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Citation for final published version:

Ottmann, Oliver G. , Müller-Tidow, Carsten, Krämer, Alwin, Schlenk, Richard F., Lübbert, Michael, Bug, Gesine, Krug, Utz, Bochtler, Tilmann, Voss, Florian, Taube, Tillmann, Liu, Dan, Garin-Chesa, Pilar and Döhner, Hartmut 2019. Phase I dose-escalation trial investigating volasertib as monotherapy or in combination with cytarabine in patients with relapsed/refractory acute myeloid leukaemia. *British Journal of Haematology* 184 (6) , pp. 1018-1021. 10.1111/bjh.15204

Publishers page: <http://dx.doi.org/10.1111/bjh.15204>

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CORRESPONDENCE

Phase I dose-escalation trial investigating volasertib as monotherapy or in combination with cytarabine in patients with relapsed/refractory AML

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Running title: Volasertib phase I in acute myeloid leukaemia

Keywords: New drug development, acute myeloid leukaemia (AML), oncology, new drugs for leukaemia, pharmacokinetic.

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Financial support for this study was provided by Boehringer Ingelheim.

Limits: 1,000 words maximum, 2 figures/tables, 10 references

Current count: 1000 words, 2 tables, 1 figure, 10 references

Supporting files: Cover letter, supporting information

Non-microtubule components of mitosis, including polo-like kinase 1 (PLK1), are required for complete cell division and have emerged as promising targets for cancer therapy. Human PLK1 is highly expressed in malignant lymphomas and acute myeloid leukaemia (AML), and elevated PLK1 is associated with poor prognosis in several cancer types (Liu *et al*, 2017)

Several PLK inhibitors have shown anti-leukaemic activity in preclinical AML models (Hikichi *et al*, 2012; Munch *et al*, 2015; Rudolph *et al*, 2015; Rudolph *et al*, 2009; Valsasina *et al*, 2012), but published clinical experience in AML is limited to BI 2536 (Müller-Tidow *et al*, 2013) and volasertib (Döhner *et al*, 2014). Volasertib is a potent, ATP-competitive and specific inhibitor of PLK1 and, to a lesser extent, the closely related kinases PLK2 and PLK3 (Rudolph *et al*, 2009). It is the most advanced PLK inhibitor currently in clinical development.

A combined phase I/II trial investigated volasertib in patient populations with AML who were ineligible for intensive treatment. The Phase II results, in patients with previously untreated AML, have been previously reported (Döhner *et al*, 2014). Here, we report the Phase I results, including maximum tolerated dose (MTD), safety, pharmacokinetics (PK) and anti-leukaemic activity, of intravenous volasertib as monotherapy or in combination with subcutaneous low-dose cytarabine (LDAC) in patients with relapsed/refractory AML considered ineligible for intensive treatment.

Patients were treated with escalating doses of volasertib (1-h intravenous infusion; starting dose 150 mg/infusion, escalated in 50 mg steps) on days 1 and 15 as monotherapy or in combination with fixed dose LDAC (2 x 20 mg/d subcutaneously on days 1–10) every 4 weeks. The study design is diagrammatically in Fig S1. All patients provided written informed consent. The trial was registered at ClinicalTrials.gov (NCT00804856).

The primary objective was to determine the MTD for volasertib monotherapy and volasertib plus LDAC combination therapy. All analyses were descriptive and exploratory, and included patients receiving at least one dose of study drug (treated set). Full methodological details are in the Supporting Information.

Eighty-eight adult patients with relapsed or refractory AML who were unsuitable for intensive salvage therapy were included between November 2008 and June 2012. Patient demographics and baseline disease characteristics are provided in Table S1. Fifty-six patients received volasertib monotherapy and thirty-two received volasertib plus LDAC combination therapy. Median age was 70 years (range, 26–84) in the monotherapy group and 71 years (40–81) in the combination group. All patients had failed prior AML treatment and had received a median of 2 and 3 previous anti-leukaemic therapy lines in the monotherapy and combination groups, respectively.

Dose escalations and dose-limiting toxicities are shown in Table I. For volasertib monotherapy, dose escalation was interrupted at 200 mg because of insufficient leukaemia control at the 150 mg and 200 mg dose and restarted from the MTD dose of 350 mg determined in the volasertib + LDAC arm. The MTD was 450 mg volasertib as monotherapy and 350 mg volasertib in combination with LDAC. An expansion cohort of 15 patients was treated with volasertib monotherapy at the 450 mg dose.

