The clinical trial information provided in this public disclosure synopsis is supplied for informational purposes only.

Please note that the results reported in any single trial may not reflect the overall potential risks or benefits of a product which are based on an evaluation of an entire research program.

Before prescribing any Takeda products, healthcare professionals should consult prescribing information for the product approved in their country.

CLINICAL STUDY REPORT C14005 SYNOPSIS

Study Title: A Phase 2 Trial of Alisertib, an Oral Aurora A Kinase Inhibitor, in Adult Patients with Acute Myelogenous Leukemia and High-Grade Myelodysplastic Syndrome

Investigator(s): PPD

Study Center(s): 19 sites in the USA (13 sites: CCI), France (5 sites: CCI), and Canada (1 site: CCI)

Publication (reference): Goldberg S, Fenaux P, Craig M, Gyan E, Lister J, Kassis J, et al. Phase 2 Study of MLN8237, An Investigational Aurora A Kinase (AAK) Inhibitor In Patients with Acute Myelogenous Leukemia (AML) or Myelodysplastic Syndromes (MDS). Blood (ASH Annual Meeting Abstracts) 2010;116:Abstract 3273.[1]

Phase: 2

Initiation Date (first patient enrolled): 16 February 2009 (last patient enrolled 22 December 2009)

Interim Analysis: Not performed, as sufficient responses were reported from the first stage of enrollment to support the planned full enrollment (interim analysis data cut would have been 18 December 2009).

Completion Date (last patient completed): 04 July 2011 (interim analysis data cut 18 December 2009)

Study Objectives:

The primary objective was:

- To estimate the antitumor activity of alisertib as measured by response rate in patients with acute myeloid leukemia (AML) and high-grade myelodysplastic syndrome (MDS).

The secondary objectives included:

- To assess additional measures of antitumor activity, including progression-free survival (PFS), duration of response (DOR), and hematologic improvement (HI) with MDS patients
- To evaluate the safety and tolerability of alisertib treatment based on vital signs, physical examination, laboratory tests, and adverse events

METHODS

Design: This was an open-label, multicenter, phase 2 study of alisertib in patients with AML and high-grade MDS. The patient population consisted of adults previously diagnosed with AML including MDS for which standard curative or life prolonging treatment either did not exist or was no longer effective. Patients who were on hydroxyurea, administered for palliative care to manage symptoms of leukocytosis, were included in the study and could continue on hydroxyurea while participating in the study. Patients were treated with alisertib at a dose of 50 mg twice daily (BID) for 7 consecutive days followed by a 14-day rest period, in 21-day cycles in order to determine the objective antitumor response rate in these malignancies. Dose reductions were implemented in the setting of drug-related toxicities. This study also evaluated PFS, DOR, and HI with MDS patients, safety and tolerability, and resistance to alisertib.

Number of Patients (planned and analyzed): Twenty-one response-evaluable patients completing 4 cycles of treatment (or discontinued therapy) were planned for the interim analysis and 41 response-evaluable patients overall were planned for the overall study. Multiple responses were reported among patients enrolled to the first stage of enrollment, and the trial proceeded with the second stage of enrollment. A total of 57 patients were enrolled (46 AML, 11 MDS). Twelve patients were not response-evaluable (11 AML, 1 MDS). There was overenrollment by 4 patients to ensure adequate response-evaluability prior to closing recruitment.

Diagnosis and Main Criteria for Inclusion: The study population consisted of patients with AML or high-grade MDS who had relapsed following or did not respond to prior therapy, or were not candidates for standard induction chemotherapy. Patients must have been at least 18 years of age and had an Eastern Cooperative Oncology Group (ECOG) performance status of 0-2.

Test Product, Dose and Mode of Administration, Batch Number: Alisertib was administered orally (PO) at a dose of 50 mg BID for 7 consecutive days followed by a 14-day rest period, in 21-day cycles. A Powder in Capsule (PIC) formulation was administered throughout the study with drug product supplied in capsule dosage forms of 5-mg or 25-mg dose strength. Lot numbers were: 18C029B, 18C030B, 18C031B, 18D008B, 18D009B, 18D010B, 18D012B, 18D013B, IB010CA04, and IC009CA03.

