Published in final edited form as:

Br J Haematol. 2016 July ; 174(2): 323–325. doi:10.1111/bjh.13765.

A Phase Ib Study of the combination of Aurora Kinase Inhibitor alisertib (MLN8237) and bortezomib in Relapsed or Refractory Multiple Myeloma

Allison Rosenthal¹, Shaji Kumar², Craig Hofmeister³, Jacob Laubach⁴, Ravi Vij⁵, Amylou Dueck¹, Katherine Gano¹, and A. Keith Stewart¹

¹Mayo Clinic, Scottsdale, Arizona

²Mayo Clinic, Rochester, Minnesota

³Ohio State, James Cancer Center, Ohio

⁴Dana Farber Cancer Institute, Boston, Massachusetts

⁵University of Washington, St Louis

Keywords

multiple myeloma; alisertib; aurora kinase; bortezomib; relapse

A cornerstone of modern therapy for multiple myeloma (MM) is the proteasome inhibitor bortezomib (BTZ). When used in combination therapy at diagnosis, response rates are 80–90%, but as a single agent, in relapse, response rates are only 30–40%. To better understand the molecular basis for response and resistance, we performed druggable genome-wide RNA interference studies (siRNA) to identify genes that, when suppressed, would synergistically enhance or abrogate the cytotoxicity of proteasome inhibition (Tiedemann, *et al* 2012, Zhu, *et al* 2011). Aurora Kinase A and Aurora Kinase B were identified as lethal targets in MM while suppression of these genes also sensitized MM cells to bortezomib.

Alisertib (MLN8237) is an oral small molecule inhibitor of Aurora A kinase (Carvajal, *et al* 2006). The safety and bioactivity of alisertib has been studied in several Phase I trials and has been generally well tolerated in patients with solid tumors (Cervantes, *et al* 2012, Dees, *et al* 2012, Falchook, *et al* 2014). With doses under 100 mg, the dose-limiting toxicities have been largely mechanistic (hematological toxicities and mucositis), and manageable (Kelly, *et al* 2014). With supportive pre-clinical work, we conducted a Phase I open-label multicenter clinical trial testing the combination of alisertib and bortezomib. No corticosteroids were used.

Patients who were age ≥ 18 with relapsed MM, measurable disease, good performance status and labs demonstrating adequate blood, kidney, and liver profiles were eligible. All patients provided written informed consent. Enrollment began February 5, 2010 and expansion

opened June 15, 2012. The study was conducted in accordance with the Declaration of Helsinki and the ICH Harmonized Tripartite Guideline for Good Clinical Practice and was approved by the relevant Regulatory and Institutional Review Boards.

A standard “3+3” design for dose escalation was utilized in Phase I. Alisertib initial dose level 0 was 25mg PO daily and BTZ was 1.3mg/m² IV on days 1, 4, 8, and 11 on a 28-day cycle. Data from concurrent Phase I trials prompted an addendum. Subsequently, alisertib was given twice daily at escalating doses from 20mg to 50mg PO BID days 1–7 on a 28 day cycle and BTZ dosing was changed to the more convenient schedule of 1.5mg/m² weekly continuously. Amended dose level 0 was alisertib 20mg PO BID with BTZ 1.5mg/m² IV. Alisertib dosing was escalated from 20mg to 50mg PO BID in successive cohorts to determine the maximum tolerated dose (MTD)(level 0: 25mg PO daily – 3 patients, amended level 0: 20mg PO BID- 3 patients plus 1 [dosing error], level 1: 30mg PO BID – 3 patients, level 2: 40mg PO BID -3 patients, and level 3: 50mg PO BID – 6 patients). Patients were observed until the end of cycle 2 and assessed for toxicity. No dose limiting toxicities (DLT) were documented, although one patient (level 3 dose) did require platelet transfusion to proceed to cycle 2 on schedule. Doses were not further escalated as information from ongoing trials indicated additional escalation would be associated with increased toxicity. If a patient failed to complete the initial cycle of therapy for reasons other than toxicity, the patient was regarded as treatment intolerant and went off study. All toxicity information was utilized in the analysis.

