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Alisertib: A review of pharmacokinetics, efficacy and toxicity in patients with hematologic malignancies and solid tumors

Susanne Liewer 1,2 and Ashley Huddleston 3

1 Nebraska Medicine, Department of Pharmacy; Omaha, NE, USA; 2 University of Nebraska Medical Center, College of Pharmacy, Omaha, NE, USA; 3 Mercy Hospital, Department of Pharmacy; Oklahoma City, OK, USA;

Correspondence:

Susanne Liewer, PharmD, BCOP
Clinical Pharmacy Coordinator, Blood and Marrow Transplant
Department of Pharmaceutical and Nutrition Care
Nebraska Medicine
Clinical Associate Professor, UNMC College of Pharmacy
981090 Nebraska Medical Center
Omaha, NE 68198-1090
(402) 552-3929
sliewer@nebraskamed.com
Fax (402) 559-8253
Key Words: Alisertib, aurora A Kinase, MLN8237, pharmacokinetics, hematologic malignancies

Abstract

Introduction: Aurora kinases are essential mediators in cell mitosis. Amplification of these kinases can lead to the development of malignancy and may be associated with inferior survival. Alisertib is an oral aurora kinase inhibitor which has been shown to induce cell-cycle arrest and apoptosis in preclinical studies. It is currently under investigation for a wide variety of malignancies including hematologic (specifically Non-Hodgkin's lymphoma) and solid tumors.

Areas covered: A PubMed search was performed to identify clinical studies reporting outcomes with alisertib. Promising results are notable in patients with peripheral T cell lymphoma in particular, forming the basis for the first phase 3 randomized trial of alisertib. Although it did show encouraging response rates, it failed to demonstrate superiority over the comparator arm at an interim analysis, halting further enrollment.

Expert Opinion: Despite disappointing early results, alisertib remains under investigation in a number of cancer types both as monotherapy and in combination with traditional cytotoxic chemotherapy, with encouraging results. Most common toxicities in early trials include myelosuppression alopecia, mucositis and fatigue. The relatively manageable toxicity profile of alisertib along with ease of dosing may allow it to be combined with other oral agents or traditional chemotherapy across a wide variety of malignancy types.
1. Introduction

Aurora kinases are a group of serine/threonine kinases which are essential for centrosome maturation and division and ultimate formation of the mitotic spindle. Aurora A kinase (AAK) has been a particular focus of recent drug development as it is overexpressed in a multitude of cancer types. Inhibition of AAK in preclinical trials led to mitotic delays, defects in chromosome segregation and cell death. (1) Alisertib (MLN8237) is a selective orally administered small molecule inhibitor of AAK that is currently under investigation for a number of hematologic and non-hematologic malignancies. This targeted agent could provide potential advantages over traditional chemotherapy including simpler dosing, fewer toxicities and potentially superior outcomes in a wide variety of malignancy types. In addition to investigating its use as monotherapy, many clinical trials are also evaluating the addition of alisertib to cytotoxic chemotherapy, with or without radiotherapy in order to elucidate cancer types most likely to benefit.

A literature search was performed to identify clinical studies reporting outcomes with the investigational agent alisertib. MEDLINE (Pubmed) was searched for studies published up to December 1, 2016. Conference proceeding from the American Society of Clinical Oncology (ASCO), American Society of Hematology (ASH), European Society for Medical Oncology (ESMO) and European Hematology Association (EHA) annual meetings (2014-2016) were also reviewed. Alisertib or MLN8237 were used as search terms. Publication titles and abstracts were screened to identify studies in vitro and in vivo studies involving alisertib. There were no restriction regarding study design or treatment.

2. Overview of the Market
There are no commercially available oral aurora kinase inhibitors on the market at this time. However, due to the potentially promising results of aurora K inhibition, several similar drugs are currently under investigation in solid tumors and hematologic malignancies.

3. Pharmacology

Conventional antimitotic agents including the taxanes and vinca alkaloids have demonstrated immense therapeutic benefit in a variety of malignancy types; however traditional chemotherapy can also demonstrate a wide variety of toxicities due to its non-targeted mechanism. To avoid these toxicities, there has been distinctive interest in the investigation of small molecule drugs which target enzymes involved in mitotic progression. Additionally, despite a multitude of therapeutic successes in hematologic and non-hematologic malignancies, there still remains a significant population of patients who relapse. Salvage therapies have modest successes, but may carry significant toxicities in heavily pretreated patients. The Aurora kinases A and B are kinases that play a key role in cell mitosis. (2) Aurora A kinase (AAK) is essential for centrosome function, spindle assembly, chromosome alignment, and mitotic entry and may play a role in resistance to paclitaxel. (3) (4) Overexpression of both the A and B subtypes have been reported in a wide variety of malignancies including myeloma, leukemia non-Hodgkin’s lymphomas, breast, bladder, colon, ovarian, pancreatic, stomach, and neuroblastoma. (5) (6) After cancer development, overexpression of Aurora kinases may be associated with shorter survival. (7) (8)

