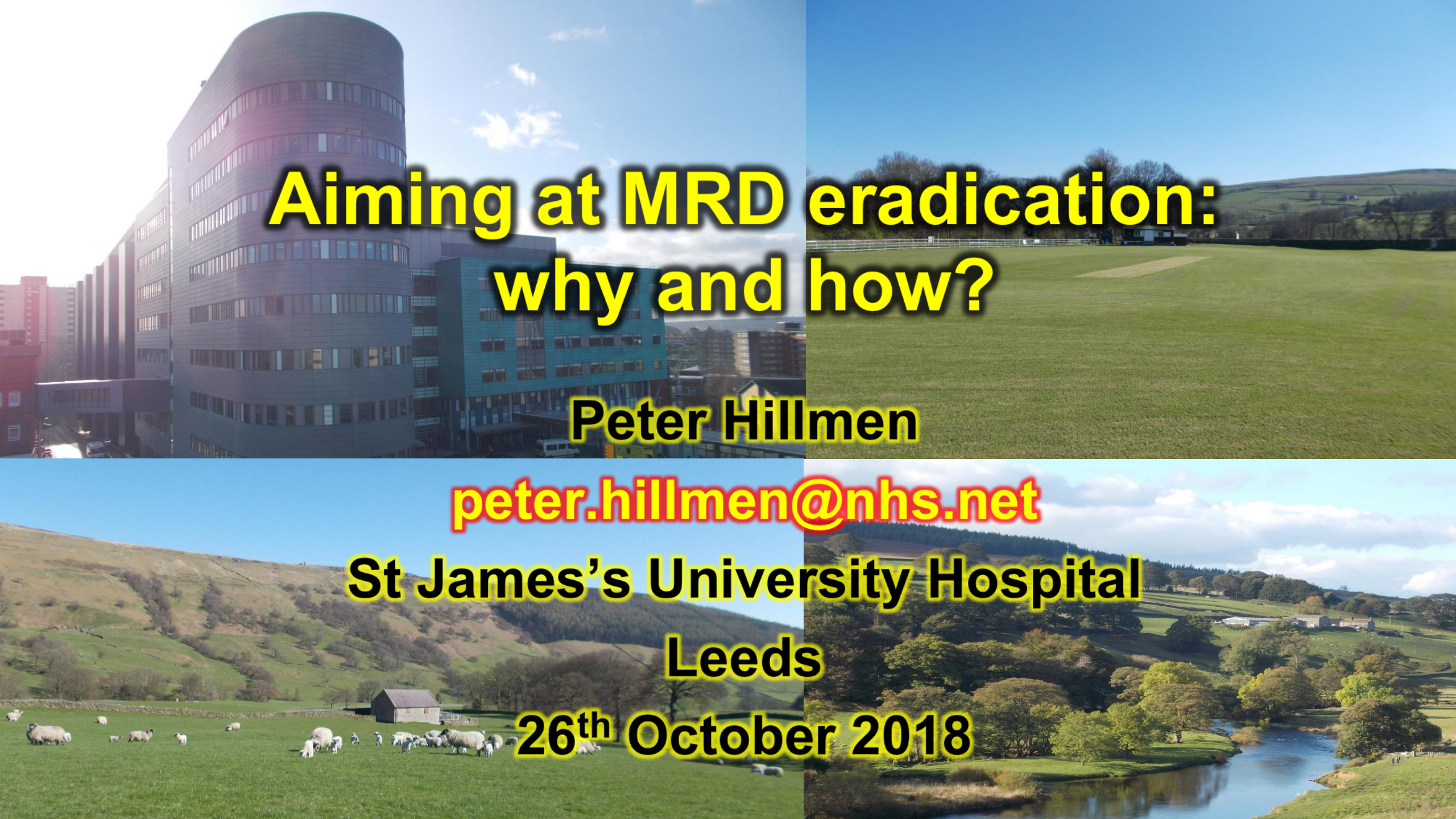


Aiming at MRD eradication: why and how?

Peter Hillmen

peter.hillmen@nhs.net

St James's University Hospital

Leeds

26th October 2018

Disclosures – Peter Hillmen

Advisor/consultant

- Abbvie
- Acerta
- Gilead
- Janssen
- Novartis/GSK
- Pharmacyclics
- Roche

Research/trial support

- Abbvie
- Gilead
- Janssen
- Novartis/GSK
- Pharmacyclics
- Roche

No share ownership, patents or board membership

Reasons to eradicate MRD in CLL?

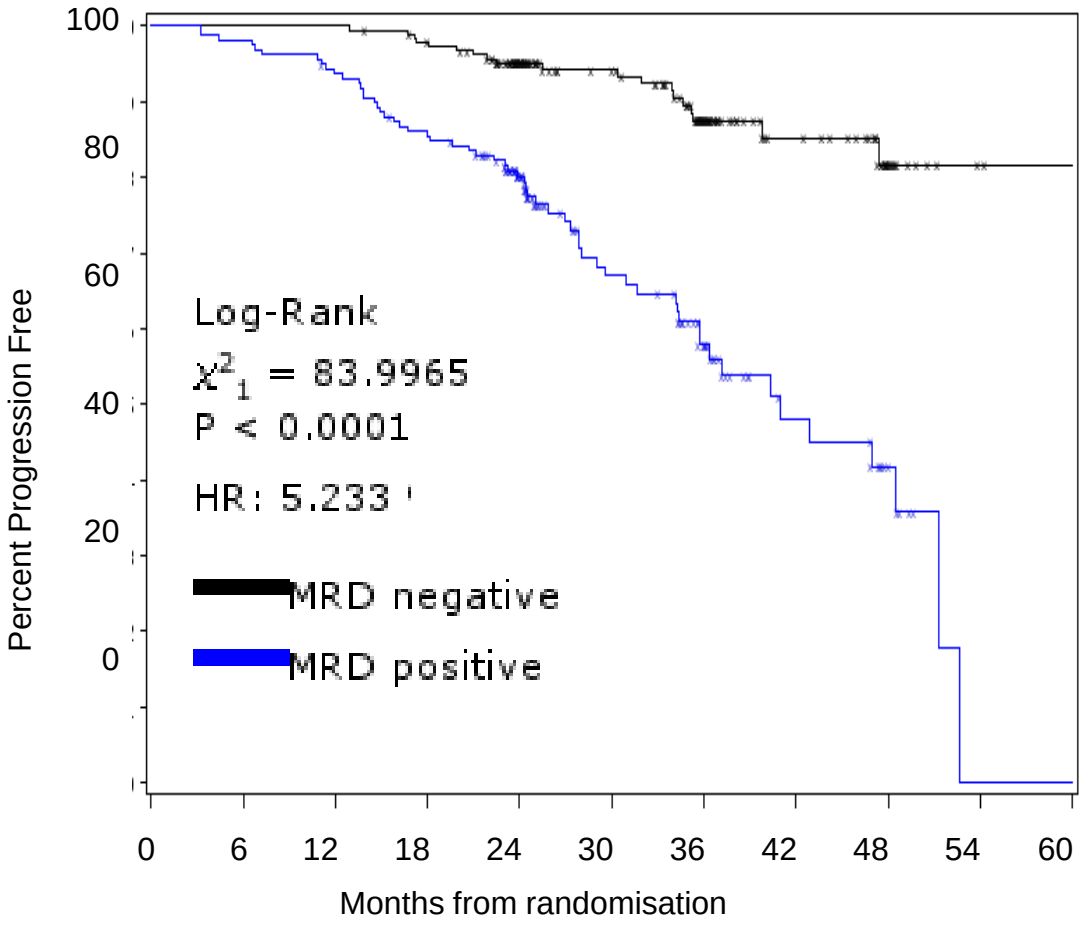
1. End-point in clinical trials
2. To predict individual patient outcome after completion of therapy
3. To define duration of therapy
4. To consider re-initiation of therapy
5. To move towards cure

Reasons to eradicate MRD in CLL?

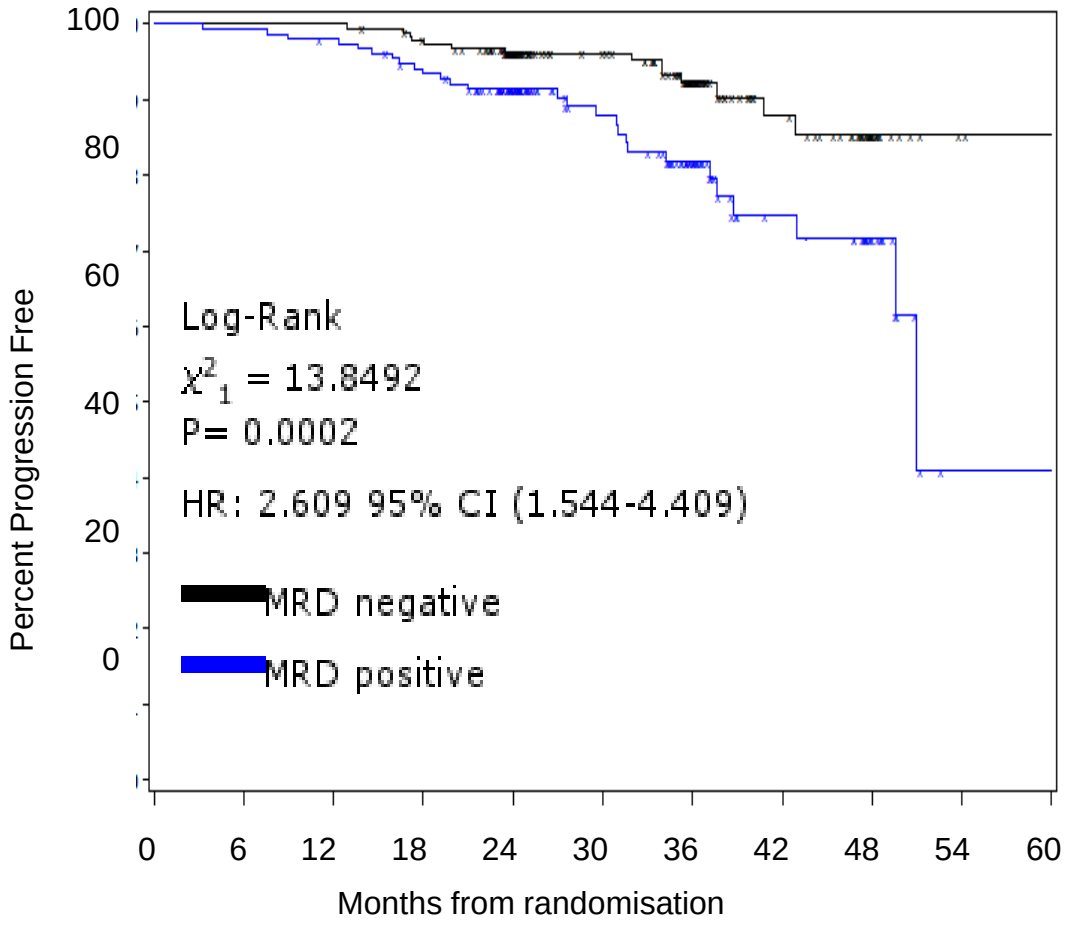
1. End-point in clinical trials
2. To predict individual patient outcome after completion of therapy
3. To define duration of therapy
4. To consider re-initiation of therapy
5. To move towards cure

NCRI ADMIRE and ARCTIC (n=345): FCR(±M) in front-line CLL
Time to PD and OS – MRD in marrow at 3 months post-FCR(±M)

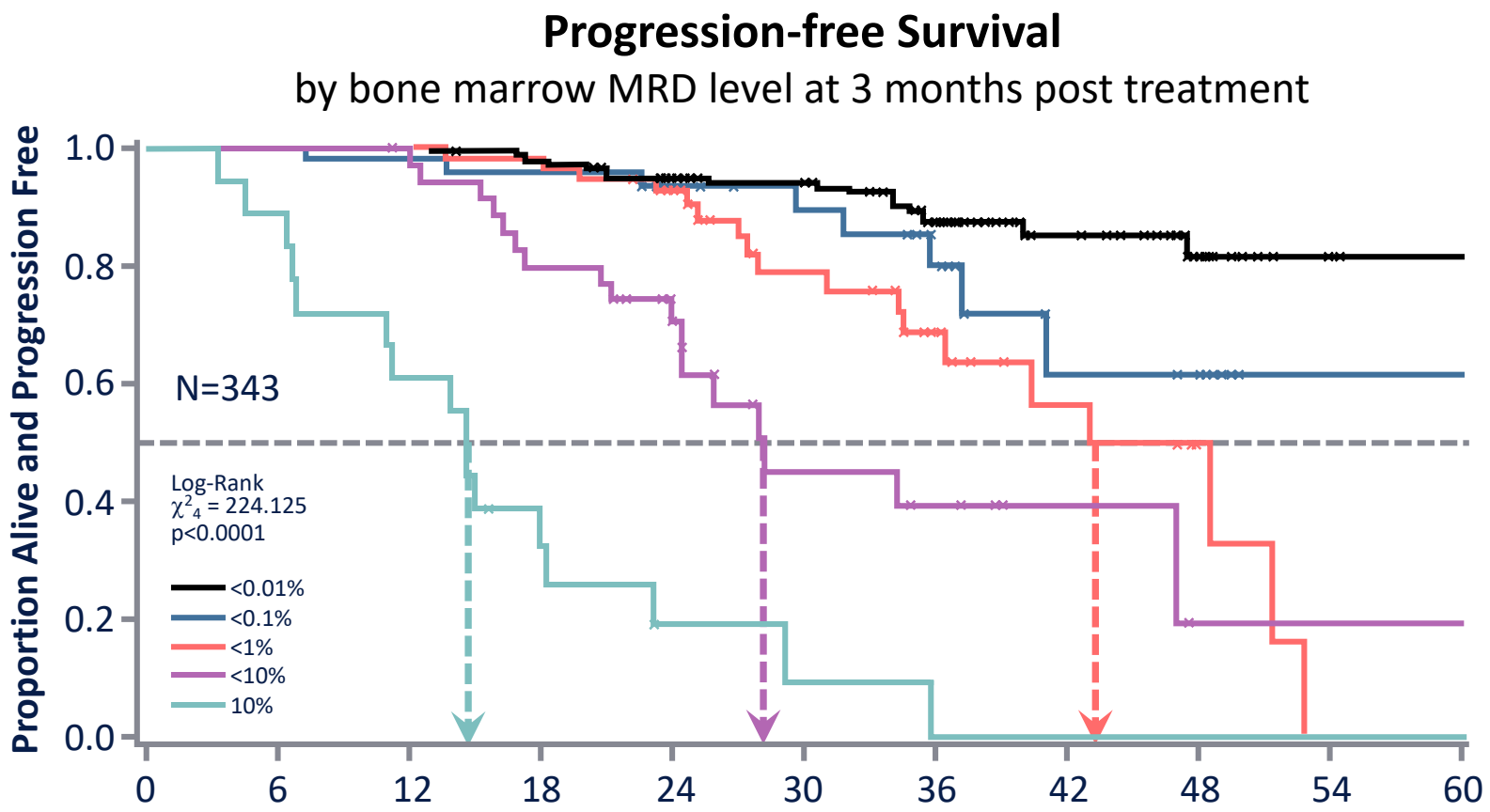
Progression-free survival



Overall survival



ADMIRE/ARCTIC Trial (FCR-Based Treatment): Sequential Benefit in PFS per Log Reduction in MRD

