A phase I dose-escalation study of MSC1992371A, an oral inhibitor of aurora and other kinases, in advanced hematologic malignancies

Graux, Carlos; Sonet, Anne; Maertens, Johan; Duyster, Justus; Greiner, Jochen; Chalandon, Yves; Martinelli, Giovanni; Hess, Dagmar; Heim, Dominik; Giles, Francis J; Kelly, Kevin R; Gianella-Borradori, Athos; Longerey, Blandine; Asatiani, Ekaterine [**and 2 more**]

How to cite

GRAUX, Carlos et al. A phase I dose-escalation study of MSC1992371A, an oral inhibitor of aurora and other kinases, in advanced hematologic malignancies. In: Leukemia research, 2013, vol. 37, n° 9, p. 1100–1106. doi: 10.1016/j.leukres.2013.04.025

This publication URL: https://archive-ouverte.unige.ch/unige:37151

Publication DOI: 10.1016/j.leukres.2013.04.025

Leukemia Research 37 (2013) 1100–1106

Contents lists available at SciVerse ScienceDirect

Leukemia Research

journal homepage: www.elsevier.com/locate/leukres

A phase I dose-escalation study of MSC1992371A, an oral inhibitor of aurora and other kinases, in advanced hematologic malignancies☆

Carlos Graux[a,*], Anne Sonet[a], Johan Maertens[b], Justus Duyster[c,1], Jochen Greiner[d], Yves Chalandon[e], Giovanni Martinelli[f], Dagmar Hess[g], Dominik Heim[h], Francis J. Giles[i,j], Kevin R. Kelly[j], Athos Gianella-Borradori[k,2], Blandine Longerey[k], Ekaterine Asatiani[k], Narmyn Rejeb[k], Oliver G. Ottmann[l]

[a] *Mont-Godinne University Hospital (UCL), Yvoir, Belgium*
[b] *University Hospital Gasthuisberg, Leuven, Belgium*
[c] *Technical University of Munich, Munich, Germany*
[d] *University of Ulm, Ulm, Germany*
[e] *University Hospital Geneva, Geneva, Switzerland*
[f] *University of Bologna, Bologna, Italy*
[g] *Kantonsspital St. Gallen, St. Gallen, Switzerland*
[h] *Basel University Hospital, Basel, Switzerland*
[i] *HRB Clinical Research Facility, Galway, Ireland*
[j] *Cancer Therapy and Research Center at the University of Texas Health Sciences Center, San Antonio, TX, USA*
[k] *Merck Serono S.A., Geneva, Switzerland*
[l] *Johann Wolfgang Goethe University, Frankfurt, Germany*

ARTICLE INFO

Article history:
Received 19 December 2012
Received in revised form 3 April 2013
Accepted 21 April 2013
Available online 5 June 2013

Keywords:
Aurora kinase inhibitor
MSC1992371A
Phase I
Hematologic malignancies

ABSTRACT

A phase I dose-escalation study of MSC1992371A, an oral aurora kinase inhibitor, was carried out in patients with hematologic malignancies. Patients received escalating doses either on days 1–3 and 8–10 ($n = 36$) or on days 1–6 ($n = 39$) of a 21-day cycle. The maximum tolerated doses were 37 and 28 mg/m^2/day, respectively. Dose-limiting toxicities included severe neutropenia with infection and sepsis, mucositis/stomatitis, and diarrhea. Complete responses occurred in 3 patients. Four disease-specific expansion cohorts then received the dose and schedule dictated by the escalation phase but the study was prematurely discontinued due to hematologic and gastrointestinal toxicity at clinically effective doses.

1. Introduction

Aurora kinases play a key role in mitosis and are over-expressed in most tumor types including leukemias [1]. Deregulation of aurora kinases is associated with tumorigenesis, making them an attractive target for small-molecule inhibitors [1]. The majority in development are multikinase inhibitors active against aurora A and B as well as other kinases such as ABL (including its T315I variant), FMS-like tyrosine kinase 3 (FLT3), and Janus kinase (JAK2). The most promising activity of aurora kinase inhibitors (AKIs) in preclinical models and early clinical trials appears to be in hematologic malignancies. This is especially so in FLT3-activated acute myeloid leukemia (AML) and imatinib-resistant Philadelphia chromosome-positive (Ph+) leukemias, particularly those with T315I mutation [2].

MSC1992371A is a potent adenine triphosphate-competitive inhibitor of aurora kinase isoforms A–C, disrupting mitotic spindle activity, blocking cell separation, and leading to polyploidy and cell death. At low nanomolar concentrations, MSC1992371A also inhibits other kinases involved in cell survival and proliferation including FLT3, BCR-ABL1, and BCR-ABL1 with T315I mutation. It also inhibits JAK2 kinase, but at higher concentrations (60 nM < IC_{50} < 600 nM). Preclinically, MSC1992371A has demonstrated potent antitumor activity as single agent and in combination treatment in leukemia cell lines, freshly isolated leukemia

☆ ClinicalTrials.gov identifier: NCT01080664.

