

The predictive value of early molecular response in chronic phase CML patients treated with dasatinib first-line therapy in the SPIRIT 2 trial

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Cell biobanking

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Data and Ethics Monitoring Committee

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Chief Investigator

Stephen O'Brien

Sites

172 sites around the UK

Patients

560 to date



560 patients recruited

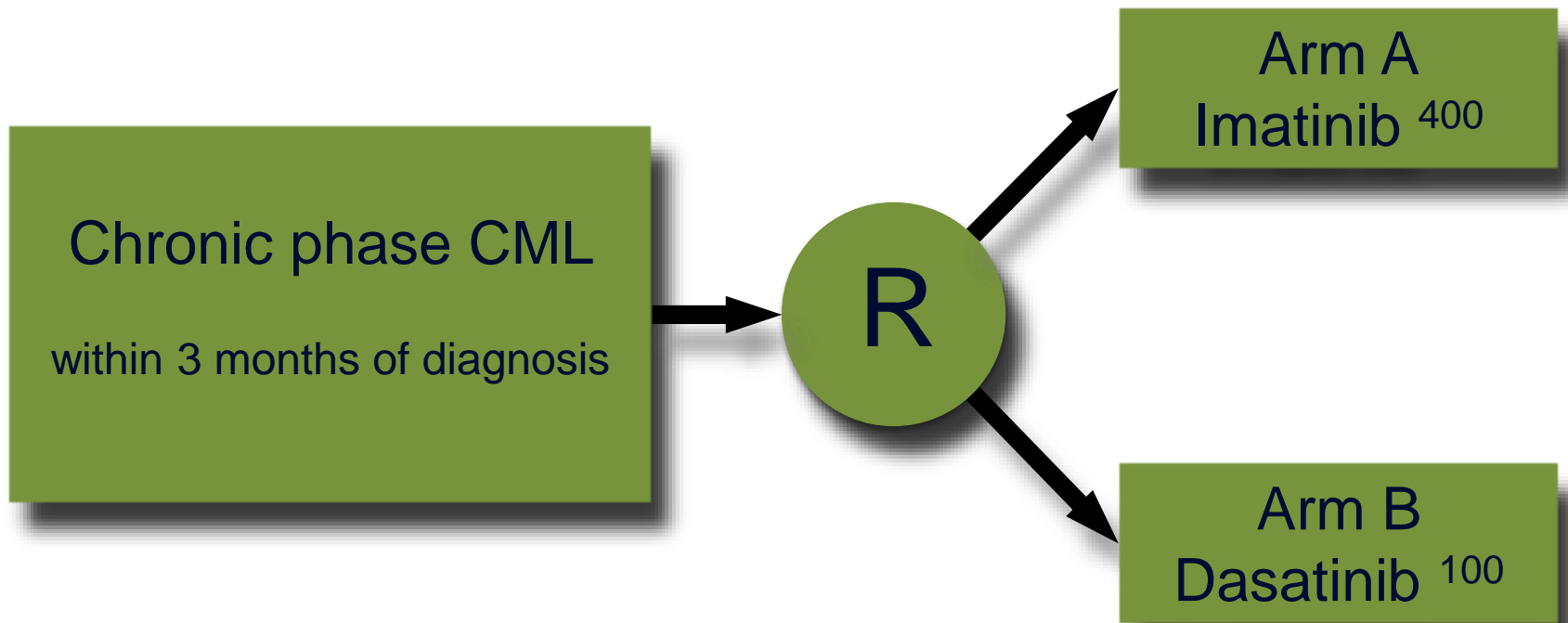
810 target

172 sites participating

123 sites have recruited



SPIRIT 2: Study Design



Randomised open label study

Primary endpoint: 5 year EFS

Secondary: cyto, molec response, tox

Background

- With imatinib, the BCR-ABL transcript level at 3 months appears to be the best predictor of outcome^{1,2,3}
- About 25% of patients on imatinib fail to reach the 10% PCR target at 3 months⁴
- Perhaps those patients should change treatment?
- Similar analyses with first-line 2G TKIs now emerging⁵

