Phase I trial of volasertib, a Polo-like kinase inhibitor, in Japanese patients with acute myeloid leukemia

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This phase I trial conducted in Japanese patients with acute myeloid leukemia evaluated the safety, maximum tolerated dose and pharmacokinetics of volasertib (BI 6727), a selective Polo-like kinase inhibitor. The primary endpoints were the maximum tolerated dose of volasertib and the incidence of dose-limiting toxicities. Secondary endpoints were best response and remission duration. Other endpoints included safety and pharmacokinetics. Patients who were ineligible for standard induction therapy or with relapsed or refractory disease received volasertib monotherapy as a 2-h infusion on days 1 and 15 of a 28-day cycle, with dose escalation following a 3 + 3 design. A total of 19 patients were treated with three volasertib doses: 350, 400 and 450 mg. One patient receiving volasertib 450 mg reported a dose-limiting toxicity of grade 4 abnormal liver function test and 450 mg was determined as the maximum tolerated dose. The most frequently reported adverse events were febrile neutropenia (78.9%), decreased appetite (42.1%), nausea and rash (36.8% each), and sepsis, fatigue, hypokalemia, stomatitis and epistaxis (26.3% each). Best responses were complete remission ($n = 3$), complete remission with incomplete blood count recovery ($n = 3$) and partial remission ($n = 1$). The median remission duration of the six patients with complete remission or complete remission with incomplete blood count recovery was 85 days (range 56–358). Volasertib exhibited multi-compartmental pharmacokinetic behavior with a fast distribution after the end of infusion followed by slower elimination phases. Volasertib monotherapy was clinically manageable with acceptable adverse events and anti-leukemic activity.

Acute myeloid leukemia (AML) is a heterogeneous clonal disorder of hematopoietic progenitor cells and represents the most common form of acute leukemia in adults.[1] Standard therapy for AML includes the nucleoside analog cytarabine in combination with an anthracycline and there have been few changes to this primary therapy over the past three decades. Therapeutic outcomes for younger patients with AML have improved over the past 30 years, possibly due to improvements in supportive care, for example, the use of antibiotics;[2] however, durable cures occur in the minority of patients with standard therapy.[3] For newly diagnosed older patients, clinical outcomes are worse because many cannot tolerate intensive remission induction chemotherapy and the disease is more often chemotherapy-resistant.[2] Patients with relapsed/refractory AML also have a poor prognosis.[4]

The current National Comprehensive Cancer Network guidelines recommend participation in clinical trials as the first choice for older patients with untreated AML, and participation in clinical trials is strongly preferred for patients with relapsed/refractory disease.[1] Along with advances in understanding the biology of AML, therapies that have novel mechanisms of action and can be tolerated by older patients are needed to improve outcomes for patients with AML.[3]

The serine/threonine kinase Polo-like kinase 1 (PLK1) controls several key steps during mitosis.[5,6] PLK1 overexpression has been demonstrated in various human cancers, including AML,[7–9] and a potential role for PLK1 overexpression in carcinogenesis has been shown both *in vitro* and *in vivo*,[7,10] making PLK1 an attractive target for novel therapeutic approaches in cancer.[5]

Volasertib (an investigational agent) is a selective and potent cell cycle kinase inhibitor that induces mitotic arrest and apoptosis by targeting PLK.[11] Volasertib has been shown to selectively inhibit PLK1 and, to a lesser extent, PLK2 and PLK3, but does not inhibit more than 50 unrelated kinases tested.[11] Preclinical studies have shown that targeting PLK with volasertib leads to cell cycle arrest with abnormal mitotic figures (polo arrest) and subsequent cell death by apoptosis.[11] In addition, volasertib has shown anti-tumor efficacy in multiple preclinical models of AML, including bone marrow samples in short-term culture as well as subcutaneous and disseminated *in vivo* models in immune-deficient mice.[12]

Volasertib has been previously investigated as monotherapy in a phase I trial in White patients with relapsed or refractory AML who are ineligible for intensive therapy[13] and demonstrate a clinically manageable safety profile at maximum tolerated dose (MTD) with anti-leukemic activity.[13] The phase I trial reported here was conducted to evaluate the MTD, the safety, the tolerability and the pharmacokinetics (PK) of volasertib, administered once every 2 weeks as monotherapy, in Japanese patients with AML.

