Chronic Myeloid Leukaemia Working Group

Richard Clark

Steve O'Brien

Chronic Myeloid Leukaemia

- SPIRIT (1): some data! Steve O'Brien
- SPIRIT 2 Steve O'Brien
- CML Registry and ELN
- CML meetings 2008

First line: current situation

- Imatinib vs IFN
  - 87% probability of 5yr PFS by KM (IRIS data)
  - Direct IFN comparison no longer possible
- Imatinib vs…
  - Imatinib + IFN, high-dose imatinib
  - SPIRIT studies and TOPS
- Imatinib vs…
  - Nilotinib - industry
  - Dasatinib - industry
  - Bosutinib, INNO-406? - industry
- No studies so far of:
  - Nilotinib vs dasatinib
  - Bosutinib vs nilotinib etc.

First line, MD Anderson

	Dasatinib	Nilotinib
No. patients	40	35
Median follow up	18 months	6.5 months
CCR at 12 months	95%	30 of 31 at 3 months
Grade 3/4 neutropenia	5%	3%
Grade 3/4 thrombocytopenia	10%	6%
3/4 pleural effusion	0%	0%
Treatment interruption	46%	43%

non randomised

European Leukemia Net

European Treatment and Outcome Study (EUTOS)

1) Standardisation of BCR-ABL transcript quantitation
   led by Prof. Nick Cross (Salisbury) ~22 UK labs

2) CML Registry: desired UK contribution is unclear

3) Plasma imatinib levels…

4) (Spread of excellence)

CML Meetings

- Autumn 2007
  - Professional: Newcastle (with MPD group)
    - Steve O'Brien
  - Patients & carers: Edinburgh
    - Tessa Holyoake
- Autumn 2008
  - Both likely to be in London/Cambridge
  - Date tbc, 7th/8th November?
    - Brian Huntly

