



## STI571 Prospective International Randomised Trial 2

A phase III, prospective randomised comparison of imatinib (STI571, Glivec or licensed generic) 400mg daily versus dasatinib 100mg in patients with newly-diagnosed chronic phase chronic myeloid leukaemia.

|                   |                                    |
|-------------------|------------------------------------|
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[www.spirit-cml.org](http://www.spirit-cml.org)

## Investigator Signature Page

SPIRIT2 - STI571 Prospective International Randomised Trial 2 - A phase III, prospective randomised comparison of imatinib (STI571, Glivec or licensed generic) 400mg daily versus dasatinib 100mg in patients with newly-diagnosed chronic phase chronic myeloid leukaemia.

Protocol version 2.1 : 12 December 2016

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.

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Principal Investigator Name (print clearly)

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Principal Investigator Signature

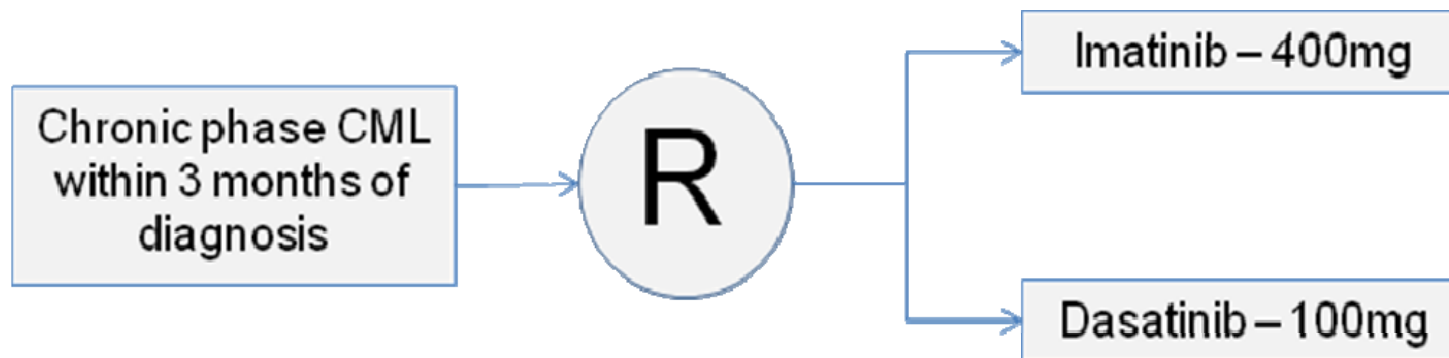
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# SPIRIT2

STI571 Prospective International Randomised Trial



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The SPIRIT team would like to acknowledge Professor John Goldman (30 November 1938 - 24 December 2013) for his significant contribution and support of the SPIRIT CML studies.

**Sponsor**

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**Funder**

Bristol Myers Squibb (BMS)

## Contents

|          |  |           |
|----------|--|-----------|
| <b>1</b> | <b>SPIRIT2: QUICK REFERENCE TO ESSENTIAL INFORMATION</b> | <b>9</b>  |
| 1.1      | What is SPIRIT2?   | 9         |
| 1.2      | Protocol v 2.1 – Summary of Major Changes from v2.0      | 10        |
| 1.3      | Eligibility check list                                   | 11        |
| 1.4      | How to randomise a patient                               | 11        |
| 1.5      | Who to contact for help                                  | 11        |
| <b>2</b> | <b>INTRODUCTION</b>                                      | <b>12</b> |
| 2.1      | Background and rationale for the study                   | 12        |
| 2.2      | Summary of study design                                  | 13        |
| <b>3</b> | <b>ENDPOINTS</b>   | <b>14</b> |
| 3.1      | Primary endpoint   | 14        |
| 3.2      | Secondary endpoints                                      | 14        |
| <b>4</b> | <b>STUDY POPULATION</b>                                  | <b>14</b> |
| <b>5</b> | <b>INCLUSION AND EXCLUSION CRITERIA</b>                  | <b>15</b> |
| 5.1      | Inclusion criteria                                       | 15        |
| 5.2      | Exclusion Criteria                                       | 15        |
| <b>6</b> | <b>SITE SET-UP AND PATIENT RANDOMISATION</b>             | <b>16</b> |
| 6.1      | Site requirements for study participation                | 16        |
| 6.2      | Randomising a new patient                                | 16        |
| <b>7</b> | <b>TREATMENT ARMS</b>                                    | <b>18</b> |
| 7.1      | Arm A: Imatinib 400 mg daily                             | 19        |
| 7.1.1    | Dose modification for imatinib at 400 mg/day             | 20        |
| 7.1.2    | Dose modification for dasatinib at 100 mg/day            | 22        |
| 7.1.3    | Patients with Shortness of Breath                        | 23        |
| <b>8</b> | <b>STUDY MEDICATIONS: PRACTICALITIES</b>                 | <b>25</b> |

|           |   |           |
|-----------|---|-----------|
| 8.1       | Arm A – 400mg daily Imatinib .....  | 25        |
| 8.2       | Arm B – 100mg daily dasatinib (Sprycel) (CA180-216).....                    | 25        |
| 8.3       | Disposal of unused study medication .....                                   | 26        |
| <b>9</b>  | <b>CONCOMITANT MEDICATIONS.....</b>   | <b>27</b> |
| 9.1       | How do I control the blood count whilst study medication is suspended?..... | 27        |
| <b>10</b> | <b>VISIT SCHEDULES AND ASSESSMENTS .....</b>                                | <b>28</b> |
| 10.1      | Screening assessments (Visit 1).....  | 28        |
| 10.2      | Assessments for visits 2 - 15 .....   | 29        |
| 10.3      | Study Drug Permanent Discontinuation.....                                   | 31        |
| 10.4      | Annual Review (for Patients Who Have Discontinued Study Drug).....          | 32        |
| 10.5      | End of Study.....   | 32        |
| <b>11</b> | <b>ASSESSMENT OF SAFETY .....</b>   | <b>33</b> |
| 11.1      | Adverse Events (AEs) .....  | 33        |
| 11.2      | Shortness of breath .....   | 34        |
| 11.3      | Serious Adverse Events (SAEs) .....   | 34        |
| <b>12</b> | <b>ASSESSMENTS OF EFFICACY .....</b>  | <b>36</b> |
| 12.1      | Event free survival.....  | 36        |
| 12.2      | Complete haematological response (CHR) .....                                | 36        |
| 12.3      | Cytogenetic response .....  | 37        |
| 12.4      | Molecular response .....  | 37        |
| 12.5      | Definition of disease progression .....                                     | 38        |
| 12.6      | Definition of treatment failure .....                                       | 38        |
| <b>13</b> | <b>QUALITY OF LIFE ANALYSIS .....</b>                                       | <b>39</b> |
| <b>14</b> | <b>HEALTH ECONOMICS EVALUATION.....</b>                                     | <b>40</b> |
| <b>15</b> | <b>ETHICS.....</b>  | <b>40</b> |
| <b>16</b> | <b>STATISTICAL CONSIDERATIONS AND DATA ANALYSIS .....</b>                   | <b>40</b> |

|             |  |           |
|-------------|--|-----------|
| <b>16.1</b> | <b>Sample size and power calculations .....</b>                            | <b>40</b> |
| 16.1.1      | Sample Size Calculation for Event Free Survival at 5 years .....           | 40        |
| 16.1.2      | Sample Size Calculation for Complete Cytogenetic Response at 2 years ..... | 41        |
| 16.1.3      | Sample Size Calculation for Treatment Failure Rates at 5 years.....        | 42        |
| <b>16.2</b> | <b>Recruitment.....</b>  | <b>42</b> |
| <b>16.3</b> | <b>Statistical Analysis .....</b>  | <b>43</b> |
| 16.3.1      | Primary Endpoint .....   | 43        |
| 16.3.2      | Secondary Endpoints.....   | 43        |
| 16.3.3      | Safety.....  | 44        |
| <b>17</b>   | <b>PRESENTATION AND PUBLICATION OF RESULTS .....</b>                       | <b>44</b> |
| 17.1        | Presentation of results .....  | 44        |
| 17.2        | Publication of results .....   | 44        |
| <b>18</b>   | <b>DATA HANDLING AND RECORD KEEPING.....</b>                               | <b>44</b> |
| <b>19</b>   | <b>DIRECT ACCESS TO SOURCE DATA/DOCUMENTS .....</b>                        | <b>45</b> |
| <b>20</b>   | <b>CML BIOBANK .....</b>   | <b>45</b> |
| <b>21</b>   | <b>CML REGISTRY.....</b>   | <b>45</b> |
| <b>22</b>   | <b>APPENDICES .....</b>  | <b>47</b> |
| 22.1        | Appendix 1 -Declaration of Helsinki .....                                  | 47        |
| 22.2        | Appendix 2 - NCI/NIH Common Toxicity Criteria (v2 30 April 1999).....      | 50        |
| 22.3        | Appendix 3 - ECOG Performance Status Scale .....                           | 74        |
| 22.4        | Appendix 4 – Schedule of assessments .....                                 | 75        |



## 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 Squibb 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 Protocol v 2.1 – Summary of Major Changes from v2.0**

|   | <b>Change</b>   | <b>Section(s)</b> |
|---|---|-------------------|
| 1 | Information regarding the use of generic imatinib   | 8.1               |
| 2 | Removal of the requirement for bone marrow aspirate samples   | 10.2              |
| 3 | The paragraph relating to planned hospital stays and SAEs, which was added in error as part of the previous amendment, has been removed | 11.3              |
| 4 | Correction of typographical errors and inconsistencies  | Various sections  |

### **1.3 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.

### **1.4 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](http://www.spirit-cml.org)). Once a site has gained local Trust Research and Development approval it is activated on the SPIRIT2 webservice 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 must be faxed to the trial office (+44 (0)191 376 0748) within 24 hours of randomisation. 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.

### **1.5 Who to contact for help**

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

|                            |                            |
|----------------------------|----------------------------|
| <b>Trial Office</b>        | <b>+44 (0)191 282 4157</b> |
| <b>+44 (0)191 282 0904</b> |                            |
| Professor Stephen O'Brien  | +44 (0)191 282 0904        |
| 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 progression free survival by Kaplan Myer analysis<sup>1</sup>. 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<sup>2</sup> 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<sup>3</sup>. 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<sup>4</sup>. 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 revised 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 now 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.

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<sup>1</sup> Druker *et al.* N Engl J Med 355:2408, December 7, 2006

<sup>2</sup> American Society for Haematology 2007, Atlanta, abstract 735

<sup>3</sup> American Society for Haematology 2007, Atlanta, abstract 30

<sup>4</sup> 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.

There have been a small number of reports of Pulmonary Arterial Hypertension (PAH) in patients taking dasatinib. A small number of case reports have emerged of patients from previous dasatinib trials presenting with mild breathlessness, approximately 0.4%. These patients have not experienced pleural effusions, but are found to have PAH on right heart catheterisation. As PAH usually presents as mild shortness of breath the evaluation processed outlined in section 0 should be followed for any patient presenting with shortness of breath.

