SPIRIT 2

STI571 Prospective International Randomised Trial

# An NCRI randomised study comparing dasatinib with imatinib in patients with newly diagnosed CML: 2 year follow up

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NCRI National Cancer Research Institute

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University of Glasgow

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www.spirit-cml.org

The Newcastle Hospitals NHS Foundation Trust

NHS

# Acknowledgements


| | |
|---|---|
| **Data analysis and presentation** | Stephen O' Brien, Corinne Hedgley, Gemma Gills, Thomas Zwingers, John McCullough, Wendy Osborne |
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| **Data Monitoring Committee** | Charles Schiffer, Keith Wheatley, Graham Dark, John Goldman |
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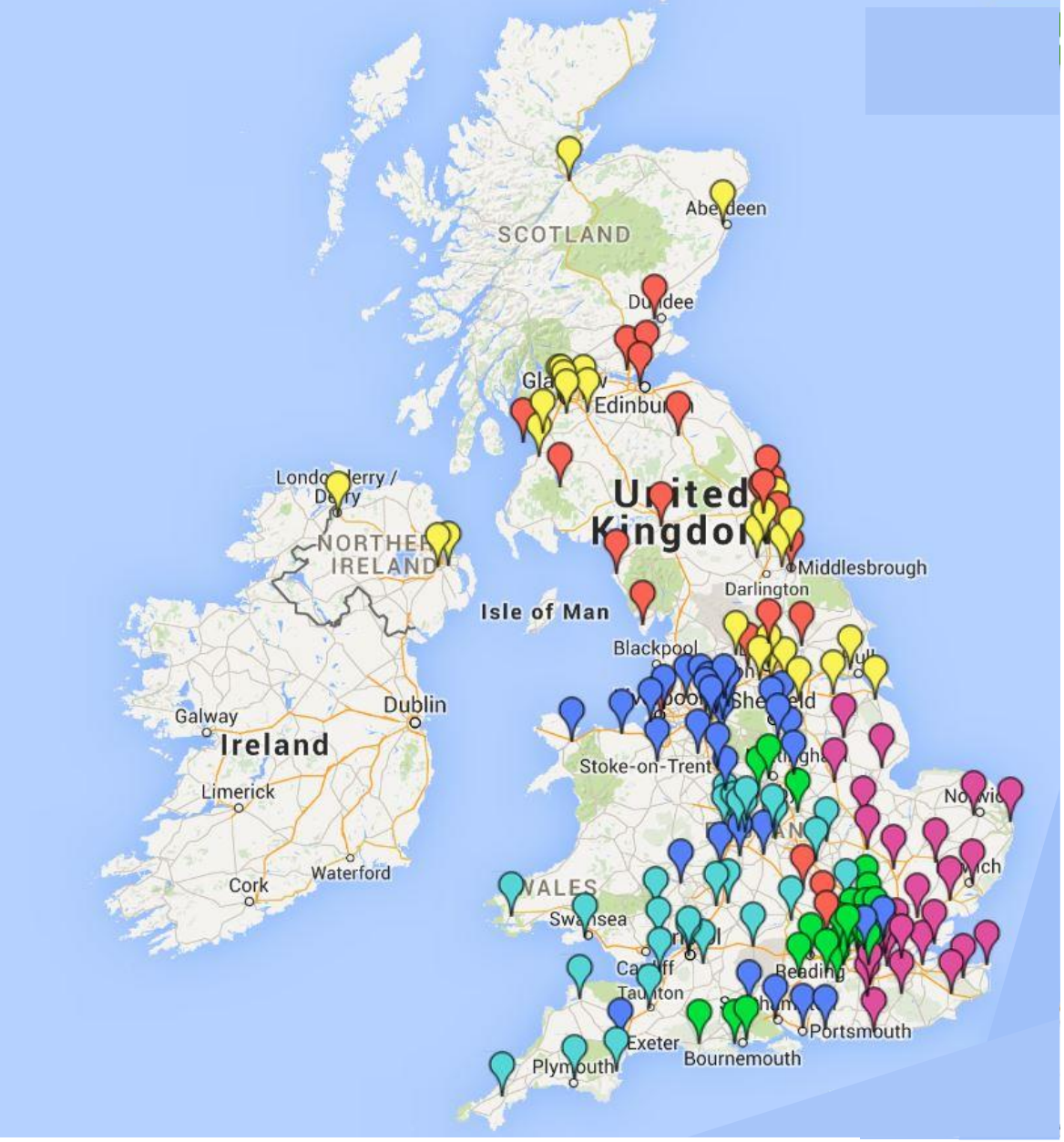
| **Chief Investigator** | Stephen O'Brien |
| **Sites** | n=172. Thanks to all our investigators and site staff. |
| **Patients** | n=814. A huge thank you to all participating patients. |
| **NCRI CML Working Group** | Dragana Milojkovic, Jenny Byrne, Hugues de Lavallade, Adam Mead, Graeme Smith, Brian Huntly, Richard Szydlo, Andy Goringe, Naumann Butt, Sameer Tulpule, Shamyla Siddique, Bernie Ramsahoye, Mhairi Copland (Chair) |




NCRI
National Cancer Research Institute

814 patients in total

Recruitment closed Feb 2013

**BSH 2015: 2 years follow up**

172 hospitals set up,145 recruited patients

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# Outline

Background

Design

What happened to all the patients?