Members of CML Working Group

Jane Apperley

Jenny Byrne

Letizia Foroni

John Goldman

Corinne Hedgley

Tessa Holyoake

Brian Huntly

Anne Lennard

Guy Lucas

David Marin

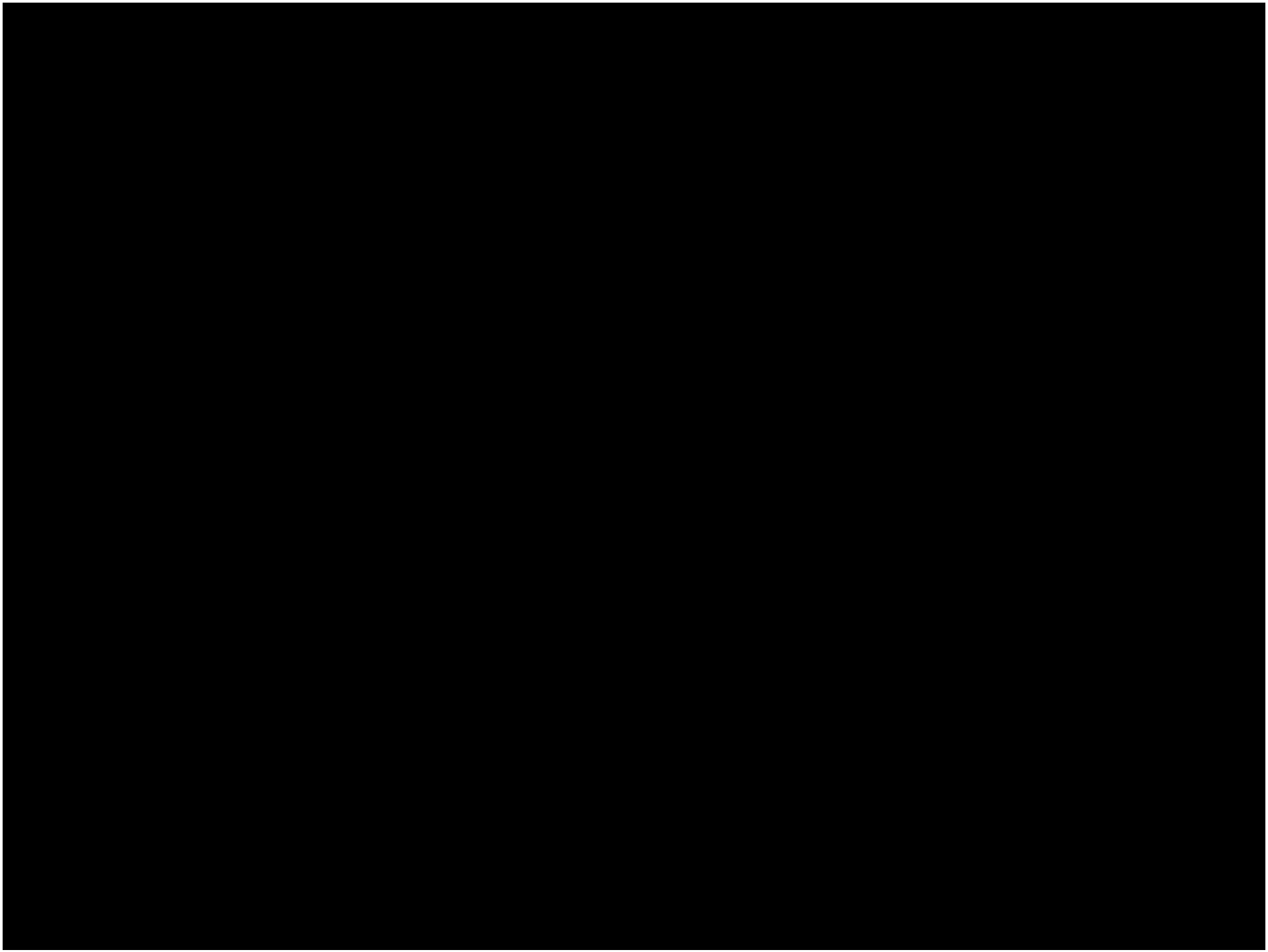
Michael O'Dwyer

Steve O'Brien (SPIRIT CI)

Pat Shepherd

Graeme Smith

Richard Clark (Chair)




