Sponsor

Novartis

Generic Drug Name

Glivec® (imatinib mesylate)

Therapeutic Area of Trial

Oncology: refractory desmoplastic small round cell tumors expressing a molecular target of imatinib

Approved Indication

Glivec® is currently approved in many countries for:

- Adult patients with metastatic or unresectable GIST.
- adjuvant treatment of adult patients with a significant risk of recurrence after resection of GIST Kit-positive.
- adult and pediatric patients with chronic myeloid leukemia (CML) with Philadelphia chromosome (bcr-abl) positive (Ph +) newly diagnosed, for which the bone marrow transplant is not considered first-line treatment.
- adult and pediatric patients with Ph + CML in chronic phase after failure of therapy with interferon-alpha, or in accelerated phase or blast crisis.
- adult patients with acute lymphoblastic leukemia with Philadelphia chromosome positive (Ph +) integrated with chemotherapy in newly diagnosed.
- adult patients with relapsed or refractory Ph + ALL as monotherapy.
- adult patients with myelodysplastic / myeloproliferative diseases (MDS / MPD) associated with rearrangements of the receptor gene for the platelet derived growth factor (PDGFR).
- adult patients with advanced hypereosinophilic syndrome (HES) and / or chronic eosinophilic leukemia (CEL) with FIP1L1-PDGFR rearrangement.
- adult patients with unresectable dermatofibrosarcoma protuberans (DFSP) and adult patients with recurrent and/or metastatic DFSP who are not eligible for surgery.

Study Number

CSTI571BIT06

Title

OPEN-LABEL TRIAL OF GLIVEC® (IMATINIB MESYLATE) IN PATIENTS WITH REFRACTORY DESMOPLASTIC SMALL ROUND CELL TUMORS (DSRCT) EXPRESSING A MOLECULAR TARGET OF GLIVEC® (PDGF-R AND/OR C-KIT)

Phase of Development

Phase II

Study Start/End Dates

Study initiation date: 25-Aug-2005 (first patient enrolled; FPFV 25-Oct-2005)

Early termination date: Not applicable

Study completion date: 23-Jun-2009 (last patient completed)

Study Design/Methodology

Open label, uncontrolled, prospective clinical trial of Glivec® 400 mg p.o./day in patients with refractory desmoplastic small round cell tumors expressing a molecular target of imatinib. Glivec® could be increased to 800 mg p.o./day (400 mg b.i.d.) if the patient was not responding after 13 weeks of treatment. Patients had to be treated for 12 months.

Centres

9 centers in Italy.

Publication

none

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Objectives

Primary objective(s)

To assess the clinical and biological activity of imatinib mesylate in the treatment of patients with refractory desmoplastic small round cell tumors expressing a molecular target of imatinib (PDGF-RA, PDGF-RB and/or c-kit), as judged by objective response rates .

Secondary objective(s)

To assess the improvement of overall survival after treatment and the safety and tolerability. Actual resectability rate after therapy had to be assessed, as compared to resectability before starting therapy.

A mutational analysis of the molecular targets of imatinib identified with the immunoistochemistry and/or molecular biology (PDGF-RA, PDGF-RB and/or c-kit) had to be performed at any time during the study, after the enrolment of the patients, in order to better understand the biology of the tumor, still unknown.

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

Glivec® 100 mg capsules packaged in polyethylene bottles. Patients had to receive Glivec® 400 mg p.o./once daily; Glivec® could be increased to 800 mg p.o./day (400 mg b.i.d), if the patient did not respond after 13 weeks of treatment.

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

Not applicable

Criteria for Evaluation

Primary Objective

Overall tumor response according to RECIST criteria.

Secondary Objective

Proportion of patients undergoing surgery

Overall survival

Progression free survival

Safety:

Safety assessments consisted of evaluating adverse events and serious adverse events, laboratory data and Performance status/body weight. Toxicity had to be evaluated according to the NCI Common Toxicity Criteria, v. 2.0.

Pharmacology:

no pharmacokinetics was planned in this study.

Statistical Methods

Efficacy evaluation

Overall tumor response had to be clinically evaluated according to §3.5.3 of the Study Protocol and reported in the CRFs.