## **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  $\geq 18$  years of age.
2. Patients must have all 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) be diagnosed with chronic phase CML confirmed by blood morphology and RT\_PRC for BCR-ABL (FISH and bone marrow cytogenetics are also acceptable for confirmation of CML are not a requirement).
    - iii)
      - (a)  $< 15\%$  blasts in peripheral blood bone marrow;
      - (b)  $< 30\%$  blasts plus promyelocytes in peripheral blood and bone marrow;
      - (c)  $< 20\%$  basophils in peripheral blood,
      - (d)  $\geq 100 \times 10^9/L$  platelets
  - iv) no evidence of extramedullary leukaemic involvement, with the exception of hepatosplenomegaly.
3. Written voluntary informed consent.

### 5.2 Exclusion Criteria

1. 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.**
2. 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.)
3. Patient who have had any form of prior haemopoietic stem cell transplant, either autograft or allograft.
4. Patients with an ECOG Performance Status Score  $\geq 3$ .
5. Patients with serum bilirubin, SGOT/AST, SGPT/ALT, or creatinine concentrations  $> 2.0 \times$  the institutional upper limit of the normal range (IULN).
6. Patients with International normalised ratio (INR) or partial thromboplastin time (PTT)  $> 1.5 \times$  IULN, with the exception of patients on treatment with oral anticoagulants.
7. 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.

8. Patients with known positivity for human immunodeficiency virus (HIV); baseline testing for HIV is not required.
9. Patients who have undergone major surgery within 4 weeks of Study Day 1, or who have not recovered from prior major surgery.
10. 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).
11. 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*.
12. 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

The standard dose is 400mg in the imatinib arm and 100mg in the dasatinib arm. Wherever possible, patients should take the 'standard' dose. There are occasions of course where patients cannot tolerate the standard dose, usually due to toxicity, and in these circumstances the following dose reduction and re-escalation schedules should be used.

If a patient cannot tolerate the standard dose, every effort should be made to give them as much study drug as possible with repeated attempts at dose escalation. This is to ensure that the patient derives the greatest benefit from the drug.

**Example.** A patient starts imatinib 400mg and within 5 days has developed a widespread (grade 3) rash. Study drug (imatinib in this case) should be stopped until the rash has subsided. If necessary the WBC and/or platelet count can be controlled by hydroxycarbamide although this is rarely necessary. Once the rash has settled (to grade 1 or 0), start imatinib 200mg for 2 weeks. If the rash does not recur, increase to 300 mg for 2 weeks, then up to 400mg. Using this strategy it is uncommon for the rash to recur and the patient can be established on the full standard dose. The same approach is often successful with cytopenias and other toxicities.

Patients will be allowed to continue allocated study drug on whatever dose they can sustain as long as there is adequate disease control. The aim is to achieve low enough dose of TKI to minimise toxicity while maintaining acceptable PCR. An acceptable PCR is defined as less or equal to 1% and preferably less or equal to 0.1%. The CI or a member of Senior Management Group are always happy to discuss individual cases. Please contact SPIRIT team by email [tnu-tr.spirittrials@nhs.net](mailto:tnu-tr.spirittrials@nhs.net) who will facilitate contact with SPIRIT CI or medic.

**Every attempt should be made to dose re-escalate to the standard dose: imatinib 400mg daily; dasatinib 100mg daily.**

### **7.1 Arm A: Imatinib 400 mg daily**

Patients randomised to this arm will receive once daily oral administration of imatinib at a dose of 400 mg. Patients usually 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 dose modification guidelines on the following page **MUST** be followed for patients with:

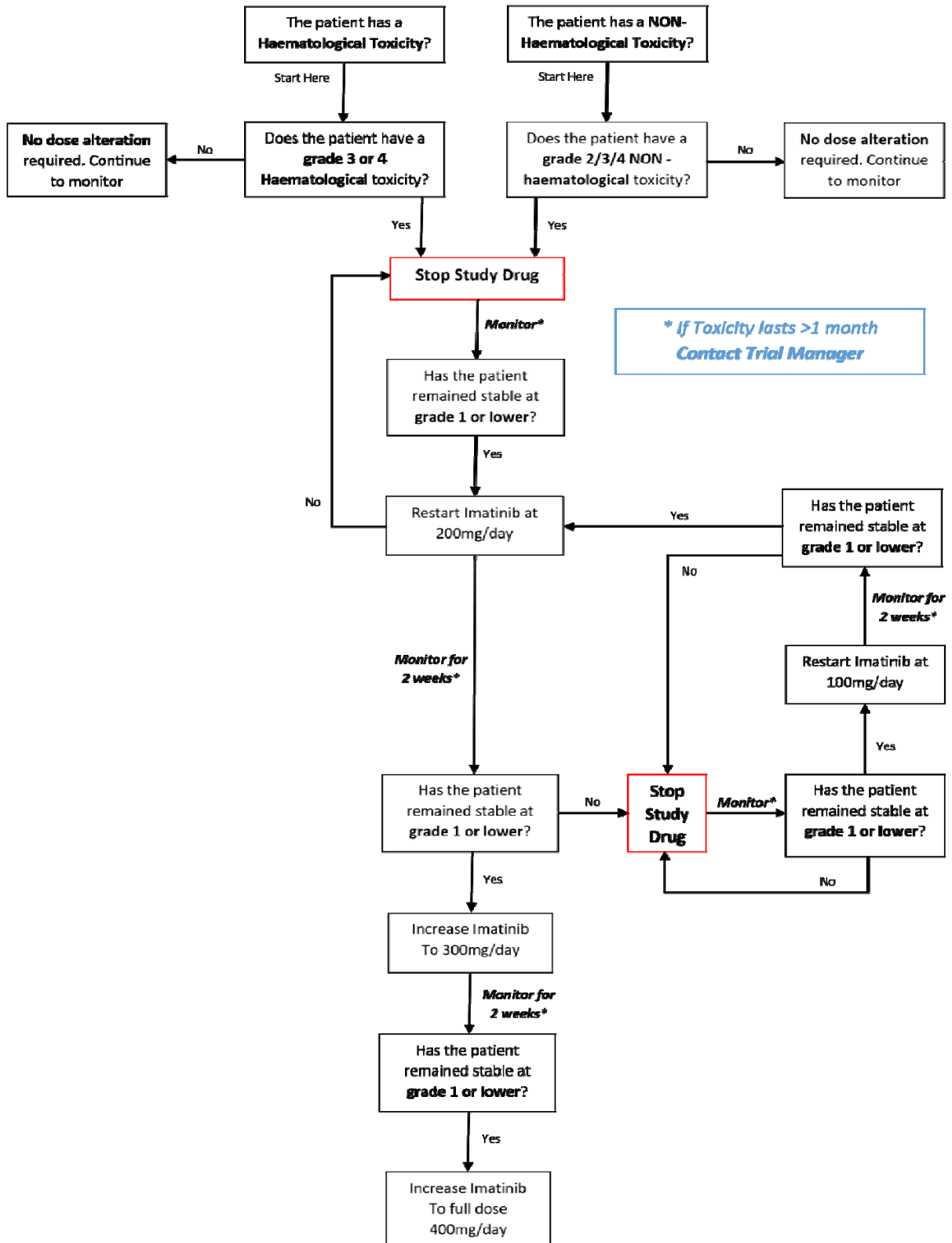
- haematological abnormalities (platelets, neutrophils, WBC)
- abnormal liver function tests (AST/ALT)
- toxicities where the study drug is the suspected cause

The aim is to achieve low enough dose of TKI to minimise toxicity while maintaining acceptable PCR. An acceptable PCR is defined as less or equal to 1% and preferably less or equal to 0.1%. The CI or a member of Senior Management Group are always happy to discuss individual cases. Please contact SPIRIT team by email [tnu-tr.spirittrials@nhs.net](mailto:tnu-tr.spirittrials@nhs.net) who will facilitate contact with SPIRIT CI or medic.

If dose reductions are made, every effort should be made to re-escalate to the standard dose (imatinib 400mg).

In certain circumstances it may not be appropriate to modify dose according to the guidelines. If there are clinical reasons for not following the dose modification guidelines please call the trial office to discuss before proceeding. Dose modification for imatinib 400 mg/day

### 7.1.1 Dose modification for imatinib at 400 mg/day



Arm B: Dasatinib 100mg daily

Patients randomised to arm B will receive once daily oral administration of dasatinib at a dose of 100 mg. Patients usually 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. Patients should avoid grapefruit juice while taking dasatinib as this may alter dasatinib levels (CYP3A4 substrate).

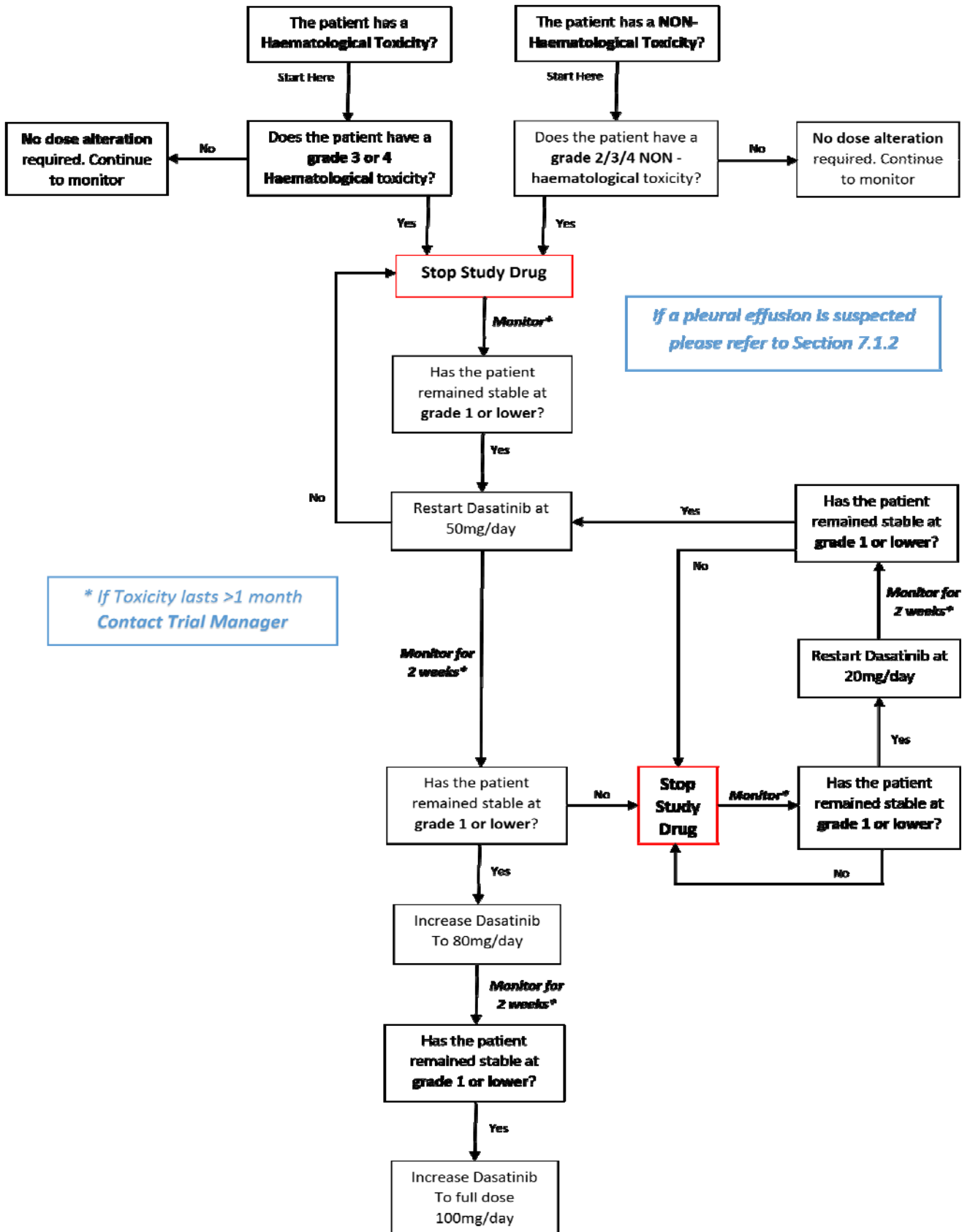
The dose modification guidelines on the following page **MUST** be followed for patients with:

- haematological abnormalities (platelets, neutrophils, WBC)
- abnormal liver function tests (AST/ALT)
- pleural effusion (diuretics, steroids and chest drains are not usually required to treat pleural effusions)
- toxicities where the study drug is the suspected cause

**The aim is to optimise PCR response whilst minimising side effects.** An acceptable PCR is defined as less or equal to 1% and preferably less or equal to 0.1%. The CI or a member of Trial Management Group are always happy to discuss individual cases. Please contact SPIRIT team by email [tun-tr.spirittrials@nhs.net](mailto:tun-tr.spirittrials@nhs.net) who will facilitate contact with SPIRIT CI or medic.

In certain circumstances it may not be appropriate to modify dose according to the guidelines. If there are clinical reasons for not following the dose modification guidelines please call the trial office to discuss before proceeding.

7.1.2 Dose modification for dasatinib at 100 mg/day

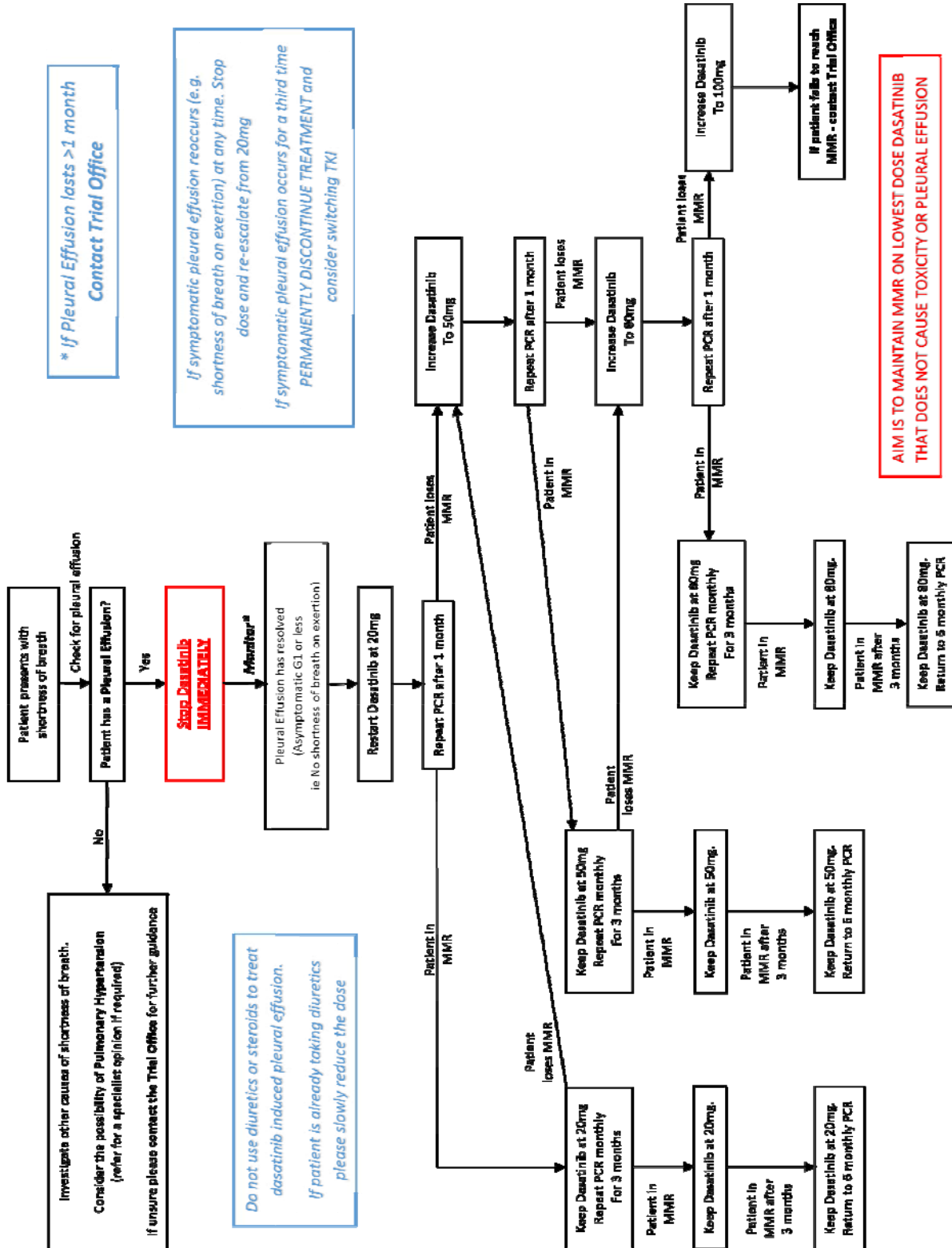


### 7.1.3 Patients with Shortness of Breath

It has been noted that dasatinib can cause Pulmonary Arterial Hypertension (PAH), pleural effusions and shortness of breath. The following steps should be followed for all dasatinib patients.

All findings should be reported according to the eCRF completion guidelines and the directions on the following page.

Dose modification for pleural effusions (Dasatinib only)





## **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**

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.

From January 2017, imatinib will be generic, meaning other supplies of imatinib other than Glivec will be available to NHS Trusts. We advise SPIRIT 2 patients randomised to Imatinib are prescribed the generic imatinib selected for use within their local NHS Trust. Ideally, the same generic imatinib will be used for the remainder of the study.

Imatinib should be stored at room temperature not to exceed 30°C.

Imatinib tablets should be taken by mouth with a drink of water and some food, to minimise gastric irritation. 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 and dasatinib, should be used with caution.

### **8.2 Arm B – 100mg daily dasatinib (Sprycel) (CA180-216)**

The dasatinib for Arm B WILL BE PROVIDED FREE OF CHARGE by BMS for 5 years for each patient 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 labels in English or multi-lingual 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.

Dasatinib may also be referred to as Sprycel and/or CA180-216 in the documentation supplied by the trial.

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

Storage temperature excursions should be documented and notified to the Trial Office according to the SPIRIT 2 Information for Pharmacists document.

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

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 and dasatinib, should be used with caution.”

### **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/dasatinib therapy. If the patient's count is such as to require these medications after the first month of imatinib/dasatinib 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. The use of GCSF is permitted and should also be recorded as a concomitant medication.

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. 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/dasatinib, should be used with caution. For further information on TKI interactions this link provides an extract from the paper by Haouala et al<sup>5</sup> [http://www.gist.ch/userfiles/TKI\\_drug\\_interactions\\_Table.pdf](http://www.gist.ch/userfiles/TKI_drug_interactions_Table.pdf)

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.

There has been some concern about prolongation of the QT interval on the ECG of patients taking Tyrosine Kinase Inhibitors. Caution should therefore be exercised in prescribing drugs which are known to prolong the QT interval and if such drugs are necessary for the patient's wellbeing more frequent ECG monitoring might be advisable.

### **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

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<sup>5</sup> Haouala A, Widmer N, Duchosal MA, Montemurro M, Buclin T, Decosterd LA. Drug interactions with the tyrosine kinase inhibitors imatinib, dasatinib, and nilotinib. *Blood* 2010.

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 0191 376 0748) 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/<br>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<br>Trepine)                         | Morphology <b>Percentage</b> of blasts, Percentage of promyelocytes (aspirate), cellularity (trepine)<br>G-Banding and/or FISH analysis should be conducted. (see section)<br>G-Banding - number of metaphases examined, number metaphases positive for Philadelphia chromosome, chromosomal abnormalities other than Ph chromosome;<br>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), alanine transaminase (ALT) / serum glutamate pyruvate transaminase (SGPT), alkaline phosphatase, creatinine, urea.   |
| Quantitative PCR (Q-PCR)<br>for BCR-ABL (see section<br>0)    | Peripheral blood sample collected for BCR-ABL transcript levels.   |
| Concomitant Medications/<br>Significant Non-Drug<br>Therapies | Record all concomitant medications and/or 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<br>Questionnaire                              | To be completed by the patient. (sub-set of patients only)   |

## 10.2 Assessments for visits 2 - 15

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 annually thereafter.

The schedule of assessments by visit is detailed in appendix 4 (section 22.4).

| Assessment   | Includes   |
|--|--|
| Physical examination   | General examination – If clinically indicated Assessment of extramedullary disease including liver, lymph nodes, spleen.   |
| Performance status   | According to ECOG criteria (see Appendix 3)  |
| Haematology  | Haemoglobin, white blood cell (WBC) count and differential to include percentage of blasts, lymphocytes, neutrophils, basophils, and eosinophils, platelet count.  |
| Biochemistry   | Total bilirubin, / alkaline phosphatase, creatinine, urea.<br>aspartate aminotransferase (AST) / serum glutamic-oxaloacetic transaminase (SGOT) <b>AND/OR</b> alanine transaminase (ALT) / serum glutamate pyruvate transaminase (SGPT),<br>lactate dehydrogenase (LDH) (Optional) |
| Quantitative PCR (Q-PCR) for BCR-ABL (see section 0)<br>(all visits except visits 2 and 3) | Blood sample collected for analysis of BCR-ABL transcript levels by central lab.   |
| Concomitant Medications/<br>Significant Non-Drug<br>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<br>Questionnaire<br>(all visits except visit 6)                            | To be completed by the patient.  |

**See SPIRIT 2 eCRF Completion Guidelines document for further information. (<http://www.spirit-cml.org/>)**

### 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.

### **QPCR samples for SPIRIT 2 study assessments are analysed by a central laboratory (MRD Group, Hammersmith Hospital), free of charge.**

#### Instructions for handling QPCR samples

- Pre-addressed, postage-paid shipping containers, shipping forms and EDTA sample tubes are provided by the Trial Office for QPCR samples.
  - To prevent sample degradation, samples for PCR analysis should be posted in time to allow them to arrive at the analysing laboratory before the weekend.
  - Please inform the Trial Office on which day(s) of the week your site will post samples as express shipping containers are available for those needing to post on a Thursday.
  - Samples are sent via first class post Mon-Wed and via special delivery on Thursdays – PLEASE ENSURE YOU HAVE THE CORRECT SAMPLE SHIPPING BOX.
  - Further details can be found in the September 2012 Newsletter on the Documents & Downloads section of the SPIRIT 2 website [www.spirit-cml.org](http://www.spirit-cml.org)
  - Please do NOT post samples on a Friday.
- 
- Each analysis requires 18ml 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
  - Please contact the Trial Office if you require additional sample shipping supplies.

