SPIRIT2

STI571 Prospective International Randomised Trial

# An NCRI randomised study comparing dasatinib with imatinib in patients with newly diagnosed CML

Stephen O'Brien, Corinne Hedgley, Sarah Adams, Letizia Foroni, Jane Apperley, Tessa Holyoake, Chris Pocock, Jenny Byrne, Lynn Seeley, Wendy Osborne, John McCullough, Mhairi Copland, John Goldman, Richard Clark.

NCRI National Cancer Research Institute

University of Liverpool

Imperial College London

University of Glasgow

Newcastle University

www.spirit-cml.org

The Newcastle Hospitals NHS Foundation Trust

NHS

# Acknowledgements


| | |
|---|---|
| **Data analysis and presentation** | Stephen O'Brien, Corinne Hedgley, Paul Terril, Philip Rowe, John McCullough |
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| **Cell biobanking** | Tessa Holyoake, Alan Hair, Heather Jorgensen, Glasgow |
| **Study Management Committee** | SO'B, CH, Richard Clark, Liverpool; Jane Apperley, Hammersmith, Mhairi Copland (Chair of CML WG) |
| **Data Monitoring Committee** | **John Goldman**, Keith Wheatley, Graham Dark, Charles Schiffer |
| **Sponsor** | Newcastle Hospitals NHS Foundation Trust |
| **Funder** | Bristol-Myers Squibb: Glenn Kroog, Milayna Subar, Sonal Chavda-Sitaram |
| **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) |


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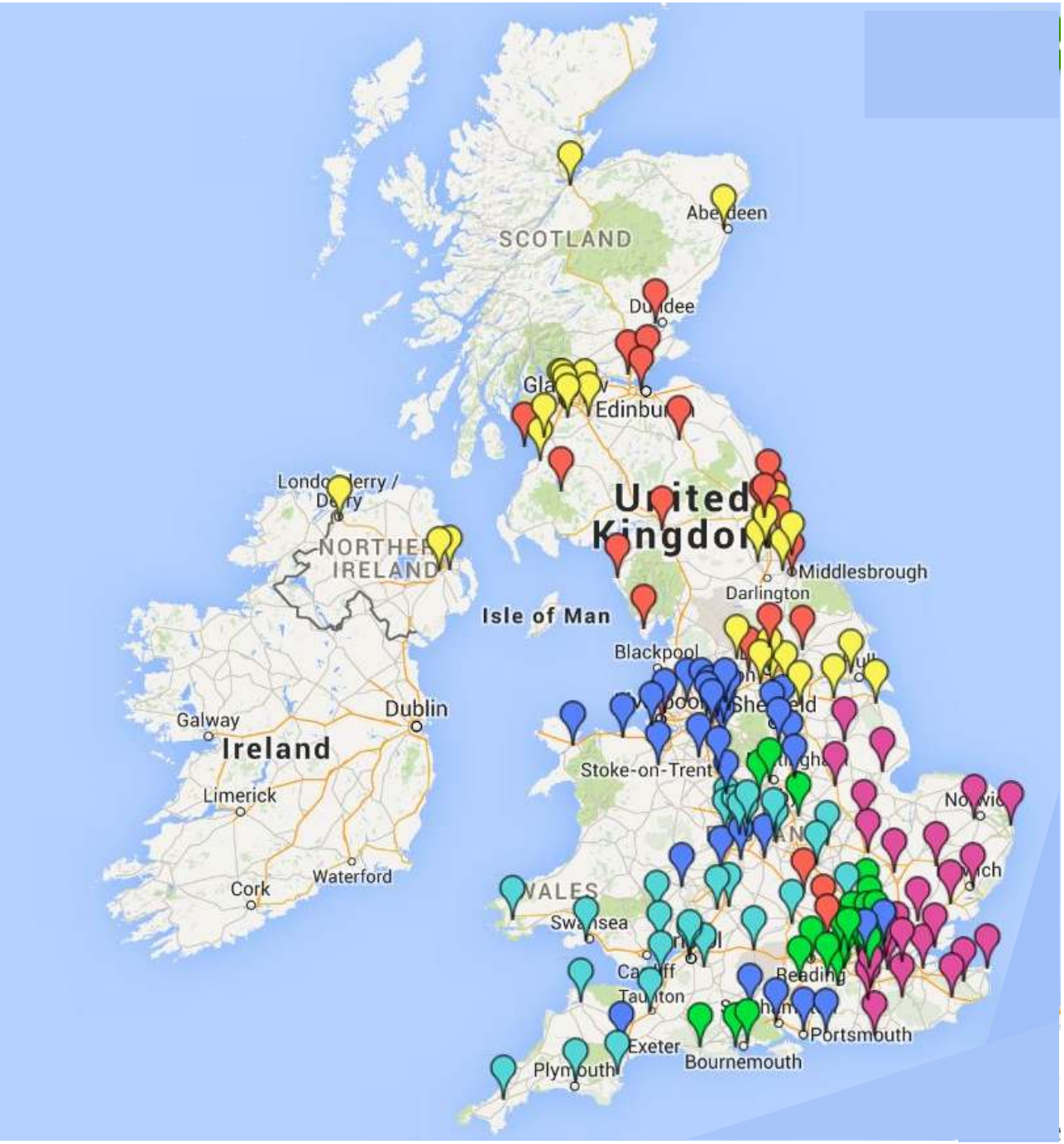
ISRCTN71971 Prospective International Randomised Trial




