A Five-Tier, Phase 2 Open-Label Study of IMC-A12 Administered as a Single Agent Every 2 Weeks in Patients With Previously-Treated, Advanced or Metastatic Soft Tissue and Ewing's Sarcoma/PNET

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The primary objective of this study is to determine the progression-free survival (PFS) rate assessed 12 weeks after the initiation of IMC-A12 monotherapy, administered every 2 weeks to patients with previously-treated, advanced or metastatic soft...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Other condition
Study type	Interventional

Summary

ID

NL-OMON33655

Source
ToetsingOnline

Brief title
IMC-A12 in patients with Soft Tissue and Ewings Sarcoma or PNET.

Condition

- Other condition
- Soft tissue neoplasms malignant and unspecified

Synonym

Ewing's sarcoma/PNET, tissue cancer

Health condition

Ewing's sarcoma and peripheral neuroectodermal tumor (PNET)

Research involving
Human

Sponsors and support

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

Intervention

Keyword: Ewing's sarcoma, IMC-A12, peripheral neuroectodermal tumor (PNET), Soft Tissue sarcoma

Outcome measures

Primary outcome

Efficacy Assessments:

Patients will be evaluated for response according to RECIST; patients will be reevaluated every 6 weeks, with confirmatory assessment at least 4 weeks subsequent to initial documentation of objective response.

The 12-week PFS will be measured as a binary variable. The treatment of a given patient will be considered *successful* if radiological evaluation performed at 12 weeks after the start of therapy indicates stable disease (SD), partial response (PR), or complete response (CR) as defined by RECIST. All other cases, including those who experience progressive disease (PD) or death before the 12 week evaluation, will be considered *unsuccessful.*

Overall PFS is the interval from the date of first treatment until date of objectively determined PD or death due to any cause.

The ORR is the best confirmed objective response from the date of first

treatment until disease progression/recurrence (taking as reference for progressive disease the smallest measurements recorded since the treatment started). ORR will be defined as the proportion of patients achieving either PR or CR.

The time to response, in patients for whom the best overall response is either PR or CR, is measured from the date of first treatment to the first occurrence of either CR or PR.

The duration of response, in patients whose best overall response is either PR or CR, is measured from the time of the first occurrence of either CR or PR to the first date of progressive disease or death.

Overall survival is defined as the interval between date of enrollment and the date of death from any cause. Patients who are alive at time of study completion will be censored at the time the patient was last known to be alive.

The CBR is defined as the percentage of patients whose best overall response is either CR, PR, or SD.

Safety Assessments:

Safety will be evaluated using the National Cancer Institute Common Terminology Criteria for Adverse Events, Version 3.0, based on recorded adverse events, physical examinations, and clinical laboratory assessments.

Secondary outcome

The secondary objectives of this study are:

• To evaluate the overall PFS rate;

• To evaluate the objective response rate (ORR);

• To determine the time to onset of response and the duration of response;

• To determine overall survival (OS);

• To determine the clinical benefit rate (CBR);

• To evaluate the safety, tolerability, and adverse event profiles of IMC-A12

in the

treatment of metastatic or advanced squamous sarcoma; and

• To assess the development of antibodies against IMC-A12.

Study description

Background summary

The term soft tissue sarcoma (STS) refers to a group of histologically distinct subtypes of cancer originating in the connective tissue. These cancers are uncommon with fewer than 1% of all diagnosed malignancies and 2% of cancer-related mortality. However, STS is the sixth most common cancer in children, with an annual incidence of approximately 8 to 9 per million in the population age < 19 years. Ewing*s sarcoma (ES), an extremely aggressive primary bone tumor, and peripheral neuroectodermal tumor (PNET) are histologically distinct from the STS but they share similar genetic characteristics and cellular physiology and are therefore often grouped together as members of the Ewing family of tumors, and addressed together for analytical purposes.
The study drug IMC-A12 is recombinant human IgG1 monoclonal antibody which possesses high affinity for type I insulin-like growth factor receptor (IGF-IR), acts as an antagonist of IGF-I and IGF-II ligand binding and signaling, and inhibits the IGF-IR pathway, leading to a reduction in surface receptor density on treated cells. However, it does not bind to or recognize the human insulin receptor.
IMC-A12 inhibits the proliferation and growth of a variety of human tumor cell lines, both in vitro and in vivo. Because IMC-A12 is a recombinant human IgG1 antibody, it is also capable of inducing antibody dependent cell-mediated cytotoxicity that may inhibit the growth of tumor cells in vivo.