Progressions and deaths

Adverse events

Cytogenetics & PCR

Summary

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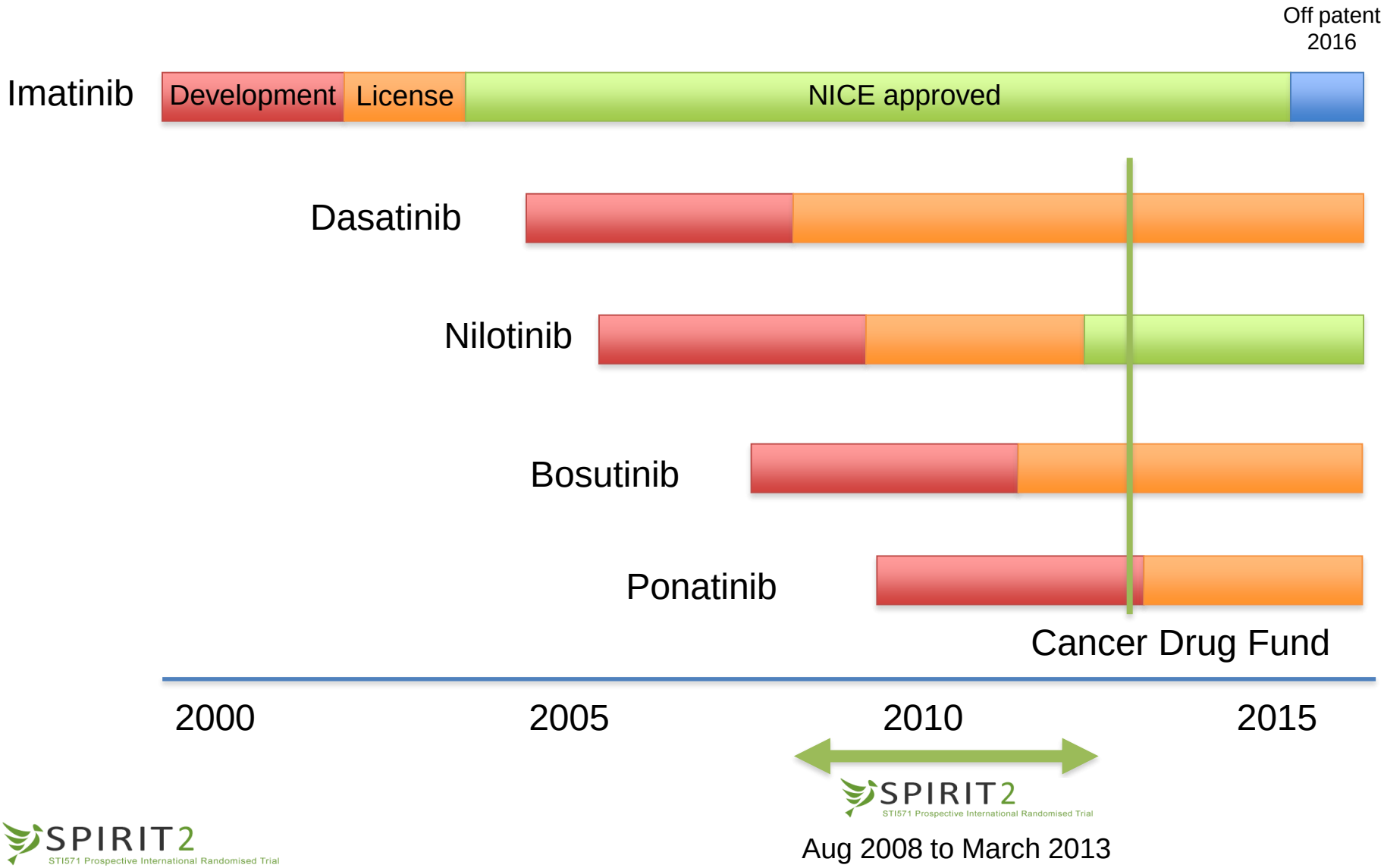
# Background

- Imatinib still commonly used as first line therapy
- 2nd generation TKIs generally produce higher rates of major molecular response
- Dasision study* (n= 519) MR3 (MMR) at 5 years:
  - Imatinib 64% (63% still on treatment)
  - Dasatinib 76% (61% still on treatment)
- No difference in OS at 5 years
- Concerns about long term safety of 2nd gen
- SPIRIT 2 (n=814) is largest dasatinib trial

Kantarjian *et al*. NEJM (2010); 362:2260
Jabbour *et al*. Blood (2014); 123: 494-500
*rates are KM cumulative incidence
Cortes *et al*. Abstract 154, ASH 2014

# TKIs in the UK




Aug 2008 to March 2013

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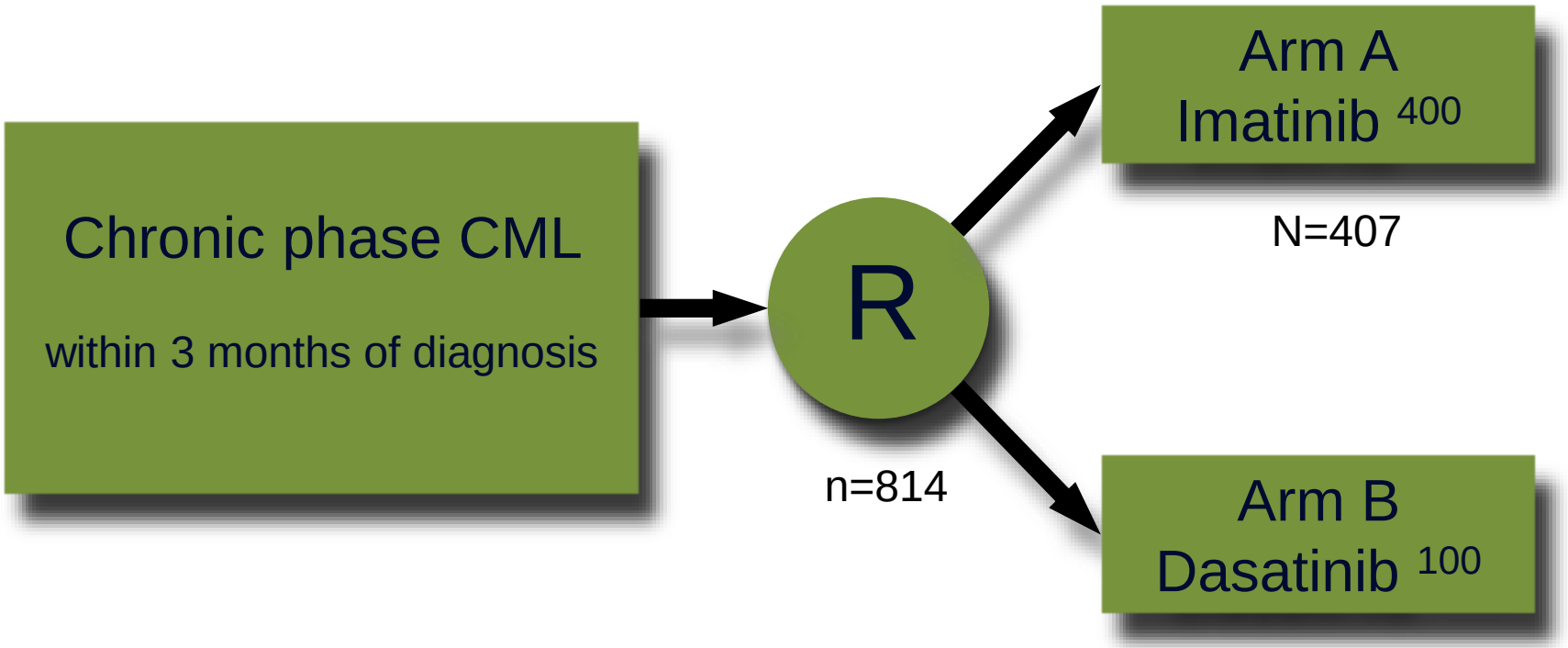
# SPIRIT 2: study design




