A Phase 2 Study of a Human Anti-PDGFRα Monoclonal Antibody (IMC-3G3) in Previously Treated Patients with Unresectable and/or Metastatic Gastrointestinal Stromal Tumors (GIST)

Published: 12-05-2011
Last updated: 29-04-2024

The primary objective of this study is to evaluate the tumor response of stable disease (SD), partial response, or complete response at at 12 weeks (according to RECIST 1.1 criteria) in two separate cohorts representing molecularly distinct subsets...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Malignant and unspecified neoplasms gastrointestinal NEC
Study type	Interventional

Summary

ID

NL-OMON38170

Source
ToetsingOnline

Brief title
IMCL CP15-1008 (625/024)

Condition

- Malignant and unspecified neoplasms gastrointestinal NEC
- Gastrointestinal neoplasms malignant and unspecified

Synonym
unresectable and/or metastatic gastrointestinal stromal tumors; tumour in het gastrointestinaltract

Research involving

Human

Sponsors and support

Primary sponsor: Imclone Systems
Source(s) of monetary or material Support: ImClone Systems

Intervention

Keyword: Anti-PDGFR&alfa, GIST, IMC-3G3

Outcome measures

Primary outcome

Efficacy assessments will include imaging studies and tumor measurements/disease response assessments, according to RECIST 1.1, every 6 weeks (± 3 days) following the first dose of study therapy until documentation of PD.

Secondary outcome

Safety Assessments:

Safety will be evaluated based on reported adverse events, physical examinations, ECGs, and clinical/laboratory tests. Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA®) and graded using the NCI-CTCAE, Version 4.03. Clinical laboratory toxicity will be graded using NCI-CTCAE criteria, Version 4.03.

Pharmacokinetic Assessments:

Blood samples will be obtained for analysis of the PK behavior of IMC 3G3, with more extensive sampling performed for 10 patients of each cohort that continues into the second stage of enrollment. PK parameters will be estimated using a noncompartmental model; parameters to be reported include, but are not limited

to, Cmax, AUC0-inf, t1/2, Cl, and Vss.

Pharmacodynamic Assessments:

Samples will be collected for nonpharmacogenetic biomarker research.

Exploratory biomarker analyses in whole blood will include potentially relevant biomarkers of IMC-3G3 pharmacodynamic activity including PDGF and VEGF and other factors related to PDGFRα. In addition, tissue samples from the primary or metastatic tumor provided at baseline will also be evaluated for biomarkers including analysis of PDGFRα expression and analyses of other factors related to PDGFRα.

Immunogenicity Assessments:

Blood samples for the assessment of antibodies against IMC-3G3 (immunogenicity) will be collected for all study patients at specified timepoints throughout the study. In addition, if a patient should have an infusion reaction to IMC-3G3, all attempts should be made to obtain a blood sample for immunogenicity analysis as close to the onset of the event as possible, at the resolution of the event, and 30 days following the event.

Study description

Background summary

Gastrointestinal stromal tumors (GIST) are a type of mesenchymal tumor specific to the gastrointestinal tract (GI). Reports of GIST have undergone a significant increase in frequency during the last two decades, as familiarity with this form of malignancy has grown; GIST is clinically malignant in 20% - 25% of gastric cases and 40% - 50% of cases affecting the small intestine. Surgical resection is the optimal approach to primary GIST without evidence of metastases. However, recurrence within five years is fairly common even for completely resected tumors. Furthermore, prior to the advent of molecularly

targeted therapy, relatively few nonsurgical treatment options were available for patients with this form of malignancy. Conventional cytotoxic chemotherapy was associated with typical response rates of 5% or less, and the median survival for patients with metastatic/unresectable GIST was only 5-12 months. Since the year 2000, imatinib is associated with significant clinical benefit when used in the treatment of unresectable or metastatic GIST, including median overall survival (OS) approaching 5 years. Recently, sunitinib has emerged as the treatment of choice for patients with GIST that becomes refractory to imatinib. Imatinib and sunitinib are now approved as single agent therapy for the treatment of unresectable or metastatic GIST in the first- and second-line, respectively. Imatinib has also been approved by regulatory authorities worldwide for post-resection adjuvant therapy of primary GIST with significant risk of relapse, since substantial improvement in recurrence-free survival has been documented with imatinib.
However, 5%-10% of unresectable or metastatic GIST have non-acquired PDGFR-alpha (PDGFRα) activating mutations in internal kinase domains. Of these patients, only approximately one-third respond to approved therapies (imatinib and sunitinib), and neither treatment is associated with clinical benefit in patients with the D842V PDGFRα mutation. Thus, the median progression-free survival (PFS) of patients with this and similar mutations is only approximately 6 weeks despite any currently available treatment. New treatments for patients with GIST and this type of mutation, and for patients whose disease becomes refractory to both imatinib and sunitinib, are needed.

