Sponsor

Novartis Pharma GmbH

Generic Drug Name

Imatinib mesylate, STI571

Therapeutic Area of Trial

Advanced breast carcinoma

Approved Indication

- Indicated for the treatment of patients (adults and children) with CML (Ph+), who are not suitable for stem cell transplantation as first line therapy, in the chronic phase after failure of IFNalpha therapy, in the accelerate phase or in the status of blasten crisis
- Indicated for the treatment of adult patients with new diagnosed Ph+ ALL in combination with chemotherapy
- Indicated for the treatment of adult patients with recurrent or refractory Ph+ ALL as monotherapy
- Indicated for the treatment of adult patients with MDS/MPD together with gene alterations of the PDGF-receptor
- Indicated for the treatment of adult patients with HES or chronic eosinophilic leucemia with FIP1L1-PDGFRz-Alterations
- Indicated for the treatment of adult patients with c-Kit +, not removable and/or metastatic malignant GIST tumors
- Indicated for the adjuvant treatment of adult patients with significant risk of a relapse after resection of cKit + GIST tumors
- Indicated for the treatment of adult patients with not removable, or relapsed and/or metastatic DFSP where no operation is taken into account

Protocol Number

CSTI571BDE28

Title

Open-label Trial of Imatinib mesylate in combination with Vinorelbine for patients with advanced breast carcinoma: ICON

Study Phase

Phase I

Study Start/End Dates

22-Jun-2006 to 05-Jul-2012

On 18-Nov-2011, only 1 patient was still under treatment. At this point, data collection in this study was considered sufficient for an evaluation of the study objectives. In February 2012 an interim analysis was performed. This report describes the results of the final analysis with data cut-off on 05-July-2012.

Study Design/Methodology

This study was an open-label, single arm, phase I dose escalating study combining imatinib mesylate with vinorelbine weekly for patients with locally advanced or metastasized breast carcinoma. Patients were supposed to be in a second or third line situation, after progression on a previous standard 1st line therapy. Tumors of patients included were required to express PDGF-receptor-α and/ or -β and/or c-kit. If possible, the malignant lesions should have been accessible from the body surface for biopsies (e.g. from skin metastasis and/or recurrent disease of the breast or thoracic wall).

Centers

1 center in 1 country: Germany (1)

Objectives

Primary objective was to assess the safety and tolerability of imatinib in combination with vinorelbine in patients with progressive or metastatic breast cancer.

Secondary objectives were to evaluate the:

- Clinical activity of the combination as best overall response (at least partial response [PR], according to Southwestern Oncology Group [SWOG]) and time to disease progression (TTP)
- Quality of life (acc. to the European Organization for Research and Treatment of Cancer [EORTC] QLQ-C30 and QLQ-BR23 questionnaire)
- Biological activity of the combination by pharmacogenetic measurements as described in the Pharmacogenetics Section of the study protocol (not subject to this report)

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

Dose escalation was to be performed as follows:

1 At dose Level 1 (40% level) patients received single drug imatinib 400 mg daily p.o. in combination with vinorelbine 10 mg/m^2 weekly i.v.

2 The second (60% level) level combined imatinib 400 mg daily p.o. and vinorelbine 15 mg/m^2 weekly i.v.

3 This was followed by a third level (80% level) combining imatinib 400 mg daily p.o. and vinorelbine 20 mg/m^2 weekly i.v.

4 Patients at the final dose level (100% level) received imatinib 400 mg daily p.o. and vinorelbine 25 mg/m^2 weekly i.v.

Statistical Methods

Analysis populations were defined as follows: The safety population included all patients who received at least one dose of imatinib or vinorelbine. The (intent to treat) ITT population included all enrolled patients who received at least one dose of imatinib+vinorelbine. The efficacy analyzable population consisted of all patients who received the study drug combination for at least 3 weeks.

Efficacy evaluation: Best overall response: The crude response rate was calculated based on the investigator's assessment. A Kaplan-Meier estimator together with the corresponding 95% confidence interval (CI) was additionally presented.

TTP was presented as Kaplan-Meier curve and median time to progression was planned to be compared against historical controls.