#### 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:

**Dr L Foroni**  
**Imperial Molecular Pathology Labs**  
**2<sup>nd</sup> Floor G Block**  
**Hammersmith Hospital,**  
**Du Cane Road,**  
**London W12 0HS**

See also CML Biobank section 20

### **10.3 Study Drug Permanent Discontinuation**

Please contact the Chief Investigator (Prof. Steve O'Brien – 0191 282 0904) to discuss before permanently discontinuing study drug.

Patients who permanently discontinue study drug will be followed up annually for the remainder of the study.

The following information is collected within the eCRF for patients permanently discontinuing study drug.

#### Study Drug:

- Study Drug (dasatinib/imitinib)
- Date of change (stop date)
- Dose (0mg)
- Reason study drug was stopped (Permanently Discontinued)
- Whether patient will continue with Annual Follow-up visits.

#### Patient Outcome

- Reason for permanent discontinuation of study treatment.
- Reason for treatment failure if applicable:
  - Death: non-CML related
  - Death: CML-related
  - Disease progression - blast crisis
  - Disease progression - accelerated phase
  - Loss of CHR (complete haematological response)
  - Loss of MCR (major cytogenetic response)
  - Intolerance - AE
  - Intolerance - Laboratory toxicity
  - Failure to achieve CHR after 6 months treatment
  - Failure to achieve MCR after 12 months treatment
  - Failure to achieve CCR after 24 months treatment
- Date of treatment failure or death

If more than one treatment failure option applies the highest option on the list is used. (eg. For a patient who has lost a MCR and gone into Blast Crisis - Choose 'Blast Crisis')

Adverse Events and Concurrent Medications should be updated.

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.

**See SPIRIT 2 eCRF Completion Guidelines document for further information. (<http://www.spirit-cml.org/>)**

**See appendix 4 for visit schedule**

#### ***10.4 Annual Review (for Patients Who Have Discontinued Study Drug)***

An Annual Review of each patient after permanent study drug discontinuation will be conducted.

The patient's survival, disease status, CML therapy and additional malignancies acquired are recorded.

QPCR samples should continue to be sent for analysis at the central laboratory following the study schedule for patients who are in follow-up but have discontinued study treatment.

**See SPIRIT 2 eCRF Completion Guidelines document for further information. (<http://www.spirit-cml.org/>)**

#### ***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 and 30 days after last dose, 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 this case the clinical signs and symptoms (or diagnosis) must be recorded on the adverse events section of the electronic CRF with the appropriate diagnostic description.**

**See SPIRIT 2 eCRF Completion Guidelines document for further information. (<http://www.spirit-cml.org/>)**

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 (refer to definitions below)
5. relationship to the study drug (s) (suspected/not suspected)
6. action(s) taken

#### Adverse Event Intensity Definitions

Mild: Transient or mild discomfort (<48 hours); no medical intervention/therapy required

Moderate: Mild to moderate limitation in activity - some assistance may be needed; no or minimal medical intervention/therapy required

Severe: Marked limitation in activity, some assistance usually required; medical intervention/therapy required, hospitalization possible

### **11.2 Shortness of breath**

There have been a small number of reports of Pulmonary Arterial Hypertension (PAH) in patients taking dasatinib. As PAH usually presents as mild shortness of breath the evaluation processes outlined in section 7.3 should be followed for any patient presenting with shortness of breath.

### **11.3 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. a congenital anomaly
5. any malignancy (other than CML)
6. CML disease progression (to accelerated phase or blast crisis)
7. any other significant medical event, that, based upon appropriate medical judgment, may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed above (including progression to accelerated phase or blast crisis of CML).

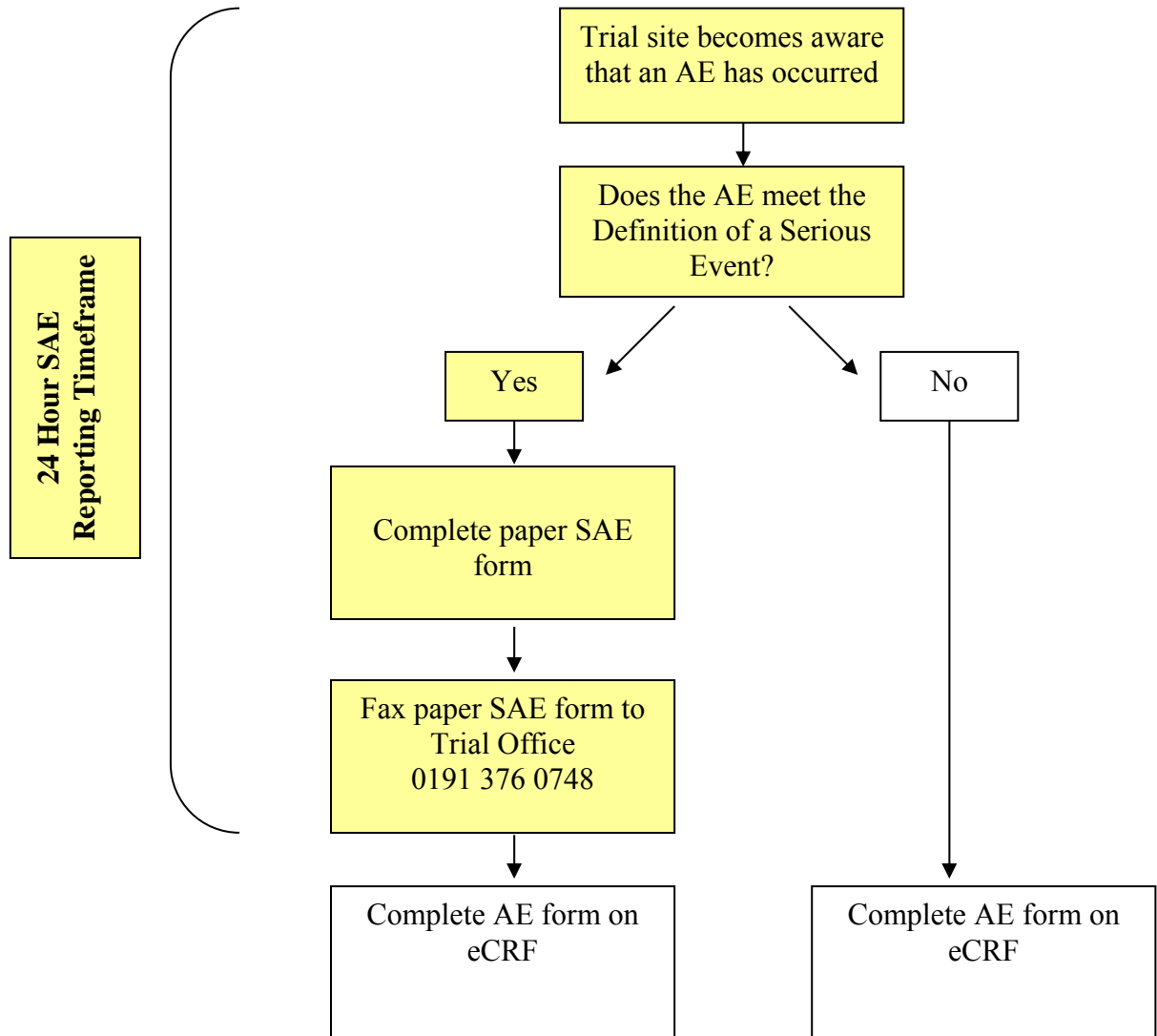
Hospitalisation is defined as an overnight stay. Prolongation of an existing hospitalisation also qualifies as a SAE.

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 of becoming aware of the event**, 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 and suspected relationship to study drug. 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 or designee, and sent by fax to the trial coordinator. Initial SAE reports can be faxed to the Trial Office without PI signature to avoid reporting delays. All follow-up information about a reported serious adverse event must also be forwarded to the SPIRIT 2 trial office.

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 of the SPC for Imatinib (Glivec™) Tablets and dasatinib (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.

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  $\geq 1$  month later:
  - WBC count that rises to  $> 20.0 \times 10^9/L$
  - Platelet count that rises to  $\geq 600 \times 10^9/L$
  - Progressive splenomegaly to a size  $\geq 5$  cm below the left costal margin
  - Appearance of  $\geq 5\%$  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  $> 20.0 \times 10^9/L$ .
- 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  $\geq 1$  month later.

### 12.2 Complete haematological response (CHR)

All of the following must be present for  $\geq 4$  weeks:

- Normal peripheral blood counts, i.e. WBC count  $< 11.0 \times 10^9/L$  and platelet count  $< 450 \times 10^9/L$ .
- 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 analysis on bone marrow samples will be collected. If FISH results are also available both results will be collected.**

#### **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.  $\leq 35\%$  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.  $\leq 35\%$  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%<sup>6</sup>. 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%.

QPCR analysis of BCR-ABL transcripts is being conducted by a central laboratory for this study (see section 0).

### **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<sup>7</sup>.

- '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

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<sup>6</sup> Hughes TP, Kaeda J, Branford S, Rudzki Z, Hochhaus A, Hensley ML, Gathmann I, Bolton AE, van Hoomissen IC, Goldman JM, Radich JP. Frequency of major molecular responses to imatinib or interferon alfa plus cytarabine in newly diagnosed chronic myeloid leukemia. *N Engl J Med.* 2003;349:1423-1432

<sup>7</sup> Baccarani *et al.* *Blood* 2006; 108: 1809-20

### 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<sup>8</sup>. 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<sup>9</sup> is the preference-based measure of choice in this trial; it has been 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 and SPIRIT(1) 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 event-free 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, and 12 months post-entry to the trial, and at 6 monthly intervals thereafter; these time-points coincide with clinical follow-up and reflect the anticipated trajectory of response to therapy. Questionnaires will normally be administered during study clinic visits.

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<sup>8</sup> Gotay CC, Korn EL, McCabe MS, Moore TD, Cheson BD. Quality-of-life assessment in cancer treatment protocols: research issues in protocol development. *Journal of the National Cancer Institute*. 1992;84:575-579

<sup>9</sup> Brooks R. EuroQol: the current state of play. *Health Policy*. 1996;37:53-72

## 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%<sup>10</sup>. 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

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<sup>10</sup> Druker *et al.* N Engl J Med 355:2408, December 7, 2006



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, $\alpha$          | 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, $\lambda_1$ | 0.0373 |
| Group 2 exponential parameter, $\lambda_2$ | 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 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<sup>11</sup>, 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  $\chi^2$  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.