* Corresponding author at: Hematology Unit, NARILIS, CHU Mont-Godinne, Avenue Docteur G. Thérasse, 1-5530 Yvoir, Belgium. Tel.: +32 81 42 47 64/38 31; fax: +32 81 42 38 32.
E-mail address: carlos.graux@uclouvain.be (C. Graux).
[1] Current address: Department of Internal Medicine I, University of Freiburg, Freiburg, Germany.
[2] Current address: Clavis Pharma, Oslo, Norway.

0145-2126/$ – see front matter © 2013 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.leukres.2013.04.025

cells, and leukemia xenograft models [3]. Toxicities appear to be related mainly to the gastrointestinal and hematopoietic systems. In animal models, activity and toxicity depend not only on dose but also on schedule of administration [3]. The compound is also known as R763. Rights are currently owned by Rigel Pharmaceuticals, Inc., CA, USA.

We report a phase l dose-escalation study of MSC1992371A in patients with a range of advanced hematologic malignancies. The primary objective was to determine the maximum tolerated dose (MTD) for 2 administration schedules. Secondary objectives included a preliminary evaluation of safety, pharmacokinetics, and antitumor activity relevant to patient selection. This was followed by an expansion phase to evaluate the tolerability and clinical activity of MSC1992371A in 4 specific types of hematologic malignancies using the dose regimens identified in the first phase of the study, or selected lower doses.

2. Materials and methods

2.1. Patients

The dose-escalation phase enrolled patients with advanced hematologic malignancies, including relapsed or refractory AML and newly diagnosed AML patients over 60 years who did not accept or were ineligible for chemotherapy (e.g., due to expected poor treatment tolerance, poor performance status, or comorbidities) as per judgment of the investigator. Patients with intermediate or high-risk myelodysplastic syndrome (MDS), myeloproliferative disease (MPD), chronic myeloid leukemia (CML), acute lymphoblastic leukemia (ALL), or non-Hodgkin's lymphoma (NHL) with no effective treatment options were also included. Eligible patients were age 18 or over with an Eastern Cooperative Oncology Group (ECOG) performance status of 0–2. Key exclusion criteria included acute promyelocytic leukemia and hyperleukocytosis ($>50 \times 10^9\ L^{-1}$ leukemic blasts), anticancer treatment within the previous 28 days, and radiotherapy involving 30% or more of the bone marrow within the prior 6 months. Other exclusion criteria were standard for a phase I study in this setting (see supplementary material). The first patient entered the trial in December 2006 and enrollment ended in February 2010.

2.2. Study design

This was a 2-part, phase l, open-label trial (Supplementary Fig. 1). In the escalation part of the study, 2 dosing schedules were investigated in parallel to determine the MTD for each. In both schedules, treatment was administered in 21-day cycles. The schedules differed in dosing frequency but the cumulative dose per cycle was the same in each. In schedule 1, study drug was given on days 1–3 followed by no drug on days 4–7 and then drug on days 8–10. In schedule 2, study drug was given on days 1–6. The starting dose of 3 mg/m^2/day was based on animal toxicology studies according to FDA guidance on phase I trials of cytotoxics [4]. Eight dose levels were tested, from 3 to 47 mg/m^2/day. Dose-escalation was conducted independently for each schedule based on the dose-limiting toxicities (DLT) occurring during the first cycle that were judged to be drug related. The definition of DLTs is given in detail in the supplementary material. Dose-escalation was performed using a standard sequential '3 + 3' cohort design (supplementary material).

The second part of the study evaluated the tolerability (and preliminary clinical activity) of the study drug at the dose regimens selected in the dose-escalation phase. The 4 groups defined for the second, expansion phase were (i) AML, (ii) Ph+ acute leukemias, ALL, or blast-phase CML, (iii) chronic or accelerated-phase CML, and (iv) MPD. Enrollment in the disease-specific groups followed the same inclusion and exclusion criteria as in the dose-escalation phase. For the CML and MPD cohorts, drug was dosed according to schedule 1. For AML, ALL, and blast-phase CML, which were likely to have a higher proliferation rate, the more dose-intense schedule 2 was used. In each part of the study, treatment was continued until progressive disease and/or unacceptable toxicity. Safety and activity were reviewed by a safety monitoring committee before each dose-escalation step and regularly during the expansion part of the study.

The trial was conducted in accordance with the International Conference on Harmonization Guidelines for Good Clinical Practice, the Declaration of Helsinki, and applicable local regulations. The study was approved by the Independent Ethics Committees of participating centers. Patients gave written informed consent. The study sponsor was Merck Serono S.A., Geneva; the trial was registered with ClinicalTrials.gov (identifier NCT01080664).

2.3. Study assessments and supportive care

In addition to establishing DLTs in cycle 1, adverse events (AEs) were recorded according to Common Terminology Criteria for Adverse Events (CTCAE version 3.0) until 31 ± 3 days after last study drug administration. Changes from baseline were assessed for laboratory parameters, vital signs, physical exam, electrocardiogram (ECG), and echocardiography (or MUGA scans). Laboratory evaluations were undertaken twice weekly during the first week of treatment and weekly thereafter. Twelve-lead ECG was performed during treatment on day 1 at 2 and 4 h post-dosing and then every 2 cycles, along with echocardiography.

