Sponsor

Novartis

Generic Drug Name

Midostaurin

Trial Indication(s)

Acute myeloid leukemia

Protocol Number

CPKC412A2106

Protocol Title

A phase IB, open-label study to determine the safety and pharmacokinetics of twice daily oral dosing of PKC412 administered in combination sequentially and concomitantly with daunorubicin and cytarabine for standard induction therapy, and high-dose cytarabine for consolidation in patients with acute myeloid leukemia (AML)

Clinical Trial Phase

Phase 1B

Phase of Drug Development

Phase III

Study Start/End Dates

01-Apr-2003 to 03-Jun-2011

Reason for Termination (If applicable)

Not applicable

Study Design/Methodology

This was a Phase IB, open label, multi-center study evaluating the safety, tolerability, and pharmacokinetics of 2 dosing schedules of midostaurin (PKC412) in patients with newly diagnosed, previously untreated AML. Midostaurin was administrated either sequentially (Arm 1) or concomitantly (Arm 2) with standard induction therapy comprising daunorubicin and cytarabine, followed by consolidation therapy with high dose cytarabine. After completion of consolidation therapy, patients were to continue to receive midostaurin as single-agent maintenance therapy according to the schedule assigned during induction. In the

absence of safety concerns, midostaurin could be continued until relapse or for up to 3 years from the time of diagnosis.

Study treatment was administered in treatment cycles that could be 28 to 42 days in duration.

In the Induction phase (Cycle 1), patients were administered daunorubicin 60 mg/m^2/day IV over 30 min for 3 days (Days 1-3) and cytarabine 200 mg/m^2/day IV over 24 hours for 7 days (Days 1-7). If a second cycle of induction therapy (Cycle 2) was required due to inadequate response, daunorubicin and cytarabine were administered on Days 1-2 and Days 1-5, respectively. Midostaurin was administered either sequentially (Arm 1) or concomitantly (Arm 2) with the induction therapy.

In the Consolidation phase, patients who obtained a complete response (CR) at the end of Cycle 1 or Cycle 2 received consolidation therapy with high-dose cytarabine for up to 3 cycles (Cycles 3-5). Midostaurin was administered at the same schedule as in the Induction phase.

In the Maintenance phase, midostaurin was administered as single-agent therapy according to the schedule assigned during induction..

During the study, 4 protocol amendments were implemented that reduced the midostaurin dose from 100 mg bid to 50 mg bid and that shortened the duration of midostaurin exposure per treatment cycle in both treatment arms. The midostaurin dosing schedules for the two treatment arms in each cycle were as follows:

Arm 1 (sequential administration):

- Core + Amendment 1 (cohort C+A1): midostaurin 100 mg bid from Day 8 to Day 28
- Amendment 2 (cohort A2): midostaurin 100 mg bid from Day 8 to Day 21
- Amendments 3 + 4 (cohort A3/4): midostaurin 50 mg bid from Day 8 to Day 21

Arm 2 (concomitant administration):

- Core + Amendment 1 (cohort C+A1): midostaurin 100 mg bid from Day 1 to Day 28
- Amendment 2 (cohort A2): midostaurin 100 mg bid from Day 1 to Day 7 and from Day 15 to Day 21
- Amendments 3 + 4 (cohort A3/4): midostaurin 50 mg bid from Day 1 to Day 7 and from Day 15 to Day 21.

Due to the change in the administration schedule for midostaurin, the data were analyzed separately for the 3 cohorts in each arm, as well as overall for each arm.

Centers

Six study centers in 2 countries: USA (4 sites) and Germany (2 sites).

Publication

Stone RM, Fisher T, Paquette R et al (2012) Phase IB study of the FLT3 kinase inhibitor midostaurin with chemotherapy in younger newly diagnosed adult patients with acute myeloid leukemia. Leukemia; 26:2061-8.

Objectives:

Primary

- To evaluate the safety, tolerability, and pharmacokinetics (PK) of midostaurin administered sequentially or concomitantly with standard induction daunorubicin and cytarabine therapy followed by consolidation therapy with high dose cytarabine in patients with newly diagnosed AML.

Secondary

- Determine the efficacy of these regimens

Test Product (s), Dose(s), and Mode(s) of Administration

Midostaurin 50 mg or 100 mg twice daily orally.

Statistical Methods

Efficacy: Evaluation of efficacy was a secondary objective. The main efficacy endpoint was complete response (CR). Only CRs that occurred on treatment or within 42 days of treatment discontinuation were included in the primary efficacy analysis. Overall survival (OS) was a secondary efficacy endpoint.

Pharmacokinetics: The plasma concentrations of midostaurin and its metabolites CGP62221 and CGP52421, of daunorubicin, and of cytarabine were summarized by time point. PK parameters were determined for daunorubicin plasma using a non-compartmental analysis.