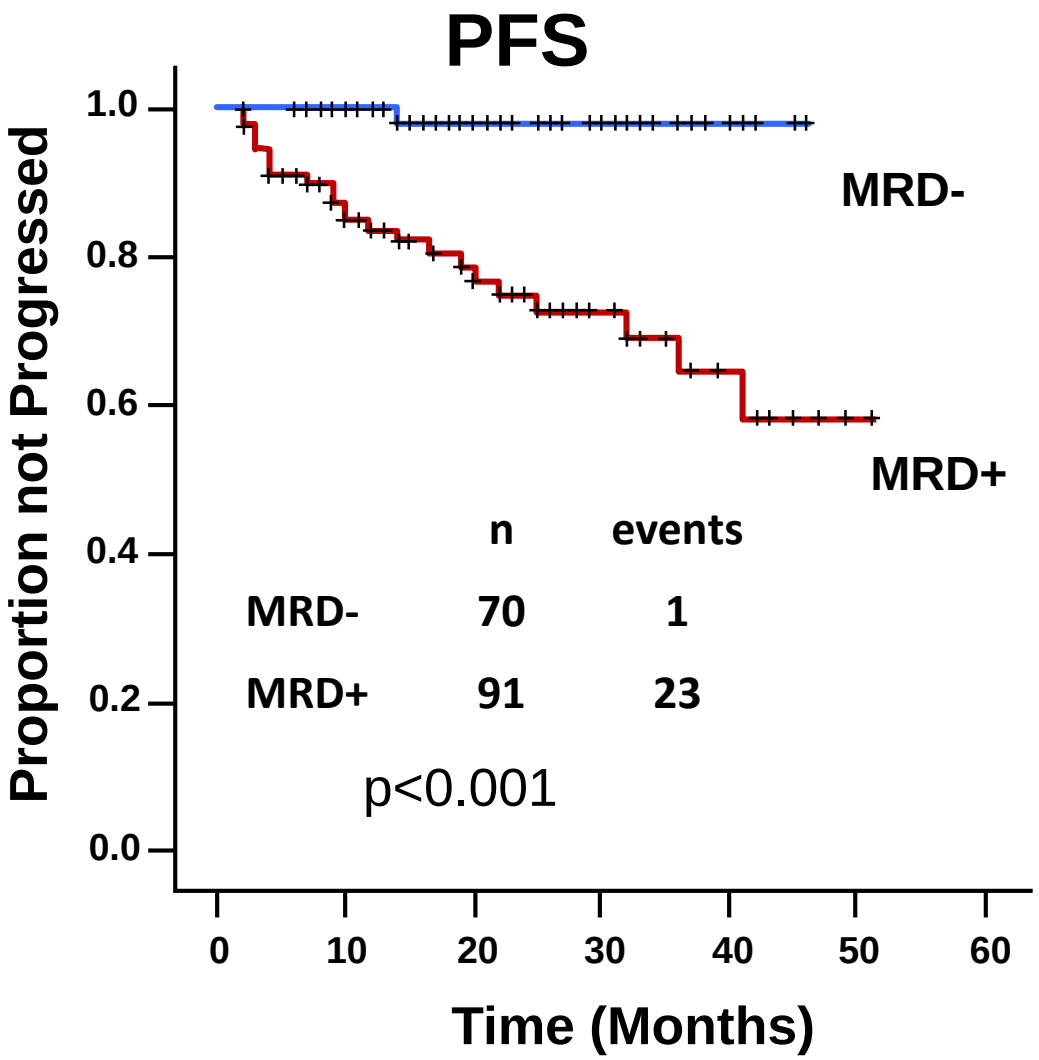


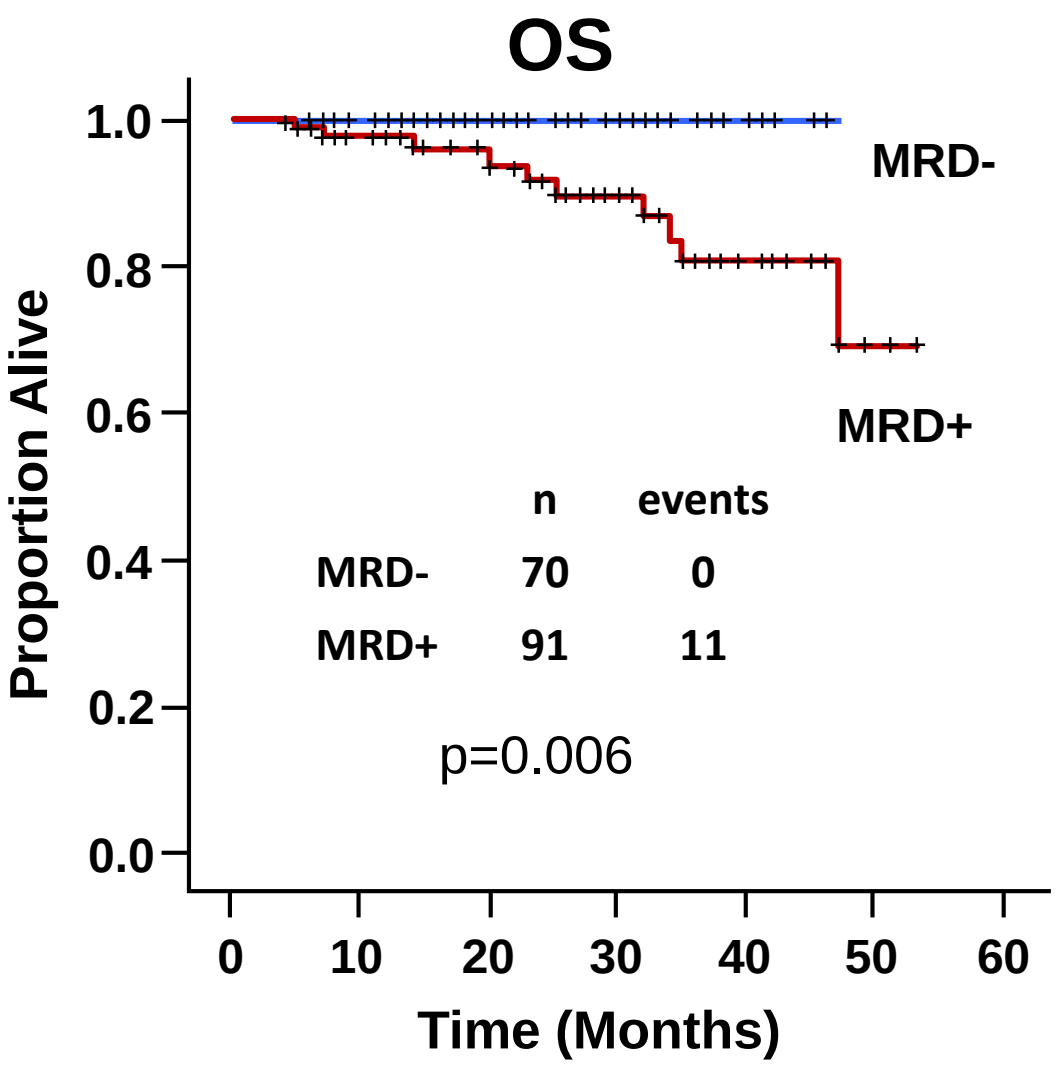
33% (95% CI = 27–38) risk reduction for disease progression per log reduction in MRD level

FCR, fludarabine, cyclophosphamide, rituximab.

Rawstron AC, *et al.* XVI iwCLL Annual Meeting 2015.

First-line FCR: PFS and OS by MRD Status

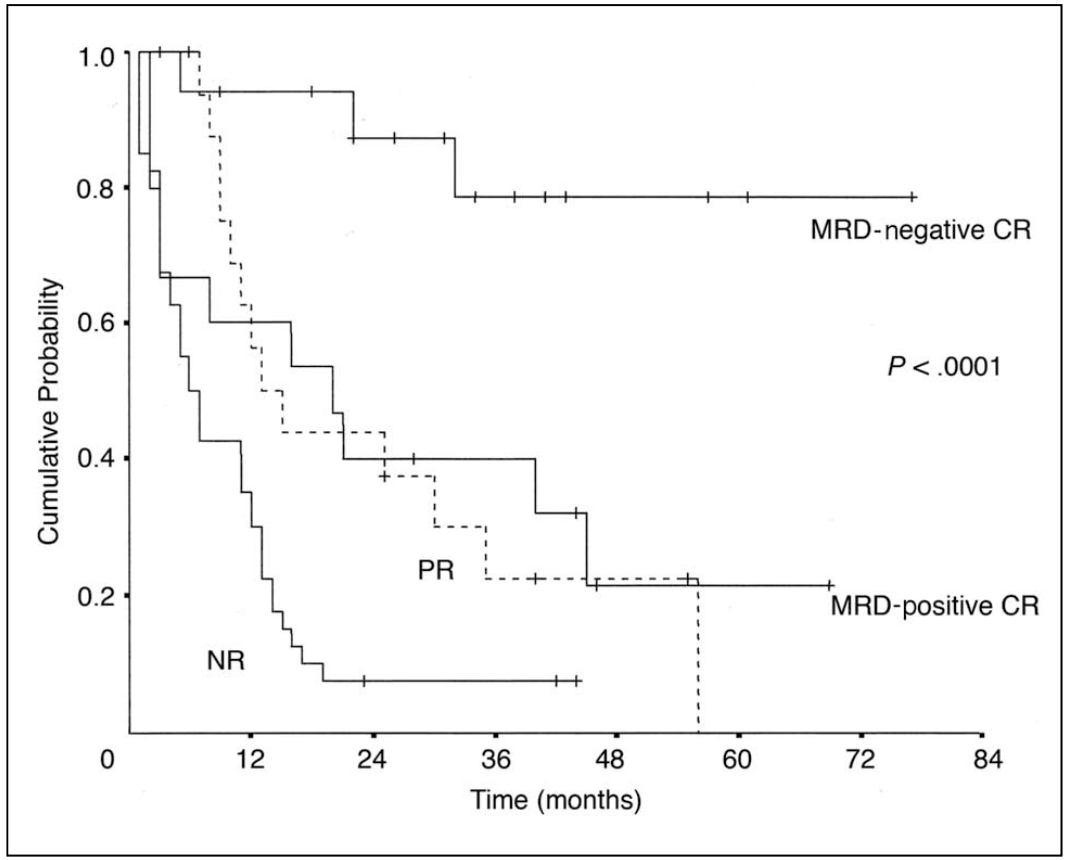




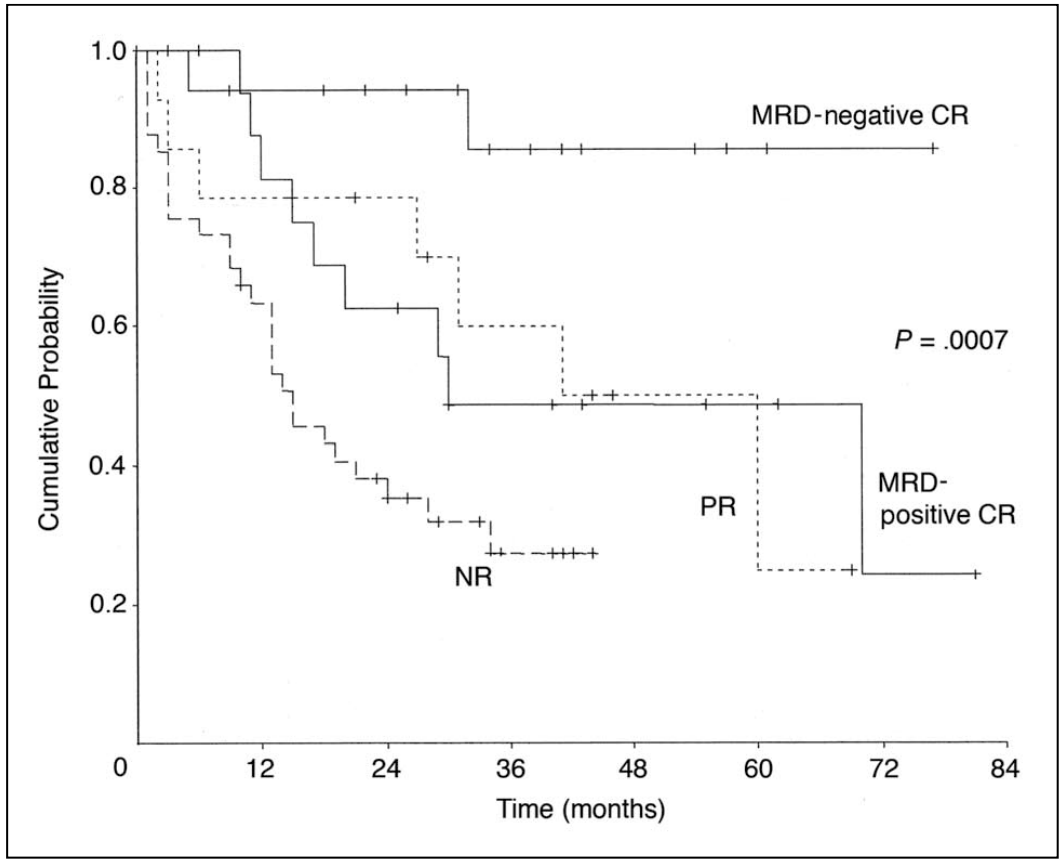
Strati P, *et al. Blood* 2014; **123:**3727–3732.

Alemtuzumab in relapsed/refractory CLL: MRD negativity associated with improved outcome

PFS

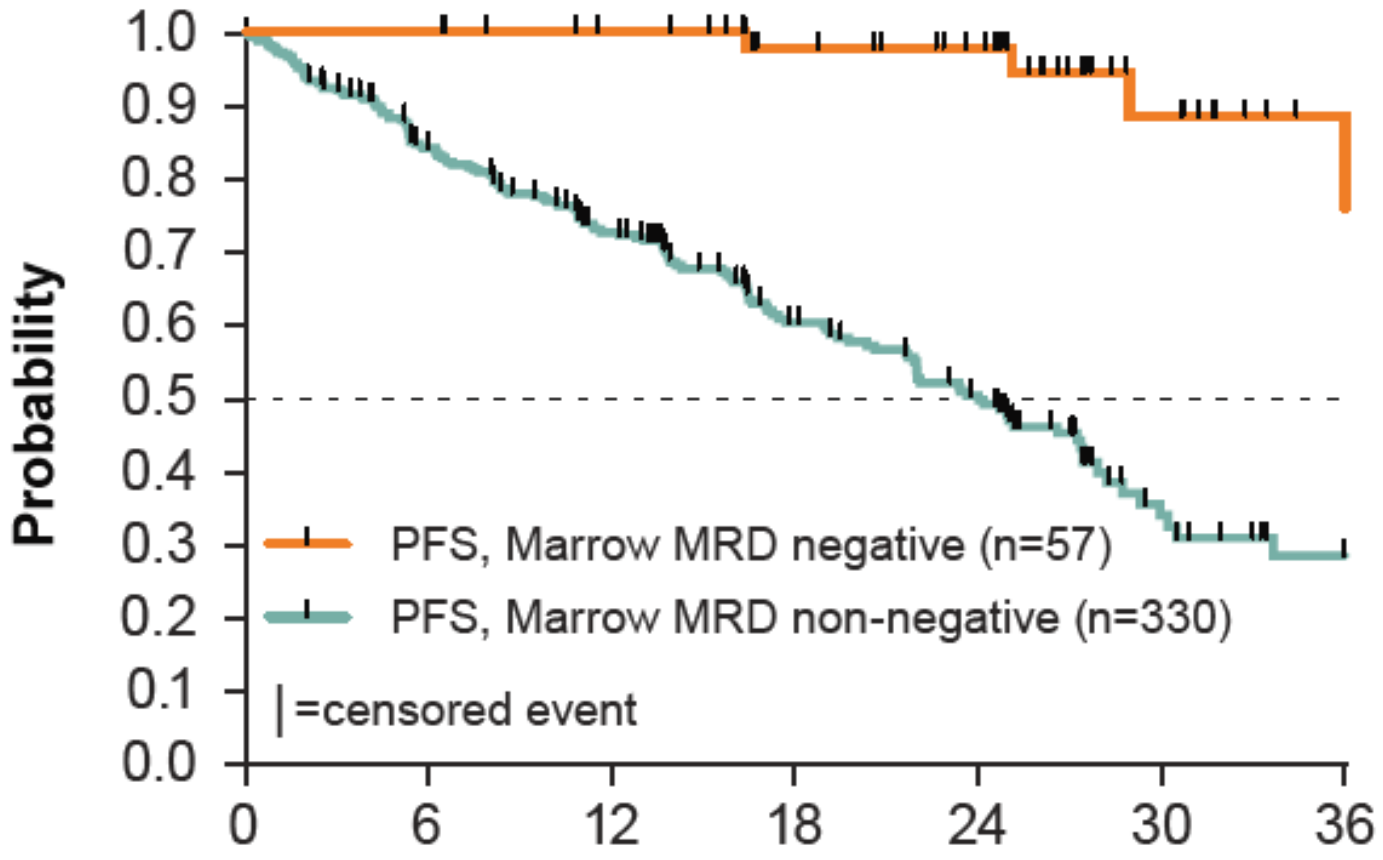


OS



Moreton P, *et al. JCO* 2005; **23,** 2971–2979

Pooled Multi-trial Analysis of Venetoclax Efficacy in R/R CLL: PFS by Marrow MRD Status



Pts at risk							
PFS (MRD negative)	57	57	50	41	35	15	7
PFS (MRD non-negative)	330	262	197	117	85	22	11

Roberts et al. ASH 2016. Abstract #3230.

