SPIRIT 2

S**TI571 **P**rospective **I**nternational **R**andom**I**sed **T**rial **2

A phase III, prospective randomised comparison of

- imatinib (STI571, Glivec/Gleevec) **400mg daily** versus
- dasatinib (Sprycel) **100mg daily**

in patients with newly-diagnosed chronic phase chronic myeloid leukaemia.

www.spirit-cml.org

Authors:	SG O'Brien, CA Hedgley

Protocol version:	1.4
Date:	20 March 2008

Investigator Signature Page

SPIRIT*2* - STI571 Prospective International RandomIsed Trial 2 - A phase III, prospective randomised comparison of imatinib (STI571, Glivec/Gleevec) 400mg daily versus dasatinib 100mg in patients with newly-diagnosed chronic phase chronic myeloid leukaemia.

Protocol version 1.4 20th March 2008

Principal Investigator Signature:

In signing below, I am confirming that I have received a copy and have read this study protocol. I agree to conduct this study in accordance with this protocol and comply with all regulatory requirements as set forth in this protocol, ICH-GCP guidelines, the Declaration of Helsinki and appropriate national regulations.

I also verify that as Principal Investigator I am the person responsible for compliance by all participating study team members at the clinical site and for supervision of the study related medical decisions for study patients.

_____

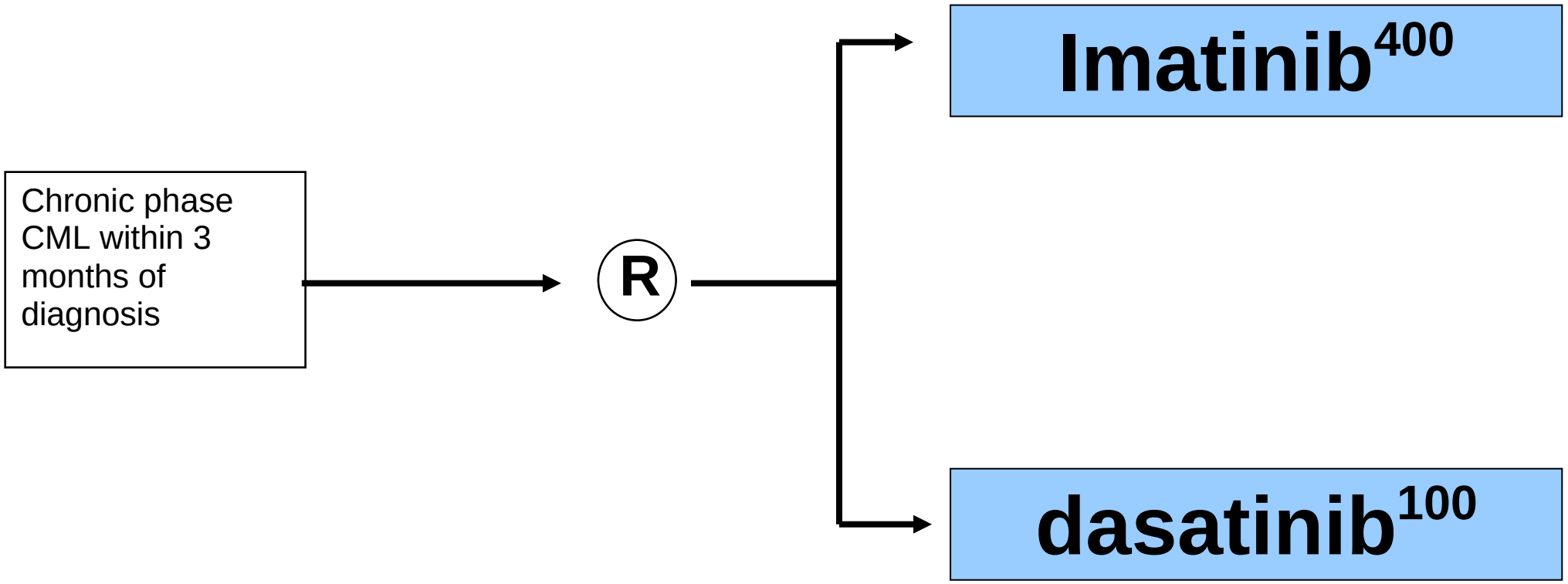
Principal Investigator Name (print clearly)

_____

Principal Investigator Signature Date

SPIRIT

STI571 Prospective International Randomised Trial 2



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Sponsor

Newcastle-upon-Tyne NHS Hospitals Trust is the research sponsor for this study. For further information regarding the sponsorship conditions, please contact the Research Governance Manager at:

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Funder

Bristol Myers Squibb (BMS)

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1 SPIRIT2: quick reference to essential information

1.1 What is SPIRIT2?

- SPIRIT2 is a Phase III, multicentre, open-label, prospective randomised trial comparing imatinib 400 mg daily versus dasatinib 100 mg daily in patients with newly-diagnosed chronic phase CML

It is expected that 810 patients will be entered into the study.

- After screening, all patients will be randomised in equal proportions to one of the following treatment groups:

  a) Imatinib 400 mg daily
  b) Dasatinib 100 mg daily

- The study treatment (imatinib or dasatinib) will be started immediately at full dose.

- The schedule of follow up and assessments can be found in appendix 4.

- The primary endpoint is to compare Event Free Survival (EFS) between the two arms at 5 years. Additional endpoints are defined in section 3.

- The Dasatinib will be provided free of charge by Bristol Myers Squib for at least 5 years per patient. There is therefore a net saving of NHS treatment costs of up to 5 years of imatinib for 50% of entrants.

1.2 Eligibility check list

Patients must be newly diagnosed (<3 months) and have been treated with only hydroxycarbamide (hydroxyurea) and/or anagrelide. The inclusion and exclusion criteria can be found in section 5.

1.3 How to randomise a patient

Any interested site in the UK can register for the trial via the SPIRIT studies website (www.spirit-cml.org). Once a site has gained ethical approval and local Trust Research and Development approval it is activated on the SPIRIT2 websystem which allows recruitment of patients at that site to commence.

SPIRIT2 will be a paperless trial and all data will be collected electronically – please follow the instructions on the web system. Access to the secure area of the SPIRIT2 web site will require a personal username and password.

A copy of the patient's consent form and cytogenetic report will need to be faxed to the trial coordinator before the patient can be randomised. Full details on patient randomisation can be found in section 6.

Patients will be randomised to either receive 400mg daily imatinib or 100mg daily dasatinib.

1.4 Who to contact for help

If you require assistance please contact the coordinating centre at the University of Newcastle or a member of the study management committee:

Trial Coordinator	**01280 814 916**
Dr Stephen O'Brien	0191 282 0605
Professor Jane Apperley	0208 383 3237
Professor Richard Clark	0151 706 4344

For full addresses/email see page 4.

2 Introduction

2.1 Background and rationale for the study

Imatinib 400mg daily has become the standard drug therapy for patients with newly-diagnosed CML. Recently-published data from the IRIS study indicate an 89% probability of five year overall survival by Kaplan Myer analysis[1]. Newer drugs are now becoming available to treat CML, notably dasatinib, nilotinib and bosutinib. These drugs have so far mainly been used to treat patients who have failed imatinib therapy but there is some experience in using these agents as first line treatment with excellent results.

Dasatinib is a potent second generation tyrosine kinase inhibitor (TKI) initially designed to overcome resistance due to TK domain mutations associated with imatinib therapy. Latest data from ASH 2007[2] indicate major and complete cytogenetic response rates of 57% and 41% respectively (median follow up 26 months) in patients who have previously failed imatinib therapy.

Very promising data are now emerging using dasatinib as first line therapy in newly-diagnosed chronic phase patients[3]. In a non-randomised study of 40 patients from the MD Anderson, with a median follow up of 18 months, 100% of patients (that's not a typo – every patient…) achieved a complete cytogenetic response (CCR) at 12 months on study. This is a quite remarkable figure and it is clear, amongst imatinib-treated patients, that higher rates of CCR translate into higher rates of long term survival[4]. One may reasonably expect therefore that dasatinib could offer superior event free survival in the longer term but this needs to be established in a phase III study. We will carefully evaluate whether additional toxicity is encountered with dasatinib 100mg and assess overall treatment failure rates as described in sections 3, 12 and 16 of the study protocol.

As described in section 16 of the protocol, we have defined 5 year Event Free Survival (EFS) as the primary endpoint of this study. The study is powered to be able to demonstrate superiority.

Anticipating that dasatinib may have more toxicity over the period of the study (although the 100mg dose that we have adopted appears better tolerated than the initial 140mg dose) we have incorporated '**treatment failure rate'** as a key secondary end point as described in section 16.1.3 of the protocol. This will incorporate progression events and those who have to stop treatment due to intolerance. We feel this is an appropriate and useful composite endpoint that will be useful to guide clinical practice in the future.

[1] [1] Druker *et al.* N Engl J Med 355:2408, December 7, 2006
[2] American Society for Haematology 2007, Atlanta, abstract 735
[3] American Society for Haematology 2007, Atlanta, abstract 30
[4] American Society for Haematology 2007, Atlanta, abstract 25

It is essential that long term studies of up-front therapy comparing these new agents with imatinib are conducted. The costs of all of these agents is considerable (between £19K and £32K per patient per annum depending on agent and dose) and in order to be evaluable by NICE and regulatory agencies, robust independent clinical and cost effectiveness data need to be generated.