NCRI
National Cancer Research Institute

814 patients in total

Recruitment closed Feb 2013

172 hospitals set up,145 recruited patients

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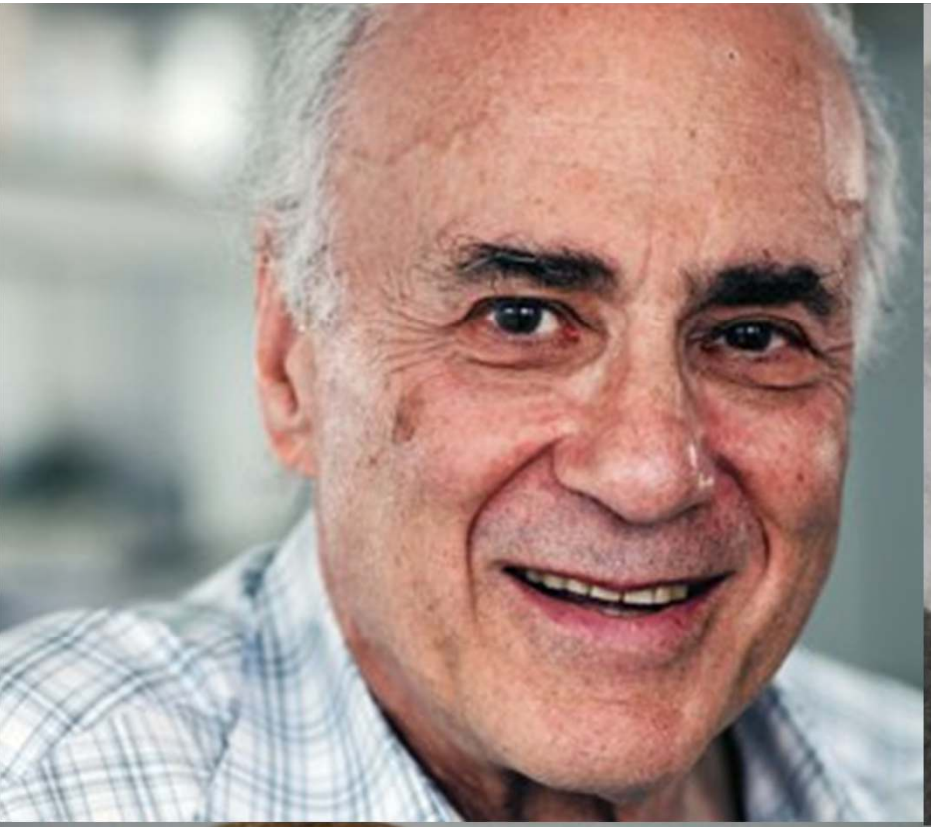

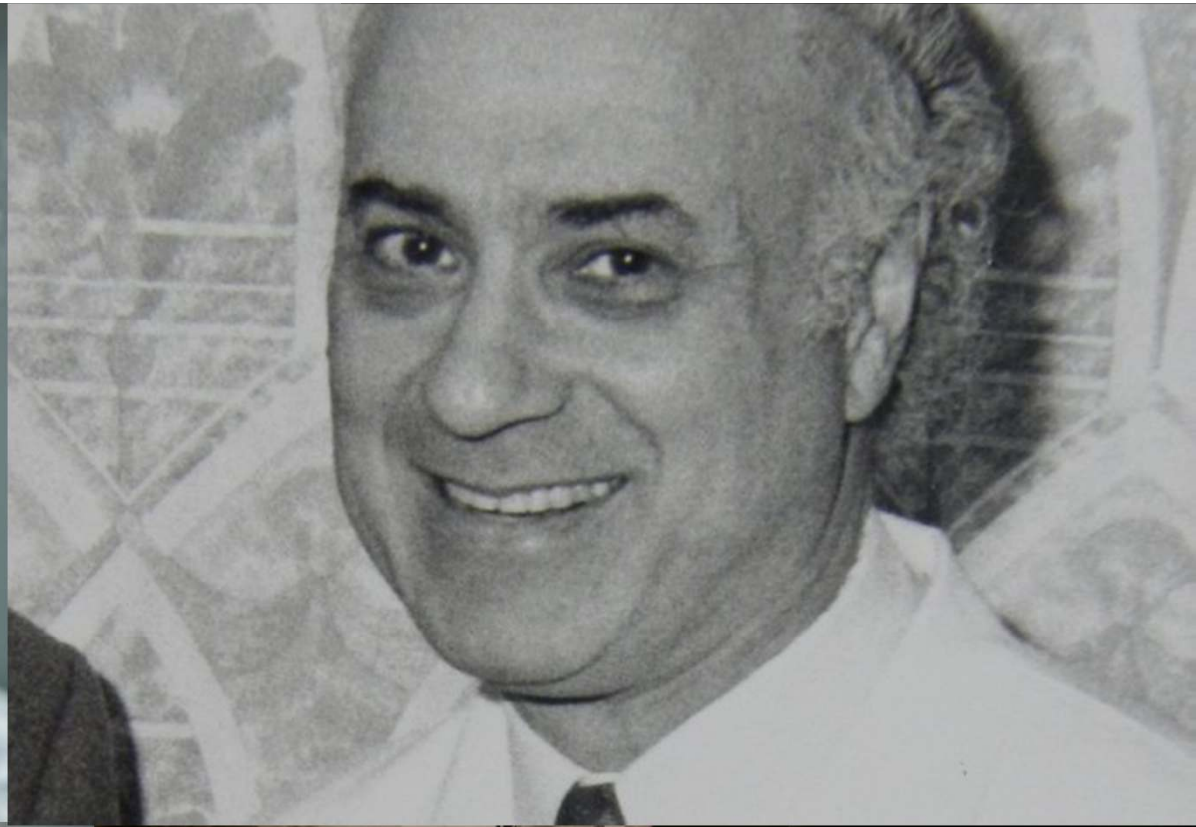


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# Outline

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 3 years:
  - imatinib 55% (69% still on treatment)
  - dasatinib 69% (71% 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