Blood samples were obtained after the single dose given on the first day and after multiple dosing (i.e., on day 10 for schedule 1 and day 6 for schedule 2, in cycle 1) for evaluation of pharmacokinetics (PK; see supplementary materials). Biomarkers of MSC1992371A target inhibition (phosphorylation of histone H3 and FLT3), cell proliferation, and cell death were explored in peripheral blood and bone marrow (see supplementary materials).

Antitumor efficacy was assessed at the end of each treatment cycle according to internationally established, disease-specific guidelines.

Patients were treated as in- or out-patients. Prophylaxis and treatment of infections with antibiotics and/or antifungals was not standardized across patients; local standard guidelines were followed and varied by country or hospital. Hematopoietic growth factors prophylaxis was not allowed by the protocol in cycle 1.

2.4. Statistical methods

For the dose-escalation part of the study, enrollment of up to 156 patients was envisaged. However, since no hypothesis was being tested, there was no calculation of sample size. The cohort expansion part of the study followed a Minimax Simon 2-stage design within each disease-specific cohort. The minimum response rate (RR) of interest was 5%, and the desired level was 20%. The study aimed to detect activity greater than 5%, with a 10% chance of 1-sided alpha error and 80% power. On this basis, accrual was planned to include a minimum of 18 and maximum of 32 evaluable patients in each disease-specific cohort. If no responses were observed in the initial 18 patients, accrual would not continue.

3. Results

3.1. Dose-escalation phase

3.1.1. Patient characteristics

Baseline demographic and disease characteristics for the dose-escalation part of the study are summarized in Table 1. Overall, 75 patients received study drug: 36 on schedule 1 and 39 on schedule 2. Overall, 91 cycles of treatment were given using schedule 1 and 70 with schedule 2 (multiple dosing). The median (range) number of completed cycles per patient in schedule 1 was 2 (0–12), and 1 (0–6) with schedule 2.

3.1.2. DLTs and determination of MTD, schedule 1

Toxicities were dose dependent; Table 2 summarizes the number of patients treated and the number of observed DLTs by dose level and schedule. The first DLT was observed at 28 mg/m^2/day, with prolonged grade 4 neutropenia in 1 of 6 patients. At the next dose, 47 mg/m^2, 2 DLTs occurred in 3 patients: grade 3 diarrhea and gastrointestinal hemorrhage occurred in 2, and grade 3 diarrhea and fatal Gram-negative sepsis in another. The dose was therefore reduced to the intermediate level of 37 mg/m^2/day, and at this dose 1 DLT was observed in the first 6 patients. The MTD was therefore established as 37 mg/m^2/day and the cohort was expanded to 12. Three patients experienced DLTs, including neutropenic infection (2 patients) and grade-3 mucositis/diarrhea (2 patients). Given that DLTs occurred in less than 33% of patients (3/12) in the expanded 37 mg/m^2 cohort, this dose was selected for further testing in 2 chronic myeloproliferative disease expansion cohorts (chronic- or accelerated-phase CML, and MPD), with the provision for dose reductions as needed.

3.1.3. DLTs and determination of MTD, schedule 2

With this schedule, no DLTs occurred until 47 mg/m^2/day, when 1 of 3 of the initial patients treated experienced a DLT and 2 further DLTs occurred in the next 2 patients. One had grade-4 mucositis and febrile neutropenia with *Clostridium* bacteremia, another had grade-4 mucositis, and a third grade-3 diarrhea. The dose was consequently reduced to 37 mg/m^2/day and enrollment continued at this level, with a total of 3 of 6 patients having a DLT. These were of similar type to those seen at 47 mg/m^2/day. The lower dose of

Table 1
Baseline patient demographics and disease characteristics (escalation phase).

Characteristic	Schedule 1 (n = 36)	Schedule 2 (n = 39)
Age, years		
Median (range)	67 (35–83)	70 (22–82)
Sex, n (%)		
Female	14 (39)	14 (36)
Male	22 (61)	25 (64)
ECOG performance status, n (%)		
0	13 (36)	15 (39)
1	15 (42)	19 (49)
2	8 (22)	5 (13)
Malignancy, n (%)		
AML	24 (67)	30 (77)
Primary	13 (36)	15 (38)
Secondary	11 (31)	15 (38)
Cytogenetics		
Favorable	0	0
Intermediate	10 (28)	11 (28)
Poor	9 (25)	10 (26)
Not known	5 (14)	9 (23)
CML	3 (8)	2 (5)
Accelerated phase	1 (3)	0
Blast phase	2 (6)	2 (5)
MDS-RAEB	3 (8)	2 (5)
MPD	4 (11)	3 (8)
ALL	1 (3)	2 (5)
Ph+	1 (3)	0
Ph–	0	2 (5)
Non-Hodgkin's lymphoma	1 (3)	–
Number of previous anticancer treatments		
Median (range)	2 (0–6)	2 (0–6)
Years since diagnosis		
Median (range)	1.0 (0–18)	0.9 (0–5.2)

ECOG, Eastern Cooperative Oncology Group; AML, acute myeloid leukemia; CML, chronic myeloid leukemia; MDS, myelodysplastic syndrome; RAEB, refractory anemia with excess blasts; MPD, myeloproliferative disorder; ALL, acute lymphoblastic leukemia; Ph+, Philadelphia chromosome-positive; Ph–, Philadelphia chromosome-negative.