SPIRIT

SPIRIT studies

Thank you!

SPIRIT studies

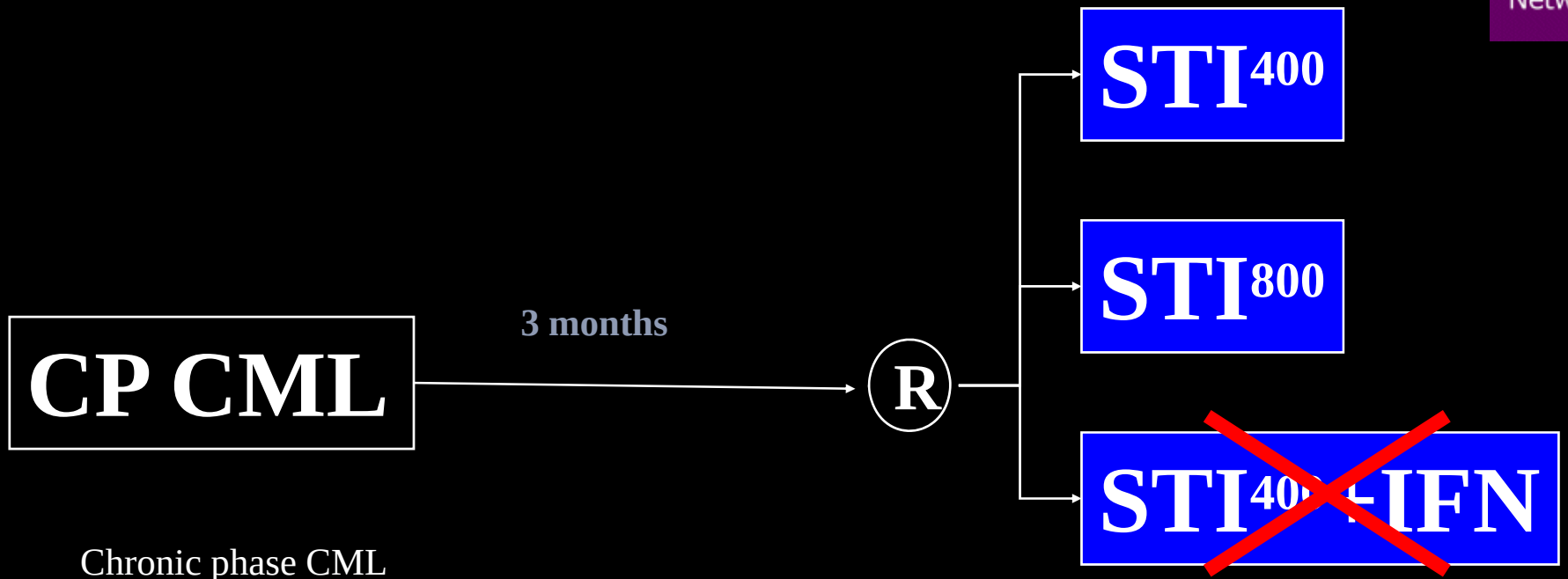
- SPIRIT ‘1’
  - Schema, state of play, recruitment
  - One year pooled results
    - Efficacy, toxicity
    - Survey results from 2007
- SPIRIT ‘2’
  - Design
  - Endpoints
  - Where we’re up to (nearly there…)