Safety: Safety assessments consisted of monitoring and recording all adverse events (AEs), serious adverse events (SAEs), with their severity and relationship to study drug, regular monitoring of hematology, clinical chemistry, vital signs, Karnofsky performance status scores, chest x-ray, electrocardiogram (ECG), multigated adquisition (MUGA) scan, and echocardiogram. Tolerability, defined as the ability of the patient to complete the study, was also assessed.

Statistical methods: Data were summarized by cohort and by treatment arm with respect to demographic and baseline characteristics, efficacy, safety and PK measurements. The statistical analyses were descriptive only, and no statistical testing was planned.

Categorical data were summarized using frequencies and percentages. Continuous data were summarized using the number of patients with non-missing values, mean, standard deviation, median, 25th and 75th percentiles, and minimum and maximum values. Time-to-event

analyses were summarized using the number and percentage of patients at risk for the event and the number and percentage of patients censored. Kaplan-Meier estimates with 95% CIs were generated.

The intent-to-treat (ITT) population was defined as all patients who received at least one dose of study medication; the safety population was defined as all patients who received at least one dose of study medication and who had at least one post-baseline safety evaluation; the PK population was defined as all patients who received at least one dose of study medication and who had at least one evaluable PK sample.

All efficacy analyses were performed using the ITT population. All safety summaries were produced using the safety set.

CR and OS were also analyzed separately for patients with FLT3 (Fms-like Tyrosine Kinase-3) mutation-positive AML and for patients with FLT3 wild-type (WT) AML.

Study Population: Key Inclusion/Exclusion Criteria

Inclusion Criteria

- Patients must have been ≥ 18 and ≤ 60 years of age.
- Patients must have had newly diagnosed histologically documented AML according to WHO criteria.
- Patients must have had a Karnofsky Performance Status of ≥ 70.

Exclusion criteria

- Patients with known impairment of gastrointestinal (GI) function or GI disease that might have significantly altered the absorption of midostaurin.
- Patients with concurrent severe and/or uncontrolled medical condition that would have compromised participation in the study.
- Patients who had received any investigational agent within 30 days prior to Day 1.
- Patients who had had any surgical procedure within 14 days of Day 1;
- Patients who had had an ejection fraction of <50% as assessed by MUGA scan or echocardiogram within 14 days of Day 1;
- Patients with presence of pulmonary infiltrates;
- Patients who had any past history of or newly diagnosed myelodysplastic syndrome; history of myeloproliferative disease or secondary AML;
- Any patient who had prior chemotherapy or radiation therapy.

Participant Flow Table

Summary of patient disposition by treatment arm and cohort - all patients

Disposition Reason	100 mg (C+A1) n (%)	100 mg (A2) n (%)	50 mg (A3/4) n (%)	Total n (%)
Arm 1 (sequential)	**N = 7**	**N = 7**	**N = 20**	**N = 34**
Enrolled	7 (100.0)	7 (100.0)	20 (100.0)	34 (100.0)
Completed*	2 (28.6)	2 (28.6)	13 (65.0)	17 (50.0)
Discontinued study	5 (71.4)	5 (71.4)	7 (35.0)	17 (50.0)
Adverse event(s)	1 (14.3)	1 (14.3)	1 (5.0)	3 (8.8)
Unsatisfactory therapeutic effect	3 (42.9)	1 (14.3)	4 (20.0)	8 (23.5)
Subject's condition no longer requires study drug	0	0	2 (10.0)	2 (5.9)
Protocol violation	0	0	0	0
Subject withdrew consent	1 (14.3)	3 (42.9)	0	4 (11.8)
Arm 2 (concomitant)	**N = 7**	**N = 8**	**N = 20**	**N = 35**
Enrolled	7 (100.0)	8 (100.0)	20 (100.0)	35 (100.0)
Completed*	1 (14.3)	1 (12.5)	9 (45.0)	11 (31.4)
Discontinued study	6 (85.7)	7 (87.5)	11 (55.0)	24 (68.6)
Adverse event(s)	2 (28.6)	1 (12.5)	2 (10.0)	5 (14.3)
Unsatisfactory therapeutic effect	2 (28.6)	2 (25.0)	4 (20.0)	8 (22.9)
Subject's condition no longer requires study drug	0	1 (12.5)	2 (10.0)	3 (8.6)
Protocol violation	1 (14.3)	0	1 (5.0)	2 (5.7)
Subject withdrew consent	1 (14.3)	3 (37.5)	2 (10.0)	6 (17.1)

*Completed: as reported by the investigator.