Duration of Treatment:

While variable for individual patients, the longest anticipated duration of study treatment for an individual patient in this study was 12 months, unless it was determined that a patient would derive benefit from continued therapy beyond 12 months.

Reference Therapy, Dose and Mode of Administration, Batch Number: This was an open-label study, and no reference or placebo treatment was used. All patients received treatment with alisertib.

Efficacy Assessments: The primary endpoint was the complete response (CR) plus partial response (PR) rate (CR + PR). Response was derived using the modified AML/MDS International Working Group (IWG) response criteria. For patients with AML, CR included patients who had morphologic complete remission with incomplete blood count recovery (CRi) as described by Cheson et al, 2003.[(2)] For patients with MDS, CR included patients who had marrow CR as described by Cheson et al, 2006,[(3)] for example, bone marrow with fewer than 5% myeloblasts and decrease by 50% or greater over pretreatment. Partial response included patients who had PR with incomplete blood count recovery (PRi) for AML and MDS patients.

The secondary endpoints included PFS and DOR, and hematologic improvement with MDS patients.

Progression-free survival was defined as the time from the date of first study drug administration to the date of first documentation of progressive disease (PD) or death.

DOR was defined as the time from the date of first documentation of a response to the date of first documentation of PD.

Hematologic improvement response category for all patients with MDS was derived using the MDS IWG criteria[(3)]

Safety Assessments: Safety endpoints included safety and tolerability of alisertib treatment based on vital signs, physical examination, laboratory tests, and adverse events (AEs). Monitoring of AEs was conducted throughout the study. Adverse events were reported from the time of alisertib administration on Day 1 of Cycle 1 through 30 days after the last dose of alisertib.

Pharmacokinetic Assessments: Blood samples (3 milliliters [mL]) for the determination of plasma concentrations of alisertib were collected during Cycle 1 of the study. For PK assessments, blood samples were drawn within 1 hour prior to the first dose of alisertib on Cycle 1, Day 1, and 1 hour

(± 15 minutes) and 3 hours (± 1 hour) after the first dose on Cycle 1, Day 1. Another sample was drawn on Day 2, ie 12 hours (± 3 hours) after the second dose on Cycle 1, Day 1 immediately prior to Cycle 1, Day 2 dosing. A final blood sample was drawn on Day 8, 12 hours (± 3 hours) following the last dose on Day 7.

Pharmacodynamic Assessments: Blood samples for the determination of Aurora A kinase (AAK) activity in peripheral blood mononuclear cells (PBMCs) were collected during Cycle 1 of the study. Blood samples were drawn within 1 hour prior to the first dose of alisertib on Cycle 1, Day 1, and 3 hours (± 1 hour) after the first dose on Cycle 1, Day 1. Another sample was drawn on Day 2, ie 12 hours (± 3 hours) after the second dose on Cycle 1, Day 1 immediately prior to Cycle 1, Day 2 dosing. A final blood sample was drawn on Day 8, 12 hours (± 3 hours) following the last dose on Day 7.

Pharmacogenetic Assessments: One peripheral blood sample was obtained prior to alisertib dosing Cycle 1, Day 1 to evaluate germ-line polymorphisms in the AAK gene and in genes encoding enzymes that may contribute to alisertib metabolism/disposition, [redacted].

Statistical Methods: Summary tabulations were presented that displayed the number of observations, mean, standard deviation, median, minimum, and maximum for continuous variables, and the number and percentage per category for categorical data. Time-to-event data were analyzed by the Kaplan-Meier life test method and results were summarized by 25th, 50th (median), and 75th percentiles with associated 2-sided 95% confidence intervals, as well as the percentage of censored observations.

Four different populations were used in the analyses in this study: Safety Population (used for all safety analyses and PFS analyses), Response-Evaluable Population (used for all efficacy analyses), PK-Evaluable Population, and Pharmacodynamic-Evaluable Population.

