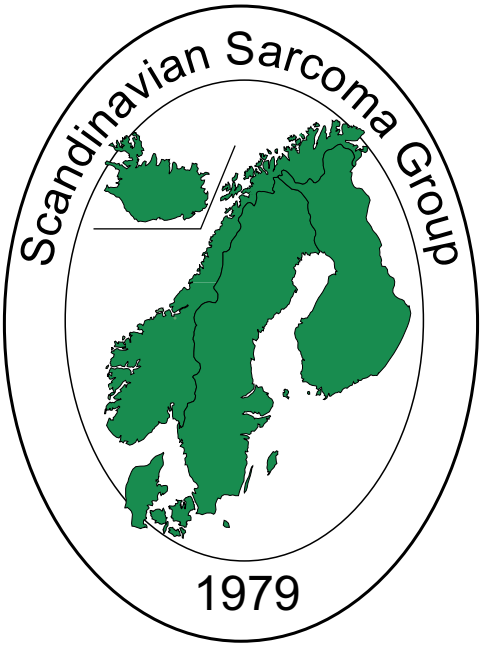
Scandinavian Sarcoma Group and
Sarcoma Group of the AIO, Germany

SSG XVIII

Short (12 months) versus long (36 months) duration of adjuvant treatment with the tyrosine kinase inhibitor imatinib mesylate of operable GIST with a high risk for recurrence

A randomized phase III study



AIO

German Working Group on Medical Oncology

www. ssg-org.net

Version: February, 2008

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Short (12 months) versus long (36 months) duration of adjuvant treatment with the tyrosine kinase inhibitor imatinib mesylate of operable GIST with a high risk for recurrence:

A randomized phase III study

Trial SSG XVIII is a Scandinavian Sarcoma Group and Sarcoma Group of the AIO multicenter, prospective, randomized study for evaluation of adjuvant treatment with the tyrosine kinase inhibitor imatinib mesylate of operable gastrointestinal stroma cells tumor (GIST) with a high risk for recurrence. The study is open to any specialized cancer center network and that fulfills all the protocol criteria.

All patients with GIST treated according to this program must be reported to the Scandinavian Sarcoma Group secretariat.

Prepared by the Working Committee of the Scandinavian Sarcoma Group and the Sarcoma Group of the AIO.

Preface

The Scandinavian countries (Denmark, Finland, Iceland, Norway and Sweden) have a total population of about 25 million. They possess similar social structures, a modern medical service covering all inhabitants, and an effective registration system for all cancer patients. This serves as a good base for cooperation. Accordingly, the Scandinavian Sarcoma Group (SSG) was founded in 1979. The aim of the Group was to improve the prognosis for sarcoma patients in the area. Guidelines for diagnosis, pathology, and treatment have been drawn which are now generally accepted by sarcoma centers in Scandinavia.

Our first randomized adjuvant chemotherapy trial for high-grade soft tissue sarcoma was done during 1981–1986. A total of 240 patients where included also in the large metaanalysis, where adjuvant chemotherapy improved metastasis-free survival and local tumor control.

In 2003 all Scandinavian Sarcoma Group members agreed on "Recommendations for the diagnosis and treatment of abdominal, pelvic and retroperitoneal sarcomas", see under www.ssg-org.net under ongoing trials. The present SSG XVIII protocol will be the third study of soft tissue sacoma with gastrointestinal stroma cell tumor (GIST) with a high risk for recurrence and this time a randomized adjuvant treatment with the tyrosine kinase inhibitor imatinib mesylate of operable GIST.

The following members have participated in the protocol design:

Pathologist

Lars-Gunnar Kindblom
Dept of Musculoskeletal Pathology
Division of Cancer Studies
University Medical School of Birmingham
Birmingham, United Kingdom
Email: lars.kindblom@roh.nhs.uk

Eva Wardelmann,
Department of Pathology,
University of Bonn Medical School
Sigmund-Freud-Strasse 25
53127 Bonn, Germany

Maarit Sarlomo-Rikala
Department of Pathology
University of Helsinki
Haartmaninkatu 3
FIN-00014 Helsinki, Finland

Surgeons

Jan Åhlén
Dept of Surgery
Karolinska Hospital
SE-171 76 STOCKHOLM
Email: jan.ahlen@ks.se

Håkan Ahlman
Dept of Surgery
Sahlgren University Hospital
SE-413 45 GOTHENBURG
Email: hakan.ahlman@vgregion.se

Oncologists

Heikki Joensuu
Dept of Oncology
University Hospital
FI-00290 HELSINKI
Email: heikki.joensuu@hus.fi

Paula Lindholm
Dept of Oncology
University Hospital
FI-20521 TURKU
Email: paula.lindholm@tyks.fi

Sigbjørn Smeland
Dept of Oncology
Montebello
The Norwegian Radium Hospital
NO-0310 OSLO 3
Email: sigbjorn.smeland@klinmed.uio.no

Kirsten Sundby Hall
Dept of Oncology
Montebello
The Norwegian Radium Hospital
NO-0310 OSLO 3
Email: k.s.hall@klinmed.uio.no

Mikael Eriksson
Dept of Oncology
University Hospital
SE-221 85 LUND
Email: mikael.eriksson@onk.lu.se

Jan-Olof Fernberg
Dept of Oncology
Karolinska Hospital
SE-171 76 STOCKHOLM
Email: jan-olof.fernberg@ks.se

Thor A Alvegård
Southern Swedish Regional Tumor Registry
University Hospital
SE-221 85 LUND
Email: thor.alvegard@cancerepid.lu.se

Principal Investigator: Heikki Joensuu, Helsinki

Data manager supervisor: Thor A Alvegård

SSG secretary: Eva-Mari Olofsson
Oncologic center, SSG secretariat
Lund University Hospital, SE-221 85 LUND, Sweden
Tel +46-46-177555, fax +46-46-188143

Printing and distribution of the final protocol will be arranged by the Oncologic Center in Lund. The SSG XVIII will be activated December 1, 2003.

Lund November 30, 2003

The following German Investigators are included in the Study Board
Peter Reichardt, Berlin
Jörg Thomas Hartmann, Tübingen
Jochen Schutte, Düsseldorf
Giuliano Ramadori, Göttingen

The Study Steering Group
Finland: Heikki Joensuu
Germany: Peter Reichardt
Norway: Kirsten Sundby Hall
Sweden: Thor Alvegård

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Protocol synopsis

Title of study: Short (12 months) versus long (36 months) duration adjuvant treatment with the tyrosine kinase inhibitor imatinib mesylate of operable GIST with a high risk for recurrence: A randomized phase III study

Number of centers: Multicenter study

Anticipated dates: First Patient First Visit: December 2003
Last Patient First Visit: August 2008
Interim safety/ toxicity analysis: Mid 2009
Final Analysis for RFS: After all randomized patients have completed their first visit following one year of adjuvant therapy (the study month 15 visit) and at least 110 events (GIST recurrence or death) have been recorded.
Follow-up Analysis for overall survival: Approximately 5 years after the Final Analysis.

Objectives

Primary objective:
To compare the recurrence-free survival (RFS) in GIST patients with a high (>50%) risk of disease recurrence within the first 5 years following the diagnosis and treated with adjuvant imatinib mesylate either for 12 or 36 months.

Secondary objectives:
To compare feasibility of adjuvant imatinib therapy, overall survival, and GIST-specific survival in GIST patients estimated to have a high risk of disease recurrence and treated with adjuvant imatinib either for 12 or 36 months following macroscopically radical surgery. Furthermore, to evaluate clinical benefit of treatment of recurred GIST after previous adjuvant treatment within the protocol.

Methodology: Open-label, randomized, prospective, phase III, multicenter study.

Number of patients: 400

Main inclusion/exclusion criteria:

Key inclusion criteria:

1. histologically confirmed GIST, CD117 (KIT) positive,
2. >50% risk of disease recurrence within the first 5-years following surgery (this is defined as tumor diameter >5.0 cm and mitotic count >5/50 high power fields (HPFs); or tumor diameter >10.0 cm, any mitotic count; or tumor of any size with a mitotic count >10/50 HPFs; or tumors ruptured into the peritoneal cavity.
3. ECOG performance status ≤2,
4. adequate organ function,
5. written informed consent.

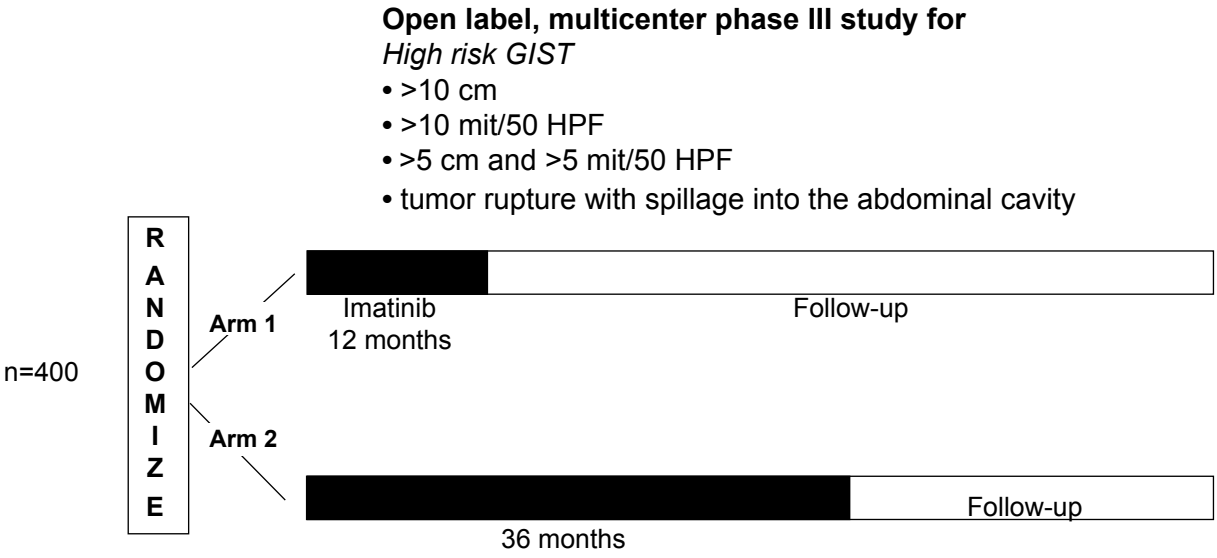
Key exclusion criteria:

1. inoperable or metastatic GIST,
2. <1 week or >12 weeks has elapsed from surgery,
3. recurrent GIST,
4. severe uncontrolled medical disease,
5. chemotherapy following surgery,
6. neoadjuvant imatinib therapy.

Treatments: Glivec 400 mg/day. Dose reduction is permitted for recurred grade 2 nonhematological toxicity, and for grade 3 or 4 hematological or nonhematological toxicity.

Investigational drug: Open label Glivec, 100 mg tablets by orally, taken with food.

Study design and duration of treatment: Arm 1: 12 months, Arm 2: 36 months.



Observation period:

For Final Analysis: Until the date when all randomized patients have completed their first visit following one year of adjuvant therapy (the study month 15 visit). At least 110 events will be required to achieve this.

For Follow-up Analysis: until the Final Analysis plus approximately 5 years counting from the date of the Final Analysis.

Criteria for evaluation

Efficacy: Primary endpoint: recurrence-free survival. Study participants are monitored longitudinally with computed tomography (CT) or MRI at 6 month intervals during the study.

Safety: Safety assessments will consist of evaluating adverse events and serious adverse events, laboratory parameters including blood hematology, serum chemistry and body weight.

Sample size and precision of statistical estimates:

The yearly RFS rate is assumed to be 7% during the study treatment, 16% for 6-12 months after the end of study treatment and 25% for later than 12 months after the end of study treatment. To show a statistically significant difference between the 12 months and 36 months treatment using a 2-sided significance level of 0.05, a total of 160 patients per group are needed to achieve a power of at least 80%. At least 110 events will be required to achieve a power of at least 80% with 160 patients. To account for a drop-out rate of 20% 400 patients will be randomized.

1 Introduction

1.1 GIST

Gastrointestinal stromal tumors (GISTs) are relatively rare tumors of the gastrointestinal tract, mesentery, omentum, and retroperitoneum. Despite their relative rarity as compared with gastrointestinal tract carcinomas, GIST is the most common sarcoma of the gastrointestinal tract and has been reported to account for about 5% of all sarcomas.[1] The annual incidence of GIST has been estimated to be about 10 to 20 cases per million.[2] Based on clinical, histopathological, ultrastructural, and molecular biology findings it is now clear that GIST is a separate entity from leiomyoma and leiomyosarcoma, which were formerly considered to be the most common types of soft tissue neoplasms in the gastrointestinal tract.[3]

GISTs occur in both genders at about similar frequency, but some series show male predominance.[3] The median age at diagnosis is about 60. GISTs are most commonly found in the stomach (40–70%), but they can occur also in all other parts of the gastrointestinal tract. About 20–40% of GISTs arise from the small intestine, and 5–15% from the colon and the rectum.[1, 2] Fifteen to 50% of GISTs present with overtly metastatic disease. The most common sites of metastases are the peritoneum and the liver, whereas regional lymph node metastases are rare.[4] Assessing the malignant potential of any given primary GIST lesion is often difficult, and even small GISTs (<2 cm in diameter) may be viewed as having uncertain malignant potential.[5] The reported overall or disease-specific 5-year survival is 28–60% among patients with malignant GIST, and the median disease-specific survival is about 5 years for primary disease, and 10 to 30 months in recurrent or metastatic disease.

Unlike leiomyosarcomas, practically all GISTs express the KIT protein (CD117) in immunohistological staining. KIT is a tyrosine kinase receptor. The ligand of the KIT receptor is the stem cell factor (SCF, also known as the mast cell growth factor or the Steel factor). GISTs often express also CD34 in immunohistochemical staining (60–70%) and occasionally also smooth muscle actin (SMA, 30–40%). GIST are rarely positive for desmin (1–2%) or S100 (about 5%), whereas smooth muscle neoplasms express SMA and desmin, and they are occasionally positive for CD34.[3] Most GISTs (about 85%) have mutated *KIT* gene, which leads to production of ceaselessly activated mutated KIT protein. Activated KIT phosphorylates down-stream proteins, which leads to constitutive activation of intracellular signal cascades and cell proliferation. Most *KIT* mutations are located in exons 11 and 9.[5–7]

GIST needs to be completely removed by surgery whenever possible. The 5-year survival following complete surgery is only about 50%, but many GISTs recur later than during the first 5 years of follow-up. Metastatic GIST is notoriously resistant to conventional chemotherapy.

1.2 Imatinib mesylate

Glivec® (Imatinib mesylate) is a protein-tyrosine kinase inhibitor that inhibits selectively the KIT tyrosine kinase. Imatinib inhibits also a few other tyrosine kinases including BCR-ABL, ABL, ARG, and the platelet derived growth factor receptors (PDGFRs). Imatinib is administered orally and taken with food to avoid upper gastrointestinal irritation. The most commonly used daily dosages range between 400 and 800 mg.

The pharmacokinetics of Glivec have been evaluated in healthy subjects and in population pharmacokinetic studies in over 900 patients. Imatinib is well absorbed after oral administration with C_{max} achieved within 2–4 hours post-dose. Mean absolute bioavailability

for the capsule formulation 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–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 Glivec 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.

1.3 Efficacy of imatinib in advanced GIST

Imatinib is the first effective systemic treatment for advanced GIST.[8, 9] In one study 147 patients with inoperable/metastatic GIST were randomized to receive either 400 mg or 600 mg imatinib orally qd for up to 24 months. Patients ranged in age from 18 to 83 years old and had a pathologic diagnosis of KIT-positive malignant GIST.

The primary outcome of the study was objective response rate. Tumors were required to be measurable at entry in at least one site of disease, and response characterization was based on South-Western Oncology Group (SWOG) criteria. All patients have had greater than 9 months of follow-up. Results are shown in table below.

Responses to Glivec in patients with advanced GIST

Best Response	Glivec 400 mg n = 74	Glivec 600 mg n = 74	All Doses n = 147
Complete response	0	0	0
Partial response	49 %	58 %	54 %
(95% CI)	(37.4–61.3)	(46.1–69.5)	(45.3–62.0)
Stable disease	32 %	24 %	28 %
(95% CI)	(21.1–43.4)	(15.1–35.7)	(20.8–35.9)
Progressive disease	16 %	11 %	14 %
Not evaluable	3 %	7 %	6 %

Complete Response: disappearance of all measurable and evaluable disease;

Partial Response: = 50 percent decrease in the summed products of the perpendicular diameters of all measurable lesions, no progression, and no new lesions;

Stable Disease: does not qualify for Complete Response, Partial Response, or Disease Progression;

Disease Progression: = 50 percent increase or an increase of 10 cm^2 (whichever is smaller) in the summed products of the perpendicular diameters of all measurable lesions, worsening of an evaluable lesion or reappearance of any lesion, a new lesion, or failure to return for evaluation due to progression.

The median time to objective response was 13 weeks. Reduction in tumor bulk for patients achieving a PR ranged from 50–96%. Responses have been durable for more than 46 weeks and median duration of response has not yet been reached (median follow-up: 24 weeks following onset of response). ECOG performance scores (PS) improved with Glivec therapy consistent with objective antitumor activity. By month 4 of the study, the number of patients with normal functional status (PS=0) increased to 64 % from 42 % at study entry.

This study was not adequately powered to distinguish efficacy between treatment groups and there was no statistically significant difference between dose levels. Three out of nine patients, however, achieved sustained partial response or stable disease following crossover to the 600

mg dose. Similar results were obtained in another study carried out by the EORTC.[10] Additional trials are currently being conducted by the NCI and EORTC to determine the optimum dose (400 mg vs. 800 mg).
Glivec was approved for use in GIST by the FDA in February, 2002. This was followed by approval in Switzerland and several other countries and European Commission approval in May, 2002.

1.4 Adverse reactions of imatinib

Treatment with Glivec was generally well tolerated in GIST, although nearly every patient experienced at least some minor adverse events. The most frequently reported adverse events were edema, nausea, diarrhea, musculoskeletal pain, fatigue, rash, headache, and abdominal pain. Most events were of mild to moderate severity. Superficial edema, most frequently periorbital or lower limb edema, was managed with diuretics, other supportive measures, or by reducing the dose of Glivec. Severe (CTC grade 3/4) superficial edema was observed in 2 patients including face edema in one patient. No major differences were seen in the severity of adverse events between the 400 mg or 600 mg treatment groups, although overall incidence of adverse events was somewhat higher in the 600 mg treatment group. Adverse events with a suspected relationship to therapy occurring in greater than 10 % of patients in any group are presented in table below.

