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An exploratory phase 2 study of investigational Aurora A kinase inhibitor alisertib (MLN8237) in acute myelogenous leukemia and myelodysplastic syndromes

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ABSTRACT

Alisertib (MLN8237) is an investigational, oral, selective, Aurora A kinase (AAK) inhibitor. In this phase 2 trial, 57 patients with acute myeloid leukemia (AML) or high-grade myelodysplastic syndrome received alisertib 50 mg BID for 7 days in 21-day cycles. Responses in 6/35 AML patients (17% response rate with an additional 49% stable disease, 34% transfusion independence) included 1 complete response lasting > 1 year. No responses were observed in MDS patients. Adverse events > 30% included diarrhea, fatigue, nausea, febrile neutropenia, and stomatitis. Results suggest modest activity in AML, supporting further research to better understand how AAK inhibition may induce leukemic cell senescence.

1. Introduction

The Aurora kinases are serine/threonine protein kinases essential for regulation of normal cell cycle mitosis. Aurora kinases A (AAK) and B are overexpressed in hematologic malignancies, including acute myeloid leukemia (AML) and myelodysplastic syndrome (MDS); reduction of intracellular AAK results in mitotic inhibition, senescence, and apoptosis in human cell lines [1].

Alisertib (MLN8237) is an investigational, orally available, selective, small-molecule AAK inhibitor [1] with antitumor activity in preclinical leukemia models [2,3].

Here we report an exploratory phase 2 trial of alisertib in a heterogeneous patient population with AML or high-grade MDS (NCT00830518). The single-agent alisertib regimen administered in this study was determined by prior phase 1 studies [4,5].

2. Methods

AML patients ineligible for potentially curative treatment options, with > 10% bone marrow (BM) or peripheral blood blasts at relapse, and who had failed to achieve complete response (CR) or relapsed after prior therapy were eligible. High-grade MDS patients were defined as follows: (a) International Prognostic Staging System (IPSS) risk Intermediate-2 or High; (b) > 10% BM blasts; and (c) treatment failure from, or not a candidate for, standard therapies. Patients were aged ≥ 18 years, with ECOG performance status 0–2, and adequate hepatic and renal function.

The study was conducted according to the Declaration of Helsinki and Good Clinical Practice. Review boards at all participating institutions approved the study protocol and all patients provided written informed consent.

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In this open-label, phase 2 study, conducted in the USA, Canada, and France, patients received alisertib 50 mg BID for 7 days plus 14-days' rest in 21-day cycles until disease progression or unacceptable toxicity.

Response was evaluated per AML and MDS International Working Group (IWG) criteria [6,7]. Primary endpoint was overall response rate (ORR; CR plus partial response [PR]). 'CR' included CR with incomplete blood count recovery (per IWG guidelines) in AML patients and marrow CR in MDS patients; 'PR' included incomplete blood count recovery in AML and MDS patients [6,7]. Secondary endpoints included progression-free survival (PFS), duration of response (DOR), and hematologic improvement in MDS patients. The response-evaluable population for the primary endpoint analysis included patients who received ≥ 1 dose of alisertib and had ≥ 1 post-baseline response assessment. Safety and tolerability were monitored throughout. Adverse events (AEs) were graded by NCI CTCAE v3.0. The safety population included patients who received ≥ 1 dose of alisertib.

A Simon optimal 2-stage design was used, with 21 patients enrolled in the first stage and ≥ 2 responses required to proceed to the second stage. Sample size was estimated using a 1-sided test at the significance level of $\alpha = 0.05$, power of 90%, a null hypothesis of response rate $\leq 5\%$, and an alternative hypothesis of response rate $\geq 20\%$. To obtain 41 response-evaluable patients, enrollment of ~44 patients was projected. Time-to-event data were analyzed by Kaplan–Meier methodology.

Table 1
Patient demographics and baseline characteristics.