SPIRIT 2 aims to partner with Bristol Myers Squibb (who have agreed to fund the study) to conduct an evaluation of imatinib 400mg vs dasatinib 100mg daily in newly diagnosed CML patients. The study will be conducted under the auspices of the NCRN CML Working Group who will have autonomous control of the study. The Sponsor will be Newcastle upon Tyne Hospitals NHS Foundation Trust.

2.2 Summary of study design

SPIRIT 2 is a Phase III, multicentre, open-label, prospective randomised trial comparing imatinib 400mg daily versus dasatinib 100 mg daily in patients with chronic phase CML. Patients must be newly diagnosed (<3 months) and have been treated with only hydroxycarbamide (hydroxyurea) and/or anagrelide.

It is expected that 810 (405 in each arm) patients will be entered into the study

After screening, all patients will be randomised in equal proportions to one of the two treatment groups:

A Imatinib 400 mg daily
B Dasatinib 100 mg daily

The treatment will be started immediately.

The primary endpoint is to compare Event Free Survival (EFS) between the two arms at 5 years. Additional endpoints are defined in section 3. Patients may also be followed for survival for up to ten years after completion of the main study period (via Office of National Statistics - ONS).

3 Endpoints

3.1 Primary endpoint

To compare 5-year Event Free Survival (EFS) between the treatment arms as shown below. The study is powered to demonstrate superiority of the dasatinib arm over the imatinib arm. See section 16 for detailed statistics.

3.2 Secondary endpoints

1. To compare the rate of complete cytogenetic response after two years of study therapy in each of the treatment arms and the cumulative incidence of such responses with each of the regimens (cytogenetic response criteria

are defined in section 12.3). The study is powered to demonstrate superiority of the dasatinib arm over the imatinib arm.

2. To compare the treatment failure rates (TFR) at 5 years between the two arms of the study (treatment failure is defined in section 12.5).

3. To compare the rates of complete haematologic response (CHR) in patients treated with these regimens in each of the treatment arms (complete haematological response is defined in section **12.2**)

4. To compare the level of 'molecular' response (BCR-ABL/ABL ratio by real time PCR) in each of the treatment arms.

5. To compare the tolerability between the regimens. This will in part be incorporated into the treatment failure assessment.

6. To assess quality of life between the regimens

7. To assess the broad comparative costs between the regimens

8. To compare overall survival at 2 and 5 years.

4 Study population

The target population includes adult patients with cytogenetically confirmed Ph-positive chronic phase CML. **Patients must be within 3 months of diagnosis and previously untreated for CML, except for hydroxycarbamide and/or anagrelide**. It is planned to enrol 405 patients per treatment arm, 810 in total.

Allografting should be considered for all appropriate CML patients and if allografting is seriously being considered in the near future, then trial entry should be discouraged.

5 Inclusion and exclusion criteria

5.1 Inclusion criteria

1. Male or female patients ≥ 18 years of age.
2. Patients must have <u>all</u> of the following:

   i) be enrolled within **3 months** of initial diagnosis of CML-CP (date of initial diagnosis is the date of first cytogenetic analysis),

   ii) cytogenetic confirmation of the Philadelphia chromosome or variants of (9;22) translocations; patients may have secondary chromosomal abnormalities in addition to the Philadelphia chromosome.

   iii) (a) < 15% blasts in peripheral blood and bone marrow;

(b) < 30% blasts plus promyelocytes in peripheral blood and bone marrow;

(c) < 20% basophils in peripheral blood,

(d) ≥ 100 x 10^9/L platelets

iv) no evidence of extramedullary leukaemic involvement, with the exception of hepatosplenomegaly.

3. Written voluntary informed consent.

5.2 EXCLUSION CRITERIA

1. Patients with Ph-negative, BCR-ABL-positive, disease are **NOT** eligible for the study.
2. Any prior treatment for CML with: any tyrosine kinase inhibitor (eg imatinib, dasatinib, nilotinib); busulphan; interferon-alpha; homoharringtonine; cytosine arabinoside; any other investigational agents (hydroxycarbamide and anagrelide are the only drugs permitted). **NB patients will be ineligible for the study if they have received ANY prior therapy with interferon-alpha or imatinib. NO exceptions.**
3. Patients who received prior chemotherapy, including regimens used in peripheral blood progenitor cells (PBPCs) mobilisation for haematopoietic progenitor-cell transplantation. (It is allowable to collect **unmobilised** PBPCs at diagnosis.)
4. Patient who have had any form of prior haemopoietic stem cell transplant, either autograft or allograft.
5. Patients with an ECOG Performance Status Score ≥ 3.
6. Patients with serum bilirubin, SGOT/AST, SGPT/ALT, or creatinine concentrations > 2.0 x the institutional upper limit of the normal range (IULN).
7. Patients with International normalised ratio (INR) or partial thromboplastin time (PTT) > 1.5 x IULN**,** with the exception of patients on treatment with oral anticoagulants.
8. Patients with *uncontrolled* medical disease such as diabetes mellitus, thyroid dysfunction, neuropsychiatric disorders, infection, angina, or Grade 3/4 cardiac problems as defined by the New York Heart Association Criteria.
9. Patients with known positivity for human immunodeficiency virus (HIV); baseline testing for HIV is not required.
10. Patients who have undergone major surgery within 4 weeks of Study Day 1, or who have not recovered from prior major surgery.
11. Patients who are:
    (a) pregnant,
    (b) breast feeding,
    (c) of childbearing potential
    without a negative pregnancy test prior to Study Day 1, and (d) male or female of childbearing potential unwilling to use barrier contraceptive

precautions throughout the trial (postmenopausal women must be amenorrhoeic for at least 12 months to be considered of non-childbearing potential).

12. Patients with a history of another malignancy either currently or within the past five years, with the exception of basal cell skin carcinoma or cervical carcinoma *in situ*.
13. Patients with a history of non-compliance to medical regimens or who are considered potentially unreliable.

6 Site Set-up and Patient Randomisation

6.1 Site requirements for study participation

Any hospital in the UK can participate in the SPIRIT 2 study if they can meet the following requirements:

- Sites must have access to the internet via Microsoft Internet Explorer version 6 or higher in order to access the electronic CRF.
- Site must gain local ethics approval (SSI)
- Site must gain local Trust Research and Development Approval
- The participating Trust must sign a Clinical Trial Agreement with the Trust sponsoring the Trial (The Newcastle-upon-Tyne Hospitals Trust)

6.2 Randomising a new patient

The following steps are taken when a site has a patient eligible for entry into the study:

1) Eligibility criteria. The investigator will assess whether the patient meets all of the trial inclusion criteria and whether any of the exclusion criteria apply (see section 5).

2) Written Informed Consent. If the patient is eligible for the trial they will be given the patient information leaflet and informed consent forms to read and will be given the opportunity to ask questions about the study. If they agree to participate in the study they will be asked to sign the informed consent forms.

3) **Randomisation.** The patient is then registered on the secure SPIRIT 2 websystem. After key data have been entered (eligibility criteria, demography, randomisation date) the system will automatically randomise the patient and generate their unique trial number. An automatic message is sent to the trial manager to alert them that a new patient has entered the trial. Patients will be randomised to either receive 400mg daily imatinib or 100mg daily dasatinib.

4) **Confirming diagnosis and consent.** Signed consent forms along with the cytogenetic report from the time of diagnosis are faxed to the trial coordinator for central monitoring and confirmation of eligibility.

7 Treatment Arms

Dosing Levels for All Arms

Dosing Level Code	**A 400mg daily imatinib**	**B 100mg daily dasatinib**
	Total daily Imatinib (mg)	Total daily dasatinib (mg)
1	*300**	*50**
2	400	*80**
3		100

(*only used for managing toxicities)

7.1 Arm A: Imatinib 400 mg daily

Dosing levels for Arm A

	Arm A 400mg daily imatinib
Dosing Level Code	Total daily Imatinib (mg)
A1 ***(only used for managing toxicities)***	*300*
A2	400

Patients randomised to this arm will receive once daily oral administration of imatinib at a dose of 400 mg. Patients may receive imatinib on an outpatient basis. Imatinib tablets should be taken by mouth with a drink of water and some food, preferably with the evening meal, to minimise gastric irritation. Patients should avoid grapefruit juice while taking imatinib as this may alter imatinib levels (CYP3A4 substrate).

The following guidelines indicate what should be done if patients develop cytopenias whilst on imatinib or if they develop other, non-haematological, side effects.