Randomised, open label

Primary endpoint: 5 year EFS

Secondary: cytogenetic, PCR response, toxicity



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# Endpoints

**Primary**

- 5 year event free survival (EFS)
  - Assessed for all patients March 2018

**Secondary**

- Rate of complete cytogenetic response (CCR)
- Rate of Major Molecular Response
  - (MMR, $MR^3$, BCR-ABL1/ABL1 ratio<0.1%)
- Toxicity
- Treatment failure rates (TFR) after 5 years
- Rates of complete haematologic response (CHR)
- Overall survival at 2 and 5 years

# Entry & exclusion criteria

## Entry

1.Male or female patients ≥ 18 years of age.

2.Patients must have all of the following:

i) be enrolled within **3 months** of initial diagnosis of **chronic phase** CML

ii) confirmation of the Philadelphia chromosome or variants of (9;22) translocations;

iii) (a) < 15% blasts in peripheral blood and bone marrow;
(b) < 30% blasts plus promyelocytes in peripheral blood and bone marrow;
(c) < 20% basophils in peripheral blood,
(d) ≥ 100 x 109/L platelets

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

3. Written voluntary informed consent.

## Exclusion

1.Ph-negative, BCR-ABL1-positive, disease not eligible

2.Any prior treatment for CML (hydroxycarbamide, anagrelide permitted)

3.Prior chemotherapy, including PBSC mobilisation

4.Prior autograft or allograft

5.ECOG Performance Status Score ≥ 3

6.>2x ULN liver, renal function; >1.5x ULN coag; warfarin OK

7.Uncontrolled medical disease; known HIV pos; major surgery within 4 weeks

8.Patients who are: pregnant; breast feeding; not on appropriate contraception

9.Other malignancy within the past five years (except BCC)

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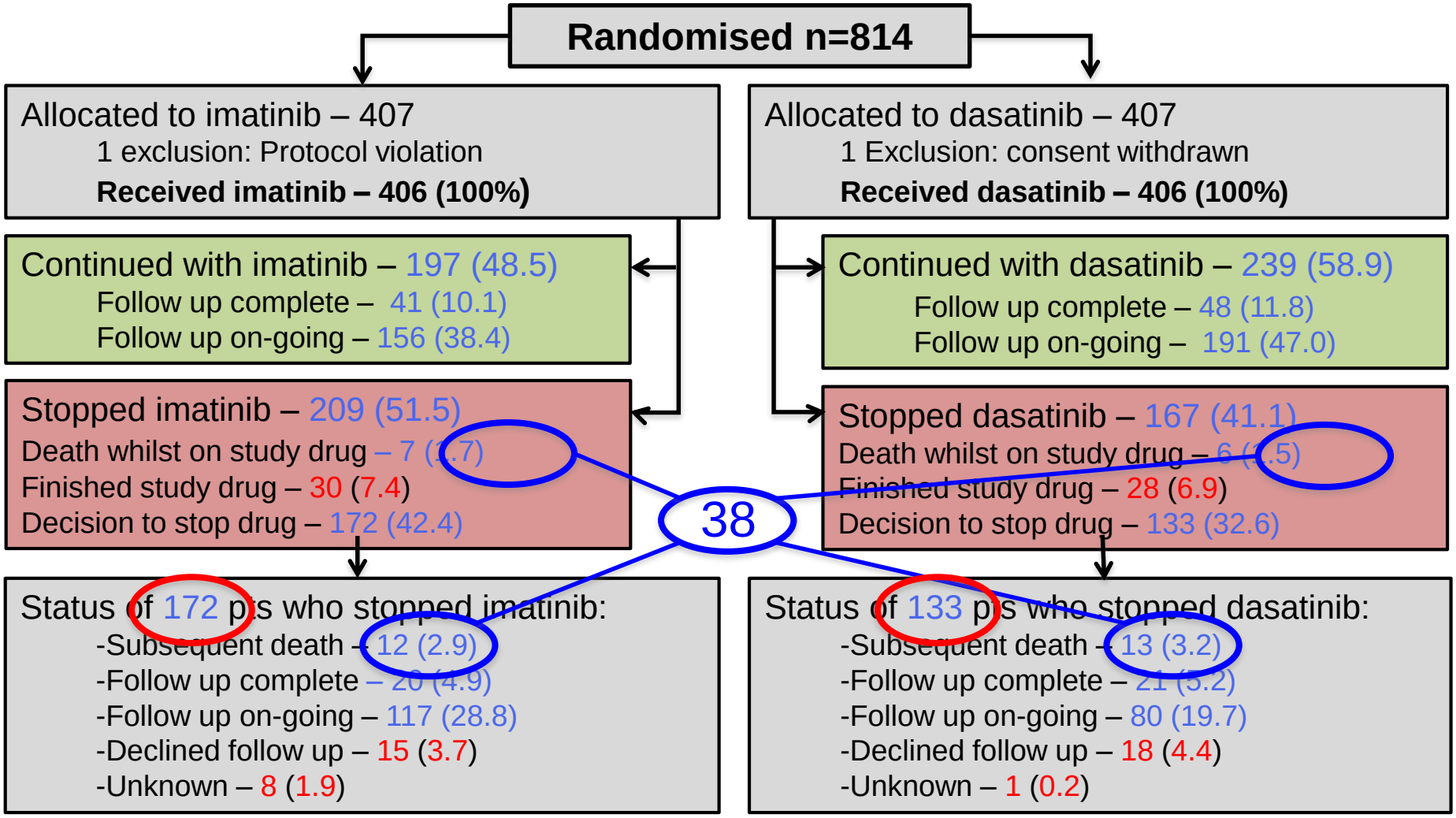
# Patients enroled