Adverse events with suspected relationship to therapy in GIST (> 10 % in any group)

	All grades			**Grade 3 / 4**		
Preferred terms	400 mg	600 mg	All doses	400 mg	600 mg	All doses
Percentage of patients	n = 73	n = 74	n = 147	n = 73	n = 74	n = 147
Any AE	97	99	98	21	22	21
Edema/fluid retention	71	77	74	1	1	1
Periorbital edema	45	50	48	0	0	0
Edema lower limb	26	15	20	0	0	0
Face edema	8	12	10	1	0	1
Edema	7	14	10	0	0	0
Eyelid edema	7	8	8	0	0	0
Nausea	51	54	52	1	1	1
Diarrhea	40	50	45	1	3	2
Myalgia / musculoskeletal pain	37	42	40	0	0	0
Fatigue	30	39	35	0	0	0
Dermatitis / rash	25	37	31	3	3	3
Headache	19	32	26	0	0	0
Abdominal pain	26	26	26	1	0	1
Flatulence	19	24	22	0	0	0
Vomiting	14	12	13	0	1	1
Any hemorrhage	11	14	12	4	5	5
Tumor hemorrhage	1	4	3	1	4	3
Upper GI bleed / perforation	4	3	3	4	1	3
Dyspepsia	10	12	11	0	0	0
Lacrimation increased	7	12	10	0	0	0
Anemia	6	12	9	1	3	2
Loose stools	7	10	8	0	0	0
Taste disturbance	3	14	8	0	0	0

There was no hyperuricemia or evidence of tumor lysis syndrome, even in patients with very rapid decreases in tumor volume. The most medically significant adverse events were gastrointestinal or intra-abdominal hemorrhage in patients with large bulky tumors, which occurred in approximately 5 % of patients.

1.5 Adjuvant use of imatinib in GIST

About 40% of all patients diagnosed with GIST have a greater than 50% risk of sarcoma recurrence within the first 5 years following surgery despite complete surgical removal of all macroscopic tumor tissue. Although imatinib mesylate has proved safe and highly effective in the treatment of patients with overtly metastatic GIST, the median time of treatment failure is between 1 to 2 years in these patients, and it is currently not known whether any proportion of GIST patients with metastatic disease can be permanently cured with imatinib. The use of imatinib in the adjuvant setting might result in a higher proportion of cured patients than can be achieved when this therapy is deferred to metastatic disease. In breast cancer, for example, adjuvant use of 5 years of tamoxifen reduces mortality by approximately one third and prevents breast cancer recurrence by almost 50% in women with estrogen receptor positive disease, whereas deferred tamoxifen therapy is no longer curative in advanced breast cancer.

Patients who have a high risk for recurrence can be identified reasonable well using a combination of prognostic factors. Large primary tumors (>10 cm in diameter), tumors with a high mitotic count (>10/50 HPFs), and tumors that manifest with both of these features (>5 cm in diamer and >5 mitotic figures/50 HPFs) are associated with less than 50% 5-year overall survival (see table below). These patients have only about 30% 5-years recurrence-free survival. Patients who have overtly metastatic disease but have been rendered free from macroscopic metastases by surgery are at a very high risk of recurrence, which approaches 100%. Of note, some recurrences may be detected only 10 to 15 years after primary surgery, further emphasizing the unfavorable long-term outcome of high-risk GIST patients when treated with surgery alone.

Assessment of the risk of recurrence in operable GIST11

	Size	Mitotic count
Very low risk	<2 cm	<5/50 HPFs
Low risk	2–5 cm	<5/50 HPFs
Intermediate risk	<5 cm 5–10 cm	6-10/50 HPFs <5/50 HPFs
High risk	>10 cm any size >5 cm	Any mitotic rate >10/50 HPFs >5/50 HPFs
Very high risk[a] -intra-abdominal metastases removed at surgery -tumor spillage at surgery	Any	Any

[a]the very high risk category is not included in the risk assessment by Fletcher et al.[11]

The optimal duration of adjuvant therapy with imatinib is not known. The median time to response is about 4 months in the metastatic setting, but the time to the best response varies considerably between patients, and a few tumors may continue to shrink up to 1 year following the start of imatinib therapy. Prolonged therapy lasting many months or a few years appears to be mandatory in most patients who have metastatic disease, and therapy interruptions may be life-threatening. Long duration of imatinib therapy might benefit also high-risk patients in the adjuvant setting, but longer treatments may also be associated with greater toxicity and costs without any clinical benefit.

Ongoing or planned U.S. and EORTC studies will randomize intermediate and high risk GIST patients to 1 or 2-year imatinib treatment or to observation without adjuvant therapy. These pivotal trials will targeted the intermediate-high risk patient population, where randomization to a no-treatment arm is considered acceptable. The current trial will focus on the high risk-very

high risk subjects (except patients with metastatic disease) with an estimated risk of disease recurrence ranging between 50 and 100%. Since 1- and 2-year treatment times are used in the U.S. and EORTC adjuvant trials, the present study on 1-year versus 3-year imatinib treatment complements the other ongoing adjuvant trials, and will generate efficacy and tolerability data on different durations of imatinib therapy.

2 Study objectives

Primary objective

To compare the recurrence-free survival (RFS) in GIST patients with a high (>50%) risk of disease recurrence within the first 5 years following the diagnosis and treated with adjuvant imatinib mesylate either for 12 or 36 months.

Secondary objectives

To compare GIST patients estimated to have a high risk of disease recurrence and treated with adjuvant imatinib either for 12 or 36 months following macroscopically radical surgery with respect to feasibility of adjuvant imatinib therapy, overall survival, and GIST-specific survival. Furthermore, to evaluate clinical benefit of treatment of recurred GIST after previous adjuvant treatment within the protocol.

3 Investigational plan

3.1 Overall study design

This is an open-label, multicenter, prospective, randomized phase III study conducted to investigate the efficacy and safety of Glivec in GIST patients who had all tumor tissue removed macroscopically at surgery, and who are estimated to be at a high risk for disease recurrence. The study participants are randomly assigned to two different durations of adjuvant treatment with Glivec. In Arm 1 Glivec is administered at a daily dosage of 400 mg p.o./day for 12 months, and in Arm 2 at the dosage of 400 mg p.o./day for 36 months. All patients will be monitored for treatment toxicity during adjuvant therapy with longitudinal blood cell counts and blood chemistry, and followed up until the date of the Final Analysis (to be carried out when all randomized patients have completed their first visit following 1 year of adjuvant treatment and at least 110 events have been recorded) and for a time period of approximately 5 years that follows the Final Analysis. Clinical follow-up visits will be performed at the same time intervals in both treatment arms. Treatment after disease recurrence is at the discretion of the investigator, but data on treatment type, duration and response to treatment will be captured on the CRFs. A total of 400 patients will be enrolled.

3.2 Study population

3.2.1 Patient population

The median overall survival time of the GIST patients in the high risk category as defined by

1) tumor diameter >5.0 cm and mitotic count >5/50 HPFs,
2) tumor diameter >10.0 cm with any mitotic count, and
3) tumors of any size, where the mitotic count is >10/50 HPFs is about 55 months. The present study will also accure patients with tumor spillage into the abdominal cavity at surgery and patients who have microscopically infiltrated margins.

3.2.2 Inclusion and exclusion criteria

Inclusion criteria

1. Patients ≥18 years of age.
2. Histologically documented diagnosis of GIST, which is resectable.
3. GIST removed at open surgery (laparoscopic and endoscopic surgery as the sole surgical procedures are not accepted).
4. Immunohistochemical documentation of KIT (immunostaining for KIT/CD117) must be positive on a tumor sample taken within 12 weeks of the study entry. Mutation analysis of the *KIT* gene is **not** required for study entry.
5. High risk of tumor recurrence as defined as one or more of the following:
   1) the largest tumor diameter greater than 10.0 cm (with any mitotic count). The tumor size needs to be 10.0 cm or greater in the resected tissue specimen when measured by a pathologist.
   2) mitotic count >10 mitoses per 50 high power fields (HPFs) (of any tumor size)
   3) the largest tumor diameter > 5.0 cm (measured by a pathologist) *and* the mitotic count > 5/50 HPFs
   4) tumor spillage into the abdominal cavity at surgery (tumor rupture may have occurred either before surgery or taken place during surgery)
   5) patients who have microscopically infiltrated margins (or suspected microscopical infiltration, R1) are allowed to enter the study.
6. Performance status 0, 1 or 2 (ECOG) (see Section 8)
7. Adequate end organ function, defined as the following:

   total bilirubin <1.5 × ULN (upper limit of normal), serum AST (SGOT) and ALT (SGPT) <2.5 × UNL, creatinine <1.5 × ULN, ANC (neutrophil count) >1.5 × 10^9/L, platelets >100 × 10^9/L.
8. Female patients of childbearing potential must have negative pregnancy test within 7 days before initiation of study drug dosing. Postmenopausal women must be amenorrheic 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.
9. Written, voluntary informed consent.

Exclusion criteria

1. Inoperable GIST.
2. Metastatic disease (within or outside the abdomen).
3. Less than 1 week or more than 12 weeks has elapsed from surgery. This time interval is counted from the date of the definite surgery aimed for cure, and cases where diagnostic or emergency surgery has been carried out >12 weeks prior to the study entry are allowed to be entered.
4. Recurrent GIST.
5. Patient has received any investigational agents within 28 days as calculated from the first day of the study drug dosing.
6. Patient is less than 5 years free of another primary malignancy except: if the other primary malignancy is not currently clinically significant nor requiring active intervention, or if other primary malignancy is a basal cell skin cancer or a cervical carcinoma in situ. Existence of any other malignant disease is not allowed.
7. Patient with Grade III/IV cardiac problems as defined by the New York Heart Association

Criteria (i.e., congestive heart failure, myocardial infarction within 6 months of study).

8. Female patients who are pregnant or breast-feeding.
9. Patient has a severe and/or uncontrolled medical disease (i.e., uncontrolled diabetes, severe chronic renal disease, or active uncontrolled infection). The concurrent use of warfarin or acetaminophen are not allowed with imatinib, and need to be replaced by other medications (e.g. by low molecular heparins in case of warfarin).
10. Patient has known chronic liver disease (i.e., chronic active hepatitis, and cirrhosis).
11. Patient has a known diagnosis of human immunodeficiency virus (HIV) infection.
12. Patient has received chemotherapy for GIST.
13. Patient received neoadjuvant imatinib therapy prior to randomization.
14. Patient has received radiotherapy to ≥25 % of the bone marrow.
15. Patient with any significant history of non-compliance to medical regimens or with inability to grant reliable informed consent.

3.3 Interruption or discontinuation of treatment

All interruptions and reductions regarding the study drug must be captured on the CRF. Patients who discontinue adjuvant imatinib will be followed up according to the same visit schedule (see Section 3.6.1) as those individuals who continue study treatment.

If the patient discontinues study medication during the trial, the reason is categorized in the CRF as one of the following:

1. Unsatisfactory therapeutic effect (GIST recurrence)
2. Adverse event(s) / Abnormal laboratory value(s)
3. Withdrawal of consent
4. Death
5. Other (for example Protocol violation, Administrative problems etc.)

A complete end of study visit must be collected for any patient discontinuing study treatment for an adverse event or an abnormal laboratory value and within 4 weeks after the last drug intake. End of study evaluations will include adverse events, physical examination, ECOG Performance Status, biochemistry, and hematology. Relevant information that is related to the reason for treatment discontinuation including contributory factors is included in the CRF. In case of recurred GIST, data regarding treatment given for recurrence will be collected.

3.4 Dose modifications for non-hematological toxicity

Grade 2

If the patient experiences a Grade 2 non-hematologic toxicity, study drug must be withheld until the toxicity has resolved to ≤ Grade 1. Glivec may then be resumed at the same daily dose. If the Grade 2 toxicity recurs, Glivec must be withheld until the toxicity has resolved to ≤ Grade 1, and the daily dose must be reduced to 300 mg once daily.

Grade 3/4

If the patient experiences Grade 3/4 toxicity study drug must be withheld until the toxicity has resolved to ≤ Grade 1 and the daily dose must be reduced to 300 mg once daily. If the Grade 3/4 toxicity recurs, Glivec must be withheld until the toxicity has resolved to ≤ Grade 1. If treatment needs to be interrupted for toxicity for a time period of 4 weeks or longer, the study treatment will be discontinued.

Dose reductions below the dose of 300 mg/day should be avoided if possible, but such dose reductions are permitted if grade 2/3/4 non-hematological toxicity recurs.

Dose modifications for hematological toxicity

Grade 2

No dose interruptions or reductions will be performed for Grade 1/2 hematological toxicity.

Grade 3/4

If patient experiences a Grade 3/4 hematological toxicity, defined as an ANC (neurophil count) $<1 \times 10^9$/L, or a platelet count $<50 \times 10^9$/L, Glivec must be withheld until the toxicity has resolved to ≤Grade 2 (ANC ≥1.0 and platelet count $\geq 50 \times 10^9$/L). ANC takes precedence over a leukocyte count (WBC) in determining the degree of neutropenia (doses should not be interrupted for a patient with a WBC $< 2.0 \times 10^9$/L but ANC $>1 \times 10^9$/L). If the toxicity resolves within two weeks, Glivec treatment may be resumed at the same dose. If the Grade 3/4 toxicity recurs or persists for longer than two weeks, Glivec must be withheld and then recommenced at the dose of 300 mg once daily, once toxicity has resolved to ≤Grade 2. If treatment needs to be interrupted for hematological toxicity for a time period of 4 weeks or longer, the study treatment will be discontinued.

No dose reductions will be performed for grade 3/4 anemia. If the patient develops anemia, she/he may be transfused at the discretion of the investigator.

Dose reductions below the dose of 300 mg/day should be avoided if possible, but such dose reductions are permitted if grade 3/4 hematological toxicity recurs.

Dose modifications for other reasons

The optimal dose of Glivec in GIST is unknown, but doses below 300 mg once daily may no longer be sufficient to inhibit KIT. If vomiting occurs, no additional trial medication should be taken that day in an effort to replace the material that has been vomited.

3.5 Treatments

3.5.1 Investigational therapy

Glivec (imatinib mesylate) 400 mg once daily. Arm 1 will be randomly assigned to 12 months of treatment and Arm 2 to 36 months of treatment. Imatinib will be administered until:

- GIST recurrence
- unacceptable toxicity
- withdrawal of consent
- the assigned duration of drug therapy has been achieved (either 12 or 36 months).

Treatment after disease recurrence is at the discretion of the investigator, but data on treatment type, duration and response to treatment will be captured on the CRFs.

Glivec will be provided as 100 mg tablets packaged in blister packs.

Daily treatment will be withheld only in the case of limiting toxicities (see Section 3.4). The prescribed dose should be administered orally, with a meal and a large glass of water. The dose of 400 mg should be administered once daily. Patients should keep normal eating habits, however low-fat (i.e. continental) breakfast is recommended avoiding xanthine (e.g. caffeine) or grapefruit containing food or beverages. Minimum of 1 hour should be allowed between last drug intake

and going to bed. If vomiting occurs, no additional trial medication should be taken that day in an effort to replace the material that has been vomited.

3.5.2 Treatment assignment

Informed consent must be obtained before any testing for the purpose of determining a patient's eligibility is performed.

Each patient will be assigned a unique patient number. Once assigned, numbers for any non-evaluable or discontinued patient will not be reused.

Randomization will be performed based on computer generated random numbers at the randomization center located at the SSG secretariat. At randomization, the patients are stratified into 2 strata: 1: local disease (1 tumor); 2: intra-abdominal disease (intra-abdominal tumor spillage, or microscopic disease left behind at surgery (R1 resection)).

Patients who meet the inclusion criteria for study treatment will be registered and given a randomization number at the SSG secretariat.

3.5.3 Concomitant therapy

In general, concomitant medications and therapies deemed necessary for the supportive care and safety of the patient are allowed, provided their use is documented in the patient records. The administration of any other anticancer agents including chemotherapy and biologic agents is NOT permitted. Similarly, the use of other concurrent investigational drugs is not allowed. Post-operative radiation therapy should not be given or re-excision done in case of suspicision of disease left behind (R1 surgery).

Because of the inherent risk of either reduced activity or enhanced toxicity of the concomitant medication and/or Glivec, drugs known to interact with the same CYP450 isoenzymes (2D6 and 3A4) as Glivec should be used with caution (Appendix 1). Patients using concomitant medications known to be metabolized by these cytochrome p450 enzymes will not be excluded from the study. However, the patients must be carefully monitored for potentiation of toxicity due to individual concomitant medication. Consideration should be given to using alternative agents with less potential for interaction with Glivec. Special care has to be given to the concomitant use of acetaminophen (paracetamol) (e.g. Panadol®, Tylenol® or Percocet®) with Glivec. A patient with leukemia who was treated with imatinib and acetamonophen died from hepatic failure.

Since warfarin is metabolized through the CYP450 system, no therapeutic anticoagulation with warfarin (e.g. Marevan®, Coumadin®, Coumadine®) will be permitted in patients participating in this study. As an alternative, therapeutic anticoagulation may be accomplished using low-molecular weight heparin (e.g. Fragmin) or heparin. In general, the use of Coumadin® is discouraged on this protocol.

The routine use of systemic corticosteroid therapy is not permitted. Corticosteroid therapy may only be administered after consultation with the principal investigator.

Prophylactic anti-emetics should be withheld until the patient has experienced grade 1 nausea or vomiting.

Prophylactic use of loperamide (e.g. Imodium®, with suggested dosing as start: 4 mg p.o. × 1, than 2 mg p.o. after each loose stool, max 16 mg/d) is recommended for patients experiencing grade 1 or 2 diarrhea, before dose interruption.

Use of erythropoietin or darbepoietin is allowed at the descretion of the treating physician to treat anaemia (B-hemoglobin <11 g/L). The use of granulocyte growth factors (G-CSF or GM-CSF) is not allowed to support the granulocyte counts.

3.5.4 Handling of study medication

All study medication will be supplied by Novartis. All drug supplies are to be used only for this protocol and not for any other purpose. Drug supplies must be kept in an appropriate, secure area (e.g. locked cabinet) and stored according to the conditions specified on the drug labels.

The patient may be dispensed up to about 3 months supply of medication (until the next study visit). The pharmacy must maintain an individual record for the patient where the drug formulation, dose, number of tablets dispensed, received, and returned must be recorded.

Patients will be asked to return all unused medication at the end of the study.

3.6 Visit schedule and assessments

3.6.1 Visit schedule

Patient must be followed at the study center according to the table "Visit schedule and assessments" on the next page. Following the 3 first years on study the subjects will be followed up at 6-month intervals until study month 84 (7 years from study entry), and at 12-month intervals thereafter for a minimum of 10 years as calculated from the date of study entry. When clinically indicated or when preferred by the investigator, more frequent follow-up visits may be organized.

All routine assessments must be performed within ± 14 days of the day indicated on the visit schedule.

Patients who discontinue imatinib prematurely for toxicity or other reasons will be followed up in a similar fashion as those who continue to take imatinib as scheduled. In case of GIST recurrence, data regarding treatment given for recurrence will be collected.