Baseline Characteristics

Baseline characteristics by cohort - Arm 1 (sequential) - ITT population

		100 mg (C+A1)	100 mg (A2)	50 mg (A3/4)	Total
		N = 7	N = 7	N = 20	N = 34
Gender – n (%)	Male	2 (28.6)	4 (57.1)	11 (55.0)	17 (50.0)
	Female	5 (71.4)	3 (42.9)	9 (45.0)	17 (50.0)
Race – n (%)	Caucasian	4 (57.1)	6 (85.7)	19 (95.0)	29 (85.3)
	Black	1 (14.3)	0	0	1 (2.9)
	Other	2 (28.6)	1 (14.3)	1 (5.0)	4 (11.8)
Age (years)	n	7	7	20	34
	Mean	50.9	46.4	44.2	46.0
	SD	10.12	12.46	12.22	11.83
	Median	55.0	49.0	48.0	48.5
	Min, Max	31, 60	21, 58	20, 60	20, 60
FLT3 status*	FLT3 mutation positive	1 (14.3)	3 (42.9)	7 (35.0)	11 (32.4)
	Wild type	6 (85.7)	4 (57.1)	13 (65.0)	23 (67.6)

* FLT3 status as recorded in the eCRF

Baseline characteristics by cohort - Arm 2 (concomitant) - ITT population

		100 mg (C+A1)	100 mg (A2)	50 mg (A3/4)	Total
		N = 7	N = 8	N = 20	N = 35
Gender – n (%)	Male	0	4 (50.0)	13 (65.0)	17 (48.6)
	Female	7 (100.0)	4 (50.0)	7 (35.0)	18 (51.4)
Race – n (%)	Caucasian	5 (71.4)	8 (100.0)	16 (80.0)	29 (82.9)
	Black	2 (28.6)	0	0	2 (5.7)
	Oriental	0	0	1 (5.0)	1 (2.9)
	Other	0	0	3 (15.0)	3 (8.6)
Age (years)	n	7	8	20	35
	Mean	46.7	35.6	48.4	45.1
	SD	8.14	14.37	10.15	11.82
	Median	49.0	30.5	49.5	49.0
	Min, Max	31, 57	23, 60	25, 65	23, 65
FLT3 mutation status*	FLT3 mutation positive	0	2 (25.0)	6 (30.0)	8 (22.9)
	Wild type	7 (100.0)	6 (75.0)	14 (70.0)	27 (77.1)

* FLT3 status as recorded in the eCRF

Summary of Efficacy

Primary Outcome Result(s)

CR rate by treatment arm and cohort – ITT population

	100 mg (C+A1)	100 mg (A2)	50 mg (A3/4)	Total
	n (%)	n (%)	n (%)	n (%)
Arm 1 (sequential)	**N = 7**	**N = 7**	**N = 20**	**N = 34**
	n (%)	**n (%)**	**n (%)**	**n (%)**
Cycle 1	n=7 3 (42.9)	n=7 3 (42.9)	n=20 11 (55.0)	n=34 17 (50.0)
Cycle 2	n=1 0	n=1 0	n=3 0	n=5 0
Overall	n=7 3 (42.9)	n=7 3 (42.9)	n=20 12 (60.0)	n=34 18 (52.9)
Arm 2 (concomitant)	**N = 7**	**N = 8**	**N = 20**	**N = 35**
	n (%)	**n (%)**	**n (%)**	**n (%)**
Cycle 1	n=7 3 (42.9)	n=8 2 (25.0)	n=20 10 (50.0)	n=35 15 (42.9)
Cycle 2	n=0 0	n=0 0	n=5 2 (40.0)	n=5 2 (40.0)
Overall	n=7 3 (42.9)	n=8 3 (37.5)	n=20 15 (75.0)	n=35 21 (60.0)

n at Cycle 1 and overall included all ITT patients. n at cycle 2 included all patients who did not have CR by the end of cycle 1 and were dosed during cycle 2.

Only CRs which occurred on treatment or within 42 days of discontinuation were taken into account.

Note: 5 patients obtained a CR after Cycle 1 or Cycle 2, and within 42 days of discontinuation. These patients are counted in the total for Overall.

Secondary Outcome Result(s)

CR rate by FLT3 mutation and treatment arm – ITT population

	FLT3 mutation positive	FLT3 WT
	n (%)	n (%)
Arm 1 (sequential)	**N = 11**	**N = 23**
	n (%)	**n (%)**
Cycle 1	n=11 8 (72.7)	n=23 9 (39.1)
Cycle 2	n=1 0	n=4 0
Overall	n=11 9 (81.8)	n=23 9 (39.1)

	FLT3 mutation positive	FLT3 WT
	n (%)	n (%)
Arm 2 (concomitant)	**N = 8**	**N = 27**
	n (%)	**n (%)**
Cycle 1	n=8 5 (62.5)	n=27 10 (37.0)
Cycle 2	n=1 1 (100.0)	n=4 1 (25.0)
Overall	n=8 6 (75.0)	n=27 15 (55.6)

n at Cycle 1 and overall included all ITT patients. n at cycle 2 included all patients who did not have CR by the end of cycle 1 and were dosed during cycle 2

Only CRs which occurred on treatment or within 42 days of discontinuation were taken into account.