Eighty-seven of 88 patients had discontinued treatment at the time of data analysis (data cut-off 07 November 2013), mostly due to disease progression (62.5%, both groups), while 20 (22.7%) discontinued due to adverse events (AEs) (monotherapy, 11 [19.6%]; combination, 9 [28.1%]). Sixteen deaths occurred while on study treatment or within 28 days of the last volasertib dose, three of which were suspected to be drug related: two with monotherapy (150 mg, cycle 1, fungal pneumonia; and 550 mg, cycle 1, pneumonia) and one with combination treatment (300 mg, cycle 1, pneumonia). Treatment-related AEs were reported in 38 (67.9%) monotherapy patients and in 19 (59.4%) combination therapy patients. The most common treatment-related AEs were cytopenias and complications related to cytopenias. The most common grade ≥ 3 AEs are listed in Table II.

Complete remission (CR)/CR with incomplete blood count recovery (CRi) was observed in 6 patients (18.8%) treated with combination therapy and 5 patients (8.9%) treated with monotherapy (Fig S2A). The duration of event-free survival

ranged from 153 to 392 days and from 64 to 566 days in the combination and monotherapy groups, respectively. CR or CRi was achieved after 1–3 treatment cycles in the combination group and after 1 treatment cycle in the monotherapy group.

PK parameters are shown in Fig S3 and Table S2.

Volasertib exposure was not affected by LDAC co-administration. For the pharmacodynamic analyses, a limited number of samples were evaluable due to technical limitations. An increase in the number of pH3-positive cells, mitotic catastrophe (mitotic arrest and subsequent apoptosis), and nuclear condensation and fragmentation, was clearly visible in evaluable bone marrow samples of volasertib-treated patients (Fig S2B).

In this study, the safety profile of volasertib in this heavily pretreated population of AML patients was demonstrated as clinically manageable at doses above the recommended phase II dose (300 mg on day 1 of a 3-week treatment cycle) previously determined in solid tumour patients (Schöffski *et al*, 2012), and was consistent with the anti-mitotic mode of action of volasertib. PK parameters in this study were similar to those observed in other studies of volasertib (Schöffski *et al*, 2012; Stadler *et al*, 2014). Pharmacodynamic activity was visible in the bone marrow 1–5 days after volasertib administration with aberrant mitotic figures and characteristic nuclear condensation and fragmentation patterns, indicating that volasertib induces mitotic arrest and apoptosis in line with the clinical observation of blast reduction.

Volasertib alone or in combination with LDAC showed preliminary anti-leukaemic activity in patients with relapsed/refractory AML, a population with very limited therapeutic options. Based on these phase I results, the safety and efficacy of volasertib 350 mg plus LDAC versus LDAC alone has been further explored in the randomised phase IIa part of this trial (Döhner *et al*, 2014) and in an ongoing confirmatory phase III trial in the same patient population (POLO-AML-2; NCT01721876).

Studies evaluating volasertib in AML and other haematological malignancies, particularly those determining the dose and schedule, should address the mechanisms of anti-leukaemic activity, and its potential to augment efficacy of other agents by targeting PLK.

ACKNOWLEDGEMENTS

All authors fulfil the three criteria required to qualify for authorship: 1) conceived and/or designed the work that led to submission, acquired data, and/or played an important role in interpreting the results; 2) drafted or revised the manuscript; and 3) approved the final version. Oliver G. Ottmann is an endowed professor of the German José Carreras Leukaemia Foundation. Financial support was provided by Boehringer Ingelheim. Medical writing assistance, financially supported by Boehringer Ingelheim, was provided by Victoria A. Robb of GeoMed, an Ashfield company, part of UDG Healthcare plc, during the preparation of this manuscript.

COMPETING INTERESTS

OO received honoraria from Boehringer Ingelheim for advisory board participation. CMT, GB and UK have received research support from Boehringer Ingelheim. RFS has received consultancy fees from Boehringer Ingelheim. FV, PGC, TT and DL are employees of Boehringer Ingelheim Pharma GmbH & Co. KG. AK, ML, TB, and HD have declared no competing interests.