Study objective

The primary objective of this study is to evaluate the tumor response of stable disease (SD), partial response, or complete response at at 12 weeks (according to RECIST 1.1 criteria) in two separate cohorts representing molecularly distinct subsets of previously treated patients with GIST when treated with IMC-3G3: Cohort 1 includes patients with GIST harboring PDGFRα mutations (D842V and any others), while Cohort 2 includes patients with GIST not harboring PDGFRα mutations.
Exploratory analyses in whole blood will include potentially relevant biomarkers of IMC-3G3 pharmacodynamic activity including PDGF and VEGF and other factors related to PDGFRα. Biomarkers will also include analysis of tumor specimens for expression of PDGFRα and analyses of other factors related to PDGFRα. Associations between exploratory biomarkers and clinical outcomes (PFS, ORR, OS, etc) will be evaluated.

Study design

In this open-label, two-stage, multicenter, multinational Phase 2 trial, patients will receive intravenous IMC 3G3 20 mg/kg every 14 days (one cycle). Patients will be assessed for tumor response every 6 weeks (± 3 days). All patients will continue to receive treatment until there is radiographic

documentation of disease progression, death, or intolerable toxicity, or other withdrawal criteria are met.
The study will utilize a Simon two-stage optimal design with two cohorts. During Stage I, in each cohort (1 and 2), patients will be enrolled until eight evaluable patients (defined in the Statistical Methods section of the synopsis) have been enrolled. If two or fewer (of eight evaluable) patients in a cohort have a response of SD or better (per RECIST 1.1) at 12 weeks following the first dose, then that cohort will be discontinued. If three or more of the first eight evaluable patients in a cohort have a response of SD or better at 12 weeks, that cohort will continue into a second stage of enrollment with accrual of an additional 24 patients to a minimum total of 32 evaluable patients. If more than 15 patients with a response of SD or better are observed at 12 weeks in this expanded cohort, the drug will be considered for further investigation.

Intervention

IMC-3G3: injection for intravenous (I.V.) use, supplied in single-use 500 mg/50 mL vials containing 10 mg/mL of product in histidine buffer, administered to patients as an I.V. infusion at 20 mg/kg every 14 days.

Study burden and risks

A detailed list of side effects of IMC-3G3 is included in Appendix 2 of the patient information sheet. Very Common Side Effects (at least 10% of patients) include: Fatigue and allergic reaction. Common side effects (1-10% of the patients are: Thrombocytopenia (low platelets), Constipation, Diarrhea, Nausea, Vomiting, Chills, Fever, Headache, Elevated liver function tests and Moderate bleeding within a patient*s liver tumor

Furthermore patients might experience discomforts during the study procedures: Blood sampling, providing urine,
Magnetic Resonance Imaging (MRI), CT scan, contrasts for MRI and CT scans. Please refer to Appendix 2 of the Patient Information Sheets for more information regarding the possible discomforts of these procedures.

Contacts

Public
Imclone Systems

33 ImClone Drive
Branchburg, NJ 08876

US
Scientific
Imclone Systems

33 ImClone Drive
Branchburg, NJ 08876
US

Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

1. The patient has histologically or cytologically confirmed, unresectable and/or metastatic GIST.
2. The patient has measurable disease (per RECIST version 1.1).
3. The patient has documented objective progression following, or intolerance to, treatment with at least both imatinib and sunitinib.
4. The patient*s Eastern Cooperative Oncology Group (ECOG) performance status is 0 to 2.
5. The patient has either:
a. prior results from KIT and PDGFRα mutation analysis that meet analytical criteria as defined for the on-study analysis of these mutations (to be confirmed by the central reader for this study) and tumor tissue (from either primary or metastatic tumor [cytology is not acceptable]) that can be submitted for analysis within 30 days after the first dose of study therapy; or
b. if prior results from KIT and PDGFRα mutation analysis are not available or do not meet analytical criteria as above, then tumor tissue (from either primary or metastatic tumor [cytology is not acceptable]) must be submitted for genotype testing at the latest 28 days prior to the first dose of study therapy. The results from the Central Lab need to be available prior to enrolling the patient.
6. The patient*s age at registration is >= 18 years.
7. The patient has adequate hematologic function as defined by an absolute neutrophil count (ANC) >= 1500/µL, hemoglobin >= 9.0 g/dL (5.58 mmol/L), and a platelet count of >=

