	-	1 (10%)	1 (10%)	2 (20%)	2 (20%)	-	-	3 (75%)
Other	6 (4%)	0 (0%)	2 (8%)	1 (9%)	-	-	-	-	1 (10%)	-	1 (10%)	1 (14%)	-
Not specified	32 (23%)	4 (16%)	3 (12%)	6 (55%)	3 (30%)	2 (20%)	2 (20%)	5 (50%)	-	3 (30%)	1 (10%)	2 (29%)	1 (25%)
Ethnicity, N (%)													
Hispanic	30 (22%)	3 (12%)	1 (4%)	4 (36%)	2 (20%)	1 (10%)	1 (10%)	3 (30%)	3 (30%)	4 (40%)	3 (38%)	4 (57%)	1 (25%)
Non-Hispanic	97 (70%)	19 (76%)	22 (92%)	5 (46%)	8 (80%)	8 (80%)	7 (70%)	6 (60%)	7 (70%)	5 (50%)	5 (62%)	2 (29%)	3 (75%)
Not reported	12 (8%)	3 (12%)	1 (4%)	2 (18%)	-	1 (10%)	2 (20%)	1 (10%)	-	1 (10%)	-	1 (14%)	-

^aMedian (range).

MRT, malignant rhabdoid tumor (2 patients with CNS atypical teratoid rhabdoid tumors and 2 patients with extracranial malignant rhabdoid tumors).

Table 2. Frequency of alisertib-related grade 3 or 4 toxicity in all cycles ($n = 500$)

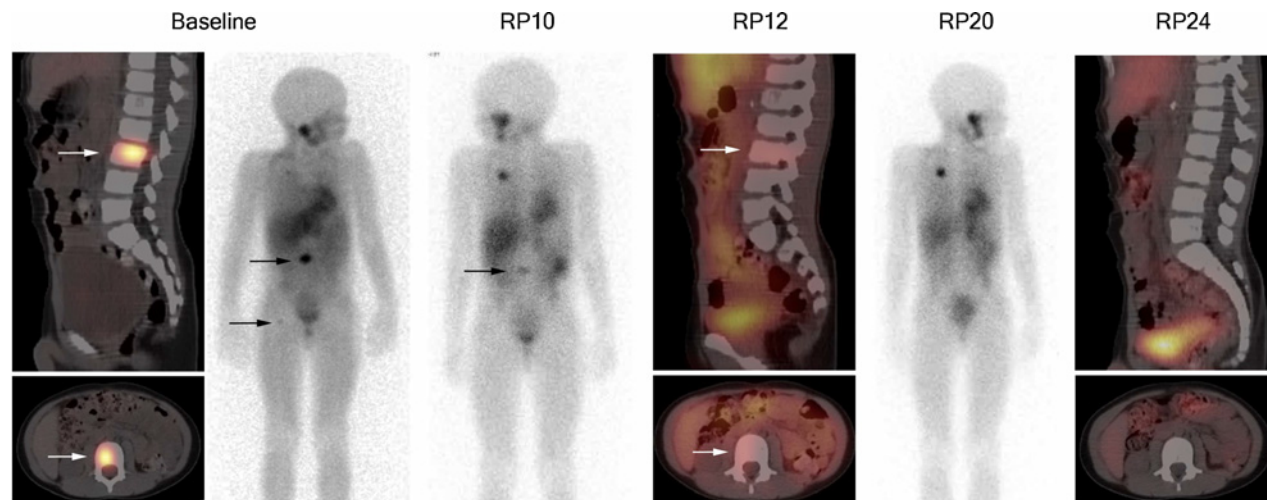
CTCAE class	Toxicity	Grade 3, n (%)	Grade 4, n (%)	Grade 5, n (%)
Hematologic	Anemia	63 (12.6%)	5 (1%)	
	Febrile neutropenia	18 (3.6%)		
	Lymphopenia	47 (9.4%)	14 (2.8%)	
	Neutropenia	124 (24.8%)	137 (27.4%)	
	Thrombocytopenia	54 (10.8%)	50 (10%)	
	Serum amylase increased	1 (0.2%)		
	Leukopenia	117 (23.4%)	48 (9.6%)	
Eye disorders	Photophobia	1 (0.2%)		
Gastrointestinal	Diarrhea	2 (0.4%)		
	Enterocolitis	1 (0.2%)		
	Oral mucositis	19 (3.8%)		
	Oral pain	5 (1%)		
	Nausea	2 (0.4%)		
	Vomiting	2 (0.4%)		
Investigations (laboratory)	ALT increased	17 (3.4%)		
	AST increased	10 (2%)		
	Hyperbilirubinemia	3 (0.6%)		
	GGT increased	1 (0.2%)		
	INR increased	1 (0.2%)		
Infection	Infection	1 (0.2%)		
	Pneumonia	1 (0.2%)		
	Urinary tract infection	1 (0.2%)		
Metabolism/nutrition	Anorexia	1 (0.2%)		
	Dehydration	6 (1.2%)		
	Hyperuricemia		1 (0.2%)	
	Hypoalbuminemia	1 (0.2%)		
	Hypocalcemia	1 (0.2%)		
	Hypokalemia	4 (0.8%)	1 (0.2%)	
	Hyponatremia	3 (0.6%)		
	Hypophosphatemia	1 (0.2%)		
Tumor lysis syndrome			1 (0.2%)	
Psychiatric	Depression		1 (0.2%)	
Neurological	Dizziness	14 (2.8%)		
	Hypersomnia	1 (0.2%)		
Hepatobiliary	Hepatic hemorrhage			1 (0.2%)
Respiratory	Respiratory failure			1 (0.2%)
Skin/dermatological	Palmar-plantar erythrodysesthesia	2 (0.4%)		