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Table I. DLTs in cycle 1 and determination of MTD

Dose level	Patients, <i>n</i>	Patients with DLTs, <i>n</i>	DLTs
<i>Volasertib + LDAC (Schedule A)</i>			
150 mg volasertib + LDAC	4	0	–
200 mg volasertib + LDAC	3	0	–
250 mg volasertib + LDAC	5	0	–
300 mg volasertib + LDAC	9	1	Pneumonia
350 mg volasertib + LDAC	8	1	Non-ST elevation myocardial infarction
400 mg volasertib + LDAC	3	2	Mucosal inflammation (<i>n</i> = 1) Hypersensitivity (<i>n</i> = 1)
<i>Volasertib monotherapy (Schedule B)</i>			
150 mg volasertib	11	1	Fungal pneumonia
200 mg volasertib	2	0	–
350 mg volasertib	5	0	–
400 mg volasertib	6	1	Mucosal inflammation
450 mg volasertib	23	1	Pyrexia
500 mg volasertib	5	2	Thrombocytopenia and epistaxis (<i>n</i> = 1) Oesophagitis and GI inflammation (<i>n</i> = 1)
550 mg volasertib	4	2	Mucosal inflammation (<i>n</i> = 1) Mucosal inflammation, GI haemorrhage, pneumonia,

haemoptysis, lung infiltration and
dyspnoea ($n = 1$)

DLT, dose-limiting toxicity; GI, gastrointestinal; LDAC, low-dose
cytarabine; MTD, maximum tolerated dose

*According to protocol, patients who were not evaluable for DLT
(did not complete at least 1 cycle for reasons other than DLT)
were replaced for determination of the MTD. Therefore, the patient
number in some dose groups differs from 3 or 6.

Table II. Grade ≥ 3 adverse events by system organ class occurring in $>10\%$ of patients in a treatment group, with preferred term displayed if reported in ≥ 2 patients in a treatment group

	Volasertib	Volasertib + LDAC
System organ class	n = 56	n = 32
preferred term	n (%)	n (%)
<i>Blood and lymphatic system disorders</i>	43 (76.8)	23 (71.9)
Thrombocytopenia	26 (46.4)	14 (43.8)
Febrile neutropenia	17 (30.4)	13 (40.6)
Anaemia	20 (35.7)	12 (37.5)
Leukopenia	13 (23.2)	10 (31.3)
Neutropenia	22 (39.3)	4 (12.5)
Pancytopenia	4 (7.1)	–
<i>Cardiac disorders</i>	2 (3.6)	4 (12.5)
Cardiac failure	1 (1.8)	2 (6.3)
<i>Gastrointestinal disorders</i>	8 (14.3)	4 (12.5)
Diarrhoea	2 (3.6)	–
<i>General disorders and administration site conditions</i>	22 (39.3)	10 (31.3)
General physical health deterioration	13 (23.2)	9 (28.1)
Pain	2 (3.6)	2 (6.3)
Mucosal inflammation	6 (10.7)	1 (3.1)
Oedema	2 (3.6)	–
<i>Infections and infestations</i>	16 (28.6)	10 (31.3)
Pneumonia fungal	1 (1.8)	4 (12.5)

Pneumonia	9 (16.1)	2 (6.3)
Sepsis	2 (3.6)	2 (6.3)
Infection	2 (3.6)	1 (3.1)
<i>Investigations</i>	14 (25.0)	11 (34.4)
C-reactive protein increased	9 (16.1)	8 (25.0)
<i>Metabolism and nutrition</i>	13 (23.2)	10 (31.3)
Hypokalaemia	6 (10.7)	3 (9.4)
Hyperglycaemia	1 (1.8)	3 (9.4)
Hypocalcaemia	3 (5.4)	2 (6.3)
Decreased appetite	2 (3.6)	1 (3.1)
Hyperuricaemia	2 (3.6)	1 (3.1)
Hyponatraemia	2 (3.6)	–
<i>Respiratory, thoracic and mediastinal disorders</i>	6 (10.7)	4 (12.5)
Dyspnoea	5 (8.9)	2 (6.3)
Epistaxis	2 (3.6)	1 (3.1)
<i>Vascular disorders</i>	4 (7.1)	5 (15.6)
Hypertension	3 (5.4)	2 (6.3)
Hypertensive crisis	–	2 (6.3)

LDAC, low-dose cytarabine

Supporting Information

Methods

Patients

Adult patients with a confirmed diagnosis of acute myeloid leukaemia (AML) according to the World Health Organization 2008 definition (Vardiman *et al*, 2009) whose disease had progressed on or following standard treatments and who were considered not suitable for intensive salvage therapy were eligible for this phase I study. All patients were required to have an Eastern Cooperative Oncology Group performance score ≤ 2 and adequate hepatic and renal function (bilirubin ≤ 1.5 mg/dl, aspartate aminotransferase/alanine transaminase ≤ 2.5 x upper limit of normal [ULN] or ≤ 5 x ULN in patients with leukaemia liver involvement; serum creatinine ≤ 2.0 mg/dl). Patients were excluded if they had acute promyelocytic leukaemia, another malignancy requiring treatment, symptomatic central nervous system leukaemia, clinically relevant QT prolongation, or other severe or uncontrollable medical conditions which would compromise evaluation of safety or efficacy based on medical judgment by the investigator.