Visit schedule and assessments

Month on Therapy	**0[a]**		**1**		**2**	**3**	**4**	**5**	**6**		**9**			**12**	**15, 18, 21, 24, 27, 30, 33, 36**	**42, 48, 54, 60, 66 72, 78, 84, 96, 108, 120[g]**	**At re-lapse**
Week on Therapy		**2**	**4**	**6**	**8**	**12**	**16**	**20**	**24**	**30**	**36**	**42**	**48**	**52**			
Medical History	X																X
Adverse Events			X			X			X		X			X	X		
Current Medication	X		X			X			X		X			X	X	X	X
Physical exam	X		X			X			X		X			X	X	X	X
Weight	X		X			X			X		X			X	X		
Height	X																
ECOG Perform. Status	X		X			X			X		X			X	X	X	X
CBC/Diff. Count/ Platelets	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[e]	X	X
AST/ALT/LDH Bilirubin/Alk Phos Creatinine/protein/ albumin	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[e]	X	X
Pregnancy test[b]	X																
Chest X-ray or CT	X																
CT or MRI of abdomen and pelvis (with contrast)	X								X					X	18, 24, 30, 36 mo	X	X[f]
FDG-PET (optional, but recommended)	X																
Serum for Banking[c]	X								X					X	18, 24, 30, 36 mo	X	X
Tumor Tissue for Central Path Review *KIT, and PDGFRA* mutation analysis[d]	X																X
Left ventricular ejection fraction (LVEF)measurement (by either echocaedio-graphy or MUGA scan (optional)	X					X								X	24 mo		

[a] baseline laboratory tests must be performed after laparotomy and within 2 weeks prior to randomization, and baseline imaging examinations within 4 weeks prior to randomization

[b] for premenopausal women and for post-menopausal women amenorrheic for less than 12 months. In case of doubt, serum FSH needs to be determined.

[c] at baseline 3 mL and >1mL during subsequent samplings.

[d] paraffin-embedded tissue required. Storage of frozen tissue recommended.

[e] blood cell counts, liver transaminase levels and creatinine will be monitored at 6 weeks intervals in patients who receive imatinib

[f] the protocol specified CT/MRI examinations need not to be repeated if recurrence is first detected in these exams

[g] blood tests and imaging examinations are optional at visits performed 96, 108 and 120 months after study entry

3.6.2 Screening assessments

Written informed consent must be obtained before any study specific medical procedures are performed. Laboratory screening assessments and physical examination including performance status, weight, and serum pregnancy test for females of child-bearing potential must be performed. In the event that hematology or biochemistry evaluation is performed within 14 days of the first dose of study drug as part of the screening evaluation, this evaluation need not be repeated, and may be used as the Day 1 values. Immunohistochemical confirmation of KIT overexpression must exist at the study entry.

Tumor measurements by CT or MRI must be performed within 28 days of the first dose of study drug. Positron emission tomography (PET) using fluorodeoxyglucose (FDG) as the tracer is recommended as a staging examination (optional).

Left ventricular ejection fraction may be measured either by echocardiography or by isotope cardiography (MUGA) prior to initiation of imatinib therapy (optional).

Screening assessments

Assessment	Includes
Inclusion/exclusion criteria	Patient eligibility is to be assessed including serum pregnancy test in females of child-bearing potential
Demographics	Date of birth and sex.
Relevant medical history / Current medical conditions	Relevant past medical history, and current medical conditions not related to the diagnosis of GIST.
Disease history	Information related to diagnosis of GIST.
Previous antineoplastic treatment	Previous: surgery, radiotherapy and systemic therapy
Physical examination / Vital signs	Total body examination, pulse rate, blood pressure.
Performance status/ Body weight	Body weight and performance status according to ECOG criteria (see Section 8).
Tumor assessment	CT or MRI of the abdomen and pelvis
Hematology	Hemoglobin, total WBC count, platelet count, and a differential count including neutrophils, lymphocytes, monocytes, eosinophils and basophils.
Biochemistry	Creatinine, total bilirubin, alkaline phosphatase, AST (SGOT), ALT (SGPT), LDH, serum total protein and albumin.
Concomitant Medications/Therapies	Concomitant medications and/or non-drug therapies and the reason for administration.

3.6.3 Efficacy assessments

Efficacy

Tumor assessments should be performed by a CT or MRI scan, throughout the study. All assessments should be performed within 14 days of the scheduled day of assessment, and whenever clinically indicated otherwise.

3.6.4 Safety assessments

Safety assessments will consist of evaluating adverse events and serious adverse events, laboratory parameters including hematology, chemistry and body weight. Monitoring of the LVEF may be carried out at the investigator's discretion. The use of the same method throughout the study is

recommended. It is recommended that the LVEFs will be measured at baseline, and 12 weeks, 52 weeks and 24 months after starting adjuvant imatinib. In case of more than 15% decrease in the LVEF as compared to the baseline value, or more than 10% decrease to a value less than 50%, consultation of a cardiologist and the principal investigator is recommended.

3.6.4.1 Adverse events

Information about adverse events, whether volunteered by the patient, discovered by investigator questioning, or detected through physical examination, laboratory test or other means, will be collected and recorded on the CRF and followed as appropriate. An adverse event is any undesirable sign, symptom or medical condition occurring after starting study treatment, even if the event is not considered to be treatment-related.

Medical conditions/diseases present before starting study treatment are only considered adverse events if they worsen after starting study treatment. Abnormal laboratory values or test results constitute adverse events only if they induce clinical signs or symptoms or require therapy, when they are recorded on the Adverse Events CRF under the signs, symptoms or diagnosis associated with them.

As far as possible, each adverse event will also be described by the NCI/NIH Common Toxicity Criteria severity grades 1–4 (Appendix 2).

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 CTC

1 = Grade 1	Mild
2 = Grade 2	Moderate
3 = Grade 3	Severe
4 = Grade 4	Life-threatening

Any Adverse Event occurring by the time of study completion (within two weeks of last drug intake) must be recorded on the Adverse Event page.

Serious Adverse Events

A Serious Adverse Event (SAE) is an undesirable sign, symptom or medical condition which:

1. is fatal or life-threatening (any grade 4 toxicity, any new cancer)
2. required hospitalization or prolonged hospitalization
3. results in persistent or significant disability/incapacity
4. constitutes a congenital anomaly or a birth defect
5. is medically significant, in that it may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed above.

Events **not** considered to be SAEs are hospitalizations for the:

- routine treatment or monitoring of the studied indication, not associated with any deterioration in condition.
- treatment, which was elective or pre-planned, for a pre-existing condition that is unrelated to the indication under study and did not worsen

- admission to a hospital or other institution for general care, not associated with any deterioration in condition
- treatment on an emergency, outpatient basis for an event **not** fulfilling any of the definitions of serious given above and **not** resulting in hospital admission.

Any SAE occurring after protocol specified procedures begin and until 4 weeks after study drug discontinuation must be reported.

In addition any pregnancy or fathering of a child within 84 days (12 weeks or 3 months) after the last Glivec intake has to be reported and recorded as an SAE.

SAEs occurring more than 4 weeks after study drug discontinuation need only to be reported if a relationship to the Novartis study drug (or therapy) is suspected.

Information about all SAEs and assessment of its relationship to Novartis treatment will be recorded in English by the investigator on the SAE Report Form. To ensure patient safety each SAE must also be reported to the SSG secretariat fax +46-46-188143 and to the local Novartis Clinical Safety & Epidemiology (CS&E) Department within 24 hours of learning of its occurrence even if it is not felt to be related to treatment.

The original copy of the SAE form and the fax confirmation sheet must be kept with the CRF documentation at the study site.

Each re-occurrence, complication or progression of the original event should be reported as a follow-up to that event. The follow-up information should describe whether the event has resolved or continues, if and how it was treated, and whether the patient continued or discontinued study participation. The follow-up SAE report should state that it is a follow-up report of a prior SAE, and the date of the initial SAE report should be included. If a SAE occurs in the same individual as a previously reported SAE and is considered completely non-associated to the previously reported one, a new SAE form should be sub-mitted as an initial report. The form and fax confirmation sheet must be retained.

Suspected Unexpected Serious Adverse Reactions

If the serious adverse event is not documented in the investigator brochure (i.e. unexpected) and is thought to be related to the Novartis study drug (or therapy), a Clinical Safety & Epidemiology Department associate may urgently require further information from the investigator prior to the submission of the reported event to the Health Authority. If warranted, to fulfill the regulatory requirement, Novartis may need to issue an investigator notification, to inform all investigators involved in any study with the same drug (or therapy) that this suspected unexpected & serious adverse reaction (SUSAR) has been reported.

Pregnancies

In the event that a female patient on study drug becomes pregnant, the pregnancy must be reported to the local Novartis CS&E Department and followed to term. All initial and follow-up information obtained regarding any pregnancy conceived during the study must be reported to the sponsor within 24 hours of the investigator's receipt of such information. A Novartis Clinical Trial Pregnancy Form is provided for this purpose. An assessment should be made between the outcome of pregnancy and the Novartis investigational drug. An abortion is to be regarded always as a SAE and assessed as 'other medically significant event' if no other seriousness criterion is fulfilled. These assessments should be entered on the Clinical Trial Pregnancy Form. A female study patient who becomes pregnant must immediately discontinue study drug. If a female study patient experiences a SAE while pregnant (associated with the pregnancy or not) this event

must be reported as instructed for SAEs, using the SAE report form. The pregnancy should be followed up to determine details of birth, outcome, including spontaneous or voluntary abortion, the presence or absence of any birth defects or congenital abnormalities or any maternal/newborn hazards.

3.6.4.2 Laboratory evaluations

The institution will perform laboratory analyses according to the Visit Schedules. Laboratory values will be recorded on the Adverse Events Form (circle the correct range) even if normal.

Hematology

Hematology includes assessment of hemoglobin, total WBC count, platelet count, and a differential count including neutrophils, lymphocytes, monocytes and eosinophils, basophils and will be performed according to the Visit Schedules. If the patient experiences any internal bleeding, analyses of bleeding time, platelet aggregation, and PT and PTT measurements, should be performed if at all possible.

Biochemistry

Biochemistry includes creatinine, albumin, total protein, total bilirubin, alkaline phosphatase, AST (SGOT), ALT (SGPT), and LDH, and will be performed according to the Visit Schedules.

Physical examinations

A physical examination including pulse rate and blood pressure will be performed according to the Visit Schedules. Information about the physical examination must be present in the source documentation at the study site. Significant GIST symptoms present prior to the start of study drug will be recorded in the CRF. Data on concomitant diseases will not be captured on the CRFs. Significant findings made after the start of study drug which meet the definition of an adverse event must be recorded on the Adverse Event Form. There are no CRF to capture routine normal findings from physical examinations assessments.

Performance status/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. In addition, patients are encouraged to otherwise measure their body weight weekly and report to the study investigator any body weight change of more than 2 kg as compared to their pre-study body weight.

4 Data management

Data items are collected to the CRF by the investigators and entered centrally into the study database, located at the SSG secretariat.

5 Mutation analyses, central pathology review, and analysis of serum KIT and the KIT ligand (SCF)

All tissue samples will be shipped to one of the three Central Laboratories of the study located at the Department of Pathology, University of Bonn Medical School (Sigmund-Freud-Strasse 25 53127 Bonn, Germany; Dr. Eva Wardelmann), Department of Pathology, University of Helsinki (Haartmaninkatu 3, FIN-00014 Helsinki, Finland, Dr. Maarit Sarlomo-Rikala) and Department of Musculoskeletal Pathology, Division of Cancer Studies, University Medical School of Birmingham, Birmingham, United Kingdom; Dr. Lars-Gunnar Kindblom) for central review.

Central pathology screening

Immunohistochemistry for CD117 (KIT) and GIST pathology will be reviewed centrally. A representative tumor tissue block and mounted tissue sections will be shipped to a Central Laboratory. Collection of tissue for histopathological screening and mutation analyses will start when the 100th patient has been randomized to the study for the first 100 patients. Collection of the paraffin blocks of the patients with a study code 101-200 will be initiated when the 200th patient has been accrued.

Mutation analysis of the KIT and PDGFR genes

Mutation analysis of *KIT* and *PDGFR* genes will be carried out from tumor tissue biopsies. A representative tumor tissue biopsy (usually a paraffin tissue block containing GIST tissue, frozen tumor tissue, or, alternatively, extracted tumor DNA) is required for this analysis. DNA extracted from the tissue is analyzed for the presence of *KIT* exon 9, 11, 13 and 17 and *PDGFR* exon 12 and 18 mutations using dHPLC, followed by sequencing of any abnormal findings. The analyses will be carried out at the University of Helsinki, Helsinki, Finland, and/or at the University of Bonn, Germany. The mutation analysis results will be correlated with patient outcome.

Serum Soluble KIT and KIT Ligand (SCF) Analyses

Serum samples are collected from the patients treated with adjuvant imatinib therapy 1) before starting imatinib and 2) at the times of disease status evaluations, and 3) at disease recurrence. Serum (≥2 ml, ≥3 ml at baseline) is collected to ordinary serum test tubes, and stored –20°C or colder. These samples will be subjected for analysis of serum soluble KIT and stem cell factor (SCF) levels, or other serum proteins relevant to the study in line with the Patient Informed Consent. The serum protein levels will be correlated with the clinical and outcome data. Samples are collected at the study center, and shipped to the P.I. of the study and on a mutually agreed date (prof. Heikki Joensuu, the Department of Oncology, Helsinki University Central Hospital, Haartmaninkatu 4, P.O. Box 180, FIN-00029 Helsinki, Finland, fax. 358-9-471 74202, email heikki.joensuu@hus.fi).

Tumor tissue microarray (TMA)

A tumor tissue microarray (TMA) may be constructed from the paraffin tissue blocks containing GIST by taking 3 to 4 coarse needle biosies (0.6 to 1.0 mm in diameter) from each block. These biopsies will be mounted on a recipient tissue block to form a TMA, each TMA containing approximately 100 small (0.6 to 1.0 mm in diameter) tissue biopsies. Thin (4 to 5 μm thick) sections may then be cut from each TMA block for staining with immunohistochemistry or for analysis of gene copy numbers using in situ hybridization. Such tissue microarrays will be used to identify proteins or amplifications or deletions of genes that may be associated with resistance or response to imatinib therapy (related to drug resistance, cell signalling, alternative growth factor receptors, cell cycle progression or apoptosis) or may be associated with prognosis and with GIST recurrence (cell cycle proliferation rate-related proteins and genes, apoptosis-related

proteins and genes, or GIST differentiation-related proteins and genes). The TMAs will be prepared and stored at the University of Helsinki, Finland, or/and at the University of Bonn, Germany. A full TMA with tissue from all study patients will be stored both at the University of Helsinki and at the University of Bonn.

Serum soluble factors related to imatinib metabolism, adverse effects of imatinib, treatment compliance or progression of GIST

Imatinib failure may be a consequence of several factors, such as new cancer cell mutations affecting either KIT or PDGFRA, cell signalling via alternative pathways, pharmacological factors or a poor patient compliance with imatinib therapy. Many of the factors related to imatinib resistance and drug toxicity are still poorly known. Adjuvant imatinib therapy may induce changes in the levels of serum electrolytes, enzymes and other proteins, hormones and soluble growth factors, which may be of importance with regard of GIST recurrence, treatment safety, and accuracy of disease outcome prediction. In the absence of metastatic disease, research serum samples collected from patients who receive adjuvant imatinib therapy are well suited for such studies. Analyses of serum electrolyte levels, and levels of soluble enzymes and cell matrix structural proteins, hormones, soluble growth factors and their cognate receptors will be analyzed from the research serum samples provided by the study participants.

6 Statistical methods

6.1 Sample size and power considerations

The sample size calculation is based on the analysis of the primary objective, i.e. comparison of the recurrence-free survival from time of randomization in patients with adjuvant imatinib either for 12 or 36 months. The patients will be allocated to the treatment groups using an even allocation (1:1).

Based on the results of the interim analysis of an adjuvant GIST study (ACOSOG Z9001) comparing 12 months on imatinib therapy, the sample size was re-estimated assuming the following event (GIST recurrence or death) rates:

- In the 12 months group, the yearly event rate will be 7% for 18 months, 16% between 18 and 24 months, and 25% after 24 months.
- In the 36 months group, the yearly event rate will be 7% until 42 months, 16% between 42 and 48 months, and 25% after 48 months.

The sample size was calculated by simulating log-rank tests using the above assumptions. A power of at least 80% is achieved with 160 patients per group. Under these assumptions, the overall hazard ratio is expected to be about 0.44 in favour of 36 months treatment group. At least 110 events will be required for the final analysis to achieve a power of at least 80% with 160 patients. Assuming a drop-out rate of 20%, altogether 400 patients will be randomized (200 patients per treatment group). The sample size calculation was performed with nQuery Advisor version 6.0. A two-sided significance level of 0.05 was used.

The final analysis comparing the treatment groups will be performed after all randomized patients have completed the visit that takes place after one year of adjuvant therapy (study month 15 visit) and at least 110 events have been recorded. To prepare for the time of the final analysis, the number of events will be monitored closely by the study statistician after all patients have been treated for 1 year.

6.2 Populations

The efficacy data will be analyzed in three populations:

- **Efficacy Population:** Primary efficacy population will consist of patients who have a confirmed GIST, signed an informed consent and were randomized to the study. In this population, patients who started using imatinib after the study treatment period will be censored at the start of the out-of-study treatment and second cancers will not be considered as RFS events.
- **Intention-To-Treat (ITT):** ITT population will consist of all randomized patients, who have signed an informed consent. In this population, patients who started using imatinib after the study treatment period will not be censored and second cancers will be considered as RFS events.
- **Per Protocol (PP):** The PP population will be similar to the primary efficacy population, but will exclude the patients with major violations in inclusion or exclusion criteria.

The Primary efficacy population will be used for the publication and is in agreement with the decisions made in the investigators' meetings. For the purposes of reporting the data to the regulatory authorities ITT population will be used by Novartis. Additionally, PP analysis may be done.

The Safety Analyzable Population includes all patients who receive at least one dose of imatinib.

6.3 Efficacy evaluation

Final analysis

The study is designed to investigate whether a longer duration of therapy (36 months) results in an improvement of recurrence free survival (RFS) as compared to a short duration of therapy (12 months). A two-sided significance level of 0.05 will be used.

The primary endpoint RFS will be measured from the date of randomization to the date of first documentation of recurrence or death (from any cause), whichever occurs first. Second cancers are not considered to be RFS events. Patients who are alive and have not recurred are censored at the date of last follow-up. Survival estimates for RFS will be calculated using the Kaplan-Meier estimator. Comparison of the treatment groups will be based on log-rank test. The overall treatment effect will be quantified by hazard ratio which will be estimated using a Cox proportional hazards regression model with the treatment group only in the model.

In the Primary efficacy population patients who started using imatinib after the study treatment period will be censored at the start of the out-of-study treatment. In ITT population, patients who started using imatinib after the study treatment period will not be censored.

