Three versus five years of adjuvant imatinib as treatment of patients with operable GIST with a high risk ofr recurrence: A randomised phase III study

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This study has been transitioned to CTIS with ID 2024-512243-23-00 check the CTIS register for the current data. Progression free survival

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

Summary

ID

NL-OMON53086

Source
ToetsingOnline

Brief title
SSGXXII

Condition

- Malignant and unspecified neoplasms gastrointestinal NEC

Synonym
Gastrointestinal Stromal Tumor, GIST

Research involving
Human

Sponsors and support

Primary sponsor: Leids Universitair Medisch Centrum
Source(s) of monetary or material Support: scandinavian sarcoma group

Intervention

Keyword: GIST

Outcome measures

Primary outcome

An open-label, 2-arm, prospective, randomised, multicentre phase III trial.

Patients diagnosed with GIST who have completed 3 years of adjuvant imatinib, who are free from GIST recurrence after 3 years of adjuvant imatinib, and who have a high risk of recurrence despite 3 years of adjuvant imatinib will be randomly allocated to one of the following 2 arms in a 1:1 ratio:

A. to further 24 months of adjuvant imatinib (i.e. the planned total duration of adjuvant imatinib is 5 years)

B. to stop imatinib (i.e. the planned total duration of adjuvant imatinib is 3 years)

The study participants will be followed up for a minimum of 10 years post-randomisation or until death.

Secondary outcome

toxiity and overall survival

Study description

Background summary

Three years of imatinib is considered the standard duration of adjuvant therapy for patients with operable high-risk GIST based on the findings of the SSGXVIII/AIO. Yet, many patients are still at a high risk of GIST recurrence after completion of 3 years of adjuvant imatinib, and might benefit from further adjuvant imatinib therapy.
The risk of GIST recurrence after 3 years of adjuvant imatinib can be estimated

using prognostic factors. Based on the analyses made on the SSGXVIII trial data, the most important factors that predict the risk of GIST recurrence in a patient population treated with 3 years of adjuvant imatinib are tumour mitotic count and tumour site. Patients with a high tumour mitotic count and GIST located at a non-gastric site have the greatest risk.
Study hypothesis: Further 2 years of adjuvant imatinib may improve recurrence-free survival (RFS) of patients who are at a high risk of GIST recurrence despite completion of 3 years of adjuvant imatinib.

Study objective

This study has been transitioned to CTIS with ID 2024-512243-23-00 check the CTIS register for the current data.

Progression free survival

Study design

An open-label, 2-arm, prospective, randomised, multicentre phase III trial.
Patients diagnosed with GIST who have completed 3 years of adjuvant imatinib, who are free from GIST recurrence after 3 years of adjuvant imatinib, and who have a high risk of recurrence despite 3 years of adjuvant matinib will be randomly allocated to one of the following 2 arms in a 1:1 ratio:
A. to further 24 months of adjuvant imatinib (i.e. the planned total duration of adjuvant imatinib is 5 years)
B. to stop imatinib (i.e. the planned total duration of adjuvant imatinib is 3 years)
The study participants will be followed up for a minimum of 10 years post-randomisation or until death.

Intervention

5 vrs 3 years of adjuvant imatinib in GIST high risk for recurrence after surgery

Study burden and risks

limited, as imatinib has limited side effects and is well known to the treating physicians

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

1. Age >= 18 years.
2. Morphological and immunohistological documentation of GIST (immunostaining for KIT [CD117] and/or DOG-1 positive, or mutation of KIT or PDGFRA present in tumour tissue).
3. Macroscopically complete surgical resection of GIST (either R0 or R1 resection).
4. Mutation analysis of KIT and PDGFR genes has been carried out.
5. A high risk of GIST recurrence, either
1) gastric GIST with mitotic count >10/50 HPFs, or >10/5mm2, or
2) non-gastric GIST with mitotic count >5/50 HPFs, or >5/5mm2, or
3) non gastric GIST with neoadjuvant imatinib and initially larger than 10 cm
4) tumour rupture
Tumour rupture (spillage of the tumour contents into the abdominal cavity) may have occurred either before or at surgery. Tumour rupture is defined by spillage of the tumour contents into the abdominal cavity. A core needle biopsy from the tumour, or tumour bleed with no apparent spillage of the tumour contents, are not considered ruptures.
If only a small amount of pretreatment tumour tissue is available from a core