Note: 5 patients obtained a CR after Cycle 1 or Cycle 2, and within 42 days of discontinuation. These patients are counted in the total for Overall.

Overall survival by FLT3 mutation status – ITT population

	FLT3 mutation positive	FLT3 WT	Total
	N=19	N=50	N=69
Patient deaths – n (%)	12 (63.2)	29 (58.0)	41 (59.4)
Patients censored – n (%)	7 (36.8)	21 (42.0)	28 (40.6)
Number of days survived (#)			
Mean	1165.3	689.3	1098.0
Median	1044.0	619.0	814.0
(95% CI)	(423.00, NC)	(473.00, NC)	(506.00, NC)

(#) Based on Kaplan-Meier survival estimates. 95% CI is on the median.
NC=not calculable

Summary of Safety

Safety Results

Adverse events by system organ class – Arm 1 (sequential) – safety population

	100 mg (C+A1)	100 mg (A2)	50 mg (A3/4)	Total
	n (%)	n (%)	n (%)	n (%)
System organ class	**N = 7**	**N = 7**	**N = 20**	**N = 34**
Any primary system organ class	7 (100.0)	7 (100.0)	20 (100.0)	34 (100.0)
Gastrointestinal disorders	7 (100.0)	7 (100.0)	19 (95.0)	33 (97.1)
Blood and lymphatic system disorders	7 (100.0)	6 (85.7)	19 (95.0)	32 (94.1)

System organ class	100 mg (C+A1) n (%) N = 7	100 mg (A2) n (%) N = 7	50 mg (A3/4) n (%) N = 20	Total n (%) N = 34
General disorders and administration site conditions	7 (100.0)	5 (71.4)	20 (100.0)	32 (94.1)
Skin and subcutaneous tissue disorders	6 (85.7)	7 (100.0)	17 (85.0)	30 (88.2)
Infections and infestations	7 (100.0)	5 (71.4)	17 (85.0)	29 (85.3)
Metabolism and nutrition disorders	7 (100.0)	7 (100.0)	15 (75.0)	29 (85.3)
Respiratory, thoracic and mediastinal disorders	7 (100.0)	5 (71.4)	15 (75.0)	27 (79.4)
Psychiatric disorders	4 (57.1)	5 (71.4)	15 (75.0)	24 (70.6)
Musculoskeletal and connective tissue disorders	4 (57.1)	5 (71.4)	14 (70.0)	23 (67.6)
Investigations	4 (57.1)	7 (100.0)	11 (55.0)	22 (64.7)
Nervous system disorders	3 (42.9)	4 (57.1)	15 (75.0)	22 (64.7)
Vascular disorders	2 (28.6)	3 (42.9)	14 (70.0)	19 (55.9)
Renal and urinary disorders	2 (28.6)	4 (57.1)	8 (40.0)	14 (41.2)
Eye disorders	2 (28.6)	4 (57.1)	5 (25.0)	11 (32.4)
Injury, poisoning and procedural complications	1 (14.3)	3 (42.9)	7 (35.0)	11 (32.4)
Cardiac disorders	3 (42.9)	4 (57.1)	3 (15.0)	10 (29.4)
Reproductive system and breast disorders	0	1 (14.3)	5 (25.0)	6 (17.6)
Ear and labyrinth disorders	0	1 (14.3)	3 (15.0)	4 (11.8)
Hepatobiliary disorders	0	0	3 (15.0)	3 (8.8)
Immune system disorders	0	0	1 (5.0)	1 (2.9)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0	0	1 (5.0)	1 (2.9)

A patient with multiple occurrences of an AE under one treatment is counted only once in the AE category for that treatment.

