Novel endpoints for MPN clinical trials

David Ross
SA Pathology, Royal Adelaide Hospital and Flinders Medical Centre
Adelaide

DISCLOSURES OF COMMERCIAL SUPPORT

Name of Company	Research support	Employee	Consultant	Stockholder	Speaker's Bureau	Scientific Advisory Board	Other
GSK	X				X		
Ground Truth	X						
Jubilant	X		X				
Keros/Takeda	X		X			X	
Menarini						X	
Merck	X					X	
Novartis	X				X	X	
Prelude	x					X	

What are clinical trials?

- Structured testing of a therapy
  - Consistent approach to dosing, response assessment
- Defined patient population – inclusion criteria
- Attempt to ensure safety and minimise interference from factors other than the disease being treated – exclusion criteria

What are endpoints?

- Pre-specified definition of success or failure of the trial
  - Primary Endpoint
- Endpoints are measures of treatment effect
  - Primary, Secondary, Exploratory
  - Should be measurable precisely and objectively

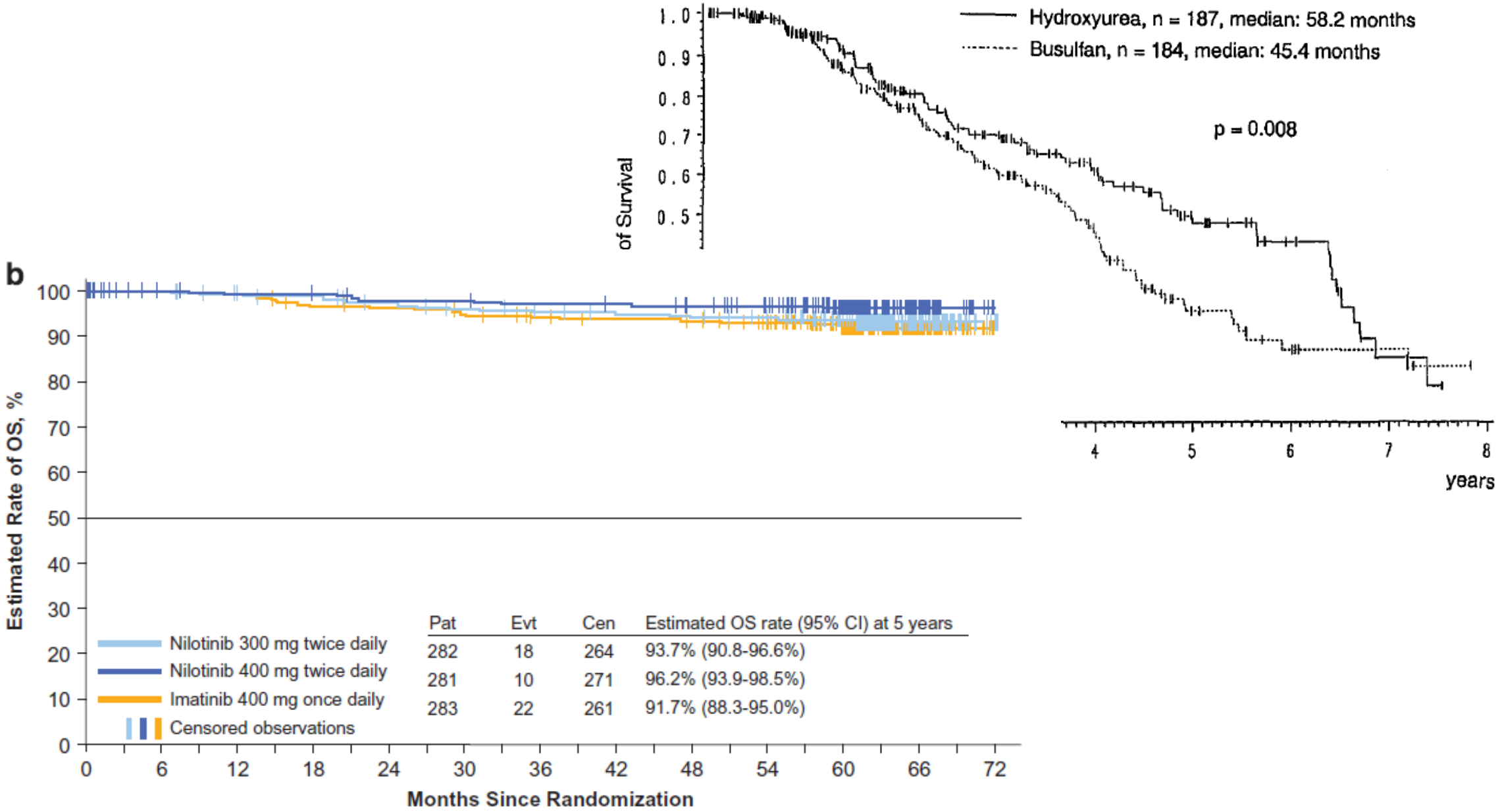
- Surrogate endpoints are measures that stand in for a true endpoint that cannot be measured directly
  - Overall survival may not be assessable for many years
  - Symptoms and quality of life cannot be measured directly

Conventional endpoints in MPN trials

- Haematological remission
  - Blood count normalisation
  - Resolution of disease-related symptoms
  - No progression or specified ‘events’
- TSS50
- SVR35

Inclusion criteria

- All newly diagnosed patients with MPN were randomized to receive either TREATMENT A or B when they fulfilled at least one of the following 6 criteria:
  - General ill feeling and fatigue
  - Weight loss of more than 10% in 6 months
  - Unexplained fever of more than 38.5 C on 5 consecutive days
  - Organomegaly-related symptoms
  - Leukocytosis of more than 50 x 10^9/L
  - Thrombocytosis of more than 1 x 10^{12}/L



Hehlmann Blood 1993 82:398;
Hochhaus Leuk 2016 30:1044.

