SPIRIT 2 Initiation: November 2009

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Key Facts

- NCRN Adopted study
- UK Multicentre study
- Looking for 810 patients from UK
- Current status

  First patient recruited Aug 2008 – Newcastle

  196 patients randomised

- Electronic Data Capture via internet
- Website: www.spirit-cml.org

Study Summary

- Randomised, Open label
- Newly Diagnosed CML (within 3 months)
- 2 treatment arms (405 patients on each)
  - Arm A: 400mg daily imatinib
  - Arm B: 100mg daily dasatinib

- Primary end point is event-free survival at 5 years
- Secondary endpoints include haematologic and cytogenetic responses

Patient recruitment

- Eligibility criteria
- Written informed Consent (consent must be prior to any study specific procedures)
- Randomisation
- Study Schedule

Eligibility - Inclusion Criteria

1. ≥ 18 years old.
2. ALL of the following should apply to patient:
    i. **within 3 months of initial diagnosis** of CML-Chronic Phase,
    ii. **Received no CML treatment (but hydroxycarbamide and/or anagrelide OK),**
    iii. Patient is **Philadelphia chromosome positive**,
    iv. Patient has
        a) < 15% blasts in peripheral blood and bone marrow;
        b) < 30% blasts plus promyelocytes in peripheral blood and bone marrow;
        c) < 20% basophils in peripheral blood;
        d) ≥ 100 x 10^9/L platelets;
        e) no extramedullary involvement (except hepatosplenomegaly).
3. **Written voluntary informed consent.**

Eligibility - Exclusion Criteria (1)

1. Patient is Ph-negative, BCR-ABL-positive.
2. Prior treatment for CML.
3. Prior chemotherapy (any type).
4. Prior haemopoietic stem cell transplant, either autograft or allograft.
5. ECOG Score ≥ 3.
6. Serum bilirubin, SGOT/AST, SGPT/ALT, or creatinine > 2.0 x IULN.
7. INR or PTT > 1.5 x IULN.
8. Uncontrolled medical disease.

Eligibility - Exclusion Criteria (2)

9. HIV-positive (HIV test not required).
10. Major surgery within 4 weeks of Study Day 1, or not recovered from prior major surgery.
11. Patient is:
    a. pregnant,
    b. breast feeding,
    c. without a **negative pregnancy test,**
    d. unwilling to use barrier contraceptive .
12. Another malignancy within the past five years.
13. History of non-compliance to medical regimens or potentially unreliable.

Informed Consent

- There are 3 consent forms **(V1.2)**
  1) Participation in the SPIRIT 2 Trial
  2) Donation of material to CML Biobank
  3) CML Patient Registry

- Only consent part (1) is necessary for inclusion in the study.
- Required prior to any study specific procedures
- Delegation log must record all personnel authorised to take consent
- Document consent procedure in source records

- **Remember:** Patient Information Sheet and Informed Consent Forms should be printed on Hospital Headed Paper.

Randomisation

1. Fax to Trial Manager (0191 376 0748)
   - Signed informed consent form(s)
   - Cytogenetics report
2. Create new patient in eCRF
3. Complete screening eCRF pages
   - Open visit – visit date
   - Eligibility criteria
   - Demography
   - Randomisation
4. Treatment arm allocation and subject number will then be displayed on screen.

Study Schedule (1)

Year 1

- Visit 1 – Screening
- Visit 2 – Day 28 (1 month)
- Visit 3 – Day 56 (2 months)
- Visit 4 – Day 84 (3 months)
- Visit 5 – 6 months
- Visit 6 – 9 months
- Visit 7 – 12 months

Years 2 – 5

- Visits 8 – 15
- Visits every 6 months

Baseline assessments must be done within 14 days prior to 1st administration of study drug

Exception = bone marrow (can be done up to 28 days prior to 1st administration of study drug)

Study Schedule (2)

- Visit Date – all visits

- Eligibility
- Demography (NHS number)
- Medical History
- CML Diagnosis Date

Screening/

Baseline

Ensure each study visit and assessment results are recorded in the source (hospital) notes

- PCR sample – every 3 months (year 1), every 6 months thereafter
- Bone marrow assessment – once a year
- Quality of Life Questionnaire - monthly (1st 3 months), month 6&12, yearly thereafter

- Physical examination
- Extramedullary Involvement Liver & Spleen
- ECOG Score
- Labs (Haem/Biochem)
- Adverse Events
- Study medication
- Concomitant medications

All visits

AE's and SAE's

- Protocol Section 11.2 - discusses Safety Reporting:

- An **adverse event** is defined as any undesirable sign, symptom, or medical condition occurring after starting study drug, whether considered study drug-related or not.
- Please ensure that all adverse events (whether related to study drug or not) are recorded in the patient's electronic case report form (via the SPIRIT 2 website).

- A **serious adverse event** is defined as an event that is:
    1. fatal, or life-threatening
    2. requires or prolongs hospitalization
    3. significantly or permanently disabling
    4. is a congenital anomaly
    5. any other significant medical event

- **SAE's must be faxed to Trial Manager within 24 hours of becoming aware of the event**

- **Fax SPIRIT 2 SAE form to 0191 376 0748**

Samples – PCR & Biobank (1)

- PCR analysis for BCR-ABL (secondary endpoint).
- CML Biobank for future studies (Consent 2)

- At Screening:
  - 11 x 6ml EDTA tubes
  - First PCR sample (visit 1) - **PRIOR** to imatinib / dasatinib treatment.

- Every 3 months in year 1 then Every 6 months years 2-5
  - 3 x 6ml EDTA tubes

Samples – PCR & Biobank (2)

- **Sample tubes** and **postage-paid pre-labeled shipping boxes provided by trial office**.
- Include **SPIRIT 2 Shipping Form**
- **Contact Trial Office when more boxes required.**

- Hammersmith Hospital – PCR analysis
  - Requires 3 x 6ml tubes
- Glasgow - CML Biobank
  - Requires 8 x 6ml tubes (at screening only)

- The samples should be sent via first class post on a Monday, Tuesday or Wednesday only (to avoid samples arriving at the weekend and degrading).

- Please notify trial office if your clinic is on a Thursday or Friday and we will provide special delivery boxes.

Treatment Arms

A. 400mg daily imatinib
   - No additional supplies required (provided via standard NHS stock)
   - A SPIRIT 2 Trial label must be applied
   - Drug accountability, etc still required – considered IMP

B. 100mg daily dasatinib
   - Dasatinib trial stock (pre-labelled) supplied to hospital pharmacy directly from BMS.
   - Initial “float” (50mg & 20mg tablets) sent on site activation
   - If patient is randomised to dasatinib, the trial manager will automatically order 3 monthly supply (50mg) for pharmacy.
   - Requests for further supplies of 20mg or 50mg tablets should be sent to Trial office using Dasatinib Order Form (on website)

Unused Study Drug should be returned to your hospital and destroyed following your normal hospital procedures. Drug destruction should be recorded on the accountability log.

Documentation

- **PI to sign protocol signature page**
- PI CV
- Delegation log
- Lab normal ranges
- Lab Accreditations

prior to recruitment – please fax copies of the above to the Trial Office (0191 376 0748).

- Staff – confirmation of all present at site initiation by email to trial office
- Logins and training certificates will be sent to sites based on attendance at initiation meeting and the nowEDC training.

Where to get information

- Trial Secretary – Wendy Banks

  ☎ 0191 282 0904

  Fax: 0191 376 0748

  ✉ wendy.banks@ncl.ac.uk

  ✉Website - www.spirit-cml.org