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Phase 1 Study of Alisertib (MLN8237) and Weekly Irinotecan in Adults with Advanced Solid Tumors

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Abstract

Purpose: Aurora kinases are overexpressed or amplified in numerous malignancies. This study was designed to determine the safety and tolerability of the Aurora A kinase inhibitor alisertib (MLN8237) when combined with weekly irinotecan.

Methods: In this single center phase 1 study, adult patients with refractory advanced solid tumors received 100 mg/m^2 irinotecan intravenously on day 1 and 8 of a 21-day cycle. Alisertib at planned escalating dose levels of 20 – 60 mg was administered orally twice per day on days 1–3 and 8–10. Patients homozygous for UGT1A1*28 were excluded. The primary objective was the safety of alisertib when combined with irinotecan in order to determine the maximum tolerated dose (MTD). Secondary objectives included overall response rate by RECIST and pharmacokinetics in a planned expansion cohort of patients with colorectal cancer treated at the MTD.

Results: A total of 17 patients enrolled at 3 dose levels. Dose limiting toxicities included diarrhea, dehydration, and neutropenia. The MTD of alisertib combined with weekly irinotecan was 20 mg twice per day on days 1–3 and 8–10. One fatal cardiac arrest at the highest dose level

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Ethics approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The study protocol was reviewed and approved by the institutional review board of the University of California, Davis.

Consent to participate

All patients provided written informed consent before treatment.

Consent for publication

All authors consent to publication.

tested was deemed possibly related to drug treatment. One partial response in 11 efficacy evaluable patients (9%) occurred in a patient with small cell lung cancer. The study was terminated prior to the planned expansion in patients with colorectal cancer.

Conclusion: In contrast to prior results in a pediatric population, adult patients did not tolerate alisertib combined with irinotecan at clinically meaningful doses due to hematologic and gastrointestinal toxicities. The study was registered with ClinicalTrials.gov under study number NCT01923337 on August 15, 2013.

Keywords

Alisertib; Irinotecan; Phase I; Aurora Kinase A

INTRODUCTION

The Aurora kinases are a group of serine/threonine protein kinases that are expressed in actively dividing cells. The Aurora A kinase localizes to centrosomes and the proximal mitotic spindle during mitosis where it functions in a diverse set of mitotic processes including chromosome alignment, centrosome function, mitotic spindle assembly, and mitotic entry [1]. The Aurora A kinase gene is amplified, overexpressed, or both in many tumor types [2–5], including colorectal cancer [6].

Alisertib is an orally bioavailable, highly selective small molecule inhibitor of the serine/threonine protein kinase Aurora A kinase. In phase 1 studies, neutropenia and stomatitis were common dose limiting toxicities (DLTs) [7, 8]. The recommended phase 2 dose of alisertib as monotherapy is 50 mg twice daily on a 7-day on, 14-day off schedule. Because alisertib may have overlapping hematologic side effects (particularly neutropenia) when used in combination with cytotoxic agents, a rodent pharmacokinetic-pharmacodynamic model was developed to predict the time course of neutropenia in humans. Preliminary results from this model suggested that a daily for 3 days each week schedule in combination with cytotoxic agents would decrease the incidence of neutropenia while maintaining efficacy with a target of 700 mg of alisertib per cycle [9].

Irinotecan and its more active metabolite, SN-38, are inhibitors of topoisomerase-I, a critical enzyme that induces transient single-stranded breaks of DNA, relieving torsional strain and permitting DNA unwinding ahead of the replication fork. Irinotecan is registered for the treatment of advanced colorectal cancer and is active in several other solid tumors including small cell lung cancer [10]. Aurora A kinase overexpression is a common event in colorectal cancer and overexpression of Aurora A kinase may lead to intrinsic or acquired resistance to SN-38 in colorectal cancer cell lines [11]. Thus, concurrent inhibition of Aurora A kinase may overcome resistance to irinotecan treatment in colorectal cancer. There is preclinical evidence for at least an additive benefit for alisertib with irinotecan in neuroblastoma and glioblastoma cell lines [12, 13]. In a subset of colorectal cancer cell lines, alisertib induces robust cell cycle arrest, polyploidy, and apoptosis with evidence of an additive effect when combined with irinotecan in patient derived xenograft models [14].

On the basis of these preclinical observations, this phase 1 study was designed to define the recommended phase 2 dose of alisertib and irinotecan for further study in colorectal, esophagogastric, small cell lung, and other solid tumors.

