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A phase 2 trial of alisertib in patients with relapsed or refractory B-cell non-Hodgkin lymphoma

Jonathon B. Cohen[a], **Kami J. Maddocks**[b], **Ying Huang**[b], **Beth A. Christian**[b], **Samantha M. Jaglowski**[b], **Christopher R. Flowers**[a], and **Kristie A. Blum**[b]

[a]Department of Hematology and Medical Oncology, Emory University – Winship Cancer Institute, Atlanta, GA, USA

[b]Division of Hematology, The Ohio State University James Comprehensive Cancer Center, Columbus, OH, USA

Alisertib (MLN8237) is an oral inhibitor of Aurora A kinase that inhibits tumor growth in murine xenograft models with diffuse large B-cell lymphoma (DLBCL) cell lines [1–3]. In a phase I study of alisertib that accrued 36 patients with NHL (DLBCL, $n = 16$; follicular lymphoma (FL), $n = 10$; mantle cell lymphoma (MCL), $n = 2$; peripheral T-cell lymphoma, $n = 2$; and others, $n = 6$), the recommended phase 2 dose was established as 50 mg twice daily on days 1–7 of a 21 day cycle [4]. In this dose escalation study, 6/36 patients with NHL experienced a partial response (PR) ranging up to >4 months in duration. Grade ≥3 hematologic toxicities included neutropenia (45%), thrombocytopenia (28%), anemia (19%), and febrile neutropenia (9%). Grade ≥3 non-hematologic toxicities included fatigue (3%), diarrhea (2%), and stomatitis (2%). We conducted a multi-site phase 2 study of alisertib in patients with relapsed and refractory B-cell NHL.

Patients with relapsed/refractory NHL after ≥1 prior therapy were enrolled to cohort A (indolent NHL) or cohort B (aggressive NHL). Additional eligibility criteria included age ≥18, ECOG performance status 0–2, absolute neutrophil count ≥1000/μL, platelet count of ≥75,000/μL, serum creatinine ≤2.0 mg/dL, and adequate liver function. This study was approved by the Institutional Review Board at participating sites, and all patients provided written informed consent in accordance with the Declaration of Helsinki.

Patients received alisertib 50 mg orally twice daily on days 1–7 of a 21 day cycle, and response assessment by computed tomography (CT) or positron emission tomography/computed tomography (PET/CT) occurred every two cycles. Non-responding patients in cohort B after cycle 2 could receive rituximab on day 1 of up cycles 3–8.

The primary objective was to determine the overall response rate (ORR) with alisertib monotherapy. We utilized a Simon minimax two stage design, with the total planned maximum accrual for each cohort of 25 patients whereas a response identified in five or

CONTACT Jonathon B. Cohen Jonathon.cohen@emory.edu Department of Hematology and Medical Oncology, Emory University – Winship Cancer Institute, 1365C Clifton Road, NE, Atlanta, GA 30322, USA.

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more patients would be considered of interest for further study. The first stage for each cohort was scheduled to be completed after the first 16 patients were accrued, and a response encountered in at least two patients in a cohort would result in progressing to the second stage. This study was open at one site from 2013 to 2015 and an additional site opened in 2015, but enrollment was slow due to early toxicities encountered and limited preliminary efficacy in this and other studies. As a result, drug supply was withdrawn and with support for the study withheld prior to completion of the first stage for each cohort, only 14 patients were enrolled, including one patient to cohort A and 13 patients to cohort B. Response was determined as defined by Cheson et al. [5]. All toxicities and adverse events were recorded according to CTCAE version 4.0.

The median age of enrolled patients was 61 years (range 35–77), and 11 were male. Twelve of 14 patients had advanced stage disease (Stage 3 = 2, Stage 4 = 10). Baseline ECOG performance status was 0 in six patients, 1 in seven patients, and 2 in one patient. Disease subtypes included DLBCL ($n = 9$) and transformed NHL ($n = 4$) enrolled on cohort B, and FL ($n = 1$) enrolled on cohort A. Enrolled patients received a median of 4 prior therapies (range 1–6), including six patients who had previously undergone autologous stem cell transplant. All patients had previously received rituximab and anthracycline-containing chemotherapy. Eleven patients had previously received a platinum-containing combination, five patients received previous bendamustine, and five patients had undergone radiation therapy at some point in their treatment. Each patient received lenalidomide, bortezomib, and ibrutinib. The patient enrolled in cohort A was a 77 year old male with stage II FL. He received two cycles and then discontinued due to progressive disease with- out any evidence of response. Survival status for this patient is unknown.