7.1.1 Dose reduction for imatinib at 400 mg/day

NCI common toxicity criteria: haematology					
Grade	**0**	**1**	**2**	**3**	**4**
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

Summary of dose reduction guidelines for patients randomised to imatinib 400mg/day				
Daily dose	**Haematological toxicity***		**Non-haematological toxicity (see NCI criteria in appendix 2)**	
Level	*Grade 1/2*	*Grade 3/4 ANC or plts*	*Grade 2*	*Grade 3/4*
A2 *400 mg*	No dose alteration	Stop imatinib If recovery to < grade 2 occurs resume @ 400 mg If toxicity recurs, stop imatinib and resume @ 300 mg after recovery to < grade 2.	Stop imatinib and resume @ 400 mg after recovery to ≤ grade 1 If toxicity recurs, stop imatinib and resume @ 300 mg after recovery to ≤ grade 1.	Stop imatinib and resume @ 300 mg after recovery to ≤ grade 1 If toxicity recurs, stop imatinib and if re-treatment is inappropriate discontinue imatinib.
A1 *300 mg*	No dose alteration	Stop imatinib and resume @ 300 mg after recovery to < grade 2 If toxicity recurs at 300 mg, consult SMC*	If Grade 2 toxicity recurs at 300 mg, consult SMC*	Discontinue imatinib treatment
* If re-challenge at a dose of 300 mg/day is not tolerable dose reduction to 200 mg/day, or discontinuation of the patient from the study may be considered after discussion with a member of the SMC, on a case-by-case basis. **Also consider dose re-escalation: see below for guidance on dose re-escalation.**				

7.1.2 Dose re-escalation

Following the dose reductions described above, the dose of imatinib may be increased to the initial dose level of 400 mg at least 1 month after dose reduction if: (a) there is no recurrence of the toxicity which led to dose reduction and (b) there is no additional ≥ grade 2 toxicity. This applies to either dose reductions due to haematological or non-haematological toxicities.

7.2 Arm B: Dasatinib 100mg daily

Dosing levels for Arm B

Dosing Level Code	**B 100mg daily dasatinib**
	Total daily dasatinib (mg)
B1 ***(only used for managing toxicities)***	*50*
B2 ***(only used for managing toxicities)***	*80*
B3	100

Patients randomised to this arm will receive once daily oral administration of dasatinib at a dose of 100 mg. Patients may receive dasatinib on an outpatient basis. Dasatinib tablets should be taken by mouth with a drink of water and swallowed whole. The following guidelines indicate what should be done if patients develop cytopenias whilst on dasatinib or if they develop other, non-haematological, side effects.

7.2.1 Dose reduction for dasatinib at 100 mg/day

NCI common toxicity criteria: haematology					
Grade	**0**	**1**	**2**	**3**	**4**
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

Summary of dose reduction guidelines for patients randomised to dasatinib 100mg/day				
Daily dose	**Haematological toxicity***		**Non-haematological toxicity (see NCI criteria in appendix 2)**	
Level	*Grade 1/2*	*Grade 3/4 ANC or plts*	*Grade 2*	*Grade 3/4*
100 mg	No dose alteration	Stop dasatinib If recovery to < grade 2 occurs resume @ 100 mg If toxicity recurs, stop dasatinib and resume @ 80 mg after recovery to < grade 2.	Stop dasatinib and resume @ 100 mg after recovery to ≤ grade 1 If toxicity recurs, stop dasatinib and resume @ 80 mg after recovery to ≤ grade 1.	Stop dasatinib and resume @ 80 mg after recovery to ≤ grade 1 If toxicity recurs, stop dasatinib and if re-treatment is inappropriate discontinue dasatinib.
80 mg	No dose alteration	Stop dasatinib If recovery to < grade 2 occurs resume @ 80 mg If toxicity recurs, stop dasatinib and resume @ 50 mg after recovery to < grade 2.	Stop dasatinib and resume @ 80 mg after recovery to ≤ grade 1 If toxicity recurs, stop dasatinib and resume @ 50 mg after recovery to ≤ grade 1.	Stop dasatinib and resume @ 80 mg after recovery to ≤ grade 1 If toxicity recurs, stop dasatinib and if re-treatment is inappropriate discontinue dasatinib.
50 mg	No dose alteration	Stop dasatinib and resume @ 50 mg after recovery to < grade 2 If toxicity recurs at 50 mg, consult SMC*	If Grade 2 toxicity recurs at 50 mg, consult SMC*	Discontinue dasatinib treatment
* If re-challenge at a dose of 50 mg/day is not tolerable dose reduction to 20 mg/day, or discontinuation of the patient from the study may be considered after discussion with a member of the SMC, on a case-by-case basis. **Also consider dose re-escalation: see below for guidance on dose re-escalation.**				

7.2.2 Dose re-escalation

Following the dose reductions described above, the dose of dasatinib may be increased to the initial dose level of 100 mg at least 1 month after dose reduction if: (a) there is no recurrence of the toxicity which led to dose reduction and (b) there is no additional ≥ grade 2 toxicity. This applies to either dose reductions due to haematological or non-haematological toxicities.

8 Study medications: practicalities

Investigational product should be stored in a secure area according to local regulations. It is the responsibility of the Investigator to ensure that investigational product is only dispensed to study subjects. The investigational product must be dispensed only from official study sites by authorised personnel according to local regulations. Storage facilities for investigational product must be securely locked and substantially constructed, with restricted access to prevent theft or diversion, as applicable by local regulations.

Although the risk of dermal exposure is considered minimal, it is recommended that only study patients should handle the study drug.

8.1 Arm A – 400mg daily Imatinib (Gleevec)

Imatinib is approved by the National Institute of Clinical Excellence for the treatment of newly diagnosed CML. Under the Health Services Act, trusts are now obliged by law to provide the standard dose (400mg daily) for newly diagnosed patients.

The imatinib for Arm A will be sourced from the participating site's NHS stock and relabelled at site with an appropriate clinical trial label.

Imatinib should be stored at room temperature not to exceed 30^{o}C.

Imatinib tablets should be taken by mouth with a drink of water and some food, to minimise gastric irritation. Patients should avoid grapefruit juice while taking imatinib as this may alter imatinib levels (CYP3A4 substrate).

8.2 Arm B – 100mg daily dasatinib (Sprycel)

The dasatinib for Arm B WILL BE PROVIDED FREE OF CHARGE by BMS for 5 years for each patients after the last patient is recruited. This guarantees each patient a minimum of 5 years supply.

This dasatinib for Arm B is supplied directly by BMS Research and Development in two different strengths. Dasatinib will be packaged in bottles as follows:

- 20 mg film-coated tablets, 30 tablets/bottle (20-mg film coated tablets, biconvex, round, white to off-white in appearance with "20" or "BMS" debossed on one side and "527" on the other side)
- 50 mg film-coated tablets, 30 tablets/bottle (50-mg film coated tablets, biconvex, oval, and white to off-white in appearance with "50" or "BMS" debossed on one side and "528" on the other side)

Each bottle will be labelled in an open label fashion with booklet labels. Labels will contain, at a minimum, the following information: product name, tablet strength, batch number, directions for use, storage conditions, and appropriate caution statements.

The SPIRIT 2 trial manager is responsible for ordering the trial-supplied dasatinib.

Dasatinib tablets should be stored at 25° C (77° F); excursions permitted between 15°–30° C (59°–86° F).

Dasatinib tablets should be taken by mouth with a drink of water and swallowed whole.

8.3 Disposal of unused study medication

Study drug is not pre-labeled with the patient's study number and therefore can be used for any patient in the appropriate treatment arm. Thus, the amount of unused study drug should be minimal.

Any study drug that has been dispensed to a patient and returned unused should be disposed of via the normal method at site. This disposal should be documented.

9 Concomitant medications

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's notes and in the case report form. The administration of anticancer agents including chemotherapy and biologic agents are NOT however permitted. Similarly, the use of other investigational drugs is not allowed. The use of allopurinol is at the discretion of the investigator.

Leukapheresis or platelet phereses should not exceed more than one procedure per week and must be documented as concomitant therapies. Anagrelide and hydroxycarbamide are NOT permitted *after* the first month of imatinib therapy. If the patient's count is such as to require these medications after the first month of imatinib therapy, this will be regarded as a treatment failure and the patient will go off study. Administration of blood products should be considered as a concomitant medication and recorded as such.

There are no comprehensive data available on drug interactions with either imatinib or dasatinib so caution is required. Particular caution is required with potentially hepatotoxic drugs including paracetamol. As imatinib is a known gastric irritant caution is also required when using drugs, such as non-steroidal anti-inflammatory agents, which may compound this effect. Little is yet known about interactions between many drugs and imatinib or dasatinib that may affect efficacy. Therefore when concomitant medication with anticonvulsants, anticoagulants or other essential drugs is necessary, close monitoring will be required. Because of the possible risk of either reduced activity or enhanced toxicity of the concomitant medication and/or imatinib/dasatinib, drugs known to be metabolised by the same CYP450 (CYP3A4) isoenzymes as imatinib, should

be used with caution. For a comprehensive list of such drugs see: http://medicine.iupui.edu/flockhart/

9.1 How do I control the blood count whilst study medication is suspended?

This issue is only relevant to non-haematological toxicity. It is likely that the interval required to allow non-haematological toxicity to resolve will be no more than 1 to 2 weeks and in most cases, no additional anti-leukaemic therapy would be required. In exceptional circumstances a brief period of hydroxycarbamide may be used but this **must** be discussed with a member of the SMC and documented in the CRF.

10 Visit schedules and assessments

10.1 Screening assessments (Visit 1)

Written informed consent must be obtained (and faxed to the SPIRIT 2 trial manager on 01280 814 916) before any study specific medical procedures are performed. Baseline assessments must be done within 14 days prior to the first administration of study drug. The only exception to this is the bone marrow which can be done up to 28 days prior to the first administration of study drug.