Safety evaluation: AEs were summarized by presenting the number and percentage of patients having any AE, having any AE in each primary system organ class and having

each individual AE based on preferred term and maximum severity using the Common Toxicity Criteria (CTC) grade (CTCAE Version 3.0). Multiple AEs within a PT and CTC grade and within a body system were only counted once. All other information collected (e.g., relationship to study treatment, action taken) were tabulated and listed as appropriate. AEs that led to death or to discontinuation or were otherwise classified as dose limiting were presented separately and if appropriate were summarized by primary system organ class and preferred term. Laboratory data were summarized presenting summary statistics for raw data and change from baseline values to last available value under combination therapy. Additionally, rates of patients with clinically significant abnormalities based on the investigator's assessment were presented. Changes between investigator's assessment at Baseline and at the last available assessment under combination therapy were presented by shift tables.

Quality of life (EORTC QLQ-C30 and QLQ-BR23 questionnaire) was analyzed presenting sample statistics for the course using the ITT population. Cancer-related symptoms were assessed at Baseline and thereafter according to the visit schedule. Changes in cancer-related symptoms were summarized.

An interim analysis was performed in February 2012.

Study Population: Inclusion/Exclusion Criteria and Demographics

Number of patients: In step 1 up to 20 patients were planned to be entered to 4 dose levels (up to 5 patients per level). Dose escalation (recruiting patients to the next higher dose level) was to be performed if ≤ 1/5 patients had to discontinue study treatment due to non acceptable toxicity. After recruiting 5 patients for the highest dose level, in a second step 10 additional patients were planned to be entered to receive the highest tolerable dose of drug combination.

A total of 33 patients entered the study and received study medication.

Indication and main criteria for inclusion:

- Women ≥ 18 years of age
- Histologically documented diagnosis of invasive breast cancer which was locally advanced or metastatic and with progression on previous 1st line standard treatment
- Immunohistochemical documentation of c-kit (CD117) and/or platelet-derived growth factor (PDGF)-receptor expression by the tumor, at least 1 measurable site of disease, Eastern Cooperative Oncology Group (ECOG) performance status of 0, 1 or 2, adequate end organ function according to defined criteria
- Exclusion of pregnancy/use of contraceptive measures and written informed consent.

Key exclusion criteria:

- Grade III/IV cardiac problems as defined by the New York Heart Association Criteria
- Severe and/or uncontrolled medical disease
- Known brain metastasis
- Rapidly progressing visceral metastases requiring other chemotherapy schedules
- Chronic liver disease
- Human immunodeficiency virus (HIV) infection
- Treatment with either vinorelbine or imatinib in previous treatment regimens

Participant Flow

	Imatinib / Vinorelbine					
	600 mg / 10 mg/m^2	**400 mg / 10 mg/m^2**	**400 mg / 15 mg/m^2**	**400 mg / 20 mg/m^2**	**400 mg / 25 mg/m^2**	**Total**
Number (%) of patients						
Treated (safety popul.)	6 (100.0)	5 (100.0)	10 (100.0)	6 (100.0)	6 (100.0)	33 (100.0)
Completed	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (16.7)	1 (3.0)
Reason for discont.:						
Adverse event(s)	5 (83.3)	1 (20.0)	2 (20.0)	0 (0.0)	2 (33.3)	10 (30.3)
Unsatisf. therap. effect	0 (0.0)	4 (80.0)	5 (50.0)	3 (50.0)	2 (33.3)	14 (42.4)
Consent withdrawn	1 (16.7)	0 (0.0)	2 (20.0)	3 (50.0)	1 (16.7)	7 (21.2)
Death	0 (0.0)	0 (0.0)	1 (10.0)	0 (0.0)	0 (0.0)	1 (3.0)
ITT population	6 (100.0)	5 (100.0)	9 (90.0)	6 (100.0)	6 (100.0)	32 (97.0)
Efficacy analyzable pop.	3 (50.0)	5 (100.0)	5 (50.0)	4 (66.7)	5 (83.3)	22 (66.7)

Note: Imatinib dose was reduced from 600 to 400 mg via Amendment 2 in order to improve tolerability of study treatment. Patient (400 mg / 15 mg/m^2) who received only 1 of the 2 study drugs was excluded from the ITT and efficacy analyzable populations.