Adverse events by system organ class – Arm 2 (concomitant) – safety population

System organ class	100 mg (C+A1) n (%) N = 7	100 mg (A2) n (%) N = 8	50 mg (A3/4) n (%) N = 20	Total n (%) N = 35
Any primary system organ class	7 (100.0)	8 (100.0)	20 (100.0)	35 (100.0)
Gastrointestinal disorders	7 (100.0)	8 (100.0)	20 (100.0)	35 (100.0)
Blood and lymphatic system disorders	7 (100.0)	8 (100.0)	19 (95.0)	34 (97.1)

System organ class	100 mg (C+A1) n (%) N = 7	100 mg (A2) n (%) N = 8	50 mg (A3/4) n (%) N = 20	Total n (%) N = 35
Skin and subcutaneous tissue disorders	7 (100.0)	8 (100.0)	19 (95.0)	34 (97.1)
General disorders and administration site conditions	5 (71.4)	8 (100.0)	18 (90.0)	31 (88.6)
Infections and infestations	6 (85.7)	6 (75.0)	19 (95.0)	31 (88.6)
Metabolism and nutrition disorders	7 (100.0)	7 (87.5)	17 (85.0)	31 (88.6)
Nervous system disorders	5 (71.4)	6 (75.0)	15 (75.0)	26 (74.3)
Respiratory, thoracic and mediastinal disorders	5 (71.4)	4 (50.0)	16 (80.0)	25 (71.4)
Investigations	5 (71.4)	7 (87.5)	12 (60.0)	24 (68.6)
Vascular disorders	6 (85.7)	5 (62.5)	13 (65.0)	24 (68.6)
Psychiatric disorders	3 (42.9)	6 (75.0)	14 (70.0)	23 (65.7)
Injury, poisoning and procedural complications	0	3 (37.5)	11 (55.0)	14 (40.0)
Musculoskeletal and connective tissue disorders	4 (57.1)	3 (37.5)	7 (35.0)	14 (40.0)
Cardiac disorders	2 (28.6)	1 (12.5)	10 (50.0)	13 (37.1)
Eye disorders	1 (14.3)	3 (37.5)	9 (45.0)	13 (37.1)
Renal and urinary disorders	4 (57.1)	3 (37.5)	6 (30.0)	13 (37.1)
Reproductive system and breast disorders	2 (28.6)	3 (37.5)	4 (20.0)	9 (25.7)
Hepatobiliary disorders	3 (42.9)	2 (25.0)	3 (15.0)	8 (22.9)
Immune system disorders	0	1 (12.5)	4 (20.0)	5 (14.3)
Ear and labyrinth disorders	2 (28.6)	1 (12.5)	1 (5.0)	4 (11.4)
Endocrine disorders	0	0	2 (10.0)	2 (5.7)

A patient with multiple occurrences of an AE under one treatment is counted only once in the AE category for that treatment.

Most frequently reported adverse events by preferred term – Arm 1 (sequential) – safety population

Preferred term	100 mg (C+A1) n (%) N = 7	100 mg (A2) n (%) N = 7	50 mg (A3/4) n (%) N = 20	Total n (%) N = 34
Any adverse event	7 (100.0)	7 (100.0)	20 (100.0)	34 (100.0)
Nausea	5 (71.4)	7 (100.0)	17 (85.0)	29 (85.3)
Diarrhoea	7 (100.0)	6 (85.7)	15 (75.0)	28 (82.4)
Thrombocytopenia	5 (71.4)	5 (71.4)	16 (80.0)	26 (76.5)

Preferred term	100 mg (C+A1) n (%) N = 7	100 mg (A2) n (%) N = 7	50 mg (A3/4) n (%) N = 20	Total n (%) N = 34
Vomiting	6 (85.7)	5 (71.4)	14 (70.0)	25 (73.5)
Pyrexia	7 (100.0)	1 (14.3)	15 (75.0)	23 (67.6)
Hypokalaemia	6 (85.7)	3 (42.9)	12 (60.0)	21 (61.8)
Neutropenia	3 (42.9)	5 (71.4)	12 (60.0)	20 (58.8)
Chills	5 (71.4)	4 (57.1)	9 (45.0)	18 (52.9)
Febrile neutropenia	4 (57.1)	5 (71.4)	9 (45.0)	18 (52.9)
Headache	3 (42.9)	3 (42.9)	11 (55.0)	17 (50.0)
Anaemia	4 (57.1)	0	12 (60.0)	16 (47.1)
Constipation	4 (57.1)	3 (42.9)	9 (45.0)	16 (47.1)
Abdominal pain	1 (14.3)	3 (42.9)	11 (55.0)	15 (44.1)
Petechiae	3 (42.9)	2 (28.6)	10 (50.0)	15 (44.1)
Insomnia	2 (28.6)	3 (42.9)	9 (45.0)	14 (41.2)
Cough	2 (28.6)	2 (28.6)	9 (45.0)	13 (38.2)
Hypomagnesaemia	4 (57.1)	3 (42.9)	6 (30.0)	13 (38.2)
Rash	4 (57.1)	3 (42.9)	6 (30.0)	13 (38.2)
Oedema peripheral	4 (57.1)	3 (42.9)	5 (25.0)	12 (35.3)
Alanine aminotransferase increased	2 (28.6)	2 (28.6)	7 (35.0)	11 (32.4)
Aspartate aminotransferase increased	2 (28.6)	3 (42.9)	6 (30.0)	11 (32.4)
Decreased appetite	3 (42.9)	2 (28.6)	6 (30.0)	11 (32.4)
Blood bilirubin increased	1 (14.3)	5 (71.4)	4 (20.0)	10 (29.4)
Depression	0	2 (28.6)	8 (40.0)	10 (29.4)
Epistaxis	1 (14.3)	2 (28.6)	7 (35.0)	10 (29.4)
Hyponatraemia	1 (14.3)	3 (42.9)	6 (30.0)	10 (29.4)
Alopecia	3 (42.9)	2 (28.6)	4 (20.0)	9 (26.5)
Anxiety	2 (28.6)	2 (28.6)	5 (25.0)	9 (26.5)
Back pain	2 (28.6)	1 (14.3)	5 (25.0)	8 (23.5)
Hypotension	1 (14.3)	3 (42.9)	4 (20.0)	8 (23.5)
Leukopenia	0	1 (14.3)	7 (35.0)	8 (23.5)
Tachycardia	3 (42.9)	3 (42.9)	2 (10.0)	8 (23.5)
Arthralgia	1 (14.3)	2 (28.6)	4 (20.0)	7 (20.6)
Fatigue	2 (28.6)	0	5 (25.0)	7 (20.6)
Haemorrhoids	0	2 (28.6)	5 (25.0)	7 (20.6)
Hypoalbuminaemia	0	2 (28.6)	5 (25.0)	7 (20.6)
Oropharyngeal pain	1 (14.3)	1 (14.3)	5 (25.0)	7 (20.6)