1
SPIRIT

STI571 Prospective International Randomlsed Trial

SPIRIT

NCRN National Cancer Research Network



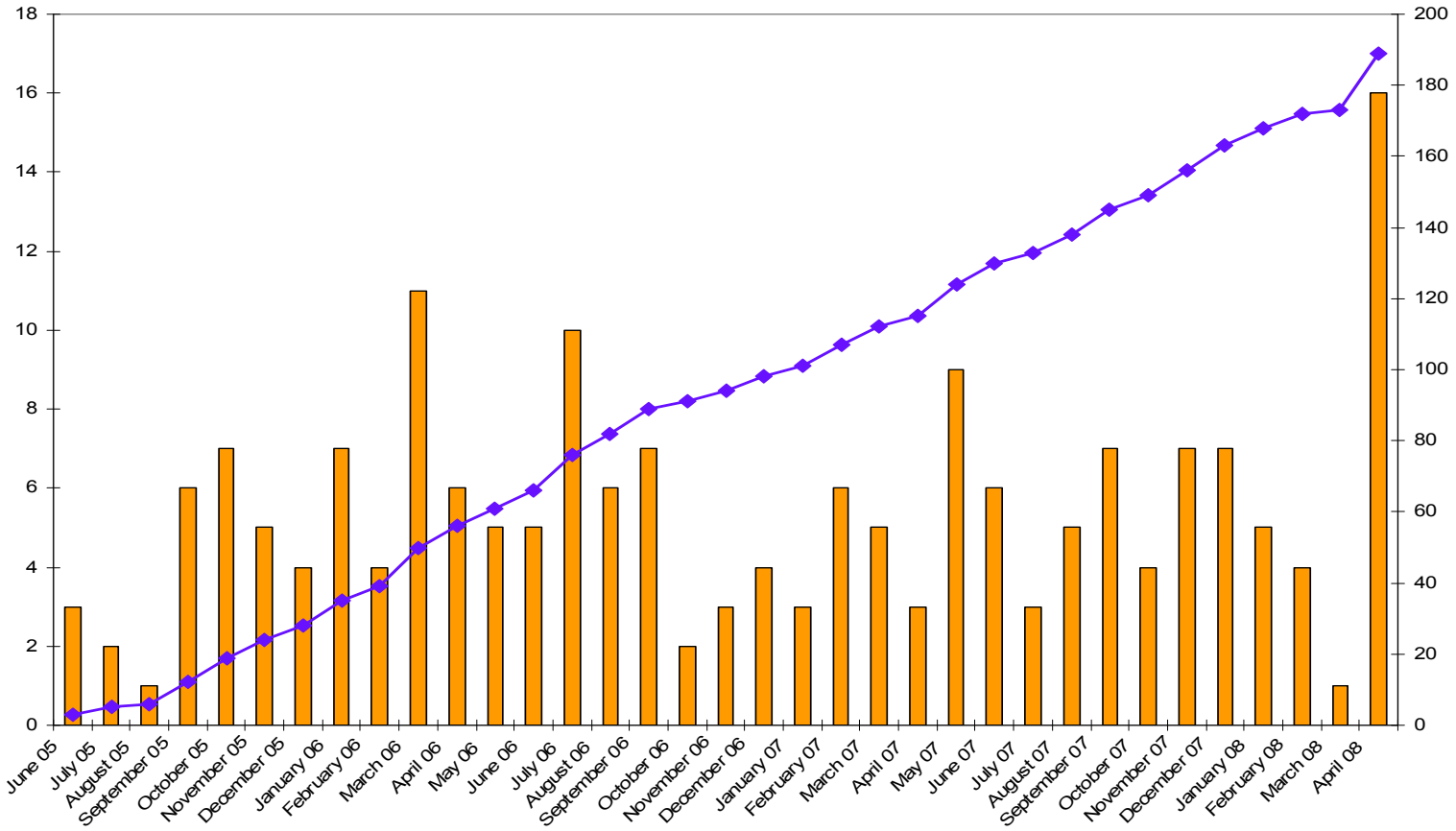
Chronic phase CML within 3 months of diagnosis

www.spirit-cml.org

SPIRIT '*1*': state of play

- Open for recruitment since June 2005
- 96 centres open for recruitment
- 194 patients recruited to-date
- Recruitment Survey May 2007
- Arm C (IFN) closed in February 2008
- Europe