Baseline Characteristics

	Imatinib / Vinorelbine					
	600 mg / 10 mg/m^2 (N=6)	**400 mg / 10 mg/m^2 (N=5)**	**400 mg / 15 mg/m^2 (N=10)**	**400 mg / 20 mg/m^2 (N=6)**	**400 mg / 25 mg/m^2 (N=6)**	**Total (N=33)**
Race - n (%)						
Caucasian	6 (100.0)	5 (100.0)	10 (100.0)	6 (100.0)	6 (100.0)	33 (100.0)
Age (years)						
Mean ± SD	60.5 ± 11.0	57.0 ± 7.2	62.1 ± 5.5	59.8 ± 6.7	60.0 ± 9.8	60.2 ± 7.7
Median	64.5	58.0	60.5	61.0	61.0	61.0
Range	45–70	46–66	57–71	47–66	42–71	42–71
Age cat. - n (%)						
< 65 years	3 (50.0)	4 (80.0)	7 (70.0)	5 (83.3)	4 (66.7)	23 (69.7)
≥ 65 years	3 (50.0)	1 (20.0)	3 (30.0)	1 (16.7)	2 (33.3)	10 (30.3)
BMI (kg/m^2)						
Mean ± SD	27.3 ± 4.4	26.1 ± 3.8	24.7 ± 5.1	25.3 ± 2.2	24.9 ± 4.8	25.5 ± 4.2
Median	27.0	24.5	24.9	24.5	22.9	24.5
Range	21.9–33.1	22.0–30.6	17.0–32.7	23.1–29.1	20.6–31.6	17.0–33.1
ECOG status - n (%)						
0	2 (33.3)	1 (33.3)	3 (60.0)	3 (100.0)	1 (100.0)	10 (55.6)
1	4 (66.7)	2 (66.7)	2 (40.0)	0 (0.0)	0 (0.0)	8 (44.4)
Missing	0	2	5	3	5	15

Abbreviations: ECOG= Eastern Cooperative Oncology Group

Safety Results

Adverse events with relationship to Glivec, by primary system organ class, preferred term and treatment

Primary system organ class Preferred term	Imatinib 600/ Vinorelb. 10 (N= 6)	Imatinib 400/ Vinorelb. 10 (N= 5)	Imatinib 400/ Vinorelb. 15 (N=10)	Imatinib 400/ Vinorelb. 20 (N= 6)	Imatinib 400/ Vinorelb. 25 (N= 6)	Total (N=33)
Any primary system organ class	6 (100.0%)	3 (60.0%)	10 (100.0%)	4 (66.7%)	5 (83.3%)	28 (84.8%)
BLOOD AND LYMPHATIC SYSTEM DISORDERS						
-Total	1 (16.7%)	-	-	-	1 (16.7%)	2 (6.1%)
ANAEMIA	1 (16.7%)	-	-	-	-	1 (3.0%)
FEBRILE NEUTROPENIA	-	-	-	-	1 (16.7%)	1 (3.0%)
EAR AND LABYRINTH DISORDERS						
-Total	-	-	-	-	1 (16.7%)	1 (3.0%)
VERTIGO	-	-	-	-	1 (16.7%)	1 (3.0%)
EYE DISORDERS						
-Total	-	1 (20.0%)	1 (10.0%)	-	1 (16.7%)	3 (9.1%)
EYE OEDEMA	-	-	-	-	1 (16.7%)	1 (3.0%)
EYELID OEDEMA	-	-	1 (10.0%)	-	-	1 (3.0%)
PERIORBITAL OEDEMA	-	1 (20.0%)	-	-	-	1 (3.0%)
GASTROINTESTINAL DISORDERS						
-Total	6 (100.0%)	3 (60.0%)	7 (70.0%)	4 (66.7%)	4 (66.7%)	24 (72.7%)
ABDOMINAL PAIN	-	-	-	-	1 (16.7%)	1 (3.0%)
ABDOMINAL PAIN UPPER	1 (16.7%)	-	-	-	-	1 (3.0%)
DIARRHOEA	3 (50.0%)	-	2 (20.0%)	-	1 (16.7%)	6 (18.2%)
DYSPEPSIA	-	-	-	1 (16.7%)	1 (16.7%)	2 (6.1%)
NAUSEA	5 (83.3%)	3 (60.0%)	7 (70.0%)	4 (66.7%)	3 (50.0%)	22 (66.7%)
VOMITING	3 (50.0%)	1 (20.0%)	4 (40.0%)	2 (33.3%)	2 (33.3%)	12 (36.4%)