28 mg/m^2/day, at which no DLTs had occurred in 3 patients, was the MTD and this cohort was expanded to 12 patients. However, 4 of the further 9 patients (4/12 in total) developed grade 3–4 mucositis and febrile neutropenia/neutropenic infection. The lower dose of 21 mg/m^2 was therefore recommended for further testing in acute-leukemia expansion cohorts (AML and Ph+ leukemias).

3.1.4. Tolerability profile

Tables 3 and 4 detail the hematologic and non-hematologic AEs reported during treatment with either schedule, irrespective of relationship to study drug. The AE profiles associated with both schedules were similar, although there were some differences in the incidence and severity of toxicities. With both schedules, the safety profile of MSC1992371A was dominated by hematologic toxicity (mainly neutropenia), infections associated with severe neutropenia, and gastrointestinal toxicities (mainly mucositis, diarrhea, and nausea). Febrile neutropenia occurred in around half of all patients. Of the non-hematologic AEs affecting ≥20% of patients, infections were the most frequent and relevant. Grades 3–4 infection was more frequent with schedule 1 than 2 (58% versus 38%).

Table 3
Hematologic adverse events (any grade and grade 3 or higher) irrespective of relationship to study drug; all cycles.

AE	Number (%) of patients with AE		
		Schedule 1 (n = 36; 91 cycles)	Schedule 2 (n = 39; 70 cycles)
Febrile neutropenia	Any grade	16 (44)	21 (54)
	≥Grade 3	16 (44)	21 (54)
Neutropenia	Any grade	33 (92)	37 (95)
	≥Grade 3	33 (92)	36 (92)
Thrombocytopenia	Any grade	36 (100)	38 (97)
	≥Grade 3	31 (86)	37 (95)
Anemia	Any grade	34 (94)	36 (92)
	≥Grade 3	22 (61)	17 (44)

AE, adverse event.

Grade ≥3 infections were mostly bacterial; pathogens reported were *Enterococcus*, *Escherichia coli*, *Staphylococcus*, *Klebsiella*, *Clostridium*. Some fungal infections were reported, including fungal pneumonia at doses ≥28 mg/m^2 and mucormycosis in 1 patient treated with schedule 1 37 mg/m^2. The second most-frequent toxicity was diarrhea, reported in about 60% of patients in both schedules, with 10–14% grades 3–4 events. With both schedules, the incidence of febrile neutropenia and severe infection increased with rising dose. The incidence and severity of GI toxicity was also dose dependent. Grades 3–4 diarrhea and stomatitis/mucosal inflammation were observed at doses of 37 mg/m^2/day and above with schedule 1, and mostly at 28 mg/m^2/day and above with schedule 2.

Twenty-three deaths were reported, 9 in schedule 1 and 14 in schedule 2. Of these, 8 were reported as related to study drug and occurred at doses of 28 mg/m^2/day and higher: 3 in schedule 1 (doses 37–47 mg/m^2/d) and 5 in schedule 2 (doses 28–47 mg/m^2/day). Sepsis was the cause of death in all drug-related cases. The organisms identified were primarily bacterial and included *E. coli* (n = 3), *Enterococcus* (n = 2), *Klebsiella pneumoniae/oxytoca* (n = 1), *Bacteroides* (n = 1) or other Gram-negative (not

Table 2
Number of patients treated and number with dose-limiting toxicities by dose level and schedule.

Schedule 1			Schedule 2		
Dose (mg/m^2/day)	Pts evaluable for DLT (n)	Pts with 1 or more DLT (n)	Dose (mg/m^2/day)	Pts evaluable for DLT (n)	Pts with 1 or more DLT (n)
3	3	–	3	3	–
6	3	–	6	3	–
10	3	–	10	3[a]	–
15	3	–	15	3	–
21	3	–	21	3	–
28	3 + 3	1	28 = MTD[c]	3 + 9	0 + 4
37 = MTD[b]	3 + 9	0 + 3	37	3 + 3	1 + 2
47	3	2	47	3 + 2	1 + 2
Total	36	6	Total	38	10

MTD, maximum tolerated dose; DLT, dose-limiting toxicity.

[a] Four patients were treated at this dose level but 1 was excluded from the DLT analysis set since this patient did not experience a DLT during the first treatment cycle and did not receive at least 90% of the cycle 1 study drug.

[b] Reduced dose level after dose-escalation from 28 to 47 mg/m^2/day.

[c] As determined per protocol. However, due to the occurrence of an unacceptable number of DLTs during the expansion phase at this dose, 21 mg was selected for use in the second, disease-specific part of the study.

Table 4
Most frequent non-hematologic adverse events (in ≥20% of patients in at least 1 schedule) or grade ≥3 (in >1 patient in at least 1 schedule), irrespective of relationship to study drug; all cycles.