Alisertib (MLN8237) is an orally administered selective AAK inhibitor which was developed as an enhancement over its predecessor, MLN8054. MLN8054, also an AAK inhibitor, was terminated in Phase I studies secondary to central nervous system (CNS) effects including dose-limiting somnolence. These off-target CNS effects were attributed to GABA$_A$ binding of MLN8054, creating undesirable benzodiazepine-like effects. (2) In pre-clinical studies, alisertib demonstrated minimal effects related to
GABA<sub>A</sub> binding, making it favorable as a less toxic alternative to MLN8054. Alisertib significantly impairs mitotic progression through activation of the mitotic checkpoint, causing abnormal spindle formation, mitotic defects, and ultimately cell death. (9) It may also have the ability to induce in vivo tumor regression. (10) Alisertib possesses selectivity of AAK over aurora B in in vitro kinase activity studies, although preclinical studies have suggested that both aurora A and aurora B kinases may be inhibited at therapeutic doses. (11) (8) This newer antimitotic agent could provide advantages over traditional antimitotic drugs including more simple and convenient dosing and administration, more manageable toxicities, and potentially improved outcomes for patients over a variety of malignancy types.

4. Pharmacokinetic Data

4.1 Animal Studies:

Preclinical animal studies have reported that alisertib is a highly permeable compound with high plasma protein binding, low plasma clearance and a moderate volume of distribution. (12) Pharmacokinetic data in mice xenograft models have reported that single doses of alisertib (3, 10 or 20 mg/kg) are absorbed within the hour, followed by a slower two-phase elimination. (13) The concentration versus time data demonstrates a linear correlation for the dose and maximum concentration and area under the plasma concentration time curve (AUC). (10) One metabolite of alisertib has been identified in the plasma. In vitro and in vivo data suggests that the activity of alisertib is affected by P-glycoprotein (P-gp) in resistant neuroblastoma cells as well as in mice xenografted with human squamous carcinoma cell lines. (14) (15) When P-gp was inhibited by verapamil, there was an increase in alisertib uptake in the in Caco2 and MKN45 cell lines. (10) Additionally when radio-labeled alisertib was administered to P-gp knockout mice there was an increased uptake compared to wild-type mice. (16) These pre-clinical animal models suggest that alisertib is slowly metabolized and is a substrate of P-gp. Due to this interaction of alisertib on p-glycoprotein, there is a potential for drug-
drug interactions with medications which are modulated through P-gp such as atorvastatin, tacrolimus, verapamil, phenobarbital, phenytoin and rifampin, although drug-drug interactions have not been formally evaluated at this time.

4.2 Pharmacokinetic Clinical Studies

Many phase I and II studies have described the pharmacokinetic profile of alisertib in cancer patients with hematologic malignancies and solid tumors (Table 1). During preclinical trials it was noted that alisertib had a decreased solubility in acidic mediums so the initial clinical trials used a buffered powdered in capsule formulation (PIC). As clinical investigations continued, an enteric coated tablet (ECT) was developed to delay dissolution until the agent reaches the upper small bowel. (17) The pharmacokinetic profiles of the ECT have been compared to the PIC formulation using the twice daily dosing for seven days treatment schedule. The formulations were found to be comparable. The steady-state bioavailability of the ECT was 90% (90% CI, 7.4-108.8) of the PIC formulation. Median times to Tmax, and peak/trough ratios were also found to be similar. (17)

Alisertib is quickly absorbed with the median time to maximum concentration (Tmax) reached in 2-3 hours. (17) (18) (19) Food does not appear to affect the absorption of alisertib. A phase I single dose pharmacokinetic study in patients with solid tumors reported their results comparing 50 mg of enteric-coated tablet after a high fat meal or under fasting conditions. After a single dose of alisertib, the median Tmax was 3 and 6 hours respectively. The geometric mean maximum concentration (Cmax) with food was 84% of that under fasting conditions. (20) Regardless of food, alisertib was well tolerated with no significant difference in the toxicity profile. This data suggests that food does not significantly impact the pharmacokinetics of alisertib, therefore it may be administered with or without food. (20)