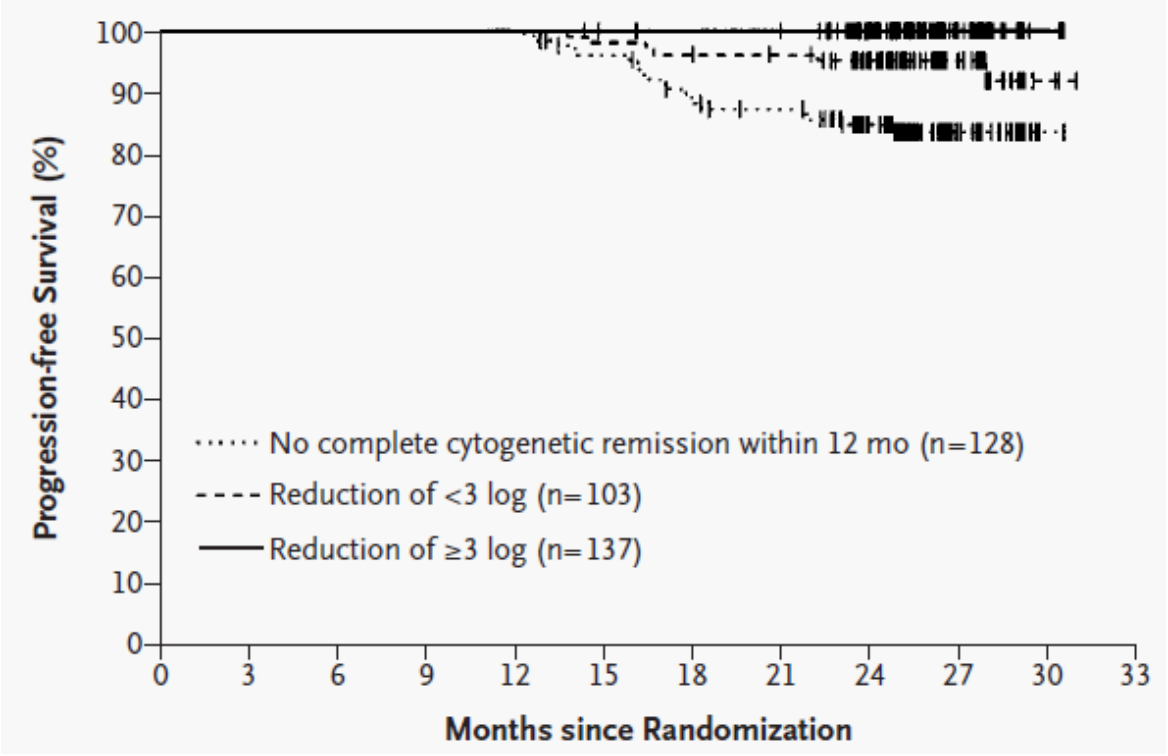
Hughes NEJM 2003 349:1423.

What enabled the transformative change?

- Highly effective therapy

- Highly accurate biomarker of response
  - Linked to disease biology
  - Early assessment of response