Efficacy Analysis: The primary efficacy analysis was based on the Response-Evaluable Population. The number and percentage of patients in each response category (CR, PR, PD, and stable disease [SD]) was tabulated, and the estimate of the response rate (rate of the sum of CR, PR) was presented with 2-sided 95% exact binomial confidence intervals for AML patients, MDS patients, and overall. CRi, marrow CR and PRi were also tabulated by subcategory of CR and PR and estimated of the response rate for AML patients, MDS patients, and overall.

All other responses were summarized as appropriate given available data. This included cytogenetic CR and Molecular CR with AML patients, relapse after CR or PR and cytogenetic response with MDS patients, and treatment failure with both AML and MDS patients.

Separate by-patient listings of the response at each cycle were also presented. This included neutrophils, platelets and bone marrow blasts for AML patients and neutrophils, platelets, hemoglobin and bone marrow blasts for MDS patients.

The numbers and percentages of patients who had transfusion independence ≥ 2, ≥ 4, and ≥ 6 treated cycles for AML patients, MDS patients, and overall were summarized and listed.

If more than 4 patients with CR + PR were observed among the 41 response-evaluable patients, then the treatment was considered worthy of further evaluation for AML and MDS patients.

Secondary efficacy analyses:

PFS was analyzed based on the Safety Population and Response-Evaluable Population using the Kaplan-Meier method, for AML patients, MDS patients, and overall.

DOR was analyzed for all responders using the Kaplan-Meier method, for AML patients, MDS patients, and overall.

For a responding patient that had not progressed and was last known to be alive, PFS was censored at the last response assessment that was SD or better.

For a patient that had not progressed, DOR was censored at the last response assessment that was SD or better.

Kaplan-Meier analyses results were presented in tables and figures.

A sensitivity analysis was performed for symptomatic deterioration that was treated as PD and was analyzed for PFS and DOR. A separate by-patient listing was also presented.

The number and percentage of patients with MDS for each HI response (erythroid response, platelet response, neutrophil response, progression or relapse) was tabulated based on the Safety Population.

Separate by-patient listings of the HI response at scheduled cycles were also presented. It included red blood cells (RBC), platelets, hemoglobins, neutrophils at scheduled cycles and those values at baseline for MDS patients.

Pharmacokinetic Analysis: C_{trough} was presented for the PK-Evaluable Population.

Pharmacodynamic Analysis: This analysis was to be explored using descriptive statistics, graphical methods, and statistical modeling as appropriate.

Safety Analysis: Safety evaluations were based on the incidence, intensity, and type of AEs, and clinically significant changes or abnormalities in the patient's physical examination vital sign measurements, and clinical laboratory results. Treatment-emergent AEs were tabulated by system organ class (SOC), high level term, preferred term, and treatment group. Exposure to study drug was tabulated.

RESULTS

Demographic Results: A total of 57 patients (46 with AML and 11 with MDS) were enrolled and received study drug.

Patient disposition is summarized below.

Overall Patient Disposition

	AML N = 46 n (%)	MDS N = 11 n (%)	Total N = 57 n (%)
Safety Population[a]	46 (100)	11 (100)	57 (100)
Response-Evaluable Population[b]	35 (76)	10 (91)	45 (79)
PK-Evaluable Population[c]	23 (50)	8 (73)	31 (54)
Reasons for End of Treatment			
Progressive Disease	18 (39)	8 (73)	26 (46)
Symptomatic Deterioration	4 (9)	1 (9)	5 (9)
Adverse Event	14 (30)	1 (9)	15 (26)
Protocol Violation	0	0	0
Study Terminated by Sponsor	0	0	0
Withdrawal by Patient	2 (4)	0	2 (4)
Lost to Follow-up	0	0	0
Other	8 (17)	1 (9)	9 (16)

Overall Patient Disposition

	AML N = 46 n (%)	MDS N = 11 n (%)	Total N = 57 n (%)

Source: Clinical Study Report C14005, Table 14.1.1.1.