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<sup>11</sup> Druker *et al.* N Engl J Med 355:2408, December 7, 2006

**Two group continuity corrected  $\chi^2$  test of equal proportions  
(odds ratio = 1) (equal n's)**

|  |                        |
|--|------------------------|
|  | <b>Exact<br/>n=257</b> |
| Test significance level, $\alpha$                            | 0.050                  |
| 1 or 2 sided test?   | 2                      |
| Group 1 proportion, $\pi_1$                                  | 0.790                  |
| Group 2 proportion, $\pi_2$                                  | 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)<sup>12</sup> 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**

|  |        |
|--|--------|
| Test significance level, $\alpha$          | 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, $\lambda_1$ | 0.0831 |
| Group 2 exponential parameter, $\lambda_2$ | 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**


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<sup>12</sup> American Society for Haematology 2007, Atlanta, abstract 25

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 superiority 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.

#### **16.3.2 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.

### 16.3.3 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](http://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, cannot 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 as listed on the Source Data Agreement and study documentation at site. Where electronic patient records are kept at site, the site must facilitate the monitor's access to these or to validated print-outs.

## 20 CML Biobank

Patients who are eligible for the SPIRIT 2 study are also offered the opportunity to donate peripheral blood to the CML Biobanks held at the Hammersmith Hospital and Glasgow Royal Infirmary. It is not an entry requirement of the SPIRIT 2 study that patients consent to the biobanking of their samples. There is a separate consent form for the Biobank.

If a patient consents to the biobank, 40mls peripheral blood is taken prior to commencement of study treatment and sent to the Glasgow Biobank (addressed, postage-paid samples boxes supplied by Trial Office).

In addition, surplus blood from samples sent for QPCR analysis by the MRD Group at the Hammersmith Hospital will be biobanked there.

The samples will be anonymised and identified by a unique study number only. Biobank samples and related clinical data will be made available to researchers subject to the appropriate regulatory and ethical approvals being in place and project approval from the NCRI CML Working Group.

## 21 CML Registry

Patients who are eligible for the SPIRIT 2 study are also offered the opportunity to join a CML Registry. It is not an entry requirement of the SPIRIT 2 study that patients consent to the CML Registry.

The full name, address, email and phone number of patients consenting to the registry are collected so that they can be contacted regarding developments in the field of CML and future research studies they may be eligible to join. The information will be stored on a secure, password protected database.

The custodians of the registry (NCRI CML Working Group) will appoint a Registry administrator who will be able to contact patients on behalf of researchers. Patient's details will not be revealed to researchers unless they give their consent.

## 22 Appendices

### 22.1 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.

**22.2 Appendix 2 - NCI/NIH Common Toxicity Criteria (v2 30 April 1999)**

| Grade   | 0            | 1  | 2  | 3   | 4  |  |
|---|--------------|--|--|---|--|--|
| <b>ALLERGY/IMMUNOLOGY</b>   |              |  |  |   |  |  |
| Allergic reaction/hypersensitivity (including drug fever)   | none         | transient rash, fever < 38°C (<100.4°F)  | drug fever 38°C  | 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  | requiring treatment  | moderate, requiring treatment   | -  | -  |
| Autoimmune reaction   | none         | serologic or evidence of autoimmune reaction but patient is asymptomatic (e.g., vitiligo), all organ function is normal and no treatment is required | other evidence of autoimmune reaction involving a non-essential organ or function (e.g., hypothyroidism), requiring treatment other than immunosuppressive drugs | of 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 organ dysfunction; progressive and irreversible reaction; long-term administration of high-dose immunosuppressive 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  | requiring medication   | symptomatic, requiring medication   | requiring steroids   | ischemic changes or requiring amputation |
| Allergy - Other Specify   | none         | mild   | moderate   | severe  | life-threatening or disabling  |  |
| <b>AUDITORY / HEARING</b>   |              |  |  |   |  |  |
| 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- (Specify)  | Other normal | mild   | moderate   | severe  | life-threatening or disabling  |  |

| Grade   |                            | 0  | 1   | 2  | 3  | 4 |
|---|----------------------------|--|---|--|--|---|
| Toxicity  |                            | 0  | 1   | 2  | 3  | 4 |
| <b>BLOOD/BONE MARROW</b>  |                            |  |   |  |  |   |
| Bone marrow cellularity   | normal for age             | 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                                    |   |
| <u>Normal ranges:</u>   |                            |  |   |  |  |   |
| children (≤ 18 years)   | 90% cellularity average    |  |   |  |  |   |
| younger adults (19-59)  | 60-70% cellularity average |  |   |  |  |   |
| older adults (≥ 60 years)   | 50% cellularity average    |  |   |  |  |   |
| Grade Bone marrow cellularity only for changes related to treatment not disease   |                            |  |   |  |  |   |
| CD4 count   | WNL                        | < LLN - 500/mm <sup>3</sup>  | 200 - < 500/mm <sup>3</sup>   | 50 - < 200/mm <sup>3</sup>   | < 50/mm <sup>3</sup>   |   |
| Haptoglobin   | normal                     | decreased  | -   | absent   | -  |   |
| Hemoglobin (Hgb)  | WNL                        | < LLN - 10.0 g/dl<br>< LLN - 100 g/L<br>< LLN - 6.2 mmol/L   | 8.0 - < 10.0 g/dl<br>80 - < 100 g/L<br>4.9 - < 6.2 mmol/L   | 6.5 - < 8.0 g/dl<br>65 - 80 g/L<br>4.0 - < 4.9 mmol/L  | < 6.5 g/dl<br>< 65 g/L<br>< 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 <sup>+</sup> ) 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 <sup>9</sup> /L<br>< LLN - 3000/mm <sup>3</sup>   | 2.0 - < 3.0 x 10 <sup>9</sup> /L<br>2000 - < 3000/mm <sup>3</sup>   | 1.0 - < 2.0 x 10 <sup>9</sup> /L<br>1000 - < 2000/mm <sup>3</sup>  | < 1.0 x 10 <sup>9</sup> /L<br>< 1000/mm <sup>3</sup>   |   |
| Lymphopenia   | WNL                        | <LLN - 1.0 x 10 <sup>9</sup> /L<br><LLN - 1000/mm <sup>3</sup>   | 0.5 - <1.0 x 10 <sup>9</sup> /L<br>500 - <1000/mm <sup>3</sup>  | <0.5 x 10 <sup>9</sup> /L<br><500/mm <sup>3</sup>  | -  |   |
| Neutrophils / granulocytes (ANC/AGC)  | WNL                        | 1.5 - <2.0 x 10 <sup>9</sup> /L<br>≥1500 - <2000/mm <sup>3</sup>   | 1.0 - <1.5 x 10 <sup>9</sup> /L<br>≥1000 - <1500/mm <sup>3</sup>  | 0.5 - <1.0 x 10 <sup>9</sup> /L<br>≥500 - <1000/mm <sup>3</sup>  | < 0.5 x 10 <sup>9</sup> /L<br>< 500/mm <sup>3</sup>  |   |
| Platelets   | WNL                        | < LLN - 75.0 x 10 <sup>9</sup> /L<br>< LLN - 75000/mm <sup>3</sup>   | 50.0 - < 75.0 x 10 <sup>9</sup> /L<br>50000 - < 75000/mm <sup>3</sup>   | 10.0 - < 50.0 x 10 <sup>9</sup> /L<br>10000 - < 50000/mm <sup>3</sup>  | < 10.0 x 10 <sup>9</sup> /L<br>< 10000/mm <sup>3</sup>   |   |

| <b>Grade</b>  |       | <b>0</b> |  | <b>1</b> |  | <b>2</b>                    |  | <b>3</b> |   | <b>4</b> |  |
|---|-------|----------|--|----------|--|-----------------------------|--|----------|---|----------|--|
| <b>Toxicity</b>   |       | <b>0</b> |  | <b>1</b> |  | <b>2</b>                    |  | <b>3</b> |   | <b>4</b> |  |
| <b>BLOOD/BONE MARROW (Cont'd)</b>   |       |          |  |          |  |                             |  |          |   |          |  |
| The following criteria may be used for leukemia studies or bone marrow infiltrative/myelophthisic process if the protocol so specifies.<br>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  | none  | -        | -  | -        | -  | -                           | yes  | -        | -   | -        | platelet transfusions and other measures required to improve platelet increment; platelet transfusion refractoriness associated with life-threatening bleeding. (e.g., HLA or cross matched platelet transfusions) |
| Also consider Platelets.  |       |          |  |          |  |                             |  |          |   |          |  |
| Transfusion: pRBCs  | none  | -        | -  | -        | -  | -                           | yes  | -        | -   | -        | -  |
| Also consider Hemoglobin.   |       |          |  |          |  |                             |  |          |   |          |  |
| Hematologic- (Specify)  | Other | none     | mild   | -        | moderate                                 | -                           | severe   | -        | -   | -        | life-threatening or disabling  |
| <b>CARDIOVASCULAR (ARRHYTHMIA)</b>  |       |          |  |          |  |                             |  |          |   |          |  |
| 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) | -        | symptomatic and requiring treatment                     | -        | 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  | -        | symptomatic and requiring treatment                     | -        | life-threatening (e.g., arrhythmia associated with CHF, hypotension, syncope, shock)   |
| Palpitations  | none  | -        | present  | -        | -  | -                           | -  | -        | -   | -        | -  |
| Grade palpitations <u>only</u> in the absence of a documented arrhythmia.   |       |          |  |          |  |                             |  |          |   |          |  |
| Prolonged interval (QTc > 0.48 seconds)   | QTc   | none     | asymptomatic, not requiring treatment  | -        | symptomatic, but not requiring treatment | -                           | symptomatic and 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  | -        | 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  | -        | symptomatic and requiring treatment of underlying cause | -        | -  |