¹Wang et al. BJH 2003; 120:990

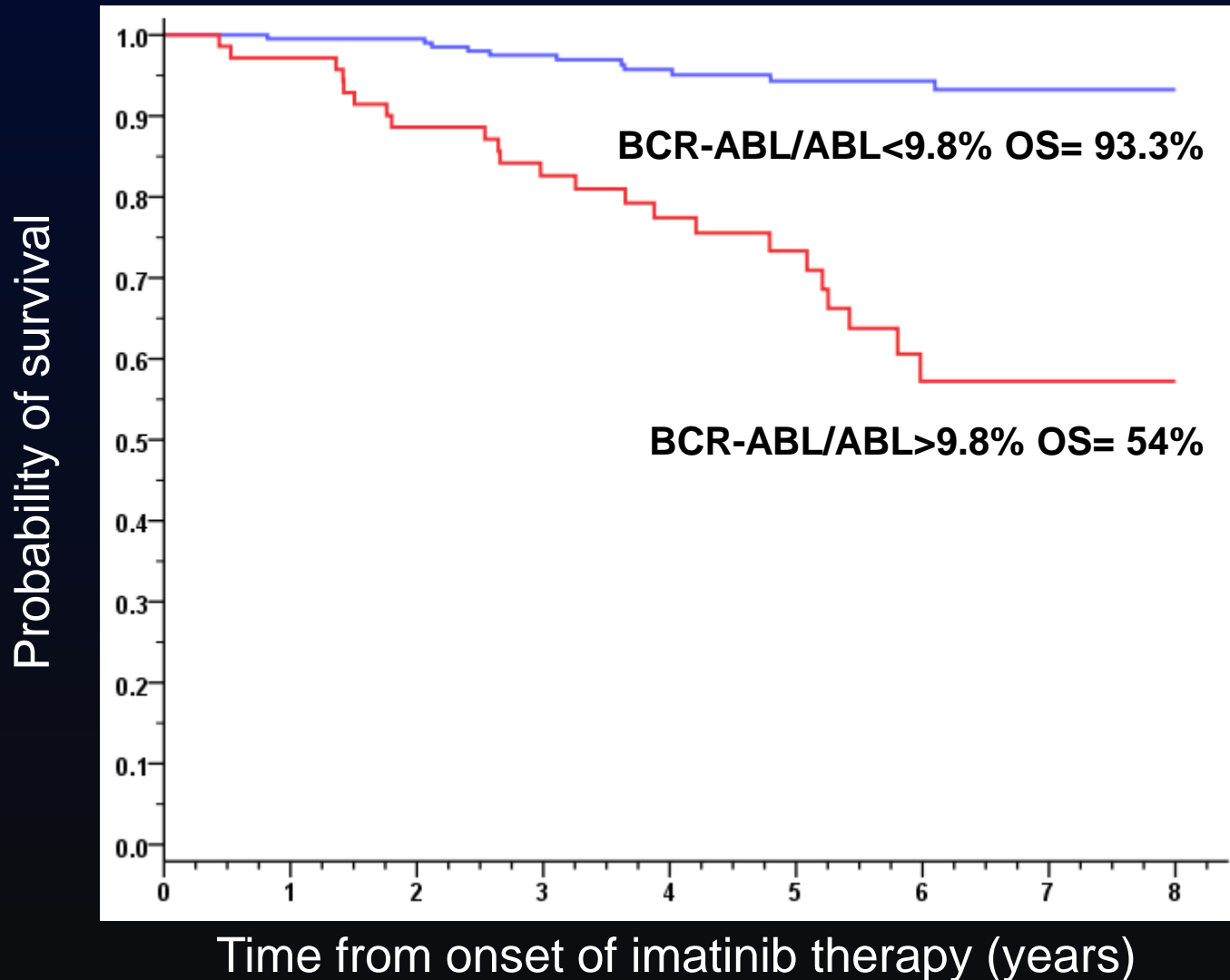
²Hughes et al. Blood 2010; 116: 3758

³Marin et al. 2010; JCO 2010; 38: 6565

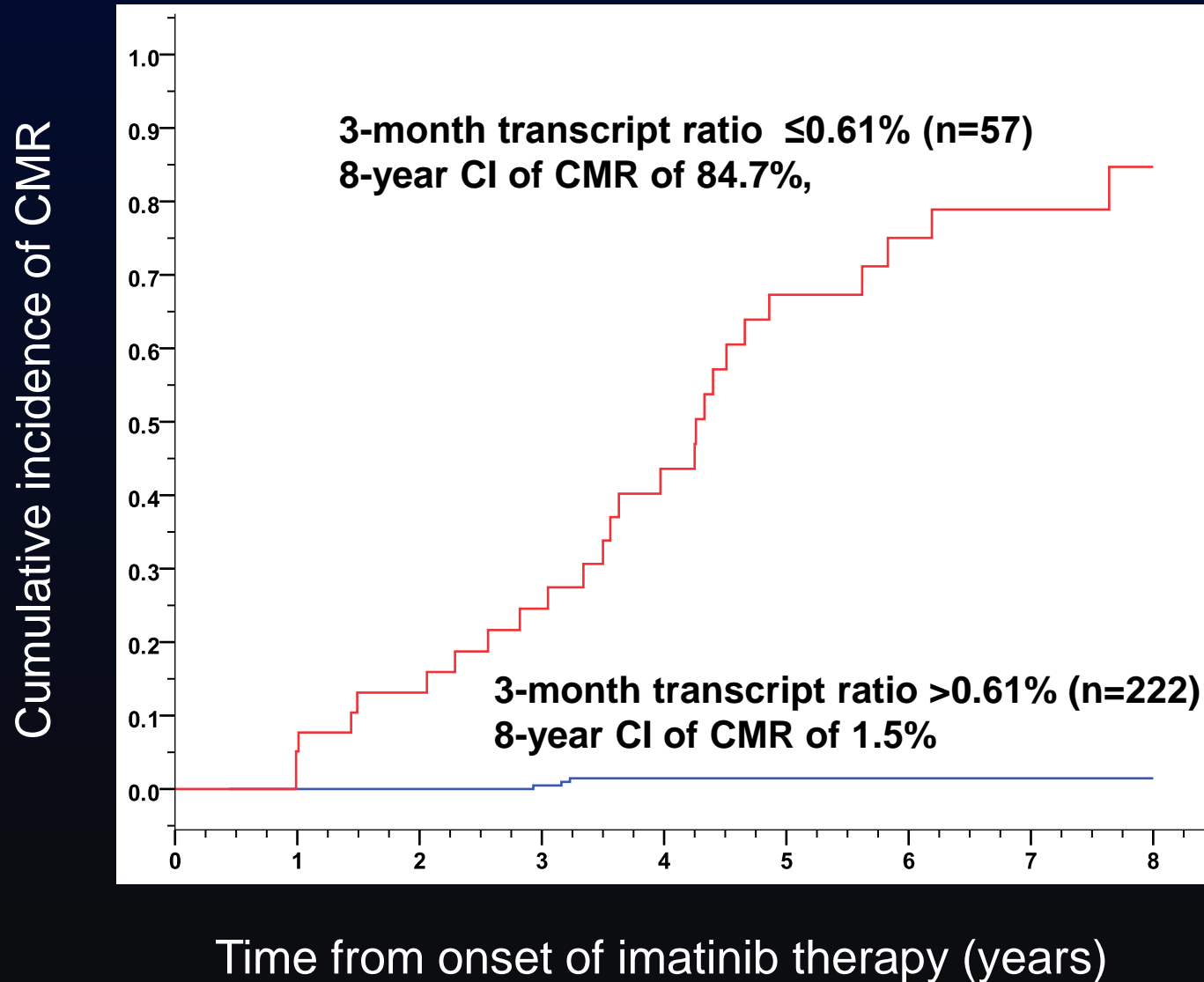
⁴Hanfstein *et al.* ASH 2011; abstract 783

⁵Hochhaus *et al.* ASH 2011; abstract 2767

Survival for 282 patients treated with imatinib first line according to molecular response achieved at 3 months



8-year cumulative incidence of CMR on imatinib therapy according to the BCR-ABL transcript level at 3 months



SPIRIT 2 dasatinib arm

- Trial continues to recruit: 560 of 810
- 5 year survival endpoint
- No disclosure of main comparisons between arms
- Evaluation of outcome on dasatinib arm based on early PCR response

Patient characteristics

- 560 patients recruited to SPIRIT 2 to date
- 280 patients on dasatinib arm
- 142 patients on dasatinib arm who have been on study long enough to contribute to a one year analysis
- Median follow up 18.2 months (range 12 - 34.9)