Aug 2008 to Feb 2013
814 in 54 months: 15 per month

| Characteristic | | Imatinib n=407 (%) | Dasatinib n=407 (%) | Total n=814 (%) |
|---|---|---|---|---|
| **Age** | Median | 53.3 | 53.1 | 53.2 |
| | Range | 18-87 | 18-89 | 18-89 |
| **Gender** | Female | 165 (40.5) | 157 (39.0) | 322 (39.4) |
| | Male | 242 (60.1) | 250 (61.4) | 492 (60.3) |
| **Available data for Sokal** | | 242 (59.6) | 246 (60.6) | 488 (60.1) |
| | | | | |
| **Follow up (months)** | Median | 41.7 | 43.0 | 42.4 |
| | Range | 2 - 69 | 0 - 71 | 0 - 71 |

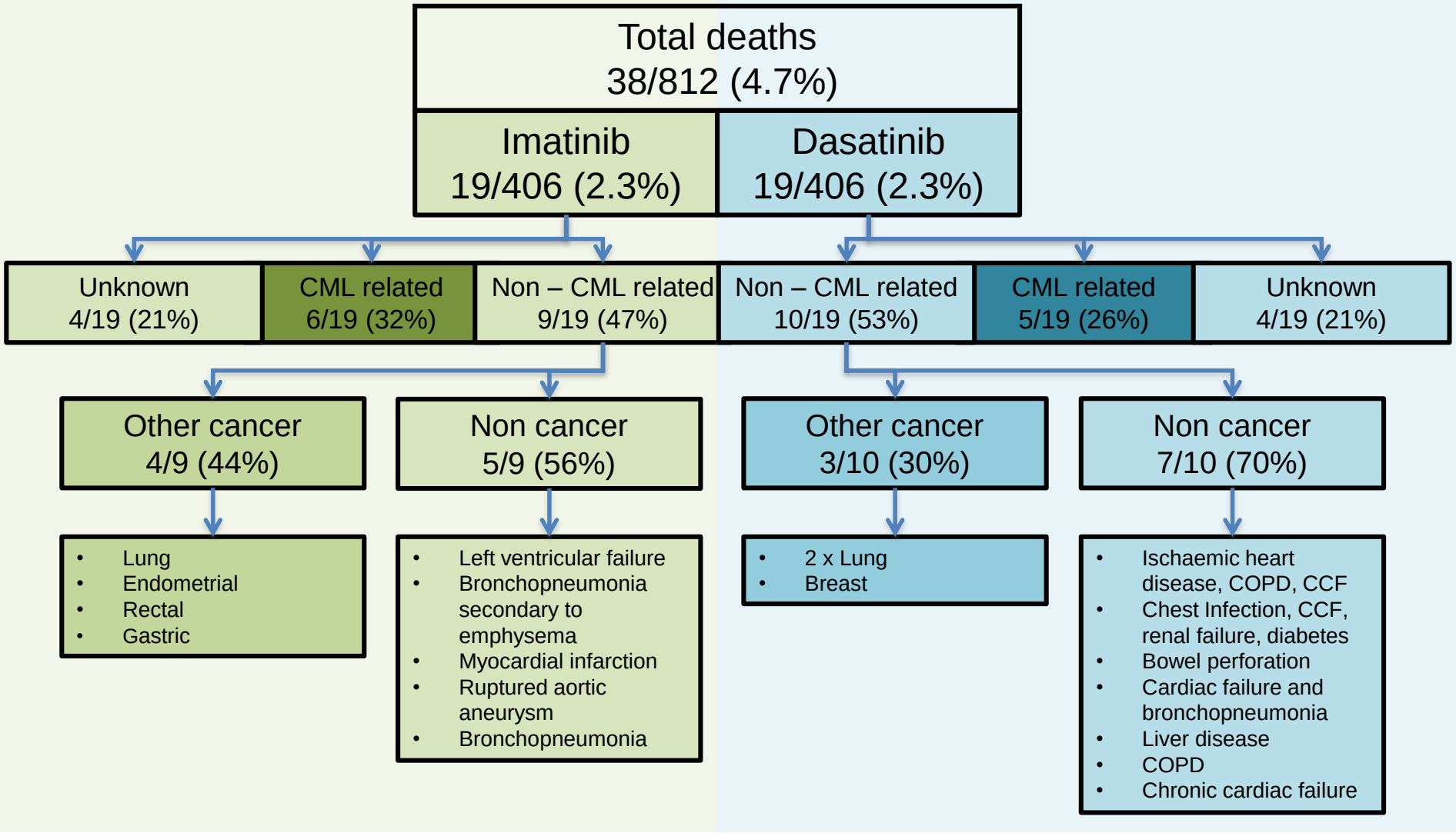
# What happened to all the patients?