n (%)	AML ($n=46$)	MDS ($n=11$)	Total ($N=57$)
Median age, years (range)	72 (48–83)	72 (46–85)	72 (46–85)
Male	24 (52)	8 (73)	32 (56)
White	36 (78)	10 (91)	46 (81)
Primary disease[a]	25 (54)	10 (91)	35 (61)
Secondary disease	21 (46)	1 (9)	22 (39)
Prior history of MDS	18 (39)	–	–
IPSS score			
Intermediate-2 (1.5 or 2.0)	–	8 (73)	–
High (≥ 2.5)	–	3 (27)	–
ECOG PS 0/1/2, n	9/29/8	3/8/0	12/37/8
Extramedullary disease	3 (7)	0	3 (5)
Median time since diagnosis, years	0.31	0.50	0.33
Classification of AML			
AML with recurrent genetic abnormalities[b]	1 (2)	–	–
AML with multilineage dysplasia[b,c,d]	21 (46)	–	–
AML, therapy-related[c]	3 (7)	–	–
AML not otherwise categorized	24 (52)		
AML minimally differentiated	4 (9)	–	–
AML without maturation	1 (2)	–	–
AML with maturation[b]	11 (24)	–	–
Acute myelomonocytic leukemia	4 (9)	–	–
Acute erythroid leukemia	1 (2)	–	–
Acute megakaryoblastic leukemia	1 (2)	–	–
Other	2 (4)	–	–
Prior therapy	39 (85)	10 (91)	49 (86)
Azacitidine	19 (41)	6 (55)	25 (44)
Cytarabine	22 (48)	3 (27)	25 (44)
Decitabine	14 (30)	4 (36)	18 (32)
Idarubicin	12 (26)	1 (9)	13 (23)
Allogeneic/autologous transplant	3 (7)[f]	0	3 (5)
Radiation therapy	2 (4)	1 (9)	3 (5)
≥ 3 prior therapies	8 (17)	1 (9)	9 (16)
Best response to prior therapy (*n*)	39	10	49[g]
CR	9 (23)	1 (10)	10 (20)
PR	4 (10)	0	4 (8)
SD	11 (28)	2 (20)	13 (27)
Median time since progression, months	1.3	1.0	1.1

AML, acute myeloid leukemia; CR, complete response; ECOG PS, Eastern Cooperative Oncology Group performance status; IPSS, International Prognostic Staging System; MDS, myelodysplastic syndrome; MPD, myeloproliferative disorder; PR, partial response; and SD, stable disease.

[a] Modified World Health Organization criteria at the time of primary diagnosis.

[b] 1 patient was classified as having AML with recurrent genetic abnormalities, AML following MDS or MDS/MPD, and AML with maturation.

[c] 1 patient was classified as having AML, therapy related and AML following MDS or MDS/MPD.

[d] 18 AML patients had multilineage dysplasia following MDS or MDS/MPD, while the remaining 3 patients with multilineage dysplasia were without antecedent MDS or MDS/MPD but had dysplasia in $\geq 50\%$ of cells in 1 or more myeloid lineage.

[f] 2 patients had prior allogeneic transplant.

[g] 21 patients had progressive disease and response was not evaluable in 1 patient.

3. Results

Fifty-seven patients were enrolled (Table 1). The median number of treatment cycles received was 2 (range 1–26) with similar medians for AML and MDS. The maximum number of cycles received for AML and MDS patients was 26 and 6, respectively, with differences between diseases driven by an increased response rate in AML patients.

Forty-five patients were response-evaluable; 12 were not due to lack of on-study response assessment. ORR for the study was 13% (response-evaluable patients). Two responses were documented in stage 1; therefore, the study continued to stage 2. Recruitment continued beyond the expected 44 patients in order to enroll 8 MDS patients.

3.1. Response – AML

Thirty-five AML patients were response-evaluable; 6 responded (CR, $n=1$; PR, $n=5$; Table 2) giving an ORR of 17%. Four of the 6 responders had a history of prior MDS. DORs for responders were 21* [asterisks denote censored observations], 27*, 57, 91*, 409, and 596 days, respectively, including 1 patient with durable CR through 16 cycles (~1 year). Seventeen patients (49%) had stable disease. Time to first response was 1–4 cycles. Changes in blasts in responding patients shown in Fig. 1. There was no apparent pattern of response according to AML subtype based on the IWG recommended classifications (Table 2).

Twelve of 35 AML patients (34%) achieved transfusion independence during the study; 10 maintained independence for ≥ 2 cycles, and 1 for ≥ 4 cycles.

Median PFS was 55 days (95% CI: 47, 67 days; range 1*–638).

Table 2
Investigator-assessed best response in response-evaluable patients receiving alisertib.

n (%)	AML ($n=35$)	MDS ($n=10$)	Total ($N=45$)
ORR (CR+PR)	6 (17)	0	6 (13)
CR	1 (3)[a]	0	1 (2)
PR	5 (14)[b]	0	5 (11)
SD	17 (49)	2 (20)	19 (42)

AML, acute myeloid leukemia; MDS, myelodysplastic syndrome; CR, complete response; PR, partial response; and SD, stable disease.

[a] The patient with CR had AML with multilineage dysplasia.