This study was conducted according to the guidelines of the Declaration of Helsinki, the International Conference on Harmonization-Good Clinical Practice and local legislation. Written informed consent was obtained from all patients. The trial was registered at ClinicalTrials.gov; registration number: NCT00804856.

Study design and patient enrolment

The primary objective of this open-label, multicentre, phase I study was to determine the maximum tolerated dose (MTD) for 2 treatment schedules, based on the number of patients with dose limiting toxicities (DLTs) in cycle 1: volasertib in combination with low-dose cytarabine (LDAC) and volasertib monotherapy. Secondary endpoints for phase I included incidence and grade of adverse events (AEs), the pharmacokinetic (PK) profile of volasertib when administered alone and in combination with LDAC and PK of LDAC after a single dose when given in combination with volasertib, pharmacodynamic monitoring for drug effect on leukaemia cells and event-free survival.

The study design is depicted in Fig S1. In the phase I part, patients eligible for study entry were assigned to 1 of 2 treatment schedules. Schedule A patients received volasertib on days 1 and 15 (1h intravenous infusion) combined with LDAC (2 x 20 mg/d subcutaneous) on days 1–10 of a 4-week treatment cycle while Schedule B patients received volasertib as monotherapy on days 1 and 15 of a 4-week treatment cycle. Initially patients were recruited to Schedules A and B in parallel, but when the 200 mg dose in Schedule B was reached, recruitment was paused while Schedule A continued recruitment to reach the MTD. After determination of the MTD for Schedule A, recruitment in Schedule B was restarted at the MTD established in Schedule A. Dose escalation was conducted for each treatment group following a

3 + 3 design (Simon *et al*, 1997). The MTD was defined as the highest dose of volasertib at which 6 patients were treated and no more than 1 patient experienced DLT within the first cycle of treatment. Toxicities were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE; v.3.0).

The criteria for DLTs were drug-related CTCAE grade ≥ 3 non-haematological toxicity (excluding: untreated nausea, untreated vomiting, CTCAE grade 3 untreated diarrhoea, CTCAE grade 3 febrile neutropenia and CTCAE grade 3 infection with grade 3 or 4 neutrophils). For haematological toxicity, the DLT definition was restricted to patients achieving bone marrow blast clearance and included persistent drug-related CTCAE grade 4 neutropenia or thrombocytopenia until 3 weeks after the end of the treatment cycle, unless the respective grade 4 cytopenia was pre-existent. In patients who required platelet substitution to maintain a CTCAE grade <4 before treatment, a CTCAE grade 4 thrombocytopenia after treatment did not constitute a DLT. Following MTD determination in the volasertib monotherapy arm (Schedule B) an additional 15 patients were evaluated for safety and efficacy in the MTD-expansion cohort.

Treatment

The starting dose of volasertib was 150 mg, with dose escalations in 50 mg steps. During the trial, no additional chemotherapy or immunotherapy was permitted, and prior anti-leukaemia

chemotherapy or immunotherapy had to be discontinued at least 2 weeks before the first administration of volasertib; hydroxyurea could be given until 1 day before the first administration of the trial drug for peripheral blast control.

Response to treatment was assessed at the end of each treatment cycle. Patients could continue treatment if there was no disease progression/relapse and if neutrophils were $\geq 500/\mu\text{l}$ ($0.5 \times 10^9/\text{l}$) and platelets $\geq 25\,000/\mu\text{l}$ ($25 \times 10^9/\text{l}$), unless grade 4 neutropenia or thrombocytopenia was pre-existent. In the case of drug-related AEs preventing immediate continuation of treatment, further volasertib treatment was delayed until recovery from the AE. In the case of DLT, treatment was paused until recovery and restarted if the patient met criteria for further treatment with a reduced dose of volasertib for all subsequent treatment cycles (LDAC dose remained unchanged). Dose reduction of volasertib was allowed only once: treatment was permanently discontinued in patients experiencing a second DLT. An inpatient dose escalation of volasertib (up to 50 mg/cycle) was permitted after the first cycle and in the absence of safety concerns to increase the probability of clinical benefit.

Safety assessments

Incidence of AEs was summarised by system organ class, severity, type and relation to study drug. Safety evaluations included assessment of haematological parameters, biochemistry panel assessment and urinalysis. At baseline, throughout

treatment and at the end of treatment electrocardiograms were recorded and cardiac enzyme assessments were performed.

Efficacy assessments

At screening, conventional cytogenetic and molecular genetic analyses were performed at a central reference laboratory.