Minimal residual disease is an independent predictor for 10-year progression-free and overall survival in CLL

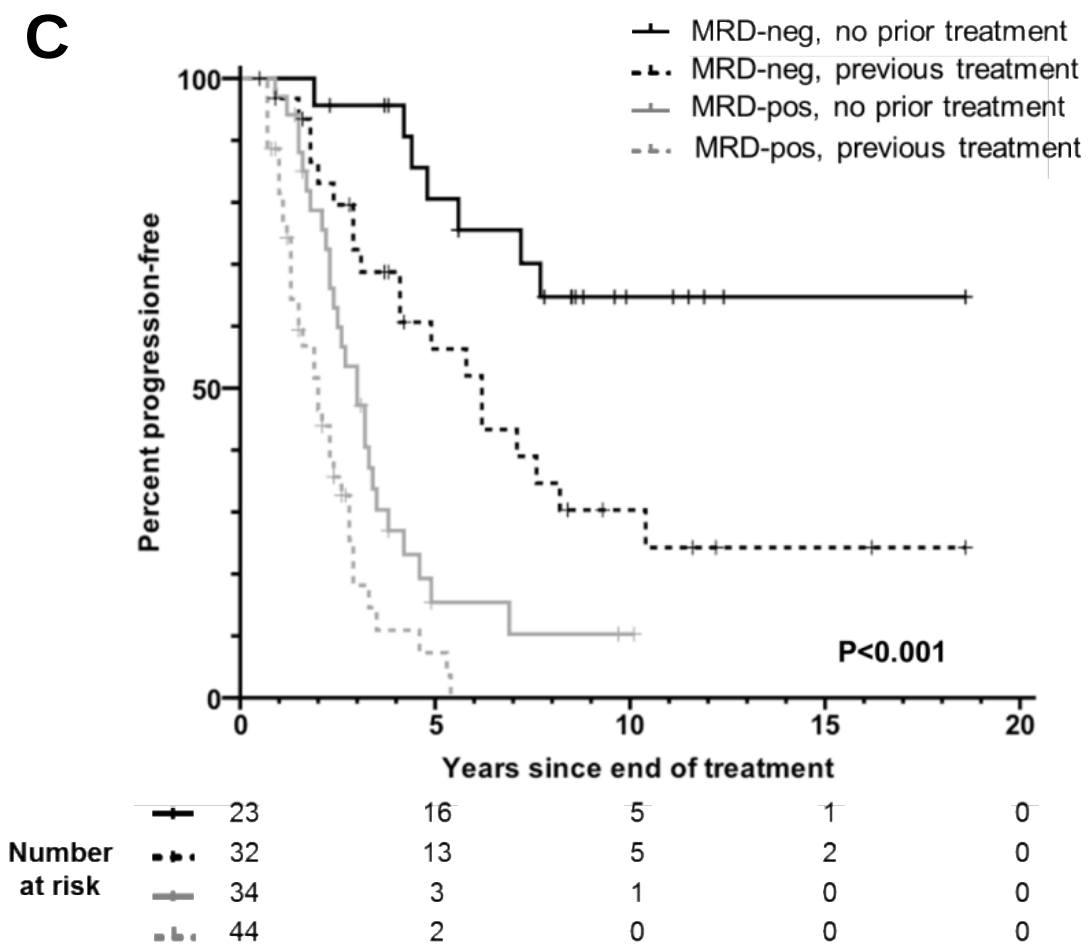
133 patients with MRD assessment in the marrow post-therapy:

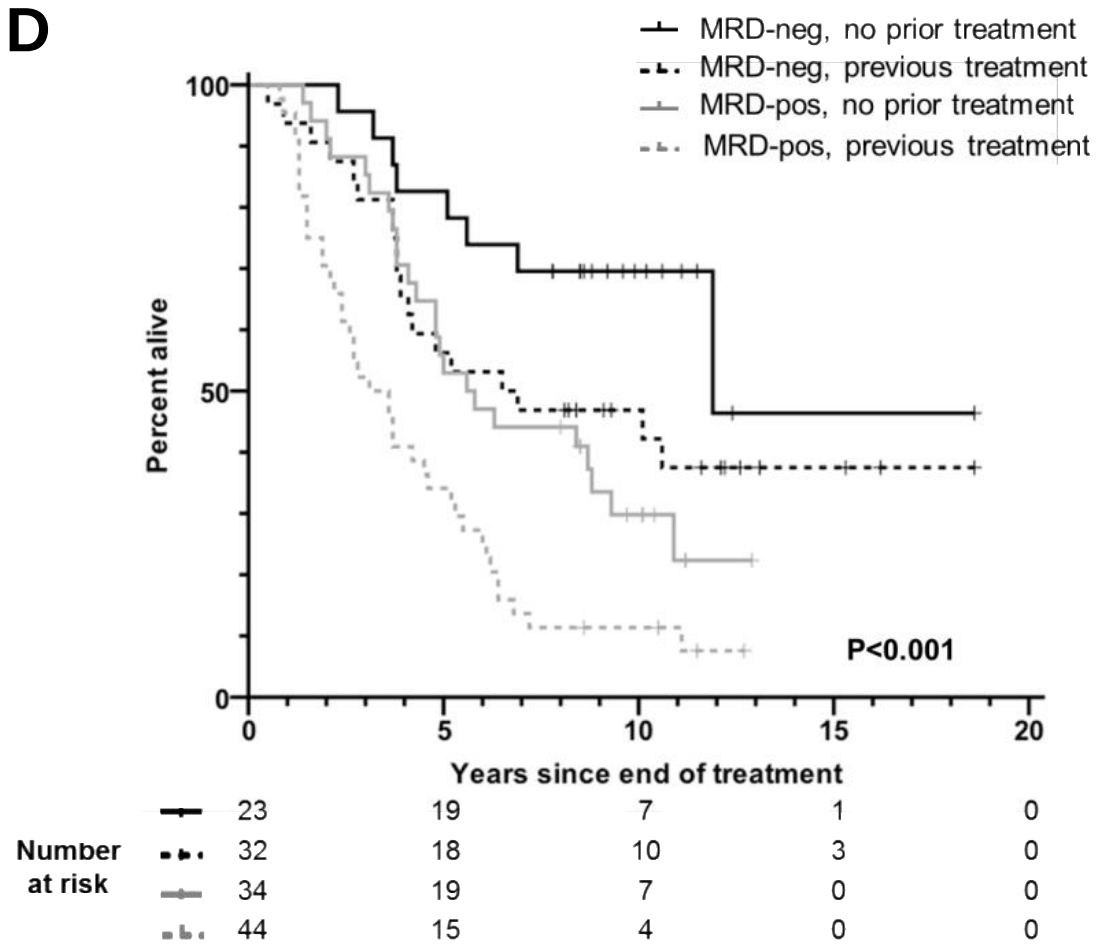
67 CIT; 31 single agent chemotherapy, 7 autologous SCT, 28 MoAB

Parameter	Progression-free Survival			Overall Survival		
	Univariate (Log-Rank) P Value	Multivariate (Cox) P Value	Hazard Ratio (95% CI)	Univariate (Log-Rank) P Value	Multivariate (Cox) P Value	Hazard Ratio (95% CI)
Age* (60 years)	.513			**.001**	**.001**	**2.41 (1.45-4.00)**
Hemoglobin* (110 g/L)	.957			.058		
Platelet* (100 x 10^9/L)	**.001**	.983		**.034**	.168	
Binet stage* (A/B vs C)	**.005**	.870		**.001**	**.018**	**2.23 (1.14-4.33)**
Prior treatment (Y/N)	**.003**	.159		**.003**	**<.001**	**2.61 (1.61-4.23)**
Treatment type	**<.001**	.265		**.004**	.886	
IWCLL Response	**<.001**	.545		**.001**	.585	
MRD level (< 0.01 / 0.01-0.1 / 0.1-1 / > 1%)	**<.001**	**<.001**	**2.07 (1.59-2.69)**	**<.001**	**.002**	**1.39 (1.13-1.70)**
Adverse cytogenetics* (del 17p/11q)†	**.024**	**.013**	**2.00 (1.16-3.45)**	.051		

Kwok *et al., Blood*, 2016 Dec 15;128(24):2770-2773.

Minimal residual disease eradication predictive in both previously untreated and treated patients





Kwok *et al., Blood*, 2016 Dec 15;128(24):2770-2773.

Regulatory approval of MRD in CLL

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

23 October 2014
EMA/629967/2014
Committee for Medicinal Products for Human Use (CHMP)

Guideline on the use of minimal residue disease a
endpoint in chronic lymphocytic leukaemia studie

Executive summary

Minimal residual disease (MRD) negativity in patients ir
rate) after induction therapy may be used as an interm
controlled studies designed to show superiority in term
the experimental regimen is well characterised in CLL a
superiority of the regimen over established regimens u

News >

FDA Updates Venetoclax CLL Label With MRD Data

Jason M. Broderick @jasoncology
Published: Tuesday, Sep 11, 2018

John F. Seymour, MBBS, PhD

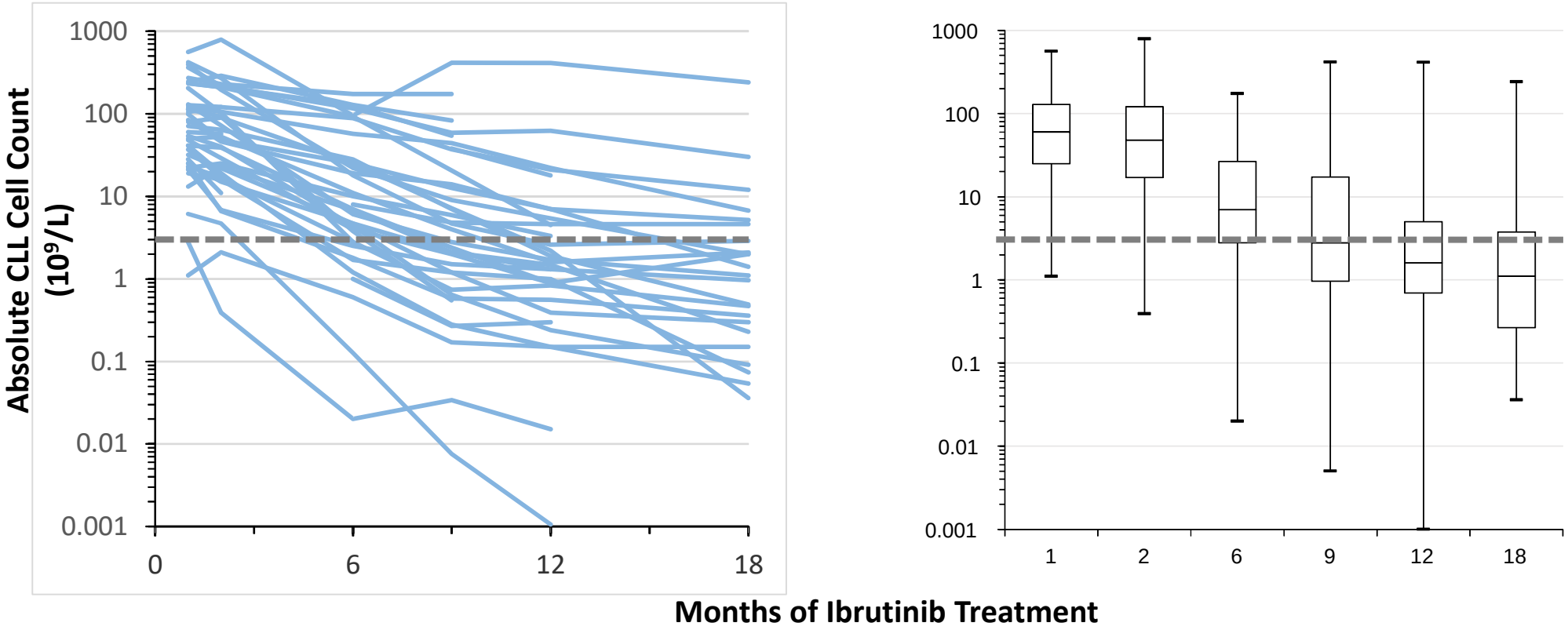
The FDA has added minimal residual disease (MRD) data from the phase III MURANO trial to the label for venetoclax (Venclexta) for its approved use in combination with rituximab (Rituxan) for previously-treated patients with chronic lymphocytic leukemia (CLL).

AbbVie, which is co-developing venetoclax with Roche, noted in a press release that, “MRD-negativity occurs when less than 1 CLL cell per 10,000 lymphocytes can be detected in the blood or bone marrow.” In MURANO, the MRD-negativity

Reasons to eradicate MRD in CLL?

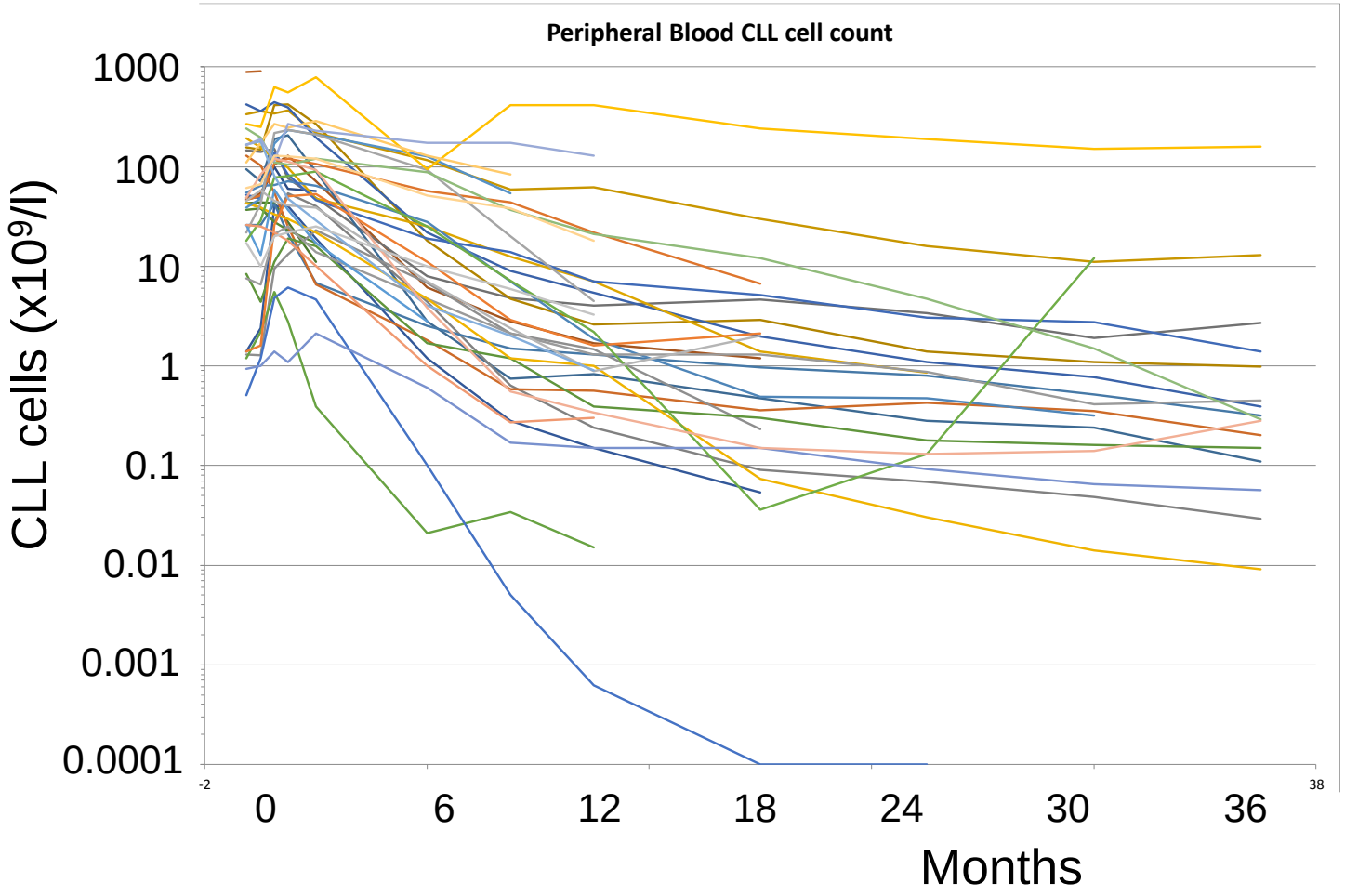
1. End-point in clinical trials
2. To predict individual patient outcome after completion of therapy
3. To define duration of therapy
4. To consider re-initiation of therapy
5. To move towards cure

Measuring the kinetics of response to ibrutinib: MRD analysis to determine “CLL halving-time”



IcICLLe: https://www.clinicaltrialsregister.eu/ctr-search/trial/2012-003608-11/GB

Measuring the kinetics of response to ibrutinib: MRD analysis to determine “CLL halving-time”



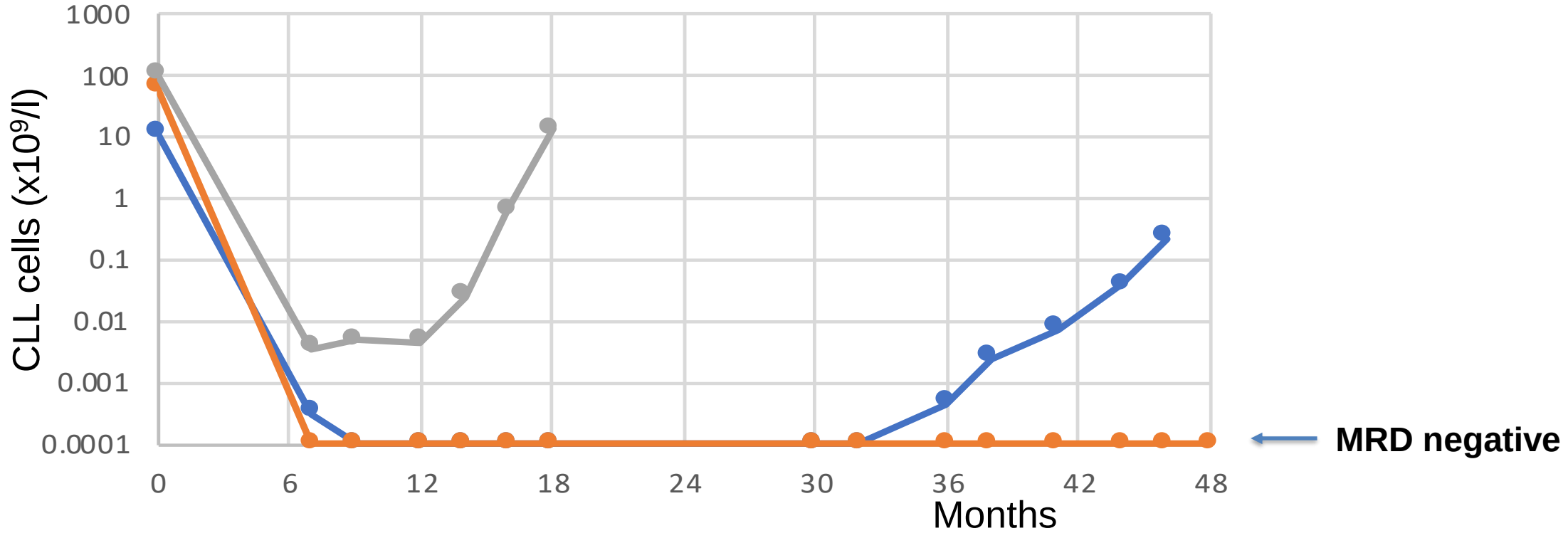
The Leeds Teaching Hospitals NHS
NHS Trust