Among patients with DLBCL, there were three patients with non-Germinal center B-cell (GCB) and four patients with GCB cell of origin determined by IHC, with two patients not assessed. Three patients were assessed for *CMYC* and *BCL2* rearrangements by FISH, with one patient having a *CMYC* rearrangement and the other two having no detected rearrangements. Two DLBCL patients were CD5+. The median number of alisertib cycles in cohort B was 2 (range: 1–5), and six patients received only one cycle. Reasons for therapy discontinuation in this cohort included progressive disease ($n = 9$), pneumonitis with hypoxia ($n = 1$), prolonged cytopenias ($n = 1$), patient choice ($n = 1$), and allogeneic transplant ($n = 1$). Only one cohort B patient who achieved stable disease after cycle 2 received combined alisertib and rituximab for one cycle before proceeding with allogeneic transplant.

Two out of 13 patients in cohort B responded to the single agent alisertib with an ORR of 15% (95%CI: 2–45%). One responding patient had transformed NHL with a *CMYC* rearrangement and discontinued study therapy after one cycle due to pancytopenia. However, this patient achieved a PR lasting 1 month based on scans obtained 1.5 months after the last dose of alisertib. The second responding patient was a 45 year old female with CD5+ non-GCB DLBCL who had previously received two prior regimens. She did not have *CMYC* or *BCL2* rearrangements. She achieved SD after receiving single agent alisertib for two cycles, converted to PR after cycle 4 and subsequently received one cycle of combined rituximab and alisertib before allogeneic transplantation. This patient ultimately progressed

6 months after transplant and died of disease. To date in cohort B, 10 patients have expired, one patient is receiving a subsequent therapy, and survival status is unknown for two patients. The median PFS in cohort B is 1.2 months (95%CI: 0.8–2.5), and the median OS is 3.1 months (95%CI: 1.7–27.6).

Grade ≥3 toxicities at least possibly associated with study treatment are summarized in Table 1. Six cohort B patients experienced grade ≥3 toxicities, including four patients with neutropenia, four with lymphopenia, one with thrombocytopenia, and two with mucositis. One patient's dose was reduced to 40 mg twice daily due to mucositis. Two additional patients discontinued therapy due to toxicity. One patient had grade 3 pneumonitis with hypoxia requiring hospitalization. An additional patient had prolonged pancytopenia for 6 weeks after one week of alisertib. This patient received three prior lines of therapy including autologous transplant. There was also one episode of grade 3 febrile neutropenia. The patient in cohort A had grade 3 neutropenia that was definitely associated with treatment.

In this small trial, alisertib was associated with significant toxicity and an ORR of 15% in patients with aggressive NHL. As most patients quickly progressed, only one patient in cohort B was eligible to receive combined alisertib and rituximab. ORR for single agent alisertib was reported in a prior phase 2 study that included 48 patients with several subtypes of B- and T-cell lymphoma. Similar to our findings of limited efficacy, the ORR was only 14% in DLBCL ($n = 21$) [6]. Grade ≥3 neutropenia (63%), thrombocytopenia (33%), and stomatitis (15%) were frequently encountered in the prior study and were also common in our study, even with the limited duration of treatment experienced by most patients. The significant myelosuppression and limited ORR of <20% observed with alisertib in these two phase 2 trials do not support further clinical evaluation of this agent in patients with relapsed/refractory DLBCL.

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Table 1

Grade 3 or 4 toxicities at least possibly related to study therapy.

Toxicity (*n* = 14)	**Grade 3, no. (%)**	**Grade 4, no. (%)**
Neutropenia	2 (14)	3 (21)
Lymphopenia	3 (21)	1 (7)
Thrombocytopenia	–	1 (7)
Febrile Neutropenia	1 (7)	–
Fatigue	1 (7)	–
Mucositis	2 (14)	–
Hyponatremia	1 (7)	–
Cough	1 (7)	–
Dyspnea	1 (7)	–
Pneumonitis with hypoxia	1 (7)	–