| <b>Grade</b>  |          |   |  |  |   |  |
|---|----------|---|--|--|---|--|
| <b>Toxicity</b>   | <b>0</b> | <b>1</b>  | <b>2</b>   | <b>3</b>   | <b>4</b>  |  |
| <b>CARDIOVASCULAR (ARRHYTHMIA) (cont'd)</b>                                   |          |   |  |  |   |  |
| Supraventricular arrhythmias (SVT/atrial fibrillation/ flutter)               | none     | asymptomatic, not requiring treatment   | not symptomatic, but 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   | not symptomatic, but 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   | not symptomatic, but 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   | T-wave changes   | asymptomatic, ST- and T-wave changes suggesting ischemia   | angina without evidence of infarction   | acute myocardial infarction  |
| <b>CARDIOVASCULAR (GENERAL)</b>   |          |   |  |  |   |  |
| Cardiac left ventricular function   | normal   | asymptomatic decline of resting ejection fraction of 10% but < 20% of baseline value; shortening fraction 24% but < 30% | decline of resting ejection fraction   | asymptomatic but resting ejection fraction below LLN for laboratory or decline of resting ejection fraction 20% of baseline value; < 24% shortening fraction | CHF responsive to treatment   | severe or refractory CHF or requiring intubation                                     |
| CNS cerebrovascular ischemia is graded under NEUROLOGY.                       |          |   |  |  |   |  |
| Cardiac troponin I (cTnI)   | normal   | -   | -  | levels consistent with unstable angina as defined by the manufacturer  | levels consistent with myocardial infarction as defined by the manufacturer                       |  |
| Cardiac troponin T (cTnT)   | normal   | ≥ 0.03 - < 0.05 ng/ml   | ≥ 0.05 - < 0.1 ng/ml   | ≥ 0.1 - < 0.2 ng/ml  | ≥ 0.2 ng/ml   |  |
| Edema   | none     | asymptomatic, not requiring therapy   | not symptomatic, 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   |   |
| <b>CARDIOVASCULAR (GENERAL) Cont'd</b>  |              |  |   |   |   |   |
| Hypotension   | none         | changes, but not requiring therapy (including transient orthostatic hypotension) | requiring brief replacement therapy but hospitalisation; physiologic consequences | fluid or other therapy but not physiologic consequences   | requiring 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).<br>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   |   |
| <b>COAGULATION</b>  |              |  |   |   |   |   |
| See the HEMORRHAGE category for grading the severity of bleeding events.  |              |  |   |   |   |   |
| DIC (disseminated intravascular coagulation)  | absent       | -  | -   | laboratory findings present with <u>no</u> bleeding       | laboratory findings <u>and</u> bleeding   |   |
| Also grade Platelets.<br>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   | 0          | 1  | 2   | 3   | 4   |
|---|------------|--|---|---|---|
| <b>Toxicity</b>   |            |  |   |   |   |
| <b>COAGULATION (cont'd)</b>   |            |  |   |   |   |
| 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 hemorrhage/bleeding or thrombosis/embolism or renal failure) requiring therapeutic intervention |
| Also consider Hemoglobin (Hgb), Platelets, Creatinine.<br>Must have microangiopathic changes on blood smear (e.g., schistocytes, helmet cells, red cell fragments). |            |  |   |   |   |
| Coag- (Specify)   | Other none | mild   | moderate  | severe  | life-threatening or disabling   |
| <b>CONSTITUTIONAL SYMPTOMS</b>  |            |  |   |   |   |
| Fatigue (lethargy, malaise, asthenia)   | none       | increased fatigue over baseline, but not altering normal activities              | moderate 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 <sup>9</sup> /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.<br>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- (Specify)  | Other none | mild   | moderate  | severe  | life-threatening or disabling   |

| Grade   |           |   |   |  |  |
|---|-----------|---|---|--|--|
| Toxicity  | 0         | 1   | 2   | 3  | 4  |
| <b>DERMATOLOGY/SKIN</b>   |           |   |   |  |  |
| Alopecia  | normal    | mild hair loss  | pronounced hair loss  | -  | -  |
| Bruising (in absence of grade 3 or 4 thrombocytopenia)  | none      | localised or dependent area                                       | in generalised  | -  | -  |
| Bruising resulting from grade 3 or 4 thrombocytopenia is graded as Petechiae/purpura <u>and</u> Hemorrhage/bleeding with grade 3 or 4 thrombocytopenia in the HEMORRHAGE category, <u>not</u> in the DERMATOLOGY/SKIN category. |           |   |   |  |  |
| Dermatitis, focal (associated with high-dose chemotherapy and bone marrow transplant)   | none      | faint erythema or dry desquamation                                | or 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 emollients   | with 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 reaction  | skin 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   |            | 0   | 1  | 2  | 3  | 4 |
|---|------------|---|--|--|--|---|
| Toxicity  |            |   |  |  |  |   |
| <b>DERMATOLOGY/SKIN (cont'd)</b>  |            |   |  |  |  |   |
| 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 medication  | no   | 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 fasciitis  |   |
| Wound- non-infectious   | non- none  | incisional separation   | incisional hernia  | fascial disruption without evisceration  | fascial disruption with evisceration   |   |
| Skin- (Specify)   | Other none | mild  | moderate   | severe   | life-threatening or disabling  |   |
| <b>ENDOCRINE</b>  |            |   |  |  |  |   |
| 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  | -  |   |

| <b>Grade</b>  |            |  |  |  |  |  |
|---|------------|--|--|--|--|--|
| <b>Toxicity</b>   | <b>0</b>   | <b>1</b>   | <b>2</b>   | <b>3</b>   | <b>4</b>   |  |
| <b>ENDOCRINE (cont'd)</b>   |            |  |  |  |  |  |
| 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- (Specify)  | Other none | mild   | moderate   | severe   | life-threatening or disabling  |  |
| <b>GASTROINTESTINAL</b>   |            |  |  |  |  |  |
| 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 |  |

| <b>Grade</b>  |          |   |  |   |   |
|---|----------|---|--|---|---|
| <b>Toxicity</b>   | <b>0</b> | <b>1</b>  | <b>2</b>   | <b>3</b>  | <b>4</b>  |
| <b>GASTROINTESTINAL (cont'd)</b>  |          |   |  |   |   |
| -Patients with a colostomy:   | none     | mild increase in 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 hospitalisation  | 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 hospitalisation 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  |
| <b>GASTROINTESTINAL (cont'd)</b>  |        |   |   |   |  |
| Gastritis   | none   | -   | requiring medical management or non-surgical treatment  | uncontrolled by out-patient medical management; requiring hospitalisation 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 <u>not due to radiation</u> is graded in the GASTROINTESTINAL category for specific sites: Colitis, Esophagitis, Gastritis, Stomatitis/pharyngitis (oral/pharyngeal mucositis), and Typhlitis; or the RENAL/GENITOURINARY category for Vaginitis. |        |   |   |   |  |
| Mucositis due to radiation  | none   | erythema of the mucosa  | patchy pseudomembranous reaction (patches generally 1.5 cm in diameter and non-contiguous)                    | confluent pseudomembranous reaction (contiguous patches generally > 1.5 cm in diameter)   | necrosis or deep ulceration; may include bleeding not induced by minor trauma or abrasion                                  |
| Also consider Pain due to radiation.  |        |   |   |   |  |
| Note: Grade radiation mucositis of the larynx here.<br>Dysphagia related to radiation is also graded as <u>either</u> Dysphagia- esophageal related to radiation <u>or</u> 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  |        | 0  | 1  | 2   | 3  | 4  |
|--|--------|--|--|---|--|--|
| Toxicity   |        |  |  |   |  |  |
| <b>GASTROINTESTINAL (cont'd)</b>   |        |  |  |   |  |  |
| Stomatitis / pharyngitis (oral/pharyngeal mucositis)   | none   | painless ulcers, erythema, or soreness in the absence of lesions | ulcers, or mild                            | painful edema, or can eat or swallow                            | erythema, ulcers, but  | 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 complication requiring surgical intervention (e.g., colostomy) |
| Also consider Hemorrhage/bleeding with 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- (Specify)  | Other  | none   | mild                                       | moderate  | severe   | life-threatening or disabling  |
| <b>HEMORRHAGE</b>  |        |  |  |   |  |  |
| 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 transfusion   | without                                    |   | 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 with grade 3 or 4 thrombocytopenia  | none   | mild transfusion   | without                                    |   | 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.  |        |  |  |   |  |  |

| <b>Grade</b>   |          |                                      |          |  |  |   |
|--|----------|--------------------------------------|----------|--|--|---|
| <b>Toxicity</b>  | <b>0</b> | <b>1</b>                             | <b>2</b> | <b>3</b>   | <b>4</b>   |   |
| <b>HEMORRHAGE</b>  |          |                                      |          |  |  |   |
| 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 transfusion                     | without  | -  | requiring transfusion  | catastrophic bleeding, requiring major non-elective intervention                          |
| Hematemesis  | none     | mild transfusion                     | without  | -  | 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 transfusion                     | without  | -  | requiring transfusion  | catastrophic bleeding, requiring major non-elective intervention                          |
| Hemorrhage /bleeding associated with surgery   | none     | mild transfusion                     | without  | -  | 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 transfusion                     | without  | -  | 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 transfusion or medication       | without  | 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 transfusion                     | without  | -  | requiring transfusion  | catastrophic bleeding, requiring major non-elective intervention                          |
| <b>HEPATIC</b>   |          |                                      |          |  |  |   |
| 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)<br>The following criteria are used only for bilirubin associated with graft versus host disease. |          |                                      |          |  |  |   |

| Grade   | 0          | 1                         | 2  | 3   | 4  |
|---|------------|---------------------------|--|---|--|
| <b>HEPATIC (cont'd)</b>   |            |                           |  |   |  |
|   | 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- (Specify)  | Other none | mild                      | moderate   | severe  | life-threatening or disabling                |
| <b>INFECTION/FEBRILE NEUTROPENIA</b>  |            |                           |  |   |  |
| 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 hospitalisation  | life-threatening sepsis (e.g., septic shock) |
| Febrile neutropenia (fever of unknown origin without clinically or microbiologically documented infection) (ANC < 1.0 x 10 <sup>9</sup> /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 <sup>9</sup> /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 hospitalisation | life-threatening sepsis (e.g., septic shock) |
| Wound-infectious is graded under DERMATOLOGY/SKIN.  |            |                           |  |   |  |