TAP
From Leukaemia & Lymphoma Research

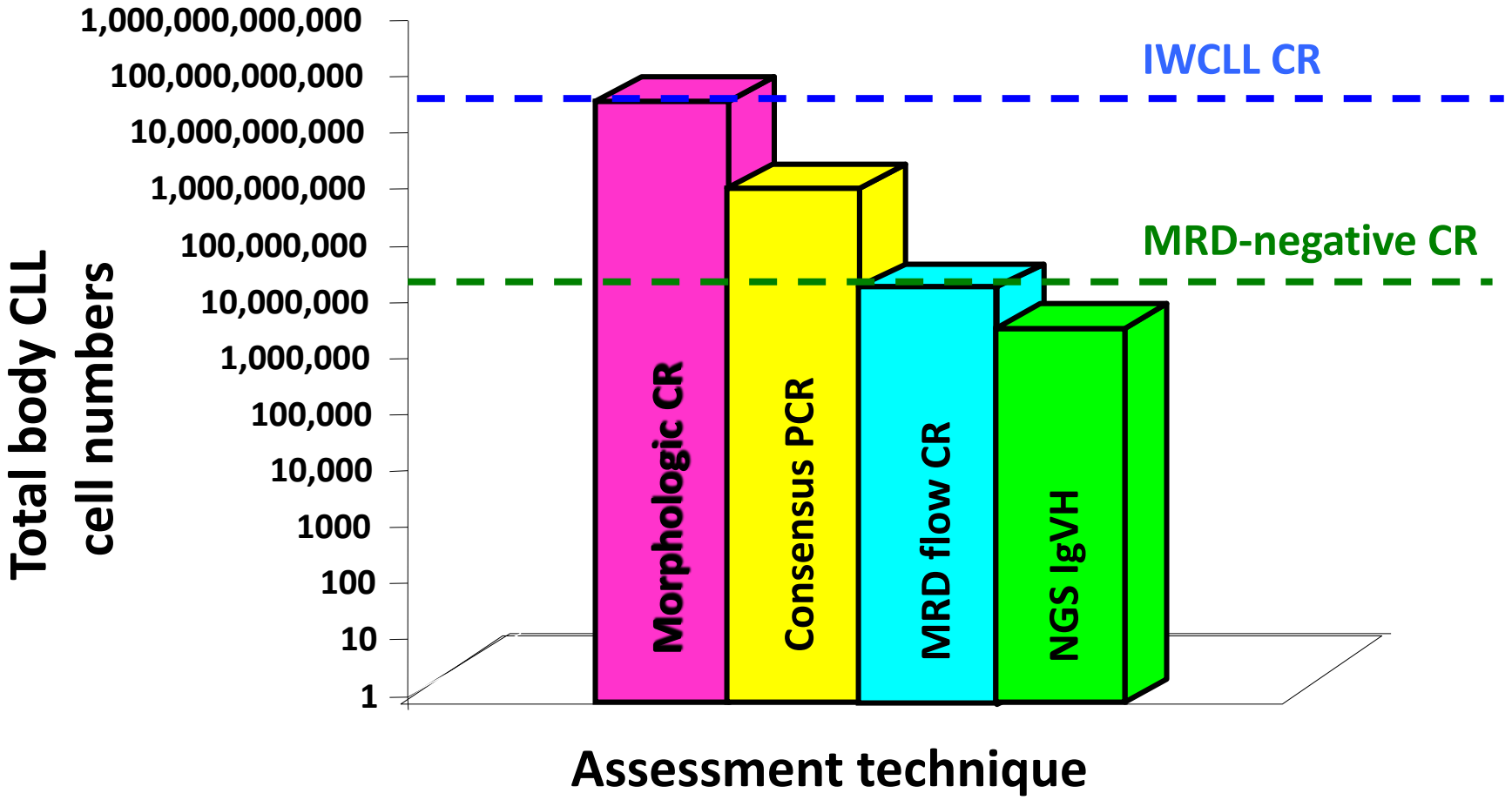
UNIVERSITY OF LEEDS

The role of MRD in patients receiving venetoclax monotherapy?

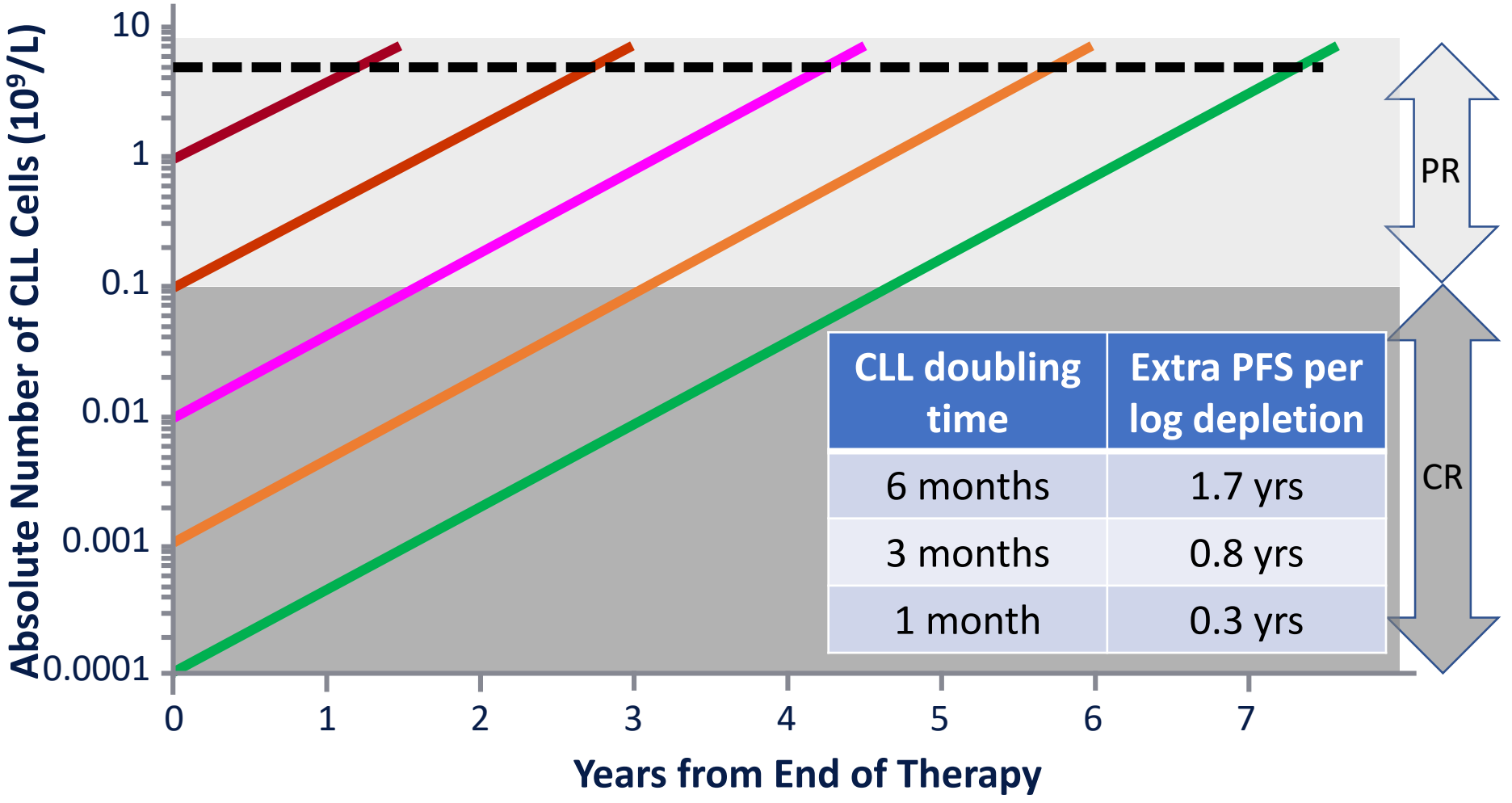
3 patients with relapsed 17p deleted CLL treated with venetoclax monotherapy



Does eradication of MRD equal eradication of disease?



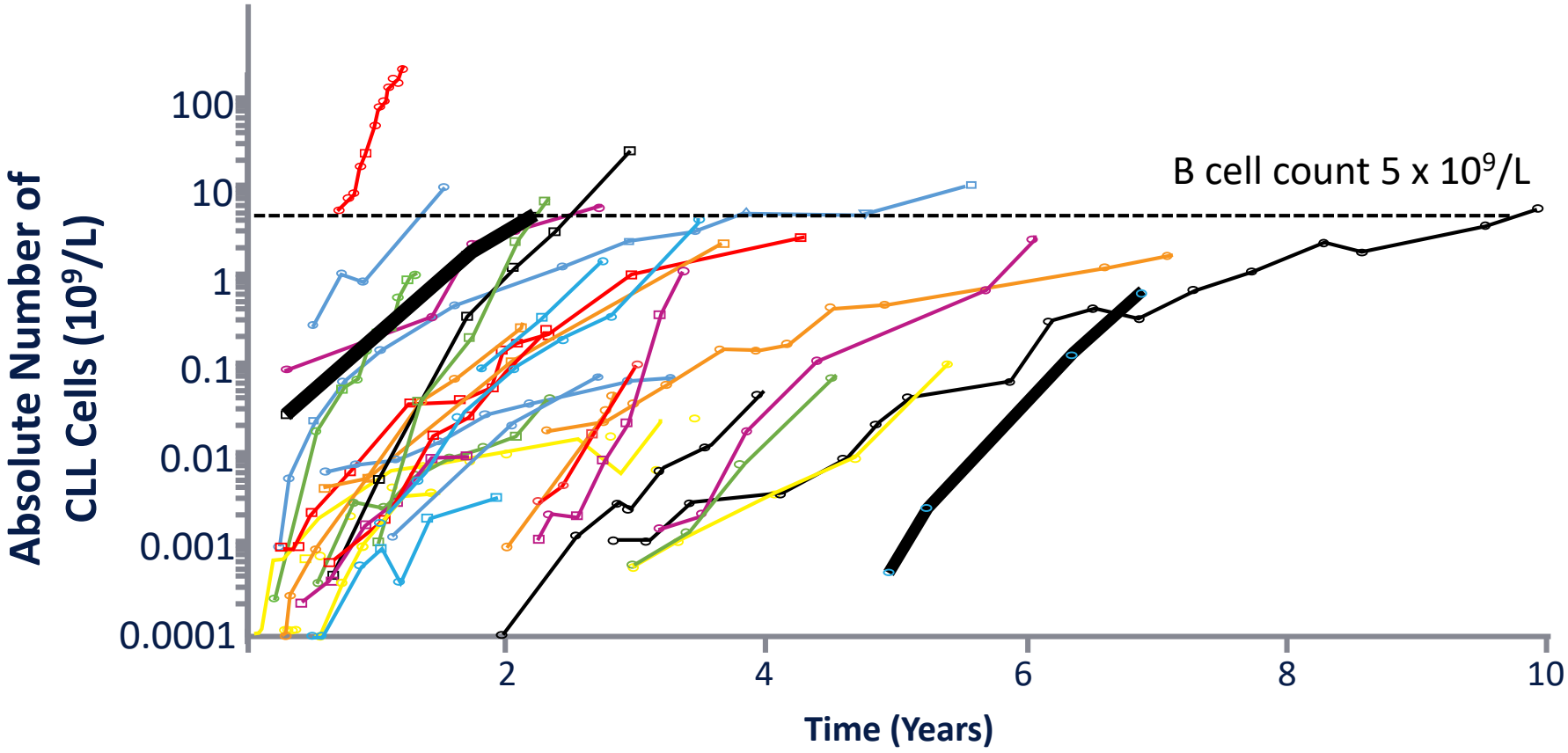
Assuming Exponential Growth at the MRD Level → Linear Increase in PFS per Log Tumour Depletion



CLL doubling time	Extra PFS per log depletion
6 months	1.7 yrs
3 months	0.8 yrs
1 month	0.3 yrs

CR, complete remission; PR, partial remission.

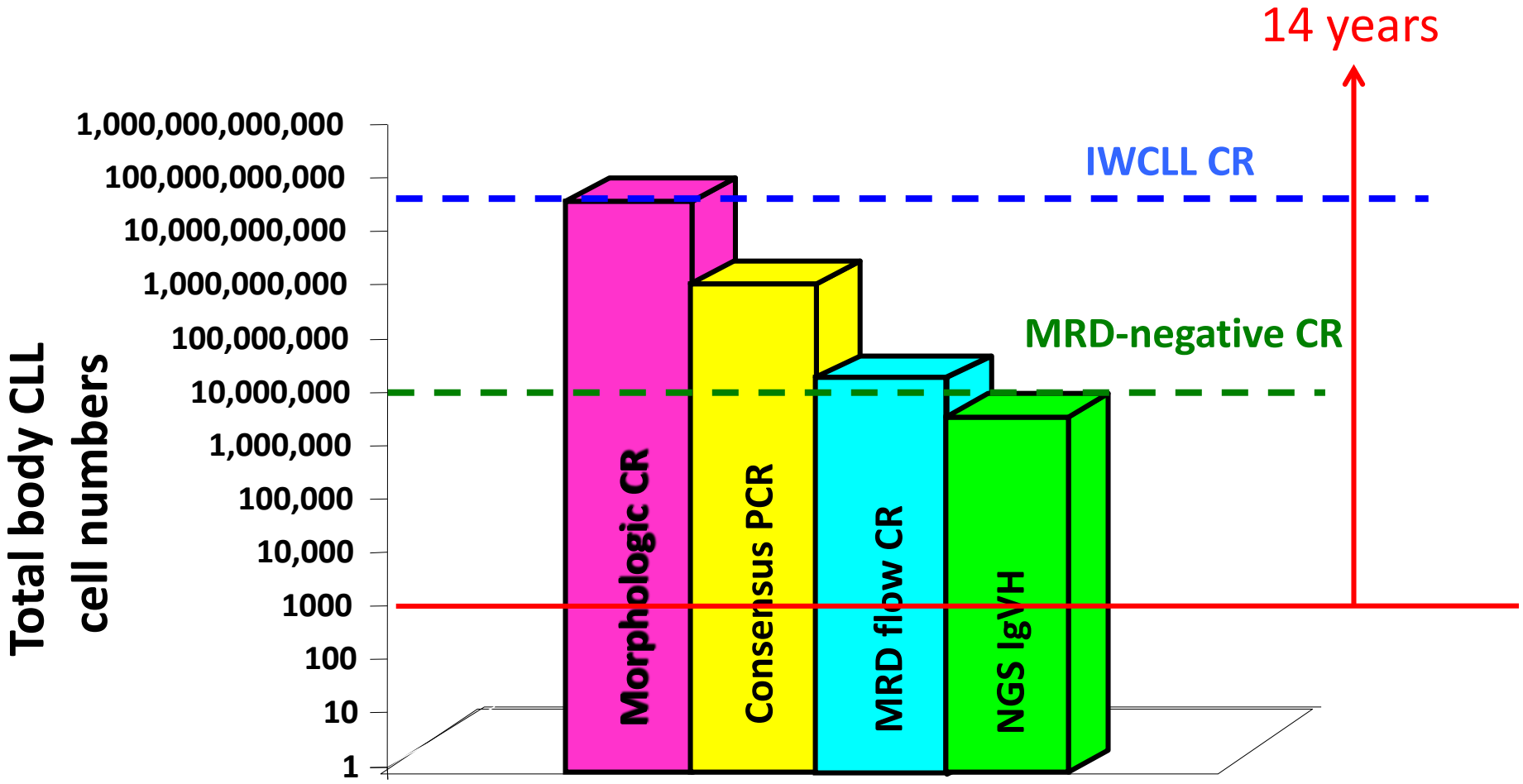
Kinetics of Relapse: Exponential Growth from the Lowest Detectable MRD Level



Serial MRD measurements in a cohort of 32 MRD+ patients in clinical remission with no absolute lymphocytosis after treatment [predominantly FCR] at Leeds

Total 68 patients monitored, 31 persistent MRD <0.01%, 5 insufficient MRD+ timepoints.

Patient with a CLL doubling time of 6 months - clinical relapse at 14 years



3 CLL doubling times = 8-fold increase in MRD

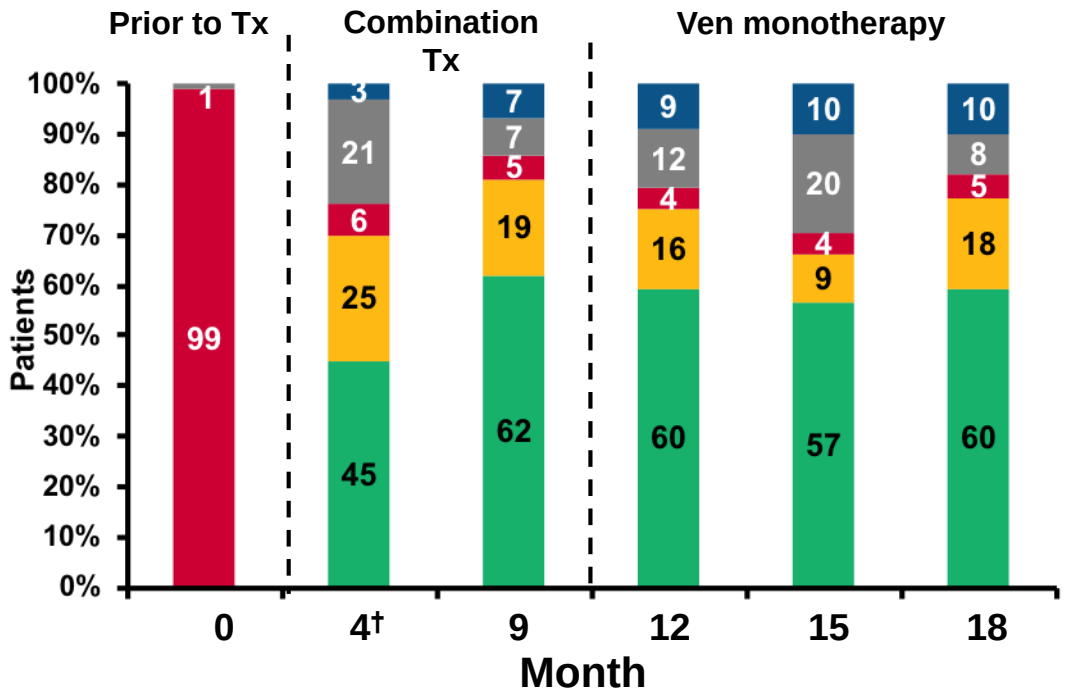
Reasons to eradicate MRD in CLL?

