SPIRIT 2

STI571 Prospective International Randomised Trial

Dose interruption/reduction of TKI in first 3 months of treatment of CML is associated with inferior early molecular responses and predicts for an increased likelihood of discontinuing 1st line agent

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NCRI National Cancer Research Institute

Newcastle University

Imperial College London

The Newcastle Hospitals NHS Foundation Trust

NHS

Background

- 10% (MR1) at 3 months seems to be important
- No data to confirm that switching at 3 months can improve outcome. Trials being designed to address this
- About 20% of newly diagnosed patients require temporary dose interruption and/or dose reduction soon after starting a TKI
- Do these dose alterations affect the achievement of RQ-PCR < 10% at 3 months, and if so, how should we manage these patients with respect to early changes of drug ?
- We used data SPIRIT2 to try to answer these questions

NCRI
National Cancer Research Institute

814 patients recruited

Recruitment closed Feb 2013

172 sites

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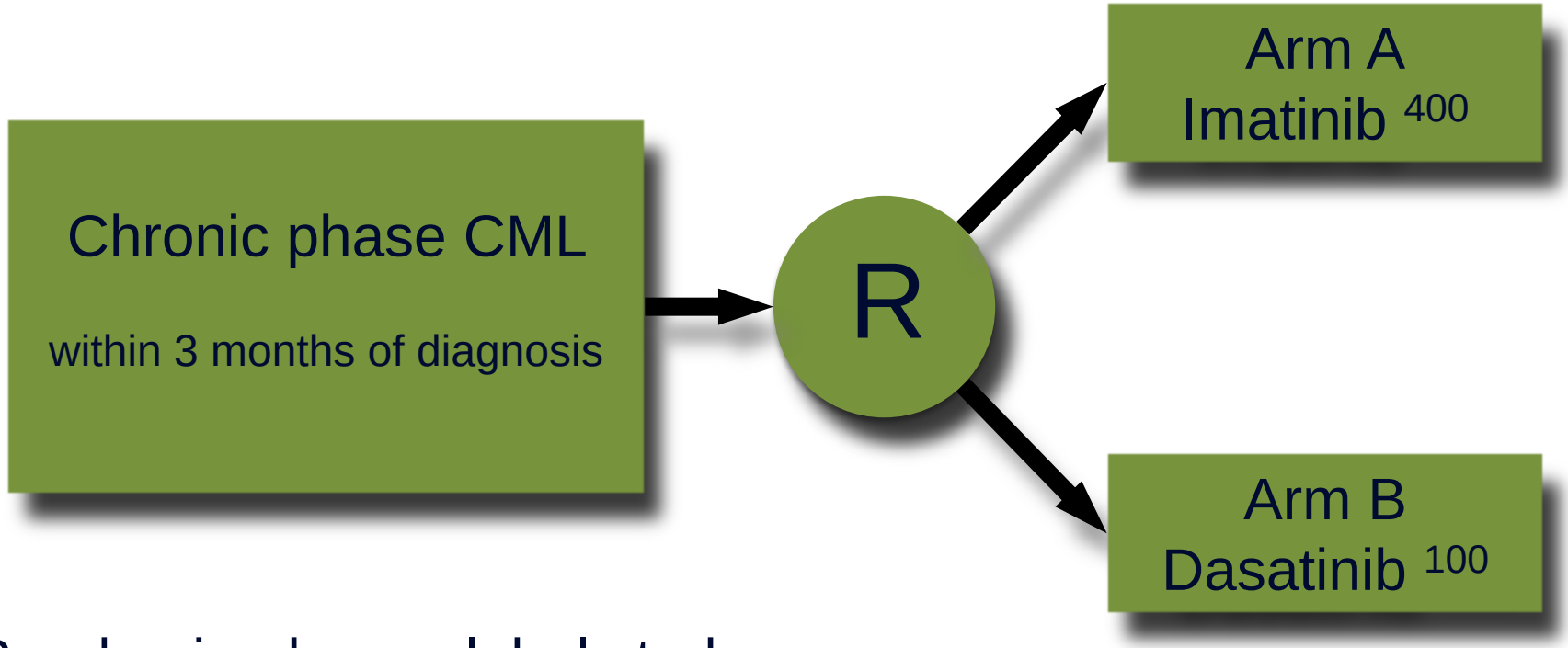
SPIRIT 2: Study Design