Assessment	Includes
Patient eligibility	Inclusion/exclusion criteria
Relevant Medical History/ Current Medical Conditions	Relevant past medical history and current medical conditions not related to the study indication.
Disease History	Date of diagnosis, summary of previous therapy for CML.
Physical examination	General examination. Includes height and weight. Assessment of extramedullary disease including liver, lymph nodes, spleen.
Performance status	According to ECOG criteria (see Appendix 3)
Bone Marrow (Aspirate and Trephine)	Morphology Percentage of blasts, Percentage of promyelocytes (aspirate), cellularity (trephine) G-Banding and/or FISH analysis should be conducted. (see section **Error! Reference source not found.**) G-Banding - number of metaphases examined, number metaphases positive for Philadelphia chromosome, chromosomal abnormalities other than Ph chromosome; FISH – number of interphase nuclei examined, number of interphase nuclei positive for BCR-ABL.
Haematology	Haemoglobin, white blood cell (WBC) count and differential to include percentage of blasts, neutrophils, basophils, and eosinophils, platelet count.
Biochemistry	Total bilirubin, lactate dehydrogenase (LDH), aspartate aminotransferase (AST)/ serum glutamic-oxaloacetic transaminase (SGOT), alananine transaminase (ALT) / serum glutamate pyruvate transaminase (SGPT), alkaline phosphatase, creatinine, urea.
Quantitative PCR (Q-PCR) for BCR-ABL (see section 10.3)	Peripheral blood sample collected for BCR-ABL transcript levels.
Concomitant Medications/	Record all concomitant medications and/or non-drug therapies,

Significant Non-Drug Therapies	including anti-leukaemic chemotherapy received within the month prior to starting the study. Include the reason for administration.
Study medication log	Changes to study drug, including drug initiation, discontinuation and dose changes.
Prognostic Scores	Sokal and Hasford scores will be automatically calculated from baseline information.
Quality of Life Questionnaire	To be completed by the patient. (sub-set of patients only)

10.2 Assessments for visits 2 - 14

Bone marrow assessment (aspirate, trephine, cytogenetics & FISH) will be performed at screening and annually thereafter.

Blood samples for Q-PCR analysis will be taken at screening and after 3, 6, 9, 12, 18 and 24 months of treatment. Sampling should then be every 6 months thereafter.

The quality of life questionnaire should be completed at screening, and after 1, 2, 3, 6 and 12 months of treatment continuing yearly thereafter.

The schedule of assessments by visit is detailed in appendix 4.

Assessment	**Includes**
Physical examination	General examination. Assessment of extramedullary disease including liver, lymph nodes, spleen.
Performance status	According to ECOG criteria (see Appendix 3)
Bone Marrow (Aspirate and Trephine) (visits 7, 9, 11, 13, 15 only)	Morphology - Percentage of blasts, Percentage of promyelocytes, (aspirate), cellularity (trephine) G-Banding and/or FISH analysis should be conducted. (see section **Error! Reference source not found.**) G-Banding - number of metaphases examined, number metaphases positive for Philadelphia chromosome, chromosomal abnormalities other than Ph chromosome; FISH – number of interphase nuclei examined, number of interphase nuclei positive for BCR-ABL.
Haematology	Haemoglobin, white blood cell (WBC) count and differential to include percentage of blasts, neutrophils, basophils, and eosinophils, platelet count.
Biochemistry	Total bilirubin, lactate dehydrogenase (LDH), aspartate aminotransferase (AST)/ serum glutamic-oxaloacetic transaminase (SGOT), alananine transaminase (ALT) / serum glutamate pyruvate transaminase (SGPT), alkaline phosphatase, creatinine, urea.
Quantitative PCR (Q-PCR) for BCR-ABL (see section 10.3) (all visits except visits 2 and 3)	Peripheral blood sample collected for BCR-ABL transcript levels.
Concomitant Medications/ Significant Non-Drug Therapies	All concomitant medications and/or non-drug therapies, since last visit
Adverse Events	All untoward experiences since last visit
Study medication log	Changes to study drug, including drug initiation, discontinuation and dose changes.
Quality of Life Questionnaire (visits 1, 2, 3, 4, 5, 7, 9, 11, 13, 15 only)	To be completed by the patient. (sub-set of patients only)

10.3 Quantitative PCR (QPCR) samples

A sample is taken for PCR analysis to detect BCR-ABL transcript levels at various timepoints throughout the study. Sampling times for PCR analysis are at screening, prior to treatment with study drug (imatinib/dasatinib) then every three months for the first year and then every six months for the remainder of the study.

Instructions for handling QPCR samples

- Samples for PCR analysis should be collected on a Monday, Tuesday or Wednesday only (to allow them to arrive at the analysing laboratory before the weekend).
- Each analysis requires 40ml of peripheral blood collected in EDTA tube(s).
- Each tube should be clearly marked with the patient's SPIRIT 2 trial number, initials, date of birth and the date and time of the sample.
- Each sample should be accompanied by a SPIRIT 2 PCR shipping form

Central Laboratory for QPCR analysis

- A central laboratory is being used to analyse the QPCR samples to ensure the results for the study are comparable between sites.
- There is no cost to the investigational site for this analysis.
- QPCR samples should be sent to:
  MRD Group,
  LRF Adult Leukaemia Centre,
  Imperial School of Medicine,
  Department of Haematology,
  Hammersmith Hospital,
  Du Cane Road,
  London W12 0NN
- The package should be clearly marked 'SPIRIT 2 Trial' and should be sent via first class post. Packaging must comply with the IATA Packing Instruction 650 (http://www.iata.org/NR/ContentConnector/CS2000/SiteInterface/sites/whatwedo/dangerousgoods/file/PI650.pdf)

10.4 Study Drug Discontinuation and Study Discontinuation (Visit 15)

If a patient is unable to continue on the treatment regime to which they were randomised for reasons of toxicity or intolerance that patient will discontinue study treatment. However, if the patient is willing to continue in the SPIRIT 2 study they will continue to be followed up within the study until the final visit.

For patients discontinuing the study, the assessments are as for visits 2 – 14 described above with the addition of a study discontinuation assessment.

Visit 15 is completed for patients discontinuing the study regardless of the point at which they are discontinuing (e.g. a patient discontinuing after 3 months will complete visit 15 instead of visit 4).

It must be documented whether each patient completes the study or discontinues prematurely for any reason. The reason for premature discontinuation must be recorded if any patient does not complete either study treatment or the study-related observations. Any patient discontinuing participation in the study must have the reason categorised on the electronic study completion forms as follows:

1. End of Study
2. Adverse Event
3. Death (non-cancer related)
4. Death (cancer-related)
5. Treatment failure
6. Disease progression
7. Protocol violation
8. Consent withdrawn
9. Lost to follow-up
10. Other

Patients who discontinue the study due to a study drug-related adverse event must be followed weekly for four weeks (and subsequently at 4-weekly intervals), or until resolution or stabilisation of the event. A complete end of study evaluation should be conducted for any patient discontinuing the study. End of study evaluations include: adverse events, concomitant medications and therapies, biochemistry, haematology, bone marrow cytogenetics, quality of life questionnaire (for a sub-set of patients only). All relevant information related to the reason for premature discontinuation including contributory factors must be included on the study completion section of the electronic case report form.

See appendix 4 for visit schedule

10.5 End of Study

The end of the study for each individual patient is defined as date on which the patient reaches study visit 15 (60 months on study) unless the patient has discontinued prematurely before reaching visit 15.

The end of the study is defined as the date on which the last patient continuing in the study reaches the last visit 15.

Patients may also be followed for survival for up to ten years after completion of the main study period (via Office of National Statistics - ONS)

11 Assessment of safety

Safety assessments will consist of evaluating adverse events, laboratory parameters including haematology (haemoglobin, percentage of blasts, WBC count, platelet count) and biochemistry (total bilirubin, LDH, AST/SGOT, ALT/SGPT, alkaline phosphatase, creatinine and urea), physical examinations, and documentation of all concomitant medications and/or therapies including blood products.

11.1 Adverse Events (AEs)

An adverse event is defined as any undesirable sign, symptom, or medical condition occurring after starting study drug, whether considered study drug-related or not. Undesirable signs, symptoms or medical conditions/diseases present before starting study drug are only considered adverse events if they worsen after starting study drug. Study drugs include any drug under evaluation in the study, including reference drug, placebo, or any other drug required by the protocol. Information about each adverse event will be collected and recorded on the adverse events section of the electronic CRF.

Adverse events, whether volunteered, discovered during general questioning, or detected through physical examination, laboratory test or other means must be recorded on the adverse event section of the electronic CRF and followed carefully until resolution. Abnormal laboratory values or test results should not generally be considered adverse events unless they induce clinical signs or symptoms or require intervention in which case they must be recorded on the adverse events section of the electronic CRF with the appropriate diagnostic description.