A number of supportive analyses will be performed for the primary endpoint:

- Log-rank test and Cox proportional hazards stratified by type of disease (local disease or intra-abdominal disease, i.e. stratification factor used in the randomization).
- A Cox proportional hazard model estimating the treatment effect while adjusting for the main prognostic variables, such as the primary tumor diameter, mitotic count, and presence of intra-abdominal implants/hepatic metastases. In addition, the center or country and other relevant baseline variables may be included in the model.
- Wilcoxon test (giving greater weight to early events).
- A piecewise Cox proportional hazards model estimating the treatment effect within specific periods (0-12 months, 12-36 months, >36 months). The hazard ratio and 95% CIs will be plotted against time.
- The recurrence rate in the short duration group after 12 months (i.e. after the study treatment

has been completed) will be compared to the recurrence rate in the long duration group after 36 months (i.e. after the study treatment has been completed). The estimated risk profiles will be presented using a smoothed hazard plot.
- The events that have occurred after 12 months treatment will be compared with similar methods as the primary analysis. The patients, who have had an event before the 12 months treatment will be considered as having withdrawn from follow-up at the time of the event[12].
- An analysis of RFS, counting also the second cancers as recurrences.
- The RFS and GIST-specific survival will also be analyzed by means of the competing risks method, i.e. estimation of the cumulative incidence function for the specific cause[13], if the proportion of competing risks is not negligible. The competing risks for RFS are deaths and withdrawals from the study and for the GIST-specific survival deaths due to other causes and withdrawals from the study.

Overall survival and GIST-specific survival will be analyzed as secondary endpoints 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 randomization 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.

GIST-specific survival will be measured from the date of randomization to the date of death considered to be caused by GIST. Patients alive are censored at the time of last follow-up, and patients who have died of a competing cause of death are censored on the date of death resulting from the intercurrent cause. Similar methods as for the primary variable will be used in the data analysis.

The presence of second cancers will be tabulated.

Follow-up analysis 5 years after the Final analysis

A follow-up analysis will be conducted approximately 5 years after the final analysis has been conducted. The follow-up analysis is designed to investigate whether a longer duration of therapy (36 months) results in an improvement of overall survival as compared to a short duration of therapy (12 months). A two-sided significance level of 0.05 will be used.

In addition to the overall survival, the analysis of other endpoints (RFS, GIST-specific survival, presence of second cancers) will be updated. Methods similar to the final analysis will be used.

A further exploratory analysis will compare data on systemic medical treatments, surgery for metastatic disease, and radiation therapy given to treat recurred (usually overtly metastastic) GIST and the best responses to first-line imatinib in the metastatic setting. These variables will be tabulated by treatment group. Time from the date of randomization to the date of first progression of overtly metastatic GIST (as defined by RECIST; a new node within a metastatic lesion, i.e. ”a node within a mass”, is also considered disease progression) or death will be compared between the treatment groups (TTP-Met). In this analysis patients whose GIST has not recurred or whose metastatic GIST has not progressed will be censored at the time of the last follow-up. Patients who had overt metastases at the time of randomization will be excluded from the TTP-Met analysis. TTP-Met will also be calculated excluding from the analysis those subjects whose first-line systemic treatment for metastatic disease was some other agent than imatinib.

6.4 Safety evaluation

Feasibility of therapy will be estimated by 1) the proportion of patients who received the study medication for the assigned period of time, 2) the total frequency of serious adverse events and the annual frequency of serious adverse events, 3) the total frequency and the annual frequency of hematological and nonhematological grade 3 or 4 adverse events.

In addition, the number of patients who reduced the imatinib dose and the imatinib treatment interruptions will be summarized.

The occurrence of the following cardiac complications will be tabulated:
- diagnosis of myocardial infarction since study entry
- diagnosis of cardiac failure since study entry
- diagnosis of coronary artery disease since study entry
- diagnosis of other cardiac diseases since study entry
- cardiac intervention (e.g. surgery, artery dilatation) since study entry.

The safety analysis will be conducted two times, in the final analysis and in the follow-up analysis. Both total frequencies and annual frequencies will be reported in the safety analysis.

7 Notable scales

See Appendix 2 for the NCI/NIH Common Toxicity Criteria

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

8 Publication policy and authorship

The final publication will be written by the principal investigator. An effort will be made to include every investigator who has entered at least 4% (n=14) of the 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 smaller number of accrued patients than 14 may also 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, pathologist, person(s) responsible for gene mutation and serum growth factor analysis, and appropriate Novartis personnel 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 multicenter study agree not to present data gathered from one center or a small group of centers 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.

Novartis must receive copies of any intended communication in advance of publication (at least 15 working days for an abstract or oral presentation and 45 working days for a journal submission). Novartis will review the communications for accuracy (thus avoiding potential discrepancies with submissions to health authorities), verify that confidential information is not being inadvertently divulged and provide any relevant supplementary information.

9 Procedures and instructions

9.1 Administrative procedures

9.1.1 Changes to the protocol

Any change or addition (excluding administrative) to this protocol requires a written protocol amendment that must be approved by the Principal Investigator before implementation. Amendments significantly affecting the safety of patient's, 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. modifications in drug dose or duration of exposure of Glivec outside of the protocol-specified rules,
2. significant changes in the study design (e.g. addition of a control group),
3. increases in the number of invasive procedures to which subjects are exposed
4. 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 or by Novartis 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,
3. minor changes in the packaging or labeling of study drug.

9.1.2 Monitoring procedures

The monitoring plan is detailed in an Appendix (Appendix 4) to the protocol.

9.1.3 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 SSG 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/randomization 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, both Novartis and the investigator 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, electrocardiograms, etc, and keep the signed informed consent form. All information on CRF 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 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 number and title of trial)
5. any other pertinent study document.

9.1.4 Auditing procedures

Auditing procedures are not required by the protocol.

9.1.5 Disclosure and confidentiality

By signing the protocol, the investigator agrees to keep all information provided by Novartis in strict confidence and to request similar confidentiality from his/her staff and the IRB/IEC/REB. Study documents (protocols, investigators' brochures, CRF and other material) will be stored appropriately to ensure their confidentiality. The information provided by Novartis to the investigator may not be disclosed to others without direct written authorization from Novartis, except to the extent necessary to obtain informed consent from patients who wish to participate in the trial.

9.1.6 Discontinuation of study

Novartis reserves the right to discontinue any study under the conditions specified in the clinical trial agreement.

9.2 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.

9.2.1 Institutional Review Board/Independent Ethics Committee

Before implementing this study, the protocol, the proposed informed consent form 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.

9.2.2 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.

10 References

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Appendix

Appendix 1: Drugs known to be metabolized by CYP450 isoenzymes

P450 enzyme	Substrates	Inhibitors	Inducers
CYP2D6	Several antidepressants Neuroleptics Beta-blockers Antiarrhythmics Codeine Dextromethorphan Ethylmorphine Nicotine	Ajmaline Chinoidine Fluoxetine Paroxetine Quinidine Ritonavir	None known
CYP3A4	Acetaminophen Carbamazepine Cyclosporin Digitoxin Diazepam Erythromycin Felodipine Fluoxetine Nifedipine Quinidine Saquinavir Steroids (e.g. cortisol) Terfenadine Triazolam Verapamil Warfarin	Clotrimazole Ketoconazole Ritonavir Troleandomycin	Dexamethasone Phenytoin Rifampin Troleandomycin

Appendix 1.5: Drugs known to be metabolized by CYP450 isoenzymes 2D6 and 3A4 (four pages)

CYP2D6	
Substrates	
Amitriptyline (hydroxylation)	Metoclopramide
Amphetamine	Metoprolol
Betaxolol	Mexiletine
Bisoprolol	Mianserin
Brofaromine	Meperidine
Bufuralol	Methadone
Bupropion	Mirtazapine (hydroxylation)
Captopril	Molindone
Carvedilol	Morphine
Cevimeline	Nortriptyline (hydroxylation)
Chlorpheniramine	Olanzapine (minor, hydroxymethylation)
Chlorpromazine	Ondansetron
Cinnarizine	Orphenadrine
Clomipramine (hydroxylation)	Oxycodone
Clozapine (minor pathway)	Papaverine
Codeine (hydroxylation, o-demelhylation)	Paroxetine (minor pathway)
Cyclobenzaprine (hydroxylation)	Penbutolol
Cyclophosphamide	Pentazocine
Debrisoquin	Perhexiline
Delavirdine	Perphenazine
Desipramine	Phenformin
Dexfenfluramine	Pindolol
Dextromethorphan (o-demethylation)	Promethazine
Dihydrocodeine	Propafenone
Diphenhydramine	Propranolol
Dolasetron	Quetiapine
Donepezil	Remoxipride
Doxepin	Risperidone
Encainide	Ritonavir (minor)
Fenlluramine	Ropivacaine
Flecainide	Selegiline
Fluoxetine (minor pathway)	Sertindole
Fluphenazine	Sertraline (minor pathway)
Haiofantrine	Sparteine
Haioperidol (minor pathway)	Tamoxifen
Hydrocodone	Thioridazine
Hydrocortisone	Tiagabine
Hydroxyamphetamine	Timolol
Imipramine (hydroxylation)	Tolterodine
Labetalol	Tramadol
Loratadine	Trazodone
Maprotiline	Trimipramine
m-Chlorophenylpiperazine (m-CPP)	Tropisetron
Methamphetamine	Venlafaxine (o-desmethylation)
	Yohimbine

Inhibitors	
Amiodarone	Methadone
Celecoxib	Mibefradil
Chloroquine	Moclobemide
Chlorpromazine	Nortluoxetine
Cimetidine	Paroxetine
Citalopram	Perphenazine
Clomipramine	Propafenone
Codeine	Quinacrine
Delavirdine	Quinidine
Desipramine	Ranitidine
Dextropropoxyphene	Risperidone (weak)
Diltiazem	Ritonavir
Doxorubicin	Sertindole
Entacapone (high dose)	Sertraline (weak)
Fluoxetine	Thioridazine
Fluphenazine	Valprolc acid
Fluvoxamine	Venlafaxine (weak)
Haloperidol	Vinblastine
Labetalol	Vincristine
Lobeline	Vinorelbine
Lomustine	Yohimbine

CYP3A3/4	
Substrates	
Acetaminophen	Cevimeline
Alfentanil	Cerivastatin
Alosetron	Chlorpromazine
Alprazolam	Cimetidine
Amiodarone	Cisapride
Amitriptyline (minor)	Citałopram
Amlodipine	Clarithromycin
Anastrozole	Clindamycin
Androsterone	Clomipramine
Antipyrine	Clonazepam
Astemizole	Clozapine
Atorvastatin	Cocaine
Benzphetamine	Codeine (demethylation)
Bepridil	Cortisol
Bexarotene	Cortisone
Bromazepam	Cyclobenzaprine (demethylation)
Bromocriptine	Cyclophosphamide
Budesonide	Cyclosporine
Bupropion (minor)	Dapsone
Buspirone	Dehydroepiandrostendione
Busulfan	Delavirdine
Caffeine	Desmethyldiazepam
Cannabinoids	Dexamethasone
Carbamazepine	Dextromethorphan (minor, N-demethylation)
Diazepam (minor; hydroxylation, N-demethylation)	Nelfinavir
Digitoxin	Nevirapine
Diltiazem	Nicardipine
Disopyramide	Nifedipine
Docetaxel	Niludipine

CYP3A3/4	
Dolasetron	Nimodipine
Donepezil	Nisoldipine
Doxorubicin	Nitrendipine
Doxycycline	Omeprazole (sulfonation)
Dronabinol	Ondansetron
Enalapril	Oral contraceptives (NOS)
Erylhromycin	Orphenadrine
Estradiol	Paclitaxel
Ethinyl estradiol	Pantoprazole
Ethosuximide	Pimozide
Etoposide	Pioglitazone
Exemestane	Pravastatin
Dofetilide (minor)	Prednisone
Felodipine	Progesterone
Fentanyl	Proguanil
Fexofenadine	Propafenone
Finasteride	Quercetin
Fluoxetine	Quetiapine
Flutamide	Quinidine
Glyburide	Quinine
Granisetron	Repaglinide
Halofantrine	Retinoic acid
Hydrocortisone	Rifampin
Hydroxyarginine	Risperidone
Ifosfamide	Ritonavir
Imipramine	Salmeterol
Indinavir	Saquinavir
Isradipine	Sertindole
Itraconazole	Sertraline
Ketoconazole	Sibutramine
Lansoprazole (minor)	Sildenafil citrate
Letrozole	Simvastatin
Levobupivacaine	Sirolimus
Lidocaine	Sufentanil
Loratadine	Tacrolimus
Losartan	Tamoxifen
Lovastatin	Temazepam
Methadone	Teniposide
Mibefradil	Terfenadine
Miconazole	Testosterone
Midazolam	Tetrahydrocannabinol
Mifepristone	Theophylline
Mirtazapine (N-demethylation)	Tiagabine
Montelukast	Tolterodine
Navelbine	Toremifene
Nefazodone	Trazodone
Tretinoin	Warfarin (R-warfarin)
Triazolam	Yohimbine
Troglitazone	Zaleplon (minor pathway)
Troleandomycin	Zatoestron
Venlafaxine (N-demethylation)	Zileuton
Verapamil	Ziprasidone
Vinblastine	Zolpidem
Vincristine	Zonisamide

CYP3A3/4	
Inducers	
Carbamazepine	Phenytoin
Dexamethasone	Primidone
Ethosuximide	Progesterone
Glucocorticoids	Rifabutin
Griseofulvin	Rifampin
Nafcillin	Rofecoxib (mild)
Nelfinavir	St John's wort
Nevirapine	Sulfadimidine
Oxcarbazepine	Sulfinpyrazone
Phenobarbital	Troglitazone
Phenylbutazone	
Inhibitors	
Amiodarone	Metronidazole
Anastrozole	Mibefradil
Azithromycin	Miconazole (moderate)
Cannabinoids	Nefazodone
Cimetidine	Nelfinavir
Clarithromycin	Nevirapine
Clotrimazole	Norfloxacin
Cyclosporine	Norfluoxetine
Danazol	Omeprazole (weak)
Delavirdine	Oxiconazole
Dexamethasone	Paroxetine (weak)
Diethyldithiocarbamate	Propoxyphene
Diltiazem	Quinidine
Dirithromycin	Quinine
Disulfiram	Quinupristin and dalfopristin
Entacapone	Ranitidine
Erythromycin	Ritonavir
Ethinyl estradiol	Saquinavir
Fluconazole (weak)	Sertindole
Fluoxetine	Sertraline
Fluvoxamine	Troglitazone
Gestodene	Troleandomycin
Grapefruit juice	Valproic acid (weak)
Indinavir	Verapamil
Isoniazid	Zafirlukast
Itraconazole	Zileuton
Ketoconazole	

Adapted from Cytochrome P-450 Enzymes and Drug metabolism. In : Lacy CF, Armstrong LL, Goldman MP, Lance LL eds. Drug Information Handbook 8th ed. Hudson, OH; LexiComp Inc. 2000: 1364-1371

Appendix 2: NCI/NIH Common Toxicity Criteria

	Grade				
Toxicity	**0**	**1**	**2**	**3**	**4**
ALLERGY/IMMUNOLOGY					
Allergic reaction/ hypersensitivity (including drug fever)	none	transient rash, drug fever < 38°C (<100.4°F)	urticaria, drug fever 38°C (100.4°F), and/or asymptomatic bronchospasm	symptomatic bronchospasm, requiring parenteral medication(s), with or without urticaria; allergy-related edema/ angioedema	anaphylaxis
Isolated urticaria, in the absence of other manifestations of an allergic or hypersensitivity reaction, is graded under DERMATOLOGY/SKIN.					
Allergic rhinitis (including sneezing, nasal stuffiness, postnasal drip)	none	mild, not requiring treatment	moderate, requiring treatment	-	-
Autoimmune reaction	none	serologic or other evidence of autoimmune reaction but patient is asymptomatic (e.g., vitiligo), all organ function is normal and no treatment is required	evidence of autoimmune reaction involving a non-essential organ or function (e.g., hypothyroidism), requiring treatment other than immunosuppressive drugs	reversible autoimmune reaction involving function of a major organ or other toxicity (e.g., transient colitis or anemia), requiring short-term immunosuppressive treatment	autoimmune reaction causing major grade 4 organ dysfunction; progressive and irreversible reaction; long-term administration of high-dose immuno-suppressive therapy required
(Also consider Hypothyroidism, Colitis, Hemoglobin, Hemolysis)					
Serum sickness	none	-	-	present	
Isolated urticaria, in the absence of other manifestations of an allergic or hypersensitivity reaction, is graded under DERMATOLOGY/SKIN.					
Vasculitis	none	mild, not requiring treatment	symptomatic, requiring medication	requiring steroids	ischemic changes or requiring amputation
Allergy - Other Specify	none	mild	moderate	severe	life-threatening or disabling
AUDITORY / HEARING					
Conductive hearing loss is graded under AUDITORY/HEARING					
Earache is graded under PAIN					
External auditory canal	normal	external otitis with erythema or dry desquamation	external otitis with moist desquamation	external otitis with discharge, mastoiditis	necrosis of the canal soft tissue or bone
Changes associated with radiation to external ear (pinnae) are graded under DERMATOLOGY/SKIN.					
Inner ear/hearing	normal	hearing loss on audiometry only	tinnitus or hearing loss, not requiring hearing aid or treatment	tinnitus or hearing loss, correctable with hearing aid or treatment	severe unilateral or bilateral hearing loss (deafness), not correctable
Middle ear/hearing	normal	serous otitis without subjective decrease in hearing	serous otitis or infection requiring medical intervention; subjective decrease in hearing; rupture of tympanic membrane with discharge	otitis with discharge, mastoiditis or conductive hearing loss	necrosis of the canal soft tissue or bone
Hearing- Other (Specify)	normal	mild	moderate	severe	life-threatening or disabling
BLOOD/BONE MARROW					
Bone marrow cellularity Normal ranges: children (≤ 18 years) younger adults (19-59) older adults (≥ 60 years)	normal for age 90% cellularity average 60-70% cellularity average 50% cellularity average	mildly hypocellular or 25% reduction from normal cellularity for age	moderately hypocellular or >25 - 50% reduction from normal cellularity for age or >2 but <4 weeks to recovery of normal bone marrow cellularity	severely hypocellular or >50 - 75% reduction in cellularity for age or 4 - 6 weeks to recovery of normal bone marrow cellularity	aplasia or >6 weeks to recovery of normal bone marrow cellularity