Alisertib dosing in cancer patients with a variety of tumor types has shown a dose dependent increase in the steady-state AUC . (20) (18) (19) Data from pre-clinical xenograft models have suggested
that the anti-tumor activity associated with alisertib is achieved with drugs levels of 1 μM. The current
dosing strategy of 50 mg by mouth BID for 7 days of a 21 day cycle used in clinical trials exceeds this
steady-state plasma concentration. (17) Alisertib appears to undergo hepatic metabolism and fecal
elimination. A two part, open label study in patients with advanced malignancies described the
pharmacokinetic properties and elimination of alisertib after a single radiolabeled dose as well as
multiple day dosing. The mean plasma exposure ratio of alisertib compared to drug related material
was 0.46, suggesting that alisertib metabolites are found within the circulation. (21) Following a single
oral dose of a radio-labeled alisertib less than 3% of drug was cleared by renal elimination and over 80%
of the radio-labeled drug was received in the feces. (21) Fecal elimination represents the primary route
of elimination for alisertib suggesting that this drug undergoes hepatic metabolism and biliary excretion
while renal clearance of unchanged drug is negligible.

A large population pharmacokinetic/pharmacodynamics multi-center trial of 363 adult cancer
patients was conducted to support phase I/II trials dosing of alisertib. Similar to other phase I/II trials,
the investigators reported a quick absorption rate and a half-life of 19.3 hours. (22) In addition to the
pharmacokinetic data, this trial also reported no clinically significant pharmacokinetic differences in
patients who received 50 mg twice daily in the following patient specific populations: UGT1A1*28
genotypes, age (25-85 years), mild/moderate renal dysfunction (CrCl > 30 mL/min), gender, body weight
(42-175 kg) or body surface area (1.31-2.97 m2). (22) In addition to the similar pharmacokinetic
parameters, there was no apparent difference in the safety and tolerability profile of alisertib across the
patient populations. This data supports the use of the fixed dosing strategy of 50 mg BID days 1
through 7 every 21 days that has been described in the earlier clinical trials.

As cancer therapies become more targeted, the development of biomarkers to predict or
monitor response to these agents may help personalize therapies. Early in vitro studies suggested
pharmacodynamic markers such as disruption of spindle alignment or the use of the mitotic index may predict response to alisertib. (23) Xenograft models reported a fast and sustained spindle alignment disruption however the mitotic index had a slower, transient response. These results indicate only the spindle alignment is likely to be clinically useful due to its quick response. Monitoring of these markers has not consistently been incorporated into the larger clinical trials.

5. **Clinical Trials in Hematologic Malignancies:**

A phase II trial of alisertib in patients with relapsed and refractory aggressive B-cell and T-cell lymphomas suggested that alisertib has activity in this population. Response rate was the primary endpoint in this trial and secondary endpoints included safety, duration of response and progression free survival (PFS). A total of 48 patients were included in the study. The median age was 68 years old (range 32-85) and the prior number of regimens was 3 (range 1-9). Diffuse large B-cell lymphoma (DLBCL) was the most common diagnosis (21/48) followed by mantle cell lymphoma (MCL) (13/48), T-cell lymphoma (TCL 8/48), transformed follicular lymphoma (FL, 5/48) and one patient with Burkitt’s lymphoma (BL). All patients were initiated on 50 mg twice daily on days 1 through 7 every 21 days. Over half of the patients (25/48) required a dose reduction, with many of the dose reductions occurring in cycle two as a result of delayed count recovery. The overall response rate (ORR) was 27% (13/48), this includes 10% complete response (CR), 17% partial response (PR) and 33% had stable disease (SD). (9) When looking at the response rates by histology, 4/8 patients with TCL and 2/5 with transformed FL had responses to alisertib. Other responses to alisertib organized by histology include: 3/21 with DLBCL, 3/13 with MCL and 1/1 with BL. (9) Alisertib was well tolerated, common adverse drug events of grade three or greater included: myelosuppression, stomatitis and fatigue. Four patients died during this trial, two of progressive disease, one due to sepsis and the final patient’s death was reported as
unknown. (9) Alisertib did demonstrate single agent activity in the patient population. Notably, half of the patients with TCL responded to therapy.