75,000/µL obtained within 2 weeks prior to registration.
8. The patient has adequate hepatic function as defined by a total bilirubin <= 1.5 mg/dL (25.65 µmol/L), and aspartate transaminase (AST) and alanine transaminase (ALT) <= 3.0 × the upper limit of normal (ULN) [or <= 5.0 x the ULN in the setting of liver metastases].
9. The patient has adequate renal function (serum creatinine <= 1.5 × the institutional ULN or calculated creatinine clearance >= 45 mL/min.
10. The patient has adequate coagulation function, as defined by international normalized ratio (INR) <= 1.5 and a partial thromboplastin time (PTT) <= 1.5 × ULN if not receiving anticoagulation therapy. Patients on full dose anticoagulation must be on a stable dose of oral anticoagulant or low molecular weight heparin, have a therapeutic INR, no active bleeding (defined as within 14 days prior to first dose of study medication), and no pathological condition that carries a high risk of bleeding (eg, tumor involving major vessels or known varices).
11. Because the teratogenicity of IMC-3G3 is not known, women of childbearing potential (WOCBP) and sexually active males must agree to use adequate contraception (hormonal or barrier method of birth control; abstinence) prior to study entry and for at least 12 weeks after the last dose of IMC-3G3.
12. The patient has resolution to Grade <= 1 by the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) Version 4.0 of all clinically significant toxic effects of prior locoregional therapy, surgery, chemoembolization, or other anticancer therapy. The exception for such effects are events that pertain to the lab values found elsewhere in these inclusion criteria. (For example, criterion #7 states that a patient with hemoglobin >= 9.0 g/dL [5.58 mmol/L] is considered eligible, even though NCI-CTCAE Version 4.0 defines this value as Grade 2 anemia.)
13. The patient has a life expectancy of >= 3 months.
14. The patient has provided signed informed consent.

Exclusion criteria

1. The patient has untreated central nervous system metastases and as a result is clinically unstable with regard to neurologic function. Patients are eligible if the following conditions are met: a) surgical resection performed at least 4 weeks prior to registration; b) at least 4 weeks have elapsed since completion of cranial irradiation (whole brain radiation therapy, focal radiation therapy, stereotactic radiosurgery); c) at least 4 weeks have elapsed since the last steroid dose; and d) central nervous system metastases are stable.
2. The patient has a history of another primary cancer, with the exception of a) curatively resected non-melanomatous skin cancer; b) curatively treated carcinoma in situ; or c) other primary solid tumor treated with curative intent, no known active disease present, and no treatment administered during the last 3 years prior to study entry.
3. The patient has received any investigational therapy within 14 days prior to registration or is concurrently enrolled in any other type of medical research judged not to be scientifically or medically compatible with this study.
4. The patient is receiving concurrent treatment with other anticancer therapy, including other chemotherapy, immunotherapy, hormonal therapy, radiotherapy, targeted therapy, chemoembolization, or an investigational agent.

5. The patient has an elective or a planned major surgery to be performed during the course of the study.
6. The patient has an uncontrolled intercurrent illness including, but not limited to, ongoing or active infection requiring parenteral antibiotics, symptomatic congestive heart failure, severe myocardial insufficiency, clinically significant cardiac arrhythmia, or psychiatric illness/social situations that would limit compliance with study requirements.
7. The patient has unstable angina pectoris, angioplasty, cardiac stenting, or myocardial infarction 6 months prior to study entry.
8. The patient has known human immunodeficiency virus (HIV) infection.
9. The patient has undergone major surgery within 28 days prior to registration.
10. The patient, if female, is pregnant or breastfeeding.
11. The patient has a known allergy to any of the treatment components.
12. The patient has a history of allergic reactions attributed to compounds of chemical or biologic composition similar to that of IMC-3G3.

Study design

Design

Study phase:	2
Study type:	Interventional
Intervention model:	Other
Allocation:	Non-randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	23-08-2011
Enrollment:	3
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	IMC-3G3

Generic name:	NA

Ethics review

Approved WMO Date:	12-05-2011
Application type:	First submission
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	18-08-2011
Application type:	First submission
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	12-04-2012
Application type:	Amendment
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	16-05-2012
Application type:	Amendment
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	18-07-2012
Application type:	Amendment
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EudraCT	EUCTR2010-022560-12-NL
CCMO	NL36622.058.11