Primary system organ class Preferred term	Imatinib 600/ Vinorelb. 10 (N= 6)	Imatinib 400/ Vinorelb. 10 (N= 5)	Imatinib 400/ Vinorelb. 15 (N=10)	Imatinib 400/ Vinorelb. 20 (N= 6)	Imatinib 400/ Vinorelb. 25 (N= 6)	Total (N=33)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS						
-Total	2 (33.3%)	1 (20.0%)	1 (10.0%)	-	2 (33.3%)	6 (18.2%)
FATIGUE	1 (16.7%)	-	1 (10.0%)	-	1 (16.7%)	3 (9.1%)
OEDEMA	-	-	-	-	1 (16.7%)	1 (3.0%)
OEDEMA PERIPHERAL	1 (16.7%)	1 (20.0%)	-	-	-	2 (6.1%)
METABOLISM AND NUTRITION DISORDERS						
-Total	-	-	-	1 (16.7%)	1 (16.7%)	2 (6.1%)
DECREASED APPETITE	-	-	-	1 (16.7%)	1 (16.7%)	2 (6.1%)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS						
-Total	-	-	1 (10.0%)	-	-	1 (3.0%)
BONE PAIN	-	-	1 (10.0%)	-	-	1 (3.0%)
NERVOUS SYSTEM DISORDERS						
-Total	2 (33.3%)	-	1 (10.0%)	-	1 (16.7%)	4 (12.1%)
DYSGEUSIA	1 (16.7%)	-	1 (10.0%)	-	1 (16.7%)	3 (9.1%)
PERIPHERAL SENSORY NEUROPATHY	1 (16.7%)	-	-	-	-	1 (3.0%)
PSYCHIATRIC DISORDERS						
-Total	1 (16.7%)	-	-	-	-	1 (3.0%)
ANXIETY	1 (16.7%)	-	-	-	-	1 (3.0%)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS						
-Total	1 (16.7%)	-	-	-	-	1 (3.0%)
DYSPNOEA	1 (16.7%)	-	-	-	-	1 (3.0%)

Primary system organ class Preferred term	Imatinib 600/ Vinorelb. 10 (N= 6)	Imatinib 400/ Vinorelb. 10 (N= 5)	Imatinib 400/ Vinorelb. 15 (N=10)	Imatinib 400/ Vinorelb. 20 (N= 6)	Imatinib 400/ Vinorelb. 25 (N= 6)	Total (N=33)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS						
-Total	-	-	1 (10.0%)	-	-	1 (3.0%)
ERYTHEMA	-	-	1 (10.0%)	-	-	1 (3.0%)
VASCULAR DISORDERS						
-Total	-	1 (20.0%)	-	-	1 (16.7%)	2 (6.1%)
HOT FLUSH	-	-	-	-	1 (16.7%)	1 (3.0%)
LYMPHOEDEMA	-	1 (20.0%)	-	-	-	1 (3.0%)

Primary system organ classes are presented alphabetically; preferred terms are sorted within primary system organ class alphabetically. A patient with multiple occurrences of an AE under one treatment is counted only once in the AE category for that treatment.A patient with multiple adverse events within a primary system organ class is counted only once in the total row.

Adverse events with relationship to the combination Glivec/vinorelbine, by primary system organ class, preferred term and treatment