responses, 1 each with RECIST-measurable NBL, MIGB evaluable NBL and HBL. The patient with HBL and partial response was previously reported in the phase I trial (29). Unlike the phase I study (ADVL0812), prolonged stable disease was not considered as a response in this trial and was not centrally reviewed. No responses were achieved in the other primary disease strata (OS, EWS, RMS, ALL, AML). The objective responses are summarized in Table 3 and includes the number of cycles of alisertib administered for patients with a best response of stable disease. Accrual to secondary strata (HBL, WT, GCT, NRSTS) was discontinued due to insufficient response in the primary strata. At the time the study was closed, accrual to the first stage was not completed for HBL, GCT, or rhabdoid tumors.

Pharmacokinetics and pharmacogenomics

Forty-five patients provided consent for optional PK samples on ADVL0912 and 2 patients from ADVL0812 had trough levels obtained on day 4. The alisertib PK parameters were highly variable (Supplementary Table S1). There was no correlation between age or gender and alisertib C_{min} or AUC. The alisertib C_{max} exceeded $1 \mu\text{mol/L}$ in 98% (44/45) of patients participating in detailed PK studies on day 1. The median C_{min} on day 4 was $1.6 \mu\text{mol/L}$, exceeding $1 \mu\text{mol/L}$ target trough concentration in 67% (26/39) of patients. The median C_{min} on day 7 was $0.9 \mu\text{mol/L}$, exceeding $1 \mu\text{mol/L}$ in 41% of patients (11/27).

A total of 87 patients underwent genotyping for AURKA and UGT1A1 (Table 4). There was no relationship between cycle 1 toxicity and either the Phe31Ile or Val57Ile SNPs in the AURKA genotype or in the AURKA haplotypes (Table 5). There was no relationship between \geq grade 2 toxicities and AURKA genotype for the Ile31Phe SNP or the AURKA haplotypes. However, patients that were heterozygous (WV) for the Val57Ile SNP appeared to have fewer \geq grade 2 toxicities (Table 5). Given the small patient cohort, it is not possible to determine if this is clinically significant. In addition, there were no relationships between treatment response and AURKA genotype for either SNP.

**Figure 1.**

Sagittal and axial SPECT/CT images from ^{125}I -MIBG examination performed at baseline, reporting periods (RP) 12 and 24; ^{125}I -MIBG anterior projection planar images at baseline, RP10 and RP 20. Each reporting period is 1 cycle. Arrows indicate MIBG-avid NBL in the L3 vertebral body and proximal right femur. The other areas of MIBG positivity on planar images include physiologic uptake in liver, salivary glands, renal collecting system, GI tract, and excretion in bladder. Uptake projecting of the thorax at RP 10 and 10 is residual tracer at the port injection site.