# Patients who stopped study drug

| Reason for stopping study drug (exc. death) | Imatinib 406 (%) | Dasatinib 406 (%) | Total 812 (%) |
|---|---|---|---|
| Consent withdrawn | 8 (1.9) | 12 (2.9) | 20 (2.5) |
| Disease progression - accelerated phase | 1 (0.2) | 2 (0.5) | 3 (0.3) |
| Disease progression - blast crisis | 7 (1.7) | 4 (1.0) | 11 (1.4) |
| Failure to achieve CCR after 24 months | 6 (1.5) | 2 (0.5) | 8 (1.0) |
| Failure to achieve MCR after 12 months | 22 (5.4) | 3 (0.7) | 25 (3.1) |
| Intolerance - non haem tox | 49 (12.0) | 89 (21.9) | 138 (16.9) |
| Intolerance - haem/lab tox | 21 (5.2) | 9 (2.2) | 30 (3.7) |
| Loss of CHR | 5 (1.3) | 0 | 5 (0.6) |
| Loss of MCR | 5 (1.3) | 2 (0.5) | 7 (0.8) |
| Other reason | 2 (0.5) | 3 (0.7) | 5 (0.6) |
| Reason unknown - Lost to follow up | 2 (0.5) | 2 (0.5) | 4 (0.5) |
| 'Inadequate response' (cytogenetic, haematological, molecular, mutation detected) | 44 (10.8) | 5 (1.3) | 49 (6.0) |
| **Total** | **172 (42.4)** | **133 (32.6)** | **305 (37.6)** |

# Cause of death



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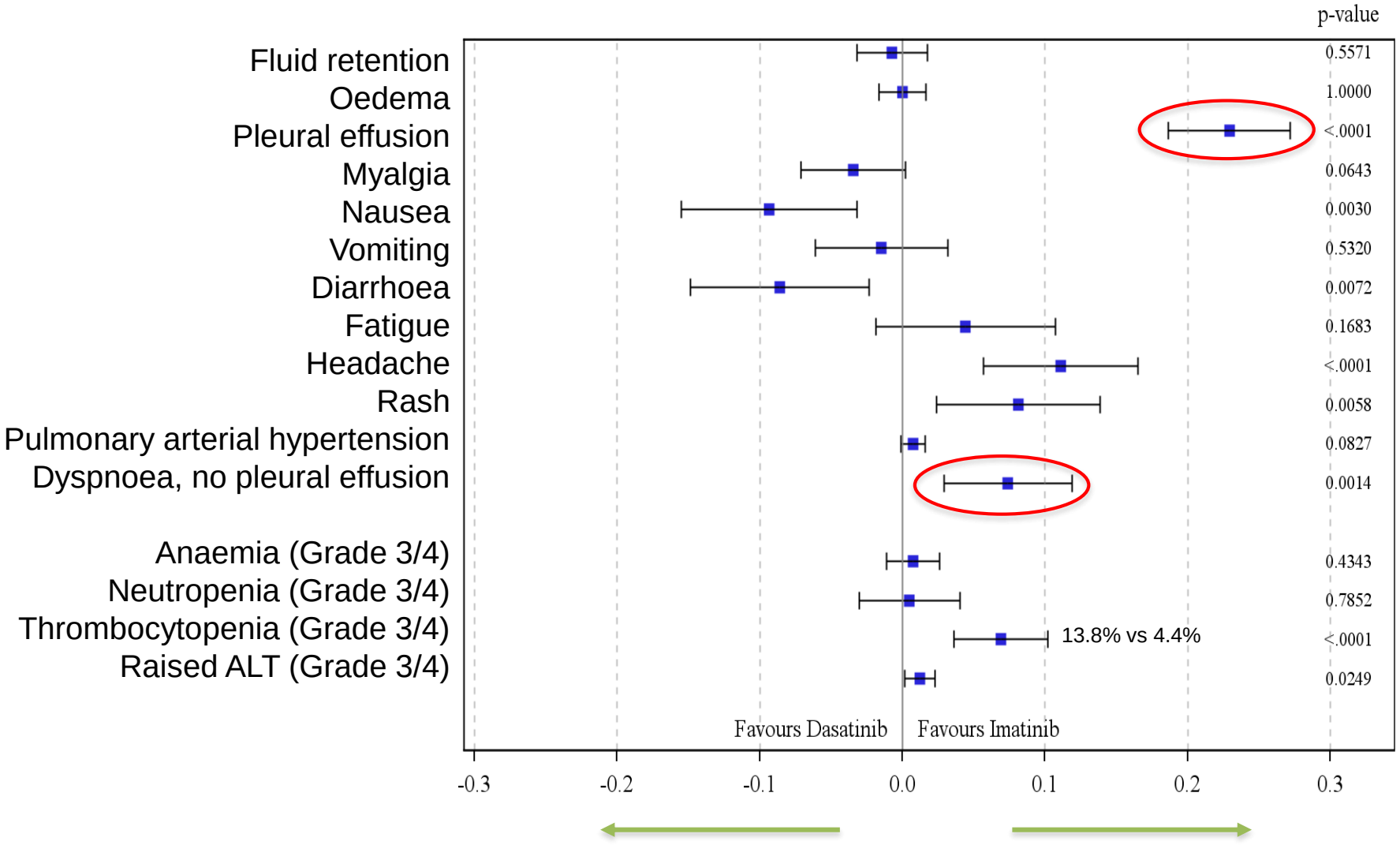
# Comparative AEs