AE		Number (%) of patients with AE	
		Schedule 1 (n = 36; 91 cycles)	Schedule 2 (n = 39; 70 cycles)
Infections[a]	Any grade	29(81)	23(59)
	≥Grade 3	21(58)	15(39)
Gastrointestinal disorders			
Diarrhea	Any grade	23(64)	24(62)
	≥Grade 3	5(14)	4(10)
Stomatitis/mucosal inflammation	Any grade	11(31)	13(33)
	≥Grade 3	4(11)	9(23)
Vomiting	Any grade	10(28)	10(26)
	≥Grade 3	1(3)	0(0)
Decreased appetite	Any grade	8(22)	6(15)
	≥Grade 3	5(14)	1(3)
Nausea	Any grade	9(25)	16(41)
	≥Grade 3	0(0)	0(0)
Abdominal pain	Any grade	6(17)	4(10)
	≥Grade 3	3(8)	0(0)
GI/intestinal hemorrhage	Any grade	4(11)	1(3)
	≥Grade 3	3(8)	1(3)
Colitis/sigmoiditis	Any grade	4(11)	1(3)
	≥Grade 3	3(8)	0(0)
GI inflammation	Any grade	1(3)	2(5)
	≥Grade 3	0(0)	2(5)
Constitutional disorders			
Asthenia/fatigue	Any grade	10(28)	18(46)
	≥Grade 3	5(14)	5(13)
Pyrexia/hyperthermia	Any grade	9(25)	8(21)
	≥Grade 3	3(8)	1(3)
General physical health deterioration/performance status decreased	Any grade	4(11)	8(21)
	≥Grade 3	2(6)	4(10)
Peripheral edema	Any grade	7(19)	11(28)
	≥Grade 3	0(0)	0(0)
Hepatic disorders			
Transaminases increased	Any grade	8(22)	12(31)
	≥Grade 3	1(3)	2(5)
Hyperbilirubinemia	Any grade	4(11)	3(8)
	≥Grade 3	2(6)	0(0)
Gamma-glutamyltransferase increased	Any grade	3(8)	5(13)
	≥Grade 3	2(6)	4(10)
Metabolic disorders			
Hypokalemia	Any grade	16(44)	14(36)
	≥Grade 3	8(22)	7(18)
Hypoalbuminemia	Any grade	11(31)	7(18)
	≥Grade 3	2(6)	3(8)
Hypocalcemia	Any grade	5(14)	1(3)
	≥Grade 3	2(6)	0(0)
Hypophosphatemia	Any grade	4(11)	1(3)
	≥Grade 3	3(8)	1(3)
Other			
Epistaxis	Any grade	11(31)	8(21)
	≥Grade 3	1(3)	1(3)
Headache	Any grade	10(28)	9(23)
	≥Grade 3	0(0)	1(3)
Dyspnea	Any grade	10(28)	9(23)
	≥Grade 3	6(17)	6(15)
Cough	Any grade	5(14)	8(21)
	≥Grade 3	0(0)	0(0)
Petechiae	Any grade	4(11)	9(23)
	≥Grade 3	0(0)	0(0)
Alopecia	Any grade	3(8)	8(21)
	≥Grade 3	0(0)	0(0)
Blood lactate dehydrogenase increased	Any grade	2(6)	6(15)
	≥Grade 3	1(3)	2(5)
Multi-organ failure	Any grade	2(6)	0(0)
	≥Grade 3	2(6)	0(0)

AE, adverse event; GI, gastrointestinal.
[a] Grade ≥3 infections were mostly bacterial; pathogens reported were *Enterococcus*, *E. coli*, *Staphylococcus*, *Klebsiella*, *Clostridium*. Some fungal infections were reported, including fungal pneumonia and mucormycosis.