The SWOG 1108 trial reported their experience with alisertib in patients with relapsed, refractory peripheral T-cell lymphoma (PTCL) and transformed mycosis fungoides. Thirty-seven patients were enrolled in this study with the median number of prior therapies was 3 (range 1-18); over half of the patient population were considered refractory to their last therapy (20/37). All patients received the standard dose of alisertib (50 mg twice daily on days 1 through 7 every 21 days). The ORR for the entire patient population was 24% (95% CI 12-41%). Patients with PTCL had a 30% ORR (95% CI, 9 to 61%). The median time to response was 12 weeks and progression free survival (PFS) was 3 months (1-18 months). (24) Like in other trials, myelosuppression was the most common grade 3 or higher toxicity reported (neutropenia 32%, anemia 30% thrombocytopenia 24%). Five patients had febrile neutropenia and 1 reported death related to sepsis. Non-hematologic toxicities included fatigue (46%), alopecia (24%) and mucositis (22%). (24) In this phase II trial, alisertib demonstrated promising activity in a heavily pretreated patient population with PTCL.

The Lumiere trial, a multi-center, randomized phase III study in patients with relapsed/refractory PTCL was initiated based on the positive responses described in phase II trials. Adult patients were enrolled after receiving at least one prior conventional therapy. Patients were randomized to single agent alisertib or investigators choice (pralatrexate weekly, romidepsin days 1, 8 and 15, gemcitabine on days 1, 8 and 15). The primary endpoints were ORR and PFS. Secondary endpoint also included OS, CR rate and safety. Over two hundred patients were randomized in the trial (120 alisertib, 118 investigator’s choice). At the interim analysis, the two groups were well balanced, with a median age of 63 and 64 years for alisertib and the comparator arm. The ORR for alisertib and the comparator arm was 33% and 43% (OR 0.65 [95% CI 0.34-1.23]) with a CR observed in 16 and 25% of the patients
respectively. The median PFS was 3.7 and 3.4 months (HR 0.939 [95% CI 0.681-1.293]). While the OS data was not mature at the time of publication, the OS survival was reported as 9.9 and 12.2 months (HR 0.901 [95% CI 0.607-1.337]) for alisertib and the investigator choice arms. Rates of grade 3 or greater toxicities were similar between the two groups (85 vs 81%). Discontinuation of therapy due to toxicity has reported in 9% and 13% of patients in alisertib and comparator arms. Alisertib did demonstrate activity in relapsed and refractory PTCL patients, but in this trial it did not show any significant benefit over the comparator arm. Based on the interim data analysis, there was a low probability of alisertib demonstrating superiority and therefore enrollment into this trial was halted.

As a single agent, alisertib has an acceptable toxicity profile in patients who have been heavily pre-treated (See Table 2). Common grade 3 or greater toxicities have been hematologic in nature, including neutropenia, anemia, leukopenia and thrombocytopenia. Treatment related deaths were reported in the phase II and the phase III trials. Sepsis and progressive diseases were often the cause of death in these trials. Non-hematologic toxicities were also associated with alisertib, these included: stomatitis, fatigue and alopecia. Early alisertib trials reported off-target CNS adverse events (somnolence, confusion, dizziness). It is believed these toxicities are due to the reversible binding of the benzodiazepine-like portion of alisertib to the GABA<sub>A</sub> receptors. These dose limiting CNS toxicities were observed at doses above 60 mg, as these effects tend to be more closely related to drug peak concentrations. Dividing the dose of alisertib to twice daily has helped mitigate some of the CNS toxicities. Based on this toxicity profile, alisertib will likely be able to be combined with more traditional chemotherapies without exposing the patient to excessive drug-related toxicities.

Alisertib has demonstrated clinical activity in other hematologic malignancies such as acute myeloid leukemia (AML), and multiple myeloma (MM). An exploratory phase II study of single agent alisertib in 45 patients with AML or myelodysplastic syndrome (MDS) reported an ORR of 13%. Of the
35 patients with AML, six responded to therapy resulting in an ORR of 17%. The median PFS was 55 days (95% CI 47, 67 days; range 1-638). None of the patients with MDS responded to therapy. (26) Alisertib has also been combined with 7 days of continuous cytarabine (200 mg/m²) and 3 days of idarubicin (7+3) in a phase I study in patients with newly diagnosed AML. Of the 12 evaluable patients, 11 (92%) have achieved remission. None of the patients received re-induction with additional cytarabine and idarubicin (5+2). These results suggest that alisertib is tolerated when combined with more traditional therapies in patients with AML. (27)

In-vitro data reported an inhibition of AAK in MM cells induces apoptosis as well as halts cell-cycle progression. When alisertib was combined with dexamethasone, doxorubicin or bortezomb, synergistic activity was reported. This benefit was confirmed in a murine xenograft model suggesting alisertib may have promising activity in MM. (28) Alisertib was combined with bortezomib in a phase I study in patients with relapsed multiple myeloma. Twenty-six patients received the combination with an ORR of 26.9% (95% CI 11.6-47.8) and a median PFS of 5.9 months demonstrating this combination had modest activity in a heavily pre-treated population. (29) To understand the benefit of alisertib combined with bortezomib in this patient population further phase II testing is needed.