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Table 3. Responses to alisertib

Stratum	Response evaluable	Responder		Nonresponders		
		Complete response	Partial response	Stable disease, <i>n</i> patients, median (range) cycles administered	Nonresponders	Progressive disease
NBL (measurable)	24		1	2 (6, 13 cycles)	5	16
NBL (MIBG evaluable)	24	1	1	9 [13 (5-35) cycles]	4	9
ALL	10			3 (1, 2, 2 cycles)	1	6
AML	10				10	
EWS	10			3 (4, 5, 5 cycles)	2	5
Rhabdo-myosarcoma	10			1 (15 cycles)	2	7
NR-ST5	10			1 (5 cycles)	2	7
OS	10				2	8
Wilms tumor	10	1		1 (31 cycles)	1	7
Hepatoblastoma	8		1 ^a	1 (5 cycles)	2	4
Germ cell tumor	7			2 (4 and 5 cycles)	1	4
Rhabdoid tumors	4				1	3
Total	137	2	3	23	33	76

^aReported previously in ADVL0812 publication (29).

Paired data for UGT1A1 phenotype and day 4 C_{min} was obtained in 32 patients. There did not appear to be a difference in day 4 C_{min} between the intermediate (IM) and poor metabolizer (PM) phenotypes, therefore, the data for these patients were pooled (Table 6). The mean \pm SE alisertib trough concentration for the extensive metabolizer group (EM, $n = 16$) was $1.01 \pm 0.23 \mu\text{mol/L}$ (95% CI, 0.53–1.49 $\mu\text{mol/L}$) and for IM/PM ($n = 16$) was $2.06 \pm 0.30 \mu\text{mol/L}$ (95% CI, 1.42–2.70 $\mu\text{mol/L}$). The difference in the population means, 1.05 $\mu\text{mol/L}$ (95% CI, 0.28–1.82 $\mu\text{mol/L}$), was statistically significant (P value of pooled t test, 0.0091). The mean alisertib trough concentration for patients with and without \geq grade 2 toxicities were $1.50 \pm 0.25 \mu\text{mol/L}$ (95% CI, 0.96–2.04 $\mu\text{mol/L}$) and $1.58 \pm 0.35 \mu\text{mol/L}$ (95% CI, 0.83–2.32 $\mu\text{mol/L}$), respectively. The difference in the population means, 0.08 $\mu\text{mol/L}$ (95% CI, -0.79 –0.94 $\mu\text{mol/L}$), was not statistically significant. Although alisertib trough concentrations were statistically significantly higher for IM/PM patients, there did not appear to be a relationship with the occurrence of \geq grade 2 toxicity (P value = 0.86). Furthermore, we found no significant interaction between EM (yes/no) and \geq grade 2 adverse events (yes/no) (P value = 1.0; Table 6).

Xenograft studies

For the T-lineage ALL-8, based on serial PB parameters, leukemia progression was significantly delayed compared to vehicle control for both of the treatment schedules, resulting in increased EFS (Fig. 2; Table 7). Leukemia progression was delayed by an additional 12.1 days in mice treated with schedule B compared

with schedule A ($P = 0.004$), with T/C values 3.6 and 2.2, respectively. However, neither of the treatment schedules induced an objective response. Data are summarized in Table 7 (Supplementary Table S2). Engraftment levels for ALL-8 engrafted mice detected in the 3 compartments analyzed at autopsy (blood, bone marrow, and spleen) are shown in Supplementary Fig. S1 and Figs. 2 and 3, respectively. Treatment with both alisertib schedules limited leukemia progression to a similar extent by day 7 in all organs analyzed. These effects were not complete, with 5% to 10% human cells in the spleen and approximately 20% human cells in the bone marrow as the lowest levels achieved. schedule B was more effective than schedule A in reducing leukemia levels measured at day 21 in the 3 compartments analyzed, but the differences between the treatments were transient and after drug treatments ceased there was a rapid progression of the disease (day 42).

