SSG XXV: The stop-GIST trial
Discontinuation of imatinib in patients with oligo-metastatic gastrointestinal stromal tumor that has become radiologically undetectable with treatment

A prospective multicenter phase II study

The trial "SSG XXV: The stop-GIST trial" is an Oslo University Hospital sponsored, prospective, open-label, 1-group, multicenter phase II trial evaluating discontinuation of imatinib in highly selected patients treated with imatinib longer than 5 years for oligo-metastatic GIST (≤ 3 metastases) and who have no detectable GIST lesions on CT/MRI imaging following complete surgical resection (R0/R1-resection) or radiofrequency ablation (RFA) of the metastases.

SPONSOR:

Oslo University Hospital
The Norwegian Radium Hospital
Department of Oncology
Ullernchausseen 70
0379 Oslo
Norway

EudraCT number: 2016-003774-40

Protocol ID: "SSG XXV: The stop-GIST trial"

ClinicalTrials.gov Identifier: NCT02924714

Version no.: 5.0
Version date: 24.AUG.2017

Innhold

Contact details 4

Signature page 5

Protocol synopsis 6

Protocol Version Log 10

Visit schedule and assessments (Table 1) 11

1 Introduction 13
- **1.1 Gastrointestinal stromal tumour (GIST)** 13
- **1.2. Treatment of metastatic GIST patients** 14
- **1.3. Imatinib mesylate** 14
- **1.4. Adverse events of imatinib in metastatic GIST trials** 14
- **1.5. Discontinuation of imatinib** 15

2 Study objectives 17

3 Investigational plan 17
- **3.1 Overall study design** 17
- **3.2 Study population** 18
  - **3.2.1 Patient population** 18
  - **3.2.2 Inclusion and exclusion criteria** 18
- **3.3 Study assignment** 19
- **3.4 Patients and treatments** 20
  - **3.4.1 Study patients** 20
  - **3.4.2 Patient discontinuation in the study** 20
  - **3.4.3 Concomitant therapy** 20
  - **3.4.4 Treatment after disease progression** 20
  - **3.4.5 End of study** 20
- **3.5 Visit schedule and assessments** 20
  - **3.5.1 Visit schedule** 20
  - **3.5.2 Screening assessments** 21
  - **3.5.3 Tumour assessments** 21
  - **3.5.4 Laboratory assessments and physical examination** 21
  - **3.5.5 Quality of Life** 22
  - **3.5.6 Toxicity reporting** 22
  - **3.5.7 Patient safety and event reporting** 23
  - **3.5.8 Potential risks and benefits** 23

4 Data management and monitoring 23
- **4.1 Case report forms (CRFs)** 23
- **4.2 Source data** 23
- **4.3 Study Monitoring** 24

5 Central pathology evaluation 24
- **5.1 Mandatory pathology information** 24

6 Central radiological review 24

7 Molecular and translational studies 24
- **7.1 Explorative analyses of GIST-related genes and gene expression** 25
- **7.2 Serum, plasma and whole blood samples** 25

8 Statistical methods 26
8.1 Sample size and power considerations 26
8.2 Populations 26
8.3 Efficacy evaluation 26
8.4 Number of analyses 27
8.5 Quality of Life 27
9 Notable scales 27
10 Publication policy and authorship 28
11 Procedures and instructions 28
11.1 Administrative procedures 28
11.1.1 Changes to the protocol 28
11.1.2 Monitoring procedures 29
11.1.3 Recording of data and retention of documents 29
11.1.4 Auditing procedures 29
11.1.5 Disclosure and confidentiality 29
11.2 Ethics and Good Clinical Practice 29
11.2.1 Institutional Review Board/Independent Ethics Committee 30
11.2.2 Informed consent 30
12 References 31
13 Appendix I 34

Contact details

Sponsor:	**Stein Kaasa, MD PhD** Department of Oncology Oslo University Hospital Tel: +47 2293 4418 E-mail: stekaa@ous-hf.no
Principal Investigator:	**Øyvind Sverre Bruland, MD PhD** Department of Oncology Oslo University Hospital Tel: +47 2293 4000/ +47 2293 4767 E-mail: osb@ous-hf.no
International coordinator	**Heikki Joensuu, MD PhD** Comprehensive Cancer Center Helsinki Phone: +35 8407210438 E-mail: heikki.joensuu@hus.fi
Sub-Investigator:	**Ivar Hompland, MD** Department of Oncology Oslo University Hospital Tel: +47 2293 4000 E-mail: ivahom@ous-hf.no
Statistician:	**Menuela Zucknick, PhD** Department of Biostatistics Oslo University Hospital
Project Manager:	**Signe Øien Fretland** Department of Oncology Oslo University Hospital Tlf: +47 2293 4714 sigfre@ous-hf.no

Signature page

Title: Discontinuation of imatinib in patients with oligo-metastatic gastrointestinal stromal tumor that has become radiologically undetectable with treatment: A prospective multicenter phase ll study

Protocol ID no: SSG XXV: The Stop-GIST trial

EudraCT no: 2016-003774-40

I hereby declare that I will conduct the study in compliance with the Protocol, ICH GCP and the applicable regulatory requirements:

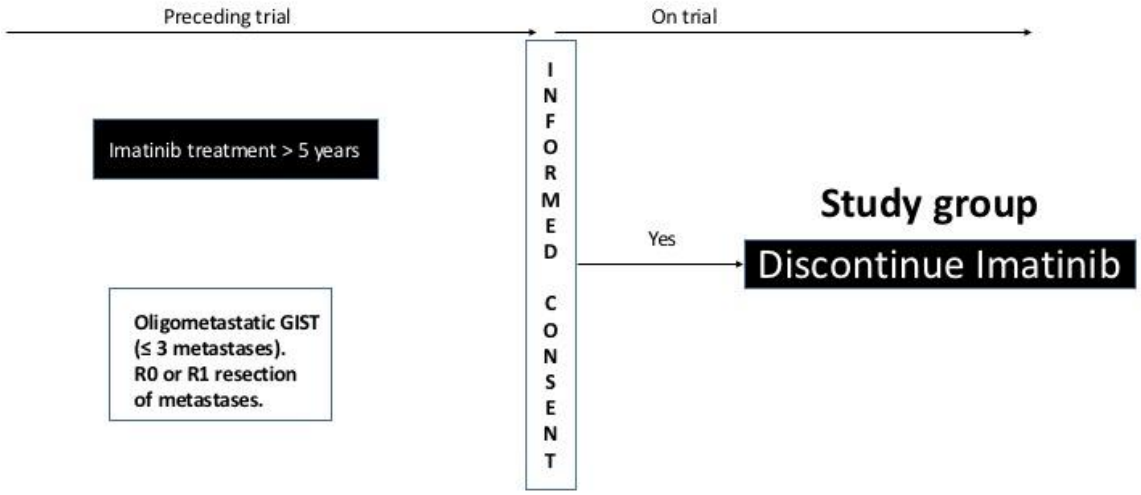
Name	Title	Role	Signature	Date
Stein Kaasa	Head of Department of Oncology	Sponsor's representative		
Øyvind Sverre Bruland	Professor in clinical oncology	Principal Investigator		

Protocol synopsis

TITLE	**Discontinuation of imatinib in patients with oligo-metastatic gastrointestinal stromal tumor that has become radiologically undetectable with treatment: A prospective multicenter phase ll study.**
SPONSOR	Oslo University Hospital, The Norwegian Radium Hospital.
STUDY RATIONALE	Patients with metastatic GIST are currently recommended to have life-long treatment with tyrosine kinase inhibitors (TKI). The standard first-line treatment is imatinib, which is switched to other drugs at progression or if the patient does not tolerate imatinib. The prevailing hypothesis is that imatinib and other TKIs fail to completely eradicate metastatic GIST and that progression is inevitable if imatinib treatment is discontinued. However, the SSGXVIII/AIO trial found that 3 years of adjuvant imatinib yielded both superior RFS and OS rates compared to 1 year of adjuvant imatinib, which finding does not exclude the hypothesis that sufficiently long administration of imatinib might sometimes eradicate subclinical GIST. Furthermore, a few retrospective studies have reported favorable survival outcomes with surgery of residual disease in metastatic GIST in patients responding to imatinib, and a subset (approximately 20%) of patients with advanced GIST do not progress within the first 10 years on imatinib. Imatinib treatment comes with potential side-effects and, as of now, considerable costs to the society. Therefore, discontinuation of imatinib in highly selected patients, i.e. those who have received imatinib for longer than 5 years and who have undergone metastasectomy of all macroscopic oligometastatic disease, needs to be explored as a novel treatment strategy. Discontinuation might lead to detection of durable complete remissions without imatinib or even cure.
TARGET GROUP	Patients treated with imatinib longer than 5 years for oligo-metastatic GIST (≤ 3 metastases) and who have no longer detectable GIST lesions on CT/MRI imaging following complete surgical resection (R0/R1-resection) or RFA of the metastases.
END POINTS	**Primary:** Three-year progression-free survival (PFS) after discontinuation of imatinib. **Secondary:** • Overall survival • Quality of life **Exploratory:** • Plasma ctDNA as a liquid biopsy in follow-up • Histologic and molecular genetics evaluation of excised tumor tissue • Changes in the blood cell counts and blood biochemistry after stopping imatinib (includes hematology, serum transaminases, electrolytes, creatinine, creatinine kinase)

TRIAL DESIGN	An open-label, 1-group, prospective, multicenter phase II trial. Patients with histologically diagnosed GIST with oligo-metastatic disease (≤ 3 metastases) who have had the metastases surgically resected (R0/R1) or radio-frequency ablated, or whose metastases (≤ 3) have become undetectable in imaging with systemic treatment, and who have been treated with imatinib for more than 5 years without signs of progression.