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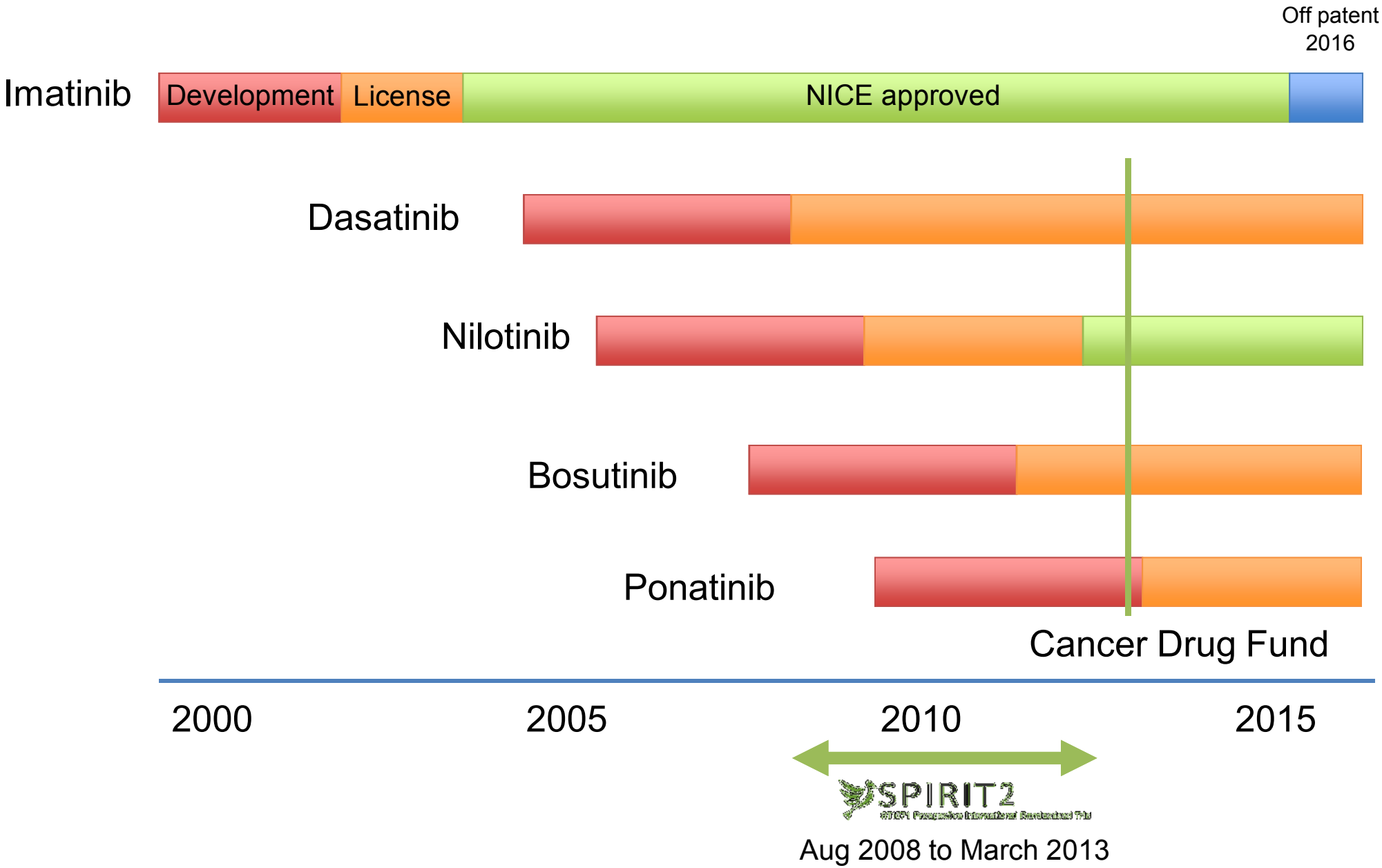
# TKIs in the UK



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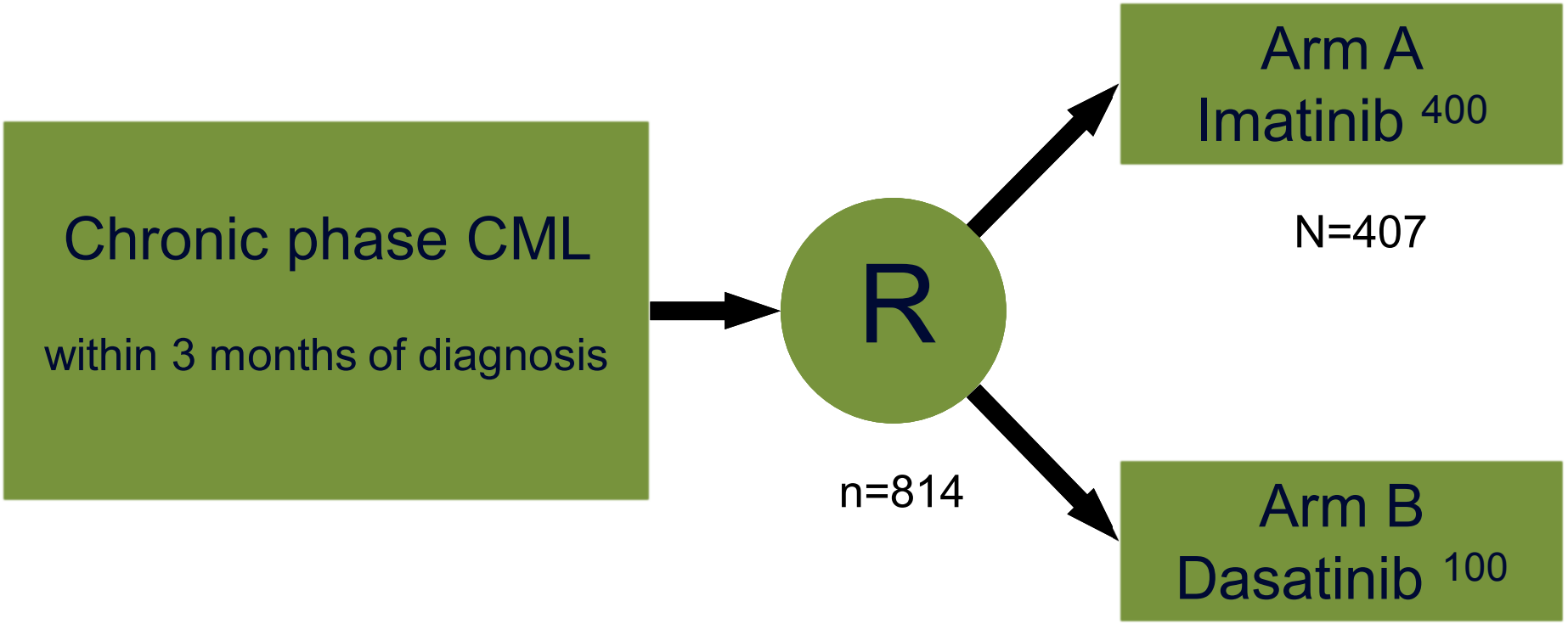
# SPIRIT 2: study design