Materials and Methods

Trial design. This was a phase I, open-label, dose-escalation study conducted in six centers in Japan (NCT01662505; Study 1230.26) that enrolled adults with relapsed/refractory or untreated AML who were ineligible for standard induction therapy. The primary endpoints of this trial were the MTD of volasertib and the incidence of dose-limiting toxicities (DLT). Secondary endpoints were best response (complete remission [CR], CR with incomplete blood count recovery [CRi] and partial remission [PR]) according to the criteria published by the International Working Group and European Leukemia Net and remission duration. Other endpoints included the incidence and intensity of adverse events (AE) graded according to the Common Terminology Criteria for Adverse Events (CTCAE), version 3.0, and safety laboratory parameters. The trial was conducted in compliance with the principles laid down in the Declaration of Helsinki, in accordance with the International Conference on Harmonisation Harmonised Tripartite Guideline for Good Clinical Practice (GCP), and in accordance with relevant Boehringer Ingelheim standard operating procedures and the Japanese GCP regulation. All participating patients gave written informed consent.

Patients. Patients were required to be aged ≥18 years with relapsed/refractory AML or untreated AML considered not suitable for standard induction therapy according to the investigator's judgment. The diagnosis of AML was made according to World Health Organization classification, and patients were required to have an Eastern Co-operative Oncology Group (ECOG) performance status ≤2 at screening and to have signed informed consent consistent with the Japanese GCP. Patients were excluded if they had: a diagnosis of acute promyelocytic leukemia, a third or later relapse, prior hematopoietic stem cell transplantation, an additional malignancy that required treatment, clinical evidence of active central nervous system leukemia at the time of screening, a resting left ventricular ejection fraction <50% at the time of screening, a clinically relevant QT prolongation (e.g. long QT syndrome, QTcF >470 ms), a treatment with systemic therapy for the primary disease within 14 days (except for hydroxyurea), lack of recovery from any acute toxicities or clinically significant AE pertinent to the prior systemic therapy, aspartate aminotransferase (AST) or alanine aminotransferase (ALT) >2.5 times the upper limit of normal, total bilirubin >2.0 mg/dL, or serum creatinine >2.0 mg/dL.

Treatments. Patients received volasertib as monotherapy on days 1 and 15 of a 28-day cycle via intravenous drip infusion over 2 h. Dose escalation followed a 3 + 3 design with a starting dose of volasertib 350 mg (level 1) per administration. The duration of one treatment cycle was 28 days, and a subsequent cycle could be started on day 29 unless study drug-related AE necessitated an additional recovery period. If a DLT occurred, the treatment was interrupted until recovery and resumed at a reduced dose. To allow close safety monitoring,

all patients were hospitalized during the first treatment cycle or until the investigator considered it appropriate to manage the patient on an outpatient basis. The use of growth factors was allowed as per institutional standards. Prophylactic anti-emetics were not requested per protocol but were allowed if medically indicated. Patients were allowed to remain on the study treatment for additional treatment cycles if the following criteria for retreatment were met: recovery from any DLT (cycle 1)/DLT-equivalent AE (cycle 2 onwards) to CTCAE grade ≤2 or baseline, whichever was higher, except for QTcF, which was required to be CTCAE grade ≤1 before retreatment; absence of any discontinuation criteria; and patient's re-consent to additional treatment cycles (before starting cycle 2).

Assessments. The frequencies of AE were tabulated by the *Medical Dictionary for Regulatory Activities* system organ class and preferred term and CTCAE grade for each dose cohort. AE were also classified by the causality relationship with the study drug. Any CTCAE grade ≥3 non-hematologic AE occurring during cycle 1, which were considered by the investigator to be related to the study treatment qualified as DLT except for: untreated nausea or vomiting of any grade; grade 3 untreated diarrhea that could be sufficiently treated and reduced to grade ≤2; grade 3 febrile neutropenia, or grade 3 infection with grade 3 or 4 neutrophils; any laboratory abnormality, which is not considered clinically significant by the investigator or resolves spontaneously or can be recovered with appropriate treatment within 5 days; and CTCAE grade 3 tumor lysis syndrome.