1. End-point in clinical trials
2. To predict individual patient outcome after completion of therapy
3. To define duration of therapy
4. To consider re-initiation of therapy
5. To move towards cure

MURANO: MRD Negative responses and prolonged PFS

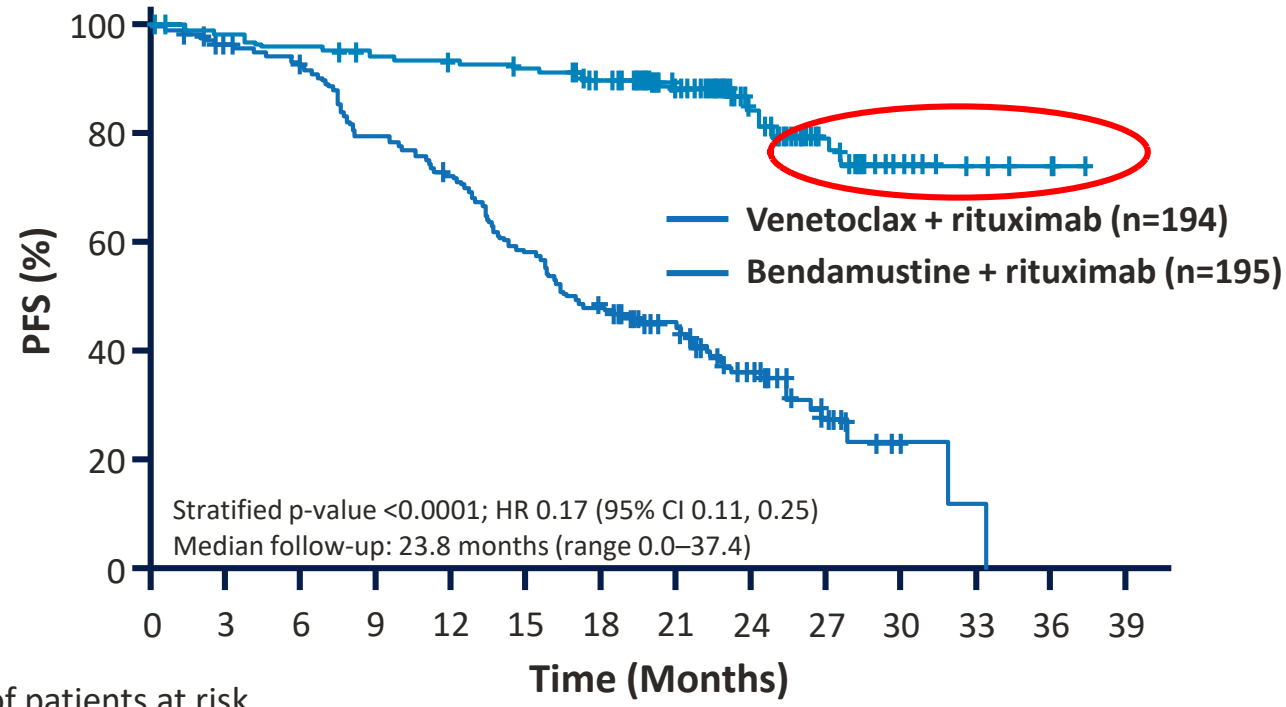
Venetoclax given for a fixed period of 24months and then stopped

MRD Response: Venetoclax + Rituximab



Negative: $<10^{-4}$ [MRD4] | Intermediate-positive: 10^{-4} to $<10^{-2}$ | High-positive: $\geq 10^{-2}$ | Missing* | PD/death/withdrew

Investigator-Assessed PFS



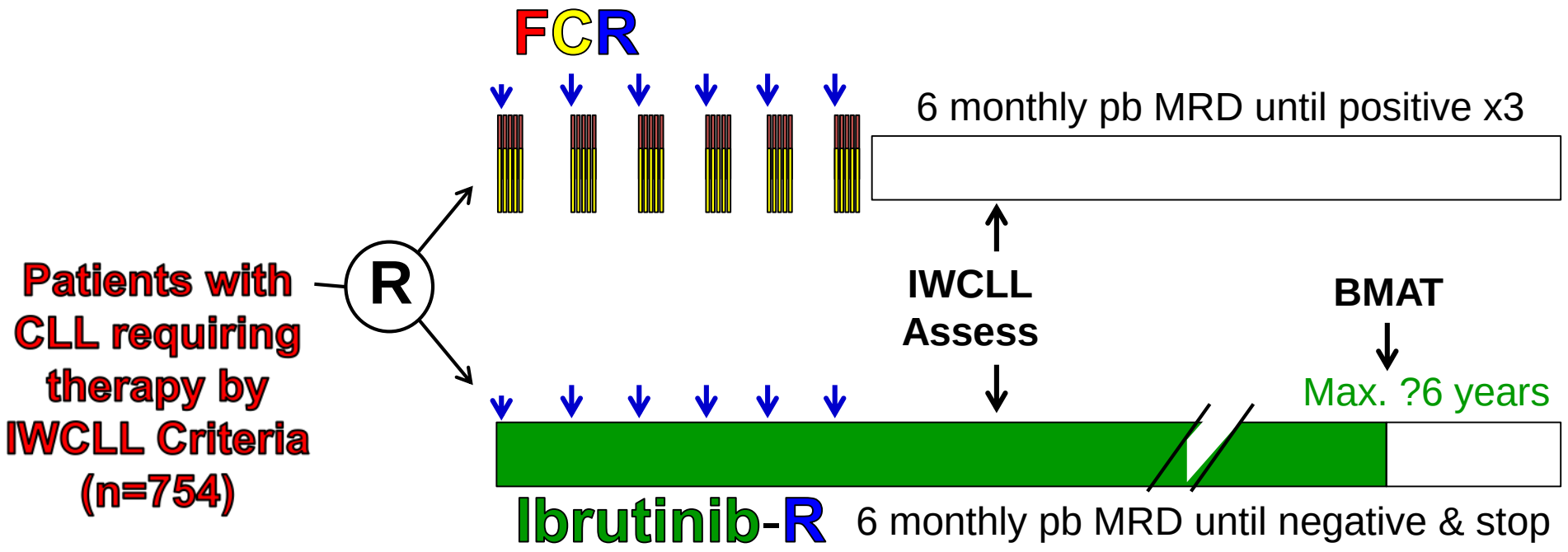
No. of patients at risk

Venetoclax + rituximab	194	190	185	179	176	173	157	115	76	33	14	5	3	0
Bendamustine + rituximab	195	177	163	141	127	102	81	57	35	12	3	1	0	0

Seymour *et al. N Engl J Med.* 2018 Mar 22;378(12):1107-1120 .

Front-line trial for patients fit for FCR:
NCRI *Flair* (CLL10) Trial

Front Line therapy in CLL: Assessment of Ibrutinib plus Rituximab



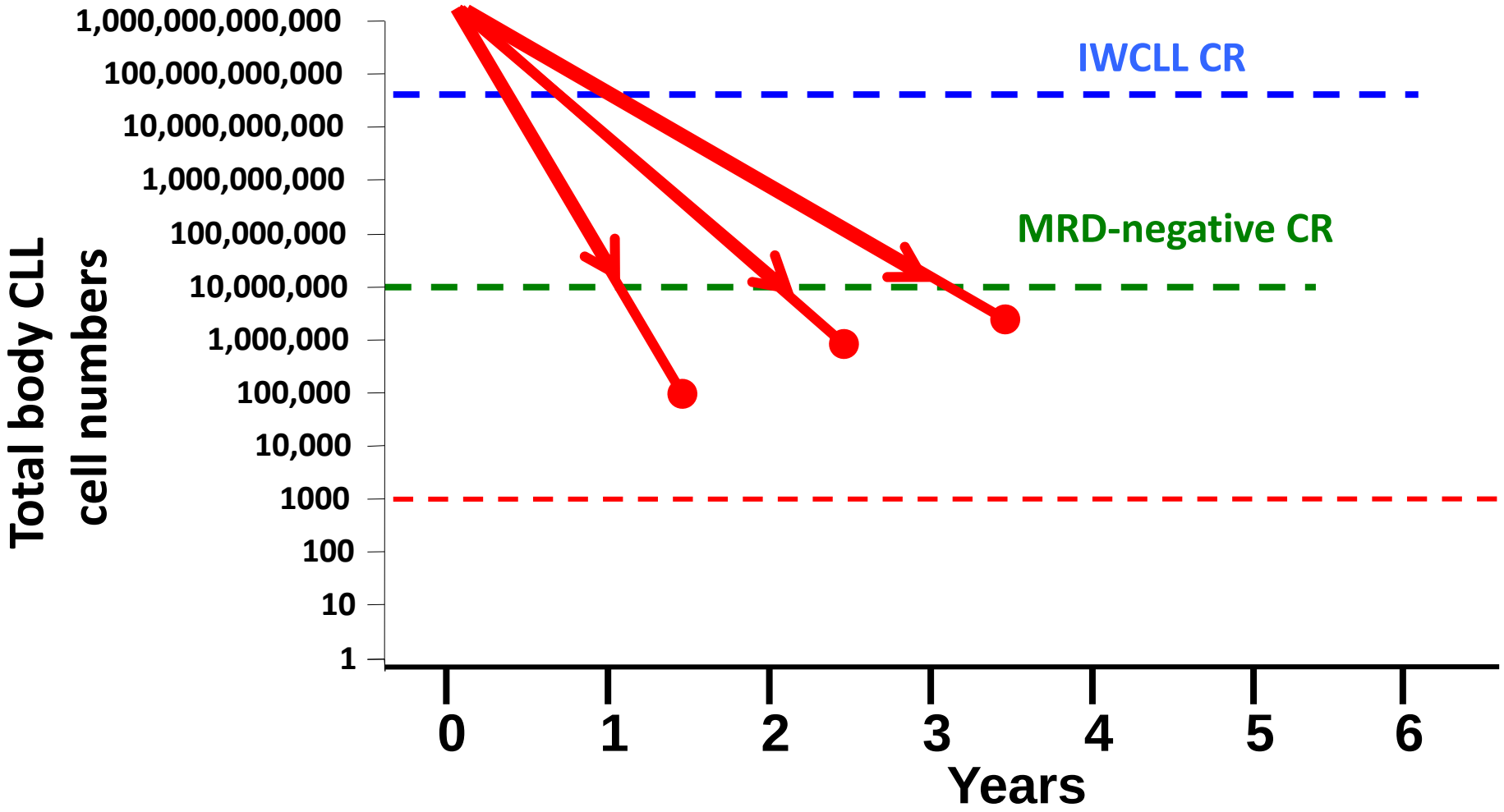
Completed recruitment of 772 patients July 2018

NCRI National Cancer Research Institute
Partners in cancer research

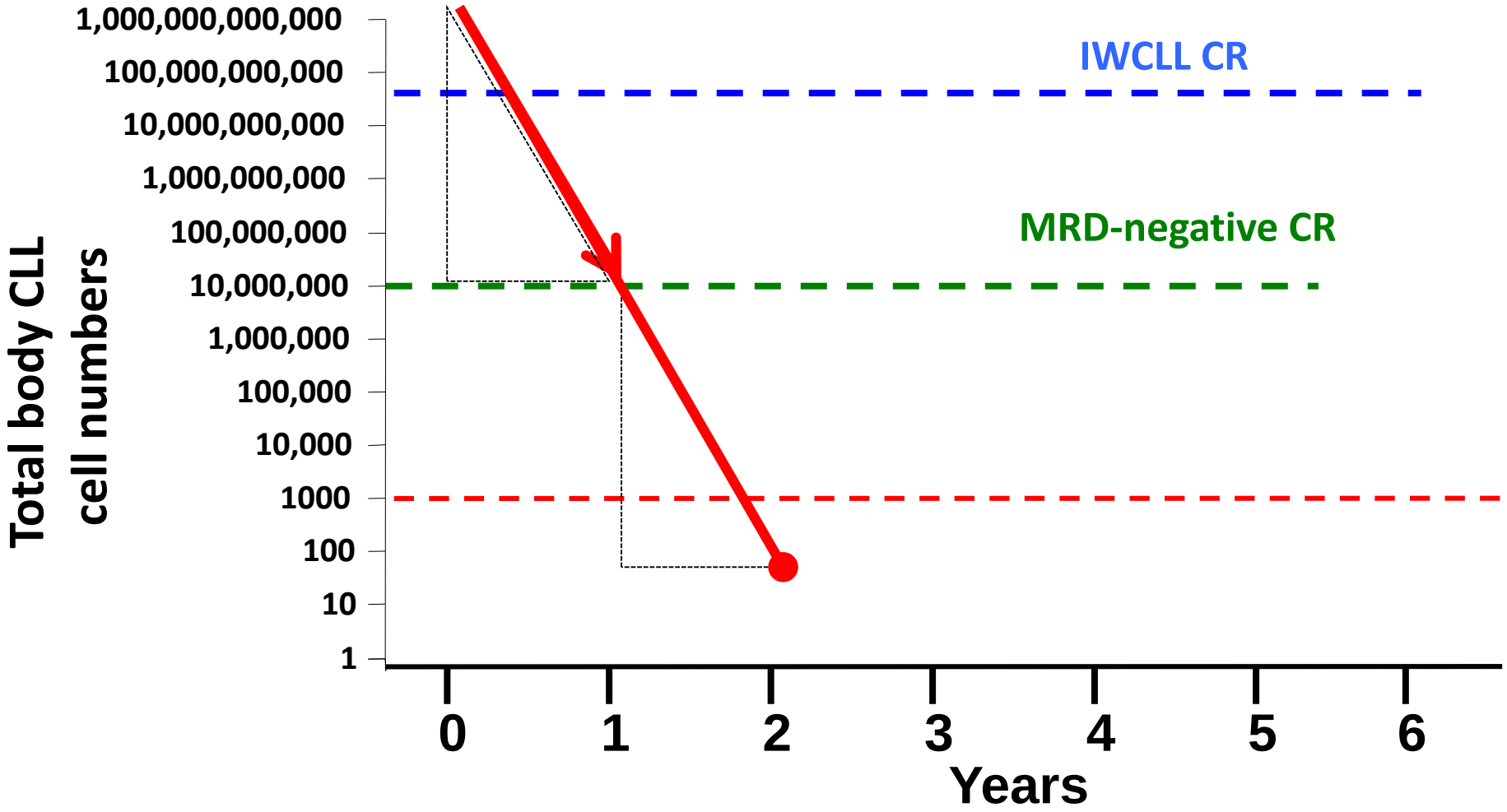
CANCER RESEARCH UK

ctru University of Leeds

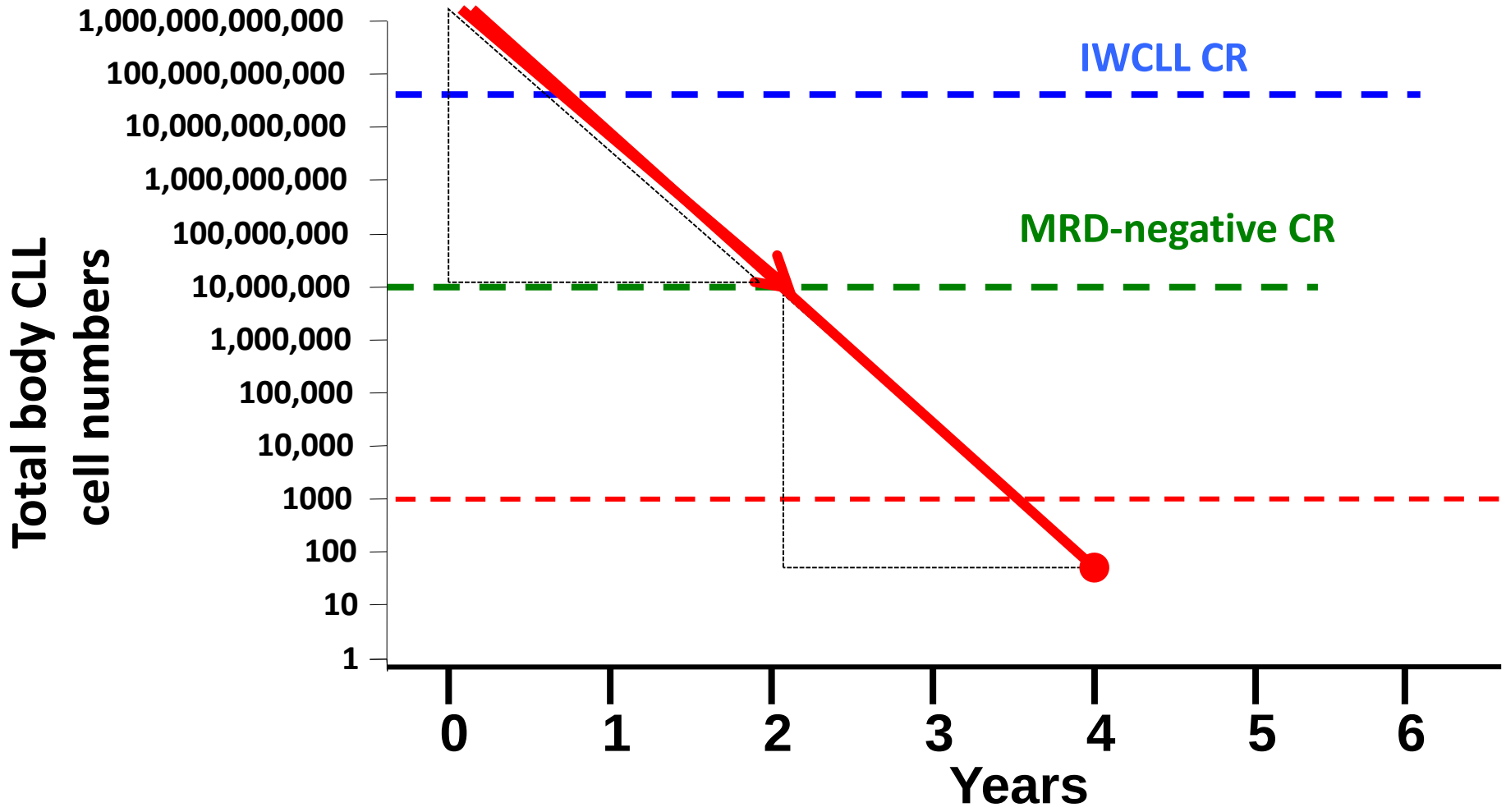
Modified treatment stopping rule in FLAIR - duration of therapy defined by speed of response