Trial Design



NUMBER OF PATIENTS	31 patients entered in the study.
TARGET POPULATION	**Inclusion criteria:** To be eligible for the inclusion in the study, each patient must fulfill each of the criteria below. 1. Age ≥ 18. 2. Morphological and immunohistochemical documentation of GIST (immunostaining for KIT/ (CD117) and/or DOG-1 (anoctamin-1)) must be positive on a tumour sample. Patients with demonstrated mutation in *KIT* or *PDGFRA* may be entered to the study despite negative immunostaining for KIT and DOG-1 provided that tumour histology is compatible with GIST. 3. Confirmed metastatic disease by radiology, histology, or both in history. 4. >5.0 years of treatment with imatinib for metastatic disease when the breaks in imatinib administration are taken into account. 5. No more than 3 detectable metastases in the liver and/or in the abdomen on imaging of the abdomen and the pelvis or at surgery during the course of the disease. 6. Macroscopically complete resection of all metastases (either R0 or R1 surgery). Patients who have microscopically infiltrated margins (or suspected

	microscopical infiltration, R1) are eligible to enter the study. Radiofrequency ablation (RFA) of liver metastases in place of surgery is also allowed. Patients whose oligometastatic disease had disappeared completely so that no remainig target lesion for surgery or RFA can be identified (including absence of residual cyst-like lesions) are allowed to enter the study. 7. Eastern Co-operative Oncology Group (ECOG) performance status ≤ 2. 8. Patient has provided a written, voluntary informed consent prior to study entry and any study-specific procedures. **Exclusion criteria:** Patients who fulfill any of the following criteria will be excluded: 1. Patients with metastases outside of the abdomen (e.g. in the bones or lungs). 2. Not willing to donate tumor tissue and/or blood samples for the molecular studies that aim at predicting of GIST recurrence. 3. Presence of a mutation in *SDH*, or other evidence for SDH deficiency. 4. Presence of neurofibromatosis-1. 5. R2 resection of the primary tumour or metastasis. 6. Patient with inability to grant reliable informed consent. 7. Inability to comply with the scheduled follow-up. 8. Progressive disease during imatinib or other systemic treatments for GIST, before or after surgery/RFA of the metastases.
STUDY TREATMENT	**Study group: Discontinuation of imatinib** No imatinib or other anti-cancer treatment will be administered.
ASSESSMENTS:	**Primary:** • Progression-free survival (PFS) is defined by the time interval between the date of imatinib discontinuation and the date of first detection of GIST progression or death, whichever occurs first. Patients alive without progression are censored on the date of last follow-up **Secondary**: • Overall survival (the time period between the date of imatinib discontinuation and the date of death). • Quality of Life (EQ-5D instrument). **Exploratory:** • To explore the relationship between study endpoints and blood biomarkers including, but not limited to, *KIT*/*PDGFRA* mutations in cell-free circulating DNA in plasma and circulating growth factor and cytokine levels. • To explore the relationships between study endpoints and biomarkers in resected tumors prior to study entry. • Changes in the blood cell counts and blood biochemistry after stopping imatinib as compared to the values on

	imatinib (includes comparisons in blood cell counts, serum transaminases, creatinine, and electrolytes between the baseline values measured on imatinib and the values measured at 2, 5 and 8 months after stopping imatinib). **Pre-planned interim analysis:** • 1-year PFS in the first 15 patients included. The study is terminated if 10 or more of the 15 patients (≥67 %) have progression of disease or withdraws from the study within the first 12 months from the date of study entry.
STATISTICAL CONSIDERATIONS	This is a superiority study as compared with historical controls regarding the main endpoint (PFS). Based on historical data, discontinuation of imatinib in patients with metastatic GIST is associated with rapid recurrence/progression. In the BRF-14 study where patients were randomised to discontinue imatinib at 1 and 3 years on treatment, the 2-years PFS was 10 % and 16 %, respectively. Based on these observations, the historical 3-year PFS can be assumed to be 15 %. An improvement in 3-year PFS from 15 % to 35 % is considered as clinically significant. To find this effect with 80% power using a one-sided statistical significance level of 0.05, 26 patients are needed. To allow a drop-out rate of 15 %, 31 patients will be included in the trial (power 0.8, one-sided alpha 0.05).

Protocol Version Log

Protocol version (date)	Substantial amendment	Changes	Section
V1.0 (13Jun2016)	NA	NA	
V2.0 (24Oct2016)	NA	New Project Manager contact	Contact Details
		Addition of Signature Page	Signature Page
		Additional section with potential risks and benefits	3.5.8
V3.0 (20Dec2016)		Added SSG and OUS logo, in addition to EudraCT number and ClinicalTrials.gov identifier	Front page
		Creatinin Kinase deleted	Protocol Synopsis
		Radiological central review included	3.5.3 Tumour assessments and 6 Central Radiological Review
		Adverse Event grade 1-2 included.	3.5.6 Toxicity reporting
V4.0 (15Mar2017)	No	Changed protocol ID / title from "SSG XXIV: The Stop-GIST trial" to "SSG XXV: The Stop-GIST trial"	Front page Synopsis
V5.0 (24Aug2017)	Yes	Defined End of Study Specified that all amendments to the protocol should also be submitted to competent authorities Added Monitoring Plan as appendix I	3.4.5 End of study 11.1.1 Changes to the protocol 13 Appendix I

Visit schedule and assessments (Table 1)

	Screening/ Baseline	Study group										Follow-up (study arm)			
Months from randomisation		**2**	**5**	**8**	**11**	**15**	**19**	**23**	**27**	**31**	**36**	**42**	**48**	**54**	**60**
Informed consent (a)	0 to -14 d														
Inclusion/ exclusion criteria	0 to -14 d														
Medical history & demographics (b)	0 to -14 d														
Regular medication (c)	0 to -14 d														
Adverse events (d)	0 to -14 d														
Physical examination (e)	0 to -14 d	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Weight	0 to -14 d	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Height	0 to -14 d														
ECOC performance status	0 to -14 d	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Haematology (f)	0 to -14 d	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Blood biochemistry (g)	0 to -14 d	x	x	x	x	x	x	x	x	x	x	x	x	x	x
CT/MRI of the abdomen & pelvis (h)	0 to -28 d	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Quality of life (i)	0 to -7 d		x		x		x		x		x		x		x
Research plasma & serum (j)	0 to -7 d	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Research blood (k)	0 to -7 d	x													
Resected metastatic tumour tissue collection (l)		x													

(a) Written informed consent must be signed and dated by the patient prior any study-specific procedures. The centre must keep a log of the patients who received the informed consent.

(b) Includes age, gender, race, date of first GIST histological diagnosis; As far as possible following should be collected: surgical margin, tumour size (cm), location, rupture, mitotic count (per 50 HPFs); date of starting imatinib; dose of imatinib (the highest and the lowest daily doses given for a period longer than 1 week), interruptions of imatinib dosing lasting longer than 2 weeks; major side-effects of imatinib recorded (grade 1- 4). As far as possible location of metastases (liver or peritoneal cavity), type of resection of metastases (R0 or R1), date of metastasis surgery if done, date of RFA if done, size of metastases (tumour longest diameter in centimetres), pathological response to treatment (complete/partial pathological response) should be collected.

(c) Daily imatinib dose in milligrams before discontinuation.

(d) Adverse events of imatinib at the time of study entry. Collected according to the CTCAE v.4.0.

(e) Includes blood pressure and pulse rate.

(f) Includes haemoglobin, total WBC count, platelet count, and a differential count including neutrophils, lymphocytes, monocytes, eosinophils and basophils. In the event that haematology evaluation has been performed within 14 days prior to the date of study inclusion, these tests do not need to be repeated.

(g) Includes serum or plasma creatinine; serum total bilirubin, ALT, AST, alkaline phosphatase. LDH, albumin, calcium, magnesium and phosphate at follow-up months 2 and 5. In the event that blood biochemistry evaluation has been performed within 14 days prior to the study entry, these tests do not need to be repeated at screening.

(h) Done with a contrast agent if possible. In the event that CT/MRI of the abdomen and the pelvis has been performed within 28 days from the date of inclusion, imaging does not need to be repeated. Further imaging examinations with CT, MRI, US, PET or CT-PET may be performed whenever considered clinically indicated after study entry.

(i) EQ-5D instrument.

(j) ≥5 mL serum and ≥5 mL plasma, stored at -70˚C or colder. The baseline sample is preferentially drawn when the patient is on imatinib. Research serum and plasma are collected also at the time of tumour recurrence.

(k) ≥5 mL whole blood, stored at -70˚C or colder. The baseline sample is drawn when the patient is on imatinib.