needle biopsy, it is acceptable to multiply the mitotic count obtained form fewer than 50 HPF's to approximate the counts obtained from 50 HPFs in surgical biopsies, or to multiply the count obtained form a tumour tissue area less than 5 mm2 to approximate the counts obtained from the 5 mm2 area. However, if only minimal amount of tumour tissue is available form a core needle biopsy (from 5 or fewer HPFs, or only 1 mitosis can be indentified), multiplication should not be attemted and is not considered acceptable.
6. ECOG performance status <= 2.
7. Adequate organ function, defined as serum total bilirubin <1.5 x ULN (upper limit of normal), serum AST (SGOT) and ALT (SGPT) <2.5 x ULN, creatinine <1.5 x ULN; blood ANC (neutrophil count) >=1.0 x 109/L, platelet count >=100 x 109/L.
8. Female patients of childbearing potential must have a negative pregnancy test within 14 days before initiation of study drug dosing. Postmenopausal women must have amenorrhoea for at least 12 months to be considered of non-childbearing potential. Male and female patients of reproductive potential must agree to employ an effective barrier method of birth control throughout the study and for up to 3 months following discontinuation of study drug. For females, a highly effective method for birth control must be used, which means that the method can achieve a failure rate of less than 1% per year when used consistently and correctly. All females of child-bearing potential must be informed of such methods, and must also, if sexually active, accept a monthly pregnancy test during treatment if randomized to prolonged imatinib use.
9. Patient willing to be followed up at the study site regardless of the result of randomisation.
10. Patient has provided a written, voluntary informed consent prior to study-specific screening procedures

Exclusion criteria

1. Presence of distant metastases or local recurrence of GIST.
2. Not willing to donate tumour tissue and/or blood samples for the study molecular studies.
3. Presence of a substitution mutation at PDGFRA codon D842 (usually D842V).
4. Administration of adjuvant imatinib longer than for 3 years is planned regardless of the result of randomisation, or *life long* imatinib administration is planned.
5. Prior adjuvant (+ neoadjuvant) therapy with imatinib mesylate for at least 35 months has not been completed, or the total duration of prior adjuvant (+ neoadjuvant) imatinib administration exceeds the total duration of 38 months.
6. Neoadjuvant imatinib for a duration that exceeds 12 months.
7. Longer than 4-week break during adjuvant imatinib administration.
8. The dose of imatinib at completion of 3 years of adjuvant imatinib was 200 mg per day or less or greater than 800 mg per day.
9. Patient has received any investigational anti-cancer agents during adjuvant imatinib or between completion of adjuvant imatinib and the date of

randomisation.
10. Patient has been free of another malignancy for less than 5 years except if the other malignancy is not currently clinically significant nor requiring active intervention, or if the other malignancy is one of the following: basal cell skin cancer,a cervical carcinoma in situ, a small (2cm or less in diameter) node negative breast cancer (pT1N0M0), a low Gleason score (,8) local (T1 or T2) prostate cancer. Recent existence of any other malignant disease is not allowed.
11. Patient with Grade III/IV cardiac disease as defined by the New York Heart Association Criteria (i.e., congestive heart failure, myocardial infarction within 6 months of study entry).
12. Female patients who are pregnant or breast-feeding.
13. Severe and/or uncontrolled medical disease (i.e., uncontrolled diabetes, severe chronic renal disease, or active uncontrolled infection).
14. Known diagnosis of human immunodeficiency virus (HIV) infection.
15. Patient with a significant history of non-compliance to medical regimens or with inability to grant reliable informed consent
16. Inability of difficulty in swallowing tablets
17. Patients with chronic or active hepatitis B

Study design

Design

Study phase:	3
Study type:	Interventional
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Completed
Start date (anticipated):	28-03-2017
Enrollment:	15
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Glivec
Generic name:	imatinib
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	30-12-2016
Application type:	First submission
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

Approved WMO Date:	09-01-2017
Application type:	First submission
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

Approved WMO Date:	21-08-2017
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

Approved WMO Date:	24-11-2017
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

Approved WMO Date:	15-01-2018
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden)

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Approved WMO Date:	02-08-2019
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
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Approved WMO Date:	26-08-2019
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
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Approved WMO Date:	12-08-2022
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
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Approved WMO Date:	22-08-2022
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
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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
EU-CTR	CTIS2024-512243-23-00
EudraCT	EUCTR2014-000898-39-NL
CCMO	NL56780.058.16