[b] 5 patients with PR had AML with multilineage dysplasia ($n=2$), or AML not otherwise categorized ($n=3$) which included acute myelomonocytic leukemia ($n=1$), acute megakaryoblastic leukemia ($n=1$), and other: post-MDS ($n=1$). Two patients transformed from MDS to AML during the study – 1 patient transformed before the first response assessment (counted as AML), and the other transformed at the second response assessment (counted as MDS).

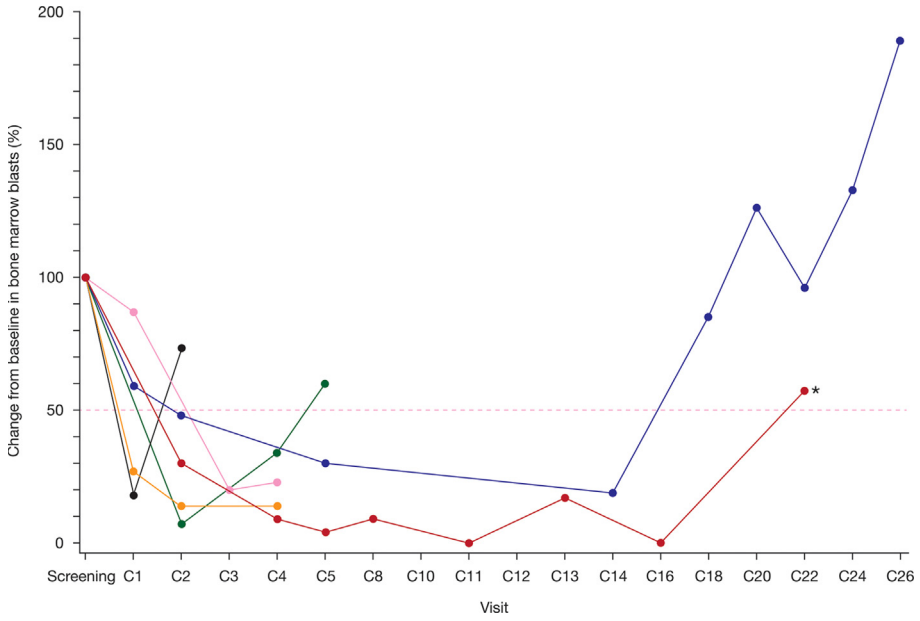

Fig. 1. Percentage change in bone marrow blasts from baseline over time (21-day cycles) in responding patients; plot lines represent individual patients ($n=6$).

Table 3
Non-hematologic (≥ 15% all grades) and hematologic AEs.

Non-hematologic AEs ($N=57$)				
n (%)	All grades		Grade ≥3	
	Treatment emergent	Drug related	Treatment emergent	Drug related
Diarrhea	23 (40)	18 (32)	1 (2)	1 (2)
Fatigue	22 (39)	15 (26)	8 (14)	4 (7)
Nausea	22 (39)	13 (23)	0	0
Stomatitis	18 (32)	9 (16)	4 (7)	2 (4)
Somnolence	14 (25)	11 (19)	3 (5)	2 (4)
Abdominal pain	14 (25)	2 (4)	1 (2)	0
Dyspnea	14 (25)	1 (2)	6 (11)	1 (2)
Pyrexia	12 (21)	0	0	0
Peripheral edema	12 (21)	0	1 (2)	0
Cough	12 (21)	0	0	0
Alopecia	11 (19)	9 (16)	0	0
Asthenia	10 (18)	5 (9)	4 (7)	3 (5)
Vomiting	10 (18)	5 (9)	0	0
Sepsis	9 (16)	1 (2)	9 (16)	1 (2)

Hematologic AEs ($N=57$)								
n (%)	*All grades*				*Grade ≥3*			
	AML ($n=46$)		MDS ($n=11$)		AML ($n=46$)		MDS ($n=11$)	
	Treatment emergent	Drug related	Treatment emergent	Drug related	Treatment emergent	Drug related	Treatment emergent	Drug related
Febrile neutropenia	17 (37)	8 (17)	4 (36)	1 (9)	12 (26)	5 (11)	4 (36)	1 (9)
Anemia	14 (30)	4 (9)	3 (27)	1 (9)	10 (22)	4 (9)	1 (9)	1 (9)
Thrombocytopenia	9 (20)	3 (7)	2 (18)	2 (18)	7 (15)	3 (7)	2 (18)	2 (18)
Neutropenia	5 (11)	2 (4)	3 (27)	2 (18)	5 (11)	2 (4)	2 (18)	2 (18)
Leukopenia	3 (7)	1 (2)	2 (18)	2 (18)	2 (4)	0	2 (18)	2 (18)
Neutrophil count decreased	3 (7)	3 (7)	0	0	3 (7)	3 (7)	0	0

AML, acute myeloid leukemia; MDS, myelodysplastic syndrome; and AE, adverse events.