(l) If possible, DNA and RNA extraction from the resected metastatic tissue block, biopsies for a tissue microarray, and 5 tumour tissue sections (4-5 um thick)

1 Introduction

1.1 Gastrointestinal stromal tumour (GIST)

Gastrointestinal stromal tumour (GIST) is a relatively rare mesenchymal neoplasm, but the most common sarcoma of the gastrointestinal tract with an annual incidence of approximately 10 cases per million.[1, 2] Furthermore, GIST is rare as compared with many gastrointestinal tract carcinomas, but it is the most common type of soft tissue sarcoma in some series.[1] GISTs occur in both genders at about similar frequency, the median age at the time of the diagnosis being approximately 63 years.[3] GISTs are most commonly found in the stomach (40-70%), but they can occur in any part of the gastrointestinal tract. About 20-40% of GISTs arise from the small intestine, and 5-15% from the colon or the rectum.[3] GIST may rarely arise outside of the gastrointestinal tract from the omentum, mesentery, retroperitoneum or other intra-abdominal sites.[3, 4] Most GISTs are local tumours when first detected, but 15-20 % have already given rise to overt metastases.[5] Metastases are commonly found in the peritoneum or the liver, whereas regional lymph node metastases are rare except in paediatric GIST.[6, 7]

The diagnosis is based on tissue morphology and a characteristic profile in immunohistochemical staining. Most (95%) of GISTs stain positively for the KIT receptor tyrosine kinase (CD117), and an equally large proportion stain positively for anoctamin-1 (DOG-1, a chloride channel protein). GISTs are usually negative for muscle immunomarkers such as desmin. The diagnosis can be confirmed in almost all cases by immunohistochemistry.[8]

Mutation analysis of *KIT*, *PDGFRA* (encodes platelet-derived growth factor receptor alpha), and preferably also other genes, such as *BRAF* and *SDH* (encodes succinate dehydrogenase), is required for the treatment planning. Most (approximately 75%) GISTs harbour *KIT* mutation that is usually found in *KIT* exon 11 (70%), and less commonly in exon 9 (5-10%), exon 13 (1%), exon 17 (1%), and rarely in other exons. *PDGFRA* mutation is present in approximately 15% of GISTs; most of these are located in *PDGFRA* exon 18, and less frequently in exon 12, exon 14, or other exons. GISTs that lack *KIT* or *PDGFRA* mutation (called *KIT*/*PDGFRA*wild-type GISTs; 10% of all GISTs) may harbour mutated succinate dehydrogenase gene (*SDHA*, *-B*, *-C* or *–D*), neurofibromatosis-1 gene (*NF1*), or rarely mutated *BRAF*, *RAS* or other genes.[8]

Most GISTs are cured by surgery, but approximately 40% of GISTs that are local at the time of first detection will eventually give rise to distant metastases. Distant metastases are usually detected within the first 10 years from the diagnosis.[3] Advanced GIST can often be successfully managed with tyrosine kinase inhibitors (TKIs) that inhibit the key molecular drivers of GIST, mutated KIT and PDGFRA.[9] The median duration of response of patients with advanced GIST when treated with the current standard first-line agent, imatinib mesylate, is approximately 2 to 3 years.[10] Most GISTs (80-90%) respond to imatinib, but certain mutated kinases and wild-type GISTs are resistant to imatinib and other TKIs. Mutations at the *PDGFRA* locus D842 (usually D842V) confer imatinib resistance, and many GISTs that are wild-type (wt) with respect of *KIT* and *PDGFRA* are unlikely to respond to imatinib, such as wild-type GISTs associated with NF-1, and likely SDH deficient GISTs.[11, 12]

1.2. Treatment of metastatic GIST patients

Imatinib revolutionized the treatment of patients with advanced GIST[9] and became the model of targeted therapy in solid tumours; it is now considered to be the standard first-line medical treatment of GIST.[13] The median duration of response to imatinib in advanced GIST is 2 to 3 years, and approximately 20% of the responses last for 10 or more years.[14, 15] Most GISTs eventually progress on imatinib, which may then be replaced by other tyrosine kinase inhibitors (TKIs), such as sunitinib (second-line therapy) and regorafinib (third-line therapy).[13] The frequently cited treatment guidelines recommend continuous and 'life-long' TKI administration for patients with advanced GIST.[13] This has served many patients well as patients now live for a median duration of approximately 5 years after the detection of metastatic disease compared to only about 18 months prior to the TKI era.[10, 16] Although there has been a dramatic improvement in GIST outcomes, the prevailing hypothesis is that imatinib and other TKIs fail to completely eradicate the disease and that progression of metastatic GIST is inevitable if imatinib treatment is discontinued.

1.3. Imatinib mesylate

Imatinib mesylate is currently the standard first-line treatment of metastatic GIST. Imatinib is a selective inhibitor of a few tyrosine kinases including KIT, BCR-ABL, ABL, ARG, and PDGFRA.[17] Imatinib is administered orally and taken with food to avoid upper gastrointestinal tract irritation. The most commonly used daily dosage is 400 mg. There is evidence from advanced GIST that patients with *KIT* exon 9 mutation benefit from a higher dose (800 mg/day) than the standard 400 mg daily dose.[18]

Imatinib is well absorbed after oral administration with C_{max} achieved within 2-4 hours post-dose. Mean absolute bioavailability is 98%. Following oral administration in healthy volunteers, the elimination half-lives of imatinib and its major active metabolite, the N-desmethyl derivative, were approximately 18 and 40 hours, respectively. Mean imatinib AUC increased proportionally with increasing dose in the range 25 mg to 1000 mg. There was no significant change in the pharmacokinetics of imatinib on repeated dosing, and accumulation is 1.5-2.5 fold at steady state when imatinib is dosed once daily. At clinically relevant concentrations of imatinib, binding to plasma proteins in *in vitro* experiments is approximately 95%, mostly to albumin and α_1-acid glycoprotein. CYP3A4 is the major enzyme responsible for metabolism of imatinib. Other cytochrome P450 enzymes, such as CYP1A2, CYP2D6, CYP2C9 and CYP2C19, play a minor role in its metabolism.

1.4. Adverse events of imatinib in metastatic GIST trials

Imatinib is moderately to well tolerated, and several of the adverse effects can be ameliorated with supportive measures or dosing modification.[19] While severe adverse effects are infrequent, virtually all treated patients have side effects, the most frequent being anaemia, periorbital oedema and watery eyes, diarrhoea, muscle cramps (typically in hands and legs), fatigue, and nausea (Table I).[9, 20] Compliance, i.e. adherence to self-administered imatinib, can be a challenge for patients on chronic therapy. In the SSGXVIII/AIO trial, the proportion of patients who discontinued imatinib during the assigned treatment period not due to disease recurrence was 26 % in the 36-month group compared to 13 % in the 12-month group.[21].

Table II. Frequently recorded adverse events in the B2222 and EORTC/ISG/AGITG trials in patients receiving 400 mg daily.

Adverse event**	Adverse event of any Grade		Adverse event of Grade 3 or 4	
	B2222 (%)	EORTC (%)	B2222 (%)	EORTC (%)
Any	97	99	21	32
Anaemia	5	89	1	7
Leukopenia	6	43	3	3
Neutropenia	8	41	7	7
Fatigue	30	68	N.A	6
Oedema	71	71	1	3
Nausea	51	49	N.A	3
Diarrhoea	40	48	1	2
Myalgia	37	24	N.A	0,2

**Graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 2.0.

1.5. Discontinuation of imatinib

There is evidence to support the current practice of administering imatinib in advanced GIST until progression, or indefinitely in the absence of progression. Only a small minority (0% to 5%) of patients with advanced GIST achieve complete response (CR) with imatinib, most responses being partial responses (PR) or stable disease (SD).[9, 20, 22] In the BFR14 trial, patients with advanced GIST who were responding to first-line imatinib were randomly assigned either to continue imatinib or to stop it at the time of randomisation. Almost all patients who stopped had GIST progression within 2 years from the date of randomisation, regardless of whether the patient had been on imatinib 1, 3, or 5 years prior to imatinib discontinuation. This led to a substantially shorter time to GIST progression in the stop group. Importantly, stopping imatinib did not significantly influence overall survival (OS), likely since most patients in the group that stopped responded to imatinib reinstitution.[23-26] This suggests that imatinib discontinuation does not influence the rate at which imatinib-resistance mutations emerge in advanced GIST.