Tumor assessments had to be made at baseline and thereafter according to visit schedule. The investigator made an evaluation of tumor response at each time point after the baseline assessment.

Patterns of tumor response had to be centrally reviewed. A judgement of tumor response had to be expressed after central review and computed for the response rate assessment.

Primary efficacy outcome are the following:

a) Proportion of “objective” responses:

This proportion was computed by dividing the number of patients showing an “objective” response (according to RECIST criteria) to drug by the total number of patients in the population. For each patient, the best response observed at any time during treatment with the experimental drug was considered.

b) Proportion of “clinical” responses

This proportion was computed by dividing the number of patients showing a “clinical” re-

sponse by the total number of patients in the population. Patients were considered in clinical response if there had been an objective response or at least ONE of the following criteria was met:

a) An unequivocal reduction in tumor density at CT scan

b) An unequivocal reduction in signal intensity and/or contrast enhancement at MRI

Confidence intervals (two-sided, 95%, Pearson-Clopper-limits) had to be calculated for the rate of responders.

Secondary efficacy outcome are the following:

a) Proportion of patients undergoing surgery

This proportion had to be computed by dividing the number of patients undergoing surgery by the number of patients who were considered not amenable to surgery at enrolment.

b) Overall Survival

This had to be computed from the first day of study treatment to the day of death from any cause.

c) Progression-free survival

This had to be computed from the first day of study treatment to the day of documented progression according to RECIST criteria or clinical criteria, or to the day of death from any cause, whichever occurred first.

Survival plots for overall survival (Kaplan-Meier-Plot), and progression-free interval (Actuarial method) had to be provided. Progression-free interval had also to be compared against historical controls.

Safety evaluation

- Adverse events

The assessment of safety was based mainly on the frequency of adverse events, particularly adverse events leading to discontinuation of treatment and on the number of abnormal laboratory values [HAEMATOLOGY: haemoglobin, platelets, total white blood cell count & differential counts; BLOOD CHEMISTRY: urea or BUN, creatinine, albumin, total protein, total bilirubin, alkaline phosphatase, γ-GT, AST (SGOT), ALT (SGPT), and LDH].

Adverse events were summarized by presenting the number and percentage (as appropriate) of patients having any adverse event by body system, type of adverse event, and maximum severity according to CTC grade. Those adverse events which resulted in death, discontinuation or were otherwise classified as dose limiting had to be presented separately.

- Laboratory data

Laboratory data were summarized using the NCI CTC criteria (Appendix 2 to the Study Protocol).

- Performance status/Body weight

Changes from baseline (screening visit) in performance status grades were summarised at de-

fined intervals.

Tables of summary statistics of body weight were produced at defined intervals.

Study Population: Inclusion/Exclusion Criteria and Demographics

The study protocol foresaw a patient population of twenty-five patients with refractory desmoplastic small round cell tumors expressing a molecular target of imatinib (PDGFRA, PDGFRB and/or c-kit), to be enrolled in about 9 Italian centers.

Inclusion criteria

1. Histologically documented diagnosis of DSRCT, unresponsive or in no complete remission after any conventional multimodality approach.
2. Immunohistochemical documentation of an imatinib mesylate target (PDGF-RA, PDGF-RB and/or C-KIT). Biomolecular assessment of the receptors activation had to be made whenever possible. To this end, if frozen material was not available, obtaining of fresh material was encouraged, if it could be obtained with no major distress for the patient, preferably through an incisional biopsy (to allow immunoprecipitation) or, if this was not feasible, a Trucut biopsy (to allow Western Blot assessment). However, if frozen or fresh material could not be obtained, paraffined material was also acceptable. The immunoistochemical and/or biomolecular assessment was centralized to the reference center **(Laboratorio di Anatomia Patologica, Istituto Clinico Humanitas di Rozzano, *Prof. Massimo Roncalli e Dr Pier Giuseppe Colombo* phone: +39 02 82244712).**
3. Measurable or evaluable disease.
4. Performance status 0, 1, 2 or 3 (ECOG) (see Section 7.1 of the Protocol) at screening and verified at basal evaluation (visit 1).
5. Adequate end organ function, defined as the following: total bilirubin < 1.5 x ULN, SGOT and SGPT < 2.5 x UNL, creatinine < 1.5 x ULN.
6. Adequate bone marrow function, defined as the following: ANC >1.5 x 10^9/L, platelets >100 x 10^9/L, Hb $\geq$9 g/dL. Blood transfusions were allowed to reach the baseline requested Hb level.
7. Female patients of childbearing potential had to have negative pregnancy test within 7 days before initiation of study drug dosing. Postmenopausal women had to be amenorrheic for at least 12 months to be considered of non-childbearing potential. Male and female patients of reproductive potential had to agree to employ an effective barrier method of birth control throughout the study and for up to 3 months following discontinuation of study drug.
8. Written, voluntary informed consent.