Genetic risk subgroups were defined according to the European LeukemiaNet (ELN) proposals (Döhner *et al*, 2010). Response was assessed in peripheral blood and bone marrow. Baseline bone marrow assessment was conducted within 2 weeks prior to the start of treatment. Bone marrow aspiration for response assessment was performed at the end of the first treatment cycle, and after subsequent treatment cycles if applicable. Responses were assessed at the trial site according to published criteria (Cheson *et al*, 2003; Döhner *et al*, 2010).

Pharmacokinetics

Blood samples for PK characterisation of volasertib and cytarabine were collected at pre-specified time points during the first and second cycles of volasertib monotherapy and combination treatment (cycle 1, day 1 before the start, 30 min after start and just before the end of the volasertib infusion, and then at 1.5, 2, 3, 4, 24, 96, 216 and 336 h after the start of infusion; cycle 1 day 15 before the start, 30 min after start and just before the end of the volasertib infusion, and then at 1.5, 2, 3, 4 and 336 h after the start of infusion; cycle 2 day 1 before the start

and just before the end of the volasertib infusion). Plasma concentrations were determined by validated assays for volasertib (Awada *et al*, 2015) and cytarabine (Unpublished data, N. Plaud 2011). The concentration–time data of volasertib and cytarabine in plasma were analyzed by non-compartmental methods, using the software WinNonlin® Professional (Pharsight Corporation, v5.02).

Pharmacodynamics

Bone marrow samples for pharmacodynamic evaluation were collected in cycle 1 before and 24–120 h after the first administration of volasertib and at the end of cycle 1.

Pharmacodynamic analyses were performed to examine cell morphology, mitotic arrest and induction of apoptosis. After Ficoll™ gradient separation to obtain the mononuclear cell fraction, cells were centrifuged onto pre-coated microscope slides, and fixed in cold acetone/methanol. The percentage of cells arrested in mitosis was analysed by immunofluorescence labelling with phosphorylated histone H3 phosphoserine 10 (Upstate, Lake Placid, NY, USA) and α -tubulin (Sigma, St. Louis, MO, USA). Apoptosis was analysed by immunocytochemistry labelling for terminal deoxynucleotidyl transferase dUTP nick end labeling (TUNEL) (Chemicon International, Temecula, CA, USA). Cytological evaluation of bone marrow aspirates was performed by staining with May–Grünwald Giemsa. Microscopy pictures were obtained using an Axioskop 40 with 1000x magnification.

Statistical analysis

All analyses were descriptive and exploratory by nature. Patients receiving at least 1 dose of study drug (treated set) were included in the analysis. Patients who had not completed at least 1 cycle for reasons other than DLT and were thus not evaluable for DLT were replaced in order to determine the MTD, but included in the treated set for all other analyses.

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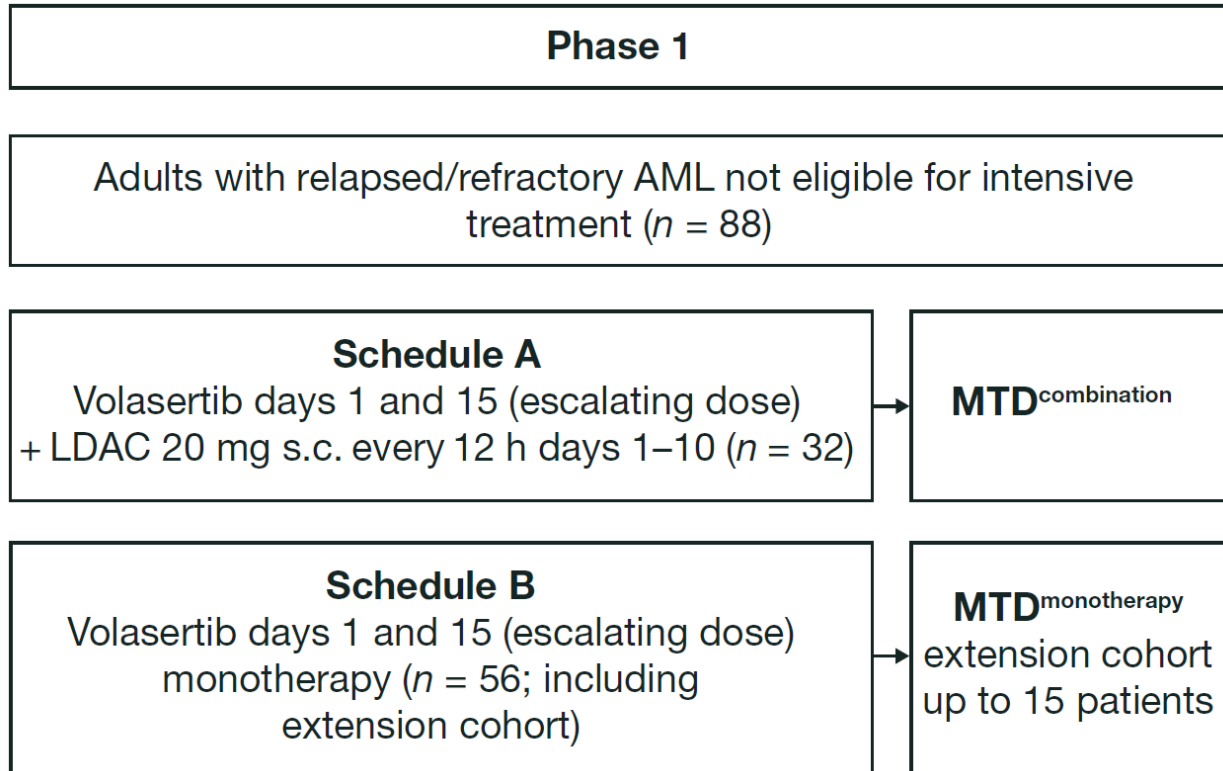
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SUPPORTING FIGURES