Electrocardiograms (ECG) were performed and QTcF calculated with every infusion of volasertib (days 1 and 15) before the start and shortly before the end of the infusion. In cycle 1, additional ECG were performed at 4, 8 and 24 h post-infusion on day 1.

Blood samples for PK analysis were collected in cycle 1 pre-dose, and 1, 2, 3, 4, 8, 24, 96, 144, 216 and 336 h after the start of the first infusion and pre-dose, 1 and 2 h after the start of the second infusion on day 15. Volasertib and the metabolite CD 10899 plasma concentrations were determined by a validated high performance liquid chromatography, tandem mass spectrometry assay. The PK parameters were calculated by standard non-compartmental methods and analyses were performed using WinNonlin (Pharsight, Mountain View, CA, USA).

Response was evaluated according to the International Working Group criteria[14] and European Leukemia Net recommendations.[15] Response was assessed in the peripheral blood and in the bone marrow. In case of extramedullary manifestations of leukemia, assessment by imaging, as necessary, was used to complement the blood and bone marrow assessment of response.

A data cut-off of 6 June 2014 was used for the safety analyses, 26 June 2014 for the PK analyses and 12 March 2015 for the efficacy analyses. All the analyses of this trial were descriptive; hence, no statistical model was adopted in this trial.

Results

A total of 24 patients were enrolled between August 2012 and March 2014, and 19 patients were treated, receiving at least one dose, at the following volasertib dose levels: cohort 1, 350 mg (*n* = 7); cohort 2, 400 mg (*n* = 4); and cohort 3, 450 mg (*n* = 8). The remaining five patients who did not receive the trial medication failed to match the inclusion criteria. By the

data cut-off, 16 patients (84.2%) had terminated treatment with trial medication, with the most frequent reason for discontinuation being progressive disease (nine patients, 47.4%).

The patient demographics and baseline disease characteristics are summarized in Table 1. The median age was 73.0 years (range 53–86 years) and the ECOG performance status was 1 for the majority of patients (11 patients, 57.9%). The disease status was refractory in seven patients (36.8%), relapsed in six patients (31.6%), both refractory and relapsed in two patients (10.5%) and untreated in four patients (21.1%). Patients received a median of two (range 1–10) cycles of therapy and the median therapy duration was 81 days (range 23–486 days).

Dose-limiting toxicities. As per the study design, any patients who could not receive treatment on day 15 of cycle 1 for reasons other than DLT were not evaluable for MTD analysis. To fulfill the 3 + 3 design, a total of four patients who were not evaluable had to be replaced for MTD determination (one patient [350 mg cohort 1] did not receive the second dose because of early withdrawal due to progressive disease; three patients [1 in the 400-mg cohort 2 and 2 in the 450-mg cohort 3] missed the second dose because of AE that did not qualify as DLT). No DLT were reported in cycle 1 in the 350-mg or 400-mg cohort.

One DLT was reported in cohort 3 cycle 1 at the 450-mg volasertib dose level in 1 of the 6 evaluable patients. This patient experienced a DLT of grade 4 abnormal liver function test in cycle 1. The patient was an 80-year-old male and had elevated transaminases (AST: 39 IU/L [reference 13–33 IU/L], ALT: 64 IU/L [reference 6–30 IU/L], total bilirubin: 0.4 mg/dL [reference 0.3–1.2 mg/dL]) 2 days before the study medication was started. On day 9 of cycle 1, an increase of transaminases was observed (AST: 131 IU/L, ALT: 116 IU/L, total bilirubin: 1.1 mg/dL) and, on day 11, the patient's transaminases and bilirubin increased further (AST: 764 IU/L,