| Grade  |       | 0      | 1   | 2  | 3  | 4  |
|--|-------|--------|---|--|--|--|
| Toxicity   |       |        |   |  |  |  |
| <b>LYMPHATICS</b>  |       |        |   |  |  |  |
| Lymphatics   |       | normal | mild lymphedema   | moderate lymphocyst                        | lymphedema compression;  | severe lymphedema function; limiting lymphocyst requiring ulceration |
| Lymphatics- (Specify)  | Other | none   | mild  | moderate                                   | severe   | life-threatening or disabling  |
| <b>METABOLIC/LABORATORY</b>  |       |        |   |  |  |  |
| Acidosis (metabolic respiratory)   | or    | normal | pH < normal, but 7.3  | -  | pH < 7.3   | pH < 7.3 with life-threatening physiologic consequences              |
| Alkalosis (metabolic respiratory)  | or    | 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 (creatinine 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<br>> ULN - 2.9 mmol/L                               | >11.5 - 12.5 mg/d<br>> 2.9 - 3.1 mmol/L    | >12.5 - 13.5 mg/dl<br>> 3.1 - 3.4 mmol/L                           | > 13.5 mg/dl<br>> 3.4 mmol/L   |
| Hypercholesterolemia   |       | WNL    | > ULN - 300 mg/dl<br>> ULN - 7.75 mmol/L                              | > 300 - 400 mg/dl<br>> 7.75 - 10.34 mmol/L | > 400 - 500 mg/dl<br>>10.34 - 12.92 mmol/L                         | > 500 mg/dl<br>> 12.92 mmol/L  |
| Hyperglycemia  |       | WNL    | > ULN - 160 mg/dl<br>> ULN - 8.9 mmol/L                               | > 160 - 250 mg/dl<br>> 8.9 - 13.9 mmol/L   | > 250 - 500 mg/dl<br>> 13.9 - 27.8 mmol/L                          | > 500 mg/dl<br>> 27.8 mmol/L<br>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<br>> ULN - 1.23 mmol/L                              | -  | > 3.0 - 8.0 mg/dl<br>> 1.23 - 3.30 mmol/L                          | > 8.0 mg/dl<br>> 3.30 mmol/L   |
| Hypernatremia  |       | WNL    | >ULN - 150 mmol/L   | >150 - 155 mmol/L                          | >155 - 160 mmol/L  | >160 mmol/L  |
| Hypertriglyceridemia   |       | 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<br>≤ 0.59 mmol/L<br>without physiologic consequences | -  | > ULN - 10 mg/dl<br>≤ 0.59 mmol/L<br>with physiologic consequences | > 10 mg/dl<br>> 0.59 mmol/L  |
| Also consider Tumor lysis syndrome, Renal failure, Creatinine and Potassium. |       |        |   |  |  |  |
| Hypocalcemia   |       | WNL    | <LLN - 8.0 mg/dl<br><LLN - 2.0 mmol/L                                 | 7.0 - < 8.0 mg/dl<br>1.75 - < 2.0 mmol/L   | 6.0 - < 7.0 mg/dl<br>1.5 - < 1.75 mmol/L                           | <6.0 mg/dl<br>< 1.5 mmol/L   |
| Hypoglycemia   |       | WNL    | < LLN - 55 mg/dl<br>< LLN - 3.0 mmol/L                                | 40 - < 55 mg/dl<br>2.2 - < 3.0 mmol/L      | 30 - < 40 mg/dl<br>1.7 - < 2.2 mmol/L                              | < 30 mg/dl<br>< 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<br>< LLN - 0.5 mmol/L                                | 0.9 - <1.2 mg/dl<br>0.4 - < 0.5 mmol/L     | 0.7 - < 0.9 mg/dl<br>0.3 - < 0.4 mmol/L                            | < 0.7 mg/dl<br>< 0.3 mmol/L  |
| Hyponatremia   |       | WNL    | < LLN - 130 mmol/L  | -  | 120 - <130 mmol/L  | <120 mmol/L  |
| Hypophosphatemia   |       | WNL    | < LLN - 2.5 mg/dl<br><LLN - 0.8 mmol/L                                | 2.0 - <2.5 mg/dl<br>0.6 - <0.8 mmol/L      | 1.0 - <2.0 mg/dl<br>0.3 - <0.6 mmol/L                              | < 1.0 mg/dl<br><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- (Specify)   | Other | none   | mild  | moderate                                   | severe   | life-threatening or disabling  |



| <b>Grade</b>   |        | <b>0</b>   |                       | <b>1</b>  |                       | <b>2</b>   |                       | <b>3</b>  |  | <b>4</b> |  |
|--|--------|--|-----------------------|---|-----------------------|--|-----------------------|---|--|----------|--|
| <b>Toxicity</b>  |        | <b>0</b>   |                       | <b>1</b>  |                       | <b>2</b>   |                       | <b>3</b>  |  | <b>4</b> |  |
| <b>MUSCULOSKELETAL</b>   |        |  |                       |   |                       |  |                       |   |  |          |  |
| Arthralgia is graded in the PAIN category.   |        |  |                       |   |                       |  |                       |   |  |          |  |
| Arthritis  | none   | mild pain with inflammation, erythema or joint swelling but interfering with function        | joint not with        | moderate pain with inflammation, erythema, or joint swelling interfering with function, but not interfering with activities of daily living | joint not with        | severe pain with inflammation, erythema, or joint swelling and interfering with activities of daily living     | joint not with        | disabling   |  |          |  |
| Muscle weakness (not due to neuropathy)  | normal | asymptomatic weakness on exam  | with physical         | symptomatic and interfering with function, but not interfering with activities of daily living  | with physical         | symptomatic and interfering with activities of daily living  | with physical         | bedridden or disabling  |  |          |  |
| Myalgia is graded under PAIN.  |        |  |                       |   |                       |  |                       |   |  |          |  |
| Myositis (inflammation / damage of muscle)   | none   | mild pain, interfering with function   | not with              | pain interfering with function, but not interfering with activities of daily living   | not with              | pain interfering with function and interfering with activities of daily living                                 | not with              | bedridden or disabling  |  |          |  |
| Also consider CPK.<br>Myositis implies muscle damage (i.e., elevated CPK).                         |        |  |                       |   |                       |  |                       |   |  |          |  |
| Osteonecrosis (avascular necrosis)   | none   | asymptomatic detected by imaging only  | and                   | symptomatic and interfering with function, but not interfering with activities of daily living  | and                   | symptomatic and interfering with activities of daily living  | and                   | symptomatic; or disabling   |  |          |  |
| Joint, muscle, or bone (osseous)- Other (Specify)  | none   | mild   |                       | moderate  |                       | severe   |                       | life-threatening or disabling   |  |          |  |
| <b>NEUROLOGY</b>   |        |  |                       |   |                       |  |                       |   |  |          |  |
| Aphasia, receptive and/or expressive, is graded under Speech impairment in the NEUROLOGY category. |        |  |                       |   |                       |  |                       |   |  |          |  |
| Arachnoiditis/meningismus/radiculitis  | absent | mild pain interfering with function  | not with              | moderate interfering with function, but not interfering with activities of daily living   | not with              | severe interfering with activities of daily living   | not with              | unable to function or perform activities of daily living; bedridden; paraplegia |  |          |  |
| Also consider Headache, Vomiting and Fever.  |        |  |                       |   |                       |  |                       |   |  |          |  |
| Ataxia (incoordination)  | normal | asymptomatic abnormal on exam, and interfering with function                                 | but physical not with | mild symptoms interfering with function, but not interfering with activities of daily living  | but physical not with | moderate symptoms interfering with activities of daily living  | but physical not with | 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 <u>NOT</u> graded here.            |        |  |                       |   |                       |  |                       |   |  |          |  |
| Cognitive disturbance/learning problems  | none   | cognitive disability; interfering with work/school performance; preservation of intelligence | not with              | cognitive disability; interfering with work/school performance; decline of 1 SD (Standard Deviation) or loss of developmental milestones    | not with              | cognitive disability; resulting in significant impairment of work/school performance; cognitive decline > 2 SD | not with              | inability to work/frank mental retardation                                      |  |          |  |

| <b>Grade</b>  |        | <b>0</b>  |    | <b>1</b>  |    | <b>2</b>   |         | <b>3</b>  |         | <b>4</b>  |                                     |
|---|--------|---|----|---|----|--|---------|---|---------|---|-------------------------------------|
| <b>Toxicity</b>   |        |   |    |   |    |  |         |   |         |   |                                     |
| <b>NEUROLOGY (cont'd)</b>   |        |   |    |   |    |  |         |   |         |   |                                     |
| Confusion   | normal | confusion or disorientation or attention deficit of brief duration; resolves spontaneously with no sequelae   | or | confusion or disorientation or attention deficit interfering with function, but not interfering with activities of daily living   | or | confusion or delirium interfering with activities of daily living  | or      | delirium interfering with activities of daily living  | or      | harmful to self; requiring hospitalisation  | or                                  |
| Cranial neuropathy is graded in the NEUROLOGY category as Neuropathy-cranial.   |        |   |    |   |    |  |         |   |         |   |                                     |
| Delusions   | normal | -   | -  | -   | -  | present  | present | present   | present | toxic psychosis   | toxic psychosis                     |
| Depressed level of consciousness  | normal | somnolence or sedation not interfering with function  | or | somnolence or sedation interfering with function, but not interfering with activities of daily living   | or | obtundation or stupor; difficult to arouse; interfering with activities of daily living  | or      | stupor; difficult to arouse; interfering with activities of daily living  | or      | coma  | coma                                |
| Syncope (fainting) is graded under NEUROLOGY.   |        |   |    |   |    |  |         |   |         |   |                                     |
| Dizziness/lightheadedness   | none   | not interfering with function   | or | interfering with function, but not interfering with activities of daily living  | or | interfering with activities of daily living  | or      | interfering with activities of daily living   | or      | bedridden or disabling  | 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  | or | moderate involuntary movements interfering with function, but not interfering with activities of daily living   | or | severe involuntary movements or torticollis interfering with activities of daily living  | or      | severe involuntary movements or torticollis interfering with activities of daily living   | or      | bedridden or disabling  | bedridden or disabling              |
| Hallucinations  | normal | -   | -  | -   | -  | present  | present | present   | present | toxic psychosis   | toxic psychosis                     |
| Headache is graded under PAIN.  |        |   |    |   |    |  |         |   |         |   |                                     |
| Insomnia  | normal | occasional difficulty sleeping not interfering with function  | or | difficulty sleeping interfering with function, but not interfering with activities of daily living  | or | frequent difficulty sleeping interfering with activities of daily living   | or      | difficultly interfering with activities of daily living   | or      | -   | -                                   |
| This toxicity is graded when insomnia is related to treatment. If pain or other symptoms interfere with sleep do NOT grade as insomnia. |        |   |    |   |    |  |         |   |         |   |                                     |
| Leukoencephalopathy associated radiological findings  | none   | mild increase in (subarachnoid space) and/or mild ventriculomegaly; and/or small (+/- multiple) focal T2 hyperintensities, involving periventricular white matter or < 1/3 of susceptible areas of cerebrum | or | 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 | or | severe increase in SAS; severe ventriculomegaly; near total white matter T2 hyperintensities or diffuse low attenuation (CT); focal white matter necrosis (cystic) | or      | severe increase in SAS; severe ventriculomegaly; diffuse low attenuation with calcification (CT); diffuse white matter necrosis (MRI) | or      | severe increase in SAS; severe ventriculomegaly; diffuse low attenuation with calcification (CT); diffuse white matter necrosis (MRI) | or                                  |
| Memory loss   | normal | memory loss not interfering with function   | or | memory loss interfering with function, but not with activities of daily living  | or | memory loss interfering with activities of daily living  | or      | memory loss interfering with activities of daily living   | or      | amnesia   | amnesia                             |
| Mood alteration-anxiety, agitation  | normal | mild mood alteration not interfering with function  | or | moderate mood alteration interfering with function, but not interfering with activities of daily living   | or | severe mood alteration interfering with activities of daily living   | or      | severe mood alteration interfering with activities of daily living  | or      | suicidal ideation or danger to self   | suicidal ideation or danger to self |

| <b>Grade</b>  |          |  |  |  |  |   |  |  |  |  |
|---|----------|--|--|--|--|---|--|--|--|--|
| <b>Toxicity</b>   | <b>0</b> | <b>1</b>   | <b>2</b>   | <b>3</b>   | <b>4</b>   |   |  |  |  |  |
| <b>NEUROLOGY (cont'd)</b>   |          |  |  |  |  |   |  |  |  |  |
| 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 hospitalisation   |   |  |  |  |  |
| 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  | 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 intermittent interfering with function  | brief or 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  | - |  |  |  |  |

| <b>Grade</b>   |            |  |  |   |  |  |  |  |  |
|--|------------|--|--|---|--|--|--|--|--|
| <b>Toxicity</b>                                      | <b>0</b>   | <b>1</b>   | <b>2</b>   | <b>3</b>  | <b>4</b>   |  |  |  |  |
| <b>NEUROLOGY (cont'd)</b>                            |            |  |  |   |  |  |  |  |  |
| 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- (Specify)                                | Other none | mild   | moderate   | severe  | life-threatening or disabling                      |  |  |  |  |
| <b>OCULAR/VISUAL</b>                                 |            |  |  |   |  |  |  |  |  |
| 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 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               | -  |  |  |  |  |