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

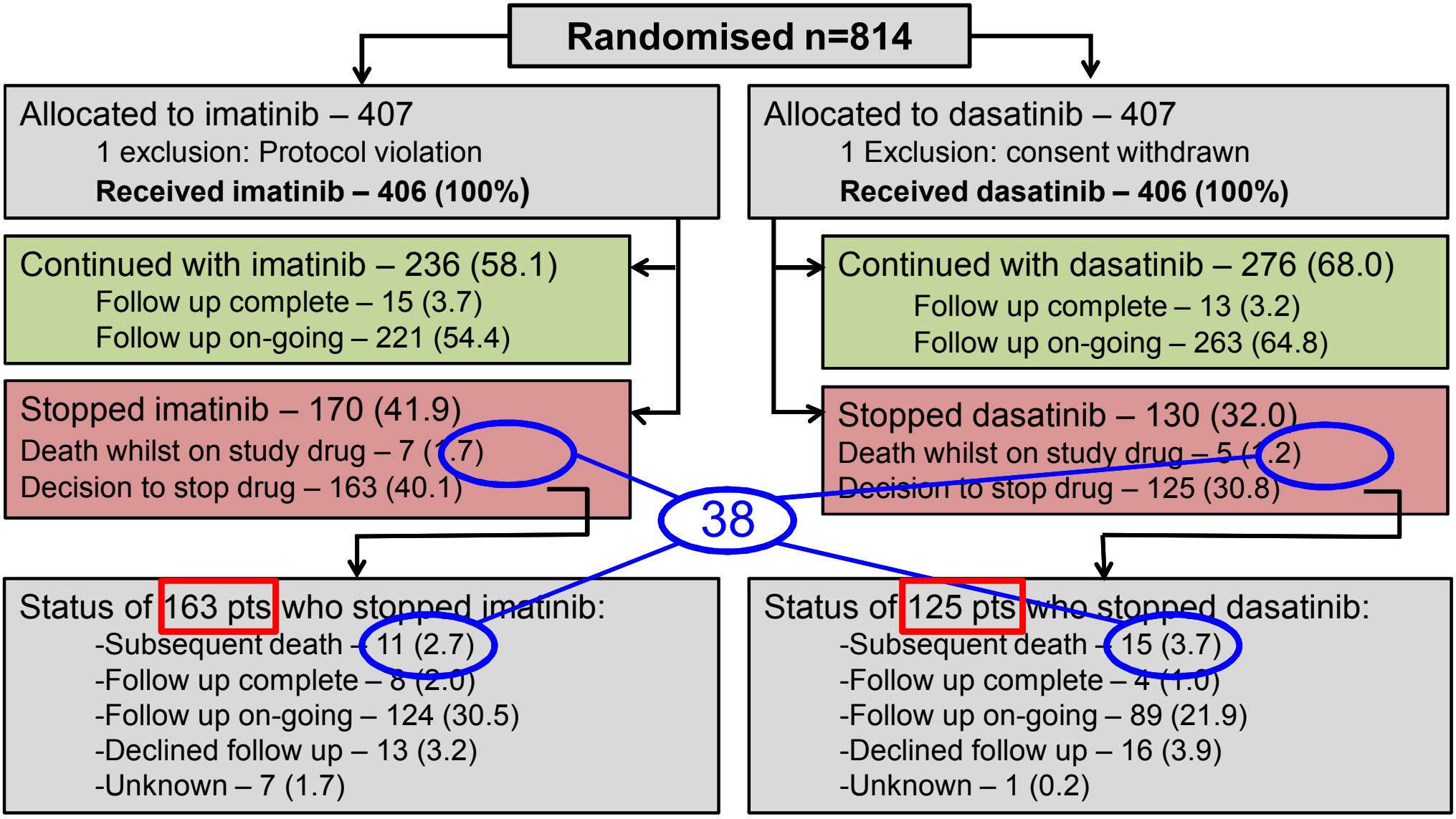
Aug 2008 to Feb 2013
814 in 54 months: 15 per month

| Characteristic | | Imatinib n=407 (%) | Dasatinib n=407 (%) | Total n=814 (%) |
|---|---|---|---|---|
| **Age** | Median | 53.0 | 53.0 | 53.0 |
| | Range | 18-87 | 18-89 | 18-89 |
| **Gender** | Female | 165 (40.5) | 156 (38.3) | 321 (39.4) |
| | Male | 241 (59.2) | 250 (61.4) | 491 (60.3) |
| | NK | 1 (0.2) | 1 (0.2) | 2 (0.2) |
| **Available data for Sokal** SA2 | | 242 (59.6) | 246 (60.6) | 488 (60.1) |
| | | | | |
| **Follow up (months)** | Median | 36.9 | 38.3 | 37.4 |
| | Range | 2 – 69 | 0 – 69 | 0 - 69 |

Slide 15

SA2 I'm not sure where these numbers came from originally? Do they need checking or as per BSH numbers is fine?
Sarah Adams, 8/15/2014

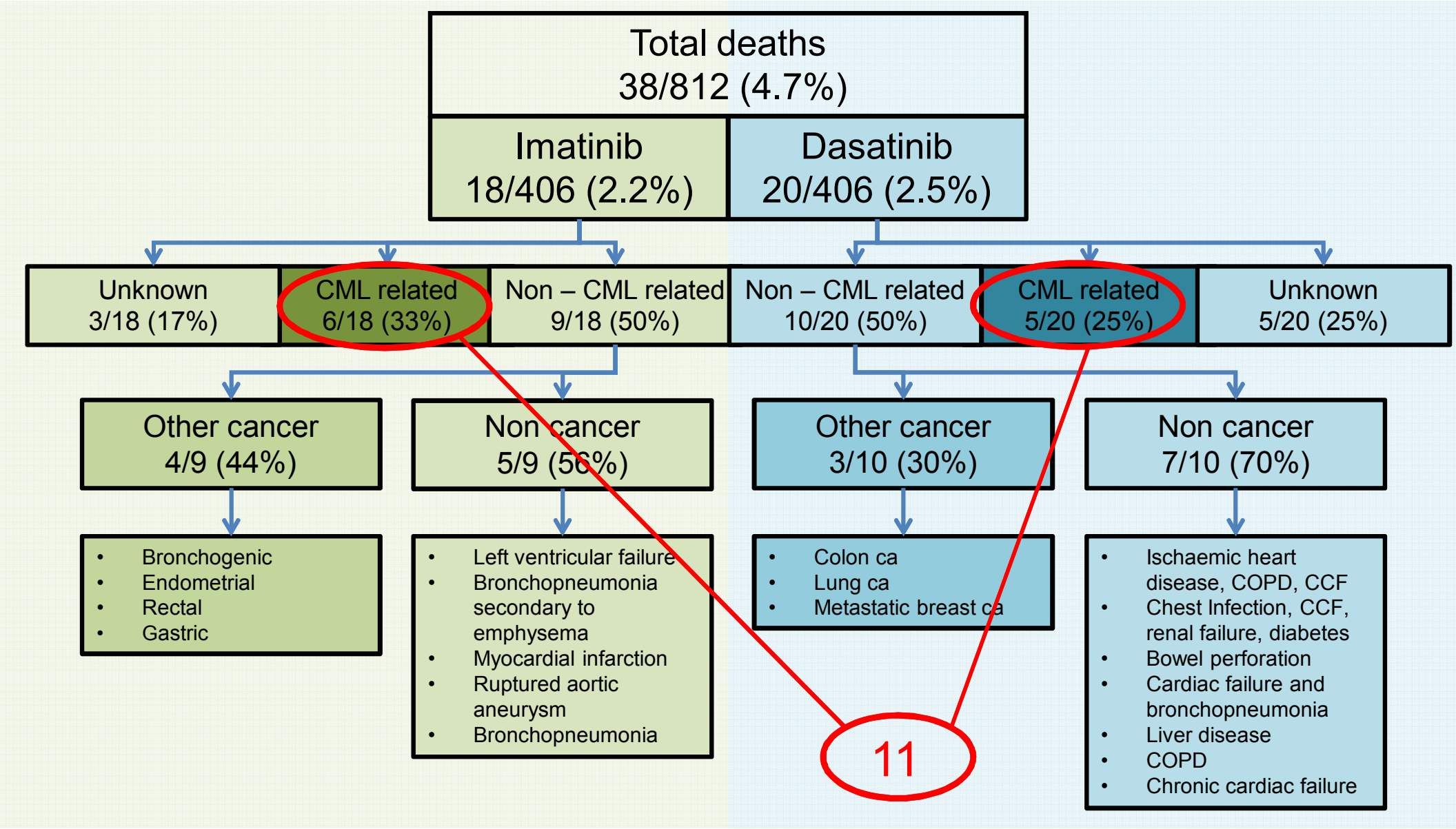
# What happened to all the patients?