For the B-lineage ALL-19, based on serial PB parameters, leukemia progression was not significantly different from that of controls for schedule A (Fig. 3; Table 7). However, schedule B significantly delayed ALL-19 progression by 24.6 days relative to controls, which was 17.6 days greater than schedule A ($P = 0.048$) with T/C values 4.7 and 2.0, respectively. Furthermore, although treatment on schedule A resulted in progressive disease (PD), schedule B induced a complete response (CR). Data are summarized in Table 7 and Supplementary Table S2. Engraftment levels for ALL-19 engrafted mice detected in the 3 compartments analyzed at autopsy (blood, bone marrow,

Table 4. AURKA, UGT1A1^{c28}, and UGT1A1 PBREM genotype distribution

Gene	RsSNP ID	Description	Genotype ^a (WW/WV/VV)
AURKA	rs2273535	91 A>T, Ile31Phe	51/27/8 ^b
	rs1047972	169 G>A, Val57Ile	63/21/2 ^b
UGT1A1 ^{c28}	rs8175347	TA repeat (5,6,7,8)	39/32/11
UGT1A1 PBREM	rs4124874	-3279 T>G	23/42/22
	rs10929302	-3156 G>A	46/33/8

^aW, wild-type allele; V, variant allele; for UGT1A1.^bOne sample could not be genotyped with the available DNA.

Five samples could not be genotyped with the available DNA.

^c28- WW = 66 or 57, WV = 67 or 68, and VV = 77 or 78.**Table 5.** Toxicity versus AURKA genotype

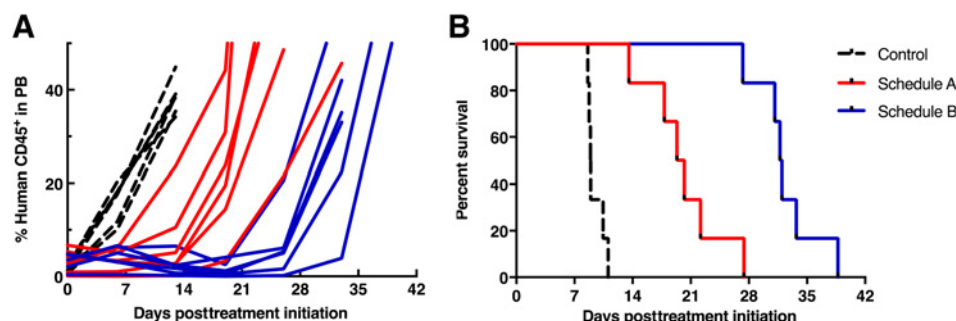
AURKA genotype		Cycle 1 DLT		Grade 2+ toxicity	
		Yes	No	Yes	No
91 A>T	Total	13	73	72	14
	WW	8	43	42	9
	WV	5	22	22	5
	VV	0	8	8	0
169 G>A	Total	13	73	72	14
	WW	10	53	54	9
	WV	3	18	17	4
	VV	0	2	1	1
Haplotype	Total	13	73	72	14
	H1	5	25	26	4
	H2	8	48	46	10

Table 6. Toxicity versus UGT1A1 metabolizer phenotype and alisertib trough concentration (C_{min}) on day 4

	EM		I/E, I, P	
	Grade \geq 2: No (n = 7)	Grade \geq 2: Yes (n = 9)	Grade \geq 2; No (n = 8)	Grade \geq 2: Yes (n = 8)
Alisertib, C_{min} (μ mol/L) mean \pm SD	0.81 \pm 0.43	1.17 \pm 1.15	2.25 \pm 1.53	1.87 \pm 0.82
Alisertib, C_{min} (μ mol/L) median (range)	0.99 (0.2-1.24)	0.53 (0.08-3.51)	2.22 (0.6-5.65)	1.80 (0.97-3.10)

Figure 2.

Percentage of huCD45⁺ cells in PB over time (A), and event-free survival curves (B) for ALL-8 engrafted NOD/SCID mice treated with alisertib at 10.4 mg/kg twice daily for 7 days (schedule A, red), or twice daily for 5 days repeated for 3 weeks (schedule B, blue) in relation to vehicle-treated controls (dotted line).



and spleen) are shown in Supplementary Fig. S1 and Figs. 2 and 3, respectively. They followed a similar pattern to those of ALL-8, with the exception of being higher at day 7, particularly in the bone marrow.