Randomised open label study

Primary endpoint: 5 year EFS

Secondary: cytogenetic, PCR response, toxicity

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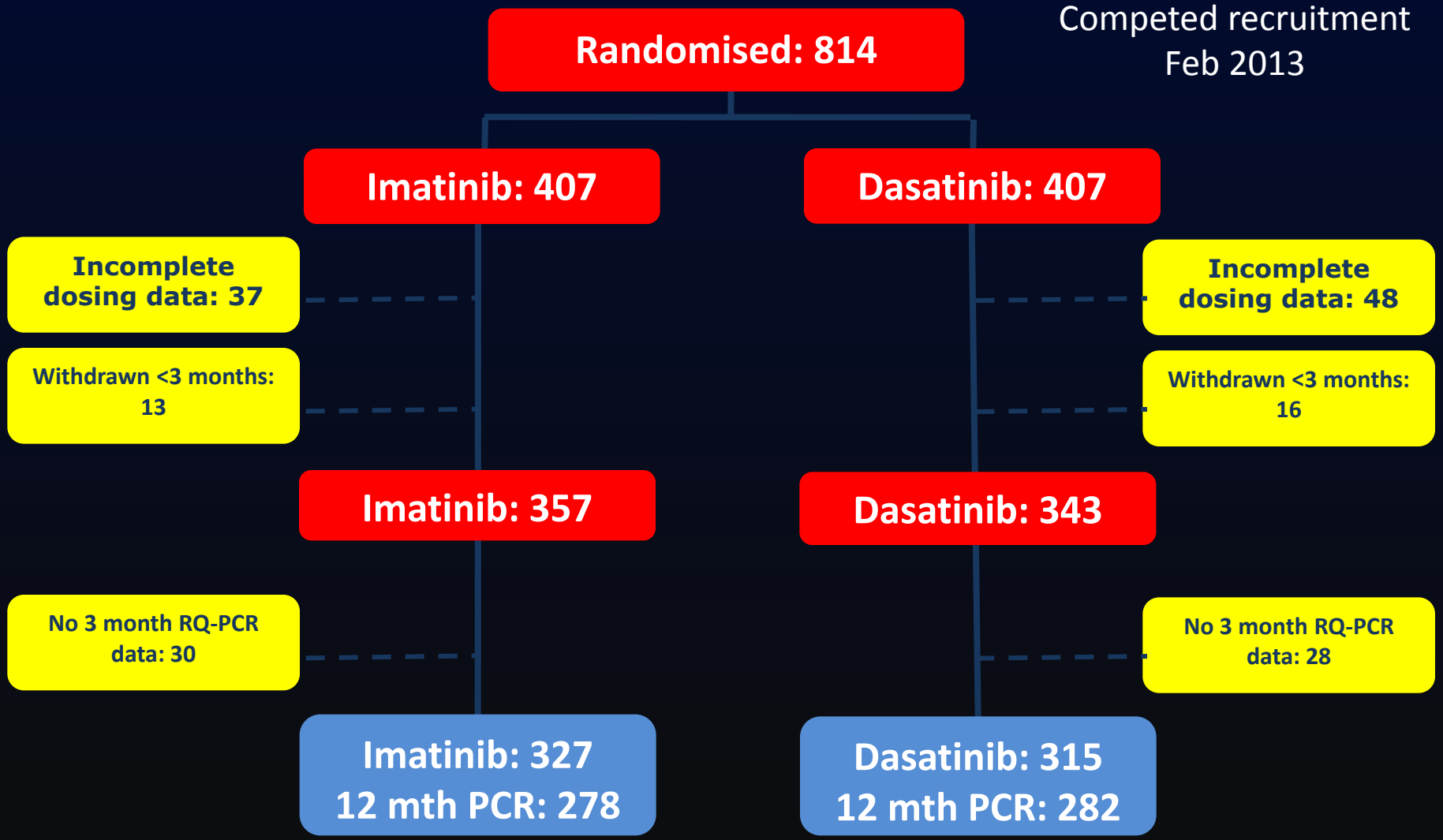
SPIRIT 2 Study Population



Achievement of RQ-PCR <1%^{IS} at 12 months by RQ-PCR at 3 months (ITT)

	12 mth RQ-PCR on Imatinib			12 mth RQ-PCR on Dasatinib	
	<1%	**>1%**		**<1%**	**>1%**
RQ-PCR at 3 months			**RQ-PCR at 3 months**		
<10% 209/278 (75%)	90.0%	10.0%	**<10% 258/282 (91%)**	94.2%	5.8%
>10% 69/278 (25%)	55.1%	44.9%	**>10% 24/282 (9%)**	70.8%	29.2%