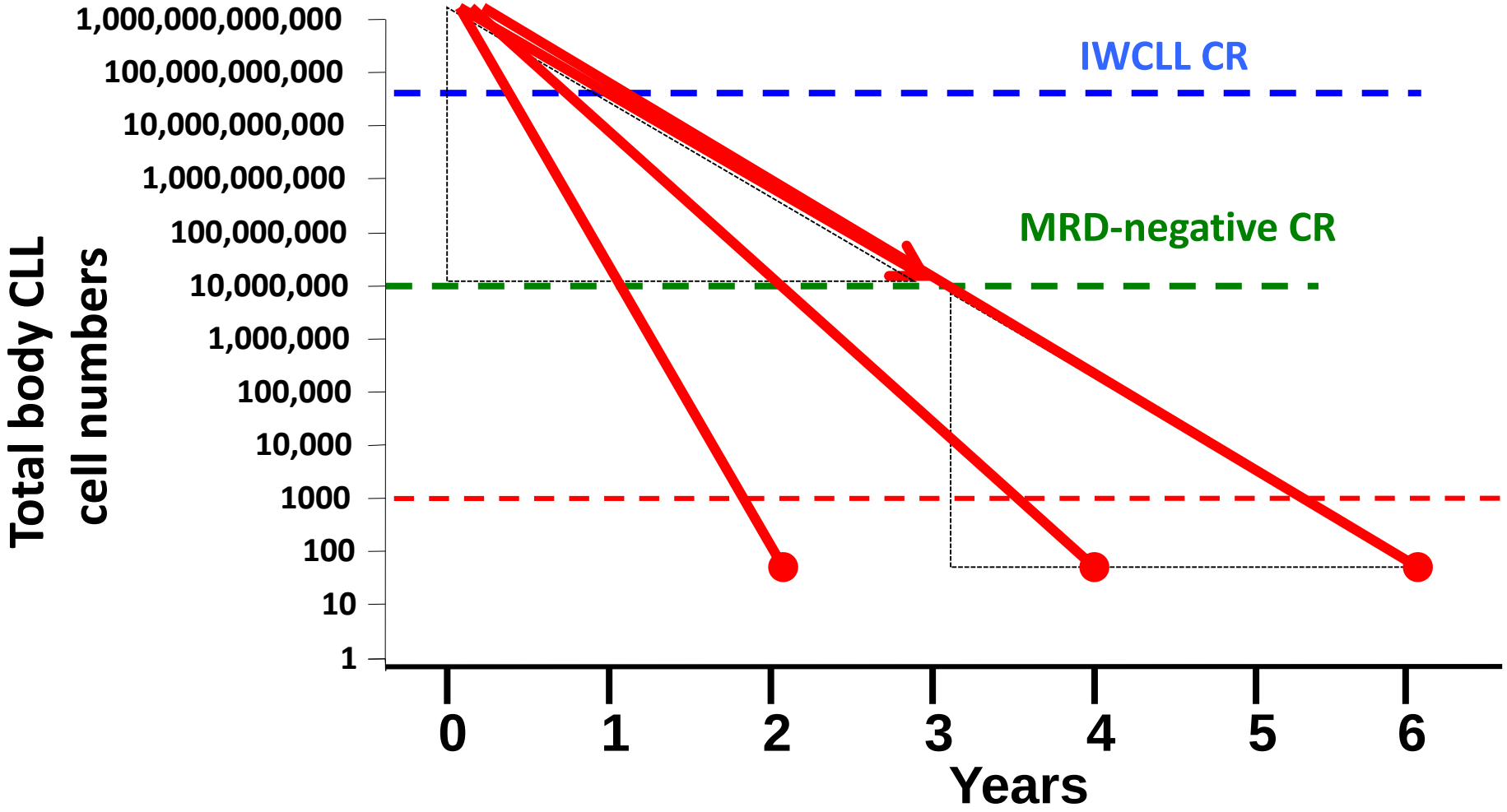
Modified treatment stopping rule in FLAIR - duration of therapy defined by speed of response



Modified treatment stopping rule in FLAIR - duration of therapy defined by speed of response



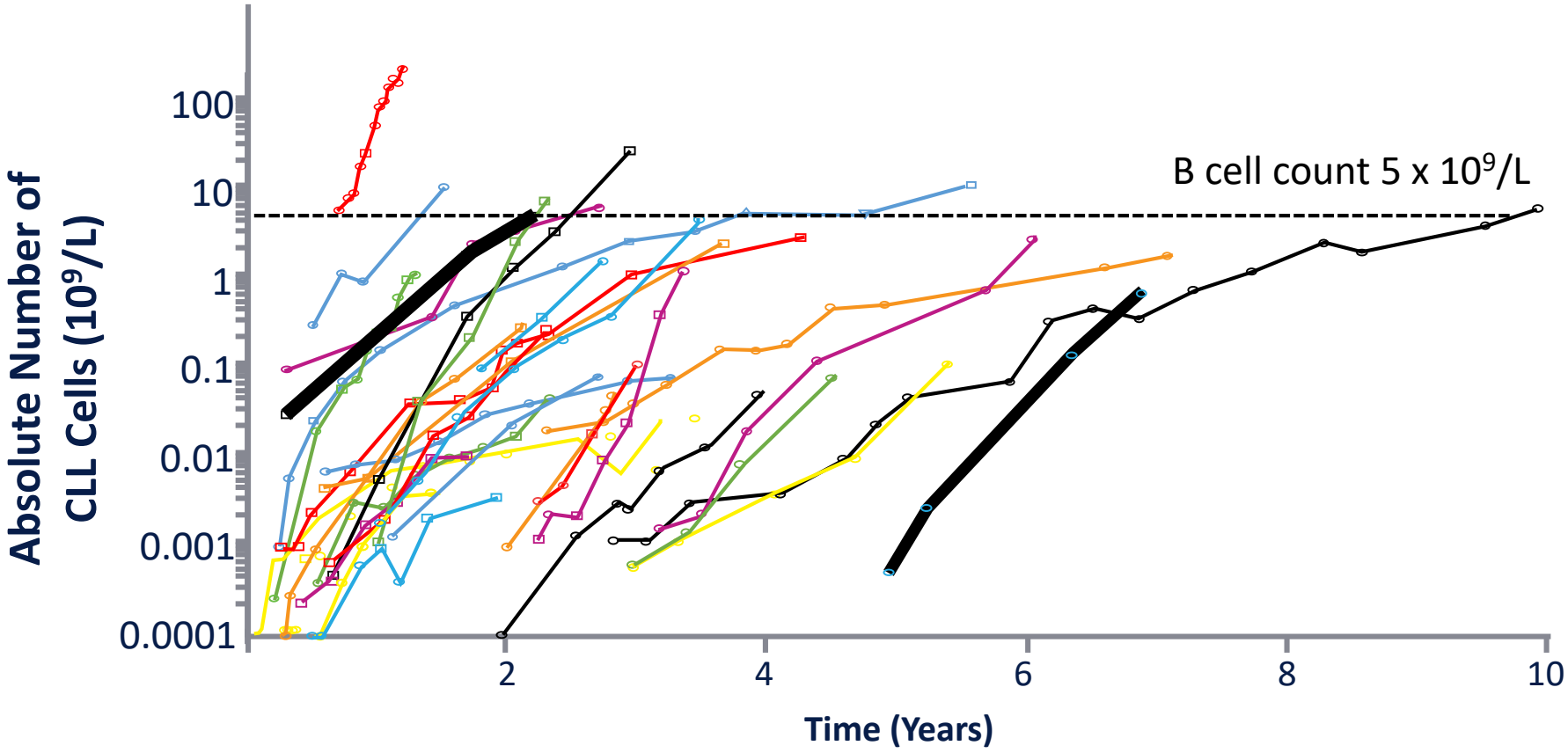
Modified treatment stopping rule in FLAIR - duration of therapy defined by speed of response



Reasons to eradicate MRD in CLL?

1. End-point in clinical trials
2. To predict individual patient outcome after completion of therapy
3. To define duration of therapy
4. To consider re-initiation of therapy
5. To move towards cure

Kinetics of Relapse: Exponential Growth from the Lowest Detectable MRD Level



Serial MRD measurements in a cohort of 32 MRD+ patients in clinical remission with no absolute lymphocytosis after treatment [predominantly FCR] at Leeds

Total 68 patients monitored, 31 persistent MRD <0.01%, 5 insufficient MRD+ timepoints.

A Proposed Randomised Phase III Trial Comparing Continuous with Intermittent Treatment in CLL ("Intermittent Treatment Trial")

RANDOMISATION (1:1). N = 800

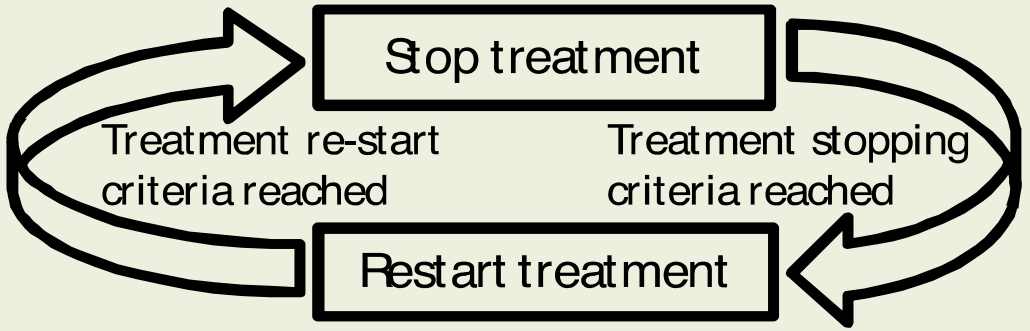
Stratification factors: no of prior therapies, time on current therapy, MRD, VH status, BTK inhibitor

Continuous treatment until disease progression

N = 400

Intermittent treatment strategy until treatment strategy failure

N = 400



Assessments until disease progression/ treatment strategy failure

3 monthly assessments: assessment for restarting/stopping treatment, standard investigations, QoL & health economics questionnaires, (data collected 6 monthly unless start/stop treatment)

Reasons to eradicate MRD in CLL?

1. End-point in clinical trials
2. To predict individual patient outcome after completion of therapy
3. To define duration of therapy
4. To consider re-initiation of therapy
5. To move towards cure

Understanding MRD – the maths!

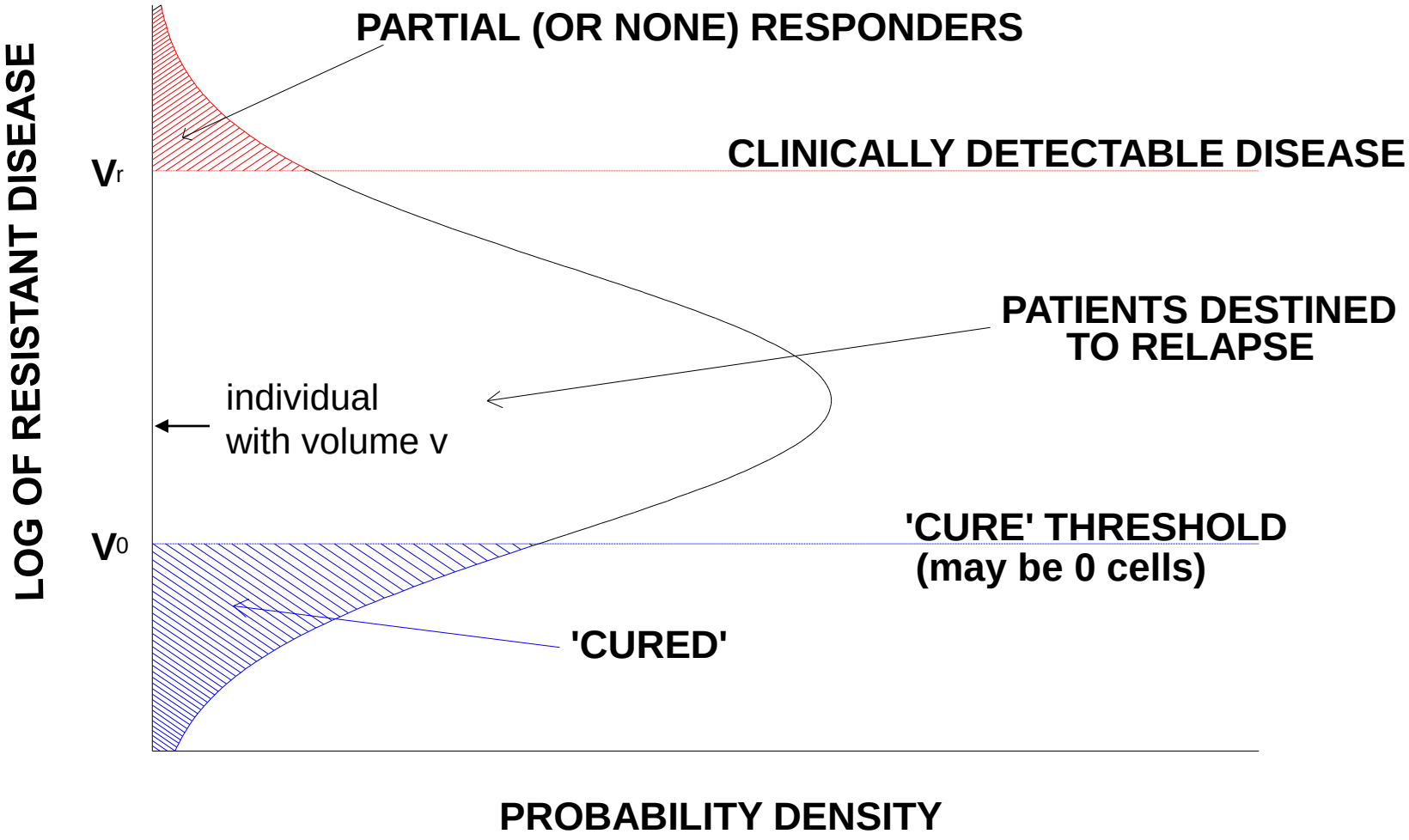
Walter Gregory *et al.* Characterizing and quantifying the effects of breast cancer therapy using mathematical modelling.