The final cohort was expanded with an additional 7 patients receiving treatment. The initial planned maximum number of treatment cycles was 10, although responding patients were considered for additional cycles. Treatment was continued until progression, unacceptable toxicity, or patient refusal, new primary malignancy or other medical problems.

The primary endpoint was defining a MTD and describing toxicities of the combination of alisertib and BTZ. The final dose cohort was expanded to evaluate overall response rate. All patients that received at least one dose of study drug were assessed for safety and response. Adverse events were monitored using the National Cancer Institute Common Toxicity Criteria for Adverse Events version 4.0. Response was evaluated using the uniform response criteria established by the International Myeloma Working Group (Durie, *et al* 2006).

Nineteen patients were treated during Phase I, with an additional 7 patients included in an expansion cohort (total 26 patients). Baseline characteristics are shown in Supplementary Table I. 14/26 (53.9%) patients were relapsed while 12 (46.1%) were relapsed and refractory. 96.2% (25/26) of patients had previous exposure to immunomodulatory drugs (IMiDs) and none were BTZ refractory.

Median follow up was 20.6 months (range 4.3–36.6). At last follow up, 22 patients had progressed, while four had not. 12 patients were still alive, while 14 had died. No patients were still actively receiving treatment.

Median number of cycles received was four (1–32 cycles). Fourteen (53.9%) patients stopped treatment due to progressive disease. Two refused further treatment, and four

stopped secondary to adverse effects. Two completed study protocol and one patient chose alternative treatment.

Significant adverse events (AEs) are shown in Table I. The majority of significant toxicities were hematologic, consistent with previous studies of alisertib (Falchook, *et al* 2014, Kelly, *et al* 2014). There was a higher incidence of grade 3/4 neutropenia than expected with BTZ alone. Additive neurotoxicity was not seen.

The overall response rate (partial response) was 26.9% (95% CI 11.6–47.8). Clinical benefit rate including minimal response was 42.3% (Supplementary Table II). One patient had a stringent CR with 2 patients experiencing a VGPR, and 4 patients with PR. Ten patients had stable disease for at least two cycles. Median progression free survival was 5.9 months (Figure 1). Median overall survival was 23.6 months (Supplementary Figure 1). Median time to treatment failure was 4.3 months. The expansion study was closed early due to poor accrual.

In summary, this study provides preliminary data on the efficacy of the combination of alisertib and BTZ for relapsed MM. Duration of response varied widely with one patient staying on therapy for more than three years. Nevertheless, the contribution of alisertib to BTZ activity cannot be determined without additional Phase II testing. Further studies looking at inhibition of Aurora A kinase alone or in combination with established or novel anti-MM therapies will be necessary.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