All adverse events will be described by:

1. duration (start and end dates),
2. toxicity grade (grade 1 – 4, refer to Appendix 2),
3. seriousness,
4. intensity
5. severity
6. relationship to the study drug (s) (suspected/not suspected),
7. action(s) taken

11.2 Serious Adverse Events (SAEs)

Information about every serious adverse event must be collected and recorded on the Serious Adverse Event Report Form. A serious adverse event is defined as an event that is:

1. fatal, or life-threatening
2. requires or prolongs hospitalisation
3. significantly or permanently disabling
4. is a congenital anomaly
5. any other significant medical event

Any hospitalisation which was planned prior to the start of study (elective in nature), which relates directly to the underlying disease or is part of the regular

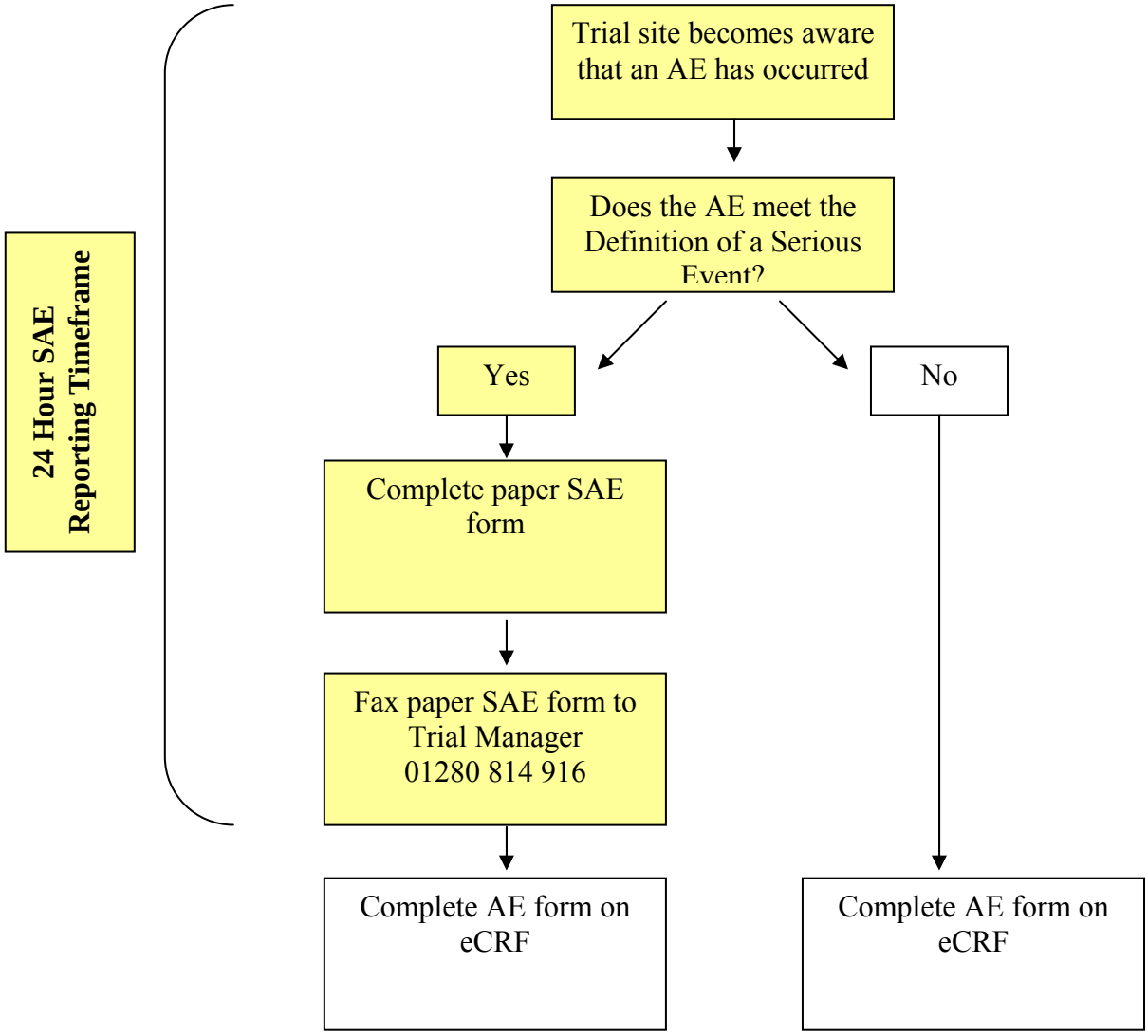
treatment for the disease and which does not lead to a deterioration in the patient's condition need NOT be reported.

Any serious adverse event, including serious laboratory abnormalities occurring after a patient receives study medication and for a period up to four weeks after stopping study drug must be reported by the local investigator, to the trial coordinator **within 24-hours**, even if not deemed to be study drug-related. The minimum information required to report an SAE is the SPIRIT 2 subject number and a description of the adverse event. The completed Serious Adverse Event Report Form (which can be found on the SPIRIT studies website) must be printed off, signed by the principal investigator, and sent by fax to the trial coordinator. All follow-up information about a reported serious adverse event must also be forwarded to the SPIRIT 2 trial coordinator.

All AE's that are serious and possibly related to one (or more) of the study drugs and are not included in the Summary of Product Characteristics (SPC) for the appropriate product will be treated as Suspected Unexpected Serious Adverse Reactions for expedited reporting purposes. The latest version on the SPC for Glivec Tablets and Sprycel tablets can be found at http://emc.medicines.org.uk/.

The trial coordinator will be responsible for notifying the appropriate regulatory and ethical bodies. The SPIRIT 2 trial coordinator will also notify BMS and Novartis.

Workflow for study sites reporting Adverse Events



12 Assessments of efficacy

12.1 Event free survival

For the purposes of the study an 'event' will be defined as the first occurrence of one of the following:

- Death from any cause
- Disease progression (as defined below)
- Loss of CHR defined as the appearance of any of the following, confirmed by a second determination ≥ 1 month later:
  - → WBC count that rises to > 20.0 x 10^9/L
  - → Platelet count that rises to ≥ 600 x 10^9/L
  - → Progressive splenomegaly to a size ≥ 5 cm below the left costal margin
  - → Appearance of ≥ 5% myelocytes + metamyelocytes in the peripheral blood
  - → Appearance of blasts or promyelocytes in the peripheral blood
- Increasing WBC count: for patients not achieving a CHR, haematological progression will be defined as a doubling of WBC count at least one month apart with at least the second value > 20.0 x 10^9/L.
- Loss of major cytogenetic response (MCR), defined as an increase in the Ph+ bone marrow cells by at least 30 percentage points (e.g., from 20% to 50%, or from 30% to 60%) confirmed by a second cytogenetic analysis ≥ 1 month later.

12.2 Complete haematological response (CHR)

All of the following must be present for ≥ 4 weeks:

- Normal peripheral blood counts, i.e. WBC count < 11.0 x 10^9/L and platelet count < 450 x 10^9/L.
- Normal WBC differential (no peripheral blood blasts and promyelocytes, a sum of myelocytes + metamyelocytes in the peripheral blood of < 5% will be permitted; more immature granulocytes will not be permitted)
- No evidence of disease-related symptoms and extramedullary disease, including hepatosplenomegaly

Duration of CHR is defined as the time from the first documentation of the complete haematologic response to the date the loss of complete haematologic response or treatment failure is documented, whichever occurs first.

12.3 Cytogenetic response

G-Banding and/or FISH analysis on bone marrow samples will be collected. If both results are available both results will be recorded. If only one is available G-banding data should be collected in preference to FISH. Cytogenetic response will be assessed annually.

G-Banding

Cytogenetic response in terms of the percentage of Ph chromosome-positive metaphases in bone marrow is defined as follows: complete (0% Ph-positive cells); partial (> 0%-35%); minor (> 35%-65%); minimal (> 65%-95%); none (> 95%-100%).

Major cytogenetic response comprises both complete and partial cytogenetic responses i.e. ≤ 35% of Ph chromosome-positive metaphases in bone marrow.

A minimum of 20 metaphases must be examined in each bone marrow sample, whenever possible. **Results from a sample with less than 5 metaphases will not be considered. A sample with 5-19 metaphases will be considered if the results are confirmed by a follow-up sample.**

FISH

Cytogenetic response (FISH) in terms of the percentage of BCR-ABL positive interphases in bone marrow is defined as follows: complete (0% BCR-ABL cells); partial (> 0%-35%); minor (> 35%-65%); minimal (> 65%-95%); none (> 95%-100%).

Major cytogenetic response comprises both complete and partial cytogenetic responses i.e. ≤ 35% of BCR-ABL-positive interphases in bone marrow.

For FISH a minimum of 100 interphases must be examined in each bone marrow sample, whenever possible..

The duration of cytogenetic response is defined as the time from the first documentation of the response to the date the loss of cytogenetic response or treatment failure is documented, whichever occurs first.

12.4 Molecular response

The main secondary objective of this study is to test whether dasatinib 100mg in patients with previously untreated CML in chronic phase will produce a molecular response rate as good as, if not better than, that of imatinib at the standard dose of 400 mg/day.

For this purpose, major molecular response is defined as a 3-log reduction in the BCR-ABL/ABL ratio, relative to baseline, after 12 months of therapy. We also wish to capture data on patients who achieve a 4 log reduction. To date, the largest study of molecular response reported a rate of 3-log reduction of approximately 38%[2]. Dasatinib would be considered promising if it increased the major molecular response rate by at least 20 percentage points, e.g., from 38% to 58%.

12.5 Definition of disease progression

Any of the following events whilst the patient is on study would define disease progression:

- Death due to leukaemia. Death due to causes other than leukaemia, e.g. myocardial infarction, traffic accident, etc. will NOT define disease progression.
- Accelerated phase or blast crisis is defined as follows:

  Accelerated phase is defined as the appearance of one of the following: blasts in the blood or bone marrow $\geq$ 15%, or percentage of blasts plus promyelocytes in the peripheral blood or bone marrow $\geq$ 30%, or peripheral blood basophils $\geq$ 20%. (There are no reliable criteria for accelerated phase based on platelet count as it is virtually impossible to distinguish the effects of treatment from the effects of accelerating disease.)

  Blast crisis is defined as blasts in the blood or bone marrow $\geq$ 30% or appearance of extramedullary involvement (e.g. chloromas), except for hepatosplenomegaly.