Breast Cancer Res Treat (2016) 155:303–311

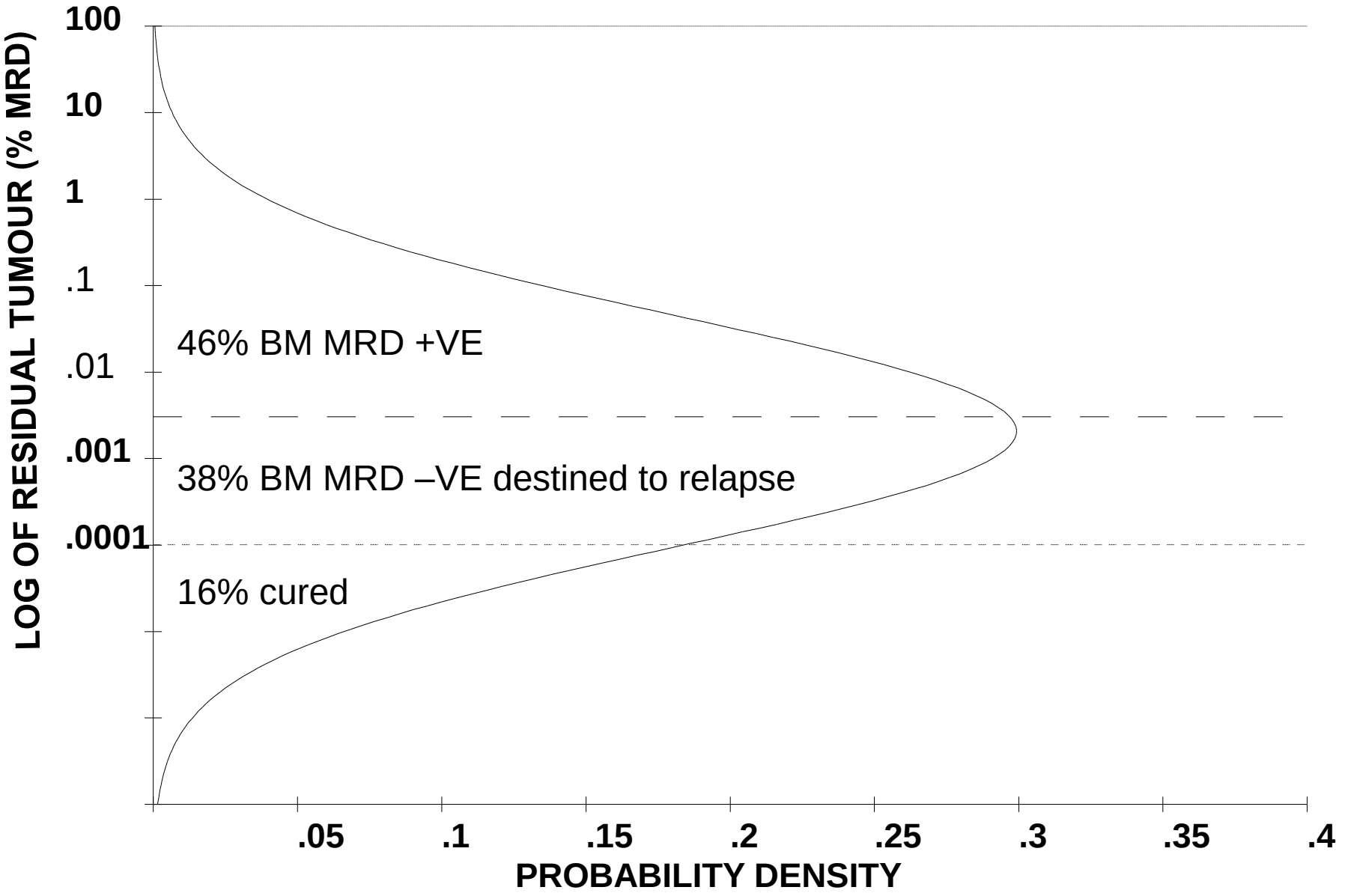
Walter M. Gregory → w.m.gregory@leeds.ac.uk

- "Designed a mathematical model to describe and quantify the mechanisms and dynamics of tumor growth, cell-kill and resistance as they affect durations of benefit after cancer treatment."
- Applied in the paper to breast cancer and AML
- Also fits with Hodgkin's disease and ALL
- Walter has applied the model to FCR-like therapy in CLL

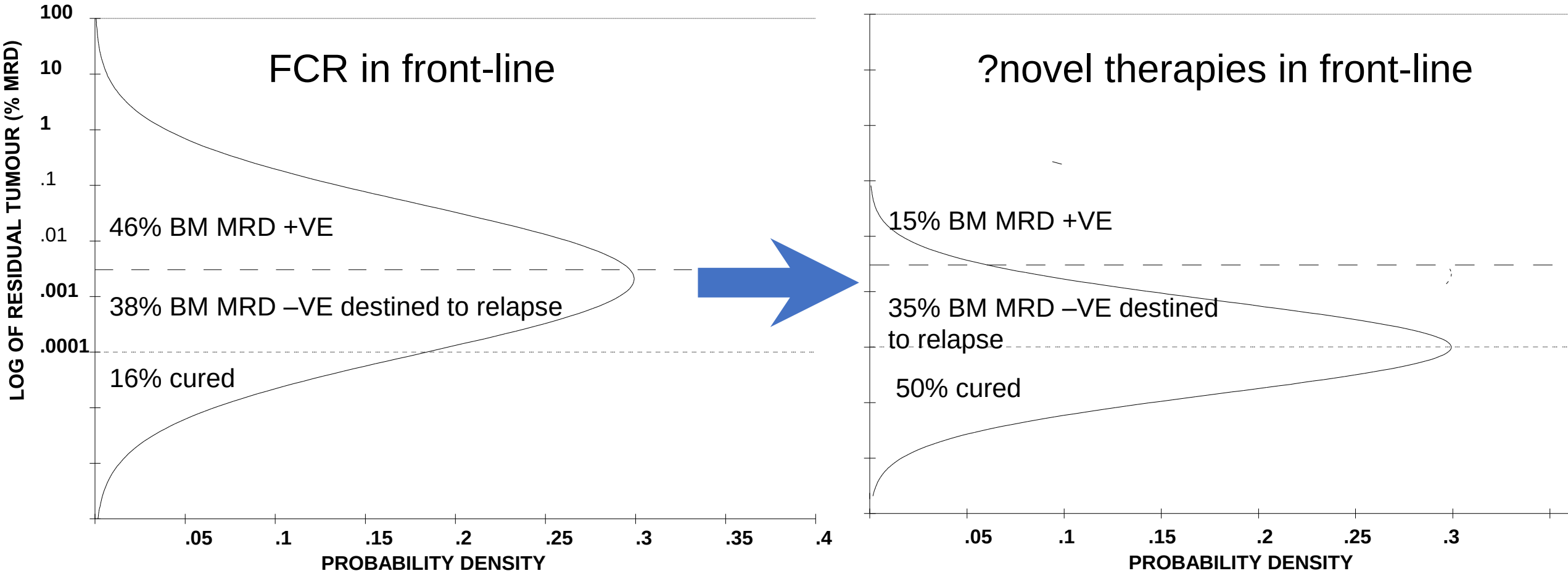
Assumed distribution of resistant disease at the start of treatment for the whole patient population



Normal distribution of MRD identifies a subset of "cured" patients (ADMIRE/ARCTIC → FCR or FCM-R)



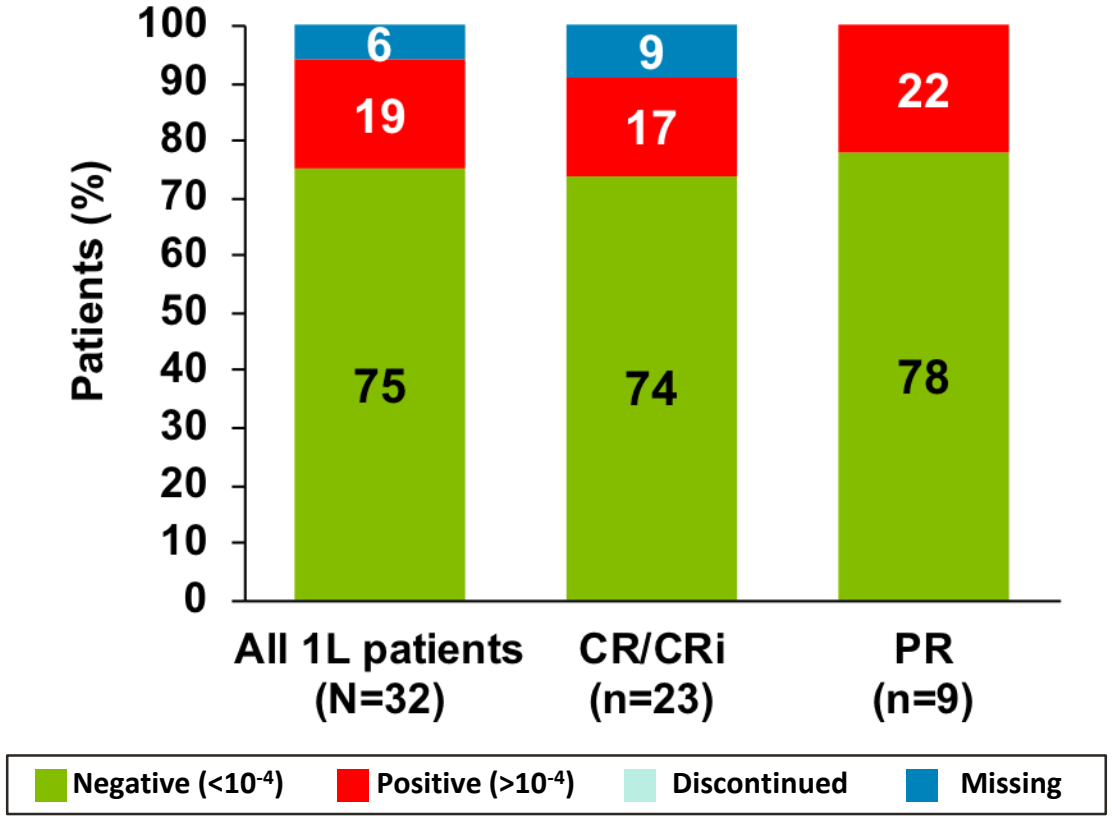
Is it realistic to expect a cure?



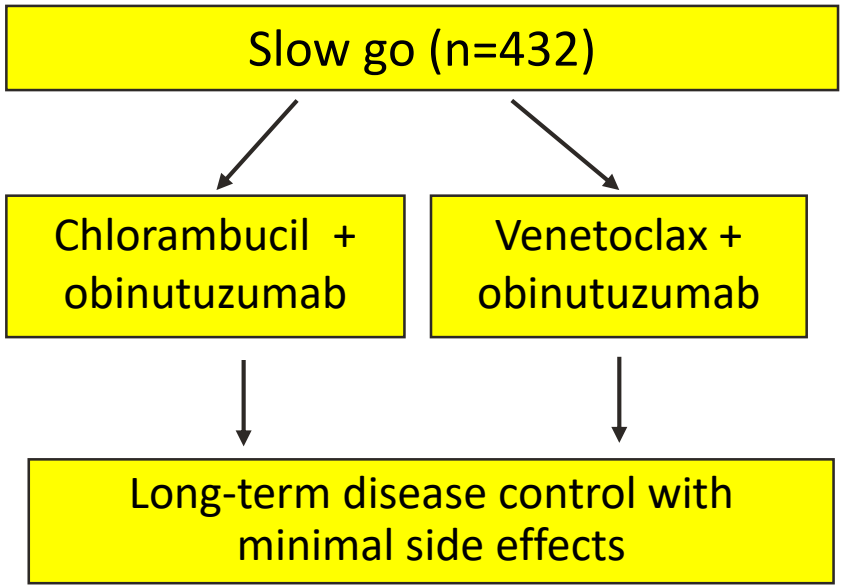
Venetoclax + obinutuzumab in frontline CLL:

Phase 1b GP28331 study (front-line cohort)

Bone marrow MRD negativity
at some point on study



GCLLSG CLL14 trial (front-line)



Study Start Date: December 2014

Inclusion Criteria: Untreated CLL requiring therapy according to the IWCLL criteria

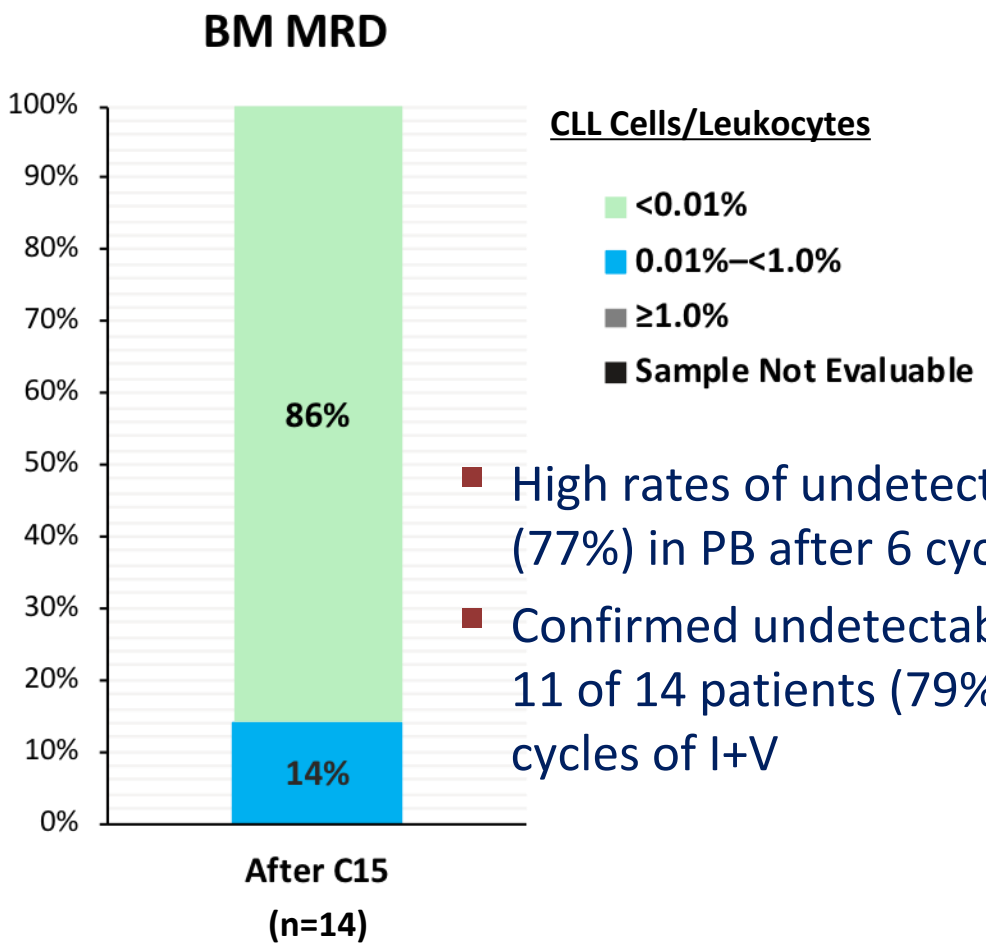
Total CIRS score > 6

Flinn I, *et al. Blood* 2017; Abstract.

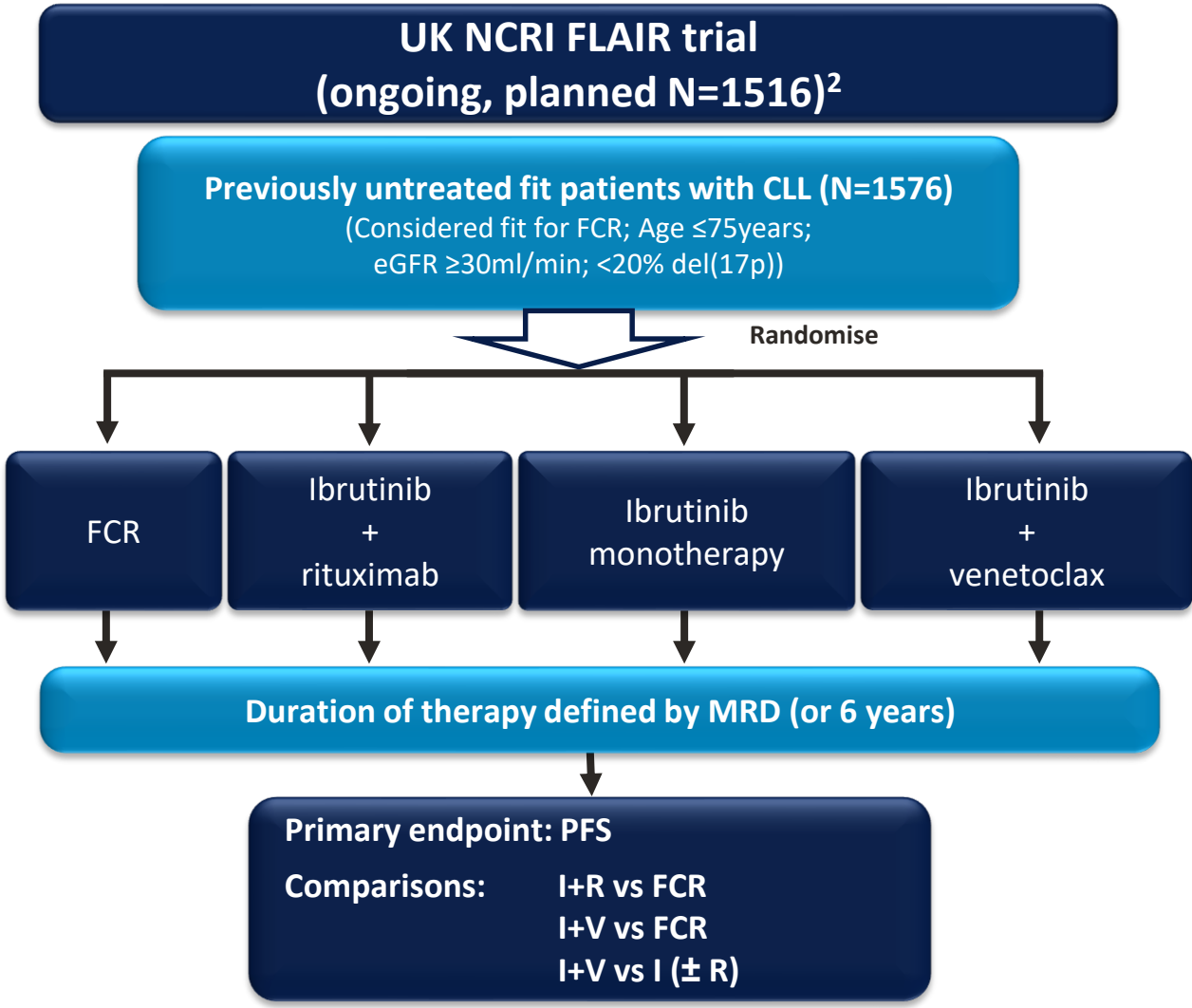
Modified the NCRI Flair Trial –opened Sept 2014