Primary system organ class Preferred term	Imatinib 600/ Vinorelb. 10 (N= 6)	Imatinib 400/ Vinorelb. 10 (N= 5)	Imatinib 400/ Vinorelb. 15 (N=10)	Imatinib 400/ Vinorelb. 20 (N= 6)	Imatinib 400/ Vinorelb. 25 (N= 6)	Total (N=33)
Any primary system organ class	2 (33.3%)	3 (60.0%)	7 (70.0%)	2 (33.3%)	4 (66.7%)	18 (54.5%)
BLOOD AND LYMPHATIC SYSTEM DISORDERS						
-Total	-	-	2 (20.0%)	2 (33.3%)	2 (33.3%)	6 (18.2%)
ANAEMIA	-	-	-	-	1 (16.7%)	1 (3.0%)
LEUKOPENIA	-	-	2 (20.0%)	2 (33.3%)	2 (33.3%)	6 (18.2%)
NEUTROPENIA	-	-	1 (10.0%)	-	-	1 (3.0%)
CARDIAC DISORDERS						
-Total	-	-	1 (10.0%)	-	-	1 (3.0%)
BUNDLE BRANCH BLOCK RIGHT	-	-	1 (10.0%)	-	-	1 (3.0%)
GASTROINTESTINAL DISORDERS						
-Total	1 (16.7%)	1 (20.0%)	1 (10.0%)	1 (16.7%)	2 (33.3%)	6 (18.2%)
ABDOMINAL PAIN UPPER	-	-	-	-	1 (16.7%)	1 (3.0%)
DIARRHOEA	-	-	1 (10.0%)	1 (16.7%)	-	2 (6.1%)
NAUSEA	1 (16.7%)	-	1 (10.0%)	-	1 (16.7%)	3 (9.1%)
STOMATITIS	-	1 (20.0%)	-	-	-	1 (3.0%)
VOMITING	-	1 (20.0%)	-	-	1 (16.7%)	2 (6.1%)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS						
-Total	-	3 (60.0%)	5 (50.0%)	1 (16.7%)	2 (33.3%)	11 (33.3%)
ASTHENIA	-	-	1 (10.0%)	-	-	1 (3.0%)
FATIGUE	-	2 (40.0%)	4 (40.0%)	1 (16.7%)	2 (33.3%)	9 (27.3%)
GAIT DISTURBANCE	-	-	-	-	1 (16.7%)	1 (3.0%)
PYREXIA	-	1 (20.0%)	1 (10.0%)	-	-	2 (6.1%)

Primary system organ class Preferred term	Imatinib 600/ Vinorelb. 10 (N= 6)	Imatinib 400/ Vinorelb. 10 (N= 5)	Imatinib 400/ Vinorelb. 15 (N=10)	Imatinib 400/ Vinorelb. 20 (N= 6)	Imatinib 400/ Vinorelb. 25 (N= 6)	Total (N=33)
INVESTIGATIONS						
-Total	-	1 (20.0%)	4 (40.0%)	1 (16.7%)	1 (16.7%)	7 (21.2%)
BLOOD POTASSIUM DECREASED	-	-	1 (10.0%)	-	-	1 (3.0%)
GRANULOCYTE COUNT DECREASED	-	-	-	1 (16.7%)	-	1 (3.0%)
HAEMOGLOBIN DECREASED	-	1 (20.0%)	3 (30.0%)	1 (16.7%)	1 (16.7%)	6 (18.2%)
LYMPHOCYTE COUNT DECREASED	-	-	2 (20.0%)	-	-	2 (6.1%)
LYMPHOCYTE COUNT INCREASED	-	-	-	1 (16.7%)	-	1 (3.0%)
PULSE ABNORMAL	-	-	1 (10.0%)	-	-	1 (3.0%)
WEIGHT DECREASED	-	1 (20.0%)	-	-	-	1 (3.0%)
METABOLISM AND NUTRITION DISORDERS						
-Total	-	-	1 (10.0%)	-	-	1 (3.0%)
DECREASED APPETITE	-	-	1 (10.0%)	-	-	1 (3.0%)
NERVOUS SYSTEM DISORDERS						
-Total	-	-	-	-	1 (16.7%)	1 (3.0%)
NEUROPATHY PERIPHERAL	-	-	-	-	1 (16.7%)	1 (3.0%)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS						
-Total	-	-	-	-	1 (16.7%)	1 (3.0%)
DYSPNOEA	-	-	-	-	1 (16.7%)	1 (3.0%)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS						
-Total	1 (16.7%)	-	1 (10.0%)	-	1 (16.7%)	3 (9.1%)
ALOPECIA	-	-	1 (10.0%)	-	1 (16.7%)	2 (6.1%)
PALMAR-PLANTAR ERYTHRODYSAESTHESIA SYNDROME	1 (16.7%)	-	-	-	-	1 (3.0%)

Primary system organ classes are presented alphabetically; preferred terms are sorted within primary system organ class alphabetically. A patient with multiple occurrences of an AE under one treatment is counted only once in the AE category for that treatment.A patient with multiple adverse events within a primary system organ class is counted only once in the total row.