MATERIALS AND METHODS

Patients

Eligible adult patients had histologically or cytologically confirmed metastatic or unresectable solid tumors for which standard curative or palliative measures did not exist or were no longer effective or a solid tumor for which irinotecan as monotherapy was considered standard. Patients could have been treated with any number of prior therapies as long as they were completed two weeks prior to study entry, the patient retained an ability to swallow oral medications and the Zubrod (ECOG) performance status remained between 0 and 2. Measurable or non-measurable disease was allowed but must have been assessed within 28-days of study entry. Laboratory criteria included adequate bone marrow function, normal serum total bilirubin, ALT and AST ≤ 1.5 times institutional upper limit of normal or ≤ 5.0 times institutional upper limit of normal in the presence of liver metastases, and a creatinine ≤ 1.5 times institutional upper limit of normal or creatinine clearance ≥ 60 mL/min/1.73m^2 measured by 24-hour urine collection.

As glucuronidation is the primary metabolism for both SN-38 and alisertib, exclusion criteria included a history of known Gilbert's syndrome or homozygous presence of the uridine diphosphate glucuronosyltransferase (UGT) 1A1*28 allele on pre-treatment testing. Additional exclusion criteria included prior radiation to greater than 25% of the bone marrow, therapeutic anticoagulation, active infection, non-healing wound, recent major surgery and symptomatic or uncontrolled brain metastasis. Previously treated brain metastases were allowed as long as the patient was neurologically stable and off steroids and anticonvulsants at the time of registration. Due to the potential for drug interactions, known strong CYP3A4 inducers or inhibitors were prohibited. Cardiac exclusion included myocardial infarction within 6 months prior to enrollment, New York Heart Association (NYHA) Class III or IV heart failure, uncontrolled angina, severe uncontrolled ventricular arrhythmias, or electrocardiographic evidence of acute ischemia or active conduction system abnormalities. An electrocardiogram was required prior to study entry.

The study protocol was reviewed and approved by the institutional review board of the University of California, Davis (IRB# 440954). All patients provided written informed consent before treatment. The study was registered with ClinicalTrials.gov under study number NCT01923337.

Treatment Plan

We enrolled patients in a standard 3 + 3 design with fixed doses of irinotecan and escalating doses of alisertib (Table 1). Irinotecan was administered by intravenous infusion at an initial dose of 100 mg/m^2 over 30 minutes on days 1 and day 8 of each 21-day (3-week) cycle. Alisertib was administered orally twice daily on days 1–3 and 8–10 of each 21-day treatment cycle at doses determined based on their assigned dose level (a total of 6 days per

cycle). The initial alisertib dose level corresponded to a total dose of 240 mg per cycle. Alisertib was administered on an empty stomach, separated from food for two hours before, and one hour after each dose, except for water and prescribed medications. No intra-patient dose escalation was allowed. Dose modification of both irinotecan and alisertib for grade 3 or higher toxicity was allowed according to a defined schedule specified by the protocol.

Dose limiting toxicity (DLT) was defined as any grade 3 non-hematologic toxicity not reversible to grade 2 or less within 96 hours, or any grade 4 toxicity. Grade 3 diarrhea was not considered dose-limiting unless it did not reverse to grade 2 or less with 96 hours of aggressive management. Transient grade 4 neutropenia was also not considered dose-limiting unless it did not resolve to grade 3 or less within 96 hours, or it was associated with febrile neutropenia. DLT was based on the first course of treatment. Decisions to escalate or expand a dose level were based on the first cycle of treatment. To be fully evaluable for DLT assessment, a patient must have received at least one complete cycle of treatment and be observed for at least 11 days after the cycle 1, day 10 dose of alisertib or have experienced DLT. All patients enrolled were followed for toxicity, but any patients who were not fully evaluable for DLT assessment were replaced. If DLT was experienced in exactly one of three patients, three more patients (for a total of six) were treated at that dose level. Escalation was planned in successive cohorts of three to six patients and would terminate as soon as two or more patients experienced any DLT at least possibly attributable to the study drugs at a given dose level.

Study Procedures

History, physical examination, vital signs, performance status and laboratory studies including complete blood count and comprehensive metabolic assessment were assessed prior to enrollment, weekly during cycle 1, and then once per cycle. Toxicity was graded using the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) criteria, version 4.0. Tumor measurements were performed with 28 days of cycle 1 and subsequently every 9 weeks during the study. Patients were required to maintain an administration diary with each cycle. Treatment was continued in 3-week cycles until unacceptable toxicity, progression of disease, symptomatic deterioration, the patient withdrew consent, treatment was delayed > 3 weeks due to drug-related toxicity, or the patient withdrew consent. Pharmacokinetic assessment of alisertib in combination with irinotecan was planned in an expanded cohort of patients with advanced colorectal cancer treated at the MTD.