CAPTIVATE Phase II Trial[1]

Ibrutinib + venetoclax (n=164) – 15 months therapy



- High rates of undetectable MRD (77%) in PB after 6 cycles of I+V
- Confirmed undetectable MRD* in 11 of 14 patients (79%) after 12 cycles of I+V

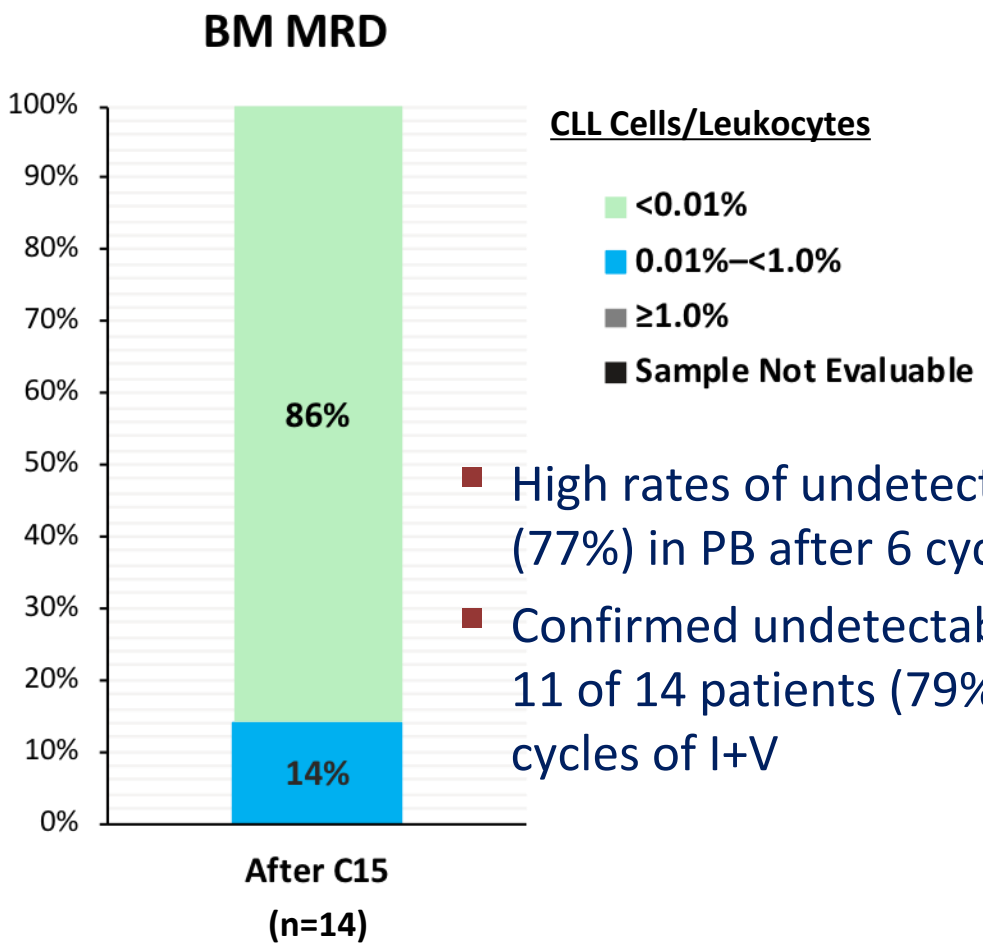


1. Wierda W , *et al. ASCO* 2018;
2. EudraCT. Available at: https://www.clinicaltrialsregister.eu/ctr-search/trial/2013-001944-76/GB

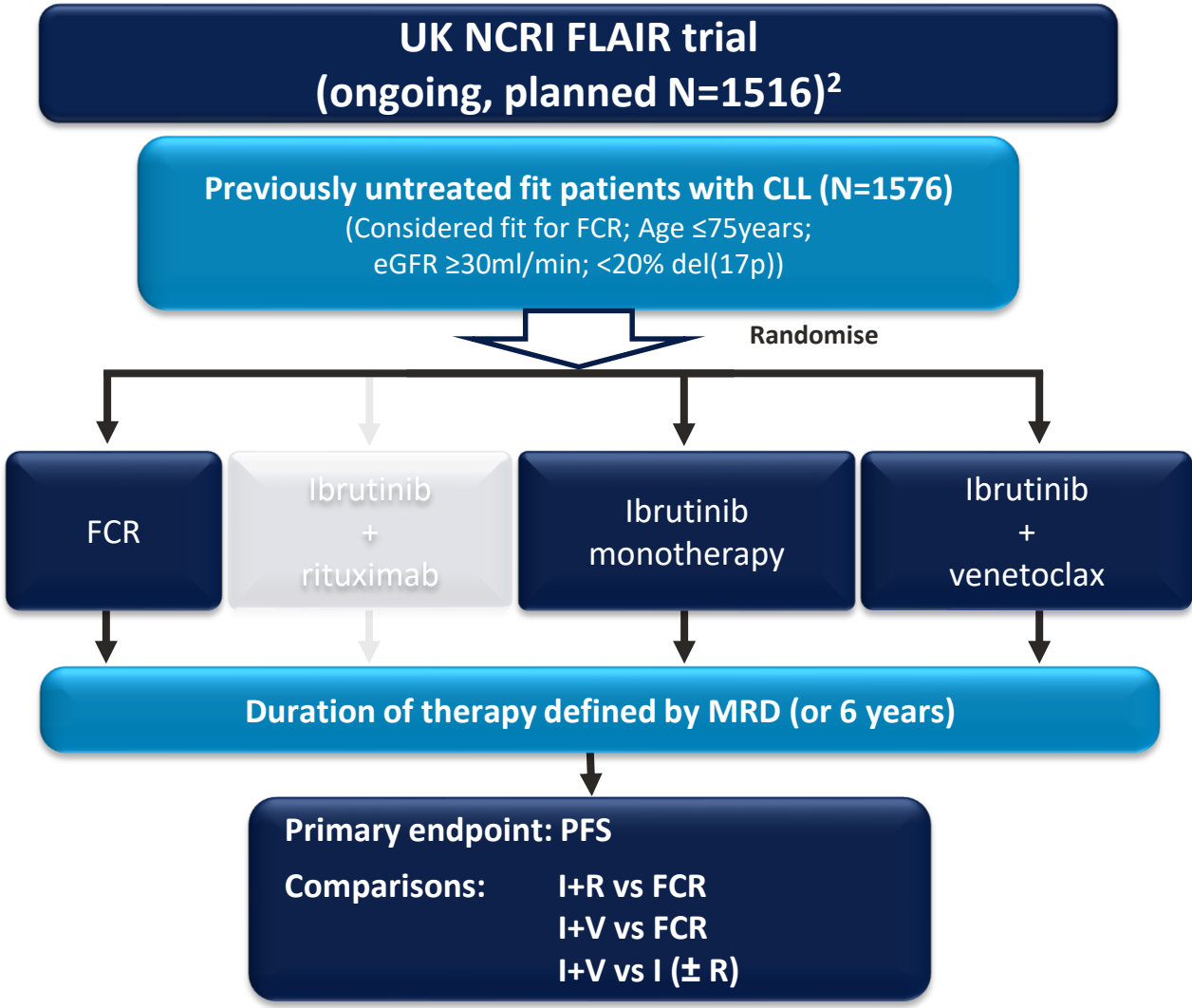
Modified the NCRI Flair Trial –modified July 2017

CAPTIVATE Phase II Trial[1]

Ibrutinib + venetoclax (n=164) – 15 months therapy



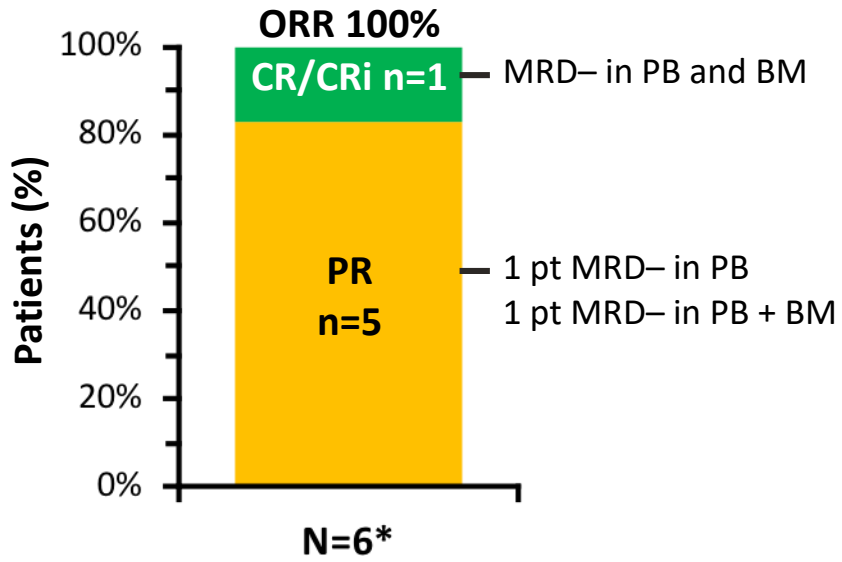
- High rates of undetectable MRD (77%) in PB after 6 cycles of I+V
- Confirmed undetectable MRD* in 11 of 14 patients (79%) after 12 cycles of I+V



1. Wierda W , *et al. ASCO* 2018;
2. EudraCT. Available at: https://www.clinicaltrialsregister.eu/ctr-search/trial/2013-001944-76/GB

Ongoing trials with obinutuzumab + ibrutinib + venetoclax (GIVe)

Phase 1b/2 study of GIVe in R/R CLL (N=12 to date)[1]



- Most common grade ≥3 AEs: neutropenia (50%), lymphopenia (33%), hypertension (25%), and fatigue (17%)
- No cases of clinical or lab TLS were observed

PB, peripheral blood.
* 6 patients have reached response assessment after completing 8 cycles of therapy;
† <65 years of age; ‡ >65 years of age.

GCLLSG CLL13 trial (ongoing, planned N=920)

Previously untreated fit patients with CLL (CIRS ≤6; normal creatinine clearance; no del(17p)/*TP53* mutation)

Randomise

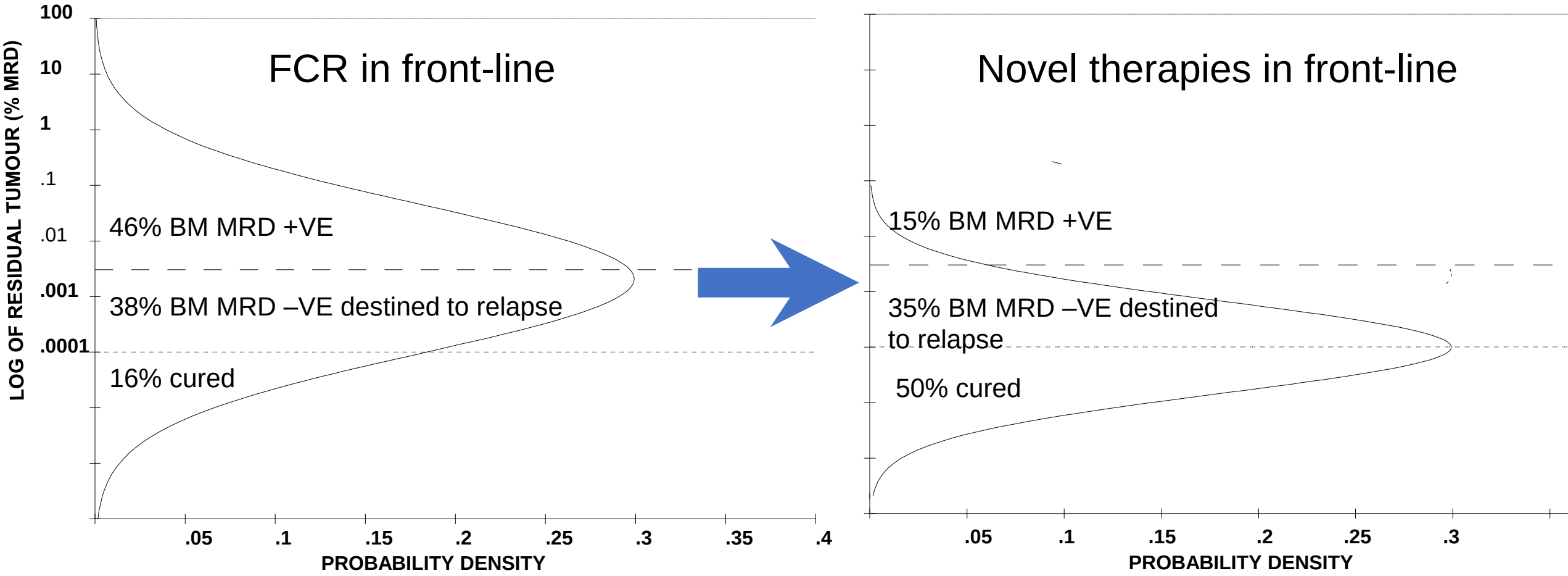
- FCR† or BR‡
- Venetoclax + rituximab
- Venetoclax + obinutuzumab
- Venetoclax, obinutuzumab ibrutinib

Follow-up for progression and survival

2 primary endpoints
- Rate of MRD negativity in PB
- PFS

1. Jones J, *et al. Blood* 2016; **128:**Abstract 639;
2. ClinicalTrials.gov. Available at: https://clinicaltrials.gov/ct2/show/NCT02950051 (accessed April 2017).

Is it realistic to expect a cure?



Conclusion: MRD in CLL

1. Deeper remissions in CLL result in more durable remissions and (theoretically) less resistance
2. MRD eradication is critical if we are going to stop therapy and move to cure
3. MRD can be used to understand the dynamics of response and early relapse for individual patients and patient populations
4. Low levels of MRD may allow prolonged drug holidays
5. Combinations may allow early cessation of therapy
6. Should we consider re-starting before clinical relapse

Thoughts to leave you with!

"There are only two types of trials

…….good trials and bad trials!"

"If we design and run trials in our *ivory towers* then there is a danger that the treatments will (or can) only be given in those *ivory towers*"

Acknowledgements

NCRI National Cancer Research Institute

NHS National Institute for Health Research

NCRI CLL Trials Sub-group

Peter Hillmen (Chair)
David Allsup
Garry Bisshopp
Adrian Bloor
Daniel Catovsky
Claire Dearden
Caroline Duncan
Martin Dyer
Chris Fegan
George Follows
Francesco Forconi
Chris Fox
John Gribben
S Hewamana
Anna Hockaday
Dena Howard
Claire Hutchinson
Ben Kennedy
Scott Marshall
Alison McCaig
Helen McCarthy
Mel Oates
Piers Patten
Andy Pettitt
Chris Pocock
Guy Pratt
Anna Schuh
Jon Strefford
Renata Walewska
Nick York

UKCLL Trials Biobank,
Melanie Oates
Melanie Goss
Emily Cass
Andy Pettitt

Bloodwise
Beating blood cancer since 1960

Pharmacyclics
Abbvie
Janssen
Roche

Bloodwise TAP Programme

Yolande Jeffferson
Rebecca Bishop
Kristian Brock
Christina Yap
Francesca Yates
Tina McLeod
Samuel Muñoz-Vicente
Shamyla Siddique

HMDS, Leeds

Andy Rawstron
Surita Dalal
Talha Munir
Abraham Varghese
Ruth de Tute
Jane Shingles
Andrew Jack

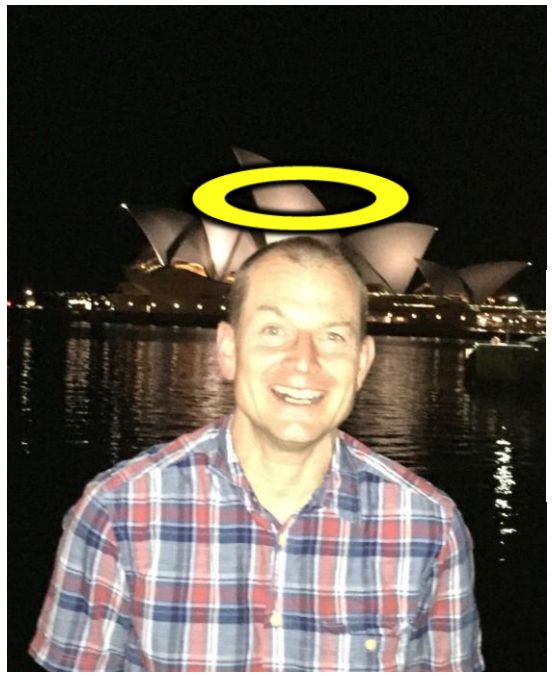
ctru University of Leeds

The Leeds Teaching Hospitals NHS Trust

Leeds CTRU

Anna Hockaday
Jamie Ougton
Seoha Shanu
Claire Dimbleby
David Philips
Kathryn McMahon
Walter Gregory
Dena Howard
Lucy McParland
Laura Collett
David Stones
Sadia Aslam
James Baglin
Julia Brown

CANCER RESEARCH UK



TAP Bloodwise
Beating blood cancer since 1960

UNIVERSITY OF LEEDS

XVIII iwCLL EDINBURGH

INTERNATIONAL WORKSHOP ON CHRONIC LYMPHOCYTIC LEUKEMIA

FOR MORE INFORMATION ABOUT PARTICIPATING IN THE 2019 PROGRAM

VISIT: ***www.iwCLL2019.org***
CALL: ***1-888-476-9129***
FOLLOW: ***@iwCLL***

20 – 23 SEPTEMBER 2019

EDINBURGH, SCOTLAND