ALT: 711 IU/L, total bilirubin: 2.6 mg/dL) and a DLT of grade 4 abnormal liver function test was recorded. By day 16, transaminases and bilirubin were improved and became equivalent to CTCAE grade 3 (AST: 156 IU/L, ALT: 450 IU/L, total bilirubin: 3.8 mg/dL). However, on day 17, the laboratory parameters were not improved to the level fulfilling the retreatment criteria; therefore, the second infusion of volasertib was suspended. By day 29 (cycle 2, day 1), the laboratory parameters indicating liver damage were mostly normalized (AST: 15 IU/L, ALT: 38 IU/L, total bilirubin: 1.0 mg/dL). According to dose-reduction criteria, treatment with volasertib in cycle 2 was started at a reduced dose (400 mg). On day 38 (cycle 2, day 10), the liver parameters were stable within the reference range and the patient was considered to have recovered from the DLT.

Volasertib 450 mg was the highest dose level planned for the trial; therefore, dose escalation was ceased at this level and 450 mg was determined as the MTD of volasertib administered intravenously on days 1 and 15 in 28-day cycles in Japanese patients with AML.

Safety. Across all treatment cycles, all 19 patients reported at least one AE irrespective of cause and one drug-related AE; 94.7% of patients reported CTCAE of grade ≥3. The most common AE (>20%) were febrile neutropenia (78.9%), decreased appetite (42.1%), nausea and rash (36.8% each), sepsis, fatigue, hypokalemia, stomatitis and epistaxis (26.3% each), vomiting and pyrexia (21.1% each), with no apparent trends for dose-related increase in frequency. AE by dose, all grades and grades 3 and 4, irrespective of relationship, occurring in ≥15% of patients overall are summarized in Table 2. Grade 4 AE were reported by one of seven patients in the 350-mg cohort 1 (neutropenia and thrombocytopenia), two of four patients in the 400-mg cohort 2 (neutropenia and thrombocytopenia), and three of eight patients in the 450-mg cohort 3 (neutropenia, hypokalemia and abnormal liver function test). No fatal (grade 5) AE were reported. No patient experienced AE that led to discontinuation of the study medication in any dose cohort. Dose reductions occurred in 2 out of 19 patients after cycle 1 at the investigator's discretion and not in accordance with the protocol. The mean (standard deviation) treatment dose per cycle was 594 mg (134 mg) for the 350-mg cohort 1, 685 mg (93 mg) for the 400-mg cohort 2, and 706 mg (219 mg) for 450-mg cohort 3.

The ECG analysis showed a maximum increase in the mean QTcF interval at 2 h after the start of the volasertib infusion. After the initial increase at 2 h, the mean QTcF intervals tended to decrease to near baseline levels by 24 h post-dosing in all dose cohorts. A >60 ms QTcF interval increase at the end of infusion compared to the QTcF interval prior to infusion was only observed in two patients treated with volasertib 450 mg cohort 3. No QTcF intervals >500 ms were reported.

Pharmacokinetics. The PK profile of volasertib demonstrated a general increase in mean plasma concentration until the end of infusion, followed by a rapid decline (Fig. 1). By 24 h after administration, the mean plasma concentration of volasertib decreased to <10% of the maximum plasma concentration. Volasertib exhibited multi-compartmental PK behavior. Exposure to volasertib increased dose-proportionally within the dose range tested. PK parameters of volasertib and its major metabolite, CD 10899, after the first infusion of volasertib 350, 400 and 450 mg are summarized in Table 3. The geometric mean (gMean) elimination half-life ranged from 108 to 130 h and was dose-independent. The gMean volume of distribution of volasertib ranged from 3540 to 4720 L, suggesting

**Table 1. Patient demographic and baseline disease characteristics**

	Volasertib (N = 19)
Median age, years (range)	73 (53–86)
<65 years	2 (10.5)
65–75 years	9 (47.4)
≥75 years	8 (42.1)
Male/female, n (%)	7 (36.8)/12 (63.2)
Baseline ECOG PS, n (%)	
0	6 (31.6)
1	11 (57.9)
2	2 (10.5)
Disease state, n (%)	
Refractory	7 (36.8)
Relapsed	6 (31.6)
Relapsed and refractory	2 (10.5)
Untreated	4 (21.1)
AML considered secondary, n (%)†	7 (36.8)
Preceding MDS	4 (21.1)
Prior therapy with topoisomerase II inhibitor	1 (5.3)
Other	2 (10.5)
Karyotype, n (%)†	
Normal	9 (47.4)
Complex	6 (31.6)
Neither	4 (21.1)

†Percentages do not sum to total due to rounding. AML, acute myeloid leukemia; ECOG PS, Eastern Co-operative Oncology Group Performance Score; MDS, myelodysplastic syndrome.