A patient with multiple occurrences of an AE under one treatment is counted only once in the AE

Preferred term	100 mg (C+A1) n (%) N = 7	100 mg (A2) n (%) N = 7	50 mg (A3/4) n (%) N = 20	Total n (%) N = 34
category for that treatment.				

Most frequently reported adverse events by preferred term – Arm 2 (concomitant) – safety population

Preferred term	100 mg (C+A1) n (%) N = 7	100 mg (A2) n (%) N = 8	50 mg (A3/4) n (%) N = 20	Total n (%) N = 35
Any adverse event	7 (100.0)	8 (100.0)	20 (100.0)	35 (100.0)
Nausea	7 (100.0)	8 (100.0)	17 (85.0)	32 (91.4)
Febrile neutropenia	5 (71.4)	4 (50.0)	18 (90.0)	27 (77.1)
Thrombocytopenia	5 (71.4)	7 (87.5)	14 (70.0)	26 (74.3)
Vomiting	6 (85.7)	7 (87.5)	13 (65.0)	26 (74.3)
Diarrhoea	4 (57.1)	7 (87.5)	13 (65.0)	24 (68.6)
Hypokalaemia	5 (71.4)	5 (62.5)	13 (65.0)	23 (65.7)
Headache	2 (28.6)	3 (37.5)	11 (55.0)	16 (45.7)
Hypomagnesaemia	4 (57.1)	3 (37.5)	9 (45.0)	16 (45.7)
Hypotension	6 (85.7)	2 (25.0)	8 (40.0)	16 (45.7)
Chills	2 (28.6)	4 (50.0)	8 (40.0)	14 (40.0)
Hypocalcaemia	3 (42.9)	3 (37.5)	8 (40.0)	14 (40.0)
Neutropenia	1 (14.3)	2 (25.0)	11 (55.0)	14 (40.0)
Oedema peripheral	2 (28.6)	3 (37.5)	9 (45.0)	14 (40.0)
Pyrexia	3 (42.9)	3 (37.5)	8 (40.0)	14 (40.0)
Constipation	2 (28.6)	2 (25.0)	9 (45.0)	13 (37.1)
Insomnia	1 (14.3)	2 (25.0)	10 (50.0)	13 (37.1)
Rash	0	4 (50.0)	9 (45.0)	13 (37.1)
Alopecia	2 (28.6)	3 (37.5)	7 (35.0)	12 (34.3)
Anaemia	3 (42.9)	3 (37.5)	6 (30.0)	12 (34.3)
Abdominal pain	5 (71.4)	3 (37.5)	3 (15.0)	11 (31.4)
Petechiae	1 (14.3)	3 (37.5)	7 (35.0)	11 (31.4)
Alanine aminotransferase increased	1 (14.3)	5 (62.5)	4 (20.0)	10 (28.6)
Aspartate aminotransferase increased	1 (14.3)	5 (62.5)	4 (20.0)	10 (28.6)
Blood bilirubin increased	1 (14.3)	4 (50.0)	5 (25.0)	10 (28.6)
Cough	1 (14.3)	3 (37.5)	6 (30.0)	10 (28.6)
Pleural effusion	2 (28.6)	3 (37.5)	5 (25.0)	10 (28.6)
Hypoxia	0	2 (25.0)	7 (35.0)	9 (25.7)