Statistical Analysis

The primary objective of this study was to investigate the feasibility and safety of alisertib when given in combination with irinotecan to adult patients with advanced solid tumors in order to define the MTD. Planned secondary objectives included preliminary evidence of efficacy for this combination in an expanded cohort of patients with advanced colorectal cancer and the pharmacokinetics of alisertib when combined with irinotecan at the MTD. Data analysis included descriptive summaries of baseline and demographic information. Toxicities were summarized by frequency and the maximum grade over the course of all

cycles of treatment. For patients with measurable disease and at least one subsequent assessment, tumor response was analyzed using RECIST v1.1 criteria.

RESULTS

Patient Characteristics

Seventeen patients were enrolled from August 2013 to December 2015 in 3 dose levels. Enrolled patients had a median age of 57, a median ECOG performance status of 1 and had been treated with a median of 2 prior regimens (Table 2). The most common disease histology was non-small cell lung cancer (n = 5).

Dose Escalation and Toxicity

Three patients were initially enrolled at dose level 1. A summary of the outcome at each dose level is provided in Table 3. None of the initial 3 patients at dose level 1 experienced DLT. Three patients were subsequently enrolled at dose level 2. One patient experienced dose limiting severe and prolonged neutropenia starting 14 days into cycle 1 and a second patient did not experience DLT. A third patient died after sustaining cardiac arrest 14 days after initiating therapy with irinotecan and alisertib. The patient had experienced grade 2 nausea at her prior clinic visit. The patient's family subsequently reported that she developed at least grade 2 diarrhea after her second dose of treatment which had not been reported to the medical team. After extensive review of Emergency Room and hospital records, it was not possible to determine the specific initiating factor for the cardiac arrest but it was deemed possibly related to study treatment. Plausible explanations included diarrhea induced electrolyte disturbance, insulin overdose and hypoglycemia, and profound hypovolemia. The study was temporarily halted and after consultations with the IRB, the FDA and the pharmaceutical company partner, the protocol was revised to expand dose level 1 and add an intermediate dose level 1B (Table 1).

Four patients were enrolled at an expanded dose level 1. One patient was ineligible for DLT assessment after developing a deep vein thrombosis unrelated to therapy early in cycle 1 that required anticoagulation and made the patient ineligible for further treatment with the study regimen. No DLT was noted in the DLT-evaluable cohort in the expansion of dose level 1. Three patients were subsequently enrolled to the newly created dose level 1B. None of these three patients experienced DLT. Acknowledging the uncertainty surrounding the death at dose level 2 and after further consultations with the IRB, the FDA and the pharmaceutical company partner, this dose level was reopened. The first patient treated developed persistent grade 3 diarrhea on cycle 1, day 11 meeting the protocol definition of DLT. Therefore, dose level 1B was expanded by 3 further patients. Grade 4 diarrhea beginning cycle 1, day 15 and persistent grade 3 diarrhea beginning cycle 1, day 13 were observed DLTs in two separate patients enrolled to this expansion cohort of dose level 1B.

Overall, 16 of 17 patients who started treatment were evaluated for DLT. The MTD was declared to be dose level 1. The toxicity profile in all patients who received at least one dose of alisertib (Table 4) suggested significant toxicity for the combination of alisertib and irinotecan including high rates of electrolyte disturbances, diarrhea, and hematologic

toxicity. Upon review of the overall toxicity profile at the low achieved dose per cycle, it was determined that further development of the regimen at the maximum tolerated dose was not warranted, and the planned expansion at the MTD was aborted.

Tumor Response

Of 17 patients who started treatment, 11 patients received sufficient treatment to be evaluable for response. The best response was a partial response that was sustained for 9 cycles in one patient with small cell lung cancer at dose level 2 (Table 3). This patient was enrolled with progression of prior limited stage small cell lung cancer that had completed treatment with platinum, etoposide and radiation approximately 6 months prior. Two other patients had stable disease as the best response, and the remaining 8 patients with follow up imaging had disease progression.

DISCUSSION

In this dose finding phase 1 study, we observed significant toxicities when alisertib was combined with irinotecan in an adult population with refractory advanced solid tumors. The primary toxicities were gastrointestinal and hematologic, with severe toxicities frequently being observed between 10 days and 2 weeks of starting treatment. At the MTD, the total exposure to alisertib was 240 mg per cycle, far less than the target exposure of 700 mg per cycle [15]. Patient numbers were too small to make meaningful conclusions regarding efficacy.