Recruitment



One year results: pooled

- We analysed patients who we would have expected to reach 1 year visit by March 2008.
- 115 patients analysed – dataset not complete
- All three original arms
- Toxicity
- Efficacy
- Discontinuations

Basic demographics

- Average age = 53 (range 19-75 years)
- 63% male
- Recruited from 41 sites across the UK

Efficacy

- Haematological Response at 3 months
  - 95% patients achieved CHR

- Cytogenetic Response at 1 year
  - 86% patients achieved a CCyR
    - Caution…

(based on 37 patients data, excluding withdrawn patients)

IRIS Comparison: Time to Achieve a CCyR

- The majority of pts (88%) achieved a CCyR in ≤ 18 months

  52% achieved a CCyR in ≤ 6 months

Time Intervals to Achieve a CCyR (N = 509)*	n	%	
≤ 6 months	265	52	} 71
> 6 ≤ 12 months	99	19	
>12 ≤ 18 months	34	7	
> 18 months	49	10	
No CCyR while on imatinib study treatment	62	12	

*Patients were evaluable after receiving ≥1 year of imatinib therapy; 42 pts who discontinued imatinib before 1 year were excluded from the analysis.
CCyR = 0% metaphases, MCyR = 0 – 35% metaphases

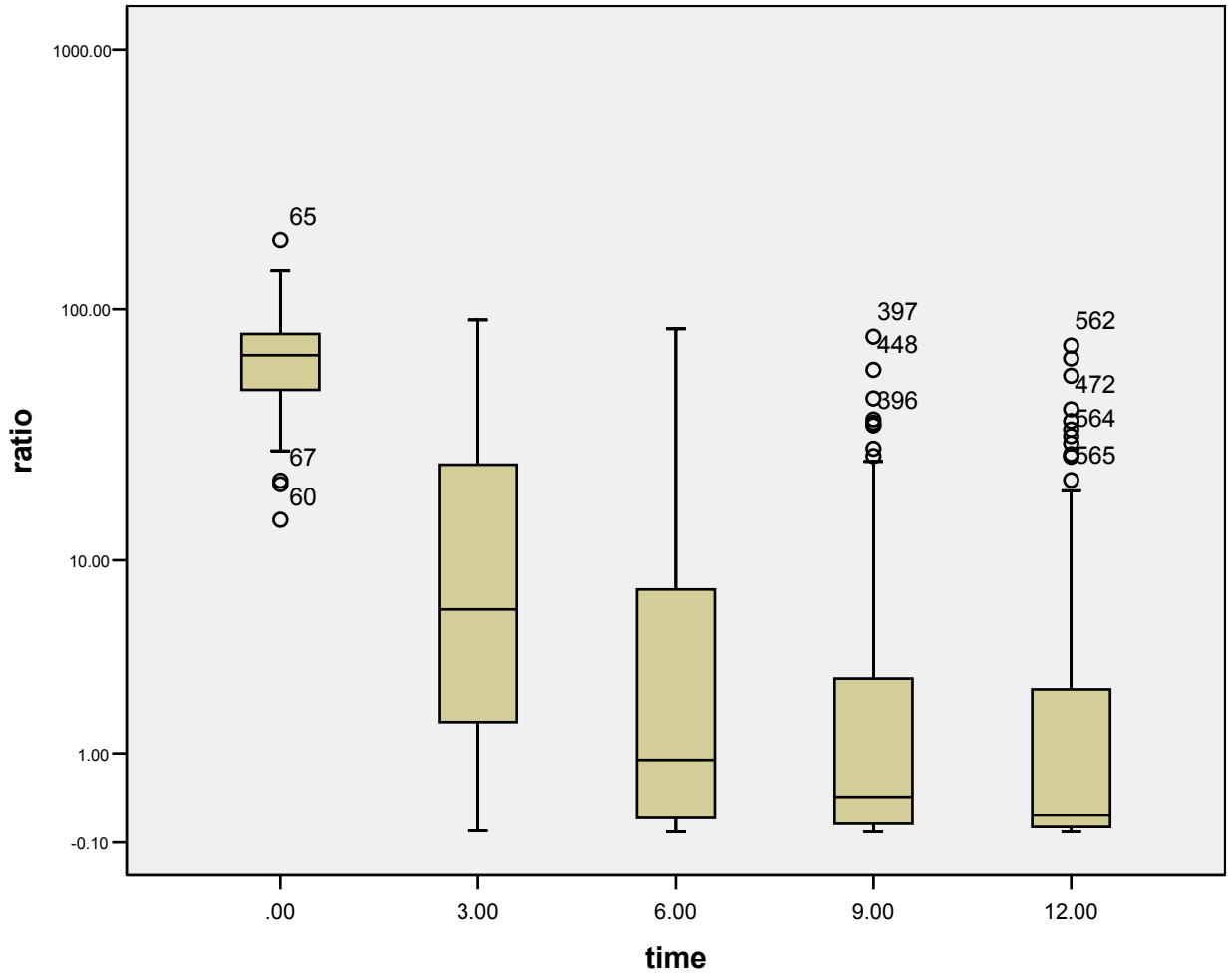
ASH 2007

Molecular response

BCR-ABL/ABL ratio at various time points after entering the trial.

Time (months)	Nos of samples	Median	Minimum	Maximum
0	66 (57%)	66.22	14.71	184.73
3	91 (79%)	7.13	0.01	90.94
6	86 (75%)	0.89	0	83.98
9	82 (71%)	0.36	0	78.33
12	78 (68%)	0.16	0	72.25

Molecular response



Haematological toxicity

Percentage of patients with neutropenia and/or thrombocytopenia

	Neutropenia	Thrombocytopenia	Combined
All Grades (1-4)	56%	55%	64%
Grades 3 / 4	28%	13%	32%

Non-haematological toxicity

- 96 (83%) patients experienced at least 1 AE
- Most AE's were mild/moderate
- The most common AE's were:
  - diarrhoea
  - fatigue
  - odema
  - myalgia/arthralgia
  - nausea/vomiting
  - rash
- 58 % of AE's had a suspected relationship to at least one on the study drugs
- 29% patients had an AE causing dose reduction or interruption
- 8% of patients had an AE causing permanent discontinuation of study treatment

Serious Adverse Events
25 events amongst 115 patients

ANGIOEDEMA
BLADDER CANCER
BLAST CRISIS OF CML
BONE AND MUSCLE PAIN
CAMPYLOBACTER GASTROENTERITIS
CHEST INFECTION
COUGH AND MILD FEVER
DIARRHOEA & DEHYDRATION (sequelae: LEFT SIDED STROKE, ACUTE CORONARY SYNDROME)
FEVER (WITH NORMAL NEUTROPHILS)
GLOSSAL SWELLING* (x2 same patient)
HAEMORRHAGE – VAGINA

Discontinuations

- 39% (45/115) patients have discontinued study treatment
- 58 % (26/45) of the discontinuations were from IFN arm
- discontinuation rate from arms A&B is 27%

Reasons for discontinuation

AE	9
Treatment failure	9
Disease progression	4
Death (cancer related)	2
Consent withdrawn	2
Protocol violation	2
Lost to follow-up	1
Other/Unknown	15