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# Pleural effusion & dyspnoea

| All grades | Imatinib n=406 (%) | Dasatinib n=406 (%) |
|---|---|---|
| Pleural effusion – number of patients | 5 (1.2) | 98 (24.1) |
| **Required drainage procedure** | **1 (20% of 5)** | **22 (22% of 98)** |
| aspiration | 0 (0) | 10 (10) |
| chest drain | 1 (20) | 8 (8) |
| drainage procedure unknown | 0 (0) | 4 (4) |
| other treatment | 1 (20) | 8 (8) |
| | | |
| Dyspnoea, no pleural effusion | 32 (7.9) | 63 (15.5) |
| all grades | 35 (8.6) | 102 (25.1) |
| grades 2/3/4 | 8 (2.0) | 50 (12.5) |

# Cardiovascular AEs

| | Imatinib n=406 (%) | Dasatinib n=406 (%) |
|---|---|---|
| **Cardiac Serious AEs** | **9 (2.2)** | **17 (4.2)** |
| | AF x3, cardiac arrest x1, cardiac failure x3, MI x1, supraventricular tachycardia x1 | ACS x2, AF x3, cardiac failure x5, MI x1, Pericardial effusion x2, cardiac tamponade x1, AV Block x1, cardiomegaly x1, palpitations x1 |
| **Vascular Serious AEs** | **4 (1)** | **6 (1.5)** |
| | AAA rupture x1, DVT x3, | DVT x1, intermittent claudication x1, arterial stenosis x1, haematoma x1, thrombosis x1, lymphoedema x1 |
| **Cerebrovascular Serious AEs** | **4 (1)** | **4 (1)** |
| | Haemorrhagic stroke x1, ischaemic stroke x3 | Haemorrhagic stroke x3, ischaemic stroke x1 |
| **Hypertension (non-serious AE)** | **4 (1)** | **8 (2)** |

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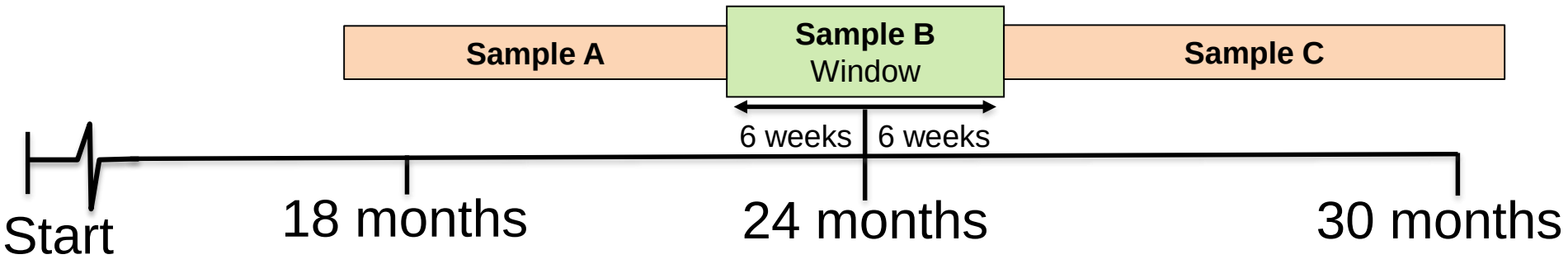
# Cytogenetics at 24 months

| | | Imatinib N=406 (%) | Dasatinib N=406 (%) | Difference (%) | p value |
|---|---|---|---|---|---|
| Major cytogenetic response (MCR) | 12 months | 211 (51.8) | 228 (56.0) | (4.2) | 0.669 |
| | 24 months | 125 (30.7) | 140 (34.4) | (3.7) | 0.787 |
| Complete cytogenetic response (CCR) | 12 months | 171 (42.0) | 217 (53.3) | (11.3) | 0.003 |
| | **24 months** | **112 (27.5)** | **137 (33.7)** | **(6.2)** | **0.189** |
| Missing analyses | 12 months | 136 (33.5) | 146 (35.9) | | |
| | 24 months | 160 (39.4) | 166 (40.9) | | |

Caution required, missing analyses included in denominator

# Definition of ‘responder’ at 24m

1. Patient remains on protocol treatment
2. PCR value available
   - » Sample window extends 6 weeks either side of 24m mark
   - » If no PCR taken within the sample window, values are imputed using windows A + C.
3. PCR <0.1% BCR-ABL1 /ABL1$^{IS}$ [MR3]