Data from SPIRIT2 confirm the association of RQ-PCR <10% at 3 months with increased likelihood of RQ-PCR <1% at 12 months

Achievement of RQ-PCR <0.1%^{IS} at 12 months by RQ-PCR at 3 months

	12 mth RQ-PCR on Imatinib			12 mth RQ-PCR on Dasatinib	
	<0.1%	**>0.1%**		**<0.1%**	**>0.1%**
RQ-PCR at 3 months			**RQ-PCR at 3 months**		
<10% 209/278 (75%)	65.1%	34.9%	**<10% 258/282 (91%)**	68.2%	31.8%
>10% 69/278 (25%)	18.8%	81.2%	**>10% 24/282 (9%)**	16.7%	83.3%

Data from SPIRIT2 confirm the association of RQ-PCR <10% at 3 months with increased likelihood of RQ-PCR <0.1% (MMR) at 12 months

Effect of reduced dosing on 3 mth RQ-PCR by total dose and by number of missed days

	Imatinib		Dasatinib	
	Number % (N=327)	**3 mth RQ-PCR < 10%**	**Number % (N=315)**	**3 mth RQ-PCR < 10%**
100% prescribed dose	272 (83%)	78.3%	222 (71%)	95.5%
80-99% prescribed dose	42 (13%)	61.9%	48 (13%)	85.4%
<80% prescribed dose	13 (4%)	46.2%	45 (4%)	80.0%
Total missed days median (range)	13.5 (1-48)		14 (1-58)	
0 days	272 (83%)	78.3%	222 (71%)	95.5%
1-14 days	41 (13%)	58.5%	48 (15%)	85.4%
> 14 days	14 (4%)	57.1%	45 (14%)	80.0%

Chance of achievement of RQ-PCR <10% decreases with increased numbers of missed doses and decreased total dosing

Effect of missing days of dosing on 12 mth RQ-PCR

	Imatinib		Dasatinib	
Missed doses in first year	**Number % Total=282**	**12 mth RQ-PCR < 1%**	**Number % Total=285**	**12 mth RQ-PCR < 1%**
0 days	227 (80%)	55.1%	187 (66%)	69.0%
1-14 days	31 (11%)	48.4%	30 (10%)	70.0%
> 14 days	24 (9%)	33.3%	68 (24%)	45.6%
		P=0.04		P=0.002

Chance of achievement of RQ-PCR <1% at 12 months decreases with increased numbers of missed dosing days

Effect of average dosing on 12 mth RQ-PCR

	Imatinib	Dasatinib
Dosing in 1st 12 months	**Achievement of MMR at 12 months (ITT)**	**Achievement of MMR at 12 months (ITT)**
100%	125/227 (55.1%)	129/187 (69.0%)
95-99.9%	14/27 (51.9%)	20/29 (69.0%)
80-95%	3/10 (30.0%)	17/37 (45.9%)
<80%	6/18 (33.3%)	13/29 (44.8%)

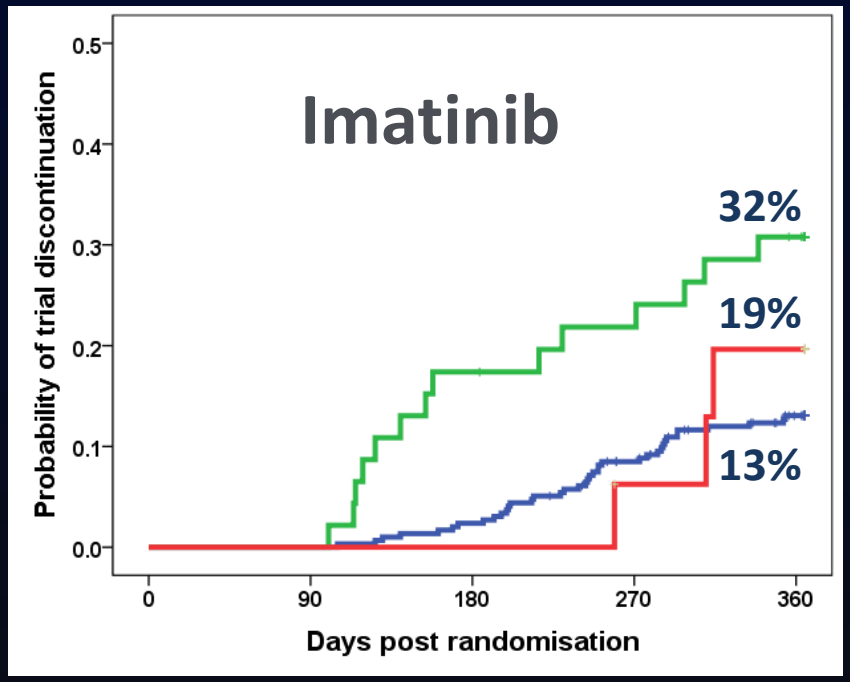
Chance of achievement of RQ-PCR <1% at 12 months decreases with decreased average dosing