Table 2. AEs by dose, all grades and grade 3 and 4 AEs irrespective of relationship, occurring in ≥15% of patients overall

AE, n	Volasertib 350 mg (n = 7)			Volasertib 400 mg (n = 4)			Volasertib 450 mg (n = 8)			Total (N = 19)		
	All grades	Grade 3	Grade 4	All grades	Grade 3	Grade 4	All grades	Grade 3	Grade 4	All grades	Grade 3	Grade 4
Sepsis	2	2	–	1	1	–	2	2	–	5	5	–
Infection	2	2	–	–	–	–	1	–	–	3	2	–
Febrile neutropenia	5	5	–	3	3	–	7	6	–	15	14	–
Neutropenia	1	–	1	1	–	1	1	–	1	3	–	3
Decreased appetite	5	1	–	1	–	–	2	2	–	8	3	–
Hypokalemia	3	1	–	–	–	–	2	–	1	5	1	1
Hyperuricemia	3	–	–	–	–	–	–	–	–	3	–	–
Hypoalbuminemia	2	–	–	–	–	–	1	–	–	3	–	–
Epistaxis	1	–	–	2	–	–	2	–	–	5	–	–
Nausea	1	–	–	2	–	–	4	–	–	7	–	–
Stomatitis	2	–	–	1	–	–	2	–	–	5	–	–
Vomiting	1	–	–	1	–	–	2	–	–	4	–	–
Rash	–	–	–	4	–	–	3	–	–	7	–	–
Fatigue	1	–	–	3	–	–	1	–	–	5	–	–
Pyrexia	2	–	–	–	–	–	2	–	–	4	–	–
Blood creatinine increased	1	–	–	2	–	–	–	–	–	3	–	–

Data cut–off June 6, 2014. AE, adverse event.
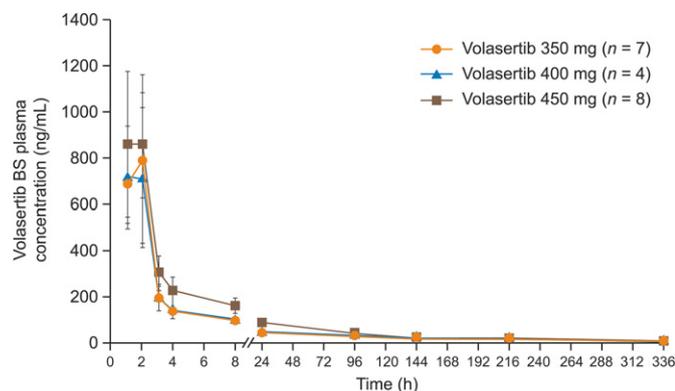
Fig. 1. Arithmetic mean plasma concentration of volasertib over time. BS, free base.

extensive distribution of volasertib into tissues and/or organs. Total plasma clearance was moderate and ranged from 606 to 669 mL/min. The gMean exposure ratios of the metabolite CD 10899 to volasertib expressed as $RAUC_{0-tz,M/P}$ after the first volasertib administration ranged from 13.3% to 15.0%.