Most Frequently Reported AEs Overall by Preferred Term n (%)

EORTC QLQ-C30 (ITT population)

			Total group (N=32)	
			n	Mean ± SD
Functional scales	Physical functioning	Baseline	24	72.1 ± 23.4
		Week 13	12	58.9 ± 23.2
	Role functioning	Baseline	24	63.9 ± 28.9
		Week 13	12	51.4 ± 30.5
	Emotional functioning	Baseline	24	66.0 ± 26.6
		Week 13	12	76.4 ± 18.7
	Cognitive functioning	Baseline	24	87.5 ± 16.5
		Week 13	12	86.1 ± 21.1
	Social functioning	Baseline	24	81.9 ± 22.5
		Week 13	12	69.4 ± 19.9
Symptom scales	Fatigue	Baseline	24	35.2 ± 19.6
		Week 13	12	49.1 ± 30.9
	Nausea/vomiting	Baseline	24	6.3 ± 15.4
		Week 13	12	16.7 ± 22.5
	Pain	Baseline	24	25.7 ± 24.1
		Week 13	12	25.0 ± 19.5
Single-item scales	Dyspnea	Baseline	24	33.3 ± 31.1
		Week XX	12	52.8 ± 36.1
	Insomnia	Baseline	24	30.6 ± 31.0
		Week 13	12	36.1 ± 33.2
	Appetite loss	Baseline	24	16.7 ± 26.0
		Week 13	12	33.3 ± 34.8
	Constipation	Baseline	24	6.9 ± 17.0
		Week 13	12	5.6 ± 13.0
	Diarrhea	Baseline	23	8.7 ± 18.0
		Week 13	12	22.2 ± 32.8
	Financial problems	Baseline	23	17.4 ± 31.6
		Week 13	11	21.2 ± 34.2
Global health status		Baseline	24	56.6 ± 21.6
		Week 13	12	55.6 ± 18.9

High scores indicate better health-related quality of life for the global health status and functional scales, and worse health-related quality of life for the symptom- and single-item scales.

EORTC QLQ-BR23 (ITT population)

			Total group (N=32)	
			n	Mean ± SD
Functional scales	**Body image**	Baseline	23	83.3 ± 23.8
		Week 13	12	86.8 ± 17.2
	Sexual functioning	Baseline	19	28.1 ± 31.9
		Week 13	10	25.0 ± 30.7
	Sexual enjoyment	Baseline	5	80.0 ± 18.3
		Week 13	4	41.7 ± 16.7
	Future perspective	Baseline	23	29.0 ± 33.8
		Week 13	12	52.8 ± 38.8
Symptom scales	**Arm symptoms**	Baseline	23	33.8 ± 27.3
		Week 13	12	24.1 ± 36.6
	Breast symptoms	Baseline	22	18.6 ± 24.9
		Week 13	12	6.3 ± 8.8
	Systematic therapy side-effects	Baseline	23	20.7 ± 16.1
		Week 13	12	26.3 ± 21.3
	Upset by hair loss	Baseline	20	15.0 ± 33.3
		Week 13	12	27.8 ± 42.2

High scores in the functional scales indicate high levels of functioning; high scores in the symptom scales indicate high levels of problems.

Number (%) of patients with most frequent AEs (>15% in total group) (safety population)

	Imatinib / Vinorelbine					
	600 mg / 10 mg/m^2	**400 mg / 10 mg/m^2**	**400 mg / 15 mg/m^2**	**400 mg / 20 mg/m^2**	**400 mg / 25 mg/m^2**	**Total**
Total number (%) of patients	6 (100.0)	5 (100.0)	10 (100.0)	6 (100.0)	6 (100.0)	33 (100.0)
Number (%) of patients with AE(s)	6 (100.0)	5 (100.0)	10 (100.0)	6 (100.0)	6 (100.0)	33 (100.0)
Total number of AEs	52	58	112	62	243	527
AE preferred term						
Nausea	6 (100.0)	4 (80.0)	9 (90.0)	5 (83.3)	5 (83.3)	29 (87.9)
Fatigue	2 (33.3)	4 (80.0)	7 (70.0)	2 (33.3)	5 (83.3)	20 (60.6)
Vomiting	3 (50.0)	2 (40.0)	5 (50.0)	3 (50.0)	3 (50.0)	16 (48.5)
Diarrhea	3 (50.0)	2 (40.0)	3 (30.0)	2 (33.3)	2 (33.3)	12 (36.4)
Dyspnea	1 (16.7)	2 (40.0)	5 (50.0)	1 (16.7)	3 (50.0)	12 (36.4)
Hemoglobin decreased	0 (0.0)	1 (20.0)	3 (30.0)	2 (33.3)	3 (50.0)	9 (27.3)
Leukopenia	0 (0.0)	0 (0.0)	2 (20.0)	3 (50.0)	4 (66.7)	9 (27.3)
Pain in extremity	0 (0.0)	2 (40.0)	4 (40.0)	1 (16.7)	2 (33.3)	9 (27.3)
Abdominal pain	0 (0.0)	1 (20.0)	1 (10.0)	2 (33.3)	3 (50.0)	7 (21.2)
Decreased appetite	1 (16.7)	0 (0.0)	2 (20.0)	1 (16.7)	2 (33.3)	6 (18.2)