SPIRIT studies

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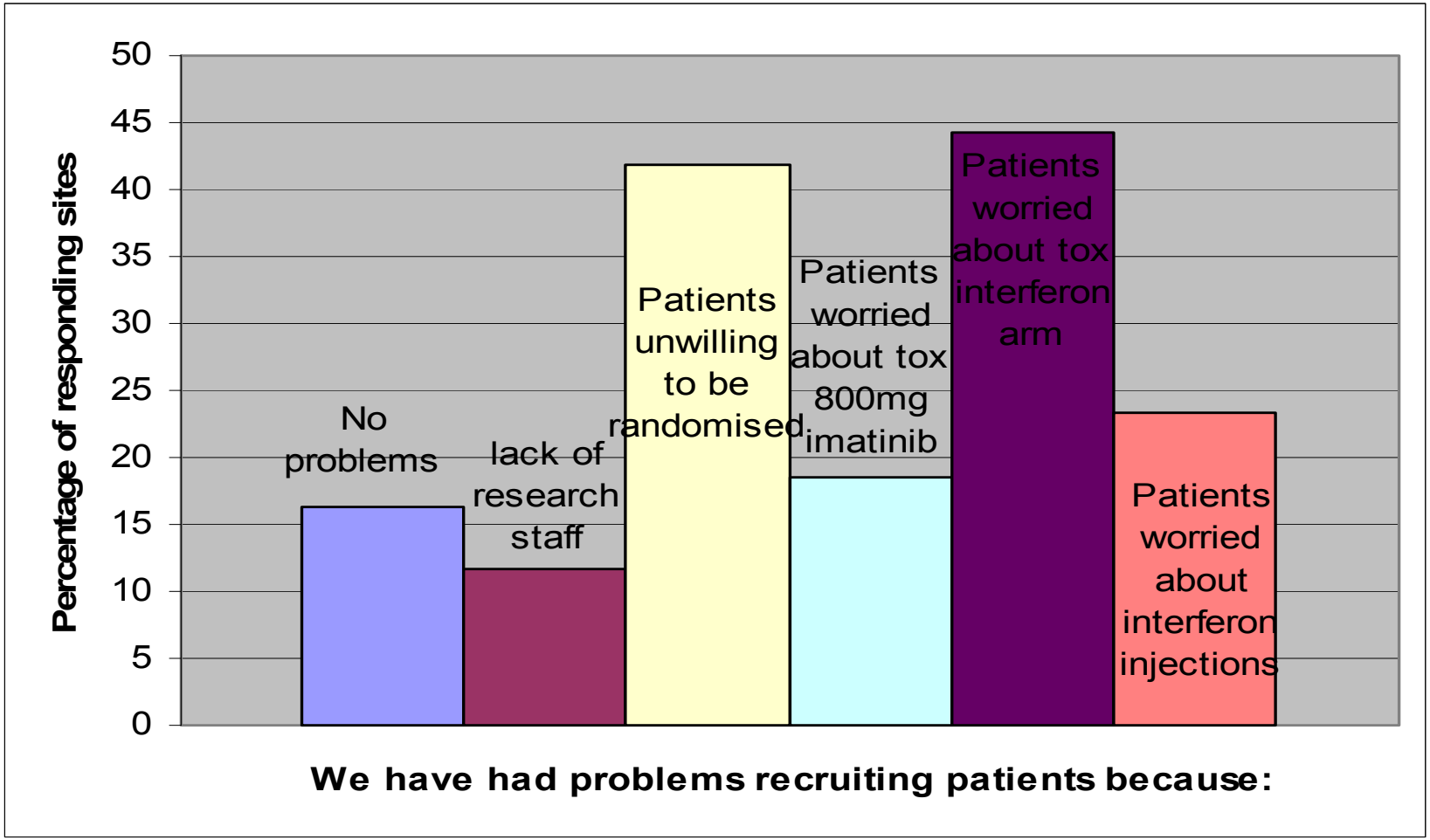
  - Schema, state of play, recruitment
  - One year pooled results
    - Efficacy, toxicity
    - Survey results from 2007
- SPIRIT ‘2’
  - Design
  - Endpoints
  - Where we’re up to (nearly there…)