More than 80% of patients with advanced GIST either respond to or achieve durable SD with first-line imatinib treatment, and less than 20% patients progress.[9, 10, 20] If a patient relapses after adjuvant imatinib, the first choice of treatment is still imatinib, and apparently similar response rates can be achieved as in imatinib-naïve patient populations with metastatic GIST. In the SSGXVIII/AIO trial, 84% of patients who completed adjuvant imatinib and then received imatinib for recurrent GIST responded to imatinib reintroduction. This was independent of the length of prior imatinib therapy in the adjuvant setting (1 or 3 years).[27]

Metastasectomy may lead to a long remission or even to cure in the treatment of some cancer types, including sarcoma. Approximately 30% of the patients with soft tissue sarcoma or osteosarcoma who relapse with lung metastases and who undergo metastasectomy become long-term survivors.[29, 30] Similarly, about 30% of selected colorectal cancer patients who have liver metastases resected survive for 5 years or longer after metastasectomy.[31]

Imatinib may not be curative despite up to 80% of patients with metastatic GIST respond or have SD on the drug,[20, 22, 32] but metastasis surgery in combination with TKI therapy might

further improve outcomes. A few retrospective studies have reported favourable outcomes with surgery in metastatic GIST patients responding to imatinib.[33-35] In a small prospective study 41 patients with liver metastases from GIST were randomised to imatinib alone versus imatinib followed by metastasis surgery and further administration of imatinib after surgery. The patients were followed up for 36 months. The 1-year and 3-year survival rates were higher in the surgery group as compared with the imatinib-only group (100% and 89% vs. 85% and 60%, respectively).[36] In another similar small randomised trial performed in China, patients treated with imatinib and metastasis surgery tended to have longer PFS and had statistically significantly longer overall survival than patients treated with imatinib alone.[37] Hence, although results from fully powered randomised trials are lacking, surgery of residual disease might prolong the duration of remission and extend survival, as excision of the macroscopic GIST tumours may delay emergence of imatinib resistance and thus the risk of subsequent disease progression.

Interestingly, studies have shown that a proportion of patients with chronic myeloid leukaemia (CML) who have maintained durable complete molecular remission did not have rapid CML recurrence despite imatinib discontinuation, suggesting that some patients with CML might be cured with imatinib.[38, 39]

An analysis of the SSGXVIII/AIO trial found that the patients who had GIST recurrence during adjuvant imatinib typically had high tumour cell proliferation rates.[40] In the subgroup analysis of the same trial, patients who had >10 mitoses within 50 high-power fields (HPFs) of the microscope in the primary GIST benefitted from 3 years of adjuvant imatinib as compared to 1 year of treatment, whereas patients with ≤10 mitoses did not.[41] Although subgroup analyses should, in general, be interpreted with great caution, these observations lead to a hypothesis that long imatinib treatments could have a potential to change the biology of GIST to more slowly progressing forms of the disease, as the quickly proliferating GISTs progress early and the rapidly proliferating cancer cells may be more efficiently eradicated by imatinib than the slowly progressing ones. Coupled with the findings from the BRF14 study that suggest that discontinuation of imatinib does not affect overall survival, these observations suggest that imatinib treatment could be discontinued in patients who no longer have macroscopic metastases and who have been on imatinib for many years without rapid recurrence of GIST, and some of such patients might even have been cured from advanced GIST.

In conclusion, we hypothesize that in highly selected patients, i.e. those who have received imatinib for longer than 5 years and who have undergone metastasectomy of all macroscopic oligometastatic disease, stopping imatinib may lead to durable maintained complete remission without the imatinib-associated side effects. Perhaps some GISTs might not recur during the entire life-time of such patients. This hypothesis prompted us to explore the possibility of stopping imatinib in highly selected GIST patients[42] and now to be further explored in is this prospective clinical trial. The patients will be followed up with frequent imaging after stopping of imatinib, and will have imatinib restarted if GIST recurs. The current study has strict selection criteria of patients, and the patient population is therefore substantially more selected than in the BRF14 trial. Due to the rarity of such highly selected patients, a randomised trial is not considered possible as was the case also in the imatinib discontinuation trials carried out in CML,[38,39] and an international multicentre design is preferred.

2 Study objectives

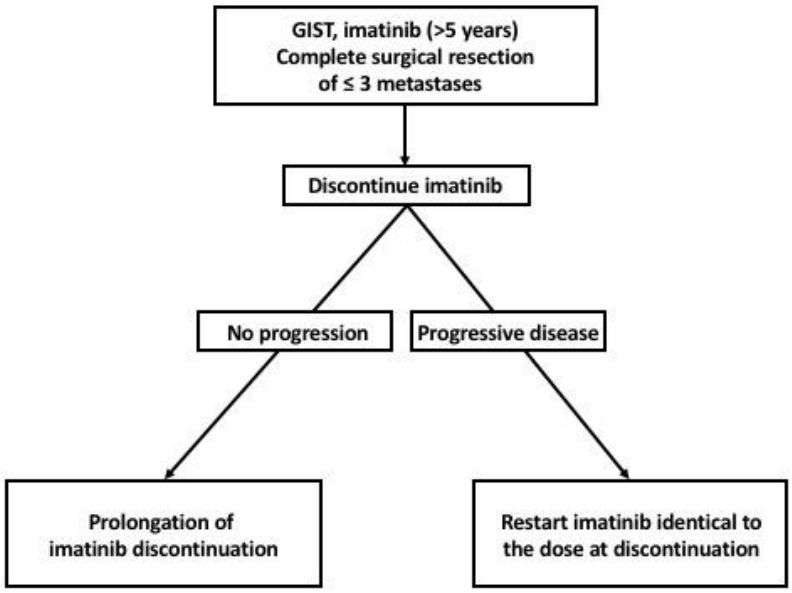
Primary objective
The primary objective of the study is to document progression-free survival (PFS) in patients who discontinue imatinib after treatment with imatinib for longer than 5 years for oligo-metastatic GIST (≤ 3 metastases) and who have no detectable overt GIST lesions in CT/MRI imaging following complete surgical resection (R0/R1-resection), radiofrequency ablation (RFA) of the metastases, or following systemic treatment for oligometastatic GIST

Secondary objectives
The secondary objectives are to study overall survival and the quality of life (QoL) in the patients who discontinue imatinib. Data about response to reinstitution of imatinib after GIST progression will be collected from the hospital records from those patients who restarted imatinib after completion of the study.

Exploratory objectives
The exploratory objectives are to study the relationship between study endpoints and circulating biomarkers, relationships between study endpoints and biomarkers in resected tumors prior to study entry, and changes in the blood cell counts and blood biochemistry after stopping imatinib as compared to the baseline values on imatinib, measured at the time of the screening examinations.

3 Investigational plan

3.1 Overall study design



This is an open-label, one-group, multicentre, phase II study conducted to investigate PFS in patients treated with imatinib longer than 5 years for oligo-metastatic GIST (≤ 3 metastases) and who have no detectable overt GIST lesions in CT/MRI imaging following complete surgical resection (R0/R1-resection), RFA of the metastases, or after systemic treatment for oligometastatic GIST.

The study participants are assigned to stop imatinib and will be monitored for cancer progression longitudinally with physical examination, measuring blood cell counts and blood chemistry, and with CT/MRI examinations. A pre-planned interim analysis will be carried out when the first 15 patients in the study have been follow-up of for one year. The study will be terminated if 10 or more of the 15 patients (≥67 %) have recurrence of GIST or discontinue the study within the first 12 months from the date of study entry. The primary analysis of the study will be carried out when the median follow-up time of the study patients is at least 36 months. A total of 31 patients will be enrolled. If GIST recurs, imatinib will be restarted at the same dose as at study entry.

3.2 Study population

3.2.1 Patient population

Patients with advanced (metastatic) GIST with
1) Imatinib treatment longer than 5 years for advanced GIST.
2) ≤ 3 metastases detected during the course of the disease and who have no detectable overt GIST lesions in CT/MRI imaging following complete surgical resection (R0/R1-resection) of the metastases, RFA of the metastases, or whose metastases are no longer detectable by imaging (CR).

3.2.2 Inclusion and exclusion criteria

Inclusion criteria:

To be eligible for inclusion in the study, each patient must fulfil each of the criteria below.

1. Age ≥ 18.

2. Morphological and immunohistochemical documentation of GIST (immunostaining for KIT/(CD117) and/or DOG-1 (anoctamin-1)) must be positive on a tumour sample. Patients with demonstrated mutation in *KIT* or *PDGFRA* may be entered to the study despite negative immunostaining for KIT and DOG-1 provided that tumour histology is compatible with GIST.

3. >5.0 years of treatment with imatinib for metastatic disease when the breaks in imatinib administration are taken into account.

4. No more than 3 detectable metastases in the liver and/or in the abdomen in imaging of the abdomen and the pelvis during the course of the disease or at surgery.

5. Confirmed metastatic GIST in history by radiology, histology, or both.

6. Macroscopically complete resection of all metastases (either R0 or R1 surgery). Patients who have microscopically infiltrated margins (or suspected microscopical infiltration, R1) are

allowed to enter the study. RFA of liver metastasis is allowed in place of surgery. Patients whose oligometastatic disease had disappeared completely so that no remaining target lesion for surgery or RFA can be identified (including absence of residual cyst-like lesions) are allowed to enter the study.

7. Eastern Co-operative Oncology Group (ECOG) performance status ≤ 2.

8. Patient has provided a written, voluntary informed consent prior to study entry and any study-specific procedures.

Exclusion criteria:
To be eligible for inclusion in the study, each patient must not have any of the criteria below.

1. Patients with metastases outside of the abdomen (e.g. in the bones or lungs).

2. Not willing to donate tumor tissue and/or blood samples for the molecular studies that aim at predicting of GIST recurrence.

3. Presence of an *SDH* mutation or other evidence for SDH deficiency.

4. Presence of neurofibromatosis-1.

5. R2 resection of the primary tumor or metastasis.

6. Patient with inability to grant reliable informed consent.

7. Inability to comply with the scheduled follow-up.

8. Progressive disease during imatinib or other systemic treatments for GIST, or before or after surgery/RFA of the metastases.