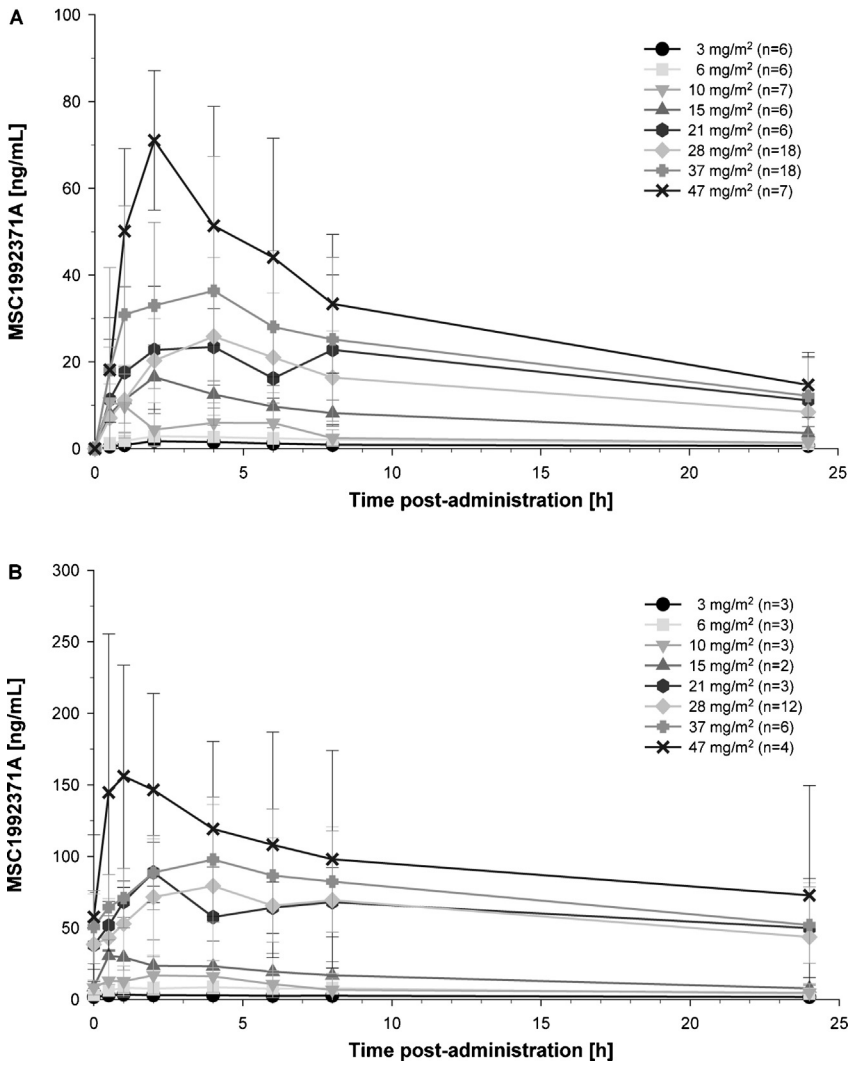

Fig. 1. Mean plasma concentration of MSC1992371A with time and according to dose level. (A) On day 1 of cycle 1 (data from the 2 schedules are combined) and (B) on day 6 of cycle 1 (i.e., after multiple dosing) in schedule 2 patients.

otherwise specified, $n = 1$), and *Candida* ($n = 1$). Other non-fatal AEs leading to permanent treatment discontinuation were predominantly infections, febrile neutropenia, and diarrhea.

3.1.5. Pharmacokinetics and pharmacodynamics

The mean plasma concentration profiles of MSC1992371A for day 1 cycle 1 in the different dose groups (and for the 2 schedules combined) are shown in Fig. 1A. Maximal plasma concentrations were reached 1–4 h (range 0.5–8.0 h) after administration. Exposure to MSC1992371A, as indicated by the maximum plasma concentration (C_{max}) and area under the plasma concentration curve (AUC_{0-t}), increased with dose. Table 5 shows PK values for both schedules at the MTD. The half-life and other derived PK parameters were not calculated for MSC1992371A since for the majority of PK profiles the extrapolated exposure (AUC_{extra}) exceeded 20% of the total exposure. However, based on the available data, the terminal half-life was estimated to be 15–25 h. Fig. 1B shows the effect of multiple dosing in patients who had drug administered for 6 successive days in schedule 2. Higher exposure to MSC1992371A was observed in schedule 2, as indicated by a 1.7- to 3.4-fold increase in geometric mean AUC_{0-t} and a 1.0- to 2.8-fold increase in geometric mean C_{max} compared to the single-dose administration in the first cycle.

Analysis of markers of MSC1992371A target inhibition, cell proliferation, and cell death did not show consistent evidence of pharmacodynamic activity associated with the administration of MSC1992371A.

3.1.6. Clinical activity

Complete response (CR) was achieved at the higher doses of 37 and 47 mg/m^2/day (schedule 2) in 2 of the 54 patients with AML. Both CRs occurred in older patients with secondary AML. Neither patient had an FLT3 mutation. Responses in both patients were maintained until relapse in cycle 4. Both patients required dose reduction of MSC1992371A to 21 mg/m^2/day in cycle 4 due to mucositis and febrile neutropenia. A CR with incomplete blood recovery (CRi) was achieved in 1 of 3 patients with Ph+ ALL treated at 37 mg/m^2/day (schedule 1). However, treatment was discontinued after 1 cycle due to grade 3 mucositis combined with severe infection, and the response was not further confirmed.

Among the 5 patients with CML, a hematologic response with an improvement in blood count and a reduction in T315I-mutated *BCR-ABL* transcripts developed in 1 patient with accelerated-phase CML (treated at 21 mg/m^2/day for 9 cycles, schedule 1) who then underwent bone marrow transplantation.

In MDS, downstaging of disease from refractory anemia with excess blasts 2 (RAEB-2) to RA was seen in 2 of 5 patients, with

Table 5
Pharmacokinetic parameters of MSC1992371A at the maximum tolerated dose for each schedule.