6. Clinical Trials in Solid Tumors

Solid tumors such as breast, small cell lung (SCLC), non-small cell lung (NSCLC), head and neck squamous cell carcinoma (HNSCC) and gastro-esophageal adenocarcinoma all express high levels of AAK. (30) A recent five-arm phase II study investigated the safety and activity of alisertib in these advanced, unresectable or relapsed cancer types. (30) Patients received alisertib 50 mg by mouth twice daily for 7 days, followed by a 14-day treatment break. Among response-assessable patients, an ORR (all partial responses) was noted in 18% of breast cancer patients and 21% of SCLC patients. Less impressively, an ORR was found in 4% of patients with NSCLC, 9% of HNSCC, and 9% of gastro-esophageal
adenocarcinoma. The most frequent grade 3-4 events were neutropenia (43%), leukopenia (21%) and anemia (10%). Results from this phase II study supported the further clinical evaluation of alisertib in patients with solid tumors, specifically patients with breast cancer and SCLC.

Amplification of AAK has been implicated in the development of ovarian cancer and is also associated with poorer survival. (31) A open-label single arm phase II study evaluated the efficacy and safety of single-agent alisertib in patients with platinum resistant or refractory epithelial ovarian, fallopian tube or primary peritoneal carcinoma. (32) Thirty-one patients were enrolled and responses were observed in 10 (30%) of patients with a 6.9 to 11.1 month duration of response noted. 52% of patients achieved SD with an average duration of response of 2.86 months. Common drug-related adverse effects (≥ grade 3) were hematologic toxicities ( neutropenia, leukopenia and thrombocytopenia) and stomatitis. Febrile neutropenia was noted in 6% of patients. Toxicities (excluding alopecia) were reversible between cycles in a majority of patients, however 4 patients discontinued therapy due to intolerable adverse effects. Cumulative toxicities (excluding alopecia) were not commonly observed in patients continuing treatment for 6-12 or more months. Results from this study support further investigation of alisertib in patients with ovarian cancer, alone or in combination with chemotherapy.

7. Expert Opinion

The novel mechanism of action, tolerability and oral formulation make alisertib a promising agent that appears to have activity in many different tumor types. Initial clinical trials generated substantial interest in alisertib in the treatment of NHL, specifically for patients with relapsed or refractory T-cell lymphoma. The phase II trial by Friedberg and colleagues investigated the activity of alisertib in patients with aggressive B-and T-cell NHL reported promising results. Patients with T-cell
lymphoma had an impressive response rate of 50% (4/8 patients). The SWOG 1108 trial confirmed the activity of alisertib in NHL patients, specifically with refractory PTCL. Patients with PTCL had a 30% response rate with a PFS of 3 months (range 1 – 18 months). While the response rate of 30% is similar to other single agents used to treat PTCL, what is notable about alisertib’s activity is many of the patients who responded were previously considered refractory to their prior therapies. Results from these early phase II trials provided a solid basis for investigating alisertib in patients with PTCL in a phase III randomized study. The Lumiere trial, the first randomized phase III study of alisertib in patients with R/R PTCL compared single agent alisertib to investigator’s choice. In over 200 patients with PTCL, single agent alisertib did show activity with an ORR of 35% with 19% of patients having a CR. However, alisertib failed to show superiority over the comparator arm (ORR 43% with 25% CR) at an interim analysis. Based on the reported outcomes and similar toxicity rates, the investigators chose to halt patient enrollment.

While alisertib failed to demonstrate superiority as a single agent over more traditional cytotoxic therapies, it still may have a role in the treatment of patients with NHL or other hematologic malignancies. In animal models, when alisertib was combined with vincristine it initially suggested synergistic activity in B-cell NHL models, unfortunately resistance eventually developed to this combination. However, when alisertib was combined with rituximab and vincristine, it demonstrated complete responses and potentially cures in the mouse xenograft model. Currently alisertib is being combined with many traditional therapies in phase I and II clinical trials. There is an ongoing phase II study that combined alisertib plus vincristine with rituximab in patients with relapsed or refractory B-NHL. Alisertib is also being studied in combination with vorinostat in patients with refractory or relapsed Hodgkin’s lymphoma, B-cell NHL or PTCL. Other novel combinations with alisertib include with bortezomib and rituximab or with combination regimen R-EPOCH (see Table 3).
Alisertib as a single agent has demonstrated a reasonable activity and toxicity profile. As alisertib is combined with more traditional chemotherapies in clinical trials, it will be important to monitor patients for excessive toxicities associated with treatment. The most common toxicities reported involve myelosuppression. This reversible toxicity led to dose reductions in almost all reported clinical trials, regardless of the malignancy. Many traditional chemotherapy agents also demonstrate dose-limiting myelosuppression. When combining alisertib with these agents, investigators will need to be thoughtful about dose reductions or perhaps the use of colony-stimulating factors in order to maintain dose intensity. There is little data describing long-term toxicities associated with alisertib. Animal data with AAK knockout mice suggests a high risk of the development of hematologic malignancies. (36) While this has not been reported in trials investigating alisertib to date, all patients enrolled on clinical trials should be monitored closely until more long-term experience is reported with this agent (see Table 4).