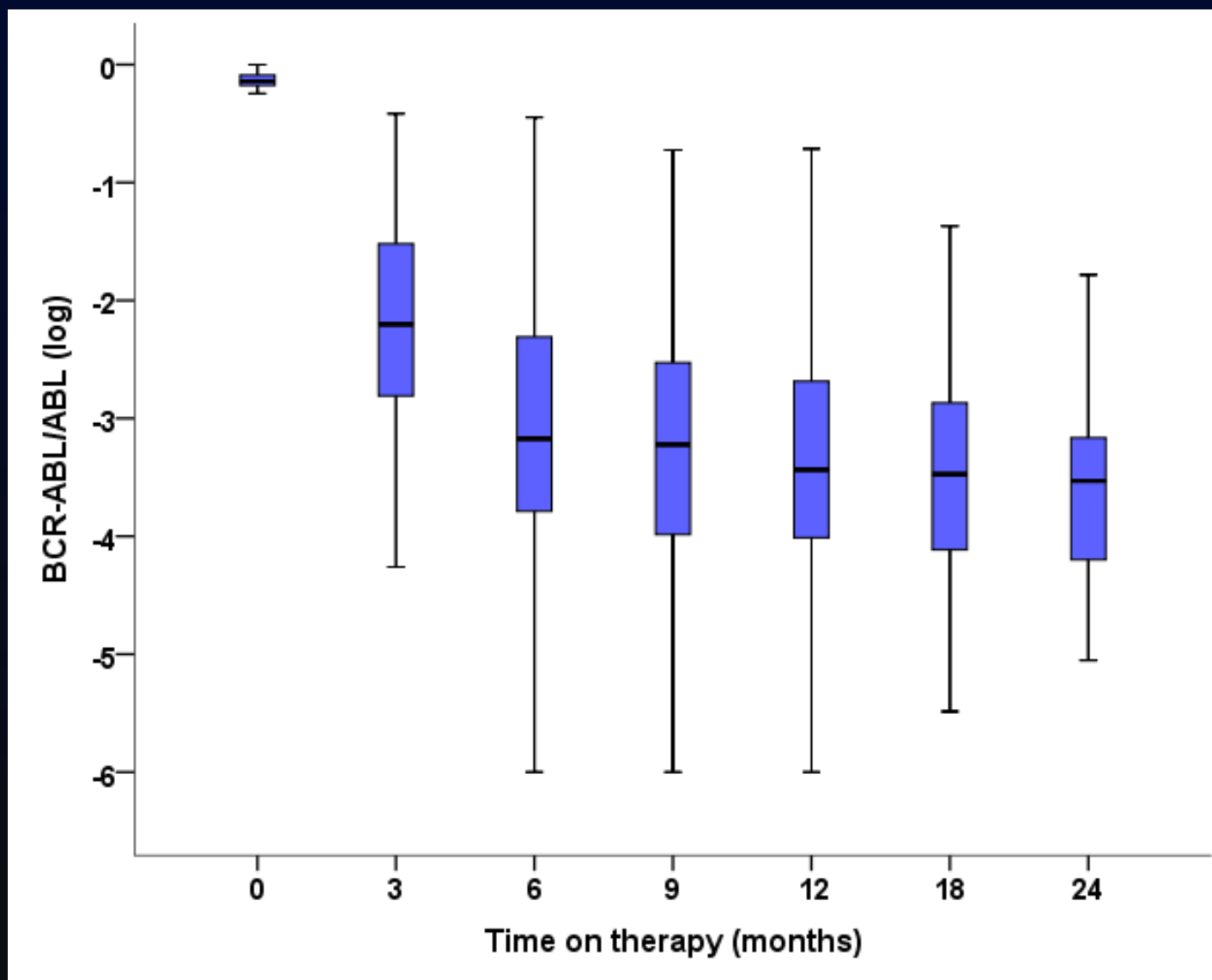
Patient characteristics

	N=142
Sex	
Male, n(%)	79 (55.6)
Female, N(%)	63 (44.4)
Age	
Median (range)	54.5 (18-82)
Sokal risk group	
Low, n(%)	35 (29.9)
Intermediate, n(%)	51 (43.6)
High n(%)	31 (26.5)
EUTOS risk group	
Low, n(%)	86 (83.5)
High, n(%)	17(16.5)

Patient characteristics

Spleen size at diagnosis Median (range)	4.9 cm (0-32)
WBC at diagnosis ($\times 10^9/l$) Median (range)	54.5 (18-82)
Haemoglobin level at diagnosis (gr/l) Median (range)	110 (42-158)
Platelet count at diagnosis ($\times 10^9/l$) Median (range)	425 (100-2433)
Blast % in peripheral blood at diagnosis Median (range)	0.6 (0-14.5)
Basophil % in peripheral blood at diagnosis Median (range)	3.9 (0-19)

Kinetics of molecular responses to dasatinib



Relative risk for cumulative incidences of CCyR, MMR and CMR^{4.5} according to a pre-therapy characteristics (variables that are predictive for at least one outcome)

Variable	RELATIVE RISK		
	CCyR	MMR	CMR ^{4.5}
Sokal	p=0.005	p=0.002	p=0.03
Low risk	1	1	1
Intermediate risk	0.813	0.789	0.838
High risk	0.510	0.350	0.328
EUTOS (high)	0.61 (p=0.09)	0.45 (p=0.04)	0.25 (p=0.06)
WBC (x10 ⁹ /l)	0.998 (p=0.04)	0.997 (p=0.05)	0.997 (p=0.13)
Haemoglobin (g/dl)	1.22 (p<0.001)	1.27 (p<0.001)	1.37 (p<0.001)