Imatinib would never achieve a TSS50



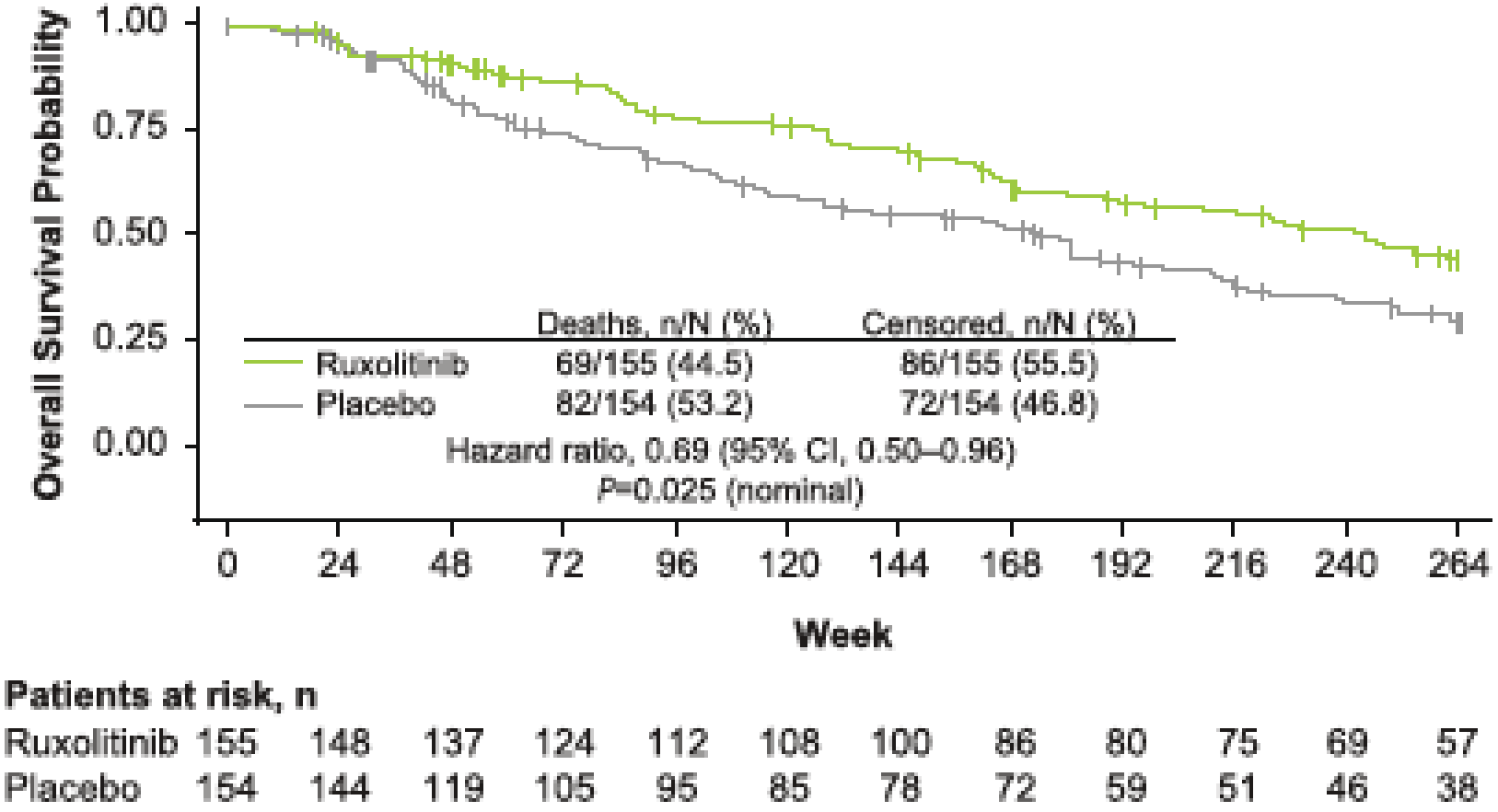
But….MF is not CML

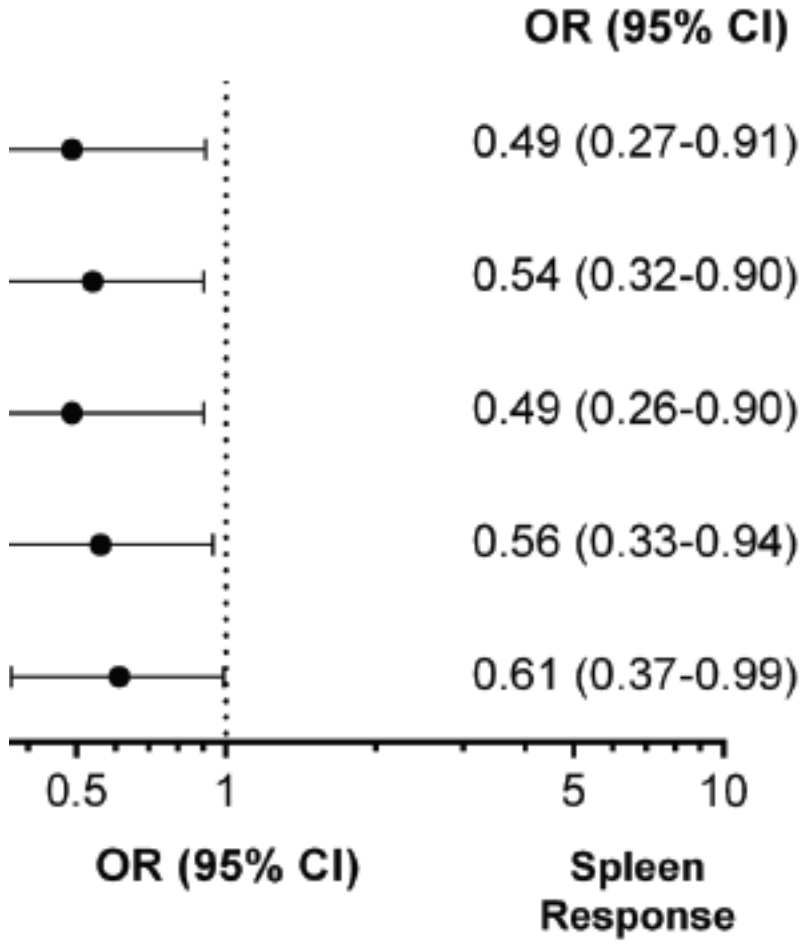
- *BCR::ABL1* is the *sine qua non*
  - JAK2, CALR, MPL, ‘triple-negative’
  - Non-driver genetic lesions ASXL1, EZH2, etc.

- *BCR::ABL1* is a founder genetic lesion
  - JAK2 can be a founder or acquired during evolution

- *BCR::ABL1* drives progression
  - Factors leading to progression are less well understood
  - Post-MPN AML can arise in JAK2-negative cells

Delayed treatment leads to inferior outcomes





Median time to crossover 40 weeks

Verstovsek JHO 2017 10:55;
Palandri Oncotarget 2017 8:79073.

What are the outcomes of highly effective therapy?

- Clinico-pathological remission
  - TSS, SVR
  - Improved cytopenia
  - Reduction in cytokines
  - Histological normalisation