Abbreviations: AML = acute myeloid leukemia; MDS = myelodysplastic syndrome; PK = pharmacokinetic(s).

Percentages for reason for end of study are based on total number of patients entering study follow-up in each column, all other percentages are based on the total number of patients in the Safety Population.

a Safety Population was defined as all patients who received any amount of alisertib.

b Response-Evaluable Population was defined as all patients who receive at least 1 dose of alisertib and had at least 1 post-baseline response assessment.

c The PK-Evaluable Population is defined as all patients who have sufficient dosing and alisertib plasma concentration-time data without dose reductions or dosing interruptions in Cycle 1.

Twelve patients were excluded from the Response-Evaluable Population since they did not have a post-baseline response assessment. There was over-enrollment by 4 patients to ensure the response-evaluable criterion was fulfilled.

Twenty six (46%) patients experienced PD and 5 patients (9%) experienced symptomatic deterioration. The other primary reasons for discontinuation from study treatment were: AEs (AML, n = 14 [30%]; MDS, n = 1 [9%]), "other" (AML, n = 8 [17%]; MDS, n = 1 [9%]), and withdrawal by patient (AML, n = 1 [2%]; MDS, n = 1 [9%]). The "other" reasons for discontinuation were investigator decision (3 patients), death of patient (2 patients), lack of response presumed to be PD but with no formal assessment completed (2 patients), prolonged platelet recovery (1 patient), and uncontrolled hyperleukocytosis under hydroxyurea (1 patient).

Note that the Patient Disposition table above lists 15 patients (14 AML and 1 MDS) with "adverse event" as their primary reason for treatment discontinuation; this includes 1 AML patient who discontinued due to a non-treatment-emergent AE (> 30 days from last dose) and who is excluded from the summary of treatment AEs resulting in study drug discontinuation in the Safety Results section.

In the Safety Population, 56% of patients were male, and 81% of patients were White. The mean age was 71.4 years (range 46 - 85 years); 51 (89%) patients were ≥ 60 years of age. Mean weight was 75.0 kg (range 47 - 110 kg), and mean baseline body surface area (BSA) was 1.86 m^2 (range 1.5 - 2.3 m^2). The mean time since the initial diagnosis was 0.68 years (range 0 - 2.9 years). Most (95%) patients did not have evidence of extramedullary disease. Either AML or MDS was primary in 61% of patients and secondary in 39%.

Baseline characteristics – AML:
Within the AML group, 21 (46%) patients were diagnosed with AML with multilineage dysplasia, of whom 18 (86%) patients were following myelodysplasia (MDA) or MDS/ myeloproliferative disease (MPD) and 3 (14%) patients were without antecedent MDS or MDS/MPD, but with dysplasia in ≥ 50% of cells in myeloid lineages. Three (7%) AML patients had therapy-related disease: 2 patients with alkylating agent/radiation related type AML and 1 patient with topoisomerase II inhibitor related type AML. Other diagnosed types of AML not otherwise categorized included: AML, minimally differentiated (4 patients), AML without maturation (1 patient), AML with maturation (11 patients), acute myelomonocytic leukemia (4 patients), acute erythroid leukemia (erythroid/myeloid and pure erythroleukemia) (1 patient), acute megakaryoblastic leukemia (1

patient), and "other" (2 patients). Eighteen (39%) AML patients had a prior history of MDS. One patient was diagnosed at baseline with AML with recurrent genetic abnormalities (unspecified).

Baseline characteristics – MDS:
Of 11 MDS patients, 1 patient was diagnosed with refractory cytopenia with multilineage dysplasia (RCMD), 2 patients had refractory anemia with excess blasts-1 (RAEB-1), and 8 patients had refractory anemia with excess blasts-2 (RAEB-2). Baseline International Prognostic Scoring System (IPSS) scores were 5-10 in 2 patients and 11-20 in 9 patients. At baseline, 3 patients had a 'good' karyotype assessment, 5 patients were 'intermediate', and 2 patients were poor (1 patient was unknown). Four patients had ≥ 1 cytopenias and 7 had 2 or 3 cytopenias. Eight MDS patients had weighted risk scores of intermediate-2 (1.5 or 2.0) and 3 patients had weighted risk scores of high (≥ 2.5) at baseline.