Irinotecan can be administered in weekly, biweekly, and triweekly schedules. While the efficacy in colorectal cancer does not appear to be impacted by schedule, the different schedules have different toxicity profiles [16]. We chose the weekly schedule in this study to minimize the risk of overlapping hematologic toxicity. Additionally, we chose a modified alisertib administration schedule predicted to reduce the risk of overlapping hematologic toxicity [9]. Nonetheless, hematologic toxicity was significant in this study. Whether alternative irinotecan and alisertib schedules might have resulted in diminished overlapping toxicity is uncertain. We excluded patients homozygous for the UGT1A1*28 polymorphism who have an increased risk of hematologic toxicity with irinotecan treatment [17, 18]. Alisertib is also metabolized via this glucuronidation pathway, but there has been no indication of an interaction between UGT1A1 genotype and toxicity from alisertib to date [19]. In contrast, drug-drug interaction studies demonstrate that medications that raise the gastric pH (e.g. proton pump inhibitors) and strong CYP3A inhibitors (e.g. itraconazole) can increase the exposure to alisertib, and drugs that induce pregnane X receptor drug metabolizing enzymes including CYP3A4 (e.g. rifamipin) can reduce the exposure to alisertib [20].

Our results contrast with those from a phase 1 study of alisertib combined with irinotecan and temozolomide conducted in a pediatric population. In that study, 80% of the pediatric single agent dose (60 mg/m^2) was tolerable when combined with irinotecan and temozolomide given on a dose and schedule developed for neuroblastoma [21]. No drug-drug interaction between irinotecan and alisertib was observed via pharmacokinetic testing in this pediatric study population. A major difference in the design of that study was the

incorporation of cephalosporin prophylaxis to reduce irinotecan-associated diarrhea [22], a strategy that has not generally been applied to adult patients treated with irinotecan. However, in an expanded study of the same combination in a pediatric population with neuroblastoma, the rate of grade 3 or higher neutropenia was as high as 70% and the rate of grade 3 diarrhea was 20% [23].

Amongst adult populations, studies combining alisertib with commonly used cytotoxic agents have encountered toxicity with increasing doses of alisertib in combination with cytotoxic agents. In a phase 1 study of alisertib day 1–7 combined with docetaxel 75 mg/m^2 every 3 weeks, the MTD was 20 mg twice daily (280 mg per cycle) [24]. Similarly, the MTD of alisertib was 10 mg twice daily days 1–3, 8–10, and 15–17 (180 mg per cycle) when combined with weekly paclitaxel 80 mg/m^2 in 28 day cycles [25]. Only when paclitaxel was reduced to 60 mg/m^2 weekly was the dose of alisertib able to safely be given at 720 mg per cycle. In a randomized phase II study of this alisertib and paclitaxel regimen, 67% of patients experienced a grade 3 or higher drug-related toxicity compared to 22% of patients treated with paclitaxel 80 mg/m^2 weekly [26]. Moreover, significant hematologic and gastrointestinal toxicity was observed when alisertib was combined with a modified FOLFOX regimen, the MTD was 10 mg twice per day for 3 days in 2 week cycles [27].

A major limitation of this study is the absence of pharmacokinetic studies in the dose escalation period. Planned pharmacokinetic studies were limited to the expansion cohort at the MTD and were not performed when this expansion was abandoned. Any assessment of the activity of the combination is limited by the small sample size and heterogenous population of patients included in this phase 1 study that was performed in patients with refractory advanced solid tumors. In general, combinations of alisertib and cytotoxic agents in adult patients with solid tumors have suggested moderate evidence for efficacy but with non-trivial toxicity concerns [25–27]. Further development of this agent will require strategies that optimize the benefit while reducing the risk of overlapping toxicity.

In conclusion, in adult patients with advanced solid tumors the maximum tolerated dose of alisertib was 20 mg orally twice per day on days 1–3 and 8–10 of a 21-day cycle when combined with irinotecan 1000 mg/m^2 on days 1 and 8. Because this dose is below the known pharmacodynamically active dose range of alisertib, this schedule is not recommended for further development. Any future studies exploring alisertib and irinotecan in adult patients should consider other dosing schedules and interventions to reduce overlapping hematologic and gastrointestinal toxicity.