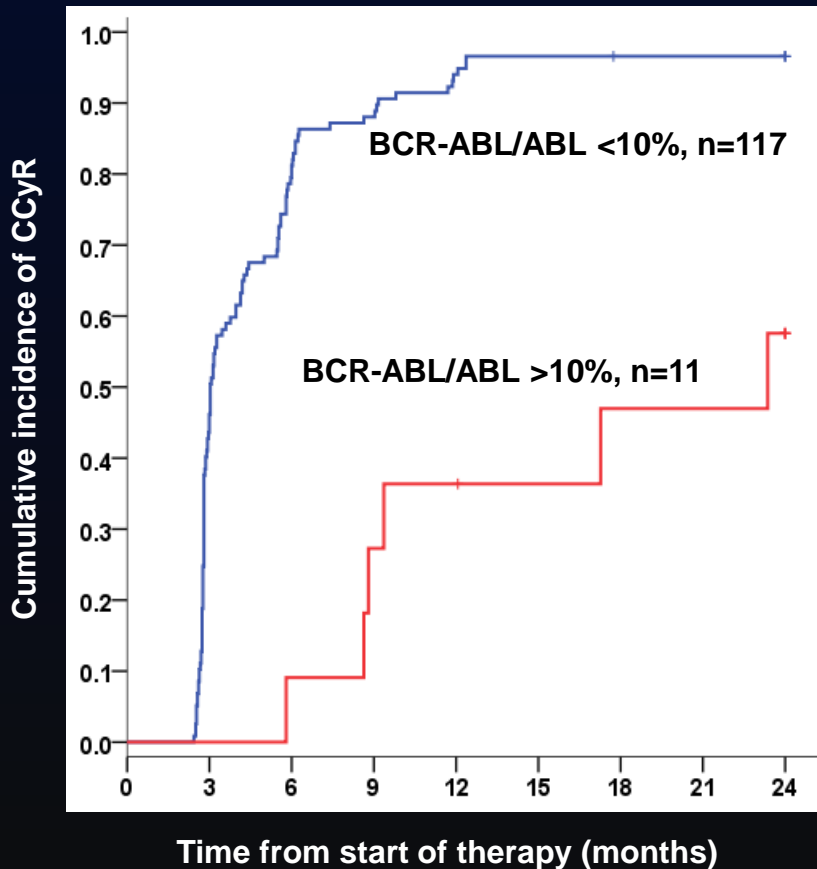
BCR-ABL transcript levels at 3 and 6 months predict for 2 year cumulative incidence of CCyR, MMR and CMR^{4.5}

	n	CCyR	MMR	CMR ^{4.5}
3 months transcript		p<0.001	p<0.001	p<0.001
>10%	11	58.8%	14.3%	0%
≤10%	117	96.6%	79.8%	45.7%
6 months transcript		p<0.001	p<0.001	p<0.001
>1%	23	68.4%	11.2%	0%
≤1%	98	100%	89.1%	52.2%

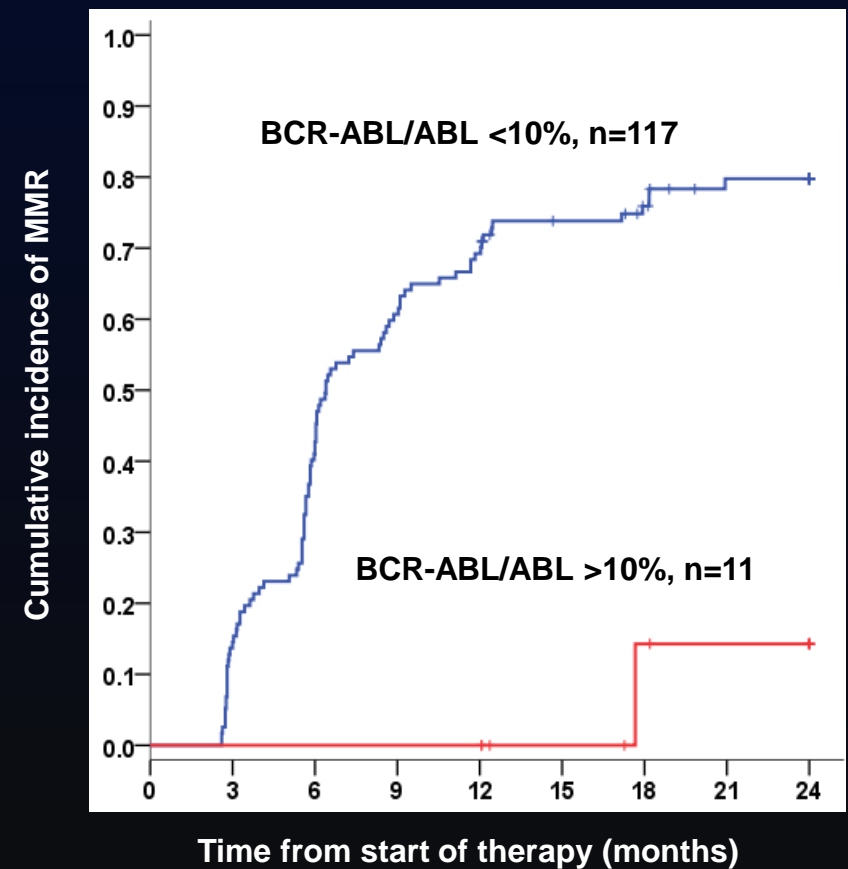
11 of 128 (8.5%) failed to reach the 10% threshold