Assessable early

- Molecular remission

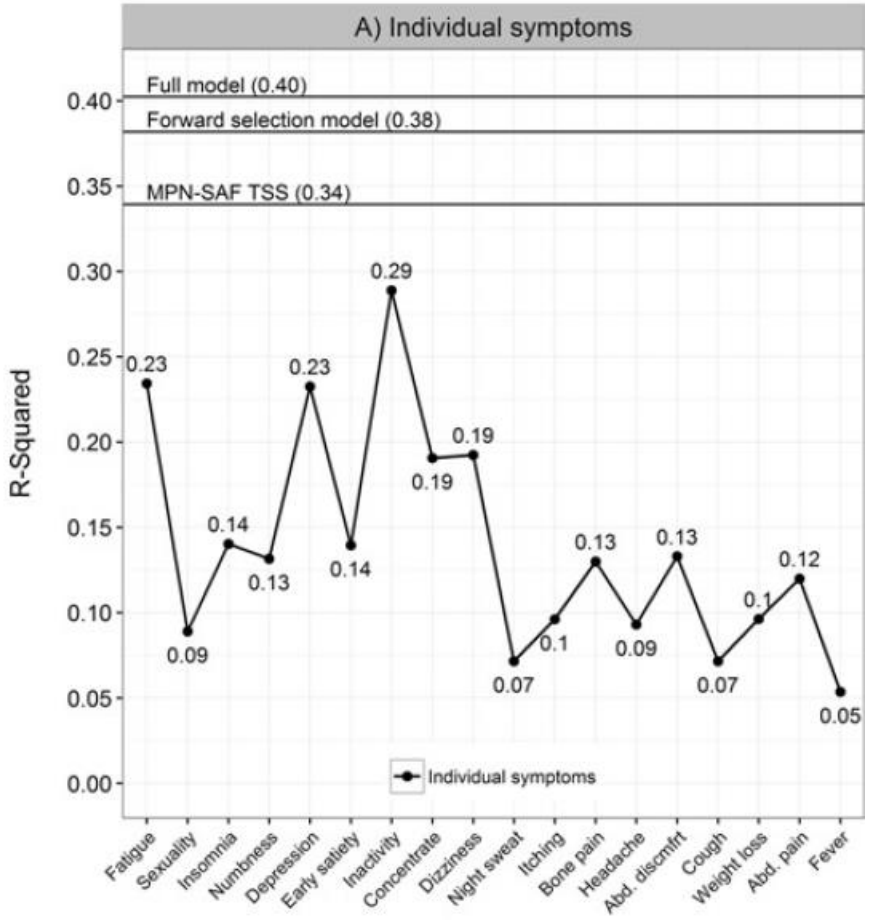
- Prevention of disease progression/transformation
- Prolonged survival (PFS, OS)

Assessable late

Limitations of current endpoints

Why TSS50?

Effect of individual symptom scores on QoL



Effect of total symptom score on PGIC

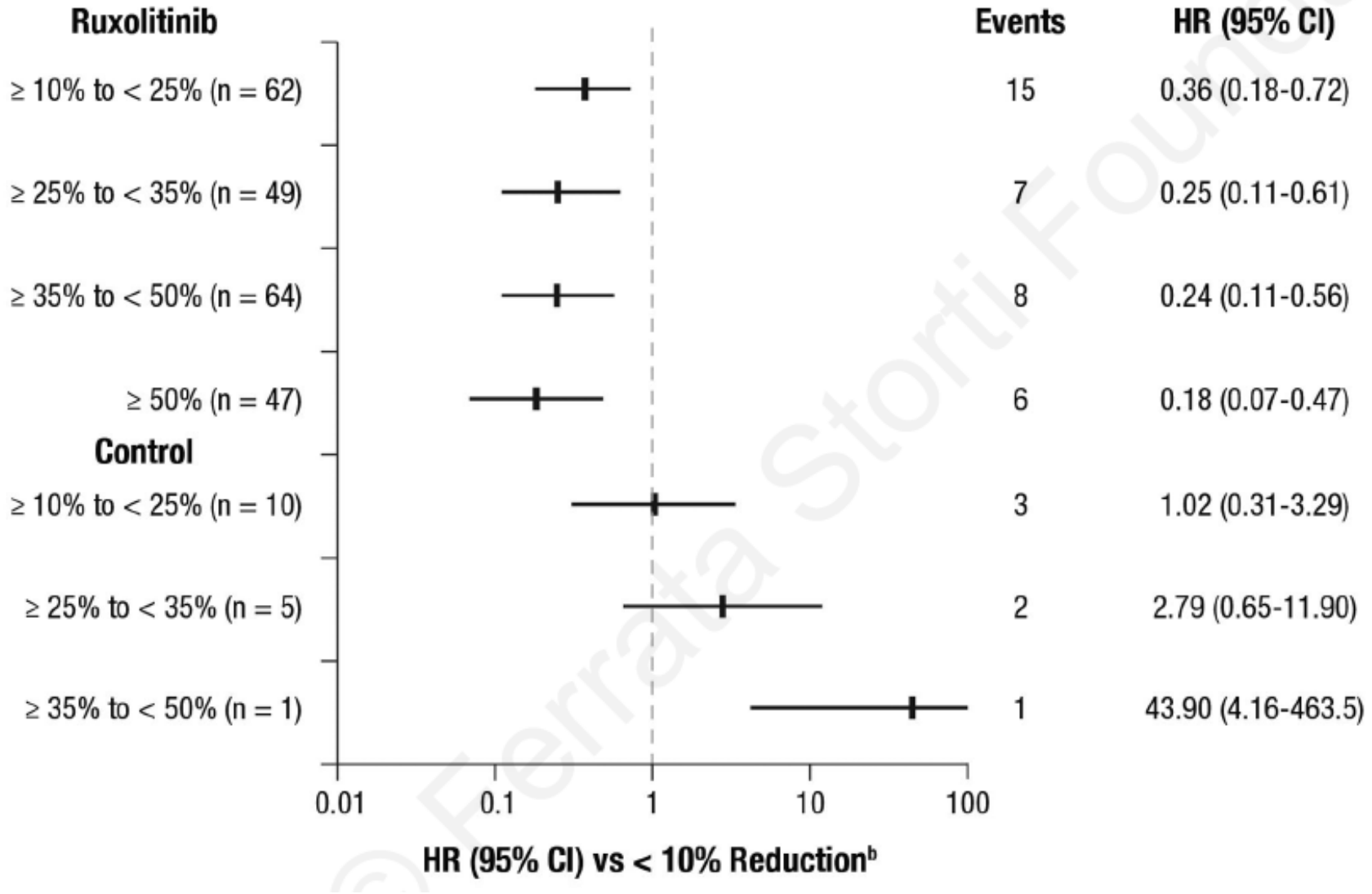
Week	Category	Change (correlation with endpoint)	N	Mean Change (SD)	Min , Max	95% Confidence Interval
24	VERY MUCH IMPROVED	0.289	29	-11.07 (10.543)	-42 , 6	(-15.082 , -7.062)
	MUCH IMPROVED		156	-8.82 (9.323)	-33 , 22	(-10.293 , -7.344)
	MINIMALLY IMPROVED		108	-4.98 (8.422)	-40 , 13	(-6.589 , -3.376)
	NO CHANGE		36	-2.31 (7.272)	-27 , 8	(-4.769 , 0.152)
	MINIMALLY WORSE		12	-0.20 (8.406)	-19 , 15	(-5.545 , 5.137)
	MUCH WORSE		7	-8.51 (6.531)	-15 , 5	(-14.551 , -2.470)
	VERY MUCH WORSE		0	N/A	N/A	N/A

Threshold for a clinically meaningful change determined as cut-off to distinguish ‘minimally improved’ from ‘much improved’. (8 points)

Langlais Leuk Lymph 2019 60:402; Hudgens Value Health 2024 27:607.