Fig S1. Study design: Phase I of a phase I/II trial assessing volasertib as monotherapy or in combination with cytarabine in AML (NCT00804856).



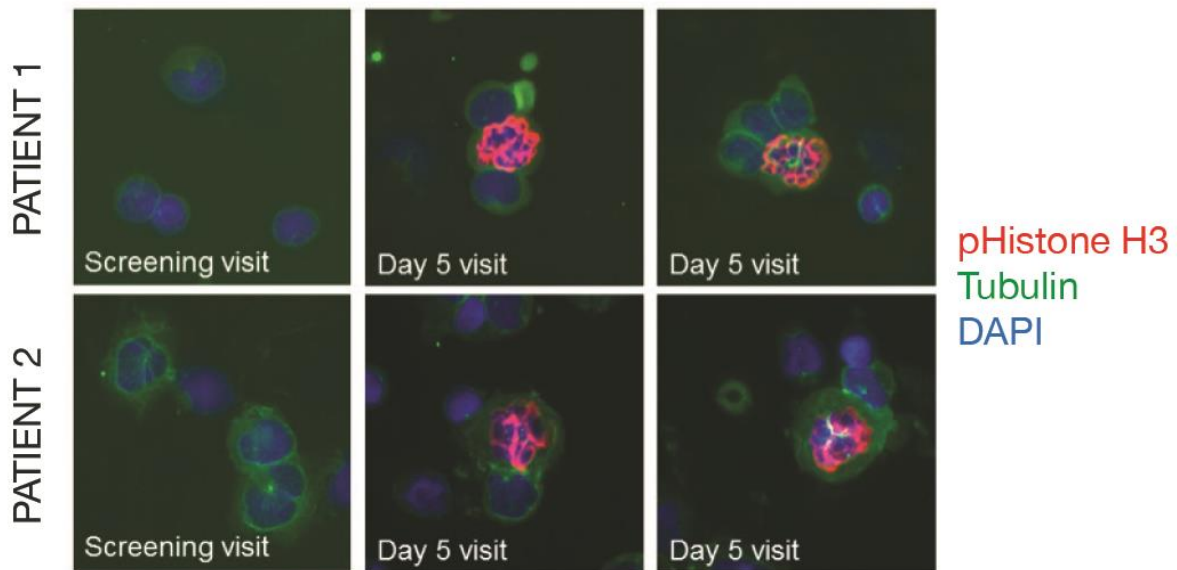
AML, acute myeloid leukemia; LDAC, low-dose cytarabine; MTD, maximum tolerated dose; s.c., subcutaneous.

Fig S2. (A) Tumour response in the two treatment groups, and (B) bone marrow samples after the first volasertib infusion, showing an increase in the number of p^H3-positive cells and a pattern of nuclear condensation and fragmentation that is characteristic of apoptosis following mitotic arrest by PLK inhibition (Polo-arrest)

(A)