Acquisition of additional chromosome abnormalities, besides a single Ph chromosome, is **NOT** considered to define disease progression.

12.6 Definition of treatment failure

Any of the following events occurring whilst patient is continuously on trial therapy would define treatment failure. Some are based on current European Leukemia Net guidelines[5].

- 'Events' as defined above.
- Intolerance such that the patient has to stop study treatment permanently.
- Failure to achieve CHR after 6 months on treatment
- Failure to achieve MCR after 12 months
- Failure to achieve CCR after 24 months

13 Quality of life analysis

Quality of life (QoL) evaluation should be included in trials where survival is expected to vary between the different arms, but the advantageous primary outcome is achieved only at the expense of major toxicity[13]. In such circumstances, data on QoL can be used to aid decision-making where the benefits of longer survival (quantity of life) need to be balanced against a negative outcome in terms of quality of life. One convenient way of expressing the relationship between length and quality of life is the Quality-Adjusted Life Year (QALY). Calculation of QALYs requires a preference-based measurement of QoL, measured on an interval scale and anchored on death vs perfect health. The EQ-5D [14] is the preference-based measure of choice in this trial; it has been

[5] Baccarani *et al.* Blood 2006; 108: 1809-20

validated for use in all participating countries, population-derived preference values are available, and it is quick to administer.

To provide a fuller picture of the impact of the chosen therapies on quality of life, the EQ-5D will be supplemented by the FACT-BRM (incorporating FACT-G). The FACT-G is a general cancer QoL measure, for evaluating outcomes in patients undergoing cancer treatment; it comprises 27 items, covering four domains: physical well-being; social/family well-being; emotional well-being; functional well-being. Originally developed in North America, it has been adapted and validated for use in the United Kingdom and France and has been demonstrated to have satisfactory discriminatory power and responsiveness to change. The FACT-G is designed to be supplemented by disease-, treatment- and condition-specific subscales. The subscale of choice for this trial is the FACT-BRM, designed for patients receiving biologic response modifiers. The FACT-BRM comprises 13 additional items, covering symptoms and side-effects of this type of therapeutic intervention. The EQ-5D, FACT-G and FACT-BRM are currently being used in the Novartis 0106 trial. Similar EORTC tools were considered but the chosen tools were considered more likely to pick up the predicted toxicities of the study regimens. Since survival is the primary outcome in this trial, sample size and power calculations have been based on anticipated differences in survival rates rather than on QoL changes. QoL will be assessed at baseline (immediately prior to randomisation), at 1, 2, 3, 6, 9 and 12 months post-entry to the trial, and at annual intervals thereafter; these time-points coincide with clinical follow-up and reflect the anticipated trajectory of response to therapy. Questionnaires will be administered via computer (Web), a proven technology in respect of the FACT instruments. A sub population of patients will be asked to complete Web and paper questionnaires for further validation.

14 Health economics evaluation

A simple health economic analysis will be conducted: we do not intend to capture detailed health economic data as patients will be predominantly treated in an outpatient setting and the costs of the trial therapies can easily be calculated. However there may be economic consequences if patients are admitted to hospital with complications of treatment or are unable to work. Data assessing these factors will be captured in order to allow an economic comparison between treatment arms.

15 Ethics

The study will be performed in accordance with Good Clinical Practice (GCP) and the Declaration of Helsinki (Appendix 1).

The clinical trial supply for patients on Arm B – 100mg daily dasatinib is guaranteed for five years for each patient from the time of the last patient being recruited into the study. Patients remaining on study treatment at 5 years on arm B will cease receiving the free trial supply at this point. It is suggested that these patients revert to the NICE approved regime of 400 mg daily imatinib at this time if dasatinib is not available on the NHS at that time. This is carefully explained in the patient information leaflet.

16 Statistical considerations and data analysis

16.1 Sample size and power calculations

The sample size is 810 in total, 405 in each arm.

All sample size calculations were performed using the software package nQuery version 6.02. The study sample size is based on detecting superiority of dasatinib over imatinib in the primary endpoint, event free survival (EFS) at 5 years. We also examined what differences in treatments this sample size would allow us to detect in two secondary endpoints; complete cytogenetic response (CCR) at 2 years and treatment failure rates (TFR) at 5 years.

16.1.1 Sample Size Calculation for Event Free Survival at 5 years

In the IRIS Study, the estimated Event Free Survival at 60 months by Kaplan Meier analysis was 83%[6]. We have taken this as the EFS baseline for the imatinib arm.

SPIRIT 2 will be powered to enable the demonstration of superiority of dasatinib over imatinib for the primary endpoint, EFS at 5 years. EFS is defined in section 12 and will be analysed using survival analysis techniques rather than proportions at 5 years. Thus the sample size calculations are performed using survival analysis estimates and terminology. The advantages of using survival analysis over proportions at 5 years are that survival analyses can use censoring to account for discontinuations, as apposed to ignoring such patients or assigning them to event status in a proportions analysis. Also, survival analysis will test for differences over the full 5 years, not just the numbers event-free at the end of the study period.

Two group test of equal exponential survival (n large), exponential dropout

Test significance level, α	0.050
1 or 2 sided test?	2
Length of accrual period	0.00
Maximum length of follow-up	5.00
Common exponential dropout rate, d	0.0325
Group 1 exponential parameter, λ_1	0.0373
Group 2 exponential parameter, λ_2	0.0187
Hazard ratio, $h=\lambda_1 / \lambda_2$	2.00
Power (%)	90
n per group	405
Total number of events required, E	87

When the sample size in each group is 405, with a total number of events required of 87, an exponential maximum likelihood test of equality of survival curves for EFS at 5 years, with a 5% two-sided significance level will have 90% power to

[6] Druker *et al.* N Engl J Med 355:2408, December 7, 2006

detect the difference between a imatinib exponential hazard parameter of 0.0373 (equates to a 5 year survival of 83%) and a dasatinib exponential hazard parameter of 0.0187 (equates to a 5 year survival of 91.1%), a constant hazard ratio of 2.00. This assumes all patients are followed for the full 5 years where possible, a maximum follow-up time of 5 years, and a common exponential dropout rate of 0.0325 (equates to a 15% drop-out over the 5 years).

16.1.2 Sample Size Calculation for Complete Cytogenetic Response at 2 years

From the IRIS study 5 year follow up paper[7], we know that the cumulative estimate of complete cytogenetic response (CCR) at 2 years is 79%. We have taken this as the CCR baseline for the imatinib arm.

Given the sample size of 405 per group (total N=810), we examined what difference in CCR proportions we could detect with 90% power.

A two group continuity corrected χ^2 test with a 5% two-sided significance level will have 90% power to detect the difference between a imatinib CCR 2 year proportion of 79% and a dasatinib CCR 2 year proportion of 87.7 (odds ratio of 1.897) when the sample size in each group is 405.

Two group continuity corrected χ^2 test of equal proportions (odds ratio = 1) (equal n's)

	Exact n=257
Test significance level, α	0.050
1 or 2 sided test?	2
Group 1 proportion, π_1	0.790
Group 2 proportion, π_2	0.877
Odds ratio, $\psi = \pi_2 (1 - \pi_1) / [\pi_1 (1 - \pi_2)]$	1.897
Power (%)	90
n per group	405

16.1.3 Sample Size Calculation for Treatment Failure Rates at 5 years

We have taken the latest data from ASH 2007 (again the IRIS study)[8] to guide us as to what proportion of patients at 5 years continue imatinib therapy without 'failing' i.e. no disease progression or other 'events' and able to tolerate the drug.

At 5 years, 66% of patients continued on imatinib without loss of response and able to tolerate the drug. We have taken this (66%) as the baseline treatment continuation rate at 5 years for the imatinib arm. This equates of course to a 34% treatment failure rate (TFR).

Two group test of equal exponential survival (n large), exponential dropout

[7] Druker *et al.* N Engl J Med 355:2408, December 7, 2006
[8] American Society for Haematology 2007, Atlanta, abstract 25

Test significance level, α	0.050
1 or 2 sided test?	2
Length of accrual period	0.00
Maximum length of follow-up	5.00
Common exponential dropout rate, d	0.0211
Group 1 exponential parameter, λ_1	0.0831
Group 2 exponential parameter, λ_2	0.0533
Hazard ratio, $h=\lambda_1 / \lambda_2$	1.5585
Power (%)	90
n per group	405
Total number of events required, E	213

When the sample size in each group is 405, with a total number of events required of 213, an exponential maximum likelihood test of equality of survival curves for TFR at 5 years, with a 5% two-sided significance level will have 90% power to detect the difference between an imatinib exponential hazard parameter of 0.0831 (equates to a 5 year treatment continuation of 66%) and a dasatinib exponential hazard parameter of 0.0533 (equates to a 5 year treatment continuation of 76.6%), a constant hazard ratio of 1.5585. This assumes all patients are followed for the full 5 years where possible, a maximum follow-up time of 5 years, and a common exponential dropout rate of 0.0211 (equates to a 10% drop-out over the 5 years).

16.2 Recruitment

Given a predicted recruitment rate of 300 – 350 patients per year we anticipate a 3 year recruitment period to reach the target sample size of 810 patients.

16.3 Statistical Analysis

A full and detailed statistical analysis plan will be written and agreed prior to database lock for the interim analysis. We plan an interim analysis after 2 years follow up, and final analysis after 5 years of follow up on all patients in the study. No stopping rules will be applied to the interim analyses.