BCR-ABL transcript levels at 3 months predicts 2 year cumulative incidence of CCyR and MMR

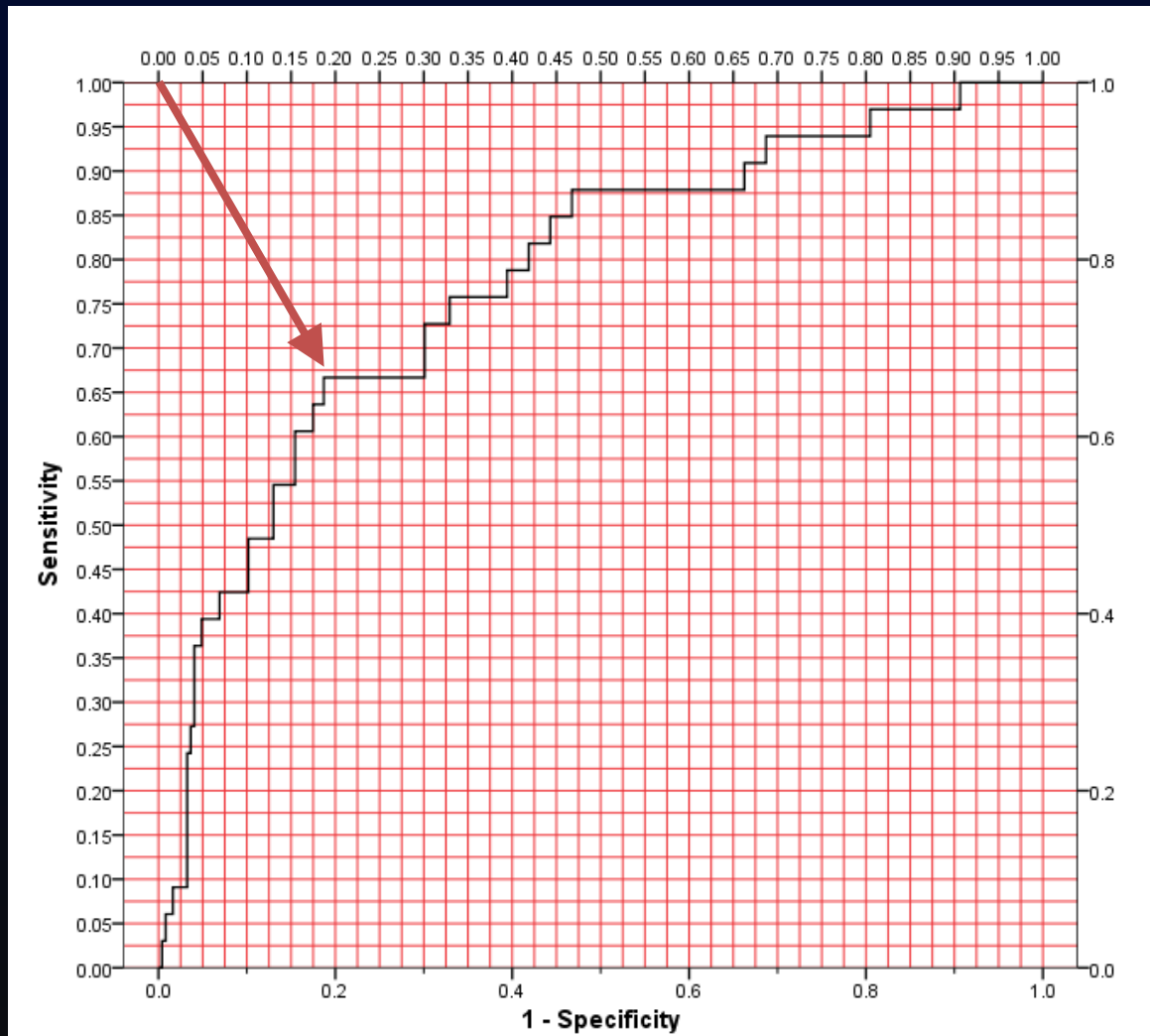
CCyR



MMR



Receiver operating characteristic (ROC) curve can identify the transcript cut off level that predicts outcomes with optimal sensitivity and specificity