NCI/NIH Common Toxicity Criteria

	Grade				
Toxicity	**0**	**1**	**2**	**3**	**4**
BLOOD/BONE MARROW (Cont´d)					
Grade Bone marrow cellularity only for changes related to treatment not disease					
CD4 count	WNL	< LLN - 500/mm^3	200 - < 500/mm^3	50 - < 200/mm^3	< 50/mm^3
Haptoglobin	normal	decreased	-	absent	-
Hemoglobin (Hgb)	WNL	< LLN - 10.0 g/dl < LLN - 100 g/L < LLN - 6.2 mmol/L	8.0 - < 10.0 g/dl 80 - < 100 g/L 4.9 - < 6.2 mmol/L	6.5 - < 8.0 g/dl 65 - 80 g/L 4.0 - < 4.9 mmol/L	< 6.5 g/dl < 65 g/L < 4.0 mmol/L
The following criteria may be used for leukemia studies or bone marrow infiltrative/myelophthisic process if the protocol so specifies.					
For leukemia studies or bone marrow infiltrative/ myelophthisic processes	WNL	10 - < 25%decrease from pretreatment	25 - < 50% decrease from pretreatment	50 - < 75% decrease from pretreatment	≥75% decrease from pretreatment
Hemolysis (e.g., immune hemolytic anemia, drug-related hemolysis)	none	only laboratory evidence of hemolysis [e.g., direct antiglobulin test (Coombs') schistocytes]	evidence of red cell destruction and 2 gm decrease in hemoglobin, no transfusion	requiring transfusion and/or medical intervention (e.g., steroids)	catastrophic consequences of hemolysis (e.g., renal failure, hypotension, bronchospasm, splenectomy)
Also consider Haptoglobin, Hgb					
Leukocytes (total WBC)	WNL	< LLN - 3.0 x 10^9/L < LLN - 3000/mm^3	2.0 - < 3.0 x 10^9/L 2000 - < 3000/mm^3	1.0 - < 2.0 x 10^9/L 1000 - < 2000/mm^3	< 1.0 x 10^9/L < 1000/mm^3
Lymphopenia	WNL	<LLN - 1.0 x 10^9/L <LLN - 1000/mm^3	0.5 - <1.0 x 10^9/L 500 - <1000/mm^3	<0.5 x 10^9/L <500/mm^3	-
Neutrophils / granulocytes (ANC/AGC)	WNL	1.5 - <2.0 x 10^9/L ≥1500 - <2000/mm^3	1.0 - <1.5 x 10^9/L ≥1000 - <1500/mm^3	0.5 - <1.0 x 10^9/L ≥500 - <1000/mm^3	< 0.5 x 10^9/L < 500/mm^3
Platelets	WNL	< LLN - <75.0 x 10^9/L < LLN - 75000/mm^3	50.0 - < 75.0 x 10^9/L 50000 - < 75000/mm^3	10.0 - < 50.0 x 10^9/L 10000 - < 50000/mm^3	< 10.0 x 10^9/L < 10000/mm^3
The following criteria may be used for **leukemia studies** or bone marrow infiltrative/myelophthisic process if the protocol so specifies.					
For leukemia studies or bone marrow infiltrative/myelop hthisic process	WNL	10 - <25% decrease from baseline	25 - <50% decrease from baseline	50 - <75% decrease from baseline	75% decrease from baseline
Transfusion: Platelets	none	-	-	yes	platelet transfusions and other measures required to improve platelet increment; platelet transfusion refractoriness associated with life-threatening bleeding. (e.g., HLA or cross matched platelet transfusions)
Also consider Platelets.					
Transfusion: pRBCs	none	-	-	yes	-
Also consider Hemoglobin.					
Hematologic-Other (Specify)	none	mild	moderate	severe	life-threatening or disabling
CARDIOVASCULAR (ARRHYTHMIA)					
Conduction abnormality/ Atrioventricular heart block	none	asymptomatic, not requiring treatment (e.g., Mobitz type I second-degree AV block, Wenckebach)	symptomatic, but not requiring treatment	symptomatic and requiring treatment (e.g., Mobitz type II second-degree AV block, third-degree AV block)	life-threatening (e.g., arrhythmia associated with CHF, hypotension, syncope, shock)
Nodal / junctional arrhythmia / dysrhythmia	none	asymptomatic, not requiring treatment	symptomatic, but not requiring treatment	symptomatic and requiring treatment	life-threatening (e.g., arrhythmia associated with CHF, hypotension, syncope, shock)
Palpitations	none	present	-	-	-

NCI/NIH Common Toxicity Criteria

Toxicity	0	1	2	3	4
CARDIOVASCULAR (ARRHYTHMIA) Cont´d					
Grade palpitations only in the absence of a documented arrhythmia.					
Prolonged QTc interval (QTc > 0.48 seconds)	none	asymptomatic, not requiring treatment	symptomatic, but not requiring treatment	symptomatic and requiring treatment	life-threatening (e.g., arrhythmia associated with CHF, hypotension, syncope, shock)
Sinus bradycardia	none	asymptomatic, not requiring treatment	symptomatic, but not requiring treatment	symptomatic and requiring treatment	life-threatening (e.g., arrhythmia associated with CHF, hypotension, syncope, shock)
Sinus tachycardia	none	asymptomatic, not requiring treatment	symptomatic, but not requiring treatment	symptomatic and requiring treatment of underlying cause	-
Supraventricular arrhythmia's (SVT/atrial fibrillation/ flutter)	none	asymptomatic, not requiring treatment	symptomatic, but not requiring treatment	symptomatic and requiring treatment	life-threatening (e.g., arrhythmia associated with CHF, hypotension, syncope, shock)
Syncope (fainting) is graded under NEUROLOGY					
Vasovagal episode	none	-	present without loss of consciousness	present with loss of consciousness	-
Ventricular arrhythmia (PVCs / bigeminy /trigeminy / ventricular tachycardia)	none	asymptomatic, not requiring treatment	symptomatic, but not requiring treatment	symptomatic and requiring treatment	life-threatening (e.g., arrhythmia associated with CHF, hypotension, syncope, shock)
Arrhythmia-Other (Specify)	none	asymptomatic, not requiring treatment	symptomatic, but not requiring treatment	symptomatic, and requiring treatment of underlying cause	life-threatening (e.g., arrhythmia associated with CHF, hypotension, syncope, shock)
Acute vascular leak syndrome	absent	-	symptomatic, but not requiring fluid support	respiratory compromise or requiring fluids	life-threatening; requiring pressor support and/or ventilator support
Cardiac- ischemic/ infarction	none	non-specific T-wave flattening or changes	asymptomatic, ST- and T-wave changes suggesting ischemia	angina without evidence of infarction	acute myocardial infarction
CARDIOVASCULAR (GENERAL)					
Cardiac left ventricular function	normal	asymptomatic decline of resting ejection fraction of 10% but < 20% of baseline value; shortening fraction 24% but < 30%	asymptomatic but resting ejection fraction below LLN for laboratory or decline of resting ejection fraction 20% of baseline value; < 24% shortening fraction	CHF responsive to treatment	severe or refractory CHF or requiring intubation
CNS cerebrovascular ischemia is graded under NEUROLOGY.					
Cardiac troponin I (cTnI)	normal	-	-	levels consistent with unstable angina as defined by the manufacturer	levels consistent with myocardial infarction as defined by the manufacturer
Cardiac troponin T (cTnT)	normal	≥ 0.03 - < 0.05 ng/ml	≥ 0.05 - < 0.1 ng/ml	≥ 0.1 - < 0.2 ng/ml	≥ 0.2 ng/ml
Edema	none	asymptomatic, not requiring therapy	symptomatic, requiring therapy	symptomatic edema limiting function and unresponsive to therapy or requiring drug discontinuation	anasarca (severe generalized edema)
Hypertension	none	asymptomatic, transient increase by >20 mmHg (diastolic) or to > 150/100* if previously WNL; not requiring treatment	recurrent or persistent or symptomatic increase by > 20 mmHg (diastolic) or to > 150/100* if previously WNL; not requiring treatment	requiring therapy or more intensive therapy than previously	hypertensive crisis

NCI/NIH Common Toxicity Criteria

Toxicity	0	1	2	3	4
CARDIOVASCULAR (GENERAL) Cont´d					
Hypotension	none	changes, but not requiring therapy (including transient orthostatic hypotension)	requiring brief fluid replacement or other therapy but not hospitalization; no physiologic consequences	requiring therapy and sustained medical attention, but resolves without persisting physiologic consequences	shock (associated with acidemia and impairing vital organ function due to tissue hypoperfusion)
Also consider Syncope (fainting). Angina or MI is graded as Cardiac- ischemia/infarction in the CARDIOVASCULAR (GENERAL).					
Myocarditis	none	-	-	CHF responsive to treatment	severe or refractory CHF
Operative injury of vein/artery	none	primary suture repair for injury, but not requiring transfusion	primary suture repair for injury, requiring transfusion	vascular occlusion requiring surgery or bypass for injury	myocardial infarction; resection of organ (e.g., bowel, limb)
Pericardial effusion/ pericarditis	none	asymptomatic effusion, not requiring treatment	pericarditis (rub, ECG changes, and/or chest pain)	physiologic consequences resulting from symptoms	tamponade (drainage or pericardial window required)
Peripheral arterial ischemia	none	-	brief episode of ischemia managed non-surgically and without permanent deficit	requiring surgical intervention	life-threatening or with permanent functional deficit (e.g., amputation)
Phlebitis (superficial)	none	-	present	-	-
Injection site reaction is graded under DERMATOLOGY/SKIN					
Syncope (fainting) is graded under NEUROLOGY					
Thrombosis / embolism	none	-	deep vein thrombosis, not requiring anticoagulant	deep vein thrombosis, requiring anticoagulant therapy	embolic event including pulmonary embolism
Vein/artery operative injury is graded as Operative injury of vein/artery in the CARDIOVASCULAR (GENERAL) category					
Circulatory or cardiac- Other (Specify)	none	mild	moderate	severe	life-threatening or disabling
COAGULATION					
See the HEMORRHAGE category for grading the severity of bleeding events.					
DIC (disseminated intravascular coagulation)	absent	-	-	laboratory findings present with no bleeding	laboratory findings and bleeding
Also grade Platelets. Must have increased fibrin split products or D-dimer in order to grade as DIC.					
Fibrinogen	WNL	0.75 - <1.0 x LLN	0.5 - <0.75 x LLN	0.25 - <0.5 x LLN	<0.25 x LLN
The following criteria may be used for leukemia studies or bone marrow infiltrative/myelophthisic process if the protocol so specifies.					
For leukemia studies:	WNL	<20% decrease from pretreatment value or LLN	20 - <40% decrease from pretreatment value or LLN	40 - <70% decrease from pretreatment value or LLN	<50 mg%
Partial thrombo-plastin time (PTT)	WNL	>ULN - ≤ 1.5 x ULN	> 1.5 - ≤ 2 x ULN	>2 x ULN	-
Phlebitis is graded in the CARDIOVASCULAR (GENERAL) category					
Prothrombin time (PT)	WNL	>ULN - ≤ 1.5 x ULN	> 1.5 - ≤ 2 x ULN	>2 x ULN	-
Thrombosis/embolism is graded in the CARDIOVASCULAR (GENERAL) category.					
Thrombotic microangiopathy (e.g., thrombotic thrombocytopenia purpura/TTP or hemolytic uremia syndrome/HUS)	absent	-	-	laboratory findings present without clinical consequences	laboratory findings and clinical consequences, (e.g., CNS hemor-rhage/bleeding or thrombosis/embolism or renal failure) requiring therapeutic intervention
Also consider Hemoglobin (Hgb), Platelets, Creatinine. Must have microangiopathic changes on blood smear (e.g., schistocytes, helmet cells, red cell fragments).					
Coag- Other (Specify)	none	mild	moderate	severe	life-threatening or disabling

NCI/NIH Common Toxicity Criteria

Toxicity	0	1	2	3	4
CONSTITUTIONAL SYMPTOMS					
Fatigue (lethargy, malaise, asthenia)	none	increased fatigue over baseline, but not altering normal activities	moderate (e.g., decrease in performance status by 1 ECOG level or 20% Karnofsky or *Lansky*) or causing difficulty performing some activities	severe (e.g., decrease in performance status by 2 ECOG levels or 40% Karnofsky or *Lansky*) or loss of ability to perform some activities	bedridden or disabling
Fever (in the absence of neutropenia, where neutropenia is defined as AGC < 1.0 x 10^9/L)	none	38.0 - 39.0°C (100.4 - 102.2°F)	39.1 - 40.0°C (102.3 - 104.0°F)	> 40.0°C (>104.0°F) for < 24 hrs	> 40.0°C (>104.0°F) for > 24 hrs
Also consider Allergic reaction/hypersensitivity. The temperature measurements listed above are oral or tympanic.					
Hot flashes/flushes are graded in the ENDOCRINE category.					
Rigors, chills	none	mild, requiring symptomatic treatment (e.g., blanket) or non-narcotic medication	severe and/or prolonged, requiring narcotic medication	not responsive to narcotic medication	-
Sweating (diaphoresis)	normal	mild and occasional	frequent or drenching	-	-
Weight gain	< 5%	5 - <10%	10 - <20%	20%	-
Also consider Ascites, Edema, Pleural effusion.					
The following criteria is to be used ONLY for weight gain associated with Veno-Occlusive Disease.					
Weight gain - veno-occlusive disease (VOD)	<2%	2 - <5%	5 - <10%	10% or as ascites	10% or fluid retention resulting in pulmonary failure
Weight loss	< 5%	5 - <10%	10 - <20%	20%	-
Also consider Vomiting, Dehydration, Diarrhea.					
Constitutional symptoms- Other (Specify)	none	mild	moderate	severe	life-threatening or disabling
DERMATOLOGY/SKIN					
Alopecia	normal	mild hair loss	pronounced hair loss	-	-
Bruising (in absence of grade 3 or 4 thrombocytopenia)	none	localized or in dependent area	generalized	-	-
Bruising resulting from grade 3 or 4 thrombocytopenia is graded as Petechiae/purpura and Hemorrhage/bleeding with grade 3 or 4 thrombocytopenia in the HEMORRHAGE category, not in the DERMATOLOGY/SKIN category.					
Dermatitis, focal (associated with high-dose chemotherapy and bone marrow transplant)	none	faint erythema or dry desquamation	moderate to brisk erythema or a patchy moist desquamation, mostly confined to skin folds and creases; moderate edema	confluent moist desquamation, 1.5 cm diameter, not confined to skin folds; pitting edema	skin necrosis or ulceration of full thickness dermis; may include spontaneous bleeding not induced by minor trauma or abrasion
Dry skin	normal	controlled with emollients	not controlled with emollients	-	-
Erythema multiforme (e.g., Stevens-Johnson syndrome, toxic epidermal necrolysis)	absent	-	scattered, but not generalized eruption	severe or requiring IV fluids (e.g., generalized rash or painful stomatitis)	life-threatening (e.g., exfoliative or ulcerating dermatitis or requiring enteral or parenteral nutritional support)
Flushing	absent	present	-	-	-
Hand-foot skin reaction	none	skin changes or dermatitis without pain (e.g., erythema, peeling)	skin changes with pain, not interfering with function	skin changes with pain, interfering with function	-

NCI/NIH Common Toxicity Criteria

Toxicity	0	1	2	3	4
DERMATOLOGY/SKIN Cont´d					
Injection site reaction	none	pain or itching or erythema	pain or swelling, with inflammation or phlebitis	ulceration or necrosis that is severe or prolonged, or requiring surgery	-
Nail changes	normal	discoloration or ridging (koilonychia) or pitting	partial or complete loss of nail(s) or pain in nailbeds	-	-
Petechiae is graded in the HEMORRHAGE category					
Photosensitivity	none	painless erythema	painful erythema	erythema with desquamation	-
Pigmentation changes (e.g., vitiligo)	none	localized pigmentation changes	generalized pigmentation changes	-	-
Pruritus	none	mild or localized, relieved spontaneously or by local measures	intense or widespread, relieved spontaneously or by systemic measures	intense or widespread and poorly controlled despite treatment	-
Purpura is graded in the HEMORRHAGE category.					
Radiation dermatitis	none	faint erythema or dry desquamation	moderate to brisk erythema or a patchy moist desquamation, mostly confined to skin folds and creases; moderate edema	confluent moist desquamation, 1.5 cm diameter, not confined to skin folds; pitting edema	skin necrosis or ulceration of full thickness dermis; may include bleeding not induced by minor trauma or abrasion
Pain associated with radiation dermatitis is graded separately in the PAIN category as Pain due to radiation.					
Radiation recall reaction (reaction following chemotherapy in the absence of additional radiation therapy that occurs in a previous radiation port)	none	faint erythema or dry desquamation	moderate to brisk erythema or a patchy moist desquamation, mostly confined to skin folds and creases; moderate edema	confluent moist desquamation, 1.5 cm diameter, not confined to skin folds; pitting edema	skin necrosis or ulceration of full thickness dermis; may include bleeding not induced by minor trauma or abrasion
Rash/desquamation	none	macular or papular eruption or erythema without associated symptoms	macular or papular eruption or erythema with pruritus or other associated symptoms covering <50% of body surface or localized desquamation or other lesions covering <50% of body surface area	symptomatic generalized erythroderma or macular, papular or vesicular eruption or desquamation covering 50% of body surface area	generalized exfoliative dermatitis or ulcerative dermatitis
Also consider Allergic reaction/hypersensitivity.					
Erythema multiforme (Stevens-Johnson syndrome) is graded separately as Erythema multiforme.					
Urticaria (hives, welts, wheals)	none	requiring no medication	requiring PO or topical treatment or IV medication or steroids for <24 hours	requiring IV medication or steroids for 24 hours	-
Wound- infectious	none	cellulitis	superficial infection	infection requiring IV antibiotics	necrotizing fascitis
Wound- non-infectious	none	incisional separation	incisional hernia	fascial disruption without evisceration	fascial disruption with evisceration
Skin- Other (Specify)	none	mild	moderate	severe	life-threatening or disabling
ENDOCRINE					
Cushingoid appearance (e.g., moon face with or without buffalo hump, centripetal obesity, cutaneous striae)	absent	-	present	-	-
Also consider Hyperglycemia and Hypokalemia					

NCI/NIH Common Toxicity Criteria

Toxicity	0	1	2	3	4
ENDOCRINE (cont'd)					
Feminization of male	absent	-	-	present	-
Gynecomastia	none	mild	pronounced or painful	pronounced or painful and requiring surgery	-
Hot flashes/flushes	none	mild or no more than 1 per day	moderate and greater than 1 per day	-	-
Hypothyroidism	absent	asymptomatic, TSH elevated, no therapy given	symptomatic or thyroid replacement treatment given	patient hospitalized for manifestations of hypothyroidism	myxedema coma
Masculinization of female	absent	-	-	present	-
SIADH (syndrome of inappropriate antidiuretic hormone)	absent	-	-	present	-
Endocrine- Other (Specify)	none	mild	moderate	severe	life-threatening or disabling
GASTROINTESTINAL					
Amylase is graded in the METABOLIC/LABORATORY category.					
Anorexia	none	loss of appetite	oral intake significantly decreased	requiring IV fluids	requiring feeding tube or parenteral nutrition
Ascites (non-malignant)	none	asymptomatic	symptomatic, requiring diuretics	symptomatic, requiring therapeutic paracentesis	life-threatening physiologic consequences
Colitis	none	-	abdominal pain with mucus and/or blood in stool	abdominal pain, fever, change in bowel habits with ileus or peritoneal signs, and radiographic or biopsy documentation	perforation or requiring surgery or toxic megacolon
Also consider Hemorrhage/bleeding with grade 3 or 4 thrombocytopenia, Hemorrhage/bleeding without grade 3 or 4 thrombocytopenia, Melena/GI bleeding, Rectal bleeding/hematochezia, Hypotension.					
Constipation	none	requiring stool softener or dietary modification	requiring laxatives	obstipation requiring manual evacuation or enema	obstruction or toxic megacolon
Dehydration	none	dry mucous membranes and/or diminished skin turgor	requiring IV fluid replacement (brief)	requiring IV fluid replacement (sustained)	physiologic consequences requiring intensive care; hemodynamic collapse
Also consider Hypotension, Diarrhea, Vomiting, Stomatitis/pharyngitis (oral/pharyngeal mucositis).					
Diarrhea Patients without colostomy:	none	increase of < 4 stools/day over pre-treatment	increase of 4-6 stools/day, or nocturnal stools	increase of 7 stools/ day or incontinence; or need for parenteral support for dehydration	physiologic consequences requiring intensive care; or hemodynamic collapse
-Patients with a colostomy:	none	mild increase in loose, watery colostomy output compared with pretreatment	moderate increase in loose, watery colostomy output compared with pretreatment, but not interfering with normal activity	severe increase in loose, watery colostomy output compared with pretreatment, interfering with normal activity	physiologic consequences, requiring intensive care; or hemodynamic collapse
Also consider Hemorrhage/bleeding with grade 3 or 4 thrombocytopenia, Hemorrhage/bleeding without grade 3 or 4 thrombocytopenia, Pain, Dehydration, Hypotension					
Duodenal ulcer (requires radiographic or endoscopic documentation)	none	-	requiring medical management or non-surgical treatment	uncontrolled by outpatient medical management; requiring hospitalization	perforation or bleeding, requiring emergency surgery
Dyspepsia / heartburn	none	mild	moderate	severe	-