Exclusion criteria

1. Patient who received any other investigational agents within 28 days of first day of study drug dosing, unless the disease was rapidly progressing.
2. Patient who was < 5 years free of another primary malignancy except: if the other primary malignancy is neither currently clinically significant nor requiring active intervention, or if other primary malignancy is a basal cell skin cancer or a cervical carcinoma in situ. Exis-

tence of any other malignant disease was not allowed.

3. Patient with Grade III/IV cardiac problems as defined by the New York Heart Association Criteria. (i.e. congestive heart failure, myocardial infarction within 6 months of study)
4. Patient with a severe and/or uncontrolled medical disease (i.e. chronic renal disease or active uncontrolled infection).
5. Patient with a known brain metastasis.
6. Patient with known chronic liver disease (i.e. chronic active hepatitis and cirrhosis).
7. Patient with a known diagnosis of human immunodeficiency virus (HIV) infection.
8. Patient who received chemotherapy within 4 weeks (6 weeks for nitrosourea or mitomycin-C) prior to study entry, unless the disease was rapidly progressing.
9. Patient with previously received radiotherapy to ≥ 25 % of the bone marrow.
10. Patient with a major surgery within 2 weeks prior to study treatment.
11. Patient with any significant history of non-compliance to medical regimens or with inability to grant reliable informed consent.

Number of Subjects

	Novartis product
Planned N	25
Randomised n	13
Intent-to-treat population (ITT) n (%)	8 (100)
Completed n (%)	0
Withdrawn n (%)	8 (100)
Withdrawn due to adverse events n (%)	0
Withdrawn due to lack of efficacy n (%)	7 (87.5)
Withdrawn for other reasons n (%)	1 (12.5)

Demographic and Background Characteristics

	Novartis product
N (ITT)	8
Females : males	1:7
Mean age, years (SD)	20.0 (SD:7.8)

Disease characteristics at diagnosis (Intention to treat analysis set)

Time from initial diagnosis (month)	
N	8
Mean	39.3
SD	45.0
Median	24.5
Min - max	6 – 148
Primary site of tumor – n(%)	
Abdomen	4 (50.0)
Pelvic mass	3 (37.5)
Abdomen and pelvis	1 (12.5)
Disease stage – n(%)	
Localised	0 (0.0)
Local advanced	2 (25.0)
Metastatic	6 (75.0)
Recurrence/progression – n(%)	
First diagnosis/stable disease	6 (75.0)
Recurrence	1 (12.5)
Progression	1 (12.5)

Source: Post text tables 14.1-6 and 14.1-7

Immunohistochemistry and biomolecular assessment at baseline (Safety analysis set)

Assessment	n (%)
PDGF-RA*	
Mild	2 (28.6)
Moderate	2 (28.6)
Strong	3 (42.9)
PDGF-RB*	
Absent	1 (14.3)
Mild	2 (28.6)
Moderate	2 (28.6)
Strong	2 (28.6)
c-KIT**	
Absent	6 (100)

* Patient 4 of center 1 with missing information
** Patient 1 and 4 of center 1 with missing information

Primary Objective Result(s)

Overall response

At the end of the study all patients had progression of the disease. Five out of eight patients had disease progression in the first two months of treatment. The best response was stable disease in one patient (12.5%) at month 3. In the other 7 patients (87.5%) the response was progressive disease from the first evaluation (month 3).

No objective response was observed in any patients. Clinical response was observed in 1 patient (12.5%) (Table 11-4).