Efficacy. All 19 patients were evaluable for response, with the results summarized in Table 4. A total of seven patients (36.8%) achieved the best response of CR, CRi or PR. One of seven patients in the 350-mg cohort achieved a CR, two of four patients in the 400-mg cohort achieved a CRi, and four of eight patients in the 450-mg cohort achieved CR (n = 2), CRi (n = 1) or PR (n = 1). The remission duration of the six patients with CR or CRi ranged from 56 to 358 days (median 85 days). Out of seven patients with a CR, CRi or PR, the baseline cytogenetic data were available for five patients: one patient with CR had a complex karyotype including −5/del(5q), del(q13), −17/del(17p), and other abnormality at baseline; one patient with CRi had a complex karyotype including −7/del(7q) and other abnormality at baseline; the 3 remaining patients had normal karyotype at baseline. Of the

seven patients who achieved CR/CRi/PR, all patients were relapsed or refractory to previous treatments for AML. One patient (male aged 69 years with primary refractory M2 de novo AML and complex karyotype) showed a rapid reduction in peripheral blast counts and aplastic bone marrow after cycle 1. Granulocyte-colony stimulating factor was used at the end of cycle 2 and during cycle 3 to support blood count recovery. This patient achieved a CR after cycle 3, which was maintained for 358 days.

Discussion

This phase I trial was the first to investigate volasertib monotherapy in Japanese patients with AML ineligible for standard therapy. The highest planned dose of volasertib (450 mg) administered intravenously on days 1 and 15 in 28-day cycles was determined to be tolerable, with one patient experiencing a DLT at 450 mg of reversible grade 4 liver function test abnormality. Dose escalation was limited to 450 mg, which was the MTD reported in a phase I study of volasertib monotherapy in White patients.[13] In contrast to the present study, DLT of mucosal inflammation and pyrexia were reported in White patients at 400 and 450 mg, respectively.

The AE profile of volasertib monotherapy in Japanese patients was considered clinically manageable and acceptable. CTCAE grade 3 febrile neutropenia, sepsis, decreased appetite and grade 4 neutropenia were among the most frequently reported severe AE with no apparent trends for dose-related increases in frequency. Grade 4 AE were mainly hematologic (neutropenia, thrombocytopenia). The overlap between the expected side effects of volasertib and the cardinal symptoms of AML, including myelosuppression, blood cytopenias, neutropenic fever and infection, make the assessment of AE with regard to relatedness challenging. These safety results are as expected from the mode of action of volasertib and the underlying disease, and are also in line with what was expected from the phase I/II trial in White patients with AML.[13,16] Because volasertib is expected to add on to the AML-related

Table 3. Summary of pharmacokinetic parameters of volasertib and CD 10899 after the first infusion of volasertib 350, 400, and 450 mg

gMean (gCV%)	Volasertib 350 mg $n = 7$		Volasertib 400 mg $n = 4$		Volasertib 450 mg $n = 8$	
	Volasertib	CD 10899	Volasertib	CD 10899	Volasertib	CD 10899
AUC_{0-tz}, ng·h/mL	7810 (29.2)	1080 (70.3)	9340 (48.8)	1280 (34.8)	11400 (20.5)	1750 (56.4)
$AUC_{0-\infty}$, ng·h/mL	8720 (27.8)	1500 (88.0)	10400 (54.7)	1680 (50.6)	12400 (22.8)	2050 (57.4)
$AUC_{0-\infty,norm}$, ng·h/mL/mg	24.9 (27.8)	4.30 (88.0)	25.9 (54.7)	4.19 (50.6)	27.5 (22.8)	4.55 (57.4)
C_{max}, ng/mL	756 (43.2)	8.45 (80.7)	762 (34.8)	8.46 (43.3)	1060 (28.6)	15.6 (78.3)
t_{max},† h	1.97 (0.967–2.15)	23.7 (3.03–96.0)	1.05 (0.867–2.05)	16.0 (7.98–120)	1.53 (0.967–2.20)	7.99 (3.97–96.0)
$t_{1/2}$, h	117 (23.3)	167 (43.0)	130 (21.6)	168 (43.2)	108 (26.4)	118 (31.5)
CL, mL/min	669 (27.8)	–	643 (54.7)	–	606 (22.8)	–
V_{ss}, L	4430 (33.5)	–	4720 (14.5)	–	3540 (28.0)	–
$RAUC_{0-tzM/P}$, %	–	13.4 (78.0)	–	13.3 (30.8)	–	15.0 (44.4)
$RAUC_{0-\infty M/P}$, %	–	16.8 (101)	–	15.8 (19.9)	–	16.1 (42.0)