NCI/NIH Common Toxicity Criteria

Toxicity	0	1	2	3	4
GASTROINTESTINAL (cont'd)					
Dysphagia, esophagitis, odynophagia (painful swallowing)	none	mild dysphagia, but can eat regular diet	dysphagia, requiring predominantly pureed, soft, or liquid diet	dysphagia, requiring IV hydration	requiring enteral or parenteral nutritional support or complete obstruction (cannot swallow saliva) or perforation
Dysphagia- esophageal related to radiation	none	mild dysphagia, but can eat regular diet	dysphagia, requiring predominantly liquid, pureed or soft diet	dysphagia requiring feeding tube, IV hydration or hyperalimentation	complete obstruction (cannot swallow saliva); ulceration with bleeding not induced by minor trauma or abrasion or perforation
Also consider Pain due to radiation, Mucositis due to radiation.					
Fistula is graded separately as Fistula- esophageal.					
Dysphagia - pharyngeal related to radiation	none	mild dysphagia, but can eat regular diet	dysphagia, requiring predominantly pureed, soft, or liquid diet	dysphagia, requiring feeding tube, IV hydration or hyperalimentation	complete obstruction (cannot swallow saliva); ulceration with bleeding not induced by minor trauma or abrasion or perforation
Fistula is graded separately as Fistula- pharyngeal.					
Fistula- esophageal	none	-	-	present	requiring surgery
Fistula- intestinal	none	-	-	present	requiring surgery
Fistula- pharyngeal	none	-	-	present	requiring surgery
Fistula- rectal/anal	none	-	-	present	requiring surgery
Flatulence	none	mild	moderate	-	-
Gastric ulcer (requires radiographic or endoscopic documentation)	none	-	requiring medical management or non-surgical treatment	bleeding without perforation, uncontrolled by outpatient medical management; requiring hospitalization or surgery	perforation or bleeding, requiring emergency surgery
Also consider Hemorrhage/bleeding with grade 3 or 4 thrombocytopenia, Hemorrhage/bleeding without grade 3 or 4 thrombocytopenia.					
Gastritis	none	-	requiring medical management or non-surgical treatment	uncontrolled by out-patient medical management; requiring hospitalization or surgery	life-threatening bleeding, requiring emergency surgery
Also consider Hemorrhage/bleeding with grade 3 or 4 thrombocytopenia, Hemorrhage/bleeding without grade 3 or 4 thrombocytopenia.					
Hematemesis is graded in the HEMORRHAGE category.					
Hematochezia is graded in the HEMORRHAGE category as Rectal bleeding/hematochezia.					
Ileus (or neuroconstipation)	none	-	intermittent, not requiring intervention	requiring non-surgical intervention	requiring surgery
Mouth dryness	normal	mild	moderate	-	-
Mucositis					
Mucositis not due to radiation is graded in the GASTROINTESTINAL category for specific sites: Colitis, Esophagitis, Gastritis, Stomatitis/pharyngitis (oral/pharyngeal mucositis), and Typhlitis; or the RENAL/GENITOURINARY category for Vaginitis.					
Mucositis due to radiation	none	erythema of the mucosa	patchy pseudomembranous reaction (patches generally 1.5 cm in diameter and non-contiguous)	confluent pseudomembranous reaction (contiguous patches generally > 1.5 cm in diameter)	necrosis or deep ulceration; may include bleeding not induced by minor trauma or abrasion
Also consider Pain due to radiation.					
Note: Grade radiation mucositis of the larynx here. Dysphagia related to radiation is also graded as either Dysphagia- esophageal related to radiation or Dysphagia- pharyngeal related to radiation, depending on the site of treatment.					
Nausea	none	able to eat	oral intake significantly decreased	no significant intake, requiring IV fluids	-
Pancreatitis	none	-	-	abdominal pain with pancreatic enzyme elevation	complicated by shock (acute circulatory failure)
Also consider Hypotension. Asymptomatic amylase and Amylase are graded in the METABOLIC/LABORATORY category.					

NCI/NIH Common Toxicity Criteria

Toxicity	0	1	2	3	4
GASTROINTESTINAL (cont'd)					
Pharyngitis is graded in the GASTROINTESTINAL category as Stomatitis/pharyngitis (oral/pharyngeal mucositis)					
Proctitis	none	increased stool frequency, occasional blood-streaked stools, or rectal discomfort (including hemorrhoids), not requiring medication	increased stool frequency, bleeding, mucus discharge, or rectal discomfort requiring medication; anal fissure	increased stool frequency/diarrhea, requiring parenteral support; rectal bleeding, requiring transfusion; or persistent mucus discharge, necessitating pads	perforation, bleeding or necrosis or other life-threatening complication requiring surgical intervention (e.g., colostomy)
Salivary gland changes	none	slightly thickened saliva/may have slightly altered taste (e.g., metallic); additional fluids may be required	thick, ropy, sticky saliva; markedly altered taste; alteration in diet required	-	acute salivary gland necrosis
Sense of smell	normal	slightly altered	markedly altered	-	-
Stomatitis / pharyngitis (oral/pharyngeal mucositis)	none	painless ulcers, erythema, or mild soreness in the absence of lesions	painful erythema, edema, or ulcers, but can eat or swallow	painful erythema, edema, or ulcers requiring IV hydration	severe ulceration or requires parenteral or enteral nutritional support or prophylactic intubation
Taste disturbance (dysgeusia)	normal	slightly altered	markedly altered	-	-
Typhlitis (inflammation of the cecum)	none	-	-	abdominal pain, diarrhea, fever, or radiographic documentation	perforation, bleeding or necrosis or other life-threatening compli-cation requiring surgical intervention (e.g., colostomy)
Also consider Hemorrhage/bleeding with grade 3 or 4 thrombocytopenia, Hemorrhage/bleeding without grade 3 or 4 thrombocytopenia, Hypotension, Febrile/neutropenia.					
Vomiting	none	1 episode in 24 hours over pretreatment	2-5 episodes in 24 hours over pretreatment	6 episodes in 24 hours over pretreatment; or need for IV fluids	Requiring parenteral nutrition; or physiologic consequences requiring intensive care; hemodynamic collapse
Also consider Dehydration					
Weight gain is graded in the CONSTITUTIONAL SYMPTOMS category.					
Weight loss is graded in the CONSTITUTIONAL SYMPTOMS category.					
GI- Other (Specify)	none	mild	moderate	severe	life-threatening or disabling
HEMORRHAGE					
Note: Transfusion in this section refers to pRBC infusion. For <u>any</u> bleeding with grade 3 or 4 platelets (< 50,000), <u>always</u> grade Hemorrhage/bleeding with grade 3 or 4 thrombocytopenia. Also consider platelets, transfusion- pRBCS, and transfusion-platelets in addition to the grade that incorporates the site or type of bleeding. If the site or type of hemorrhage/bleeding is listed, also use the grading that incorporates the site of bleeding: CNS hemorrhage/bleeding, Hematuria, Hematemesis, Hemoptysis, Hemorrhage/bleeding with surgery, Melena/lower GI bleeding, Petechiae/purpura (Hemorrhage/bleeding into skin), Rectal bleeding/hematochezia, Vaginal bleeding. If the platelet count is 50,000 and the site or type of bleeding is listed, grade the specific site. If the site or type is <u>not</u> listed and the platelet count is 50,000, grade Hemorrhage/bleeding without grade 3 or 4 thrombocytopenia and specify the site or type in the OTHER category.					
Hemorrhage /bleeding with grade 3 or 4 thrombocytopenia	none	mild without transfusion		requiring transfusion	catastrophic bleeding, requiring major non-elective intervention
Also consider Platelets, Hemoglobin, Transfusion-platelet, Transfusion-pRBCs This toxicity must be graded for any bleeding with grade 3 or 4 thrombocytopenia. Also grade the site or type of hemorrhage/bleeding. If the site is not listed, grade as Other in the HEMORRHAGE category..					
Hemorrhage /bleeding without grade 3 or 4 thrombocytopenia	none	mild without transfusion		requiring transfusion	catastrophic bleeding requiring major non-elective intervention
Also consider Platelets, Hemoglobin, Transfusion-platelet, Transfusion-pRBCs Bleeding in the absence of grade 3 or 4 thrombocytopenia is graded here only if the specific site or type of bleeding is not listed elsewhere in the HEMORRHAGE category. Also grade as Other in the HEMORRHAGE category.					

NCI/NIH Common Toxicity Criteria

Toxicity	0	1	2	3	4
HEMORRHAGE Cont´d					
CNS hemorrhage /bleeding	none	-	-	bleeding noted on CT or other scan with no clinical consequences	hemorrhagic stroke or hemorrhagic vascular event (CVA) with neurologic signs and symptoms
Epistaxis	none	mild without transfusion	-	requiring transfusion	catastrophic bleeding, requiring major non-elective intervention
Hematemesis	none	mild without transfusion	-	requiring transfusion	catastrophic bleeding, requiring major non-elective intervention
Hematuria (in the absence of vaginal bleeding)	none	microscopic only	intermittent gross bleeding, no clots	persistent gross bleeding or clots; may require catheterization or instrumentation, or transfusion	open surgery or necrosis or deep bladder ulceration
Hemoptysis	none	mild without transfusion	-	requiring transfusion	catastrophic bleeding, requiring major non-elective intervention
Hemorrhage /bleeding associated with surgery	none	mild without transfusion	-	requiring transfusion	catastrophic bleeding, requiring major non-elective intervention
Expected blood loss at the time of surgery is not graded as a toxicity.					
Melena/GI bleeding	none	mild without transfusion	-	requiring transfusion	catastrophic bleeding, requiring major non-elective intervention
Petechiae/purpura (hemorrhage /bleeding into skin or mucosa)	none	rare petechiae of skin	petechiae or purpura in dependent areas of skin	generalized petechiae or purpura of skin or petechiae of any mucosal site	-
Rectal bleeding /hematochezia	none	mild without transfusion or medication	persistent, requiring medication (e.g., steroid suppositories) and/or break from radiation treatment	requiring transfusion	catastrophic bleeding, requiring major non-elective intervention
Vaginal bleeding	none	spotting, requiring < 2 pads per day	requiring ≥ 2 pads per day, but not requiring transfusion	requiring transfusion	catastrophic bleeding, requiring major non-elective intervention
Hemorrhage-Other (Specify site)	none	mild without transfusion	-	requiring transfusion	catastrophic bleeding, requiring major non-elective intervention
HEPATIC					
Alkaline phosphatase	WNL	> ULN - 2.5 x ULN	> 2.5 - 5.0 x ULN	> 5.0 - 20.0 x ULN	> 20.0 x ULN
Bilirubin	WNL	> ULN - 1.5 x ULN	> 1.5 - 3.0 x ULN	> 3.0 - 10.0 x ULN	> 10.0 x ULN
Bilirubin- graft versus host disease (GVHD) The following criteria are used only for bilirubin associated with graft versus host disease.					
	normal	2 - <3 mg/100 ml	3 - <6 mg/100 ml	6 - <15 mg/100 ml	15 mg/100 ml
GGT (- Glutamyl transpeptidase)	WNL	> ULN - 2.5 x ULN	> 2.5 - 5.0 x ULN	> 5.0 - 20.0 x ULN	> 20.0 x ULN
Hepatic enlargement	absent	-	-	present	-
Grade Hepatic enlargement only for changes related to VOD or other treatment related toxicity.					
Hypoalbuminemia	WNL	<LLN - 3 g/dl	2 - <3 g/dl	<2 g/dl	-
Liver dysfunction/failure (clinical)	normal	-	-	asterixis	encephalopathy or coma
Documented viral hepatitis is graded in the INFECTION category.					
Portal vein flow	normal	-	decreased portal vein flow	reversal/retrograde portal vein flow	-

NCI/NIH Common Toxicity Criteria

Toxicity	0	1	2	3	4
HEPATIC (cont'd)					
SGOT (AST) (serum glutamic oxaloacetic transaminase)	WNL	> ULN - 2.5 x ULN	> 2.5 - 5.0 x ULN	> 5.0 - 20.0 x ULN	> 20.0 x ULN
SGPT (ALT) (serum glutamic pyruvic transaminase)	WNL	> ULN - 2.5 x ULN	> 2.5 - 5.0 x ULN	> 5.0 - 20.0 x ULN	> 20.0 x ULN
Hepatic- Other (Specify)	none	mild	moderate	severe	life-threatening or disabling
INFECTION/FEBRILE NEUTROPENIA					
Catheter-related infection	none	mild, no active treatment	moderate, localized infection, requiring local or oral treatment	severe, systemic infection, requiring IV antibiotic or antifungal treatment or hospitalization	life-threatening sepsis (e.g., septic shock)
Febrile neutropenia (fever of unknown origin without clinically or microbiologically documented infection) (ANC < 1.0 x 10^9/L, fever 38.5°C)	none	-	-	present	life-threatening sepsis (e.g., septic shock)
Hypothermia instead of fever may be associated with neutropenia and is graded here.					
Infection (documented clinically or microbiologically) with grade 3 or 4 neutropenia (ANC < 1.0 x 10^9/L)	none	-	-	present	life-threatening sepsis (e.g., septic shock)
Hypothermia instead of fever may be associated with neutropenia and is graded here. In the absence of documented infection with grade 3 or 4 neutropenia, grade as Febrile neutropenia.					
Infection with unknown ANC	none	-	-	present	life-threatening sepsis (e.g., septic shock)
This toxicity criterion is used in the rare case when ANC is unknown					
Infection without neutropenia	none	mild, no active treatment	moderate, localized infection, requiring local or oral treatment	severe, systemic infection, requiring IV antibiotic or antifungal treatment, or hospitalization	life-threatening sepsis (e.g., septic shock)
Wound-infectious is graded under DERMATOLOGY/SKIN.					
LYMPHATICS					
Lymphatics	normal	mild lymphedema	moderate lymphedema requiring compression; lymphocyst	severe lymphedema limiting function; lymphocyst requiring surgery	severe lymphedema limiting function with ulceration
Lymphatics- Other (Specify)	none	mild	moderate	severe	life-threatening or disabling
METABOLIC/LABORATORY					
Acidosis (metabolic or respiratory)	normal	pH < normal, but 7.3	-	pH < 7.3	pH < 7.3 with life-threatening physiologic consequences
Alkalosis (metabolic or respiratory)	normal	pH > normal, but 7.5	-	pH > 7.5	pH > 7.5 with life-threatening physiologic consequences
Amylase	WNL	> ULN - 1.5 x ULN	> 1.5 - 2.0 x ULN	> 2.0 - 5.0 x ULN	>5.0 x ULN
Bicarbonate	WNL	< LLN - 16 mEq/dl	11 - 15 mEq/dl	8 - 10 mEq/dl	< 8 mEq/dl
CPK (creatine phosphokinase)	WNL	> ULN - 2.5 x ULN	> 2.5 - 5 x ULN	> 5 - 10 X ULN	> 10 x ULN
Hypercalcemia	WNL	>ULN - 11.5 mg/dl > ULN - 2.9 mmol/L	>11.5 - 12.5 mg/d > 2.9 - 3.1 mmol/L	>12.5 - 13.5 mg/dl > 3.1 - 3.4 mmol/L	> 13.5 mg/dl > 3.4 mmol/L
Hypercholestero-lemia	WNL	> ULN - 300 mg/dl > ULN - 7.75 mmol/L	> 300 - 400 mg/dl > 7.75 - 10.34 mmol/L	> 400 - 500 mg/dl >10.34 - 12.92 mmol/L	> 500 mg/dl > 12.92 mmol/L
Hyperglycemia	WNL	> ULN - 160 mg/dl > ULN - 8.9 mmol/L	> 160 - 250 mg/dl > 8.9 - 13.9 mmol/L	> 250 - 500 mg/dl > 13.9 - 27.8 mmol/L	> 500 mg/dl > 27.8 mmol/L or ketoacidosis