In summary, Alisertib has demonstrated a broad range of activity in both solid tumors as well as in patients with hematologic malignancies such as NHL. Initial phase I and II trials in patients with relapsed and refractory NHL showed promising activity as a single agent. While the confirmatory phase III trial failed to demonstrate single agent superiority over investigators choice in R/R PTCL, alisertib still has the potential to positively impact survival in patients with relapsed or refractory malignancies. Alisertib has shown promising activity in animal models when combined with more traditional therapies as well as demonstrating single agent activity in patients with solid tumors such as breast cancer, SCLC and ovarian cancer. Further clinical trials as a single agent and in combination with more traditional chemotherapy will help further define the role of alisertib.

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Declarations of Interest

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

Table 1: Pharmacokinetic/Pharmacodynamic Trials

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>Absorption</th>
<th>Tmax (range)</th>
<th>T1/2</th>
<th>Misc</th>
</tr>
</thead>
</table>
| Cervantes^  
2012  
N = 59 | Phase I  
Advanced Solid tumors | Fasting  
Rapid absorption | 2 hours  
(1-5) | 19.2 hours;  
SSC = 1 week | Dose dependent increase in SSC |
| Dees^  
2012  
N = 83 | Phase I  
Solid Tumors | Fasting | 2 hours  
(1-6 hours) | 23 hours  
SSC = 1 week | Dose dependent increase in SSC |
| Kelly  
2014  
N = 47 | Phase I  
MM/NHL/CLL | Rapid | 2 vs 2.6 hours | 19 hours | |

^ = No lymphoma or hematologic malignancies included; SSC = Steady state conditions achieved; Tmax = Maximum serum concentration; T1/2 = mean steady-state half-life; NHL = Non-Hodgkin Lymphoma

Table 2: Common Toxicities Reported with Alisertib

<table>
<thead>
<tr>
<th>Trial</th>
<th>Grade &gt;3 Hematologic Toxicities</th>
<th>Treatment Related Deaths</th>
<th>Non-Hematologic Toxicities</th>
</tr>
</thead>
</table>
| Freidberg  
2013; N = 48 | Neutropenia (63%)  
Leukopenia (54%)  
Anemia (35%)  
Thrombocytopenia (33 %) | 4 patient deaths (1 sepsis, 2 progressive dx,1 unknown) | Stomatitis (15%)  
Fatigue (6%) |
| SWOG 1108  
2015; N = 37 | Neutropenia (32%)  
Anemia (30%)  
Thrombocytopenia (24%)  
Febrile Neutropenia (14%) | 1 death related to sepsis | Fatigue (50%)  
Alopecia (24%)  
Mucositis (22%) |
| Kelly  
2014; N = 47 | Neutropenia (45%)  
Thrombocytopenia (28%) | 6 reported deaths, none considered | Fatigue (26%)  
Nausea (21%) |

This paper was not funded.
<table>
<thead>
<tr>
<th>Sponsor</th>
<th>Trial Description</th>
<th>Regimen</th>
<th>Patient Population</th>
<th>Trial Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ohio State University Comprehensive Cancer Center with Millennium Pharmaceuticals</td>
<td>Phase II</td>
<td>Alisertib, rituximab</td>
<td>R/R NHL</td>
<td>Ongoing, Not Recruiting</td>
</tr>
<tr>
<td>NCI</td>
<td>Phase I Ongoing</td>
<td>Alisertib, vorinostat</td>
<td>R/R HL, B-cell NHL, PTCL</td>
<td>Ongoing, Not Recruiting</td>
</tr>
<tr>
<td>NCI</td>
<td>Phase I</td>
<td>Alisertib, bortezomib and rituximab</td>
<td>R/R MCL</td>
<td>Recruiting</td>
</tr>
<tr>
<td>Northwestern</td>
<td>Open Label Pilot Study</td>
<td>Single agent Alisertib</td>
<td>Myelofibrosis or R/R acute megakaryoblastic leukemia</td>
<td>Recruiting</td>
</tr>
<tr>
<td>University of North Carolina</td>
<td>Phase I</td>
<td>Alisertib with R-EPOCH</td>
<td>Myc (+) Aggressive Lymphoma</td>
<td>Recruiting</td>
</tr>
<tr>
<td>Massachusetts General Hospital</td>
<td>Phase I</td>
<td>Single agent Alisertib</td>
<td>Acute Myeloid Leukemia</td>
<td>Recruiting</td>
</tr>
</tbody>
</table>