16.3.1 Primary Endpoint

The primary endpoint for this study is the superiotrity of 100mg daily dasatinib over 400mg daily imatinib in EFS at 5 years.

In order to compare the treatments, we will fit a parametric (exponential) survival model to estimate the treatment hazard ratio and associated 95% confidence interval. We will check the adequacy of the exponential model fit to the data by comparing the exponential survival curves for each treatment against their Kaplan-Meier survival plots. If the exponential survival distributions prove to be unreasonable then the hazard ratios and confidence intervals will be estimated using a Cox proportional hazards model. We may also perform a log rank test to compare the treatments as a sensitivity analysis.

This analysis will be performed on the full analysis population, consisting of all patients that received at least one day's treatment on an 'intention to treat' basis.

Secondary Endpoints

The following secondary endpoints will be analysed. Further details will be given in the statistical analysis plan.

- Rate of complete cytogenetic responses after two years of study therapy. These responses will be analysed in two ways; firstly as a 5 category variables (complete, partial, minor, minimal, none), and secondly as a 2 category variable (complete/partial vs minor/minimal/none). Each version of the response will be analysed using chi-squared tests, and we may perform a chi-squared test for trend for the 5-category response if appropriate.
- Treatment failure rates (TFR) after 5 years between the two arms of the study (treatment failure is defined in section 12.5). This endpoint will be analysed using Kaplan-Meier plots and log-rank tests
- Rates of complete haematologic response (CHR) (complete haematological response is defined in section 12.2). Chi-squared tests will be used to compare this binary response between treatment groups.
- Level of 'molecular' response (BCR-ABL/ABL ratio by real time PCR) .
- Overall survival at two and 5 years. This endpoint will be analysed using Kaplan-Meier plots and log-rank tests, though no significant differences between treatment groups are expected.

Safety

Data on the safety and tolerability of the treatments will be collected and summarised. We will perform descriptive summaries of adverse events, serious adverse events, drug-related adverse events and treatment-limiting adverse events.

Data and all appropriate documentation will be stored for a minimum of 5 years after the completion of the study, including the follow-up period.

17 Presentation and publication of results

17.1 Presentation of results

Participating investigators and personnel from BMS must agree not to present data gathered individually or by a subgroup of centres before the full, initial presentation/publication.

It is agreed that the data from SPIRIT2 will be presented by a member of the Study Management Committee at the conclusion of the study. Participating investigators agree not to present data in any form prior to the first presentation of the overall study results. Such data includes any individual centre or national sub group analysis of response, survival or toxicity data as well as individual case reports of patients enrolled in the study. Reporting of overall trial recruitment and recruitment to national groups/individual cooperative groups is acceptable.

17.2 Publication of results

The results of SPIRIT2 will be published under a cooperative group name (such as 'The CML SPIRIT2 Group') rather than individual authors. The respective committee members will be acknowledged in an appendix to the paper. The Study Management Committee will form the core writing committee and will be acknowledged as such. Participating investigators agree not to publish data in any form prior to the first publication of the overall study results. Such data includes any individual centre or national sub group analysis of response, survival or toxicity data as well as individual case reports of patients enrolled in the study.

18 Data Handling and Record Keeping

Source Documents:

The investigator must maintain accurate patient records detailing all observations on each patient enrolled in the study.

Data entered in the CRF (including forms such as the SAE form) should be consistent with the source documents or the discrepancies must be explained.

Electronic Case Report Form (eCRF)

The eCRF for the study can be accessed via the SPIRIT Studies website www.spirit-cml.org.

The eCRF uses system controls to ensure that unauthorised users can not access or modify data and uses 128-bit encryption to ensure that data, if intercepted, can not be interpreted by third parties. The system has been validated against all standard industry requirements, including those of the FDA under 21 CFR Part 11.
All data for the study is captured via the eCRF with the exception of paper forms for the reporting of SAE's and pregnancies.

19 Direct Access to Source Data/Documents

The study monitor must be allowed to visit all study site locations from time to time to review the study conduct at site, perform source document verification and drug accountability checks. The study monitor must be allowed access to all source documents and study documentation at site.

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21 Appendices

21.1 Appendix 1 -Declaration of Helsinki

Ethical Principles for Medical Research Involving Human Subjects

Adopted by the 18th WMA General Assembly Helsinki, Finland, June 1964 and amended by the 29th WMA General Assembly, Tokyo, Japan, October 1975, 35th WMA General Assembly, Venice, Italy, October 1983, 41st WMA General Assembly, Hong Kong, September 1989, 48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996 and the 52nd WMA General Assembly, Edinburgh, Scotland, October 2000.

A. INTRODUCTION

1. The World Medical Association has developed the Declaration of Helsinki as a statement of ethical principles to provide guidance to physicians and other participants in medical research involving human subjects. Medical research involving human subjects includes research on identifiable human material or identifiable data.
2. It is the duty of the physician to promote and safeguard the health of the people. The physician's knowledge and conscience are dedicated to the fulfilment of this duty.
3. The Declaration of Geneva of the World Medical Association binds the physician with the words, "The health of my patient will be my first consideration," and the International Code of Medical Ethics declares that, "A physician shall act only in the patient's interest when providing medical care which might have the effect of weakening the physical and mental condition of the patient."
4. Medical progress is based on research which ultimately must rest in part on experimentation involving human subjects.
5. In medical research on human subjects, considerations related to the well-being of the human subject should take precedence over the interests of science and society.
6. The primary purpose of medical research involving human subjects is to improve prophylactic, diagnostic and therapeutic procedures and the understanding of the aetiology and pathogenesis of disease. Even the best proven prophylactic, diagnostic, and therapeutic methods must continuously be challenged through research for their effectiveness, efficiency, accessibility and quality.
7. In current medical practice and in medical research, most prophylactic, diagnostic and therapeutic procedures involve risks and burdens.
8. Medical research is subject to ethical standards that promote respect for all human beings and protect their health and rights. Some research populations are vulnerable and need special protection. The particular needs of the economically and medically disadvantaged must be recognised. Special attention is also required for those who cannot give or refuse consent for themselves, for those who may be subject to giving consent under duress, for those who will not benefit personally from the research and for those for whom the research is combined with care.
9. Research Investigators should be aware of the ethical, legal and regulatory requirements for research on human subjects in their own countries as well as applicable international requirements. No national ethical, legal or regulatory requirement should be allowed to reduce or eliminate any of the protections for human subjects set forth in this Declaration.

B. BASIC PRINCIPLES FOR ALL MEDICAL RESEARCH

1. It is the duty of the physician in medical research to protect the life, health, privacy, and dignity of the human subject.
2. Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and on adequate laboratory and, where appropriate, animal experimentation.
3. Appropriate caution must be exercised in the conduct of research which may affect the environment, and the welfare of animals used for research must be respected.
4. The design and performance of each experimental procedure involving human subjects should be clearly formulated in an experimental protocol. This protocol should be submitted for consideration, comment, guidance, and where appropriate, approval to a specially appointed ethical review committee, which must be independent of the investigator, the sponsor or any other kind of undue influence. This independent committee should be in conformity with the laws and regulations of the country in which the research experiment is performed. The committee has the right to monitor ongoing trials. The

researcher has the obligation to provide monitoring information to the committee, especially any serious adverse events. The researcher should also submit to the committee, for review, information regarding funding, sponsors, institutional affiliations, other potential conflicts of interest and incentives for subjects.

5. The research protocol should always contain a statement of the ethical considerations involved and should indicate that there is compliance with the principles enunciated in this Declaration.
6. Medical research involving human subjects should be conducted only by scientifically qualified persons and under the supervision of a clinically competent medical person. The responsibility for the human subject must always rest with a medically qualified person and never rest on the subject of the research, even though the subject has given consent.
7. Every medical research project involving human subjects should be preceded by careful assessment of predictable risks and burdens in comparison with foreseeable benefits to the subject or to others. This does not preclude the participation of healthy volunteers in medical research. The design of all studies should be publicly available.
8. Physicians should abstain from engaging in research projects involving human subjects unless they are confident that the risks involved have been adequately assessed and can be satisfactorily managed. Physicians should cease any investigation if the risks are found to outweigh the potential benefits or if there is conclusive proof of positive and beneficial results.
9. Medical research involving human subjects should only be conducted if the importance of the objective outweighs the inherent risks and burdens to the subject. This is especially important when the human subjects are healthy volunteers.
10. Medical research is only justified if there is a reasonable likelihood that the populations in which the research is carried out stand to benefit from the results of the research.
11. The subjects must be volunteers and informed participants in the research project.
12. The right of research subjects to safeguard their integrity must always be respected. Every precaution should be taken to respect the privacy of the subject, the confidentiality of the patient's information and to minimise the impact of the study on the subject's physical and mental integrity and on the personality of the subject.
13. In any research on human beings, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail. The subject should be informed of the right to abstain from participation in the study or to withdraw consent to participate at any time without reprisal. After ensuring that the subject has understood the information, the physician should then obtain the subject's freely-given informed consent, preferably in writing. If the consent cannot be obtained in writing, the non-written consent must be formally documented and witnessed.
14. When obtaining informed consent for the research project the physician should be particularly cautious if the subject is in a dependent relationship with the physician or may consent under duress. In that case the informed consent should be obtained by a well-informed physician who is not engaged in the investigation and who is completely independent of this relationship.
15. For a research subject who is legally incompetent, physically or mentally incapable of giving consent or is a legally incompetent minor, the investigator must obtain informed consent from the legally authorised representative in accordance with applicable law. These groups should not be included in research unless the research is necessary to promote the health of the population represented and this research cannot instead be performed on legally competent persons.
16. When a subject deemed legally incompetent, such as a minor child, is able to give assent to decisions about participation in research, the investigator must obtain that assent in addition to the consent of the legally authorised representative.
17. Research on individuals from whom it is not possible to obtain consent, including proxy or advance consent, should be done only if the physical/mental condition that prevents obtaining informed consent is a necessary characteristic of the research population. The specific reasons for involving research subjects with a condition that renders them unable to give informed consent should be stated in the experimental protocol for consideration and approval of the review committee. The protocol should state that consent to remain in the research should be obtained as soon as possible from the individual or a legally authorised surrogate.
18. Both authors and publishers have ethical obligations. In publication of the results of research, the investigators are obliged to preserve the accuracy of the results. Negative as well as positive results should be published or otherwise publicly available. Sources of funding, institutional affiliations and any possible conflicts of interest should be declared in the publication. Reports of experimentation not in accordance with the principles laid down in this Declaration should not be accepted for publication.