NCI/NIH Common Toxicity Criteria

Toxicity	0	1	2	3	4
METABOLIC/LABORATORY Cont´d					
Hyperkalemia	WNL	> ULN - 5.5 mmol/L	> 5.5 - 6.0 mmol/L	> 6.0 - 7.0 mmol/L	> 7.0 mmol/L
Hypermagnesemia	WNL	> ULN - 3.0 mg/dl > ULN - 1.23 mmol/L	-	> 3.0 - 8.0 mg/dl > 1.23 - 3.30 mmol/L	> 8.0 mg/dl > 3.30 mmol/L
Hypernatremia	WNL	>ULN - 150 mmol/L	>150 - 155 mmol/L	>155 - 160 mmol/L	>160 mmol/L
Hypertriglyceride-mia	WNL	> ULN - 2.5 x ULN	> 2.5 - 5.0 x ULN	> 5.0 - 10 x ULN	> 10 x ULN
Hyperuricemia	WNL	> ULN - 10 mg/dl ≤ 0.59 mmol/L without physiologic consequences	-	> ULN - 10 mg/dl ≤ 0.59 mmol/L with physiologic consequences	> 10 mg/dl > 0.59 mmol/L
Also consider Tumor lysis syndrome, Renal failure, Creatinine and Potassium.					
Hypocalcemia	WNL	<LLN - 8.0 mg/dl <LLN - 2.0 mmol/L	7.0 - < 8.0 mg/dl 1.75 - < 2.0 mmol/L	6.0 - < 7.0 mg/dl 1.5 - < 1.75 mmol/L	<6.0 mg/dl < 1.5 mmol/L
Hypoglycemia	WNL	< LLN - 55 mg/dl < LLN - 3.0 mmol/L	40 - < 55 mg/dl 2.2 - < 3.0 mmol/L	30 - < 40 mg/dl 1.7 - < 2.2 mmol/L	< 30 mg/dl < 1.7 mmol/L
Hypokalemia	WNL	< LLN - 3.0 mmol/L	-	2.5 - <3.0 mmol/L	<2.5 mmol/L
Hypomagnesemia	WNL	<LLN - 1.2 mg/dl < LLN - 0.5 mmol/L	0.9 - <1.2 mg/dl 0.4 - < 0.5 mmol/L	0.7 - < 0.9 mg/dl 0.3 - < 0.4 mmol/L	< 0.7 mg/dl < 0.3 mmol/L
Hyponatremia	WNL	< LLN - 130 mmol/L	-	120 - <130 mmol/L	<120 mmol/L
Hypophosphatemia	WNL	< LLN -2.5 mg/dl <LLN - 0.8 mmol/L	2.0 - <2.5 mg/dl 0.6 - <0.8 mmol/L	1.0 - <2.0 mg/dl 0.3 - <0.6 mmol/L	< 1.0 mg/dl <0.3 mmol/L
Hypothyroidism is graded in the ENDOCRINE category.					
Lipase	WNL	> ULN - 1.5 x ULN	> 1.5 - 2.0 x ULN	> 2.0 - 5.0 x ULN	> 5.0 x ULN
Metabolic- Other (Specify)	none	mild	moderate	severe	life-threatening or disabling
MUSCULOSKELETAL					
Arthralgia is graded in the PAIN category.					
Arthritis	none	mild pain with inflammation, erythema or joint swelling but not interfering with function	moderate pain with inflammation, erythema, or joint swelling interfering with function, but not interfering with activities of daily living	severe pain with inflammation, erythema, or joint swelling and interfering with activities of daily living	disabling
Muscle weakness (not due to neuropathy)	normal	asymptomatic with weakness on physical exam	symptomatic and interfering with function, but not interfering with activities of daily living	symptomatic and interfering with activities of daily living	bedridden or disabling
Myalgia is graded under PAIN.					
Myositis (inflammation / damage of muscle)	none	mild pain, not interfering with function	pain interfering with function, but not interfering with activities of daily living	pain interfering with function and interfering with activities of daily living	bedridden or disabling
Also consider CPK. Myositis implies muscle damage (i.e., elevated CPK).					
Osteonecrosis (avascular necrosis)	none	asymptomatic and detected by imaging only	symptomatic and interfering with function, but not interfering with activities of daily living	symptomatic and interfering with activities of daily living	symptomatic; or disabling
Joint, muscle, or bone (osseous)-Other (Specify)	none	mild	moderate	severe	life-threatening or disabling
NEUROLOGY					
Aphasia, receptive and/or expressive, is graded under Speech impairment in the NEUROLOGY category.					
Arachnoiditis/ meningismus/radiculitis	absent	mild pain not interfering with function	moderate interfering with function, but not with activities of daily living	severe interfering with activities of daily living	unable to function or perform activities of daily living; bedridden; paraplegia
Also consider Headache, Vomiting and Fever.					
Ataxia (incoordination)	normal	asymptomatic but abnormal on physical exam, and not interfering with function	mild symptoms interfering with function, but not interfering with activities of daily living	moderate symptoms interfering with activities of daily living	bedridden or disabling

NCI/NIH Common Toxicity Criteria

Toxicity	0	1	2	3	4
NEUROLOGY (cont'd)					
CNS cerebrovascular ischemia	none	-	-	transient ischemic event or attack (TIA)	permanent event (e.g., cerebral vascular accident)
CNS hemorrhage/bleeding is graded in the HEMORRHAGE category is NOT graded here.					
Cognitive disturbance/ learning problems	none	cognitive disability; not interfering with work/school performance; preservation of intelligence	cognitive disability; interfering with work/school performance; decline of 1 SD (Standard Deviation) or loss of developmental milestones	cognitive disability; resulting in significant impairment of work/ school performance; cognitive decline > 2 SD	inability to work/frank mental retardation
Confusion	normal	confusion or disorientation or attention deficit of brief duration; resolves spontaneously with no sequelae	confusion or disorientation or attention deficit interfering with function, but not interfering with activities of daily living	confusion or delirium interfering with activities of daily living	harmful to others or self; requiring hospitalization
Cranial neuropathy is graded in the NEUROLOGY category as Neuropathy-cranial.					
Delusions	normal	-	-	present	toxic psychosis
Depressed level of consciousness	normal	somnolence or sedation not interfering with function	somnolence or sedation interfering with function, but not interfering with activities of daily living	obtundation or stupor; difficult to arouse; interfering with activities of daily living	coma
Syncope (fainting) is graded under NEUROLOGY.					
Dizziness/lighthead edness	none	not interfering with function	interfering with function, but not interfering with activities of daily living	interfering with activities of daily living	bedridden or disabling
Dysphasia, receptive and/or expressive, are graded under Speech impairment in the NEUROLOGY category.					
Extrapyramidal/involuntary movement/restlessness	none	mild involuntary movements not interfering with function	moderate involuntary movements interfering with function, but not interfering with activities of daily living	severe involuntary movements or torticollis interfering with activities of daily living	bedridden or disabling
Hallucinations	normal	-	-	present	toxic psychosis
Headache is graded under PAIN.					
Insomnia	normal	occasional difficulty sleeping not interfering with function	difficulty sleeping interfering with function, but not interfering with activities of daily living	frequent difficulty sleeping interfering with activities of daily living	-
This toxicity is graded when insomnia is related to treatment. If pain or other symptoms interfere with sleep do NOT grade as insomnia.					
Leukoencephalopathy associated radiological findings	None	mild increase in SAS (subarachnoid space) and/or mild ventriculomegaly; and/or small (+/- multiple) focal T2 hyperintensities, involving peri-ventricular white matter or < 1/3 of susceptible areas of cerebrum	moderate increase in SAS; and/or moderate ventriculomegaly; and/or focal T2 hyperintensities extending into centrum ovale; or involving 1/3 to 2/3 of susceptible areas of cerebrum	severe increase in SAS; severe ventriculomegaly; near total white matter T2 hyperintensities or diffuse low attenuation (CT); focal white matter necrosis (cystic)	severe increase in SAS; severe ventriculomegaly; diffuse low attenuation with calcification (CT); diffuse white matter necrosis (MRI)
Memory loss	Normal	memory loss not interfering with function	memory loss interfering with function, but not with activities of daily living	memory loss interfering with activities of daily living	amnesia
Mood alteration-anxiety, agitation	Normal	mild mood alteration not interfering with function	moderate mood alteration interfering with function, but not interfering with activities of daily living	severe mood alteration interfering with activities of daily living	suicidal ideation or danger to self

NCI/NIH Common Toxicity Criteria

Toxicity	0	1	2	3	4
NEUROLOGY (cont'd)					
Mood alteration-depression	Normal	mild mood alteration not interfering with function	moderate mood alteration interfering with function, but not interfering with activities of daily living	severe mood alteration interfering with activities of daily living	suicidal ideation or danger to self
Mood alteration-euphoria	Normal	mild mood alteration not interfering with function	moderate mood alteration interfering with function, but not interfering with activities of daily living	severe mood alteration interfering with activities of daily living	danger to self
Neuropathic pain is graded under PAIN.					
Neuropathy-cranial	absent	-	present, not interfering with activities of daily living	present, interfering with activities of daily living	life-threatening, disabling
Neuropathy-motor	Normal	subjective weakness but no objective findings	mild objective weakness interfering with function, but not with activities of daily living	objective weakness interfering with activities of daily living	paralysis
Neuropathy-sensory	Normal	loss of deep tendon reflexes or paresthesia (including tingling) but not interfering with function	objective sensory loss or paresthesia (including tingling), interfering with function, but not with activities of daily living	sensory loss or paresthesia interfering with activities of daily living	permanent sensory loss that interferes with function
Nystagmus	Absent	present	-	-	-
Also consider Vision-double vision.					
Personality /behavioral	normal	change, but not disruptive to patient or family	disruptive to patient or family	disruptive; requiring mental health intervention	harmful to others or self; requiring hospitalization
Pyramidal tract dysfunction (e.g., tone, hyperreflexia, positive Babinski, fine motor coordination)	normal	asymptomatic with abnormality on physical examination	symptomatic and interfering with function but not interfering with activities of daily living	interfering with activities of daily living	bedridden or disabling; paralysis
Seizure(s)	none	-	seizure(s) self-limited and consciousness is preserved	seizure(s) in which consciousness is altered	seizure of any type which is prolonged, repetitive, or difficult to control (e.g., status epilepticus, intractable epilepsy)
Speech impairment (e.g., dysphasia or aphasia)	normal	-	awareness of receptive or expressive dysphasia, not impairing ability to communicate	receptive or expressive dysphasia, impairing ability to communicate	inability to communicate
Syncope (fainting)	absent	-	-	present	-
Also consider CARDIOVASCULAR (ARRHYTHMIA), Vasovagal episode, TIA, CVA.					
Tremor	none	mild and brief or intermittent but not interfering with function	moderate tremor interfering with function, but not interfering with activities of daily living	severe tremor interfering with activities of daily living	-
Vertigo	none	not interfering with function	interfering with function, but not interfering with activities of daily living	interfering with activities of daily living	bedridden or disabling
Neurologic-Other (Specify)	none	mild	moderate	severe	life-threatening or disabling
OCULAR/VISUAL					
Cataract	none	asymptomatic	symptomatic, partial visual loss	symptomatic, visual loss requiring treatment or interfering with function	-

NCI/NIH Common Toxicity Criteria

Toxicity	0	1	2	3	4
OCULAR/VISUAL Cont´d					
Conjunctivitis	none	abnormal ophthalmologic changes, but asymptomatic or symptomatic without visual impairment (i.e., pain and irritation)	symptomatic and interfering with function, but not interfering with activities of daily living	symptomatic and interfering with activities of daily living	-
Dry eye	normal	mild, not requiring treatment	moderate or requiring artificial tears	-	-
Glaucoma	none	increase in intraocular pressure but no visual loss	increase in intraocular pressure with retinal changes	visual impairment	unilateral or bilateral loss of vision (blindness)
Keratitis (corneal inflammation/ corneal ulceration)	none	abnormal ophthalmologic changes but asymptomatic or symptomatic without visual impairment (i.e., pain and irritation)	symptomatic and interfering with function, but not interfering with activities of daily living	symptomatic and interfering with activities of daily living	unilateral or bilateral loss of vision (blindness)
Tearing (watery eyes)	none	mild: not interfering with function	moderate: interfering with function, but not interfering with activities of daily living	interfering with activities of daily living	-
Vision- blurred vision	normal	-	symptomatic and interfering with function, but not interfering with activities of daily living	symptomatic and interfering with activities of daily living	-
Vision- double vision (diplopia)	normal	-	symptomatic and interfering with function, but not interfering with activities of daily living	symptomatic and interfering with activities of daily living	-
Vision- flashing lights/floaters	normal	mild, not interfering with function	symptomatic and interfering with function, but not interfering with activities of daily living	symptomatic and interfering with activities of daily living	-
Vision- night blindness (nyctalopia)	normal	abnormal electro-retinography but asymptomatic	symptomatic and interfering with function, but not interfering with activities of daily living	symptomatic and interfering with activities of daily living	-
Vision- photophobia	normal	-	symptomatic and interfering with function, but not interfering with activities of daily living	symptomatic and interfering with activities of daily living	-
Ocular- Other (Specify)	normal	mild	moderate	severe	unilateral or bilateral loss of vision (blindness)
PAIN					
Abdominal pain or cramping	none	mild pain not interfering with function	moderate pain: pain or analgesics interfering with function, but not interfering with activities of daily living	severe pain: pain or analgesics severely interfering with activities of daily living	disabling
Arthralgia (joint pain)	none	mild pain not interfering with function	moderate pain: pain or analgesics interfering with function, but not interfering with activities of daily living	severe pain: pain or analgesics severely interfering with activities of daily living	disabling

NCI/NIH Common Toxicity Criteria

Toxicity	0	1	2	3	4
PAIN Cont´d					
Arthritis (joint pain with clinical signs of inflammation) is graded under MUSCULOSKELETAL .					
Bone pain	none	mild pain not interfering with function	moderate pain: pain or analgesics interfering with function, but not interfering with activities of daily living	severe pain: pain or analgesics severely interfering with activities of daily living	disabling
Chest pain (non-cardiac and non-pleuritic)	none	mild pain not interfering with function	moderate pain: pain or analgesics interfering with function, but not interfering with activities of daily living	severe pain: pain or analgesics severely interfering with activities of daily living	disabling
Dysmenorrhea	none	mild pain not interfering with function	moderate pain: pain or analgesics interfering with function, but not interfering with activities of daily living	severe pain: pain or analgesics severely interfering with activities of daily living	disabling
Dyspareunia	none	mild pain not interfering with function	moderate pain interfering with sexual activity	severe pain preventing sexual activity	-
Dysuria is graded under RENAL/GENITOURINARY.					
Earache (otalgia)	none	mild pain not interfering with function	moderate: pain or analgesics interfering with function, but not with activities of daily living	severe pain: pain or analgesics severely interfering with activities of daily living	disabling
Headache	none	mild pain not interfering with function	moderate: pain or analgesics interfering with function, but not with activities of daily living	severe pain: pain or analgesics severely interfering with activities of daily living	disabling
Hepatic pain	none	mild pain not interfering with function	moderate: pain or analgesics interfering with function, but not with activities of daily living	severe pain: pain or analgesics severely interfering with activities of daily living	disabling
Myalgia (muscle pain)	none	mild pain not interfering with function	moderate: pain or analgesics interfering with function, but not with activities of daily living	severe pain: pain or analgesics severely interfering with activities of daily living	disabling
Neuropathic pain (e.g., jaw pain, neurologic pain, phantom limb pain, post-infectious neuralgia, or painful neuropathies)	none	mild pain not interfering with function	moderate pain: pain or analgesics interfering with function, but not with activities of daily living	severe pain: pain or analgesics severely interfering with activities of daily living	disabling
Pelvic pain	none	mild pain not interfering with function	moderate pain: pain or analgesics interfering with function, but not with activities of daily living	severe pain: pain or analgesics severely interfering with activities of daily living	disabling
Pleuritic pain	none	mild pain not interfering with function	moderate pain: pain or analgesics interfering with function, but not with activities of daily living	severe pain: pain or analgesics severely interfering with activities of daily living	disabling
Rectal or perirectal pain (proctalgia)	none	mild pain not interfering with function	moderate: pain or analgesics interfering with function, but not with activities of daily living	severe pain: pain or analgesics severely interfering with activities of daily living	disabling
Tumor pain (onset or exacerbation of tumor pain due to treatment)	none	mild pain not interfering with function	moderate pain: pain or analgesics interfering with function, but not with activities of daily living	severe pain: pain or analgesics severely interfering with activities of daily living	disabling
Tumor flair is graded in the SYNDROME category.					

NCI/NIH Common Toxicity Criteria

Toxicity	0	1	2	3	4
PAIN Cont´d					
Pain- Other (Specify)	none	mild	moderate	severe	
PULMONARY					
Adult respiratory distress syndrome (ARDS)	absent	-	-	-	present
Apnea	none	-	-	present	requiring intubation
Carbon monoxide diffusion capacity (DL_{CO})	90% of pretreatment or normal value	75 - <90% of pretreatment or normal value	50 - <75% of pretreatment or normal value	25 - <50% of pretreatment or normal value	< 25% of pretreatment or normal value
Cough	absent	mild, relieved by non-prescription medication	requiring narcotic antitussive	severe cough or coughing spasms, poorly controlled or unresponsive to treatment	-
Dyspnea (shortness of breath)	normal	-	dyspnea on exertion	dyspnea at normal level of activity	dyspnea at rest or requiring ventilator support
FEV_1	90% of pretreatment or normal value	75 - <90% of pretreatment or normal value	50 - <75% of pretreatment or normal value	25 - <50% of pretreatment or normal value	< 25% of pretreatment or normal value
Hiccoughs (hiccups, singultus)	none	mild, not requiring treatment	moderate, requiring treatment	severe, prolonged, and refractory to treatment	-
Hypoxia	normal	-	decreased O_2 saturation with exercise	decreased O_2 saturation at rest, requiring supplemental oxygen	decreased O_2 saturation, requiring pressure support (CPAP) or assisted ventilation
Pleural effusion (non-malignant)	none	asymptomatic and not requiring treatment	symptomatic, requiring diuretics	symptomatic, requiring O_2 or therapeutic thoracentesis	life-threatening (e.g., requiring intubation)
Pleuritic pain is graded under PAIN.					
Pneumonitis /pulmonary infiltrates	none	radiographic changes but asymptomatic or symptoms not requiring steroids	radiographic changes and requiring steroids or diuretics	radiographic changes and requiring oxygen	radiographic changes and requiring assisted ventilation
Pneumothorax	none	no intervention required	chest tube required	sclerosis or surgery required	life-threatening
Pulmonary embolism is graded as Thrombosis/embolism under CARDIOVASCULAR (GENERAL).					
Pulmonary fibrosis	none	radiographic changes, but symptoms not requiring steroids	requiring steroids or diuretics	requiring oxygen	requiring assisted ventilation
Voice changes / stridor / larynx (e.g., hoarseness, loss of voice, laryngitis)	normal	mild or intermittent hoarseness	persistent hoarseness, but able to vocalize; may have mild to moderate edema	whispered speech, not able to vocalize; may have marked edema	marked dyspnea/ stridor requiring tracheostomy or intubation
Pulmonary- Other (Specify)	none	mild	moderate	severe	life-threatening or disabling
RENAL/GENITOURINARY					
Bladder spasms	absent	mild symptoms, not requiring intervention	symptoms requiring antispasmodic	severe symptoms requiring narcotic	-
Creatinine	WNL	> ULN - 1.5 x ULN	> 1.5 - 3.0 x ULN	> 3.0 - 6.0 x ULN	> 6.0 x ULN
Dysuria (painful urination)	none	mild symptoms requiring no intervention	symptoms relieved with therapy	symptoms not relieved despite therapy	-
Fistula or GU fistula (e.g., vaginal, vesicovaginal)	none	-	-	requiring intervention	requiring surgery
Hemoglobinuria	-	present	-	-	-
Hematuria (in the absence of vaginal bleeding) is graded under HEMORRHAGE.					
Incontinence	none	with coughing, sneezing, etc.	spontaneous, some control	no control(in the absence of fistula)	-

NCI/NIH Common Toxicity Criteria

Toxicity	0	1	2	3	4
RENAL/GENITOURINARY Cont´d					
Operative injury to bladder and/or ureter	none	-	injury of bladder with primary repair	sepsis, fistula, or obstruction requiring secondary surgery; loss of one kidney; injury requiring anastomosis or re-implantation	septic obstruction of both kidneys or vesicovaginal fistula requiring diversion
Proteinuria	normal or < 0.15 g/24 hour	1+ or 0.15 - 1.0 g/24 hour	2+ to 3+ or 1.0 - 3.5 g/24 hour	4+ or > 3.5 g/24 hour	nephrotic syndrome
If there is an inconsistency between absolute value and uristix reading, use the absolute value for grading.					
Renal failure	none	-	-	requiring dialysis, but reversible	requiring dialysis and irreversible
Ureteral obstruction	none	unilateral, not requiring surgery	-	bilateral, not requiring surgery	stent, nephrostomy tube, or surgery
Urinary electrolyte wasting (e.g., Fanconi's syndrome, renal tubular acidosis)	none	asymptomatic, not requiring treatment	mild, reversible and manageable with oral replacement	reversible but requiring IV replacement	irreversible, requiring continued replacement
Also consider Acidosis, Bicarbonate, Hypocalcemia, Hypophosphatemia.					
Urinary frequency/urgency	normal	increase in frequency or nocturia up to 2 x normal	increase > 2 x normal but < hourly	hourly or more with urgency, or requiring catheter	-
Urinary retention	normal	hesitancy or dribbling, but no significant residual urine; retention occurring during the immediate postoperative period	hesitancy requiring medication or occasional in/out catheterization (<4 x per week), or operative bladder atony requiring indwelling catheter beyond immediate postoperative period but for < 6 weeks	requiring frequent in/out catheterization (4 x per week) or urological intervention (e.g., TURP, suprapubic tube, urethrotomy)	bladder rupture
Urine color change (not related to other dietary or physiologic cause e.g., bilirubin, concentrated urine, hematuria)	normal	asymptomatic, change in urine color	-	-	-
Vaginal bleeding is graded under HEMORRHAGE.					
Vaginitis (not due to infection)	none	mild, not requiring treatment	moderate, relieved with treatment	severe, not relieved with treatment, or ulceration not requiring surgery	ulceration requiring surgery
Renal/GU- Other (Specify)	none	mild	moderate	severe	life-threatening or disabling
SECONDARY MALIGNANCY					
Secondary malignancy, other (Specify type) excludes metastatic tumors	none	-	-	-	present
SEXUAL/REPRODUCTIVE FUNCTION					
Dyspareunia is graded under PAIN.					
Dysmenorrhea is graded under PAIN .					
Erectile impotence	normal	mild (erections impaired but satisfactory)	moderate (erections impaired, unsatisfactory for intercourse)	no erections	-
Female sterility	normal	-	-	sterile	-
Feminization of male is graded under ENDOCRINE.					