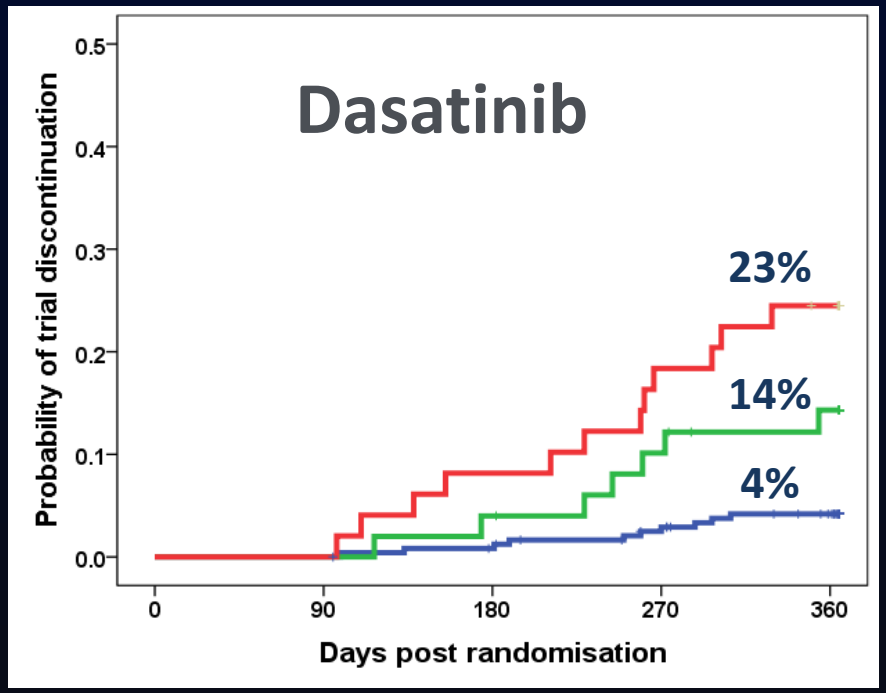
Effect of missing days of dosing on 3-12 month dosing and trial discontinuation rate

	Imatinib	Dasatinib	Either drug
Missed doses	**Probability of 1yr trial discontinuation**	**Probability of 1yr trial discontinuation**	**Ability to take drug months 3-12**
0 days	13.1% (N=295)	4.6% (N=234)	92.7%
1-14 days	31.8% (N=46)	14.3% (N=43)	59.5%
>14 days	19.6% (N=16)	22.9% (N=37)	67.3%

Increasing numbers of missed dosing days in the first 3 months is associated with less ability to take the trial drug consistently through months 3-12 and with increased likelihood of permanent discontinuation of first line treatment