3.3 Study assignment

Informed consent must be obtained before any testing of a patient's eligibility is carried out.

Patients who meet the inclusion criteria and none of the exclusion criteria for the study will be registered and given a specific study identity number at the Oslo University Hospital (OUS) secretariat.

The centre must keep a log of all patients who received patient information and/or the consent form of the study, **including also those patients who were eligible to the study but who did not wish to participate in the study.** The log contains the patient initials, the date when the patient information/consent form was received by the patient, patient eligibility to the study, the decision on study participation, and the decision to consent for collection of survival outcome data.

3.4 Patients and treatments

3.4.1 Study patients

The patients assigned to the study arm discontinue imatinib within 14 days of the date of study inclusion (the date of registration to the study).

Imatinib will remain discontinued until one of the following will occur:

• GIST recurrence
• Withdrawal from the study

3.4.2 Patient discontinuation in the study

The reasons for patient discontinuation in the study must be captured on the CRFs. If the patient discontinues the study, the reason is categorized in the CRFs as one of the following:

1. Withdrawal from the study
2. GIST progression
3. Death (from GIST or from an inter-current cause)
4. Other (for example, severe protocol violation, administrative problems)

Relevant information that is related to the reason for study discontinuation, including possible contributory factors, will be included on the CRF.

3.4.3 Concomitant therapy

Administration of any other anticancer agents including other TKIs, chemotherapy, biological agents, or experimental agents is NOT permitted. The patients should receive the medication indicated for their concomitant diseases.

3.4.4 Treatment after disease progression

Treatment after disease progression is usually imatinib, which may be restarted at the same dose as was given before study entry. Imatinib after GIST progression will be administered and monitored according to the institute standard procedures.

3.4.5 End of study

The end of study is defined as the last subject's last visit, defined as either the date of the last visit of the last subject to complete the study or the date at which the last data point from the last subject (required for statistician analysis) was received, whichever is the later date.

3.5 Visit schedule and assessments

3.5.1 Visit schedule

Patient must be followed at the study centre according to the table 1 "Visit schedule and assessments".

The subjects will be followed with CT/MRI at 3-month intervals during the first year in the study arm, 4-month intervals the second and third year, and at 6-month intervals year four and five. The minimum duration of follow-up is 5 years as calculated from the date of study entry, but follow-up for 10 years after study entry is recommended using annual imagining of the abdomen. When clinically indicated, more frequent follow-up visits and CT/MRI imaging

may be organized. All routine assessments must be performed within ± 28 days of the day indicated on the visit schedule.

3.5.2 Screening assessments

Written informed consent must be obtained before any study specific medical procedures are performed. The screening assessments are done when the patient is on imatinib.

Immunohistochemical evidence of KIT or DOG-1 overexpression must exist at the study entry, and tumour *KIT* and *PDGFRA* mutation analysis needs to be available. However, patients with demonstrated mutation in *KIT* or *PDGFRA* may be entered to the study despite negative immunostaining for KIT and DOG-1 provided that tumour histology is compatible with GIST. An attempt to sequence all frequently mutated *KIT* and *PDGFRA* exons may be made during the study from the stored tumour material.

The demographic data collected includes age, gender and race. As far as possible other data will be collected and includes the date of first GIST histological diagnosis, type of surgical resection (R0 or R1) and GIST characteristics (tumour longest diameter in centimetres, location in the GI tract/abdomen, tumour rupture before or at surgery, and mitotic count per 50 HPFs and/or 5 mm^2 of the microscope), and whether adjuvant imatinib was given, for how long, and at which dose. Also, if possible, location of metastases (liver or peritoneal cavity), type of resection of metastases (R0 or R1), whether RFA is done, size of metastases (the longest diameter in centimetres), and response to imatinib treatment (complete/partial pathological response) should be collected. The dates of metastasis surgery and/or RFA will also be captured on the CRFs (if done). The imatinib dose administered is recorded, as well as the starting date of imatinib, the highest and the lowest dose of imatinib used for a time period longer than 2 weeks, interruptions of imatinib dosing lasting longer than 2 weeks, and major prior imatinib side-effects (grade 1-4), if any.

Physical examination and assessment of the ECOG performance status are carried out, and height and weight are recorded. In the event that haematology or biochemistry evaluation have been performed within 14 days from the date of inclusion, this evaluation needs not to be repeated, and may be used as the Day 1 values.

CT or MRI of the abdomen and the pelvis must be performed within 28 days prior to the study entry. If CT or MRI has been performed within 28 days from the date of inclusion, it does not need to be repeated.

3.5.3 Tumour assessments

Tumour assessments should be performed with the same method (CT or MRI) throughout the study. All assessments should be performed within 28 days of the scheduled day of assessment, and whenever clinically indicated otherwise.
Radiological tumour assessment at inclusion and if progression should be stored at the local study site and submitted for central review per request.

3.5.4 Laboratory assessments and physical examination

3.5.4.1 Laboratory evaluations

Laboratory analyses will be carried out according to the Visit Schedule. Laboratory values will be recorded on the Follow-up Form (circle the correct range) even when normal.

Haematology
Haematology includes assessment of haemoglobin, total WBC count, platelet count, and a differential count including neutrophils, lymphocytes, monocytes, eosinophils and basophils.
Biochemistry
Biochemistry includes serum or plasma creatinine; serum albumin, total protein, total bilirubin, alkaline phosphatase, AST (SGOT), ALT (SGPT). Lactate dehydrogenase (LDH), and magnesium, calcium and phosphate (Pi) will be performed at 2 months and 5 months on study.

3.5.4.2 Physical examinations
A physical examination including pulse rate and blood pressure will be performed according to the Visit Schedule. Information about the physical examination must be present in the source documentation at the study site.
There is no CRF to capture routine normal findings from physical examinations assessments. Data on concomitant diseases will not be captured on the CRFs.

3.5.4.3 Performance status and body weight
Measurements of performance status and body weight will be performed according to the Visit Schedules. The ECOG Performance Status Scale will be used in this study.

3.5.5 Quality of Life
Quality of life (QoL) will be measured at baseline and at the follow-up according to the Visits schedule. The EuroQol (EQ)-5D instrument will be used (http://www.euroqol.org/).

The patient is requested to fill the EQ-5D instrument prior to attending the treating physician, preferable at home in tranquil surroundings. The EQ-5D instrument is available in different languages, and the instrument written in the native language of the patient should be used.

3.5.6 Toxicity reporting
As there is no study drug, toxicity reporting is not relevant to the study. The adverse effects related to imatinib prior to study entry will be collected on the CRFs, and the study patients will be monitored for persistence/disappearance of the adverse effects during the study.

As far as possible, adverse event grade 1-4 will be described by the NCI/NIH Common Terminology Criteria for Adverse Events (CTCAhE) version 4.0 using severity grades 1-5 (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm).[29]

The severity grade of an adverse event provides a qualitative assessment of the extent or intensity of an adverse event, as determined by the investigator or as reported by the patient. The severity grade does not reflect the clinical seriousness of the event, only the degree or extent of the affliction or occurrence (e.g. severe nausea, mild seizure), and does not reflect the relationship to study drug.

Severity grade for events not listed in the NCI/NIH CTCAE v.4.0
1 = Grade 1 Mild
2 = Grade 2 Moderate
3 = Grade 3 Severe
4 = Grade 4 Life-threatening
5 = Grade 5 Death

3.5.7 Patient safety and event reporting

Feasibility and adherence to the discontinuation of imatinib will be reported for all trial subjects. Each GIST patient must be carefully monitored during the course of the protocol. Necessary assessments will include physical examinations, vital signs (systolic/diastolic blood pressure and pulse rate), clinical laboratory tests (haematology, blood biochemistry), and CT/MRI evaluations. CRF reporting after discontinuation of imatinib will be conducted according to the visit schedule. A CRF has to be completed at all visits for the time period the patient is on study after discontinuation of imatinib.

Since there is now study drug in the trial, SAEs related to a study drug cannot be reported.

3.5.8 Potential risks and benefits

When the patient discontinues imatinib, eventual side effects of the medication will disappear. The patient will be followed very closely, and additional radiological examination is performed at each control.
By attending this study and discontinue imatinib the patient may have a greater risk of progression of the disease. However, available data indicate that if a patient develops progression the patient will again achieve stable disease by restarting imatinib.

4 Data management and monitoring

4.1 Case report forms (CRFs)

Data items are collected to the CRFs by the investigators and entered into the electronic study database, located at the OUS secretariat, Oslo, Norway. Principal Investigator is responsible for assuring that data entered into the CRF is complete, accurate, and that entry is performed in a timely manner. The signature or initials of the investigator will attest the accuracy of the data on each CRF. If any assessments are omitted, the reason for such omissions will be noted on the CRFs. Corrections, with the reason for the corrections will also be recorded. Paper CRF will be used in this study.

4.2 Source data

The medical records for each patient should contain information which is important for the patient's safety and continued care, and to fulfill the requirement that critical study data should be verifiable.

