Sponsor

Novartis Pharma GmbH Germany

Generic Drug Name

Imatinib mesylate
Everolimus

Therapeutic Area of Trial

Metastatic GIST

Approved Indication

Imatinib Mesylate:

- cKIT pos. metastasized GIST, cKIT pos. adjuvant GIST,
- not resectable DFSB or not eligible for resection
- (bcr-abl)-positive (Ph+) CML
- Ph+ CML in chronic phase after failure einer Interferon-Alpha-Therapy, in the accelerated phase or in the blastencrises
- new diagnosed Ph+ ALL in combination with chemotherapy
- refractory Ph+ ALL as monotherapy
- MDS/MPD with PDGFR rearrangement
- Advanced HES and/or CEL with FIP1L1-PDGFR rearrangement

Everolimus:

- advanced Her2pos Mammacarcinoma
- inoperabel or metastized pNET
- advanced RCC

Protocol Number

CRAD001C2454

Title

Multicenter, single-arm, two-stage phase II trial of RAD001 (everolimus) with Glivec® in Glivec®-resistant patients with progressive GIST

Study Phase

Phase II

Study Start/End Dates

First patient recruited: 11-Oct-2006 Last patient completed: 28-Nov-2012

This study was terminated by Amendment 2 after inclusion of 27/53 planned patients (28 were screened by then) because of the slow recruitment rate and the availability of new promising treatment options.

Study Design/Methodology

This was a non-randomized, multicenter, single-arm, Simon's two-stage, phase II trial evaluating the combination of RAD001 plus imatinib in adult imatinib-resistant patients with GIST showing progression on 400 mg/day of imatinib.

Centers

Seven centers in Germany.

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

The investigational drug, RAD001 (everolimus), was formulated in tablets of 2.5 mg strength. Imatinib, which was used for the combination therapy, was formulated as tablets of 100 and 400 mg strength. RAD001 was to be taken once a day as a single dose of 2.5 mg, followed by a single dose of 600 mg imatinib.

Statistical Methods

This was a non-randomized, multicenter, single-arm, Simon's two-stage, phase II trial evaluating the combination of RAD001 plus imatinib in adult imatinib-resistant patients with GIST showing progression on 400 mg/day of imatinib.
The primary variable was the rate of patients achieving progression-free survival at 4 months based on the evaluation of the central radiologist. Due to the small number of patients in the primary analysis population (PP population), all analyses were descriptive. In general, all variables measured on a metric scale were presented by descriptive statistics; categorical and binary variables were displayed using frequency tables.

Study Population: Inclusion/Exclusion Criteria and Demographics

Inclusion criteria:

Patients were eligible for inclusion if they met all of the following criteria:

1. Age ≥ 18 years
2. Histologically proven diagnosis of GIST
3. Objectively documented evidence of progressive disease according to the RECIST criteria despite at least 2 months' continuous treatment with imatinib at a dosage of 400 mg/day. A treatment period of 2 weeks before study entry with an increased dosage of imatinib due to progression was allowed.
4. Clinical evidence of resistance to imatinib on treatment with 400 mg/day imatinib
5. Progression had to be documented on CT or MRI scans. The scans on which progression was documented should be 2 weeks old at maximum. New scans were only required as baseline scans if they were older than approx. 2 weeks
6. At least one measurable lesion (longest diameter ≥ 20 mm on conventional CT or MRI scan; ≥ 10 mm on spiral CT)
7. ECOG Performance Status 0-2
8. Adequate bone marrow, liver and renal function on imatinib treatment, as shown by:
   - WBC ≥ 3 x 10^9/L
   - Absolute neutrophil count (ANC) ≥ 1.5 x 10^9/L
     Hemoglobin ≥ 9 g/dL
   - Platelet count ≥ 100 x 10^9/L
   - Serum transaminase activity (AST/SGOT & ALT/SGPT) < 2.5 X ULN
   - Serum total bilirubin < 1.5 x ULN
   - Serum creatinine < 1.5 x ULN or a creatinine clearance of ≥ 60 mL/min.
9. Patients had to be at least 4 weeks since prior major surgery and recovered, at least 2 weeks since prior minor surgery and recovered

10. Written informed consent had to be obtained prior to any screening procedures

Exclusion criteria:

Patients were to be excluded from participation if they met any of the following criteria:

1. Female patients who were pregnant or breast feeding, or patients of reproductive potential not employing an effective method of birth control. Because oral, implantable or injectable contraceptives might have been affected by cytochrome P450 interactions, an appropriate method of birth control was to be used throughout the trial in both sexes. Women of childbearing potential had to have a negative serum pregnancy test ≤ 48 hours prior to the administration of study medication
2. Patients presenting with known or symptomatic central nervous system (CNS) metastases or leptomeningeal involvement
3. Use of other investigational cancer therapies within 28 days prior to enrollment or which were at the time being or planned to be received during the course of the study
4. Patients who previously received rapamycin in combination with imatinib
5. Patients with any concurrent major medical condition liable to compromise the patient's participation in the study (e.g. known HIV infection, uncontrolled diabetes, serious cardiac dysrhythmia or condition, New York Heart Association classification of III or IV, congestive cardiac failure, myocardial infarction within 6 months, unstable angina, chronic or acute renal or liver disease, uncontrolled infections including abscess or fistulae, etc.)
6. Patients with a history of another malignancy within 5 years prior to study entry, except curatively treated non-melanotic skin cancer or in-situ cervical cancer
7. Patients receiving glucocorticoids (only if the p70s6 kinase-1 assay was being performed), since glucocorticoids had been shown to inhibit p70s6 kinase-1 activity
8. Patients unwilling to or unable to comply with the protocol
9. Patients committed to an institution by order of the authorities or court decision

Participant Flow

Patient disposition for each treatment period

	All patients n (%)
Number (%) of patients	
Screened	28 (100.0)
Enrolled	28 (100.0)
Exposed	28 (100.0)
Completed core study	10 (35.7)
Discontinued core study	18 (64.3)
Continued in follow-up	5 (17.9)
Completed follow-up	3 (10.7)
Discontinued follow-up	2 (7.1)
Main reason for discontinuation	
Adverse event(s) during core study	6 (21.4)
Unsatisfactory therapeutic effect during core study	10 (35.7)
Consent withdrawn during core study	2 (7.1)
Unsatisfactory therapeutic effect during follow-up	2 (7.1)

Baseline Characteristics

Demographic summary (safety population)

		Safety population (N=28)
Age (years)	Mean	59.1
	SD	12.6
	Median	61.0
	Range	30.0-80.0
Gender – n (%)	Male	17 (60.7)
	Female	11 (39.3)
Race – n (%)	Caucasian	27 (96.4)
	Black	1 (3.6)
Weight (kg)	Mean	75.8
	SD	18.6
	Median	73.2
	Range	53.0-145.0

Outcome Measures

Tumor assessment at Week 16 (LOCF)

	ITT population N=26	
	Response n (%)	95% CI (%)
Central assessment		
Complete response (CR)	0 (0.0)	0.0 – 13.2
Partial response (PR)	1 (3.8)	0.1 – 19.6
CR or PR	1 (3.8)	0.1 – 19.6
Stable disease (SD)	19 (73.1)	52.2 – 88.4
CR or PR or SD	20 (76.9)	56.4 – 91.0
Progressive disease (PD)	2 (7.7)	0.9 – 25.1
Not done	4 (15.4)	4.4 – 34.9
Local assessment		
Complete response (CR)	0 (0.0)	0.0 – 13.2
Partial response (PR)	0 (0.0)	0.0 – 13.2
CR or PR	0 (0.0)	0.0 – 13.2
Stable disease (SD)	11 (42.3)	23.4 – 63.1
CR or PR or SD	11 (42.3)	23.4 – 63.1
Progressive disease (PD)	15 (57.7)	36.9 – 76.6
Not done	0 (0.0)	0.0 – 13.2

LOCF= Last observation carried forward

Secondary efficacy results

ECOG performance status (observed values)

	ITT population N=26 n (%)	
	Baseline	**Week 16**
Grade 0	21 (80.8)	10 (38.5)
Grade 1	5 (19.2)	10 (38.5)
Grade 2	0	2 (7.7)
Grade 3	0	1 (3.8)
Grade 4	0	0
Not done	0	3 (11.5)