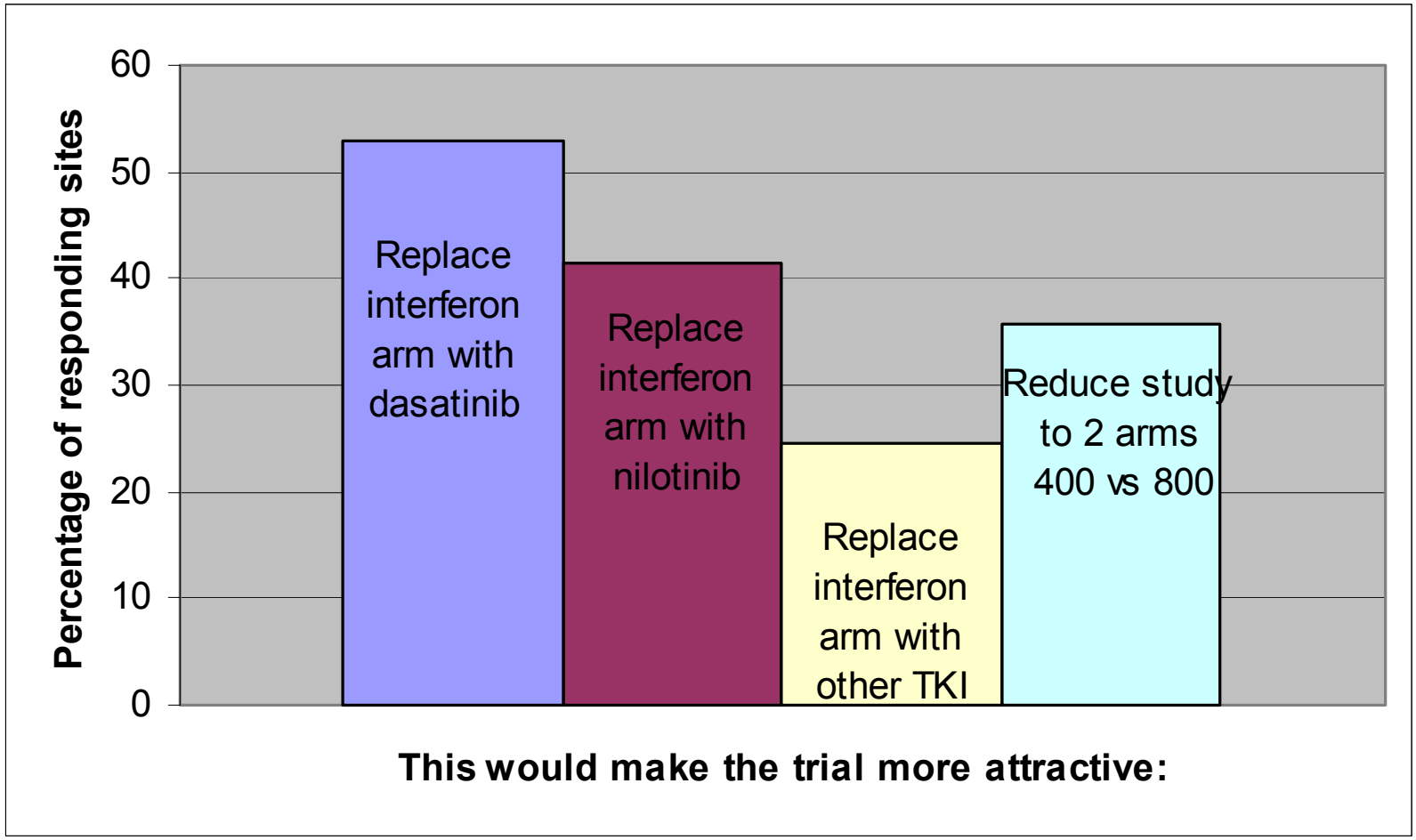
Recruitment Survey May 2007

- Distributed at the NCRI Annual Review of Leukaemia meeting May 2007
- Sent to 98 SPIRIT sites
- 53 Responses

Problems with recruitment



What would make the study more attractive?



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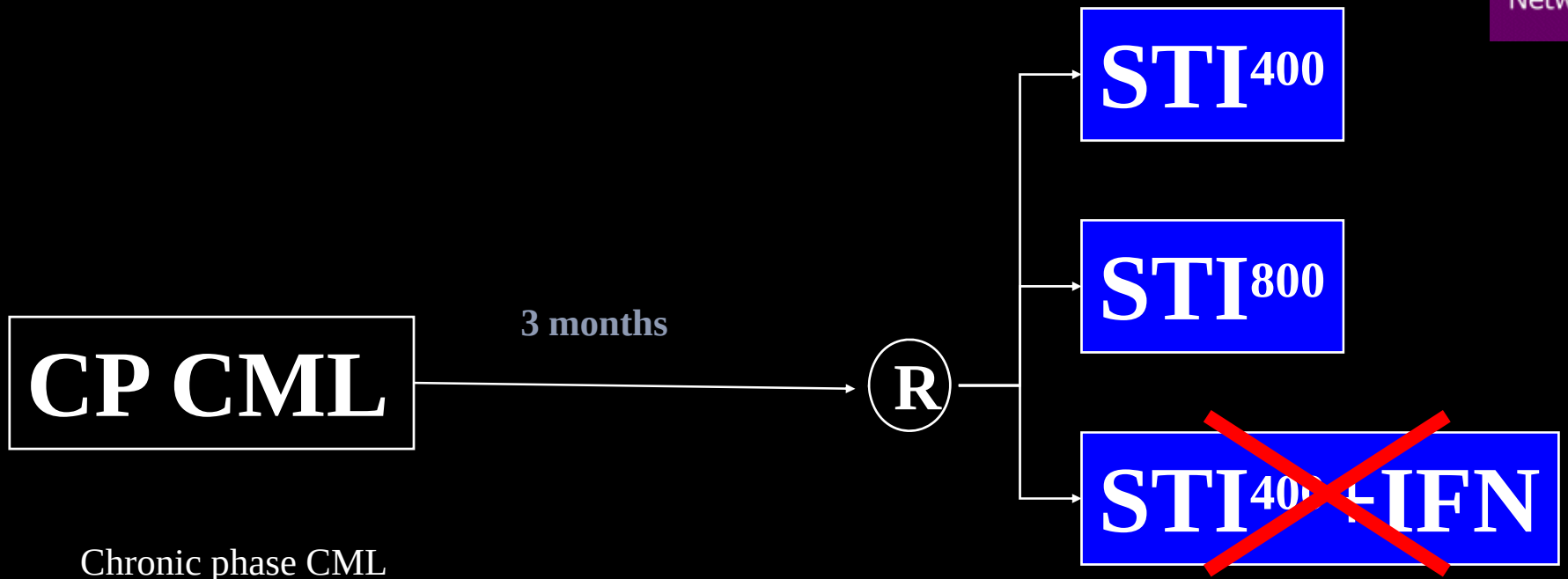