3.2. Response – MDS

None of 10 response-evaluable MDS patients responded; 1 patient achieved transfusion independence, maintained for at least 2 cycles.

Median PFS was 38 days (95% CI: 35, 113; range 22*–113).

3.3. Safety

All patients experienced ≥1 AE (Table 3). Drug-related grade ≥3 AEs were reported in 26 patients (46%; $n=19$ AML, $n=7$ MDS). Serious AEs were documented in 44 patients (77%; drug-related in $n=15$, 26%). Fourteen patients (25%) discontinued due to AEs.

There were 22 on-study deaths (20 AML; 2 MDS), including 10 deaths prior to cycle 2. All deaths were considered unrelated to alisertib; causes were progressive disease ($n=10$, 46%), sepsis ($n=5$, 23%), cerebral/intracranial hemorrhage ($n=2$, 9%), gastrointestinal infection, multi-organ failure, respiratory failure, renal failure, and subdural hematoma (each $n=1$, 5%).

4. Discussion

These results suggest that alisertib has modest single-agent anti-leukemic activity, demonstrating a 13% ORR. Six responses (17% ORR) were observed among AML patients, all of whom had pre-treated disease. An additional 49% of AML patients achieved stable disease, indicating a potentially clinically beneficial effect. Responses were generally observed by cycle 4 rather than during cycle 1, suggesting that, in the absence of disease progression, multiple cycles may be necessary to achieve anti-leukemic activity. Overall median PFS in this study was 51 days.

The population in this exploratory phase 2 trial primarily consisted of patients with progressive disease, including 21 patients (43%) refractory to most recent prior therapy and 3 having failed prior transplant (2 allogeneic). Improved clinical outcomes with alisertib may be possible in more selected populations, such as those without refractory disease and those robust enough to receive adequate drug to be effective.

The lack of response in MDS patients compared with AML patients may point to important clues in alisertib clinical mechanism of action. Failure of hematopoeisis in MDS is principally driven by increased apoptosis in the malignant clone, in contrast to marrow suppression by a proliferative clone in AML. In-vitro studies have shown that reduction of intracellular AAK results in mitotic inhibition, senescence, and apoptosis in human cell lines [1]. Thus, alisertib may be unable to stimulate an apoptotic clone in MDS but may suppress a proliferative clone in AML.

Transfusion independence was achieved in 13 patients and maintained for 2–5 cycles in 11 patients, suggesting that recovery of normal hematopoiesis can occur. Additional studies are needed to identify predictors of response and to understand how AAK inhibition may induce leukemic cell senescence, a property described with preclinical model systems [8], which may complement an antimitotic effect. In conclusion, alisertib demonstrated modest single-agent anti-leukemic activity, mostly limited to AML patients in this study. The toxicity profile was generally acceptable, and consistent with expected effects of Aurora kinase inhibition in proliferative tissues [9,10]. To allow for potentially delayed treatment effects by alisertib, improved clinical outcomes in larger populations will likely require additional strategies to enable early disease control. Results of this study of alisertib in AML/MDS highlight the need to develop predictors of response, combination regimens, and other strategies to enhance the clinical utility of treatment with this novel AAK inhibitor.

Role of the funding source

Research funded by Takeda Pharmaceuticals International Co.; alisertib was manufactured and supplied by Takeda Pharmaceuticals International Co. The sponsor declares a role in the study design, collection and analysis of data, as reflected by the inclusion of company authors. The final decision to submit the manuscript for publication lay solely with the authors.

Contributions

SLG, PF, MDC, EG, JL, JK, AP, GJS, and PW recruited and treated patients. JJ, EJL, and HF participated in study design and data collation. All authors participated in the preparation of the manuscript and approval of the final version to be submitted.

Conflicts of interest

Employment: HF, EJL, JJ (Takeda Pharmaceuticals International Co.).

Research Funding: SLG (Millennium: The Takeda Oncology Company); EG (Amgen, Janssen-Cilag, Celgene); GJS (Millennium: The Takeda Oncology Co.); PF (Celgene, Janssen-Cilag, Amgen, Roche, GSK, Novartis, Merck, Cephalon).

Honoraria: EG (Janssen, Celgene); PW (Novartis, speakers bureau); PF (Celgene, Janssen-Cilag, Amgen,Roche, GSK, Novartis, Merck, Cephalon).

Membership: MDC (Genentech).

AP, JK, JL have no conflicts of interest to disclose.

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