†Median (range). gMean, geometric mean; gCV%, geometric coefficient of variation; AUC, area under the concentration–time curve of the analyte in plasma; AUC_{0-tz}, AUC of the analyte in plasma over the time interval from 0 to time of the last quantifiable plasma concentration; $AUC_{0-\infty}$, AUC of the analyte in plasma over the time interval from 0 extrapolated to infinity; C_{max}, maximum plasma concentration; t_{max}, time from dosing to the maximum concentration of the analyte in plasma; $t_{1/2}$, terminal half-life; CL, total plasma clearance; V_{ss}, apparent volume of distribution after intravenous infusion at steady state; norm, dose normalized; $RAUC_{0-\infty M/P}$, ratio of the AUC in plasma of metabolite versus parent over the time interval from 0 extrapolated to infinity; $RAUC_{0-tzM/P}$, ratio of the AUC in plasma of metabolite versus parent over the time interval from 0 to time of the last quantifiable plasma concentration.

Table 4. Best overall response (including remission duration)

	Volasertib 350 mg (n = 7)	Volasertib 400 mg (n = 4)	Volasertib 450 mg (n = 8)	Total (N = 19)
Best overall response, n (%)				
CR	1	–	2	3 (15.8)
CRi	–	2	1	3 (15.8)
PR	–	–	1	1 (5.3)
SD	3	2	3	8 (42.1)
PD	3	–	1	4 (21.1)
Remission duration†				
CR/CRi, n	1	2	3	6
Median, days (range)	358	72 (70–74)	96 (56–262)	85 (56–358)

†One patient was receiving ongoing treatment in CR at the time of analysis. Data cut-off March 12, 2015. CR, complete remission; CRi, CR with incomplete blood count recovery; PD, progressive disease; PR, partial remission; SD, stable disease.

blood count changes and complications thereof, these AE require close monitoring and management through supportive care, prophylaxis and prompt start of infection treatment, if necessary.

Kinase inhibitors, including volasertib, are known to cause a reversible prolongation of the QT interval.[17,18] The magnitude of QTcF prolongation at the end of the volasertib infusion tended to be greatest in the 450 mg cohort-3, and returned to near baseline within 24 h. No patients in any cohort developed clinically relevant abnormalities in cardiologic assessment during treatment with volasertib.

Volasertib plasma concentration increased until the end of infusion and declined rapidly after the end of infusion. Volasertib exhibited multi-compartmental PK behavior with fast distribution after the end of infusion followed by slower elimination phases and exposure increased dose-proportionally within the dose range tested. The volasertib exposure observed in Japanese patients appears to be comparable or slightly higher than exposure reported in studies with White, Asian and Japanese patients with solid tumors (Nokihara *et al.*, 2015, manuscript in preparation).[19,20] The difference in exposure could be due to differences in weight between the study populations; however, patient numbers are low and so this observation should be interpreted with caution. Overall, the PK of volasertib in Japanese patients with AML are within the expected range observed in the previous trials in Japanese, Asian and White patients (Nokihara *et al.*, 2015, manuscript in preparation).[19,20]

In a preliminary evaluation of best response, volasertib monotherapy demonstrated anti-leukemic activity in Japanese patients with AML. The best response of CR, CRi, or PR was achieved by 7 out of 19 treated patients (36.8%) and the remission duration of the six patients with CR or CRi ranged from 56 to 358 days; one patient was receiving treatment in CR at the time of analysis. Given the poor prognosis of the trial population, this result was considered to indicate anti-leukemic activity of volasertib, supporting PLK as a potential therapeutic target in AML.

In conclusion, volasertib monotherapy at the investigated doses showed a clinically manageable safety profile and anti-leukemic activity. Overall, the safety and efficacy results, as well as the determined MTD, were consistent with the previous study in White patients with AML[19] and justify participation of Japanese patients in global volasertib AML trials without dose modification.