Preferred term	100 mg (C+A1) n (%) N = 7	100 mg (A2) n (%) N = 8	50 mg (A3/4) n (%) N = 20	Total n (%) N = 35
Back pain	3 (42.9)	3 (37.5)	2 (10.0)	8 (22.9)
Epistaxis	1 (14.3)	2 (25.0)	5 (25.0)	8 (22.9)
Hyperglycaemia	1 (14.3)	4 (50.0)	3 (15.0)	8 (22.9)
Abdominal distension	3 (42.9)	2 (25.0)	2 (10.0)	7 (20.0)
Anxiety	1 (14.3)	2 (25.0)	4 (20.0)	7 (20.0)
Asthenia	2 (28.6)	1 (12.5)	4 (20.0)	7 (20.0)
Decreased appetite	1 (14.3)	1 (12.5)	5 (25.0)	7 (20.0)
Fatigue	0	2 (25.0)	5 (25.0)	7 (20.0)
Haematuria	3 (42.9)	2 (25.0)	2 (10.0)	7 (20.0)
Hypoalbuminaemia	0	4 (50.0)	3 (15.0)	7 (20.0)
Hypophosphataemia	0	2 (25.0)	5 (25.0)	7 (20.0)
Pneumonia	2 (28.6)	1 (12.5)	4 (20.0)	7 (20.0)
Procedural pain	0	2 (25.0)	5 (25.0)	7 (20.0)
Pruritus	0	0	7 (35.0)	7 (20.0)
Transfusion reaction	0	2 (25.0)	5 (25.0)	7 (20.0)

A patient with multiple occurrences of an AE under one treatment is counted only once in the AE category for that treatment.

Deaths, serious adverse events, and adverse events leading to discontinuation – safety population

Event*	100 mg (C+A1) n (%)	100 mg (A2) n (%)	50 mg (A3/4) n (%)	Total n (%)
Arm 1 (sequential)	**N = 7**	**N = 7**	**N = 20**	**N = 34**
Deaths	0	1 (14.3)	0	1 (2.9)
Drug-related deaths during induction phase	0	0	0	0
SAEs	5 (71.4)	5 (71.4)	10 (50.0)	20 (58.8)
Discontinued due to AEs	1 (14.3)	1 (14.3)	1 (5.0)	3 (8.8)
Other significant events	7 (100.0)	7 (100.0)	20 (100.0)	34 (100.0)
Arm 2 (concomitant)	**N = 7**	**N = 8**	**N = 20**	**N = 35**
Deaths	0	0	0	0
Drug-related deaths during induction phase	0	0	0	0
SAEs	7 (100.0)	4 (50.0)	16 (80.0)	27 (77.1)
Discontinued due to AEs	2 (28.6)	1 (12.5)	2 (10.0)	5 (14.3)
Other significant events	7 (100.0)	8 (100.0)	20 (100.0)	35 (100.0)

*Events are not mutually exclusive.
Other significant AEs are those that caused discontinuation, dose adjustment/interruption, or required significant additional therapy.

Serious adverse events (>5% in the total column) regardless of study drug relationship by preferred term – safety population

Preferred term	100 mg (C+A1) n (%)	100 mg (A2) n (%)	50 mg (A3/4) n (%)	Total n (%)
Arm 1 (sequential)	**N = 7**	**N = 7**	**N = 20**	**N = 34**
Any SAE	5 (71.4)	5 (71.4)	10 (50.0)	20 (58.8)
Febrile neutropenia	4 (57.1)	3 (42.9)	7 (35.0)	14 (41.2)
Aspartate aminotransferase increased	2 (28.6)	1 (14.3)	0	3 (8.8)
Alanine aminotransferase increased	1 (14.3)	1 (14.3)	0	2 (5.9)
Pyrexia	0	0	2 (10.0)	2 (5.9)
Bacterial sepsis	0	1 (14.3)	1 (5.0)	2 (5.9)
Pneumonia	2 (28.6)	0	0	2 (5.9)
Hypotension	1 (14.3)	0	1 (5.0)	2 (5.9)
Arm 2 (concomitant)	**N = 7**	**N = 8**	**N = 20**	**N = 35**
Any SAE	7 (100.0)	4 (50.0)	16 (80.0)	27 (77.1)
Febrile neutropenia	4 (57.1)	2 (25.0)	8 (40.0)	14 (40.0)
Nausea	3 (42.9)	1 (12.5)	0	4 (11.4)