	Imatinib / Vinorelbine					
	600 mg / 10 mg/m^2	**400 mg / 10 mg/m^2**	**400 mg / 15 mg/m^2**	**400 mg / 20 mg/m^2**	**400 mg / 25 mg/m^2**	**Total**
Pleural effusion	2 (33.3)	2 (40.0)	1 (10.0)	1 (16.7)	0 (0.0)	6 (18.2)
Pyrexia	1 (16.7)	2 (40.0)	1 (10.0)	1 (16.7)	1 (16.7)	6 (18.2)
AST increased	0 (0.0)	0 (0.0)	2 (20.0)	1 (16.7)	2 (33.3)	5 (15.2)
Blood LDH increased	1 (16.7)	0 (0.0)	2 (20.0)	1 (16.7)	1 (16.7)	5 (15.2)
Bone pain	0 (0.0)	0 (0.0)	2 (20.0)	2 (33.3)	1 (16.7)	5 (15.2)
Cough	0 (0.0)	0 (0.0)	2 (20.0)	1 (16.7)	2 (33.3)	5 (15.2)

Sort order is by decreasing incidence in the total group.
Abbreviations: AST= aspartate aminotransferase; LDH= lactate dehydrogenase

Serious Adverse Events and Deaths

Number (%) of patients who died, had other serious or clinically significant AEs or discontinued because of them (safety population)

	Imatinib / Vinorelbine					
	600 mg / 10 mg/m^2	**400 mg / 10 mg/m^2**	**400 mg / 15 mg/m^2**	**400 mg / 20 mg/m^2**	**400 mg / 25 mg/m^2**	**Total**
Total number (%) of patients	6 (100.0)	5 (100.0)	10 (100.0)	6 (100.0)	6 (100.0)	33 (100.0)
Number (%) of patients with						
AEs	6 (100.0)	5 (100.0)	10 (100.0)	6 (100.0)	6 (100.0)	33 (100.0)
AEs requiring dose adjustment or SD interruption	1 (16.7)	1 (20.0)	4 (40.0)	5 (83.3)	6 (100.0)	17 (51.5)
AEs causing SD discontinuation	5 (83.3)	1 (20.0)	2 (20.0)	0 (0.0)	2 (33.3)	10 (30.3)
AEs requiring significant additional therapy	6 (100.0)	4 (80.0)	9 (90.0)	6 (100.0)	6 (100.0)	31 (93.9)
AEs related to imatinib	6 (100.0)	3 (60.0)	10 (100.0)	4 (66.7)	5 (83.3)	28 (84.8)
AEs related to vinorelbine	0 (0.0)	3 (60.0)	3 (30.0)	2 (33.3)	4 (66.7)	12 (36.4)
AEs related to comb. imatinib/vinorelbine	2 (33.3)	3 (60.0)	7 (70.0)	2 (33.3)	4 (66.7)	18 (54.5)
SAEs	4 (66.7)	3 (60.0)	5 (50.0)	2 (33.3)	2 (33.3)	16 (48.5)
SAEs causing SD discontinuation	2 (33.3)	1 (20.0)	1 (10.0)	0 (0.0)	1 (16.7)	5 (15.2)
SAEs related to any SD	3 (50.0)[a]	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (9.1)
Deaths	0 (0.0)	2 (40.0)	2 (20.0)	0 (0.0)	0 (0.0)	4 (12.1)

[a]= All cases were suspected to be related to imatinib.
Abbreviations: SD= study drug

Other Relevant Findings

Not applicable

Date of Clinical Trial Report

15-Mar-2013

Date Inclusion on Novartis Clinical Trial Results Database

28-May-2013

Date of Latest Update