Why SVR35?

SVR at 24 weeks and overall survival



Pooled analysis of COMFORT studies

Vannucchi Haem 2015 100:1139.

Chow Radiol 2016 279:306.

Response versus normalisation

Applies also to
TSS
Cytokines
Fibrosis
MR

Maximum possible SVR90

1500 mL

150 mL

Normal volume (USS)
M 179 mL (90-334)
F 134 mL (64-231)

Pathological enlargement

600 mL

300 mL

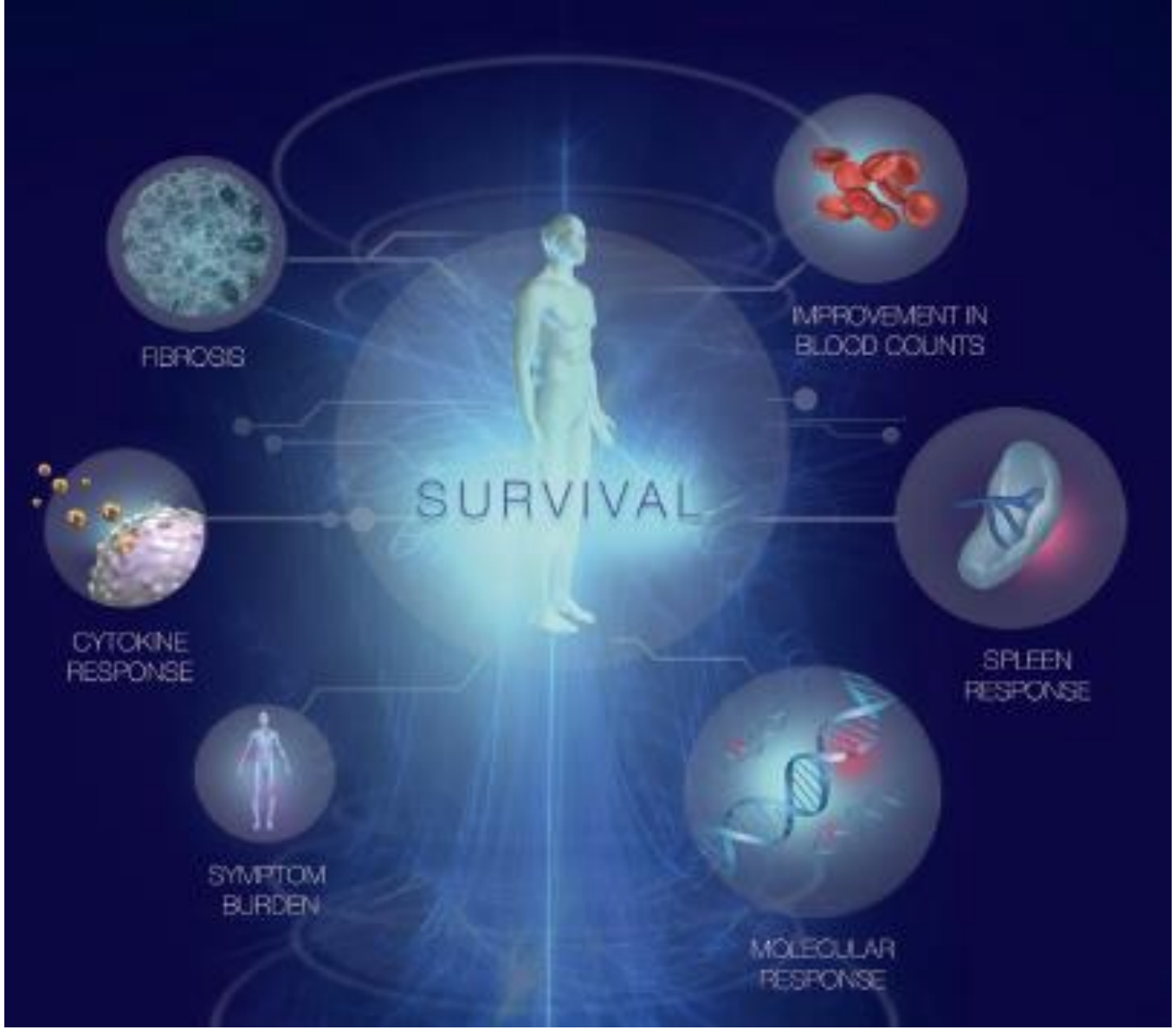
Normal volume

Maximum possible SVR50

Ideal surrogate endpoint

- Highly predictive of genuine endpoint of interest (OS/PFS)
- Assessable in every patient
- Applicable with every treatment