Discussion

In this phase II study, antitumor activity of alisertib was evaluated in 137 children and adolescents in 7 primary and 5 secondary disease strata. We demonstrated that children achieved target concentrations established in adults and preclinical models. The higher alisertib trough concentration in patients with intermediate and poor metabolizer UGT1A1 phenotypes compared with the extensive metabolizer phenotype was statistically significant. However, we did not find a difference in frequency of toxicity among these groups. Evaluation of AURK somatic mutation status and AAK expression in archival tumor specimens from children enrolled on this study was not performed; therefore, the impact of enrollment stratification by somatic mutation or expression in tumors of children enrolled on this trial is unknown. Pharmacogenomic profiling of germline AURKA in adults has focused on cancer susceptibility and early adverse reactions (14). In this study, we evaluated germline AURKA SNPs and did not find correlation with toxicity during cycle 1 or response.

Despite striking efficacy in pediatric xenograft models in which objective responses were reported in 80% of solid tumor pediatric solid tumor models and all leukemia models (26), the objective response rate in children and adolescents receiving single-agent alisertib on this trial was less than 5%. In patients receiving 50 mg

twice a day, the C_{max} and AUC_{0-24 h} were 1.3 and 40 μ mol/L h, respectively (25). At the recommended phase II dose of 50 mg twice a day for 7 days, average trough concentrations exceeded 1 μ mol/L, the efficacious concentration estimated in previous preclinical work. In mice receiving alisertib at 10 mg/kg, the C_{max} and AUC_{0-24 h} were 16 and 39 μ mol/L h, respectively, with the 12 hours level being 1.2 μ mol/L (25). These data suggest that continuous drug exposure above 1 μ mol/L throughout each 24-hour dosing period which can only be achieved with twice-daily dosing in mice, is crucial for antitumor activity. The initial preclinical studies evaluating alisertib in pediatric patient-derived xenograft models used a dose and schedule that was used in preclinical assessment of adult cancer models in an attempt to mirror pharmacokinetic-pharmacodynamic relationships expected to be tolerated in humans. However, the continuous treatment schedule was too myelosuppressive in adult phase I studies and a 7-day on, 14-day off regimen was adopted to minimize toxicity. Thus, we hypothesized that the dose and schedule used in our trial might account for the discordance between the preclinical and clinical activity observed.

Concurrent with this trial, we tested alisertib in ALL xenograft models utilizing an intermittent dose and schedule, and found significantly less efficacy compared with the previously tested schedule. This demonstrates an important point in the clinical translation of new agents. Although careful consideration is made to maximize the clinical relevance and translatability of preclinical oncology studies, numerous variables can influence the extent to which a drug against a given target will cause toxicity. This study highlights the critical importance of performing reverse translational studies to rigorously reproduce results when dose or

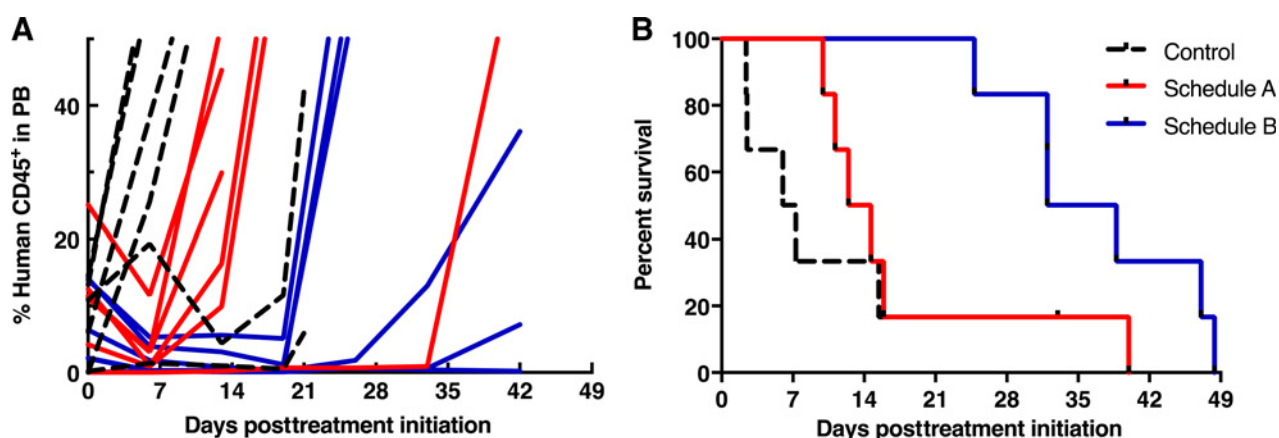
Table 7. Leukemic growth delay summary and clinical scoring for the 2 treatment schedules for xenografts ALL-8 and ALL-19