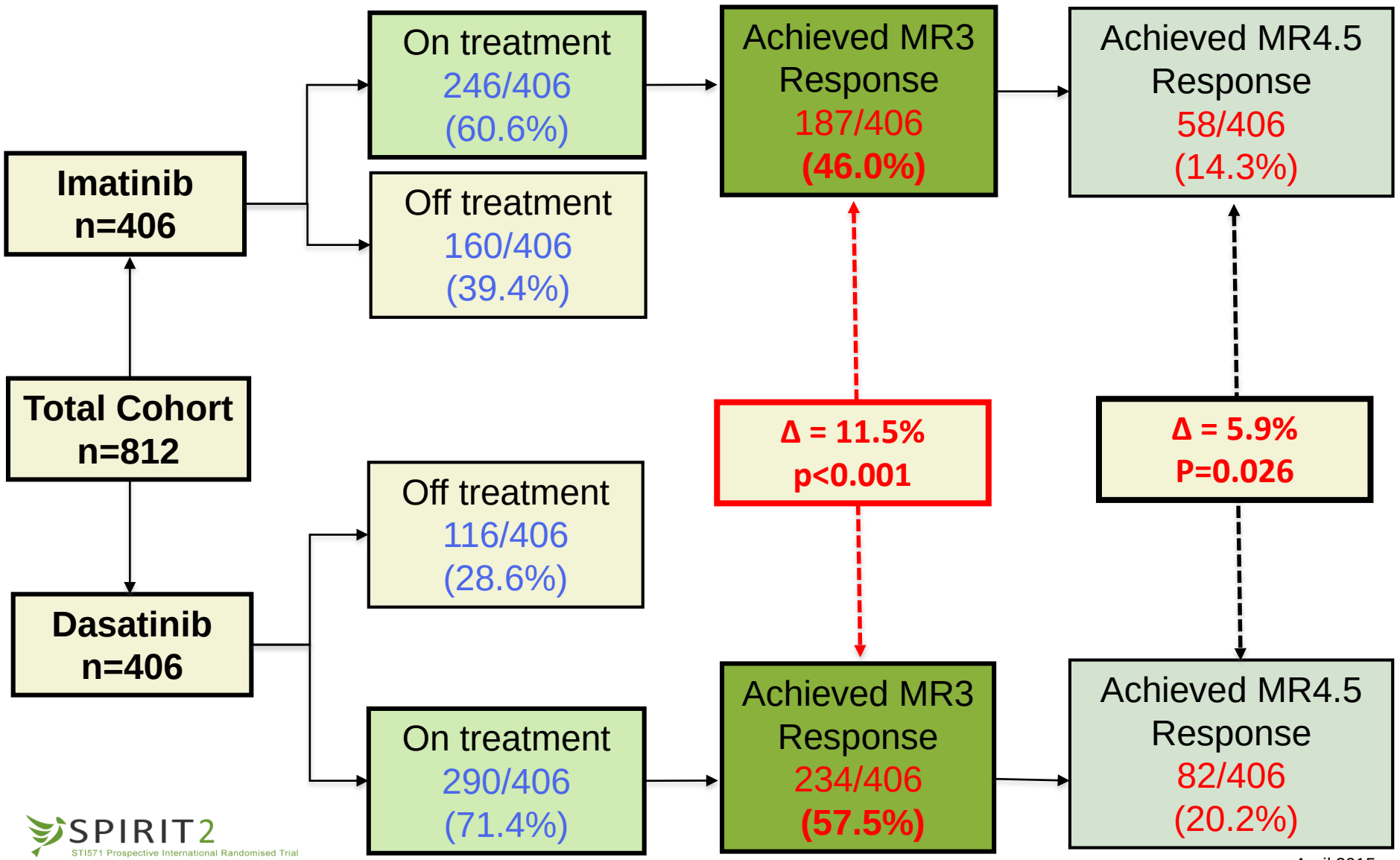
# Imputation

On treatment: 536/812 (66.0%)
Sample B available: 469/536 (87.5% of 536)
Imputated response when no 24m sample: 22 /536 (4.1% of 536)

| Example scenarios: | 18 month sample A | 24 month sample B | 30 month sample C | MR3 response |
|---|---|---|---|---|
| **No imputation needed** | - | MR3 | - | ✓ |
| | - | >MR3 | - | ✗ |
| **Imputed as "response"** | MR3 | No sample | MR3 | ✓ |
| **Imputation not applied (inc. not on study Rx)** | No sample | No sample | MR3 | ✗ |

| Actual values: | | |
|---|---|---|
| **Imatinib** | **Dasatinib** | **Total** |
| 177 | 222 | 399 |
| 40 | 30 | 70 |
| 10 | 12 | 22 |
| 179 | 142 | 321 |