Many therapies being tested



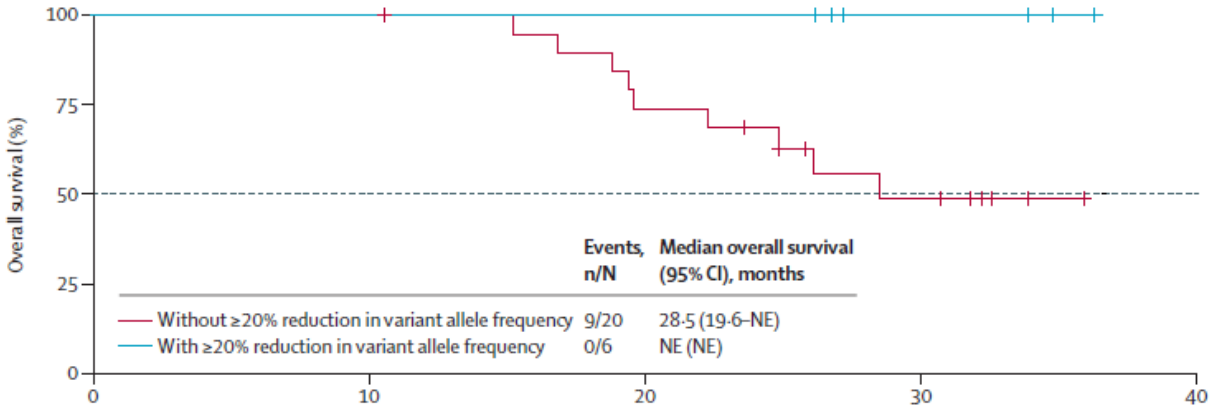
Many endpoints being reported

Only MR is a direct measure of the neoplastic clone

 Pemmaraju Lancet Haem 2022 9:e434; Harrison JCO 2023 41:3534.

Molecular response

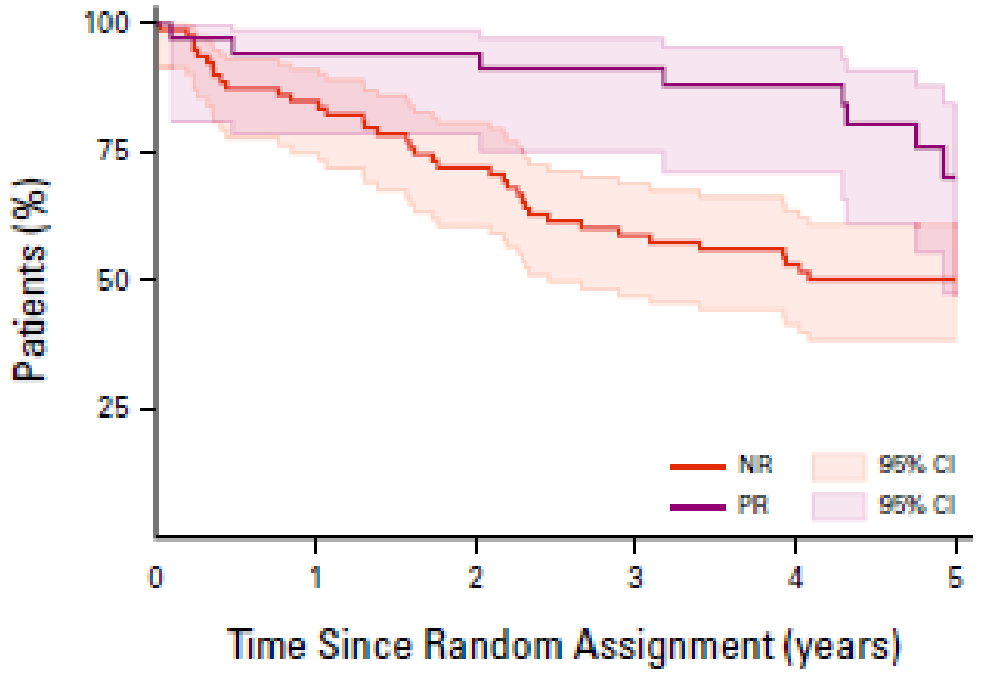
Overall survival by MR at 24 weeks (20% decrease)



Number at risk (number censored)								
Without ≥20% reduction in variant allele frequency	20 (0)	..	20 (0)	19 (1)	14 (1)	10 (3)	7 (4)	1 (10)	..
With ≥20% reduction in variant allele frequency	6 (0)	..	6 (0)	6 (0)	6 (0)	6 (0)	3 (3)	1 (5)	..

REFINE Phase 2 navitoclax added to RUX after suboptimal response or progressive disease

EFS by MR at 12 months (50% decrease)



No. at risk:						
NR	79	66	56	43	36	11
PR	34	32	32	29	26	10

MAJIC-PV Phase 2 RUX versus BAT for HU res/intol PV

Endpoint	Treatment	Trial	Overall survival
SVR	Ruxolitinib	COMFORT-1	HR 0.69 (0.50-0.96)
		COMFORT-2	*HR 0.67 (0.44-1.02)*
		SIMPLIFY-1	HR 0.45 (p=0.008)
	Momelotinib	SIMPLIFY-1	*HR 1.15 (0.61-2.16)*
TI	Momelotinib	SIMPLIFY-1	HR 0.31 (0.17-0.56)
MR20	Rux+navitoclax second-line	REFINE	Median OS 28.5 mo vs 100% at 36 mo
TSS	Momelotinib	SIMPLIFY-1	*0.85 (0.47-1.56)*

May need composite endpoints to identify disease-modifying potential, e.g. SVR+MR