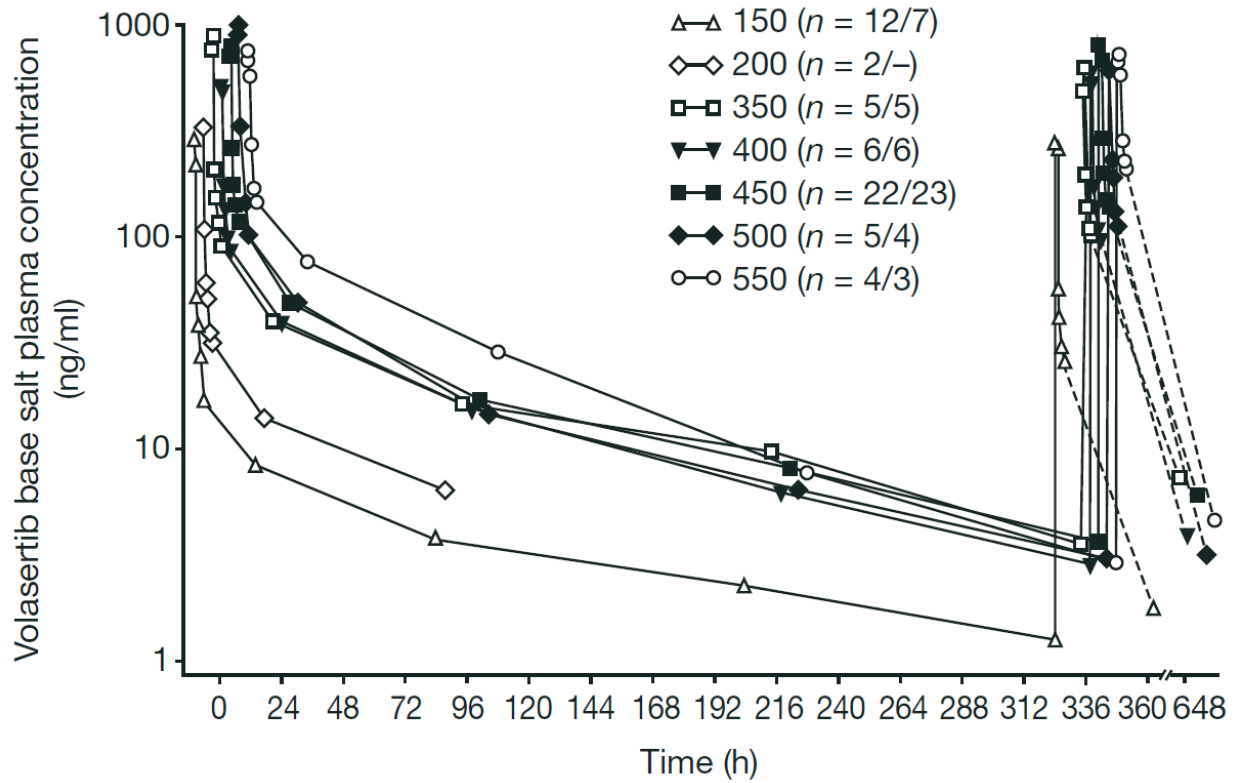
	Volasertib + LDAC combination therapy (<i>n</i> = 32) <i>n</i> (%)	Volasertib monotherapy (<i>n</i> = 56) <i>n</i> (%)
CR/CRi	6 (18·8)	5 (8·9)
PR	0 (0·0)	4 (7·1)

(B)



CR, complete remission; CRi, complete remission with incomplete blood count recovery; DAPI, 4',6-diamidino-2-phenylindole; LDAC, low-dose cytarabine; PLK, polo like kinase; PR, partial response

Fig S3. Plasma concentration–time profile of volasertib following 1 h intravenous infusion of 150 mg to 550 mg of volasertib in cycle 1 (first infusion at time 0 and second infusion at time 336 h).



h, hours

SUPPORTING TABLES

Table S1. Patient and disease characteristics.

	Volasertib monotherapy	Volasertib + LDAC
	(n=56)	(n=32)
Gender (male), %	27 (48.2)	21 (65.6)
Age, years (median, range)	70 (26–84)	71 (40–81)
<i>ECOG performance score, n (%)</i>		
0	16 (28.6)	9 (28.1)
1	31 (55.4)	18 (56.3)
2	9 (16.1)	5 (15.6)
WBC, 10 ⁹ /L (median, interquartile range)	3.7 (1.9–7.6)	3.1 (1.1–9.9)
Secondary AML*, n (%)	20 (35.7)	13 (40.6)
<i>Gene mutations, n (%)</i>		
<i>NPM1</i> mutated	8 / 49 (16.3)	3 / 26 (11.5)
<i>NPM1</i> results missing	7	6
<i>FLT3</i> -ITD	6 / 50 (12)	3 / 26 (11.5)
<i>FLT3</i> -ITD results missing	6	6
<i>ELN genetic risk subgroup, n (%)</i>		
Favourable	3 / 49 (6.1)	3 / 27 (11.1)
Intermediate I/II	36 / 49 (73.5)	19 / 27 (70.4)
Adverse	10 / 49 (20.4)	5 / 27 (18.5)
Missing	7	5
Previous systemic anti-leukaemic therapy lines (median, range)	2 (1–5)	3 (1–13)