# PCR data *at* 24 months

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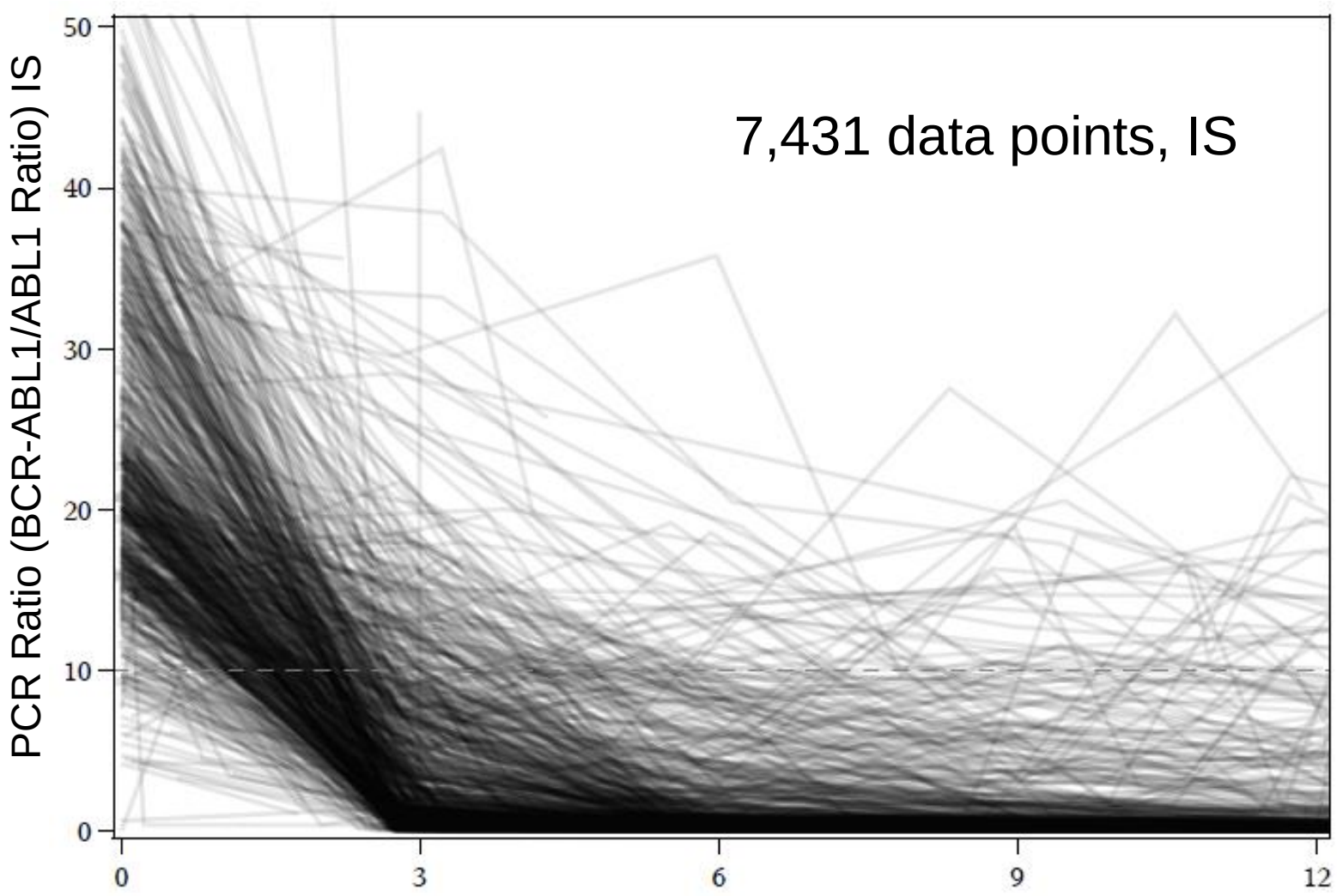
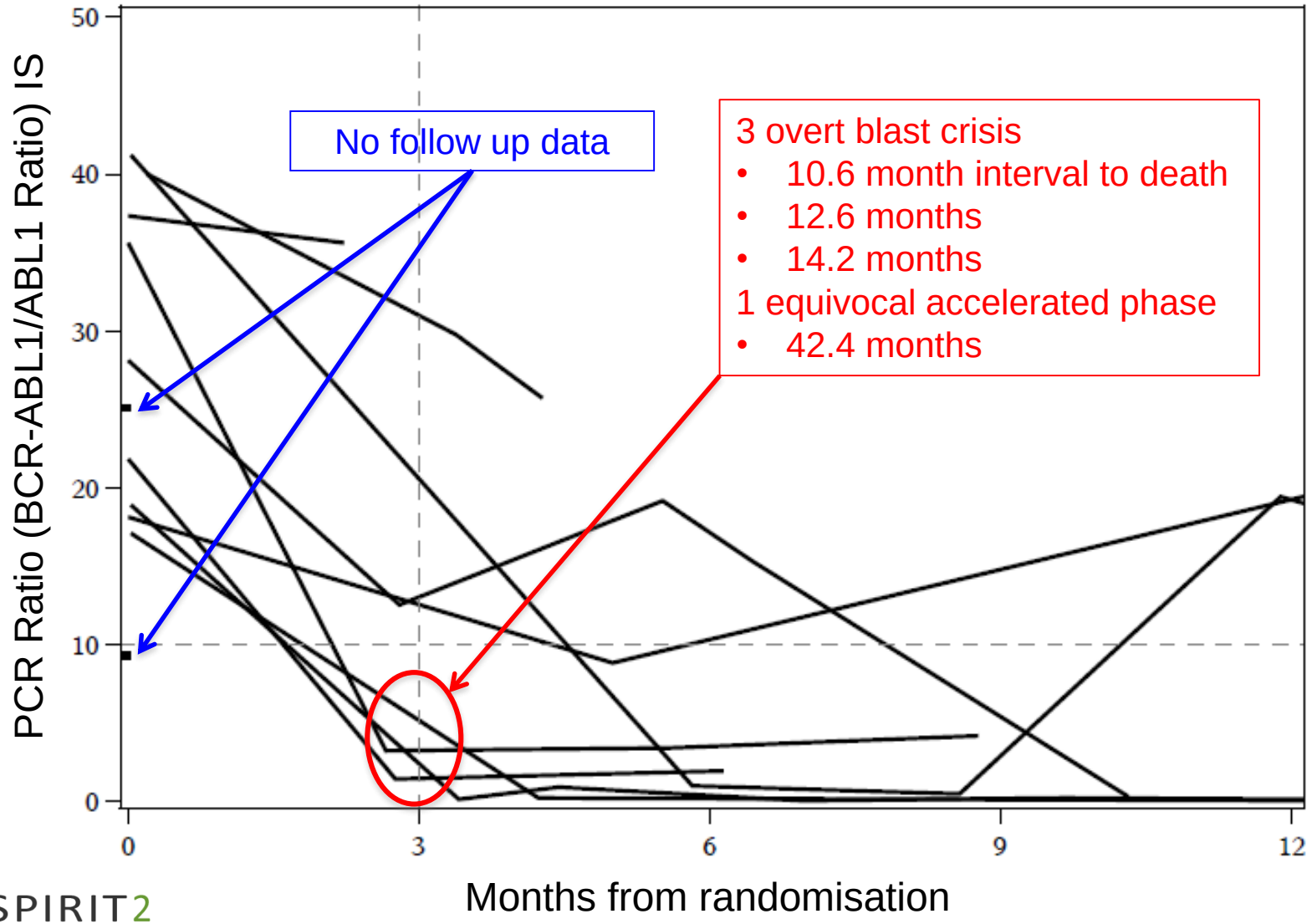
April 2015

# PCR data: all patients, both arms



# 11 patients who ‘died from CML’

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# SPIRIT 2: two year summary

- Largest randomised trial of dasatinib vs imatinib
  - n=814
  - median follow up 3.5 years; 2 years follow up on all patients
- Both drugs generally well tolerated
  - 436 of 812 (53.7%) continue on study medication
  - Imatinib: GI tox;  Dasatinib: pleural effusions, headaches
  - No difference in cardiovascular events
- MR3 rate at two years is: imatinib 46.0%, dasatinib 57.5%
  - $\Delta = 11.5\%$  $p<0.001$
- 774/812 (95.3%) remain alive overall
- No difference in progression or overall survival
- 5yr EFS can be evaluated in 2018

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