| <b>Grade</b>   |         |          |                           |          |  |  |  |      |  |
|--|---------|----------|---------------------------|----------|--|--|--|------|--|
| <b>Toxicity</b>  |         | <b>0</b> | <b>1</b>                  | <b>2</b> | <b>3</b>   | <b>4</b>   |  |      |  |
| <b>OCULAR/VISUAL</b>   |         |          |                           |          |  |  |  |      |  |
| Vision- blindness (nyctalopia)   | night   | normal   | abnormal                  | electro- | symptomatic  | and  | symptomatic  | and  | -  |
|  |         |          | retinography asymptomatic | but      | interfering with function, but not interfering with activities of daily living | with   | interfering with activities of daily living  | with |  |
| Vision- photophobia  |         | normal   | -                         |          | symptomatic  | and  | symptomatic  | and  | -  |
|  |         |          |                           |          | interfering with function, but not interfering with activities of daily living | with   | interfering with activities of daily living  | with |  |
| Ocular- (Specify)  | Other   | normal   | mild                      |          | moderate   |  | severe   |      | unilateral or bilateral loss of vision (blindness) |
| <b>PAIN</b>  |         |          |                           |          |  |  |  |      |  |
| Abdominal cramping   | pain or | none     | mild                      | pain     | not  | 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  |
|  |         |          | interfering function      | with     | with   |  |  |      |  |
| Arthralgia (joint pain)  |         | none     | mild                      | pain     | not  | 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  |
|  |         |          | interfering function      | with     | with   |  |  |      |  |
| Arthritis (joint pain with clinical signs of inflammation) is graded under MUSCULOSKELETAL . |         |          |                           |          |  |  |  |      |  |
| Bone pain  |         | none     | mild                      | pain     | not  | 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  |
|  |         |          | interfering function      | with     | with   |  |  |      |  |
| Chest (non-cardiac and non-pleuritic)  | pain    | none     | mild                      | pain     | not  | 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  |
|  |         |          | interfering function      | with     | with   |  |  |      |  |
| Dysmenorrhea   |         | none     | mild                      | pain     | not  | 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  |
|  |         |          | interfering function      | with     | with   |  |  |      |  |

| <b>Grade</b>  |          |                                     |          |  |  |           |  |  |  |  |
|---|----------|-------------------------------------|----------|--|--|-----------|--|--|--|--|
| <b>Toxicity</b>   | <b>0</b> | <b>1</b>                            | <b>2</b> | <b>3</b>   | <b>4</b>   |           |  |  |  |  |
| <b>PAIN</b>   |          |                                     |          |  |  |           |  |  |  |  |
| Dyspareunia   | none     | mild pain interfering with function | not with | moderate pain interfering with sexual activity   | severe pain preventing sexual activity   | -         |  |  |  |  |
| Dysuria is graded under RENAL/GENITOURINARY.  |          |                                     |          |  |  |           |  |  |  |  |
| Earache (otalgia)   | none     | mild pain interfering with function | not with | 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 interfering with function | not with | 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 interfering with function | not with | 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 interfering with function | not with | 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 interfering with function | not with | 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 interfering with function | not with | 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 interfering with function | not with | 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 interfering with function | not with | 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 interfering with function | not with | 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- (Specify)   | Other    | none                                | mild     | moderate   | severe   | disabling |  |  |  |  |

| <b>Grade</b>  |                      | <b>0</b>                            |  | <b>1</b>   |  | <b>2</b>  |  | <b>3</b> |   | <b>4</b> |                                       |
|---|----------------------|-------------------------------------|--|--|--|---|--|----------|---|----------|---------------------------------------|
| <b>Toxicity</b>   |                      | <b>0</b>                            |  | <b>1</b>   |  | <b>2</b>  |  | <b>3</b> |   | <b>4</b> |                                       |
| <b>PULMONARY</b>  |                      |                                     |  |  |  |   |  |          |   |          |                                       |
| Adult respiratory distress (ARDS)   | respiratory syndrome | absent                              | -  | -  | -  | -   | -  | -        | - | -        | present                               |
| Apnea   |                      | none                                | -  | -  | -  | -   | -  | present  | - | -        | requiring intubation                  |
| Carbon monoxide diffusion capacity (DL <sub>CO</sub> )                              | capacity             | 90% of pretreatment or normal value | of 75 - <90% of pretreatment or normal value                             | of 50 - <75% of pretreatment or normal value                                 | of 25 - <50% of pretreatment or normal value   | of < 25% of pretreatment or normal value  | -  | -        | - | -        | < 25% of pretreatment or normal value |
| Cough   |                      | absent                              | mild, relieved by non-prescription medication                            | requiring narcotic antitussive   | 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 <sub>1</sub>  |                      | 90% of pretreatment or normal value | of 75 - <90% of pretreatment or normal value                             | of 50 - <75% of pretreatment or normal value                                 | of 25 - <50% of pretreatment or normal value   | of < 25% 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 <sub>2</sub> saturation with exercise  | decreased O <sub>2</sub> saturation at rest, requiring supplemental oxygen      | decreased O <sub>2</sub> saturation, requiring pressure support (CPAP) or assisted ventilation | -        | - | -        | -                                     |
| Pleural effusion (non-malignant)  |                      | none                                | asymptomatic and not requiring treatment                                 | symptomatic, requiring diuretics   | symptomatic, requiring O <sub>2</sub> 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- (Specify)  | Other                | none                                | mild   | moderate   | severe   | life-threatening or disabling   | -  | -        | - | -        | -                                     |
| <b>RENAL/GENTOURINARY</b>   |                      |                                     |  |  |  |   |  |          |   |          |                                       |
| 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 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  | -  | -        | - | -        | -                                     |

| <b>Grade</b>  |       | <b>0</b> | <b>1</b>   | <b>2</b>  | <b>3</b>   | <b>4</b>                                      |
|---|-------|----------|--|---|--|---|
| If there is an inconsistency between absolute value and uristix reading, use the absolute value for grading.          |       |          |  |   |  |   |
| Renal failure   |       | none     | -  | -   | requiring dialysis, but reversible   | requiring dialysis and irreversible           |
| Ureteral obstruction  |       | none     | unilateral, not requiring surgery  | -   | bilateral, not requiring surgery   | stent, nephrostomy tube, or surgery           |
| Urinary electrolyte wasting (e.g., Fanconi's syndrome, renal tubular acidosis)  |       | none     | asymptomatic, not requiring treatment  | mild, reversible and manageable with oral replacement   | reversible but requiring IV replacement  | irreversible, requiring continued replacement |
| Also consider Acidosis, Bicarbonate, Hypocalcemia, Hypophosphatemia.  |       |          |  |   |  |   |
| Urinary frequency/urgency   |       | normal   | increase in frequency or nocturia up to 2 x normal   | increase > 2 x normal but < hourly  | hourly or more with urgency, or requiring catheter   | -   |
| Urinary retention   |       | normal   | hesitancy or dribbling, but no significant residual urine; retention occurring during the immediate postoperative period | hesitancy requiring medication or occasional in/out catheterization (<4 x per week), or operative bladder atony requiring indwelling catheter beyond immediate postoperative period but for < 6 weeks | requiring frequent in/out catheterization (4 x per week) or urological intervention (e.g., TURP, suprapubic tube, urethrotomy) | bladder rupture                               |
| Urine color change (not related to other dietary or physiologic cause e.g., bilirubin, concentrated urine, hematuria) |       | normal   | asymptomatic, change in urine color  | -   | -  | -   |
| <b>RENAL/GENITOURINARY</b>  |       |          |  |   |  |   |
| 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- (Specify)   | Other | none     | mild   | moderate  | severe   | life-threatening or disabling                 |
| <b>SECONDARY MALIGNANCY</b>   |       |          |  |   |  |   |
| Secondary malignancy, (Specify type) excludes metastatic tumors   | Other | none     | -  | -   | -  | present                                       |
| <b>SEXUAL/REPRODUCTIVE FUNCTION</b>   |       |          |  |   |  |   |
| 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- (Specify)   | Other | none     | mild   | moderate  | severe   | disabling                                     |
| <b>SYNDROMES (not included in previous categories)</b>  |       |          |  |   |  |   |
| Acute vascular leak syndrome is graded under CARDIOVASCULAR (GENERAL) .   |       |          |  |   |  |   |
| ARDS (adult respiratory distress syndrome) is graded under PULMONARY.   |       |          |  |   |  |   |



| Grade  | 0      | 1                                   | 2        | 3  | 4   |                               |
|--|--------|-------------------------------------|----------|--|---|-------------------------------|
| <b>Toxicity</b>  |        |                                     |          |  |   |                               |
| Autoimmune reactions are graded under ALLERGY/IMMUNOLOGY.  |        |                                     |          |  |   |                               |
| DIC (disseminated intravascular coagulation) is graded under COAGULATION.  |        |                                     |          |  |   |                               |
| Fanconi's syndrome is graded as Urinary electrolyte wasting in the RENAL/GENITOURINARY category.   |        |                                     |          |  |   |                               |
| Renal tubular acidosis is graded as Urinary electrolyte wasting in the RENAL/GENITOURINARY category.   |        |                                     |          |  |   |                               |
| Stevens-Johnson syndrome (erythema multiforme) is graded in the DERMATOLOGY/SKIN category.   |        |                                     |          |  |   |                               |
| <b>SYNDROMES (not included in previous categories)</b>   |        |                                     |          |  |   |                               |
| 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 interfering with function | not with | 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.<br>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- (Specify)   | Other  | none                                | mild     | moderate   | severe  | life-threatening or disabling |

### **22.3 Appendix 3 - ECOG Performance Status Scale**

| <b>DESCRIPTION</b>   | <b>Grade</b> |
|--|--------------|
| 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

## 22.4 Appendix 4 – Schedule of assessments

|  | Screening/<br>Baseline | 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                      |  |   |   |   |   |    |    |    |    |    |    |    |    |    |
| 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  |
| ECOG 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  |
| G-band analysis (Bone Marrow aspirate) | x                      |  |   |   |   |   |    |    |    |    |    |    |    |    |    |
| QPCR 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 treatment with IMP and for four weeks post discontinuation of IMP                      |   |   |   |   |    |    |    |    |    |    |    |    |    |
| Study medication log                   |                        | Continuous throughout study and whilst remains on dasatinib IMP  |   |   |   |   |    |    |    |    |    |    |    |    |    |
| Concomitant medications                |                        | Continuous for patients on IMP until visit 15  |   |   |   |   |    |    |    |    |    |    |    |    |    |
| Patient Outcome                        |                        | When study drug is permanently discontinued  |   |   |   |   |    |    |    |    |    |    |    |    |    |
| Annual Review                          |                        | On the randomisation anniversary each year after study drug discontinuation until 5 years post randomisation |   |   |   |   |    |    |    |    |    |    |    |    |    |

\*Screening Assessments are listed in section 10.1