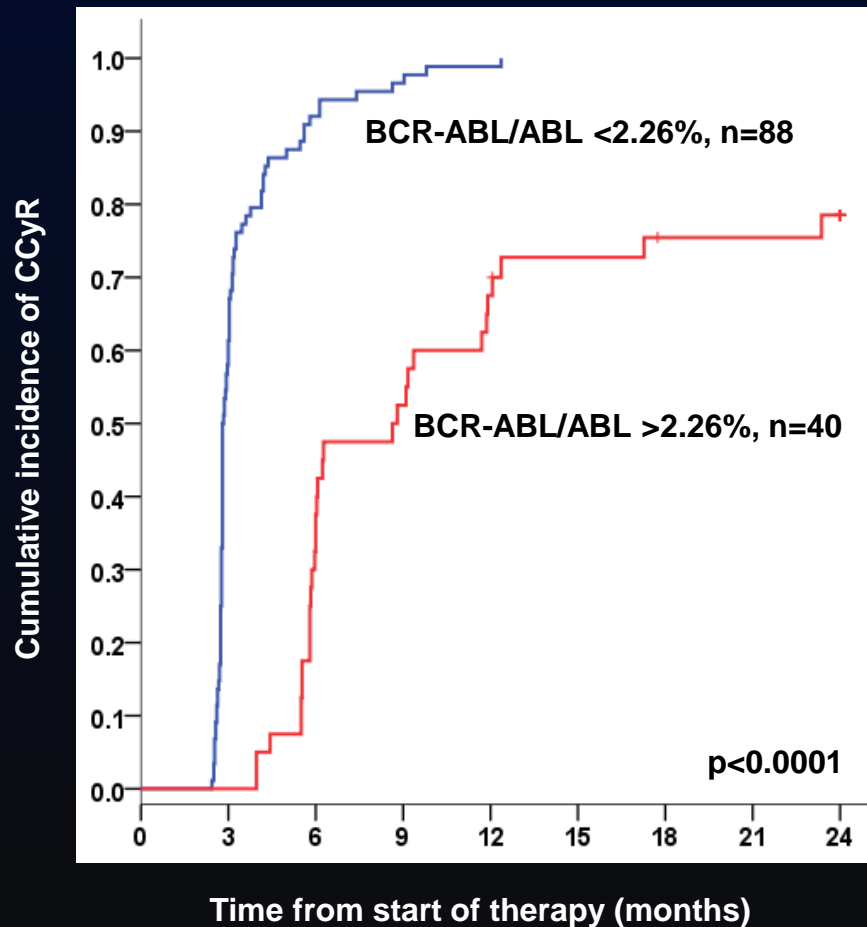


ROC curve: the 'optimal' threshold

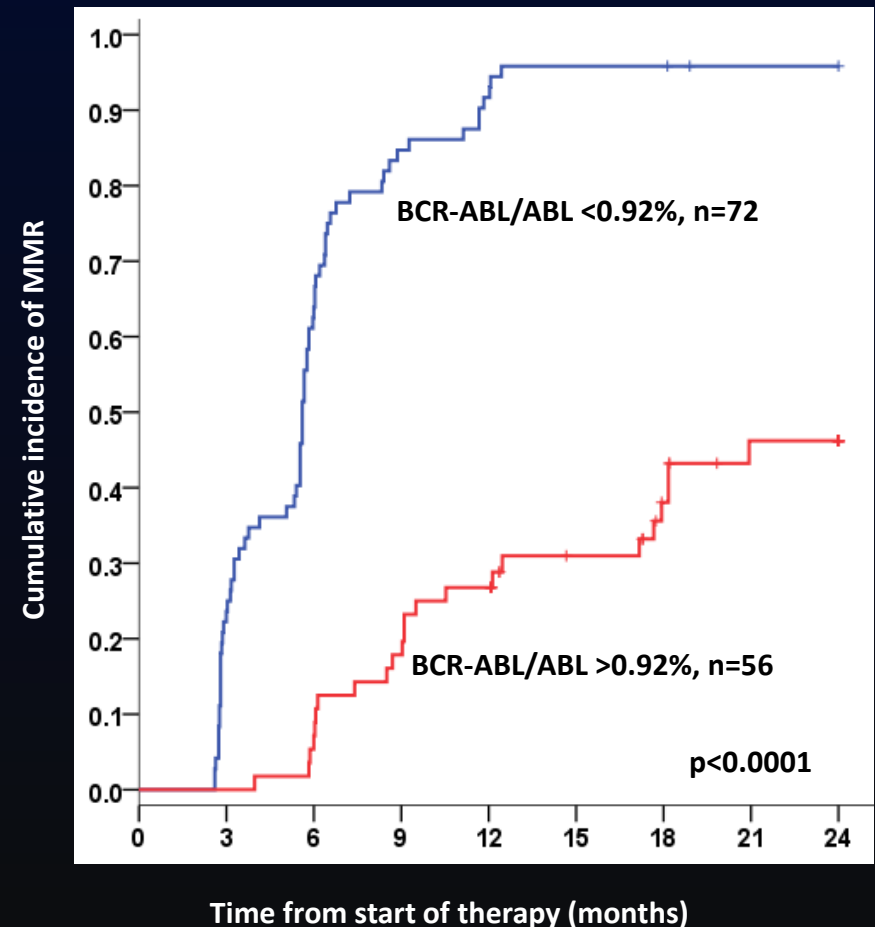
	n	Cumulative incidence of Response
CCyR		p<0.0001
<2.26	88	100%
>2.26	40	58.8
MMR		p<0.0001
<0.92	72	79.8
>0.92	56	14.3
CMR ^{4.5}		p<0.0001
<0.57	62	70.9
>0.57	66	14.5