References

- Carvajal RD, Tse A, Schwartz GK. Aurora kinases: new targets for cancer therapy. *Clinical cancer research : an official journal of the American Association for Cancer Research*. 2006; 12:6869–6875. [PubMed: 17145803]
- Cervantes A, Elez E, Roda D, Ecsedy J, Macarulla T, Venkatakrishnan K, Roselló S, Andreu J, Jung J, Sanchis-Garcia JM, Piera A, Blasco I, Maños L, Pérez-Fidalgo J-A, Fingert H, Baselga J, Tabernero J. Phase I Pharmacokinetic/Pharmacodynamic Study of MLN8237, an Investigational, Oral, Selective Aurora A Kinase Inhibitor, in Patients with Advanced Solid Tumors. *Clinical Cancer Research*. 2012; 18:4764–4774. [PubMed: 22753585]
- Dees EC, Cohen RB, von Mehren M, Stinchcombe TE, Liu H, Venkatakrishnan K, Manfredi M, Fingert H, Burris HA, Infante JR. Phase I Study of Aurora A Kinase Inhibitor MLN8237 in Advanced Solid Tumors: Safety, Pharmacokinetics, Pharmacodynamics, and Bioavailability of Two Oral Formulations. *Clinical Cancer Research*. 2012; 18:4775–4784. [PubMed: 22767670]
- Durie BGM, Harousseau JL, Miguel JS, Blade J, Barlogie B, Anderson K, Gertz M, Dimopoulos M, Westin J, Sonneveld P, Ludwig H, Gahrton G, Beksac M, Crowley J, Belch A, Boccadaro M, Turesson I, Joshua D, Vesole D, Kyle R, Alexanian R, Tricot G, Attal M, Merlini G, Powles R, Richardson P, Shimizu K, Tosi P, Morgan G, Rajkumar SV. International uniform response criteria for multiple myeloma. *Leukemia*. 2006; 20:1467–1473. [PubMed: 16855634]
- Falchook G, Kurzrock R, Gouw L, Hong D, McGregor K, Zhou X, Shi H, Fingert H, Sharma S. Investigational Aurora A kinase inhibitor alisertib (MLN8237) as an enteric-coated tablet formulation in non-hematologic malignancies: Phase 1 dose-escalation study. *Investigational New Drugs*. 2014; 32:1181–1187. [PubMed: 24879333]

- Kelly K, Shea T, Goy A, Berdeja J, Reeder C, McDonagh K, Zhou X, Danaee H, Liu H, Ecsedy J, Niu H, Benaïm E, Padmanabhan Iyer S. Phase I study of MLN8237—investigational Aurora A kinase inhibitor—in relapsed/refractory multiple myeloma, Non-Hodgkin lymphoma and chronic lymphocytic leukemia. *Investigational New Drugs*. 2014; 32:489–499. [PubMed: 24352795]
- Tiedemann RE, Zhu YX, Schmidt J, Shi CX, Sereduk C, Yin H, Mousses S, Stewart AK. Identification of Molecular Vulnerabilities in Human Multiple Myeloma Cells by RNA Interference Lethality Screening of the Druggable Genome. *Cancer research*. 2012; 72:757–768. [PubMed: 22147262]
- Zhu, YX.; Tiedemann, R.; Shi, C-X.; Yin, H.; Schmidt, JE.; Bruins, LA.; Keats, JJ.; Braggio, E.; Sereduk, C.; Mousses, S.; Stewart, AK. RNAi screen of the druggable genome identifies modulators of proteasome inhibitor sensitivity in myeloma including CDK5. 2011. <http://www.bloodjournal.org/bloodjournal/117/14/3847.full.pdf>

Figure 1.
Progression Free Survival (N=26, Events=22, Median=5.9 months, 95% CI 4.1 – 15.8 months)

Table 1

Adverse events at least partially related

Adverse Event Type	Grade							
	1		2		3		4	
	N	%	N	%	N	%	N	%
Platelet count decreased	10	38.5	3	11.5	6	23.1	2	7.7
Fatigue	12	46.2	5	19.2	2	7.7		
Nausea	13	50.0	4	15.4				
Diarrhea	10	38.5	5	19.2	1	3.8		
Peripheral sensory neuropathy	10	38.5	5	19.2				
Neutrophil count decreased	2	7.7	2	7.7	6	23.1	4	15.4
Anemia			8	30.8	2	7.7		
Lymphocyte count decreased			3	11.5	4	15.4	1	3.8
White blood cell decreased			4	15.4	1	3.8	3	11.5
Alopecia	1	3.8	6	23.1				
Vomiting	5	19.2	2	7.7				
Infections and infestations			2	7.7	4	15.4		
Mucositis oral	4	15.4	1	3.8				
Peripheral motor neuropathy	5	19.2						
Aspartate aminotransferase increase	3	11.5	1	3.8				
Creatinine increased	3	11.5						
Generalized muscle weakness					3	11.5		
Rash maculo-papular	2	7.7	1	3.8				
Weight loss	2	7.7	1	3.8				