To achieve this, the medical records of each patient should clearly describe at least:

- That the patient is participating in the study, e.g. by including the enrollment number and the study code or other study identification;
- Date when Informed Consent was obtained from the patient;
- Results of all assessments confirming a patient's eligibility for the study;
- Diseases (past and current; both the disease studied and others, if relevant);
- Surgical history, as relevant;
- Results of assessments performed during the study;
- WHO performance status assessments conducted as part of the study, if applicable;
- Visits to the clinic / telephone contacts during the study;
- Date of, and reason for, withdrawal from study;
- Date of death and cause of death, if available;
- Additional information according to local regulations and practice

4.3 Study Monitoring

The investigator will be visited based on a monitoring plan (appendix I) by the Clinical Study Monitor, who will check the following:

- Informed consent process
- Adherence to protocol
- Maintenance of required regulatory documents
- The dates of study entry, GIST progression, TKI restarting and death
- Data completion on the CRFs including query resolution and source data verification (SDV).

The monitor will review the relevant CRFs for accuracy and completeness and will ask the site staff to adjust any discrepancies as required.

When the responsible study monitor has checked and verified the CRFs, the data will be entered into a computer database for further handling and statistical evaluation.

Sponsor's representatives (e.g. monitors, auditors) and/or competent authorities will be allowed access to source data for source data verification in which case a review of those parts of the hospital records relevant to the study may be required. Monitoring may be organized locally for each participating country.

5 Central pathology evaluation

The pathology reports from the primary tumour and metastasis will be sent to a Central Pathology Lab of the study located at the OUS, Norway, for evaluation. Tumour tissue samples of any deviant reports will be shipped for secondary review.

5.1 Mandatory pathology information

Immunohistochemistry for CD117 (KIT) and/or DOG-1, and GIST morphology should have been conducted at each clinical site. A representative tumour tissue block will be shipped to the Central Pathology Lab only if a deviant pathology report exists. Collection of tissue for histopathological screening and mutation analyses (*KIT* and *PDGFRA* status) will be done locally during the study. The representative paraffin block will reside at the local hospital for future research purposes.

6 Central radiological review

Radiological tumour assessment at inclusion and at progression should be stored at the local study site and submitted for central secondary review at the OUS, Norway, per request.

7 Molecular and translational studies

The key purpose of the molecular studies is to discover molecular markers that could be used in the prediction of GIST recurrence/progression, and thus in identification of the patients who benefit from life-long imatinib therapy.

Blood samples will be shipped to the same Central Laboratory of the study located at the OUS, Norway. The samples will be shipped to the Department of Oncology, Oslo University Hospital, Oslo, Norway; for analyses described below.

7.1 Explorative analyses of GIST-related genes and gene expression

Mutation analysis of genes related to GIST genesis, progression, drug sensitivity, drug resistance, imatinib metabolism or host defence may be carried out from tumour tissue and/or peripheral blood DNA. DNA extracted from the tissue will be analysed for the presence of *KIT* and *PDGFRA* mutations when needed, as well as mutations and expression of other genes deemed important, including genes such as *BRAF*, *RAS*, or gene mutational signatures. An attempt to analyse mutations and gene copy number alterations of a large panel of potentially GIST-related genes and to perform whole exome analysis using next generation sequencing will be made. The results of such future analyses will be correlated to patient outcomes. Besides DNA, RNA and microRNA will be extracted from the tumour tissue, and used for gene expression analyses or other analyses related to the study. The data generated will be linked with the clinical data to study factors associated with GIST progression and recurrence, patient outcome, drug resistance, and host defence.

Protein analyses may also be conducted using paraffin tissue blocks, either using whole sections or tissue microarrays. We will attempt to identify protein or gene aberrations that may be associated with resistance or response to imatinib therapy (such as aberrations related to drug resistance, cell signalling, alternative growth factor receptors, cell cycle progression or apoptosis) or may be associated with patient prognosis and with GIST recurrence (such as cell cycle proliferation rate-related proteins and genes, apoptosis-related proteins and genes, GIST differentiation-related proteins and genes, or host-defence-associated proteins and genes).

7.2 Serum, plasma and whole blood samples

Serum samples (≥ 5 mL of serum) and plasma samples (≥ 5 mL of plasma) are collected longitudinally as indicated in the Visit Schedule (Table 1), and stored at -70˚C or colder. A whole blood sample (≥ 5 mL of blood) is collected at baseline. **The baseline samples should be collected when the patient is still on imatinib**.

Samples will be subjected for analysis of serum and plasma proteins, DNA or other molecules relevant to GIST. The serum and plasma protein levels will be correlated with the clinical and outcome data. Samples are collected at the study centres, and shipped on a mutually agreed date to the Central Laboratory (OUS, Oslo, Norway).

A small fraction of the circulated DNA is derived from tumour cells. DNA extracted from plasma samples will be subjected to gene mutation analyses, in particular *KIT* and *PDGFRA* mutations. Plasma samples may also be used for proteomics analyses, and other protein or DNA analyses that might be associated with GIST progression, recurrence, survival or drug resistance. Serum samples are planned to be subjected to analysis of circulating growth factors and to metabolomics assays using mass spectrometry, and of other factors that might be associated with GIST progression, recurrence, survival or drug resistance.

8 Statistical methods

8.1 Sample size and power considerations

The sample size calculation is based on the analysis of the primary objective: PFS at three years after discontinuation of imatinib. PFS is defined as the time interval between the date of discontinuation of imatinib and the date of first detection of GIST progression or death, whichever occurs first. The progression date is defined as the date when the physician first suspects GIST progression in a sequence of events that leads to the diagnosis of progressive GIST. This date will be documented on the CRF by the investigator and will be used as such in the analysis.
The power of the study was derived from comparison to historical controls regarding the main endpoint (PFS). Based on historical data, discontinuation of imatinib in patients with metastatic GIST is associated with rapid recurrence/progression. In the BRF-14 study where patients were randomized to discontinue imatinib at 1 and 3 years of treatment, the 2-years PFS was 10 % and 16 %, respectively. The historical 3-years PFS is expected to be 15 %. An improvement in 3-years PFS from 15 % to 35 % in the study arm is considered clinically significant. To find this effect with 80% power using a one-sided significance level of 0.05, 26 patients are needed. To allow a drop-out rate of 15 %, 31 patients will be included in the trial (power 0.8, one-sided alpha 0.05).

8.2 Populations

The data analysis will be performed in:

• **Efficacy Population (EP):** The primary efficacy population will consist of patients who have a confirmed GIST, were eligible for the study and signed an informed consent, and were included in the study.

The EP will be the primary analysis population. For the potential purposes of reporting the data to the regulatory authorities the EP population will be used.

8.3 Efficacy evaluation

Final analysis
The study is designed to investigate the proportion of patients who are alive without GIST progression after a median follow-up of approximately 36 months after study entry.

The primary endpoint PFS will be measured from the date of discontinuation of imatinib to the date of first documentation of progression or death (from any cause), whichever occurs first. Patients alive without GIST progression are censored on the date of last follow-up. Survival estimates will be calculated using the Kaplan-Meier estimator. Comparison between subgroups, if relevant, will be based on the log-rank test and univariate Cox models. Estimates for hazard ratios will be provided with 95% confidence intervals.

The overall subgroup effects will be quantified by a hazard ratio, which will be estimated using a Cox proportional hazards regression model (or a suitable generalisation such as concordance regression, [43] if the model assumptions for the Cox model are not met) with the discontinuation group in the model.
A number of exploratory analyses may be performed for the primary endpoint:
• Log-rank test and Cox proportional hazards model (or a suitable generalisation) stratified by relevant parameters such as, but not limited to the tumour site (gastric or non-gastric),

localization of metastasis (liver, intraperitoneal, both), metachronous and synchronous metastasis.
• A Cox proportional hazard model (or a suitable generalisation) estimating survival while adjusting for the established prognostic variables. In addition, the centre or country and other relevant baseline variables may be included in the model.

Overall survival will be analysed as a secondary endpoint in the final analysis, based on the early data detected by the time of the analysis. Overall survival will be measured from the date of discontinuation of imatinib to the date of death resulting from any cause. Patients alive are censored at the time of last follow-up. Similar methods as for the primary variable will be used in the data analysis.

Exploratory analyses will be carried out to evaluate the data of the molecular analyses carried out. The statistical analyses will be dependent on the biological factors investigated and the analysis methodology used, and will be defined separately for each molecular study.

8.4 Number of analyses

Two analyses are planned, one interim and one final analysis. The interim analysis is planned in the first 15 patients included. The analysis will be performed when 15 patients will have one year of follow-up and the following key parameters will be checked: the enrolment of the patients and the rate of progression. The study is terminated if 10 or more of the 15 patients (≥67 %) have progression of disease or withdraws from the study within the first 12 months from the date of study entry. The final analysis will be performed when the patients without an event have a median follow-up time ≥ 36 months.

8.5 Quality of Life

The QoL analyses will be done as described in 3.5.5 (http://www.euroqol.org/).

9 Notable scales

NCI/NIH Common Terminology Criteria for Adverse Events (CTCAE) v. 4.0, see http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

Eastern Cooperative Oncology Group performance status scale Grade Description

0 Fully active, able to carry on all pre-disease activities without restriction.
1 Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature e.g. light housework, office work.
2 Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours.
3 Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4 Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5 Dead

10 Publication policy and authorship

The final publication will be written by the principal investigator(s). An effort will be made to include every investigator who has entered eligible study patients as a co-author, who have participated in analysis of the study data, in drafting of the manuscript, and who can assume responsibility of the study report, if the space allows. A small number of accrued patients may suffice for authorship if the space allows, and provided that the investigator has significantly contributed to acquisition of data and drafting of the manuscript.