NR = Not reported

Table 3: Ongoing Clinical Trials with Alisertib

Hematologic Malignancies

NCI = National Cancer Institute; R/R = relapsed or refractory; NHL = Non-Hodgkin’s lymphoma; PTCL = Peripheral T-cell lymphoma; MCL = Mantle cell lymphoma; R-EPOCH = rituximab, etoposide, doxorubicin, cyclophosphamide and prednisone
## Solid Tumors

<table>
<thead>
<tr>
<th>Sponsor</th>
<th>Trial Description</th>
<th>Regimen</th>
<th>Patient population</th>
<th>Trial Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>St. Jude Children's Research Hospital</td>
<td>Phase II</td>
<td>Alisertib, cyclophosphamide, methotrexate, vincristine, cisplatin or carboplatin, etoposide, topotecan</td>
<td>R/R Rhabdoid tumors</td>
<td>Recruiting</td>
</tr>
<tr>
<td>US Oncology Research</td>
<td>Phase II</td>
<td>Alisertib, paclitaxel</td>
<td>Metastatic or locally recurrent breast cancer</td>
<td>Recruiting</td>
</tr>
<tr>
<td>NCI</td>
<td>Phase I</td>
<td>Alisertib, FOLFOX</td>
<td>M/U gastrointestinal tumors</td>
<td>Recruiting</td>
</tr>
<tr>
<td>NCI</td>
<td>Phase I</td>
<td>Alisertib, fulvestrant</td>
<td>Advanced HR (+) breast cancer</td>
<td>Ongoing, not recruiting</td>
</tr>
<tr>
<td>NCI</td>
<td>Phase II</td>
<td>Alisertib, fulvestrant</td>
<td>Advanced HR (+) breast cancer</td>
<td>Not yet recruiting</td>
</tr>
<tr>
<td>MD Anderson Cancer Center</td>
<td>Phase II</td>
<td>Alisertib alone</td>
<td>R/R unresectable malignant mesothelioma</td>
<td>Recruiting</td>
</tr>
<tr>
<td>Thomas Jefferson University</td>
<td>Phase I</td>
<td>Alisertib, stereotactic radiosurgery</td>
<td>R/R high grade glioma</td>
<td>Recruiting</td>
</tr>
<tr>
<td>Institution</td>
<td>Phase</td>
<td>Treatment</td>
<td>Disease/Cancer Type</td>
<td>Status</td>
</tr>
<tr>
<td>-----------------------------------------------</td>
<td>---------</td>
<td>------------------------------------</td>
<td>----------------------------------------------------------</td>
<td>-----------------------</td>
</tr>
<tr>
<td>Thomas Jefferson University</td>
<td>I/II</td>
<td>Alisertib, abiraterone/prednisone</td>
<td>Relapsed metastatic CRPC</td>
<td>Ongoing, not recruiting</td>
</tr>
<tr>
<td>Millennium Pharmaceuticals, Inc.</td>
<td>Ib</td>
<td>Alisertib, paclitaxel</td>
<td>East Asian patients with solid tumor malignancy (escalation) or R/R ovarian or SCLC (expansion)</td>
<td>Ongoing, not recruiting</td>
</tr>
<tr>
<td>Children’s Oncology Group</td>
<td>II</td>
<td>Alisertib alone</td>
<td>Young patients with R/R solid tumors or leukemia</td>
<td>Ongoing, not recruiting</td>
</tr>
<tr>
<td>Fox Chase Cancer Center</td>
<td>I/II</td>
<td>Alisertib, erlotinib</td>
<td>Recurrent advanced or metastatic NSCLC</td>
<td>Recruiting</td>
</tr>
<tr>
<td>NCI</td>
<td>II</td>
<td>Alisertib alone</td>
<td>R/R uterine LMS</td>
<td>Ongoing, not recruiting</td>
</tr>
<tr>
<td>University of California, Davis</td>
<td>I</td>
<td>Alisertib, gemcitabine</td>
<td>M/U solid tumors (escalation) or pancreatic cancer (expansion)</td>
<td>Recruiting</td>
</tr>
<tr>
<td>University of California, Davis</td>
<td>I</td>
<td>Alisertib, irinotecan</td>
<td>M/U solid tumors (escalation) or colorectal adenocarcinoma (expansion)</td>
<td>Ongoing, not recruiting</td>
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<tr>
<td>Weill Medical College of Cornell University</td>
<td>II</td>
<td>Alisertib alone</td>
<td>Metastatic neuroendocrine or CRPC</td>
<td>Ongoing, not recruiting</td>
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<tr>
<td>Millennium Pharmaceuticals, Inc.</td>
<td>II</td>
<td>Alisertib, paclitaxel</td>
<td>Recurrent ovarian cancer</td>
<td>Ongoing, not recruiting</td>
</tr>
<tr>
<td>University of Illinois, Chicago</td>
<td>I</td>
<td>Alisertib, pazopanib</td>
<td>R/R advanced solid tumors</td>
<td>Ongoing, not recruiting</td>
</tr>
<tr>
<td>Trial</td>
<td>Length of therapy</td>
<td>ORR</td>
<td>CR</td>
<td>PFS</td>
</tr>
<tr>
<td>-------</td>
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<td>-----</td>
</tr>
<tr>
<td>Freidberg 2013; N = 48</td>
<td>Single agent alisertib up to 1 year therapy</td>
<td>27%</td>
<td>10%</td>
<td>NR</td>
</tr>
<tr>
<td>SWOG 1108 2015; N = 37</td>
<td>Single agent alisertib Median 4 cycles (1-17 range)</td>
<td>24%</td>
<td>NR</td>
<td>Estimated median 3 months</td>
</tr>
<tr>
<td>Lumiere Trial 2015; N = 238 patients</td>
<td>Alisertib vs investigators choice 12 weeks vs 10 weeks</td>
<td>33 vs. 43% (OR 0.65 [95% CI: 0.34-1.23])</td>
<td>16 vs 25%</td>
<td>3.7 vs 3.4 months (HR 0.93 [95% CI, 0.607-1.337])</td>
</tr>
</tbody>
</table>