Preferred term	100 mg (C+A1) n (%)	100 mg (A2) n (%)	50 mg (A3/4) n (%)	Total n (%)
Thrombocytopenia	0	0	3 (15.0)	3 (8.6)
Vomiting	2 (28.6)	1 (12.5)	0	3 (8.6)
Bacterial sepsis	0	0	3 (15.0)	3 (8.6)
Pneumonia	0	0	3 (15.0)	3 (8.6)
Atrial fibrillation	0	0	2 (10.0)	2 (5.7)
Generalized oedema	0	1 (12.5)	1 (5.0)	2 (5.7)
Pyrexia	2 (28.6)	0	0	2 (5.7)
Sepsis	0	1 (12.5)	1 (5.0)	2 (5.7)
Transfusion reaction	0	1 (12.5)	1 (5.0)	2 (5.7)
Aspartate aminotransferase increased	1 (14.3)	1 (12.5)	0	2 (5.7)
Blood bilirubin increased	1 (14.3)	1 (12.5)	0	2 (5.7)
Dehydration	2 (28.6)	0	0	2 (5.7)
Depressed level of consciousness	1 (14.3)	0	1 (5.0)	2 (5.7)
Renal failure acute	1 (14.3)	0	1 (5.0)	2 (5.7)
Respiratory failure	0	0	2 (10.0)	2 (5.7)
Deep vein thrombosis	1 (14.3)	0	1 (5.0)	2 (5.7)

A patient with multiple occurrences of an AE under one treatment is counted only once in the AE category for that treatment

Other Relevant Findings

Tolerability to study medication – safety population

Event*	100 mg (C+A1) n (%)	100 mg (A2) n (%)	50 mg (A3/4) n (%)	Total n (%)
Arm 1 (sequential)	**N = 7**	**N = 7**	**N = 20**	**N = 34**
Tolerability	5 (71.4)	3 (42.9)	19 (95.0)	27 (79.4)
Arm 2 (concomitant)	**N = 7**	**N = 8**	**N = 20**	**N = 35**
Tolerability	3 (42.9)	4 (50.0)	15 (75.0)	22 (62.9)

Note: Tolerability is the ability of a patient to complete the study (i.e. complete up to 2 cycles of induction and 3 cycles of consolidation therapy given with midostaurin, unless discontinued for reasons specifically related to disease e.g. lack of remission, or death due to leukemia, while on study). Patients who died or discontinued prior to completion due to disease reasons (lack of remission) are also included in the count.

Summary of daunorubicin PK parameter comparison (alone versus combined with midostaurin)

Daunorubicin PK parameters (adjusted geometric mean)	**Midostaurin 100 mg bid (C+A1, A2)**			**Midostaurin 50 mg bid (A3/A4)**		
	Concomitant arm (n=11)	Sequential arm (n=7)	conc:seq Geometric mean ratio [90%CI]	Concomitant arm (n=16)	Sequential arm (n=14)	conc:seq Geometric mean ratio [90%CI]
AUC0-24 (ng.h/mL)	139.51	328.08	0.43 [0.16-1.12]	205.88	210.82	0.98 [0.56-1.69]
Cmax (ng/mL)	80.89	180.15	0.45 [0.23-0.86]	97.08	89.33	1.09 [0.63-1.86]

Conc: concomitant arm (daunorubicin + midostaurin)
Seq: sequential arm (daunorubicin alone)

Conclusions:

The initial dosing regimen of midostaurin 100 mg bid was poorly tolerated and was associated with a high rate of treatment discontinuation. Following optimization of the midostaurin dosing regimen, administration of midostaurin 50 mg bid (cohort A3/4) was associated with an acceptable safety and tolerability profile. The tolerability of sequential administration (Arm 1) was slightly higher than that of concomitant administration (Arm 2).

For all dosing schedules considered together, the CR rate was 52.9% and 60.0% in Arm 1 and Arm 2, respectively. Overall, the CR rate was higher for patients with FLT3 mutation-positive AML (78.9%) compared to that for patients with WT FLT3 AML (48.0%). The median OS was also longer in patients with FLT3 mutation-positive AML (~2.9 years) compared to that for patients with WT FLT3 AML (~1.7 years).

No effect of midostaurin was observed on cytarabine plasma concentrations, whereas exposure to daunorubicin appeared to decrease 2-fold at the 100 mg bid midostaurin dose. However, the large variability in the PK parameters for daunorubicin did not allow for a firm conclusion that this decrease was caused by a drug-drug interaction. The PK of midostaurin was not affected by the co-administration of daunorubicin and cytarabine.

Based on its acceptable safety and tolerability profile, the midostaurin 50 mg bid sequential regimen is considered to be the recommended regimen for further clinical investigation in AML.

Date of Clinical Trial Report

22 January 2015