ECOG= Eastern Cooperative Oncology Group

Safety Results

Number (%) of patients with AEs overall and by system organ class

	Core study	Follow-up	Total
No. (%) of patients studied	28 (100.0)	5 (100.0)	28 (100.0)
No. (%) of patients with AE(s)	28 (100.0)	5 (100.0)	28 (100.0)
System organ class affected	n (%)	n (%)	n (%)
Gastrointestinal disorders	26 (92.9)	5 (100.0)	26 (92.9)
General disorders and administration site conditions	21 (75.0)	5 (100.0)	22 (78.6)
Blood and lymphatic system disorders	18 (64.3)	4 (80.0)	18 (64.3)
Metabolism and nutrition disorders	15 (53.6)	1 (20.0)	16 (57.1)
Eye disorders	14 (50.0)	4 (80.0)	14 (50.0)
Investigations	14 (50.0)	3 (60.0)	14 (50.0)
Skin and subcutaneous tissue disorders	14 (50.0)	1 (20.0)	14 (50.0)
Nervous system disorders	11 (39.3)	2 (40.0)	11 (39.3)
Respiratory, thoracic and mediastinal disorders	10 (35.7)	2 (40.0)	10 (35.7)
Musculoskeletal and connective tissue disorders	6 (21.4)	3 (60.0)	7 (25.0)
Injury, poisoning and procedural complications	5 (17.9)	2 (40.0)	6 (21.4)
Psychiatric disorders	6 (21.4)	-	6 (21.4)
Infections and infestations	4 (14.3)	1 (20.0)	4 (14.3)
Cardiac disorders	2 (7.1)	-	2 (7.1)
Hepatobiliary disorders	2 (7.1)	-	2 (7.1)
Renal and urinary disorders	2 (7.1)	-	2 (7.1)
Vascular disorders	2 (7.1)	1 (20.0)	2 (7.1)
Ear and labyrinth disorders	1 (3.6)	1 (20.0)	1 (3.6)
Immune system disorders	1 (3.6)	-	1 (3.6)
Neoplasms benign, malignant and unspecified	1 (3.6)	-	1 (3.6)

System organ classes listed by overall incidence.

Number (%) of patients with most frequent (>10%) AEs

	All AEs during the study			Drug-related AEs
	Core study	Follow-up	Total	Total
No. (%) of patients studied	28 (100.0)	5 (100.0)	28 (100.0)	28 (100.0)
No. (%) of patients with AE(s)	28 (100.0)	5 (100.0)	28 (100.0)	28 (100.0)
AE preferred term	n (%)	n (%)	n (%)	n (%)
Diarrhoea	17 (60.7)	5 (100.0)	18 (64.3)	17 (60.7)
Fatigue	12 (42.9)	2 (40.0)	12 (42.9)	9 (32.1)
Hypokalaemia	11 (39.3)	1 (20.0)	12 (42.9)	10 (35.7)
Anaemia	11 (39.3)	2 (40.0)	11 (39.3)	10 (35.7)
Nausea	11 (39.3)	1 (20.0)	11 (39.3)	10 (35.7)

	All AEs during the study			Drug-related AEs
	Core study	Follow-up	Total	Total
Oedema peripheral	8 (28.6)	3 (60.0)	10 (35.7)	9 (32.1)
Rash	10 (35.7)	1 (20.0)	10 (35.7)	10 (35.7)
Decreased appetite	8 (28.6)	1 (20.0)	9 (32.1)	6 (21.4)
Leukopenia	9 (32.1)	4 (80.0)	9 (32.1)	9 (32.1)
Flatulence	8 (28.6)	1 (20.0)	8 (28.6)	7 (25.0)
Mucosal inflammation	7 (25)	1 (20.0)	8 (28.6)	8 (28.6)
Vomiting	7 (25.0)	1 (20.0)	8 (28.6)	6 (21.4)
Eyelid oedema	7 (25.0)	2 (40.0)	7 (25.0)	7 (25.0)
Headache	7 (25.0)	2 (40.0)	7 (25.0)	6 (21.4)
Stomatitis	5 (17.9)	1 (20.0)	6 (21.4)	6 (21.4)
Weight decreased	6 (21.4)	1 (20.0)	6 (21.4)	5 (17.9)
Eye oedema	5 (17.9)	2 (40.0)	5 (17.9)	4 (14.3)
Hypocalcaemia	4 (14.3)	1 (20.0)	5 (17.9)	3 (10.7)
Pyrexia	5 (17.9)	-	5 (17.9)	1 (3.6)
Thrombocytopenia	5 (17.9)	-	5 (17.9)	5 (17.9)
Abdominal pain	4 (14.3)	-	4 (14.3)	4 (14.3)
Dry mouth	4 (14.3)	-	4 (14.3)	2 (7.1)
Epistaxis	4 (14.3)	-	4 (14.3)	2 (7.1)
Temperature intolerance	4 (14.3)	2 (40.0)	4 (14.3)	4 (14.3)
Constipation	3 (10.7)	-	3 (10.7)	2 (7.1)
Dry skin	3 (10.7)	-	3 (10.7)	2 (7.1)
Dysgeusia	3 (10.7)	1 (20.0)	3 (10.7)	2 (7.1)
Dyspnoea	3 (10.7)	-	3 (10.7)	1 (3.6)
Haemoglobin decreased	3 (10.7)	-	3 (10.7)	3 (10.7)
Insomnia	3 (10.7)	-	3 (10.7)	1 (3.6)