# Patients who stopped study drug

| Reason for stopping study drug (exc. death) | Imatinib 406 (%) | Dasatinib 406 (%) | Total 812 (%) |
|---|---|---|---|
| Consent withdrawn | 7 (1.7) | 9 (2.2) | 16 (2.0) |
| Disease progression - accelerated phase | 1 (0.2) | 2 (0.5) | 3 (0.4) |
| Disease progression - blast crisis | 7 (1.7) | 4 (1.0) | 11 (1.4) |
| Failure to achieve CCR after 24 months | 4 (1.0) | 1 (0.2) | 5 (0.6) |
| Failure to achieve MCR after 12 months | 23 (5.7) | 3 (0.7) | 26 (3.2) |
| Intolerance - non haem tox | 53 (13.1) | 80 (19.7) | 133 (16.4) |
| Intolerance - haem/lab tox | 10 (2.5) | 10 (2.5) | 20 (2.5) |
| Loss of CHR | 5 (1.2) | 0 | 5 (0.6) |
| Loss of MCR | 5 (1.2) | 2 (0.5) | 7 (0.9) |
| Other reason | 4 (1.0) | 11 (2.7) | 29 (3.6) |
| Reason unknown - Lost to follow up | 2 (0.5) | 0 | 2 (0.2) |
| 'Inadequate response' (cytogenetic, haematological, molecular, mutation detected) | 42 (10.3) | 3 (0.7) | 45 (5.5) |
| **Total** | **163 (40.1)** | **125 (30.8)** | **288 (35.5)** |

# Cause of death



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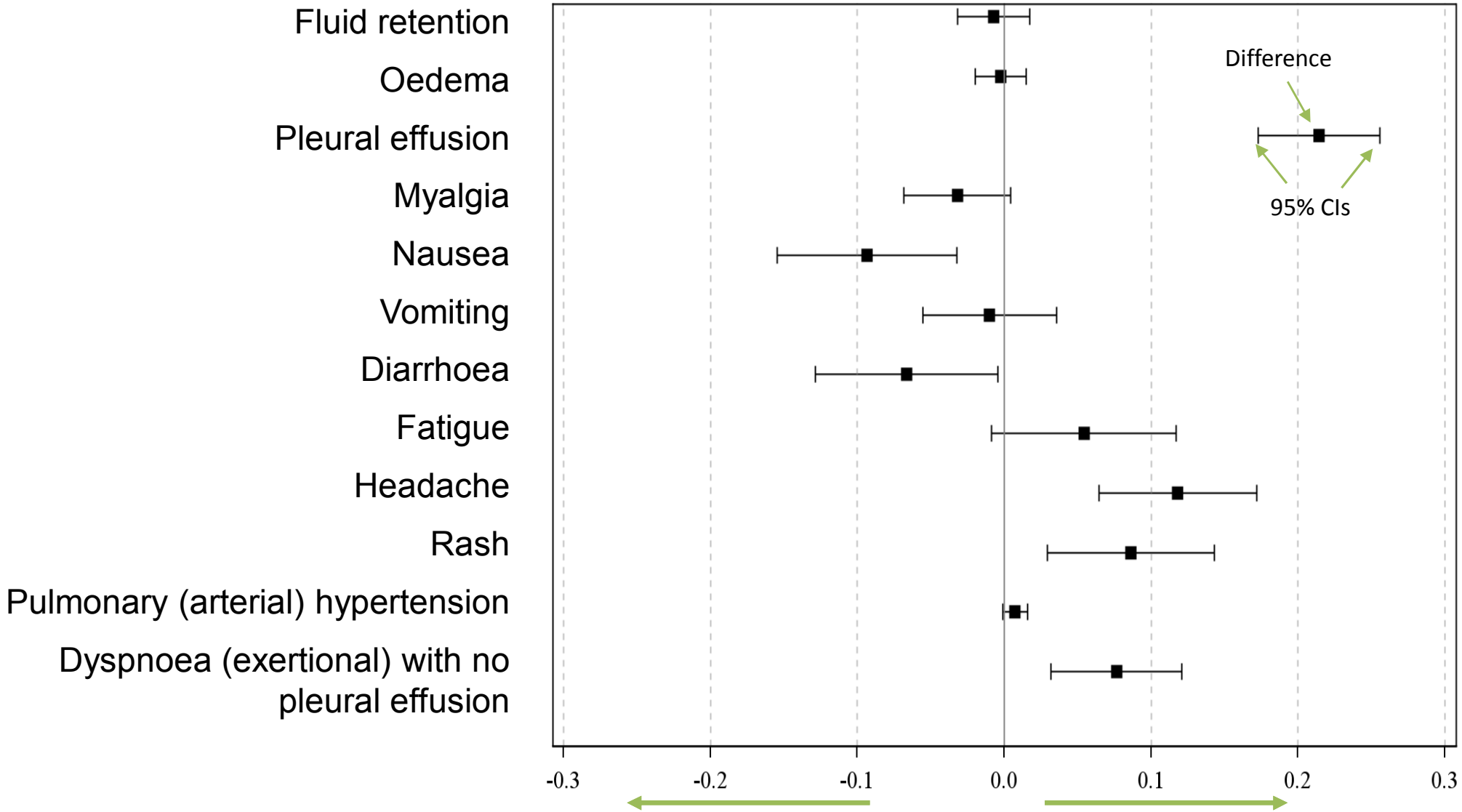
# Comparative AEs