Treatment schedule ^a	Median EFS (days)		EFS T-C (days)	EFS T/C	P value ^b	Median response score	
	Control	Treated					
ALL-8	Schedule A	8.9	19.8	10.9	2.2	0.002	PD2
	Schedule B	8.9	31.9	23.0	3.6	0.002	SD
ALL-19	Schedule A	6.6	13.6	7.0	2.0	0.584	PD2
	Schedule B	6.6	31.2	24.6	4.7	0.002	CR

^aSchedule A, twice daily \times 7 days; schedule B, twice daily \times 5 days \times 3 weeks.

^bStatistically significant results.

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**Figure 3.**

Percentage of huCD45⁺ cells in PB over time (A), and event-free survival curves (B) for ALL-19 engrafted NOD/SCID mice treated with alisertib at 10.4 mg/kg twice daily for 7 days (schedule A, red), or twice daily for 5 days repeated for 3 weeks (schedule B, blue) in relation to vehicle-treated controls (dotted line).

schedule significantly change as a result of early-phase human clinical trials. The continuous treatment schedule of alisertib, which was shown to be more effective in preclinical models than the 1-week administration schedule, was not feasible due to toxicity to pursue in the clinical setting, providing a potential explanation for the differential observed between preclinical and clinical antitumor activity. To increase our confidence in the translation of results from preclinical studies, there needs to be continued efforts to redesign preclinical experiments as we learn from the corresponding human experience.

Identifying applicable preclinical cancer models remains a major challenge in augmenting the effectiveness of drug development and predicting success in the clinic. All models are limited and interrogating the complexity of human cancers in the laboratory remains a challenge that contributes appreciably to attrition in drug development. In recent years, patient-derived xenografts obtained by direct implants of human tumors in immunodeficient mice and then passaged directly from mouse to mouse have emerged as an important platform for translational oncology research (36). The ability of these models to predict clinical outcomes is being optimized through murine humanization strategies to improve the reach of these models as reliable tools for exploring tumor intrinsic and extrinsic heterogeneity, clonal evolution under the selective pressure of our therapies, discovery of integral biomarkers and predictability of drug response in the clinic (36). Numerous challenges and limitations remain, including the lack of a proper anatomical and metastatic niche, engraftment failure of certain tumor subtypes, access to imaging technologies for robust tumor visualization, and hurdles to achieve complete human immune system reconstitution (36).

To improve the efficiency of this 2-stage phase II trial, this trial was prospectively designed to include data from 21 patients on the phase I single-agent alisertib trial (ADVL0812), who were treated at the recommended dose and met eligibility criteria for this trial, including 5 patients with NBL-measurable disease, 12 patients with NBL-MIGB evaluable disease, 2 patients with non-RMS soft tissue sarcoma, and 2 patients with hepatoblastoma. Given the rarity of relapsed pediatric cancers, trial designs that improve efficiency are essential.

Clinical trials evaluating alisertib in combination with cytotoxic agents have shown antitumor activity in children and

adolescents with relapsed solid tumors including NBL (37, 38). Given the lack of objective response observed in this comprehensive single-agent clinical trial of alisertib as well as dose-limiting myelosuppression, alternative strategies, including novel: novel combinations simultaneously targeting other oncogenic signaling pathways or exploiting the pro-apoptotic machinery (39), should be explored to harness this pathway and simultaneously minimize toxicity.

Disclosure of Potential Conflicts of Interest

D.T. Teachey is a consultant/advisory board member for Janssen. No potential conflicts of interest were disclosed by the other authors.

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A Phase II Study of Alisertib in Children with Recurrent/Refractory Solid Tumors or Leukemia: Children's Oncology Group Phase I and Pilot Consortium (ADV0921)

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