Most (86%) patients had a baseline ECOG performance status of 0 or 1. Eight (14 %) patients (all in the AML group) had a baseline ECOG status of 2.

Efficacy Results: Overall, the response rate (CR + PR) for the Response-Evaluable Population based on Investigator assessments was 13% (6 patients) (95% confidence interval [CI] 0.051, 0.268).

Of the 45 response-evaluable patients, 36 (80%) achieved PFS events and 9 (20%) were censored prior to progression for the determination of PFS. The median PFS was 51 days (95% CI: [43 days, 67 days]). The 30-day and 60-day PFS estimates were 81.21% and 37.38%, respectively.

Of the 6 responders in this study, 3 patients ultimately experienced disease progression (PPD , PPD , and PPD); DOR was 596 days, 57 days, and 409 days, respectively. For the other 3 patients (PPD , PPD , and PPD), DOR was estimated as 27 days, 21 days, and 91 days, respectively, with DOR censored at the last assessment of stable disease or better. The primary reasons for these patients going off treatment were symptomatic deterioration, AE (septic shock), and 'other' (prolonged platelet recovery), respectively.

Safety Results: A total of 57 patients received at least 1 dose of alisertib and were included in the Safety Population. The median number of treatment cycles was 2 across both patient groups (AML/MDS). Four AML patients remained on treatment for at least 6 cycles, including one patient who received 26 cycles of alisertib treatment. Mean total dose taken was 1914.6 mg (min 400, max 18200) at a mean relative dose intensity of 93.52% (min 48.6%, max 100%). Of 57 patients treated overall, 7 (12%) had the dose held for an AE, 9 (16%) had dose reduced due to an AE, and 4 (7%) had their dose discontinued for an AE.

All patients in the Safety Population experienced at least 1 treatment-emergent AE (TEAE). The most commonly reported TEAEs were diarrhea (40% overall; 46% AML, 18% MDS), fatigue (39% overall; 35% AML, 55% MDS), nausea (39% overall; 41% AML, 27% MDS), febrile neutropenia (37% overall; 37% AML, 36% MDS), and stomatitis (32% overall; 28% AML, 45% MDS).

The most common (≥10% of overall patients) drug-related TEAEs included diarrhea, fatigue, nausea, somnolence, stomatitis, febrile neutropenia, and alopecia. Overall, the most common Grade 3 or higher drug-related TEAE was febrile neutropenia (11%).

A total of 24 patients (42%) died during the study and follow up (22 [48%] patients in the AML group, 2 [18%] patients in the MDS group); of these, 22 patients (39%) died within 30 days of their last alisertib dose (20 [43%] patients in the AML group, 2 [18%] patients in the MDS group). Two additional patients died during follow up >30 days after their last dose of alisertib. None of the deaths was considered to be treatment related. Ten of these on-study deaths were attributed to disease progression (including AML). Other causes of death included gastrointestinal infection, septicemia, cerebral hemorrhage, pneumonia, subdural hematoma, intracranial bleeding, septic shock, bacterial sepsis, respiratory failure, sepsis, multi-organ failure, and renal failure acute.

Overall, a total of 44 patients (77%) experienced SAEs, of whom 15 (26%) had SAEs that were considered to be study drug related. Related SAEs included febrile neutropenia (6 patients), fatigue (2 patients), diarrhea, dehydration, stomatitis, pneumonia, dysphagia, deafness unilateral, mucositis, fall, dyspnea, febrile bone marrow aplasia, sepsis, depressed level of consciousness, and dizziness.