C. ADDITIONAL PRINCIPLES FOR MEDICAL RESEARCH COMBINED WITH MEDICAL CARE

1. The physician may combine medical research with medical care, only to the extent that the research is justified by its potential prophylactic, diagnostic or therapeutic value. When medical research is combined with medical care, additional standards apply to protect the patients who are research subjects.
2. The benefits, risks, burdens and effectiveness of a new method should be tested against those of the best current prophylactic, diagnostic, and therapeutic methods. This does not exclude the use of placebo, or no treatment, in studies where no proven prophylactic, diagnostic or therapeutic method exists.
3. At the conclusion of the study, every patient entered into the study should be assured of access to the best proven prophylactic, diagnostic and therapeutic methods identified by the study.
4. The physician should fully inform the patient which aspects of the care are related to the research. The refusal of a patient to participate in a study must never interfere with the patient-physician relationship.
5. In the treatment of a patient, where proven prophylactic, diagnostic and therapeutic methods do not exist or have been ineffective, the physician, with informed consent from the patient, must be free to use unproven or new prophylactic, diagnostic and therapeutic measures, if in the physician's judgement it offers hope of saving life, re-establishing health or alleviating suffering. Where possible, these measures should be made the object of research, designed to evaluate their safety and efficacy. In all cases, new information should be recorded and, where appropriate, published. The other relevant guidelines of this Declaration should be followed.

21.2 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

Grade					
Toxicity	**0**	**1**	**2**	**3**	**4**
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
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

Grade					
Toxicity	**0**	**1**	**2**	**3**	**4**
BLOOD/BONE MARROW (Cont'd)					
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 process	WNL	10 - <25% decrease from baseline	25 - <50% decrease from baseline	50 - <75% decrease from baseline	75% decrease from baseline
Transfusion: Platelets Also consider 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)
Transfusion: pRBCs Also consider Hemoglobin.	none	-	-	yes	-
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	-	-	-
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	-

Grade					
Toxicity	**0**	**1**	**2**	**3**	**4**
CARDIOVASCULAR (ARRHYTHMIA) (cont'd)					
Supraventricular arrhythmias (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 ventilatory support
Cardiac- ischemia/ 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	$\geq$ 0.03 - < 0.05 ng/ml	$\geq$ 0.05 - < 0.1 ng/ml	$\geq$ 0.1 - < 0.2 ng/ml	$\geq$ 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 generalised 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

Grade					
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 hospitilisation; 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	-

Grade					
Toxicity	**0**	**1**	**2**	**3**	**4**
COAGULATION (cont'd)					
Thrombosis/embolism is graded in the CARDIOVASCULAR (GENERAL) category.					
Thrombotic microangiopathy (e.g., thrombotic thrombocytopenic purpura/TTP or hemolytic uremic 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
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

Grade					
Toxicity	**0**	**1**	**2**	**3**	**4**
DERMATOLOGY/SKIN					
Alopecia	normal	mild hair loss	pronounced hair loss	-	-
Bruising (in absence of grade 3 or 4 thrombocytopenia)	none	localised or in dependent area	generalised	-	-
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 generalised eruption	severe or requiring IV fluids (e.g., generalised 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	-
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	localised pigmentation changes	generalised pigmentation changes	-	-
Pruritus	none	mild or localised, relieved spontaneously or by local measures	intense or widespread, relieved spontaneously or by systemic measures	intense or widespread and poorly controlled despite treatment	-

Grade					
Toxicity	**0**	**1**	**2**	**3**	**4**
DERMATOLOGY/SKIN (cont'd)					
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 localised desquamation or other lesions covering <50% of body surface area	symptomatic generalised erythroderma or macular, papular or vesicular eruption or desquamation covering 50% of body surface area	generalised 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					
Feminization of male	absent	-	-	present	-
Gynecomastia	none	mild	pronounced or painful	pronounced or painful and requiring surgery	-

Grade					
Toxicity	**0**	**1**	**2**	**3**	**4**
ENDOCRINE (cont'd)					
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 hospitalised 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

Grade					
Toxicity	**0**	**1**	**2**	**3**	**4**
GASTROINTESTINAL (cont'd)					
-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 hospitilisation	perforation or bleeding, requiring emergency surgery
Dyspepsia / heartburn	none	mild	moderate	severe	-
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 hospitilisation 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.					

Grade					
Toxicity	**0**	**1**	**2**	**3**	**4**
GASTROINTESTINAL (cont'd)					
Gastritis	none	-	requiring medical management or non-surgical treatment	uncontrolled by out-patient medical management; requiring hospitilisation 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 pseudomem-branous 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.					
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	-	-

Grade					
Toxicity	**0**	**1**	**2**	**3**	**4**
GASTROINTESTINAL (cont'd)					
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.					

Grade					
Toxicity	**0**	**1**	**2**	**3**	**4**
HEMORRHAGE					
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	generalised 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.					

Grade					
Toxicity	**0**	**1**	**2**	**3**	**4**
HEPATIC (cont'd)					
	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	-
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, localised infection, requiring local or oral treatment	severe, systemic infection, requiring IV antibiotic or antifungal treatment or hospitilisation	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, localised infection, requiring local or oral treatment	severe, systemic infection, requiring IV antibiotic or antifungal treatment, or hospitilisation	life-threatening sepsis (e.g., septic shock)
Wound-infectious is graded under DERMATOLOGY/SKIN.					

Grade					
Toxicity	**0**	**1**	**2**	**3**	**4**
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
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

Grade					
Toxicity	**0**	**1**	**2**	**3**	**4**
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) Also consider CPK. Myositis implies muscle damage (i.e., elevated CPK).	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
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 Also consider Headache, Vomiting and Fever.	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
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
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

Grade					
Toxicity	**0**	**1**	**2**	**3**	**4**
NEUROLOGY (cont'd)					
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 hospitilisation
Cranial neuropathy is graded in the NEUROLOGY category as Neuropathy-cranial.					
Delusions	normal	-	-	present	toxic psychosis
Depressed level of consciousness Syncope (fainting) is graded under NEUROLOGY.	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
Dizziness/lightheadedness	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 This toxicity is graded when insomnia is related to treatment. If pain or other symptoms interfere with sleep do NOT grade as 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	-
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

Grade					
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 hospitilisation
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	-

Grade					
Toxicity	**0**	**1**	**2**	**3**	**4**
NEUROLOGY (cont'd)					
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	-
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	-

Grade					
Toxicity	**0**	**1**	**2**	**3**	**4**
OCULAR/VISUAL					
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) Arthritis (joint pain with clinical signs of inflammation) is graded under MUSCULOSKELETAL .	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
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

Grade					
Toxicity	**0**	**1**	**2**	**3**	**4**
PAIN					
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.					
Pain- Other (Specify)	none	mild	moderate	severe	disabling

Grade					
Toxicity	**0**	**1**	**2**	**3**	**4**
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)	-
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.					

Grade					
Toxicity	**0**	**1**	**2**	**3**	**4**
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	-	-	-
RENAL/GENITOURINARY					
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.					
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.					

Grade					
Toxicity	**0**	**1**	**2**	**3**	**4**
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.					
SYNDROMES (not included in previous categories)					
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 characterised 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

21.3 Appendix 3 - ECOG Performance Status Scale

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

US Eastern Cooperative Oncology Group

21.4 Appendix 4 – Schedule of assessments

	Screening	**Assessment Schedule**													
Visit Number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**
Months on treatment	**0**	**1**	**2**	**3**	**6**	**9**	**12**	**18**	**24**	**30**	**36**	**42**	**48**	**54**	**60**
Screening assessments*	x														
Sokal & Hasford Score	x														
Physical examination	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Extramedullary Involvement	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Performance status	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Quality of Life Questionnaire	x	x	x	x	x		x		x		x		x		x
Bone marrow assessment	x						x		x		x		x		x
RT-PCR for BCR-ABL	x			x	x	x	x	x	x	x	x	x	x	x	x
Haematology	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Biochemistry	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
AEs/SAEs		Continuous throughout study													
Study medication log		Continuous throughout study													
Concomitant medications		Continuous throughout study													
Survival information		Continuous throughout study													
*Screening Assessments are listed in section 10.1															