# Adverse events

| All grades | Imatinib n=406 (%) | Dasatinib n=406 (%) |
|---|---|---|
| Fluid retention | 15 (3.7) | 12 (3.0) |
| Oedema | 7 (1.7) | 6 (1.5) |
| Pleural effusion | 3 (0.7) | 90 (22.2) |
| Required chest drain | 0 | 13 (3.2)<br>*13 of 90 is 14.4%* |
| Myalgia | 37 (9.1) | 24 (5.9) |
| Nausea | 131 (32.2) | 93 (22.9) |
| Vomiting | 53 (13.1) | 49 (12.1) |
| Diarrhoea | 130 (32.0) | 103 (25.4) |
| Fatigue | 109 (26.8) | 131 (32.3) |
| Headache | 55 (13.5) | 103 (25.4) |
| Rash | 73 (18.0) | 108 (26.6) |
| Dyspnoea, no pleural effusion | 34 (8.4) | 65 (16.0) |

# Cardiovascular AEs

| | Imatinib n=406 (%) | Dasatinib n=406 (%) |
|---|---|---|
| Arterial CV events | 3 (0.7)* | 9 (2.2)* |
| | myocardial infarction x1, myocardial ischaemia x1, cardiac arrest x1 | acute coronary syndrome x1, angina pectoris x4, angina unstable x1, arterial stenosis x1, intermittent claudication x1, myocardial infarction x1, myocardial ischaemia x1 |
| Hypertension | 3 (0.7)* | 8 (2.0)* |
| Venous events | 4 (1.0)* | 4 (1.0)* |

*Differences not significant

# Lab AEs

| | Imatinib 406 (%) | | Dasatinib 406 (%) | | Total 812 (%) | |
|---|---|---|---|---|---|---|
| | All grades | Grade 3/4 | All grades | Grade 3/4 | All grades | Grade 3/4 |
| **Anaemia** | 363 (89.4) | 101 (24.9) | 372 (91.6) | 124 (30.5) | 735 (90.5) | 225 (27.7) |
| **Neutropenia** | 189 (46.6) | 42 (10.3%) | 212 (52.2) | 46 (11.3) | 401 (49.4) | 88 (10.8) |
| **Thrombocytopenia** | 197 (48.5) | 19 (4.7) | 281 (69.2) | 55 (13.5) | 478 (58.9) | 74 (9.1) |
| **Elevated ALT** | 153 (37.7) | 7 (1.7) | 182 (44.8) | 0 | 335 (41.3) | 7 (0.9) |
| **Elevated creatinine** | 83 (20.4) | 13 (3.2) | 76 (18.7) | 18 (4.4) | 159 (19.6) | 31 (3.8) |

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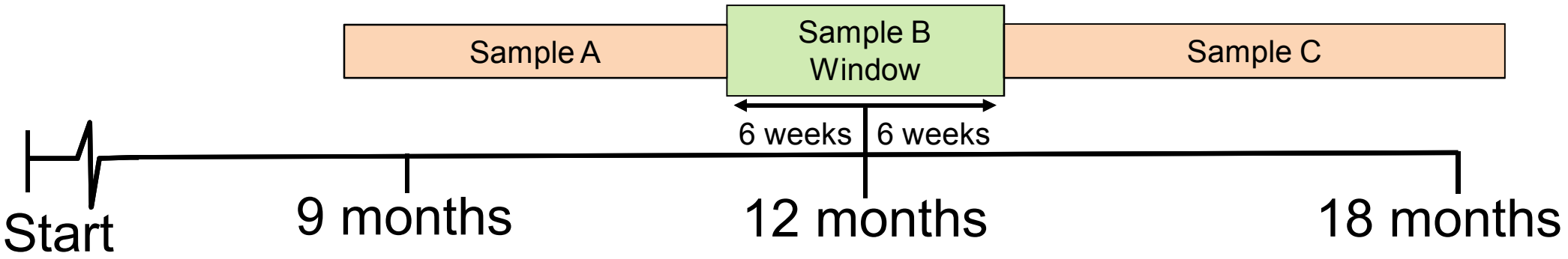
# Cytogenetics at 12 months

| | Imatinib (%) | Dasatinib (%) | Difference (%) | p value |
|---|---|---|---|---|
| Major cytogenetic response (MCR) | 209/406 (51.5) | 228/406 (56.2) | (4.7) | 0.181* |
| Complete cytogenetic response (CCR) | 169/406 (41.6) | 217/406 (53.4) | (11.8) | <0.001* |
| Missing analyses | 181/406 (44.6) | 166/406 (40.9) | | |

*caution required, missing analyses included in denominator

# Definition of ‘responder’ at 12m

1. Patient remains on protocol treatment
2. PCR value available
   - » Sample window extends 6 weeks either side of 12m 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]