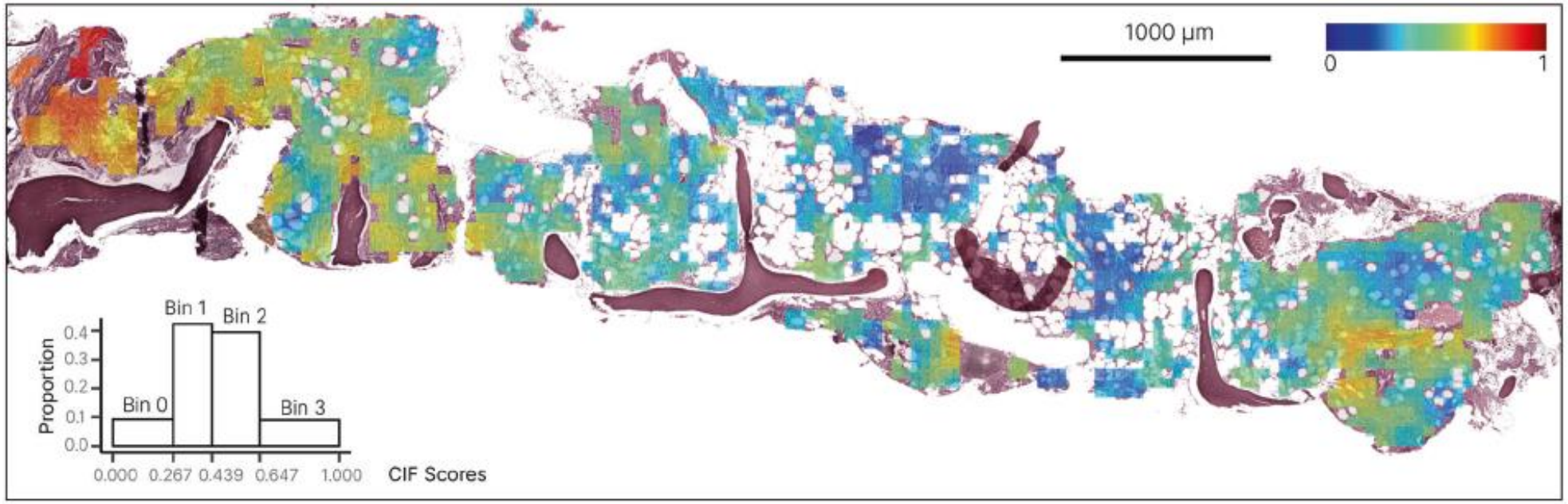
Pemmaraju Lancet Haem 2022 9:e434;
Mesa Leuk 2022 36:2261;
Verstovsek JHO 2017 10:55;
Harrison Leuk 2016 30:1701.

Tefferi JCO 2011 29:1356; Ryou Leuk 2023 37:348; Pemmaraju Cancer 2022 128:2420; Ross Blood 2024 144:1679.