The number of patients entered will be the major determinant of the sequence of co-authors. The study statistician, surgeons, and person(s) responsible for translational analyses may also be included as a co-author. All investigators who have included an eligible patient in the study will be acknowledged. Investigators participating in this multicentre study agree not to present data gathered from one centre or a small group of centres before the full publication, unless formally agreed to by all other investigators.

The results of this study may be published as one or more publications and presented at scientific meetings. The final report will be published. The Safety Analysis report and results of analyses of tissue or serum biological variables may be published provided that the Study Steering Committee considers their publication to be valuable to the scientific community and/or to advance management of GIST.

11 Procedures and instructions

11.1 Administrative procedures

11.1.1 Changes to the protocol

Changes (excluding minor administrative, technical or grammar changes) to this protocol requires a written protocol amendment that must be approved by the Principal Investigator Ethics Committee, and competent authorities (medical agency) where relevant, before implementation.
Amendments significantly affecting the safety of the patients, the scope of the investigation or the scientific quality of the study require additional approval by the Institutional Review Board/Independent Ethics Committee/Research Ethics Board (IRB/IEC/REB) and by the regulatory authorities. Examples of amendments requiring such approval are:

1. significant changes in the study design,
2. increases in the number of invasive procedures to which subjects are exposed,
3. addition or deletion of a test procedure required for safety monitoring.

These requirements for approval should in no way prevent any immediate action from being taken by the investigator in the interests of preserving the safety of all patients included in the trial. Examples of administrative changes not requiring formal protocol amendments and IRB/IEC/REB approval include:

1. changes in the staff,
2. minor changes to the exclusion or inclusion criteria used to select study patients,

11.1.2 Monitoring procedures
The monitoring plan is enclosed as appendix I.

11.1.3 Recording of data and retention of documents
The investigator must complete the CRF provided, must store copies of the CRF in a secure place and transmit the data to the OUS secretariat. Data on subjects collected on CRF during the trial will be documented in an anonymous fashion and the subject will only be identified by the subject identity number, and by his/her initials if also required. If, as an exception, it is necessary for safety or regulatory reasons to identify the subject, the investigators are bound to keep this information confidential.

The investigator must maintain source documents for each patient in the study, consisting of all demographic and medical information, including laboratory data, imaging results etc, and keep the signed informed consent form. All information on CRFs must be traceable to these source documents in the patient's file.

Essential documents, as listed below, must be retained by the investigator for as long as needed to comply with the national and international regulations. The investigator agrees to adhere to the document retention procedures by signing the protocol. Essential documents include:

1. IRB/IEC/REB approvals for the study protocol and all amendments,
2. all source documents and laboratory records,
3. CRF copies,
4. patients' informed consent forms (with study identity number and title of trial),
5. any other pertinent study document.

11.1.4 Auditing procedures
Auditing procedures are not required by the protocol.

11.1.5 Disclosure and confidentiality
By signing the protocol, the investigator agrees to keep all information not previously published or not generally available in strict confidence and to request similar confidentiality from his/her staff and the IRB/IEC/REB. Study documents will be stored appropriately to ensure their confidentiality.

11.2 Ethics and Good Clinical Practice
This study must be carried out in compliance with the protocol and the principles of Good Clinical Practice:

1. ICH Harmonized Tripartite Guidelines for Good Clinical Practice 1996, Directive 91/507/EEC, The Rules Governing Medicinal Products in the European Community,
2. Declaration of Helsinki and amendments, concerning medical research in humans (Recommendations Guiding Physicians in Biomedical Research Involving Human Subjects).

The investigator agrees to adhere to the instructions and procedures described in the protocol and thereby to adhere to the principles of Good Clinical Practice that it conforms to.

11.2.1 Institutional Review Board/Independent Ethics Committee

Before implementing this study, the protocol, the proposed informed consent forms and other information to subjects, must be reviewed by a properly constituted IRB/IEC/REB. A signed and dated statement that the protocol and informed consent have been approved by the IRB/IEC/REB must be given to the principal investigator before study initiation. Any amendments to the protocol, other than administrative ones, must be approved by this committee.

11.2.2 Informed consent

The investigator must explain to each subject (or legally authorized representative) the nature of the study, its purpose, the procedures involved, the expected duration, the potential risks and benefits involved and any discomfort it may entail. Each subject must be informed that participation in the study is voluntary and that he/she may withdraw from the study at any time and that withdrawal of consent will not affect his/her subsequent medical treatment or relationship with the treating physician.

This informed consent should be given by means of a standard written statement, written in non-technical language. The subject should read and consider the statement before signing and dating it, and should be given a copy of the signed document. If the subject cannot read or sign the documents, oral presentation may be made or signature given by the subject's legally appointed representative, if witnessed by a person not involved in the study, mentioning that the patient could not read or sign the documents. No patient can enter the study before his/her informed consent has been obtained.

12 References

1. Ducimetière F, Lurkin A, Ranchère-Vince D, et al: Incidence of Sarcoma Histotypes and Molecular Subtypes in a Prospective Epidemiological Study with Central Pathology Review and Molecular Testing. PLoS ONE 6:e20294–14, 2011

2. Nilsson B, Bümming P, Meis-Kindblom JM, et al: Gastrointestinal stromal tumors: The incidence, prevalence, clinical course, and prognostication in the preimatinib mesylate era. Cancer 103:821–829, 2005

3. Joensuu H, Vehtari A, Riihimäki J, et al: Risk of recurrence of gastrointestinal stromal tumour after surgery: an analysis of pooled population-based cohorts. Lancet Oncol 13:265–274, 2012

4. Kim K-H, Nelson SD, Kim D-H, et al: Diagnostic relevance of overexpressions of PKC-θ and DOG-1 and KIT/PDGFRA gene mutations in extragastrointestinal stromal tumors: a Korean six-centers study of 28 cases. Anticancer Res 32:923–937, 2012

5. Emile JF, Brahimi S, Coindre JM, et al: Frequencies of KIT and PDGFRA mutations in the MolecGIST prospective population-based study differ from those of advanced GISTs. Med Oncol 29:1765–1772, 2011

6. Agaimy A, Wünsch PH: Lymph node metastasis in gastrointestinal stromal tumours (GIST) occurs preferentially in young patients ≤40 years: an overview based on our case material and the literature. Langenbecks Arch Surg 394:375–381, 2008

7. Zhang L, Smyrk TC, Young WF Jr, et al: Gastric Stromal Tumors in Carney Triad Are Different Clinically, Pathologically, and Behaviorally From Sporadic Gastric Gastrointestinal Stromal Tumors: Findings in 104 Cases. The American Journal of Surgical Pathology 34:53–64, 2010

8. Corless CL, Barnett CM, Heinrich MC: Gastrointestinal stromal tumours: origin and molecular oncology. Nature Reviews Cancer 11:865–878, 2011

9. Demetri GD, Mehren von M, Blanke CD, et al: Efficacy and safety of imatinib mesylate in advanced gastrointestinal stromal tumors. N Engl J Med 347:472–480, 2002

10. Blanke CD, Demetri GD, Mehren von M, et al: Long-Term Results From a Randomized Phase II Trial of Standard- Versus Higher-Dose Imatinib Mesylate for Patients With Unresectable or Metastatic Gastrointestinal Stromal Tumors Expressing KIT. Journal of Clinical Oncology 26:620–625, 2008

11. Corless CL, Schroeder A, Griffith D, et al: PDGFRA mutations in gastrointestinal stromal tumors: frequency, spectrum and in vitro sensitivity to imatinib. Journal of Clinical Oncology 23:5357–5364, 2005

12. Cassier PA, Fumagalli E, Rutkowski P, et al: Outcome of patients with platelet-derived growth factor receptor alpha-mutated gastrointestinal stromal tumors in the tyrosine kinase inhibitor era. Clinical Cancer Research 18:4458–4464, 2012

13. The ESMO/European Sarcoma Network Working Group: Gastrointestinal stromal

tumours: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Annals of Oncology 25:iii21–iii26, 2014

14. Joensuu H, P Hohenberger and Corless CL: Gastrointestinal stromal tumour. The Lancet 382:973–983, 2013

15. Demetri GD, Rankin CJ, Benjamin RS, et al: Long-term disease control of advanced gastrointestinal stromal tumors (GIST) with imatinib (IM): 10-year outcomes from SWOG phase III intergroup trial S0033. J Clin Oncol s, suppl; abstr

16. Gastrointestinal Stromal Tumor Meta-Analysis Group (MetaGIST): Comparison of Two Doses of Imatinib for the Treatment of Unresectable or Metastatic Gastrointestinal Stromal Tumors: A Meta-Analysis of 1,640 Patients. Journal of Clinical Oncology 28:1247–1253, 2010

17. Buchdunger E, Cioffi CL, Law N, et al: Abl protein-tyrosine kinase inhibitor STI571 inhibits in vitro signal transduction mediated by c-kit and platelet-derived growth factor receptors. J Pharmacol Exp Ther 295:139–145, 2000