Patients with concomitant

diagnosis,[†] n (%)

Blood and lymphatic system disorders	54/56 (96.4)	32/32 (100.0)
Cardiac disorders	33/56 (58.9)	25/32 (78.1)
Respiratory, thoracic and mediastinal disorders	29/56 (51.8)	21/32 (65.6)
Gastrointestinal disorders	35/56 (62.5)	23/32 (71.9)
General disorders and administration site conditions	43/56 (76.8)	22/32 (68.8)
Hepatobiliary disorders	19/56 (33.9)	16/32 (50.0)
Infections and infestations	39/56 (69.6)	18/32 (56.3)
Investigations	38/56 (67.9)	27/32 (84.4)
Metabolism and nutrition disorders	41/56 (73.2)	28/32 (87.5)
Musculoskeletal and connective tissue disorders	32/56 (57.1)	24/32 (75.0)
Renal and urinary disorders	21/56 (37.5)	21/32 (65.6)
Skin and subcutaneous tissue disorders	28/56 (50.0)	19/32 (59.4)
Surgical and medical procedures	29/56 (51.8)	19/32 (59.4)
Vascular disorders	47/56 (83.9)	28/32 (87.5)

*Defined as secondary to MDS or MPN.

[†]By system organ class in ≥50% of patients in either treatment group

AML, acute myeloid leukaemia; ECOG, Eastern Cooperative Oncology Group; ELN, European;

ITD, internal tandem duplication; LeukemiaNet; LDAC, low-dose cytarabine MDS,

myelodysplastic syndrome; MPN, myeloproliferative neoplasm; WBC, white blood cell count.

Table S2. Non-compartmental PK parameters of volasertib monotherapy after intravenous infusion (1 h) on day 1 of cycle (Schedule B).

PK parameters of volasertib	150 mg			200 mg			350mg			400 mg			450 mg			500 mg			550 mg		
	n	gMean	gCV [%]	n	gMean	gCV [%]	n	gMean	gCV [%]	n	gMean	gCV [%]	n	gMean	gCV [%]	n	gMean	gCV [%]	n	gMean	gCV [%]
AUC _{0-∞} [ng·h/mL]	10	1880	29.3	–	–	–	5	7200	35.1	6	5980	62.1	22	8160	36.2	5	7320	38.5	3	9760	93.2
AUC _{0-∞,norm} [ng·h/mL/mg]	10	12.5	29.3	–	–	–	5	20.6	35.1	6	14.9	62.1	22	18.1	36.2	5	14.6	38.5	3	17.7	93.2
C _{max} [ng/mL]	12	299	40.3	2	326	95.8	5	905	33.0	6	584	35.4	22	870	29.6	5	1190	35.0	4	867	55.6
C _{max,norm} [ng/mL/mg]	12	2.00	40.3	2	1.63	95.8	5	2.59	33.0	6	1.46	35.4	22	1.93	29.6	5	2.38	35.0	4	1.45	61.2
t _{max} [h]*			0.383			0.467			0.517			0.500			0.450			0.467			0.517
	12	0.542	–	2	0.484	–	5	0.933	–	6	0.934	–	22	0.909	–	5	0.917	–	4	1.21	–
			1.02			0.500			1.00			1.03			1.15			1.00			1.45
t _{1/2} [h]	10	127	26.1	–	–	–	5	116	27.2	6	108	28.7	22	112	28.7	5	102	19.6	3	103	26.6
MRT [h]	10	130	26.6	–	–	–	5	119	18.2	6	107	37.7	22	104	34.9	5	93.1	22.0	3	101	31.2
CL [mL/min]	10	1330	29.3	–	–	–	5	810	35.1	6	1120	62.1	22	920	36.2	5	1140	38.5	3	939	93.2
V _{ss} [L]	10	10300	36.3	–	–	–	5	5800	35.1	6	7150	70.6	22	5740	38.7	5	6360	50.1	3	5680	81.9

*Data are median and range (min–max) values.

AUC_{0-∞}, area under the plasma concentration–time curve from time zero to infinity; CL, total plasma clearance; C_{max}, maximum measured concentration of the analyte in plasma; gCV, geometric coefficient of variance; gMean, geometric mean; MRT, mean residence time; PK, pharmacokinetic; norm, dose-normalized; t_{max}, the time at which C_{max} is observed; t_{1/2}, terminal half-life; V_{ss}, apparent volume of distribution at steady state