Other measures of disease burden

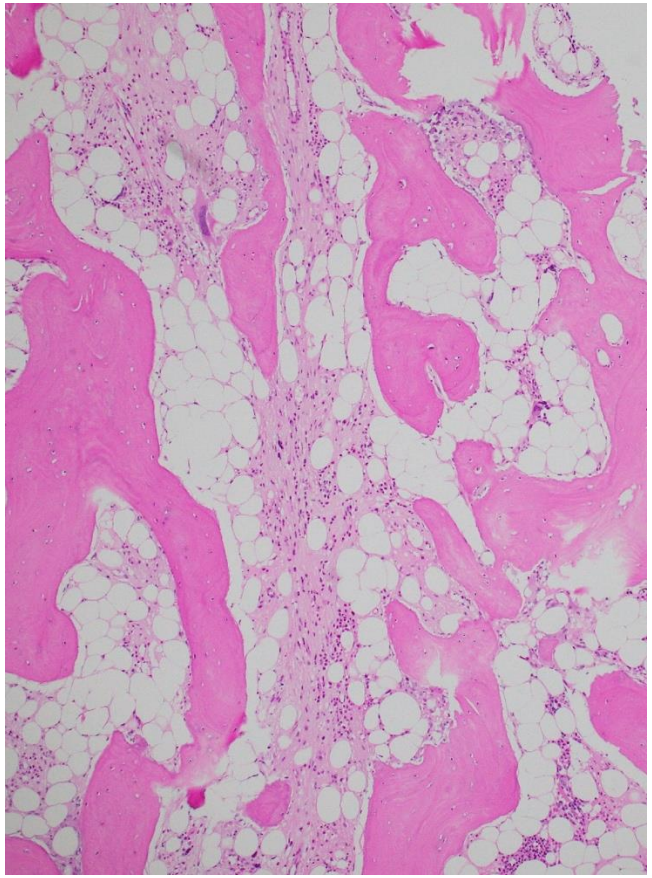
- Cytokines

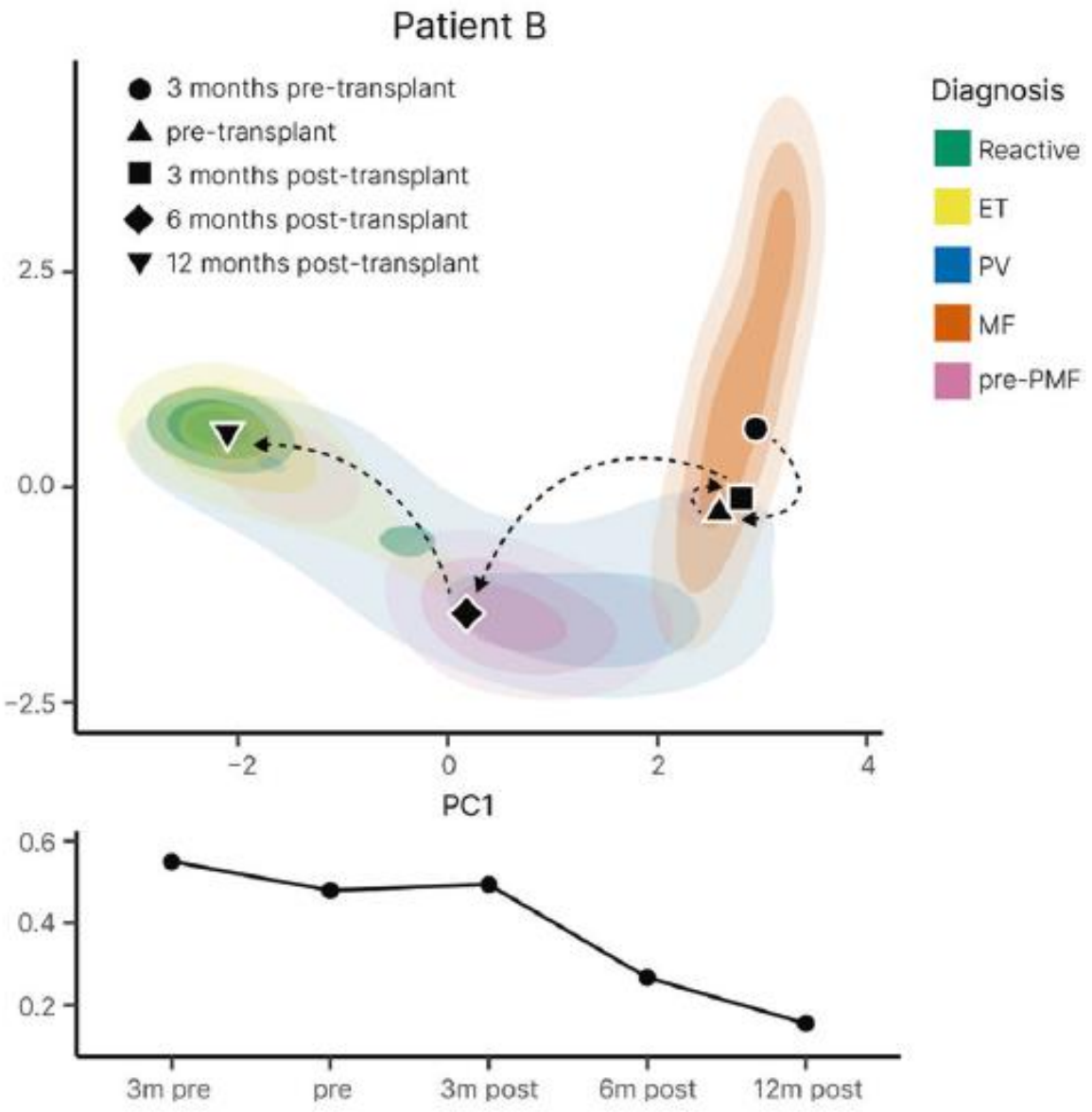
- Histomorphometry



Ryou Leuk 2023 37:348.

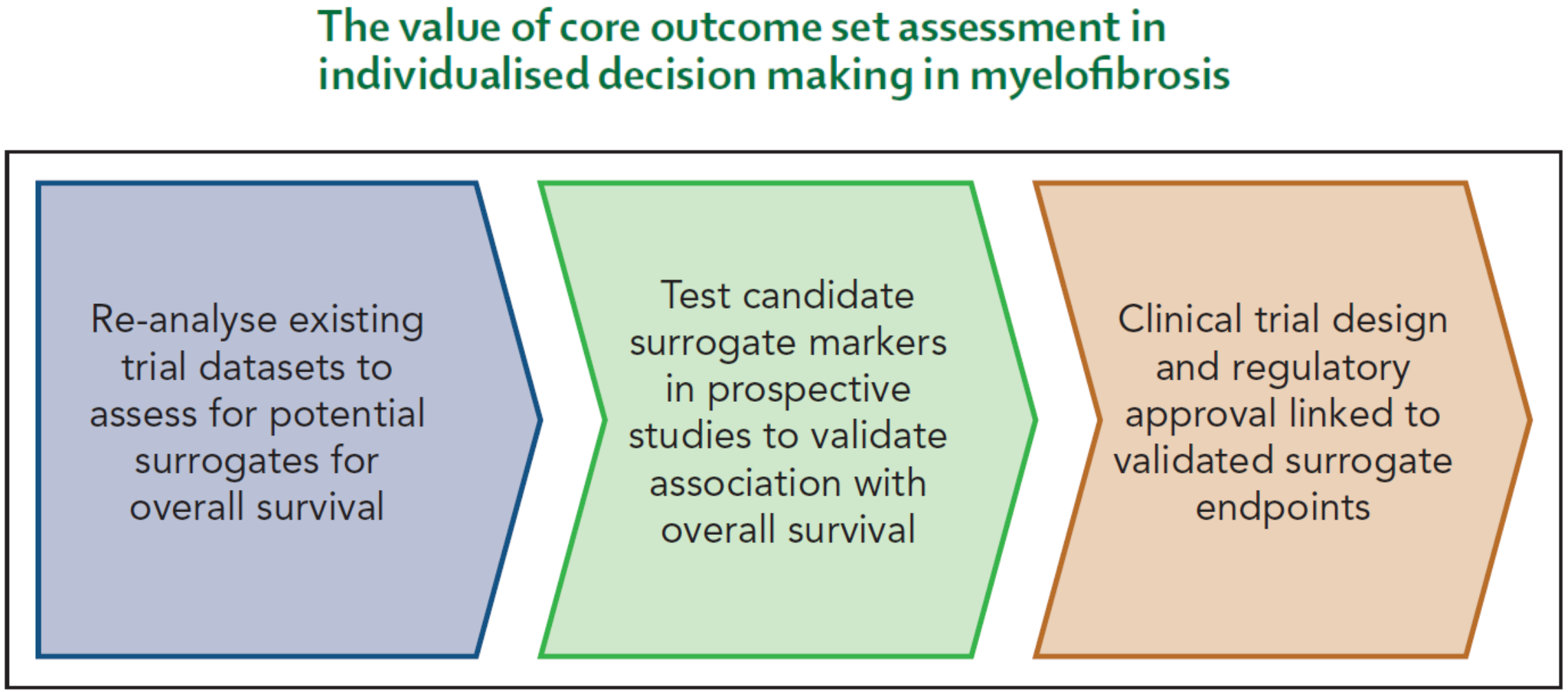
Marrow morphology contains latent information





Barosi Lancet Haem 2024 11 e383; Ross Blood 2024 144:1679.

How to find a way forward



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