NCI/NIH Common Toxicity Criteria

Toxicity	0	1	2	3	4
SEXUAL/REPRODUCTIVE FUNCTION Cont´d					
Irregular menses (change from baseline)	normal	occasionally irregular or lengthened interval, but continuing menstrual cycles	very irregular, but continuing menstrual cycles	persistent amenorrhea	-
Libido	normal	decrease in interest	severe loss of interest	-	-
Male infertility	-	-	oligospermia (low sperm count)	azoospermia (no sperm)	-
Masculinization of female is graded in the ENDOCRINE category.					
Vaginal dryness	normal	mild	requiring treatment and/or interfering with sexual function, dyspareunia	-	-
Sexual/reproductive function-Other (Specify)	none	mild	moderate	severe	disabling
SYNDROMES (not included in previous categories)					
Acute vascular leak syndrome is graded under CARDIOVASCULAR (GENERAL) .					
ARDS (adult respiratory distress syndrome) is graded under PULMONARY.					
Autoimmune reactions are graded under ALLERGY/IMMUNOLOGY.					
DIC (disseminated intravascular coagulation) is graded under COAGULATION.					
Fanconi's syndrome is graded as Urinary electrolyte wasting in the RENAL/GENITOURINARY category.					
Renal tubular acidosis is graded as Urinary electrolyte wasting in the RENAL/GENITOURINARY category.					
Stevens-Johnson syndrome (erythema multiforme) is graded in the DERMATOLOGY/SKIN category.					
SIADH (syndrome of inappropriate antidiuretic hormone) is graded in the ENDOCRINE category.					
Thrombotic microangiopathy (e.g., thrombotic thrombocytopenic purpura/TTP or hemolytic uremic syndrome/HUS) is graded in the COAGULATION category.					
Tumor flare +	none	mild pain not interfering with function	moderate pain; pain or analgesics interfering with function, but not with activities of daily living	severe pain; pain or analgesics interfering with function and with activities of daily living	disabling
Also consider Hypercalcemia. Tumor flare is characterized by a constellation of symptoms and signs in direct relation to initiation of therapy (e.g., anti-estrogens/androgens or additional hormones). The symptoms/signs include tumor pain, inflammation of visible tumor, hypercalcemia, diffuse bone pain, and other electrolyte disturbances.					
Tumor lysis syndrome	absent	-	-	present	-
Also consider Hyperkalemia and Creatinine.					
Urinary electrolyte wasting (e.g., Fanconi's syndrome, renal tubular acidosis) is graded under the RENAL/GENITOURINARY category.					
Syndromes-Other (Specify)	none	mild	moderate	severe	life-threatening or disabling

Appendix 3: Contact addresses

Southern Swedish Tumor Registry
SSG Secretariat
Lund University Hospital
221 85 LUND
Phone: +46-46-177555
Fax +46-46-188143
Email: evy.nilsson@cancerepid.lu.se

Heikki Joensuu
Editor, Acta Oncologica
Department of Oncology
Helsinki University Central Hospital
Haartmaninkatu 4
P.O. Box 180
FIN-00029 Helsinki, Finland
Phone: +358-9-471 73208
Fax: +358-9-471 74202
Email: heikki.joensuu@hus.fi

Bengt Gustavsson
Novartis Sweden AB
Box 1150
183 11 TÄBY
Phone: +46-8-7323200
Fax: +46-8-7322507
Email: bengt.gustavsson@pharma.novartis.com

Appendix 4: Serious Adverse Event Report

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PREPARATION NAME OR NO STUDY CODE	ID Center No. Subject No. Subject's initials 1. 2. fam. Randomization number	

SERIOUS ADVERSE EVENT REPORT

Page 1 of 3

1. REPORT TYPE: ☐ Initial ☐ Follow-up | 2. Country: | 3. CASE ID:

I. ADVERSE EVENT INFORMATION

4. DATE OF BIRTH: day month year	5. AGE yrs./mo.	6. RACE ☐Caucasian ☐Oriental ☐Black ☐Other	7. SEX ☐Male ☐Female	8. HEIGHT cm	9. WEIGHT kg	10. ONSET OF FIRST SIGN/SYMPTOM OF SAE day month year

11. SERIOUS ADVERSE EVENT(S) IN MEDICAL TERMS (diagnosis if possible)

Case description of the above SAE (include related sign/symptoms, treatment, course/outcome and suspected cause of the SAE) (continue on p.3 if more space is required):

Is the event due to lack of efficacy? ☐ No ☐ Yes
Is the event due to progression of underlying illness? ☐ No ☐ Yes

EXPEDITED REPORTING CRITERIA
12. CHECK ALL APPROPRIATE TO EVENT

☐ Patient died day month year
☐ Involved or prolonged inpatient hospitalization
☐ Results in persistent or significant disability/ incapacity
☐ Life-threatening

Other Seriousness Criteria:
☐ Congenital anomaly/birth defect
☐ Other significant medical events

II. TRIAL DRUG INFORMATION

13. TRIAL DRUG(S) AT OR BEFORE ONSET OF SAE (If blinded, provide drug package no.)

TRIAL DRUG PACKAGE NO.:

Comments (Continue on P.3 if more space is required):

Drug code broken ☐ No ☐ Yes

14. LAST VISIT/WEEK BEFORE ONSET OF SAE

VISIT NO.: WEEK NO.:

15. DOSES AT OR BEFORE ONSET OF SAE (total daily dose or specify if other- ADD additional pages)	16. ROUTE OF ADMINISTRATION	17. THERAPY DATES FROM: day month year TO: day month year

18. TRIAL INDICATION	19. THERAPY DURATION UNTIL ONSET OF FIRST SIGNS/SYMPTOM OF SAE hrs/days/months	20. TIME ELAPSED BETWEEN LAST DRUG ADMINISTRATION AND ONSET OF FIRST SIGNS/SYMPTOM OF SAE mins/hrs/days/months

III. HISTORY

21. PATIENT'S PAST MEDICAL HISTORY (e.g. co-existing medical conditions such as disease, allergies, similar experiences)

IV. MANUFACTURER INFORMATION (FOR INTERNAL USE ONLY)

22. DATE MANUFACTURER NOTIFIED OF SAE day month year	23. DATE OF THIS REPORT day month year

24. NAME AND ADDRESS OF REPORTING MANUFACTURER

PLEASE FAX FORM TO LOCAL CS&E FAX NO.

n

PREPARATION NAME OR NO STUDY CODE	ID Center No. Subject No. Subject's initials 1. 2. fam. Randomization number	

SERIOUS ADVERSE EVENT REPORT

1. REPORT TYPE: ☐ Initial ☐ Follow-up | 3. CASE ID:

25. CONCOMITANT DRUGS RELEVANT TO THE SAE (exclude therapy to treat SAE)

DRUG NAME(S)	DOSE / ROUTE	UNIT / SCHEDULE	DATE STARTED day month year	CONT. 0=No 1=Yes	DATE DISCONTINUED day month year	REASON FOR USE

26. COMMENTS (if adverse event is considered to be caused by a comedication, please note it here)

27. ACTION TAKEN (mark all as appropriate)

☐ No Action Taken
☐ Trial drug permanently discontinued due to this adverse event
☐ Concomitant medication taken
☐ Trial drug dosage adjusted/ temporarily interrupted*
☐ Non-drug therapy given**
☐ Hospitalization/prolonged hospitalization

* If ticked, enter new dosage information in field 11
** If ticked, provide therapeutic measures in field 11

28. TEST/LABORATORY FINDINGS (enter only those findings necessary for SAE diagnosis or course description)

TEST/ LAB NAME	UNIT	DATE day month year	VALUE	DATE day month year	VALUE	DATE day month year	VALUE

29. COMMENTS ON TEST/LABORATORY FINDINGS (Provide normal ranges on Pg. 3 if not already provided.)
(If the SAE is a laboratory abnormality, enter comments on clinical findings and/or treatment in field 11.)

30. OUTCOME OF THE PATIENT/SAE

☐ Completely recovered Date of recovery: day month year
☐ Recovered with sequelae
☐ Condition improving
☐ Condition still present and unchanged
☐ Condition deteriorated
☐ Death Autopsy: ☐ No ☐ Yes

31. ASSESSMENT OF CAUSALITY
Relationship to study drug: ☐ Not suspected ☐ Suspected

V. **INFORMATION SOURCE**

32. NAME, ADDRESS AND TELEPHONE NUMBER OF INVESTIGATOR

Signature

33. REPORTING DATE BY INVESTIGATOR/ PERSON REPORTING EVENT
day month year

PLEASE FAX FORM TO LOCAL CS&E FAX NO.

n

PREPARATION NAME OR NO STUDY CODE	ID Center No. Subject No. Subject's initials 1. 2. fam. Randomization number	

SERIOUS ADVERSE EVENT REPORT

1. REPORT TYPE: ☐ Initial ☐ Follow-up	3. CASE ID:

FOR ADDITIONAL INFORMATION:

V. **INFORMATION SOURCE**

32. NAME, ADDRESS AND TELEPHONE NUMBER OF INVESTIGATOR Signature	33. REPORTING DATE BY INVESTIGATOR/PERSON REPORTING EVENT day month year

PLEASE FAX FORM TO LOCAL CS&E FAX NO.

NOVARTIS

Appendix 5: A Novartis Clinical Trial Pregnancy Form

Trial Drug **Protocol** **Tip No.**	**ID** Centre No. ____ Subject No. ____ Subject's Initials ____ (1. 2. fam.) Randomisation Number ____	**REPORT TYPE** ☐ Initial ☐ Follow-Up

CLINICAL TRIAL PREGNANCY FORM

1. Country:	2. LOCAL CASE ID:

I. MATERNAL INFORMATION

3. DATE OF BIRTH day month year	4. AGE yrs./mo.	5. RACE ☐ Caucasian ☐ Oriental ☐ Black ☐ Other	6. HEIGHT cm	7. WEIGHT kg

8. Date of Last Menstrual Period day month year	9. Expected Date of Delivery day month year
10. Method of Contraception	11. Contraception used as instructed ☐ yes ☐ no ☐ uncertain

II. HISTORY

12. PATIENT'S PAST MEDICAL HISTORY (include information on familial disorders, known risk factors or conditions that may affect the outcome of the pregnancy e.g. alcohol, smoking, other substance consumption, infections, hypertension, diabetes including gestational, environmental or occupational exposure that may pose a risk factor).

13. PREVIOUS OBSTETRIC HISTORY – provide details on all previous pregnancies below, including abortion or stillbirth (use page 3 if needed)

	Gestation week	Outcome including any abnormalities
1		
2		
3		
4		

14. DRUG INFORMATION – please list the Novartis drug(s) first and all other therapies taken prior to or during pregnancy

Drug Names	Daily Dose	Route	Treatment Dates Start	Treatment Dates Stop	Indication	(specify week of pregnancy) Start	(specify week of pregnancy) Stop

MANUFACTURER INFORMATION (FOR INTERNAL USE ONLY)

15. DATE MANUFACTURER NOTIFIED day month year	16. DATE OF THIS REPORT day month year
17. NAME AND ADDRESS OF REPORTING MANUFACTURER	*PLEASE FILL IN THE CORRECT LOCAL CS-E ADDRESS*

PLEASE SEND FORM TO LOCAL CLINICAL SAFETY & EPIDEMIOLOGY

Trial Drug **Protocol** **Tip No.**	**ID** Centre No. ⌊____⌋ Subject No. ⌊____⌋ Subject's Initials ⌊___⌋⌊___⌋⌊___⌋ 1. 2. fam. Randomisation Number ⌊____⌋	**REPORT TYPE** ☐ Initial ☐ Follow-Up

CLINICAL TRIAL PREGNANCY FORM

2. LOCAL CASE ID:

III. PREGNANCY INFORMATION

18. PRENATAL
Have any specific tests, e.g. amniocentesis, ultrasound, maternal serum AFP, been performed during the pregnancy so far?
☐ No ☐ Yes ☐ Not known
If yes, please specify test date and results:

19. PREGNANCY OUTCOME
Delivery
☐ Normal ☐ Forceps/Ventouse ☐ Caesarean section
Maternal complications or problems related to birth: _____
Abortion
☐ Therapeutic ☐ Planned ☐ Spontaneous Please, specify reason and any abnormalities (if known) _____
_____
Date of abortion/delivery day month year
at week _____ ⌊___⌋⌊___⌋⌊___⌋

20. MATERNAL PREGNANCY ASSOCIATED EVENTS:

If the mother experiences a serious adverse event (SAE) during a pregnancy, please complete an SAE form and submit as requested

IV. CHILD INFORMATION

21. Neonate
☐ Normal ☐ Abnormal ☐ Stillbirth please specify any abnormalities with dates: _____

Sex	Height	Weight	Apgar Scores	Head circumference
☐ Male ☐ Female	cm	kg	1 min. 5 mins. 10 mins.	cm

For additional information, please use page 3 (please provide copies of relevant documentation)

V. ASSESSMENT OF PREGNANCY OUTCOME

22. SERIOUSNESS CRITERIA
☐ Non Serious
☐ Mother died day month year ⌊___⌋⌊___⌋⌊___⌋
☐ Stillbirth / Neonate died day month year ⌊___⌋⌊___⌋⌊___⌋
☐ Involved or prolonged inpatient hospitalisation ☐ Life-threatening
☐ Results in persistent or significant disability/incapacity
Other Seriousness Criteria: ☐ Congenital anomaly/birth defect ☐ Other significant medical events

23. ASSESSMENT OF CAUSALITY
Please indicate the relationship between pregnancy outcome and Novartis investigational drug
☐ Not suspected ☐ Suspected

INFORMATION SOURCE

24. NAME, ADDRESS AND TELEPHONE NUMBER OF INVESTIGATOR	25. REPORTING DATE BY INVESTIGATOR/PERSON REPORTING EVENT day month year

PLEASE SEND FORM TO LOCAL CLINICAL SAFETY & EPIDEMIOLOGY

Trial Drug **Protocol** **Tip No.**	**ID** Centre No. Subject No. Subject's Initials 1. 2. fam. Randomisation Number	**REPORT TYPE** ☐ Initial ☐ Follow-Up

CLINICAL TRIAL PREGNANCY FORM

2. LOCAL CASE ID:

FOR ADDITIONAL INFORMATION:

INFORMATION SOURCE

32. NAME, ADDRESS AND TELEPHONE NUMBER OF INVESTIGATOR Signature:	32. REPORTING DATE BY INVESTIGATOR/PERSON REPORTING EVENT day month year

PLEASE SEND FORM TO LOCAL CLINICAL SAFETY & EPIDEMIOLOGY

SSG XVIII
Registration **Form 1**

Fax this form to:
The SSG secretariat
Fax: +46-46-18 81 43

Patient Initials ___ ___ ___

Year Month

Date of birth 1 9 | | | |

Sex: ☐ Male ☐ Female

Doctor (in block letters)

Hospital and department (in block letters)

Screening visit date Day Month Year | | | | | | | | |

A. Inclusion criteria

	No	Yes
Age ≥ 18	☐	☐
Histologically confirmed, resectable GIST	☐	☐
CD117 (KIT) staining positive	☐	☐
>50% Risk for recurrence (tumor >10 cm; >10 mitoses/50 HPFs; tumor >5cm and >5 mitoses/50 HPFs; tumor spillage)	☐	☐
ECOG PS ≤2	☐	☐
Bil <1.5xN, AST/ALT <2.5 xN, crea <1.5xN, ANC >1.5, platelets >100	☐	☐
Written informed consent obtained	☐	☐

Exclusion criteria

Residual GIST detectable in screening examinations	☐	☐
Metastases	☐	☐
<1 week and >12 weeks has elapsed from surgery	☐	☐
Severe uncontrolled medical disease, severe cardiac or liver disease	☐	☐
Chemotherapy for GIST, investigational agents within 28 days	☐	☐
Neoadjuvant or prior adjuvant imatinib therapy	☐	☐
Prior radiation therapy to ≥25% of the bone marrow	☐	☐
Pregnancy or breast-feeding	☐	☐
HIV infection	☐	☐
Significant history of non-compliance with medical regimens	☐	☐
Evidence of another malignancy within 5 years of study entry (except for effectively treated basal cell or squamous skin carcinoma, carcinoma in-situ of the cervix, or lobular carcinoma in situ of the breast)	☐	☐

B. Stratification criteria

Local disease (one tumor)	☐	☐
Intra-abdominal disease defined as tumor spillage, or microscopic disease left behind at surgery (R1 resection)	☐	☐

If the answer to all above **inclusion criteria** questions was **Yes** and **exclusion criteria** questions was **No**, *and* you have answered **the questions in B above**, fax this form to the randomization center.

Filled in by the randomization center

Patient randomization number: | | |

Duration of adjuvant imatinib ☐ Arm 1 (12 months) ☐ Arm 2 (36 months)

Day Month Year

Randomization date | | | | | | | | |

Name ..... (in block letters)

March 2008/MM