NCI = National Cancer Institute; R/R = relapsed or refractory; M/U = metastatic or unresectable; HR = hormone receptor; SCLC = small-cell lung cancer; NSCLC = Non small-cell lung cancer; CRPC = castration-resistant prostate cancer; HNSCC = head and neck squamous cell carcinoma
<table>
<thead>
<tr>
<th></th>
<th>Study Details</th>
<th>ORR</th>
<th>PFS</th>
<th>OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Melichar 2015; N = 249</td>
<td>Single agent alisertib up to 2 years therapy Median 4 (1-23 range) in safety population</td>
<td>18%</td>
<td>NR</td>
<td>NR</td>
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<tr>
<td>Matulonis 2012; N = 31</td>
<td>Single agent alisertib Median 1.5 cycles (platinum-refractory) and 3 cycles (platinum resistant)</td>
<td>10%</td>
<td>1.9 months</td>
<td>NR</td>
</tr>
</tbody>
</table>

ORR = overall response rate; CR = complete response; PFS = progression free survival; OS = overall survival; NR = not reported

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### Drug Summary

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Alisertib (MLN8237)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phase</td>
<td>Currently undergoing phase II and III trials</td>
</tr>
<tr>
<td>Indication</td>
<td>None</td>
</tr>
<tr>
<td>Pharmacology</td>
<td>Aurora kinase A inhibitor</td>
</tr>
<tr>
<td>Route of administration</td>
<td>Oral</td>
</tr>
<tr>
<td>Chemical Structure</td>
<td>Pyrimidobenzapine</td>
</tr>
</tbody>
</table>

**Pivotal Trials**
- SWOG 1108: Barr PM et al. J Clin Oncol. 2015 Jul 20;33:2399-404
Bibliography

Papers of special note have been highlighted as either of interest (•) or of considerable interest (••) to readers.


• A phase II study of alisertib that demonstrated activity in both B and T-cell aggressive lymphomas.


- The promising results were further investigated in a phase III trial


- The first phase III study published in patients with R/R PTCL. Alisertib failed to show any efficacy benefit versus its comparator.


- Alisertib was coined was combined with standard 7+3 induction in patient with newly diagnosed AML. Aliserti was well tolerated without excess toxicity.


- Alisertib demonstrated antitumor activity in R/R ovarian, fallopian tube or primary peritoneal carcinoma.