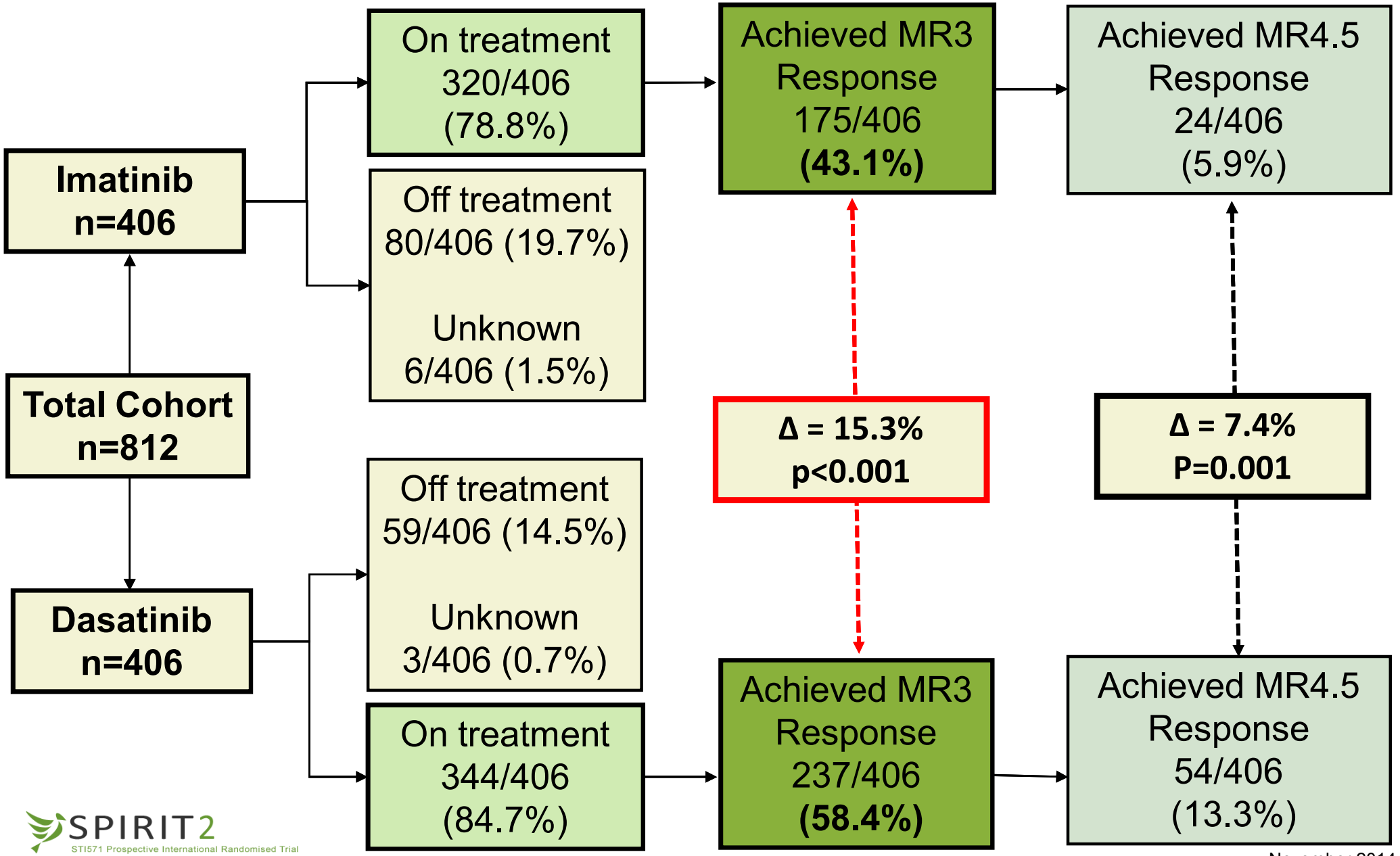


# Imputation

| | |
|---|---|
| On treatment: | 664/812 (81.8%) |
| Sample B available: | 619/664 (93.2% of 664) |
| Imputation applied as no 12m sample: | 45/664 (6.7% of 664) |

| Example scenarios: | 9 month sample A | 12 month sample B | 18 monts sample C | MR3 response | Actual values: Imatinib | Dasatinib | Total |
|---|---|---|---|---|---|---|---|
| **No imputation needed** | - | MR3 | - | ✓ | 172 | 230 | 402 |
| | - | >MR3 | - | ✗ | 124 | 93 | 217 |
| **Imputed as "response"** | MR3 | No sample | MR3 | ✓ | 3 | 7 | 10 |
| **Imputed as "No response" (e.g)** | No sample' | No sample | MR3 | ✗ | 107 | 76 | 183 |

# 12 month PCR

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November 2014

# PCR response and pleural effusion

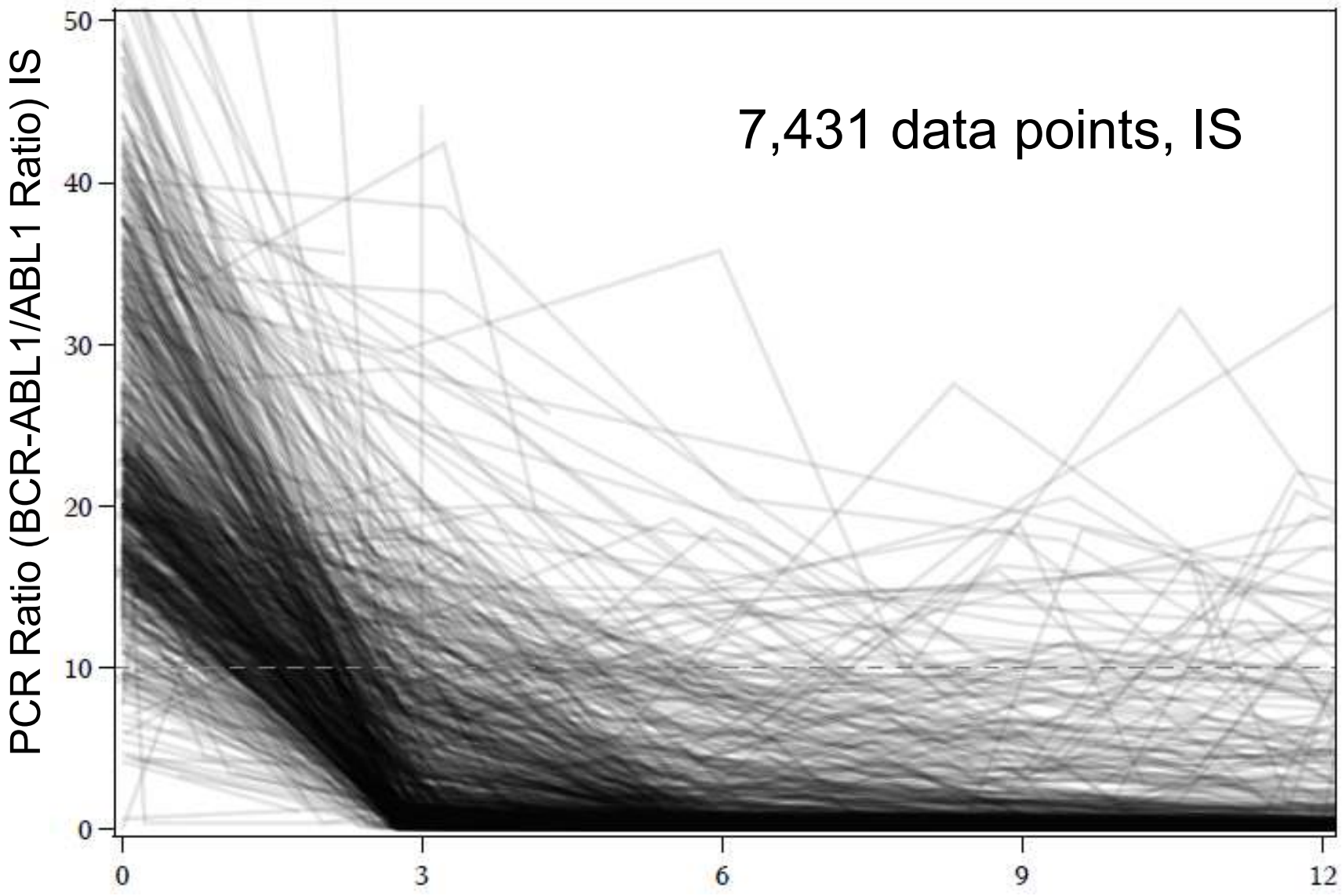
| | Imatinib n=406 | Dasatinib n=406 | Total n=812 |
|---|---|---|---|
| PCR <0.1% (MR3) | 175 (43.1%) | 237 (58.4%) | 412 (50.7%) |
| **No pleural effusion** | 403 | 316 | 719 |
| PCR <0.1% (MR3) | 174 (43.2%) | *178 (56.3%) | 352 (49.0%) |
| **With pleural effusion** | 3 | 90 | 93 |
| PCR <0.1% (MR3) | 1 (33.3%) | *59 (65.6%) | 60 (64.5%) |