Preferred terms are listed by overall incidence of all AEs during the study

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

	Core study	Follow-up	Total
No. (%) of patients studied	28 (100.0)	5 (100.0)	28 (100.0)
No. (%) of patients with AE(s)	28 (100.0)	5 (100.0)	28 (100.0)
Number (%) of patients with serious or other significant events	n (%)	n (%)	n (%)
Any SAE(s)	10 (35.7)	1 (20.0)	10 (35.7)
Death	2 (7.1) [a]	-	2 (7.1) [a]
Non-fatal SAE	9 (32.1)	1 (20.0)	9 (32.1)
Premature discontinuation due to non-fatal SAE	2 (7.1)	-	2 (7.1)
Dose adjustment/interruption due to non-fatal SAE	4 (14.3)	-	4 (14.3)
Premature discontinuation due to non-serious AE	3 (10.7)	-	3 (10.7)
Dose adjustment/interruption due to non-serious AE	10 (35.7)	2 (40.0)	12 (42.9)

[a] Including 1 case of death due to progression of the GIST tumor which occurred 30 days after the last dose of everolimus.

Number (%) of patients with non-fatal SAEs overall and by preferred term

	All SAEs during the study			Drug-related SAEs
	Core study	**Follow-up**	**Total**	**Total**
No. (%) of patients studied	28 (100.0)	5 (100.0)	28 (100.0)	28 (100.0)
No. (%) of patients with SAE(s)	9 (32.1)	1 (20.0)	9 (32.1)	5 (17.9)
SAE preferred term	n (%)	n (%)	n (%)	n (%)
Anaemia	2 (7.1)	-	2 (7.1)	1 (3.6)
Gastric haemorrhage	2 (7.1)	1 (20.0)	2 (7.1)	1 (3.6)
Blood creatine phosphokinase increased	1 (3.6)	-	1 (3.6)	1 (3.6)
Cholestasis	1 (3.6)	-	1 (3.6)	-
Colitis	1 (3.6)	-	1 (3.6)	1 (3.6)
Diarrhoea	1 (3.6)	-	1 (3.6)	1 (3.6)
Disease progression	1 (3.6)	-	1 (3.6)	-
Gastric ulcer haemorrhage	1 (3.6)	-	1 (3.6)	-
Haematoma	1 (3.6)	-	1 (3.6)	1 (3.6)
Hypersensitivity	1 (3.6)	-	1 (3.6)	-
Impaired healing	1 (3.6)	-	1 (3.6)	1 (3.6)
Metastases to spine	1 (3.6)	-	1 (3.6)	-
Pneumonitis	1 (3.6)	-	1 (3.6)	1 (3.6)

Other Relevant Findings

Three patients (10.7%) discontinued the core study due to non-serious AEs

Dose adjustments/interruptions due to non-serious AEs were made in 12 patients (42.9%).

Number (%) of patients with non-serious AEs leading to dose adjustment and/or interruption by preferred term

	Core study	Follow-up	Total
No. (%) of patients studied	28 (100.0)	5 (100.0)	28 (100.0)
No. (%) of patients with significant AE(s)	10 (35.7)	2 (40.0)	12 (42.9)
AE preferred term	n (%)	n (%)	n (%)
Diarrhoea	2 (7.1)	-	2 (7.1)
Neutropenia	2 (7.1)	-	2 (7.1)
Oedema peripheral	2 (7.1)	-	2 (7.1)
Blood bilirubin increased	1 (3.6)	-	1 (3.6)
Blood phosphorus decreased	1 (3.6)	-	1 (3.6)
Eye oedema	1 (3.6)	-	1 (3.6)
Fatigue	1 (3.6)	-	1 (3.6)
Hyperkalaemia	1 (3.6)	-	1 (3.6)
Hypersensitivity	1 (3.6)	-	1 (3.6)
Interstitial lung disease	-	1 (20.0)	1 (3.6)
Leukopenia	1 (3.6)	-	1 (3.6)
Melaena	1 (3.6)	-	1 (3.6)
Mucosal inflammation	1 (3.6)	-	1 (3.6)
Nasopharyngitis	1 (3.6)	-	1 (3.6)
Pharyngitis	-	1 (20.0)	1 (3.6)
Pneumonitis	-	1 (20.0)	1 (3.6)
Rash	1 (3.6)	-	1 (3.6)
Stomatitis	1 (3.6)	-	1 (3.6)
Thrombocytopenia	1 (3.6)	-	1 (3.6)
Vomiting	1 (3.6)	-	1 (3.6)
White blood cell count decreased	1 (3.6)	-	1 (3.6)

Date of Clinical Trial Report

November 13, 2013

Date Inclusion on Novartis Clinical Trial Results Database

November 22, 2013

Date of Latest Update