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Conflict of Interest

Dr. Semrad reports grants (to the University of California, Davis for conduct of this study) from Millennium Pharmaceuticals, Inc.; Dr. Kim reports personal fees from Eisai, personal fees from Celgene, grants from BMS, grants from Astellas, grants from Samumed, grants from Boston Biomedical, grants from Halozyme, grants from EpicentRx, grants from Merck, grants from Oncomed, grants from Dynavax, personal fees from Lilly, grants from NGM Biopharmaceuticals, grants from Erytech, grants from Fibrogen, grants from Eureka Therapeutics, outside

the submitted work; Dr. Gong has nothing to disclose; Dr. Li reports personal fees from Eisai, grants from Pfizer, grants from Merck, grants from Eureka, grants from OncoImmune (OncoC4), grants from Hengrui, grants from Tempus, outside the submitted work; Dr. Christensen has nothing to disclose; Dr. Arora has nothing to disclose; Dr. Riess reports personal fees from Blueprint, personal fees and non-financial support from Novartis, personal fees and non-financial support from Boehringer Ingelheim, personal fees from Celgene, non-financial support from AstraZeneca, personal fees and non-financial support from Spectrum, personal fees from Loxo Oncology, personal fees from Genentech, personal fees from Medtronic, non-financial support from Merck, non-financial support from Revolution Medicines, outside the submitted work; Dr. Gandara has nothing to disclose; Dr. Kelly reports grants and personal fees from Takeda.

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Table 1.

Dose Escalation Schema. Cycle length was 21 days.

Dose Level	Irinotecan (mg/m^2 IV) days 1 and 8	Alisertib (mg PO BID) days 1–3 and 8–10
1	100	20
1B *	100	20 AM, 30 PM
2	100	30
3	100	40
4	100	50
5	100	60

* Dose Level 1B was added during the course of the study.

Table 2.

Patient demographic, clinical, and treatment characteristics (n=17)

Characteristic	n	%
Age, years		
Median (range)	57 (22–80)	
Prior Regimens		
Median (range)	2 (1–6)	
ECOG performance status		
0	8	47
1	9	53
Gender		
Female	11	65
Male	6	35
Race/Ethnicity		
African American	3	18
Non-Hispanic White	11	65
Asian	3	18
Primary Site		
Non-Small Cell Lung	5	29
Small Cell Lung	3	18
Ampulla of Vater	2	12
Breast	2	12
Thymus	1	6
High-grade Neuroendocrine (not lung)	1	6
Head and Neck	1	6
Ovarian	1	6
Pancreas	1	6
Disease Status		
Measurable	17	100

Table 3.

Summary of Dose Escalation

Dose Level	Number of Patients		Median Cycles Started (range)	DLTs (n)	Dose Limiting Toxicity (DLT) Description	RECIST Response
	Treated	Evaluable for DLT				
1	7	6	2 (1–6)	0	None	0 PR 1 SD 4 PD 2 NA
1B	6	6	2 (1–4)	2	Grade 4 Diarrhea and Grade 3 Dehydration Grade 3 Diarrhea and Grade 3 Dehydration	0 PR 1 SD 3 PD 2 NA
2	4	4	2 (1–9)	3	Grade 4 Neutropenia Grade 5 Cardiac Arrest Grade 3 Diarrhea	1 PR 0 SD 1 PD 2 NA

PR=partial response; SD=stable disease; PD=progressive disease; NA=not assessed (did not complete 2 cycles of therapy)

Table 4.

Major Treatment-Related Toxicities by Grade

	Any Grade[1]		Grade 3–5[2]	
	N	%	N	%
Any	16	94	11	65
Abdominal pain	3	18	0	0
Alanine aminotransferase increased	4	24	0	0
Alkaline phosphatase increased	3	18	1	6
Anemia	14	82	3	18
Anorexia	5	29	0	0
Aspartate aminotransferase increased	6	35	1	6
Blood bilirubin increased	4	24	0	0
Constipation	4	24	0	0
Creatinine increased	5	29	2	12
Dehydration	4	24	2	12
Diarrhea	13	76	4	24
Dizziness	4	24	0	0
Fatigue	10	59	1	6
GGT increased	3	18	0	0
Generalized muscle weakness	4	24	0	0
Hypoalbuminemia	5	29	1	6
Hypocalcemia	3	18	1	6
Hypokalemia	3	18	0	0
Hypomagnesemia	3	18	0	0
Hyponatremia	10	59	2	12
Lymphocyte count decreased	12	71	4	24
Nausea	12	71	0	0
Neutrophil count decreased	11	65	4	24
Platelet count decreased	3	18	1	6
Vomiting	8	47	1	6
White blood cell decreased	14	82	4	24

[1] Toxicities of any grade occurring in 3 or more individuals

[2] Grade 3–5 toxicities occurring in 2 or more individuals, Note: one patient had grade 5 cardiac arrest possibly related to treatment