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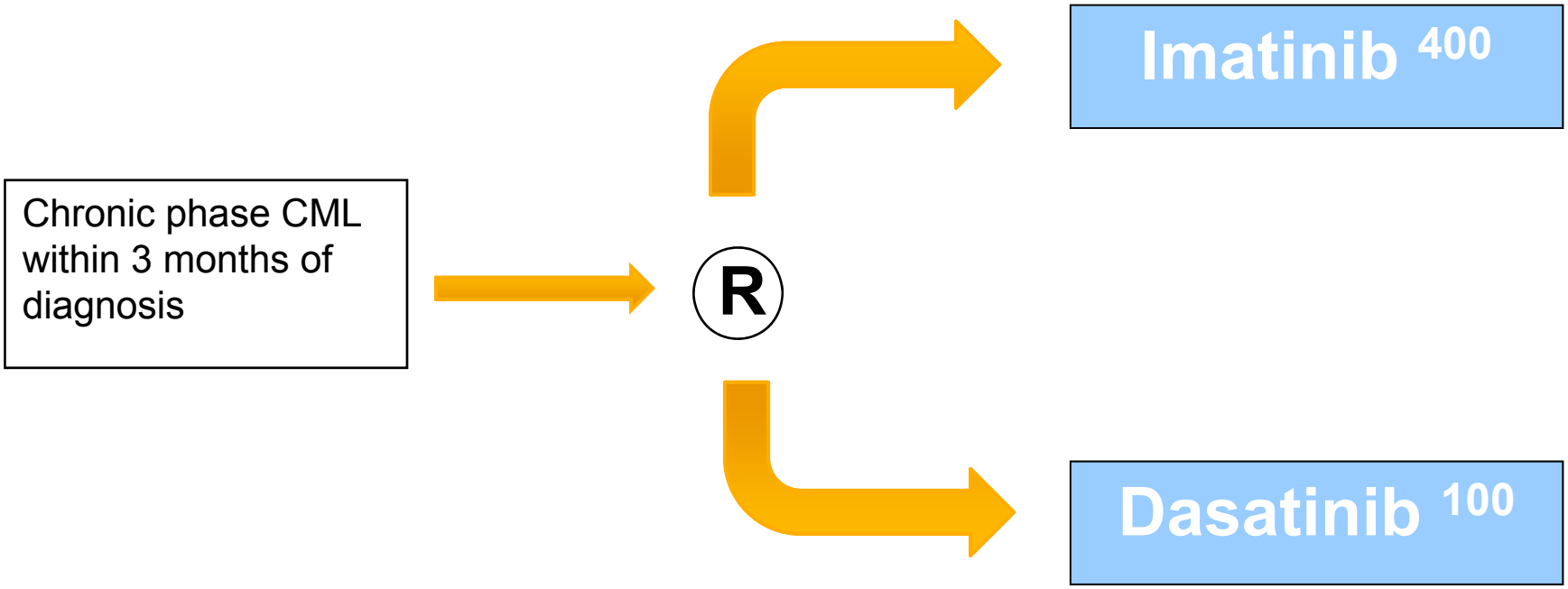
2
SPIRIT

SPIRIT *2:* design



N=850: 425 per arm

SPIRIT 2: endpoints

- ***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 dasatinib over imatinib arm.
- ***Secondary endpoints***
  - Rate of CCyR after two years
  - Treatment failure rates at 5 years
  - Rates of CHR
  - Rates of ‘molecular’ response (BCR-ABL/ABL ratio by real time PCR)
  - Tolerability
  - Quality of life
  - Pharmecoeconomics
  - Overall and progression-free survival at 2 and 5 years.

SPIRIT *2:* arrangements

- Sponsor: Newcastle Hospitals Trust
- Administration: Newcastle Clinical Trials Unit
- Funder: BMS
- SMC, DMC
- Free dasatinib for 425 patients for minimum of 5 years from date *last* patient recruited e.g. up to 8 years
  - £98M of drug
  - Potential saving to NHS: estimated £47M

SPIRIT *2:* progress

- Ethics (London REC) ✓
- Funding ✓
- MHRA ✓
  - Amendment pending
- NCRN adoption
  - Via CTAAC (Clinical Trials Awards Advisory Committee)
  - CRUK – submitted November 2007.
  - 13th June 2008 decision
- Transition from SPIRIT 1 to SPIRIT 2
- Future studies, other drugs, NICE


2
SPIRIT

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