Cumulative incidence of CCyR and MMR according to the 'optimised' transcript level at 3 months

CCyR

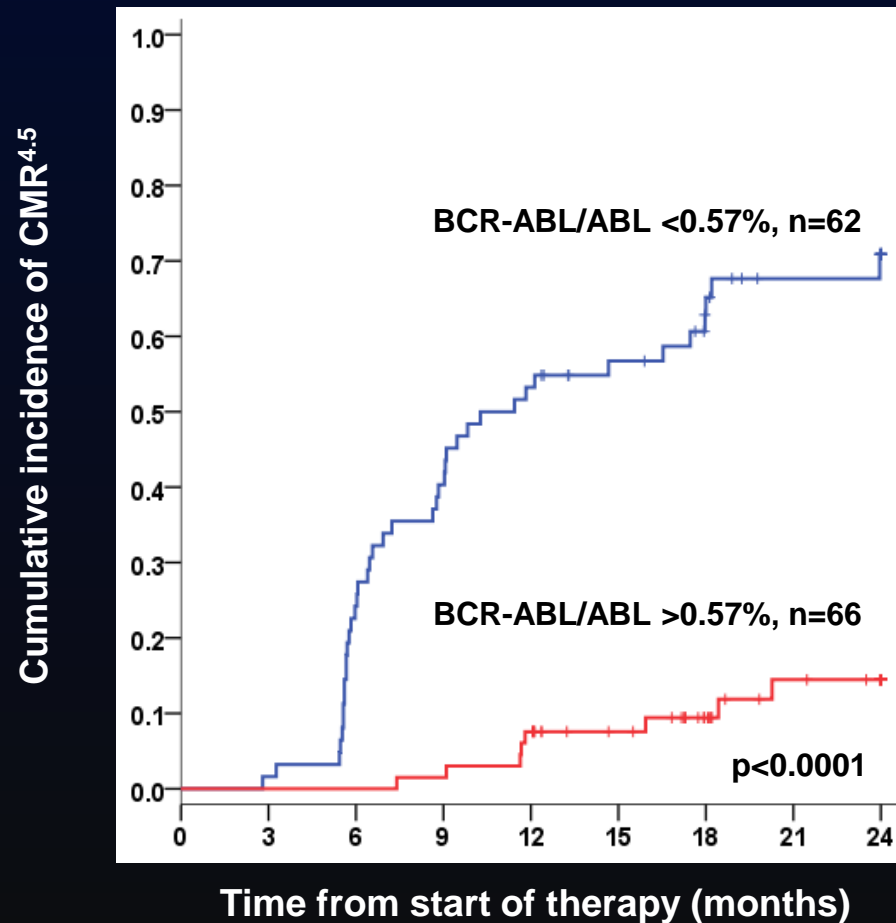


MMR



Cumulative incidence of CMR^{4.5} according to the 'optimised' transcript level at 3 months

CMR^{4.5}



Transcript level at 3 months is an independent predictor for CCyR

- 10% threshold
 - Multivariate Cox model including pre-therapy variables and transcript levels measured at 3 months
 - 3-month transcript level (higher or lower than 10%) and Hb at diagnosis (higher and lower than 11 g/dl) were the only independent predictor for the achievement of CCyR
 - Transcript level (>10%), RR= 0.176 (p<0.001)
 - Haemoglobin (>11 g/dl) RR= 1.72 (p=0.004)
- Using optimal threshold
 - Transcript level is only independent predictor of CCyR
 - >2.26%: RR=0.170 (95CI 0.107-2.70)

Conclusions

- Patients who are more likely to obtain CCyR, MMR and CMR on dasatinib can be identified at 3 months by measuring the PCR transcript level
- 10% is a useful threshold for dasatinib as well as imatinib
- 8.5% of dasatinib patients in SPIRIT 2 did not achieve 10% by 3 months (~25% on imatinib)

Conclusions

- An optimised threshold improves discrimination
 - 2.26% for CCR
 - 0.92% for MMR
 - 0.57% for CMR^{4.5}
- Further follow up required to see whether differences in PCR response at 3 months translate into differences in survival in SPIRIT 2
- Comparative analysis with imatinib in due course