References

1 National Comprehensive Cancer Network (NCCN). Clinical Practice Guidelines in Oncology. Acute Myeloid Leukemia. Version 1.2015. [Cited 10 August 2015.] Available from URL: http://www.nccn.org.
2 Kantarjian H, O'Brien S. Questions regarding frontline therapy of acute myeloid leukemia. *Cancer* 2010; **116**: 4896–901.
3 DiNardo CD, Cortes JE. New treatment for acute myelogenous leukemia. *Expert Opin Pharmacother* 2015; **16**: 95–106.
4 Craddock C, Tauro S, Moss P, Grimwade D. Biology and management of relapsed acute myeloid leukaemia. *Br J Haematol* 2005; **129**: 18–34.
5 Schöffski P. Polo-like kinase (PLK) inhibitors in preclinical and early clinical development in oncology. *Oncologist* 2009; **14**: 559–70.
6 Strebhardt K. Multifaceted polo-like kinases: drug targets and antitargets for cancer therapy. *Nat Rev Drug Discov* 2010; **9**: 643–60.
7 Renner AG, Dos Santos C, Recher C *et al.* Polo-like kinase 1 is overexpressed in acute myeloid leukemia and its inhibition preferentially targets the proliferation of leukemic cells. *Blood* 2009; **114**: 659–62.
8 Takai N, Hamanaka R, Yoshimatsu J, Miyakawa I. Polo-like kinases (Plks) and cancer. *Oncogene* 2005; **24**: 287–91.
9 Chopra P, Sethi G, Dastidar SG, Ray A. Polo-like kinase inhibitors: an emerging opportunity for cancer therapeutics. *Expert Opin Investig Drugs* 2010; **19**: 27–43.
10 Smith MR, Wilson ML, Hamanaka R *et al.* Malignant transformation of mammalian cells initiated by constitutive expression of the polo-like kinase. *Biochem Biophys Res Commun* 1997; **234**: 397–405.
11 Rudolph D, Steegmaier M, Hoffmann M *et al.* BI 6727, a Polo-like kinase inhibitor with improved pharmacokinetic profile and broad antitumor activity. *Clin Cancer Res* 2009; **15**: 3094–102.
12 Rudolph D, Impagnatiello MA, Blaukopf C *et al.* Efficacy and mechanism of action of volasertib, a potent and selective inhibitor of Polo-like kinases, in preclinical models of acute myeloid leukemia. *J Pharmacol Exp Ther* 2015; **352**: 579–89.
13 Döhner H, Bug G, Müller-Tidow C *et al.* Phase I/II study of volasertib, an intravenous Polo-like kinase inhibitor (Plk), in patients with relapsed/refractory acute myeloid leukemia (AML): updated phase I results for volasertib monotherapy. *Haematologica* 2014; **99**: S649.
14 Cheson BD, Bennett JM, Kopecky KJ *et al.* 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. *J Clin Oncol* 2003; **21**: 4642–9.
15 Döhner H, Estey EH, Amadori S *et al.* Diagnosis and management of acute myeloid leukemia in adults: recommendations from an international expert panel, on behalf of the European LeukemiaNet. *Blood* 2010; **115**: 453–74.
16 Döhner H, Lübbert M, Fiedler W *et al.* Randomized, phase 2 trial comparing low-dose cytarabine with or without volasertib in AML patients not suitable for intensive induction therapy. *Blood* 2014; **124**: 1426–33.
17 Force T, Kolaja KL. Cardiotoxicity of kinase inhibitors: the prediction and translation of preclinical models to clinical outcomes. *Nat Rev Drug Discov* 2011; **10**: 111–26.
18 Kloth JSL, Pagani A, Verboom MC *et al.* Tyrosine kinase inhibitors and QTc intervals: a class effect. *ASCO Meeting Abstracts* 2014; **32**: 2590.
19 Schöffski P, Awada A, Dumez H *et al.* A phase I, dose-escalation study of the novel Polo-like kinase inhibitor volasertib (BI 6727) in patients with advanced solid tumours. *Eur J Cancer* 2012; **48**: 179–86.
20 Lin C-C, Su W, Yen C-J *et al.* A phase I study of two dosing schedules of volasertib (BI 6727), an intravenous Polo-like kinase inhibitor, in patients with advanced solid malignancies. *Br J Cancer* 2014; **110**: 2434–40.