Fourteen (25%) patients experienced TEAEs (treatment-emergent per the protocol definition of AE onset ≤ 30 days after the patient's last dose of study drug) that led to discontinuation (13 [28%] patients in the AML group, 1 [9%] patient in the MDS group). In addition, 1 patient discontinued due to a non-treatment-emergent AE (> 30 days from last dose). Of the 14 patients who discontinued due to TEAEs, 4 patients discontinued during the 7 days of treatment and 10 patients discontinued during the rest period but ≤ 30 days post last dose. Of the 14 patients discontinuing treatment due to TEAEs, 9 experienced Grade 5 events (resulting in death). The TEAEs leading to treatment discontinuation were reported to be treatment-related in 3 of the 14 patients (2 AML and 1 MDS).

There were no unexpected trends over the course of the study for changes in any hematology or chemistry laboratory parameter. Overall, the most commonly reported hematology laboratory abnormality reported as a TEAE was febrile neutropenia, which was reported in 21 (37%) patients. Anemia was reported in 17 (30%) and thrombocytopenia in 11 (19%) patients. The difference between treatment groups in the incidence of these events was small. The incidence of serum chemistry abnormalities reported as TEAEs was low (≤ 7%) for all parameters.

Vital signs changes from baseline to end of treatment were generally small and similar between the AML and MDS groups.

Pharmacokinetic Results: The geometric mean of alisertib Day 8 trough plasma concentrations was 1.5 μM (CV: 48%), which is above the estimated EC90 (1 μM) for pharmacodynamic and antitumor activity, estimated from preclinical results in mouse xenograft models.

Pharmacodynamic Results: Forty-three of 57 patients (75%) had samples obtained and were evaluable for assessment of Aurora A kinase inhibition in blood PBMCs. Based on the preliminary analysis of the data evaluating cell cycle changes and exposures to alisertib, no significant associations between the PD results and plasma concentrations were observed.

CONCLUSIONS

Alisertib demonstrated modest single-agent anti-leukemia activity, limited to the subset of patients with AML. In the Response-Evaluable Population, the response rate (CR+PR) was 13% (6 patients) (95% CI 0.051, 0.268). The toxicity profile was consistent with prior phase 1 experience, including immediate effects in proliferative tissues. Patients enrolled to this study often exhibited poor tolerance to alisertib treatment, due in part to disease comorbidities. Nonetheless, some clinically significant anti-leukemic activity was observed after administration of this dose and schedule in some patients, including durable CR in an elderly patient with AML, recovery of bone marrow with improvement in transfusion requirements in some other patients. Additional clinical and laboratory research will be needed to support the clinical utility of alisertib in management of AML or MDS. In the setting of rapidly progressive disease, alternative treatment strategies such as combination regimens or alternative dose-schedules, coupled with intense support of toxicities and comorbidities, may be needed to achieve disease control, and to allow potentially delayed treatment effects by alisertib. The results of this first single-agent, phase 2 study of alisertib in advanced AML/MDS highlight the need to develop predictors of response, combination regimens, and other strategies that will enhance clinical utility of treatment with this novel AAK inhibitor.

REFERENCES

1. Goldberg S, Fenaux P, Craig M, Gyan E, Lister J, Kassis J, et al. Phase 2 Study of MLN8237, An Investigational Aurora A Kinase (AAK) Inhibitor In Patients with Acute Myelogenous Leukemia (AML) or Myelodysplastic Syndromes (MDS). Blood (ASH Annual Meeting Abstracts) 2010;116:Abstract 3273.
2. Cheson BD, Bennett JM, Kopecky KJ, Buchner T, Willman CL, Estey EH. Revised recommendations of the International Working Group for diagnosis, standardization of response criteria, treatment outcomes, and reporting standards for therapeutic trials in acute myeloid leukemia. Journal of Clinical Oncology 2003;21(24):4642-9.
3. Cheson BD, Greenberg PL, Bennett JM, Lowenberg B, Wijermans PW, Nimer SD, et al. Clinical application and proposal for modification of the International Working Group (IWG) response criteria in myelodysplasia. Blood 2006;108(2):419-25.

Date of Report: 10 April 2012