Best tumor response as assessed with RECIST and disease indicators - (Intention to treat analysis set)

Patients with objective response - n(%)	0 (0.0)
95% CI of objective response rate	
Patients with clinical response - n(%)	1 (12.5)
95% CI of clinical response rate	0.0 – 35.4

Secondary Objective Result(s)

Overall survival

One patient (12.5%) died, after 18 days from the beginning of the treatment, and 7 were censored. The Kaplan-Meier curve of the overall survival was not done. Further details are reported in Section 14, Table 14.2-3.

Progression free survival

According to the RECIST criteria, five (cumulative rate 62.5%) events (documented progression or death from any cause) were observed, namely two in the time period 0-84 days, 2 in 85-168, and one in 169-336, respectively. According to disease indicators, cumulative rate was 100%.

The Kaplan-Meier curve of the progression free interval was not done.
Further details are reported in Section 14, Tables 14.2-4 and 14.2-5.

Time to progression

Time to progression was one in 0-84 day-period (4 patients censored), 2 in 85-168 and one in 169-336, respectively.
Further details are reported in Section 14, Tables 14.2-6 and 14.2-7.

Other efficacy topics

Six patients had unresectable tumor and two unresectable in a radical fashion at baseline. All 8 patients were classified as unresectable at the end. ECOG performance did not change in two patients and worsened in 6 patients at the end.

Frequency distribution of change in tumor resectability and frequency distribution of change in ECOG performance are reported in Section 14, Tables 14.2-9 and 14.2-10.

Safety Results

The adverse events observed during the study were expected for this drug with regard to type and frequency. Only in 3 patients (37,5%) they led to drug discontinuation. Serious adverse events were reported in 4 patients (50%, one of which died) but in no case they were judged as drug related

Number of patients with AEs by primary system organ class - number (%) of patients (Intention to treat analysis set)

	Total (N=8)
Patients with AEs	8 (100.0)
System organ class	
Gastrointestinal disorders	5 (62.5)
General disorders and administration site conditions	4 (50.0)
Investigations	3 (37.5)
Skin and subcutaneous tissue disorders	2 (25.0)
Psychiatric disorders	1 (12.5)
Cardiac disorders	1 (12.5)
Respiratory, thoracic and mediastinal disorders	1 (12.5)
Hepatobiliary disorders	1 (12.5)
Neoplasms benign, malignant and unspecified	1 (12.5)

Patients are only counted once in each body system regardless of the number of AEs experienced in that body system
Arranged in descending order of frequency

Adverse events overall by preferred term - number (%) of patients (Intention to treat analysis set)

	Total (N=8)
Patients with AEs	8 (100.0)
Ascites	3 (37.5)
B-lymphocyte count decreased	2 (25.0)
Pain	2 (25.0)
Vomiting	2 (25.0)
Abdominal pain	1 (12.5)
Fatigue	1 (12.5)
Gastritis	1 (12.5)
Hepatic failure	1 (12.5)
Insomnia	1 (12.5)
Lymphocyte morphology abnormal	1 (12.5)
Nausea	1 (12.5)
Neoplasm progression	1 (12.5)
Oedema peripheral	1 (12.5)
Periorbital oedema	1 (12.5)
Platelet count decreased	1 (12.5)
Productive cough	1 (12.5)
Purpura	1 (12.5)
Pyrexia	1 (12.5)
Tachycardia	1 (12.5)

Arranged by descending frequencies

Deaths, other serious or clinically significant adverse events or related discontinuation - number (%) of patients (Intention to treat analysis set)

	Total (N=8)
Patients with AEs	8 (100.0)
Serious or other significant events	

Death	1 (12.5)
SAEs	4 (50.0)
Clinically significant AEs	8 (100.0)
Discontinued due to SAEs	3 (37.5)
Discontinued due to clinical significant AEs	0 (0.0)

Any serious adverse event occurred after the patient has provided informed consent and until 4 weeks after the patient has stopped trial treatment was reported

Other Relevant Findings

There were no other relevant findings on safety.

Date of Clinical Trial Report

17-Dec-2010

Date Inclusion on Novartis Clinical Trial Results Database

4 Jan 2011

Date of Latest Update