MTD	Schedule 1 37 mg/m^2/day		Schedule 2 28 mg/m^2/day	
	Day 1	Day 10	Day 1	Day 6
n	12	12	12	12
C_{max} (ng/mL)				
Median (range)	42 (17–145)	83 (38–216)	32 (13–71)	97 (21–183)
Geometric mean	45	83	31	71
Geometric CV	78	69	58	92
t_{max} (h)				
Median (range)	2 (0.5–6)	2 (0.5–8)	4 (1–6)	4 (2–6)
Geometric mean	2.3	2.5	3.0	3.5
Geometric CV	90	89	73	57
AUC_{last} (ng/mL h)				
Median (range)	384 (128–1009)	1091 (256–4285)	351 (72–787)	1133 (182–3121)
Geometric mean	422	1036	337	1057
Geometric CV	74	109	78	112

MTD, maximum tolerated dose; CV, coefficient of variation.

a reduction in bone marrow blasts to <5% but without normalization of blood cell count. Among the 7 patients with MPD, 1 patient with atypical myelofibrosis, treated with 47 mg/m^2/day (schedule 1), experienced a partial response with complete disappearance of splenomegaly and complete normalization of peripheral blood. However, this response was not confirmed after 4 weeks since the patient withdrew from the trial. A second patient treated at 37 mg/m^2/day (schedule 2) experienced a transient reduction in splenomegaly and peripheral blasts. Both MPD patients had V617F-JAK2 mutations and the second an additional JAK2 mutation.

3.2. Tolerability and clinical activity in specific hematologic malignancies

Four disease-specific expansion cohorts were initiated in the cohort-expansion phase. Patients in the chronic CML and MPD cohorts received 3 consecutive days of dosing during weeks 1 and 2 (schedule 1, MTD 37 mg/m^2/day). Patients in the AML and ALL/blast-phase CML cohorts received 6 successive days of dosing during week 1 (schedule 2, MTD 21 mg/m^2/day). A total of 26 patients received study medication. Ten patients were in the AML cohort, 9 in the ALL or blast-phase CML cohort, 5 in the MPD cohort, and 2 had accelerated-phase CML.

Baseline patient characteristics in the expansion cohorts were not different from those of the patients enrolled in the dose-escalation phase (see Table 1). Median age of patients with AML was 63.5 years (range 28–76) and 69 years (range 47–74) for patients in the Ph+ ALL/blast-phase CM cohort treated with schedule 2. Median number of prior treatment regimens was 2 (range 0–5) in the AML cohort expansion. The proportion of patients with primary and secondary AML was 6 and 4, respectively. In the MPD cohort treated with schedule 1, median age was 60 (range 48–77). Median number of prior treatment regimens was 2 (range 1–5).

After 16 patients had been enrolled in the expansion phase, the toxicity observed led to a reduction in the dose given to patients with AML or MPD. A further 7 patients were treated before the Safety Monitoring Committee recommended cessation of enrollment because of continuing toxicity and limited evidence of efficacy.

The most frequently observed treatment-emergent AEs among the 26 patients were diarrhea (65%), infections (62%), febrile neutropenia (46%), stomatitis/mucositis (46%), and neutropenia (42%). Almost half experienced grades 3–4 AEs.

Indications of clinical activity were seen in 3 patients with myelofibrosis. Signals of activity were also observed in 2 patients with accelerated-phase CML. However, none of the 20 patients with acute leukemia enrolled in the AML or ALL/blast-phase CML cohorts achieved clinical benefit.

4. Discussion

In patients with advanced hematologic malignancies, the MTD of MSC1992371A was determined as 37 mg/m^2/day MSC1992371A with intermittent 3-day dosing and 28 mg/m^2/day during 6-day continuous dosing. The most frequent AEs included myelosuppression and associated infections, along with diarrhea and mucositis. However, it should be noted that the majority of patients enrolled had heavily pretreated AML, with severe bone marrow failure at baseline and hence a high risk of infections regardless of study treatment. Schedule 2 involving 6 days continual dosing, was less well tolerated than 3 days intermittent dosing used in schedule 1, and was accompanied by a higher incidence of grades 3–4 stomatitis/mucositis and febrile neutropenia, a higher incidence of fatal events, and a lower MTD.

The AEs observed with MSC1992371A (myelosuppression and associated infections, along with diarrhea and mucositis) were similar to those reported with another AKI, barasertib, investigated in a similar clinical setting [5,6]. The similarity of the AEs observed with MSC1992371A (a pan-aurora kinase inhibitor) and barasertib (a selective aurora B inhibitor) indicates that toxicities with this class of compounds are driven predominantly by aurora kinase B inhibition. In terms of activity, barasertib differs from MSC1992371A in that CRs and CRis in AML were reported at tolerable doses, and an overall RR of 25% with manageable toxicity has recently been reported [5]. This has warranted further investigation of barasertib in AML. AT9283, an inhibitor of aurora kinases A and B and other kinases related to myeloid cell proliferation, has also demonstrated early evidence of activity in refractory AML and CML [7]. A fourth AKI, MK-0457, has achieved clinical responses in 3 patients with T315I-phenotype-refractory CML or Ph+ ALL at doses not associated with AEs [8].