*Difference not significant

# Partial PCR responses

| | Imatinib | | Dasatinib | | Totals | |
|---|---|---|---|---|---|---|
| **3 month PCR samples available** | **317** | **100%** | **319** | 100% | **636** | 100% |
| PCR > 10% (MR1) at 3 months | 66 | **20.8%** | 20 | **6.3%** | 86 | 13.5% |
| PCR < 10% (MR1) at 3 months | 251 | 79.2% | 299 | 93.7% | 550 | 86.5% |
| **12 month PCR samples available** | **210** | **100%** | **267** | **100%** | 477 | 100% |
| PCR > 1% (MR2) at 12 months* | 20 | **9.5%** | 10 | **3.7%** | 30 | 6.3% |
| PCR < 1% (MR2) at 12 months* | 190 | 90.5% | 257 | 96.3% | 447 | 93.7% |
| | | | | | | |
| Total with 'less than ideal' progress | 86/317 | **27.1%** | 30/319 | **9.4%** | 116/636 | 18.2% |

# PCR data: all patients, both arms

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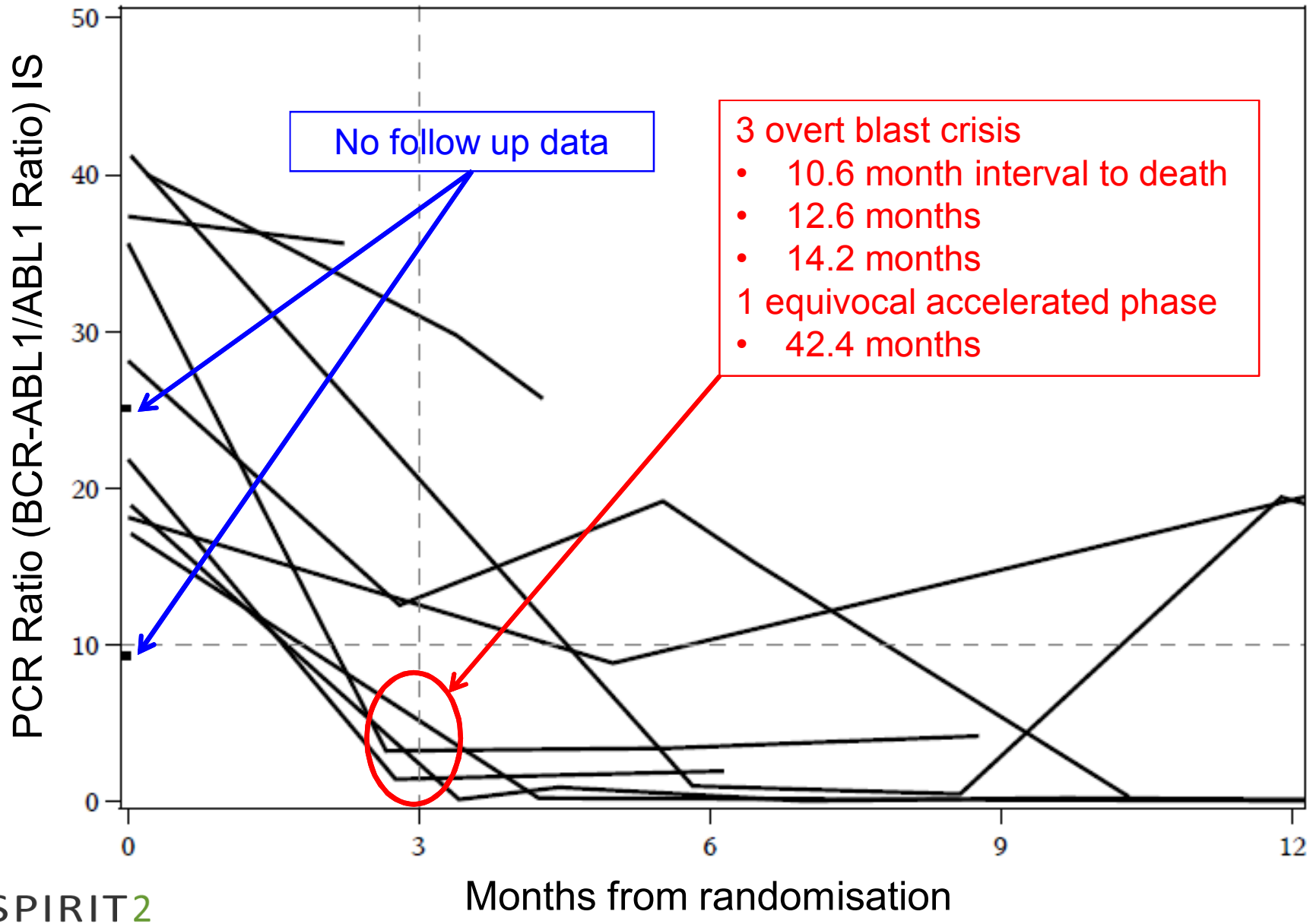
# 11 patients who ‘died from CML’



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# SPIRIT 2 summary

- Largest investigator-conducted randomised trial of dasatinib vs imatinib
  - n=814
  - median follow up 3 years
- Both drugs generally well tolerated
  - 512 of 812 (62.9%) continue on study medication
  - Imatinib: GI tox;  Dasatinib: pleural effusions, headaches
  - No difference in cardiovascular events
- MR3 rate at one year is: imatinib 43%, dasatinib 58%
- 774/812 (95.3%) remain alive overall
  - imatinib 388/406 (95.5%); dasatinib 386/406 (95.0%)
- No difference in progression or overall survival

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# Comparison with Dasision

| | Imatinib (%) | Dasatinib (%) | Difference (%) | p value |
|---|---|---|---|---|
| **Dasision[1,2]** | | | | |
| MR[3] at 1 year[1] | 28 | 46 | 18 | <0.0001 |
| MR[3] at 3 years*[2] | 55 | 69 | 14 | <0.0001 |
| **SPIRIT 2** | | | | |
| MR[3] at 1 year | 43 | 58 | 15 | <0.001 |

[1]Kantarjian *et al*. NEJM (2010); 362:2260
[2]Jabbour *et al*. Blood (2014); 123: 494-500
*rates are KM cumulative incidence
See also Cortes *et al*. Abstract 154

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