Impact of missed days of dosing on discontinuation of trial medication





Missed dose = 0

Missed dose = 1-14

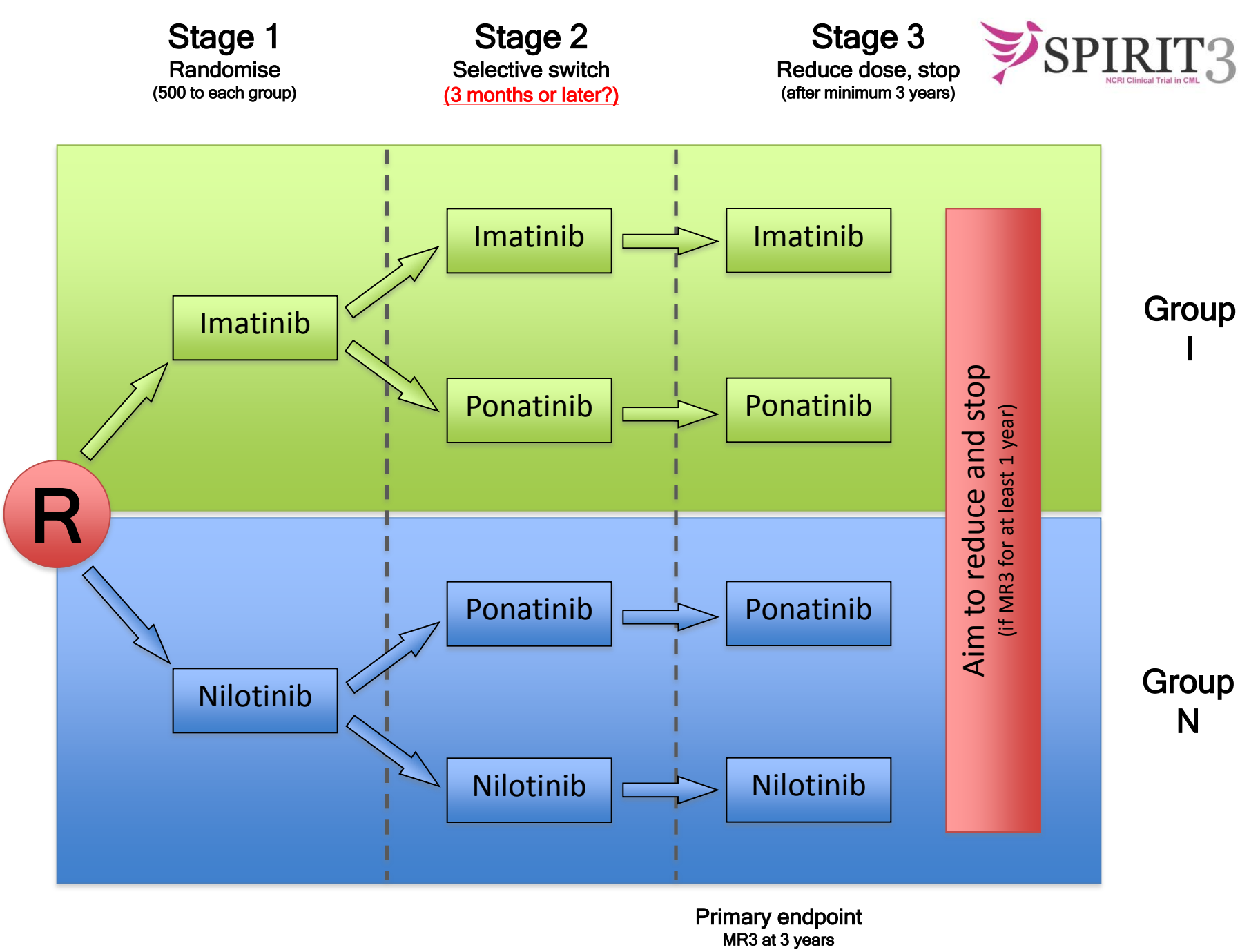
Missed dose = >14

Conclusions 1

- Data from SPIRIT2 confirm the association of <10% (MR1) at 3 months with increased likelihood of <1% (MR2) & <0.1% (MR3) at 12 months
- Achievement of MR1 at 3 months and MR2/MR3 at 12 months occurs at a higher rate with dasatinib than with imatinib, although dasatinib is less well tolerated: this suggests that higher potency of dasatinib can compensate for missed doses
- The probabilities of achieving MR2/MR3 at 12 months are similar with imatinib and dasatinib in patients who achieve MR1 at 3 months

Conclusions 2

- The probability of achieving MR1 at 3 months and MR2 at 12 months decreases if reduced amount of drug is taken within first 3 months: whether this is due to reduced drug dosage *per se* or an inherent biological effect is unclear
- Inability to tolerate full dose in first 3 months is associated with an on-going failure to tolerate drug at full dose
- Inability to tolerate full dose in first 3 months is associated with increased likelihood discontinuing first line therapy


Stage 1
Randomise
(500 to each group)
Stage 2
Selective switch
(3 months or later?)
Stage 3
Reduce dose, stop
(after minimum 3 years)
SPIRIT3
NCRI Clinical Trial in CML
Imatinib
Imatinib
Imatinib
Ponatinib
Ponatinib
R
Ponatinib
Ponatinib
Nilotinib
Nilotinib
Nilotinib
Aim to reduce and stop
(if MR3 for at least 1 year)
Group I
Group N
Primary endpoint
MR3 at 3 years

Acknowledgements

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Cell biobanking	Tessa Holyoake, Alan Hair, Glasgow
Study Management Committee	Richard Clark, Liverpool; Jane Apperley, Hammersmith (& CH, SO'B). Mhairi Copeland (Chair of CML WG)
Data and Ethics Monitoring Committee	John Goldman, Keith Wheatley, Graham Dark
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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.

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