Study objective

The primary objective of this study is to determine the progression-free survival (PFS) rate assessed 12 weeks after the initiation of IMC-A12

monotherapy, administered every 2 weeks to patients with previously-treated, advanced or metastatic soft tissue and Ewing*s sarcoma/PNET.

Study design

This is an open label, five-tier, phase 2 trial. Patients will receive intravenous (I.V.) IMC-A12 10 mg/kg over 1 hour every 2 weeks. Patients will continue to receive treatment until there is evidence of progressive disease, unacceptable toxicity, or withdrawn consent.
A two-stage design to allow interim analysis of efficacy will be employed for each of the study*s five tiers.

Intervention

Test Products, Dose, and Mode of Administration:
IMC-A12 injection for intravenous use, supplied in single-use 90 mg/20-mL or 250 mg/50-mL vials containing 4.5 mg/mL in phosphate-buffered saline or 5 mg/mL in citrate-based saline, respectively, and administered intravenously at a dose of 10 mg/kg every 2 weeks.

Duration of Treatment:
A treatment cycle will be defined as 6 weeks, with radiological evaluation every cycle. There will be no interruption between treatment cycles. Patients will be treated until there is evidence of disease progression, toxicity requiring cessation, or withdrawal of consent.

Study burden and risks

The following examinations will be made:
• Medical history: at study start.
• Physical examination: height and weight, temperature, number of heartbeats and breaths per minute and blood pressure: at study start, at every 2 weeks, at end of therapy, and during follow-up period.
• Vital signs (temperature, number of heart beats and breaths, and blood pressure): at study start and every 2 weeks, before and after each IMC-A12 infusion, at end of therapy, and during follow-up period.
• BSA calculation: at every 2 weeks.
• Toxicity / adverse event assessment: at every 2 weeks, at end of therapy, and during follow-up period.
• ECOG PS evaluation: at study start, at every 2 weeks, at end of therapy, and during follow-up period.
• Electrocardiogram: at study start
• MUGA scan: at study start
• Routine imaging studies such as CT or MRI scans: at study start and at least every 6 weeks, or as clinically indicated.
• Blood taking approximately 10 ml: at study start, at every 2 weeks, at end of

therapy, and during follow-up period.
• Pregnancy Test - serum or urine pregnancy test: at study start and every 12 weeks.
• Upon enrollment, patients will receive one IV infusion of IMC-A12 every 2 weeks over about one hour.
• Tumor Measurements/Disease Response Assessment: at least every 6 weeks, or as clinically indicated.

Upon completion of the follow-up evaluation, all patients or family members will be contacted every 3 months to obtain information regarding subsequent therapy and survival. Survival information will be collected for all patients until patient death, up to a maximum of 1 year.

The following adverse reactions might occur:
• Allergic reactions/hypersensitivity to IMC-A12 such as flushing, rash, drug fever, urticaria, dyspnea, bronchospasm, allergy-related edema/angioedema, hypotension, anaphylaxis, stridor, hoarseness.
• Hyperglycemia (Diabetes).