Both parts of this study demonstrated that the clinical use of MSC1992371A is limited by a very narrow therapeutic window. The doses at which signs of clinical benefit were seen in the dose-escalation part of the trial resulted in unacceptable toxicity in the expansion cohorts, while the decreased, less-toxic doses needed in the disease-specific cohorts lacked efficacy and in many cases could not prevent early progression. Although individual patients benefited from durable responses and tolerated several months of treatment, the overall picture showed that the dose required for

clinical activity was intolerable to a high proportion of patients, and the clinical development of this agent in hematologic malignancies has currently been halted. Even though the dual mechanism of action of AKIs is of interest, in practice it is unlikely that this class of agents can be combined with cytotoxics due to overlapping toxicities. However, preclinical studies indicate that there may be the potential to combine MSC1992371A with other agents such as histone deacetylase and BCR-ABL inhibitors, with non-overlapping toxicities [9,10]. Alternatively, modifications of dose and schedule, such as continuous administration of AKIs at a lower dose, might reduce toxicity but maintain positive clinical effects.

Acknowledgments

The authors would like to thank the patients and their families, and the many staff at the hospitals involved who contributed such valuable work. OG Ottmann is an endowed Professor of the German Jose Carreras Leukemia Foundation and would like to thank the foundation for their support.

Role of the funding source: This work was supported by Merck Serono S.A., Geneva. Currently, Rigel Pharmaceuticals Inc., CA, USA, owns the rights to MSC1992371A (R763). Editorial and writing assistance was provided by Rob Stepney, TRM Oncology, The Hague, The Netherlands, funded by Merck KGaA, Darmstadt, Germany.

Authors' contributions: OGO, NR, FJG, AG-B, and EA conceived and designed the study, and acquired, analyzed and interpreted the data. BL performed statistical analysis and interpreted the statistical output. CG, AS, JM, JD, JG, YC, GM, D Hess, D Heim, and KK acquired and interpreted the data. All authors contributed to manuscript drafting, critically reviewed the manuscript, and approved the final manuscript.

Conflict of interest: C Graux, A Sonet, J Maertens, J Duyster, J Greiner, D Hess, D Heim, K Kelly and Y Chalandon: no relevant financial relationships to disclose. F Giles and OG Ottmann have received research support from Merck Serono S.A.–Geneva. A Gianella-Borradori was and N Rejeb, B Longerey, and E Asatiani are employees of Merck Serono S.A., Geneva. G Martinelli has relevant financial activities outside the submitted work with Novartis – BMS – Pfizer.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.leukres.2013.04.025.

References

[1] Kelly KR, Ecsedy J, Mahalingam D, et al. Targeting aurora kinases in cancer treatment. Curr Drug Targets 2011;12:2067–78.
[2] Moore AS, Blagg J, Linardopoulos S, Pearson AD. Aurora kinase inhibitors: novel small molecules with promising activity in acute myeloid and Philadelphia-positive leukemias. Leukemia 2010;24:671–8.
[3] McLaughlin J, Markovtsov V, Li H, et al. Preclinical characterization of Aurora kinase inhibitor R763/AS703569 identified through an image-based phenotypic screen. J Cancer Res Clin Oncol 2010;136:99–113.
[4] US Food and Drug Administration. Center for Drug Evaluation and Research. Oncologic Drugs Advisory Committee Meeting Briefing Material. General guideline for starting dose selection for a cytotoxic agent in cancer patients; 2006. p. 128. http://www.fda.gov/OHRMS/DOCKETS/AC/06/briefing/2006_4203b1_02_FDA.Backgrounder.pdf [accessed 14.08.12].
[5] Löwenberg B, Muus P, Ossenkoppele G, et al. Phase 1/2 study to assess the safety, efficacy and pharmacokinetics of barasertib (AZD1152) in patients with advanced acute myeloid leukemia. Blood 2011;118:6030–6.
[6] Tsuboi K, Yokozawa T, Sakura T, et al. A Phase I study to assess the safety, pharmacokinetics and efficacy of barasertib (AZD1152), an Aurora B kinase inhibitor, in Japanese patients with advanced acute myeloid leukemia. Leuk Res 2011;35:1384–9.
[7] Foran JM, Ravandi F, O'Brien SM, Borthaker G, Rios M, Boone P. Phase I and pharmacodynamic trial of AT9283, an aurora kinase inhibitor, in patients with refractory leukemia. J Clin Oncol 2008;26 (abstract 2518).
[8] Giles FJ, Cortes J, Jones D, Bergstrom D, Kantarjian H, Freedman SJ. MK-0457, a novel kinase inhibitor, is active in patients with chronic myeloid leukemia or acute lymphocytic leukemia with the T315I BCR-ABL mutation. Blood 2007;109:500–2.
[9] Okabe S, Tauchi T, Ohyashiki K. Efficacy of MK-0457 and in combination with vorinostat against Philadelphia chromosome positive acute lymphoblastic leukemia cells. Ann Hematol 2010;89:1081–7.
[10] Kelly KR, Ecsedy J, Medina E, et al. The novel Aurora A kinase inhibitor MLN8237 is active in resistant chronic myeloid leukaemia and significantly increases the efficacy of nilotinib. J Cell Mol Med 2011;15:2057–70.