18. Debiec-Rychter M, Sciot R, Le Cesne A, et al: KIT mutations and dose selection for imatinib in patients with advanced gastrointestinal stromal tumours. European Journal of Cancer 42:1093–1103, 2006

19. Joensuu H, Trent JC, Reichardt P: Practical management of tyrosine kinase inhibitor-associated side effects in GIST. Cancer Treatment Reviews 37:75–88, 2011

20. Verweij J, Casali PG, Zalcberg J, et al: Progression-free survival in gastrointestinal stromal tumours with high-dose imatinib: randomised trial. The Lancet 364:1127–1134, 2004

21. Joensuu H, Eriksson M, Sundby Hall K, et al: One vs three years of adjuvant imatinib for operable gastrointestinal stromal tumor: a randomized trial. JAMA 307:1265–1272, 2012

22. Blanke CD, Rankin C, Demetri GD, et al: Phase III Randomized, Intergroup Trial Assessing Imatinib Mesylate At Two Dose Levels in Patients With Unresectable or Metastatic Gastrointestinal Stromal Tumors Expressing the Kit Receptor Tyrosine Kinase: S0033. Journal of Clinical Oncology 26:626–632, 2008

23. Blay JY, Le Cesne A, Ray-Coquard I, et al: Prospective Multicentric Randomized Phase III Study of Imatinib in Patients With Advanced Gastrointestinal Stromal Tumors Comparing Interruption Versus Continuation of Treatment Beyond 1 Year: The French Sarcoma Group. Journal of Clinical Oncology 25:1107–1113, 2007

24. Le Cesne A, Ray-Coquard I, Bui BN, et al: Discontinuation of imatinib in patients with advanced gastrointestinal stromal tumours after 3 years of treatment: an open-label multicentre randomised phase 3 trial. Lancet Oncology 11:942–949, 2010

25. Blay JY, Perol D, Le Cesne A: Imatinib rechallenge in patients with advanced gastrointestinal stromal tumors. Annals of Oncology 23:1659–1665, 2012

26. Patrikidou A, Chabaud S, Ray-Coquard I, et al: Influence of imatinib interruption and rechallenge on the residual disease in patients with advanced GIST: results of the BFR14 prospective French Sarcoma Group randomised, phase III trial. Annals of Oncology 24:1087–

1093, 2013

27. Reichardt P, Hartmann JT, Hall KS, et al: Response to imatinib rechallenge of GIST that recurs following completion of adjuvant imatinib treatment: the first analysis in the SSGXVIII/AIO trial patient population. Eur J Cancer, Volume 47 , 15, 2011

28. Le Cesne A, Ray-Coquard I, Bui-Nguyen B: Time to secondary resistance (TSR) after interruption of imatinib (IM) in advanced GIST: updated results of the prospective French Sarcoma Group randomized phase III trial on long-term survival. J Clin Oncol 29: 2011 (suppl; abstr 10015)

29. Billingsley KG, Burt ME, Jara E, et al: Pulmonary metastases from soft tissue sarcoma: analysis of patterns of diseases and postmetastasis survival. Ann Surg 229:602–10– discussion 610–2, 1999

30. Kager L, Zoubek A, Pötschger U, et al: Primary metastatic osteosarcoma: presentation and outcome of patients treated on neoadjuvant Cooperative Osteosarcoma Study Group protocols. Journal of Clinical Oncology 21:2011–2018, 2003

31. Adams RB, Aloia TA, Loyer E, et al: Selection for hepatic resection of colorectal liver metastases: expert consensus statement. HPB 15:91–103, 2013

32. Demetri GD, Wang Y, Wehrle E, et al: Imatinib Plasma Levels Are Correlated With Clinical Benefit in Patients With Unresectable/Metastatic Gastrointestinal Stromal Tumors. J Clin Oncol 27:3141–3147, 2009

33. Raut CP, Posner M, Desai J, et al: Surgical management of advanced gastrointestinal stromal tumors after treatment with targeted systemic therapy using kinase inhibitors. J Clin Oncol 24:2325–2331, 2006

34. Gronchi A, Fiore M, Miselli F, et al: Surgery of Residual Disease Following Molecular-targeted Therapy With Imatinib Mesylate in Advanced/Metastatic GIST. Ann Surg 245:341–346, 2007

35. Tielen R, Verhoef C, van Coevorden F, et al: Surgical treatment of locally advanced, non-metastatic, gastrointestinal stromal tumours after treatment with imatinib. Eur J Surg Oncol 39:150–155, 2013

36. Xia L, Zhang MM, Ji L, et al: Resection combined with imatinib therapy for liver metastases of gastrointestinal stromal tumors. Surg Today 40:936–942, 2010

37. Du CY, Zhou Y, Song C, et al. Is there a role of surgery in patients with recurrent or metastatic gastrointestinal stromal tumours responding to imatinib: a prospective randomised trial in China. Eur J Cancer 50:1772-1778, 2014

38. Mahon F-X, Réa D, Guilhot J, et al: Discontinuation of imatinib in patients with chronic myeloid leukaemia who have maintained complete molecular remission for at least 2 years: the prospective, multicentre Stop Imatinib (STIM) trial. Lancet Oncol 11:1029–1035, 2010

39. Benjamini O, Kantarjian H, Rios MB, et al: Patient-driven discontinuation of tyrosine kinase inhibitors: single institution experience. Leuk Lymphoma 55:2879–2886, 2014

40. Joensuu H, Eriksson M, Hall KS et al. Risk factors for gastrointestinal stromal tumor recurrence in patients treated with adjuvant imatinib. Cancer 120:2325-2333, 2014

41. Joensuu H, Eriksson M, Sundby Hall K, et al. Adjuvant imatinib for high-risk GI stromal tumor: Analysis of a randomized trial. J Clin Oncol 34:244-250, 2016

42. Hompland I, Bruland ØS: Can Imatinib Be Safely Withdrawn in Patients with Surgically Resected Metastatic GIST? Anticancer Res 35:5759–5765, 2015

43. Dunkler D, Schemper M, Heinze G. Gene selection in microarray survival studies under possibly non-proportional hazards. Bioinformatics, 26(6), 784-790, 2010

13 Appendix I

Monitoring Plan for the Stop-GIST trial

Discontinuation of imatinib in patients with oligo-metastatic gastrointestinal stromal tumor that has become radiologically undetectable with treatment

This clinical trial should be monitored in accordance with the ethical principles that have their origin in the Declaration of Helsinki, and that are consistent with ”Good Clinical Practice” including ”International Conference on Harmonization Guidelines for Good Clinical Practice ICH-GCP” and applicable regulatory requirements.

Responsibilities

The monitoring activities will be performed by independent monitors from respective country. The national coordinator in each participating country is responsible for appointing the monitor and that he/she is appropriately trained, and has the scientific and/or clinical knowledge needed to monitor the trial adequately.

Monitoring will take place at all participating institutions in the respective countries.

Extent of monitoring

The need of initial monitoring of each site will be managed by a set of actions:

a) A common start meeting for investigators and research coordinators will be arranged in each participating country or group of countries.
b) The monitor will have a telephone contact with the site to ensure that all documents are in place, that the study team is educated and other necessary preparations done before the site will be allowed to enrol patients.
c) Each site should be visited as early as possible after the first subject has entered the trial in order to check protocol understanding and compliance.

When having on-going patients in the trial, a site must be visited once every 12 months, thereafter as needed. A more frequent monitoring may be indicated, e.g., if the recruitment is high or any specific problems have been identified at a site.

A closing visit will be done to each site at the end of the study.

Data to verify
At all study centres:

- Determining whether the investigator is maintaining the essential documents
- Determining whether the data required by the protocol are reported accurately on the CRFs and are complete, consistent with the source documents and ready for data entry.
- Determining protocol compliance
- Determining whether storage of study documents is accurate
- Determining whether handling and storage of biological samples are accurate.

Source data verification (SDV) for all patients:
Verify all variables (100 % SDV) in at least one patient in all centres and one out of five if ≥ five patients have been included (20 %).

Variables	Patient number (%) for source data verification
Patient identity (1)	100
Informed consent (2)	100
Eligiblity criteria (3)	100
Visit dates	20
Progression free survival (4)	100
Tests and examinations	20
AE	20

1. Verify that the patient number and year of birth in the CRFs are consistent with the medical record.
2. Verify that written informed consent was obtained before each subjects participation in the trial and that this is documented in the medical record at the right time.
3. Verify that the patient is correctly included in the study, ie that all eligibility criteria are fulfilled and that relevant information about the patients participation in the trial (protocol name and purpose, patient number, treatment arm and study medication) are documented in the medical record.
4. Progression free survival (PFS) defined as the time from date of enrolment to the date of first detection of GIST progression or death.

Reporting
The monitor should submit a written report to the national coordinator after each trial-site visit.
The investigator at each study site will also receive a written report with comments of the findings and requests of changes/corrections if necessary. The national coordinator will submit a summary of the monitoring activities and results to the principal coordinator.

For more detailed description of responsibilities and requirements for monitoring, see the Monitoring SOP from the Norwegian Clinical Research Infrastructures Network (NorCRIN).