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adolescents (12-15 years)
Adolescents (16-17 years)
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

1. The patient has histologically or cytologically-confirmed sarcoma of one of the following histologies: (1) Ewing*s sarcoma / PNET; (2) rhabdomyosarcoma; (3) leiomyosarcoma; (4) adipocytic sarcoma; or (5) synovial sarcoma.
2. The patient has measurable disease, defined as at least one lesion that can be accurately measured in at least one dimension (longest diameter to be recorded), with minimum lesion size >= 2 cm on conventional measurement techniques or >= 1 cm on spiral computed tomography (CT) scan.
3. The patient has at least one measurable lesion located outside of a previously irradiated area.
4. The patient has radiographic documentation of disease progression within 6 months prior to study entry (see Section 11.4 for a full definition of disease progression).
5. The patient has relapsed, refractory, and/or metastatic disease, incurable by surgery, radiotherapy, or other conventional systemic therapy.
6. The patient must have either been considered ineligible for systemic chemotherapy or received at least one previous regimen for relapsed, refractory, and/or metastatic disease.
7. The patient is age >= 12 years.
8. The patient has a life expectancy of > 3 months.
9. The patient has an Eastern Cooperative Oncology Group performance status (ECOG PS) of 0-1.
10. The patient has adequate hematologic function as defined by absolute neutrophil count >= 1500/µL, hemoglobin >= 9 g/dL, and platelet count >=100,000/µL.
11. The patient has adequate hepatic function as defined by a total bilirubin <= 1.5 x the upper limit of normal (ULN), and aspartate transaminase (AST) and alanine transaminase (ALT) <= 3 x the ULN (or <= 5 x the ULN in the presence of known liver metastases).
12. The patient has adequate coagulation function as defined by international normalized ratio (INR) <= 1.5 and partial thromboplastin time (PTT) no more than 5 seconds above the ULN.
13. The patient has adequate renal function as defined by serum creatinine <= 1.5 x the institutional ULN or creatinine clearance >= 60 mL/min for patients with creatinine levels above 1.5 x the ULN.
14. The patient has fasting serum glucose < 120 mg/dL or below the ULN.
15. Because the teratogenicity of IMC-A12 is not known, women of childbearing potential and men must agree to use adequate contraception (hormonal or barrier method of birth control; abstinence) prior to study entry and for the duration of study participation.
16. The patient or his or her legal guardian has the ability to understand and the willingness

to sign a written informed consent document.

Exclusion criteria

1. The patient has uncontrolled brain or leptomeningeal metastases.
2. The patient has not recovered to grade <= 1 from adverse events due to agents administered more than 3 weeks prior to study entry.
3. The patient is receiving any other investigational agent(s).
4. The patient has undergone major surgery, hormonal therapy (other than replacement), chemotherapy, radiotherapy, or any form of investigational therapy within 3 weeks prior to enrollment.
5. The patient has a history of treatment with other agents targeting the IGFR.
6. The patient has a history of allergic reactions attributed to compounds of chemical or biologic composition similar to that of IMC-A12.
7. The patient has poorly controlled diabetes mellitus. Patients with a history of diabetes mellitus are allowed to participate, provided that their blood glucose is within normal range (fasting < 120 mg/dL or below ULN) and that they are on a stable dietary or therapeutic regimen for this condition.
8. The patient has an uncontrolled intercurrent illness including, but not limited to, ongoing or active infection requiring parenteral antibiotics, symptomatic congestive heart failure, uncontrolled hypertension, clinically significant cardiac arrhythmia, or psychiatric illness/social situations that would limit compliance with study requirements.
9. The patient is receiving therapy with immunosuppressive agents.
10. The patient is pregnant or breastfeeding.
11. The patient is known to be positive for infection with the human immunodeficiency virus.
12. The patient has a history of another primary cancer, with the exception of: a) curatively resected non-melanomatous skin cancer; b) curatively treated cervical carcinoma in-situ; or c) other primary solid tumor curatively resected treated with no known active disease present and no treatment administered for the last 3 years.

Study design

Design

Study phase:	2
Study type:	Interventional
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	20-07-2009
Enrollment:	6
Type:	Actual

Ethics review

Approved WMO Date:	13-01-2009
Application type:	First submission
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	16-01-2009
Application type:	First submission
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	11-02-2009
Application type:	Amendment
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	02-04-2009
Application type:	Amendment
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	11-05-2009
Application type:	Amendment
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	16-12-2009
Application type:	Amendment
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	12-04-2010

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	EUCTR2007-0006719-2-NL
ClinicalTrials.gov	NCT00668148
CCMO	NL23496.058.09