
Is it possible to stop treatment with the new targeted therapies?
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14th November 2017

Why should we stop targeted therapy in CLL?

Toxicity of ibrutinib in the Resonate and Resonate-2

Figure 2. Most Common AEs (>15% All Grade or >2% Grade 3/4)

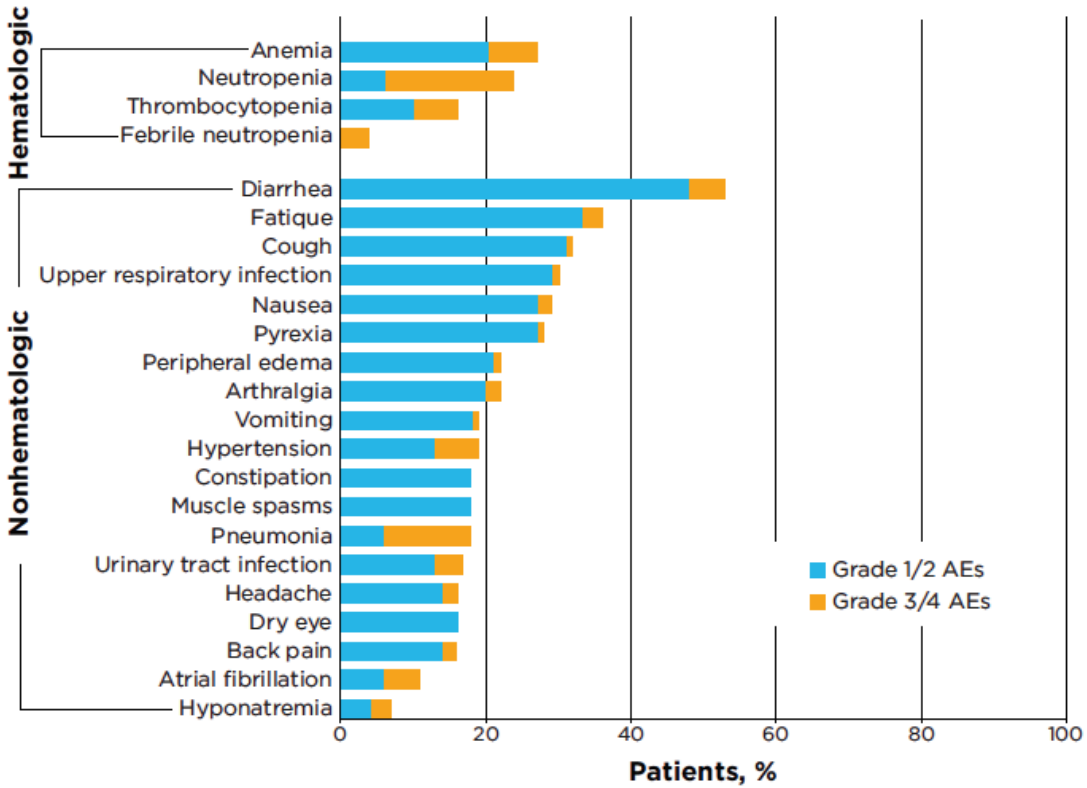
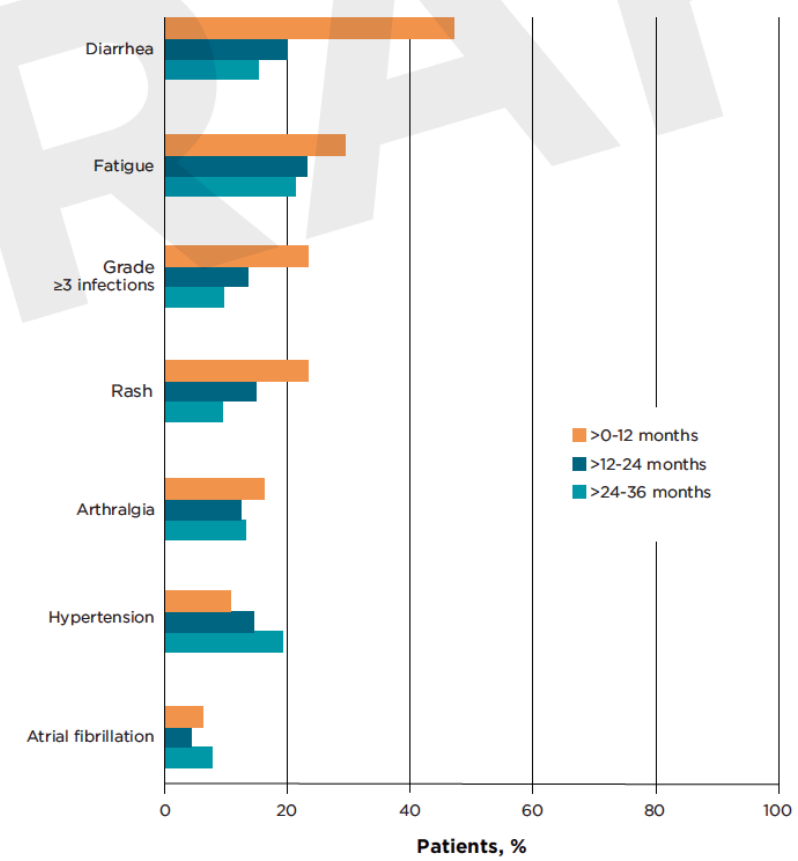


Figure 3. Prevalence of Select AEs of Clinical Relevance Over Time

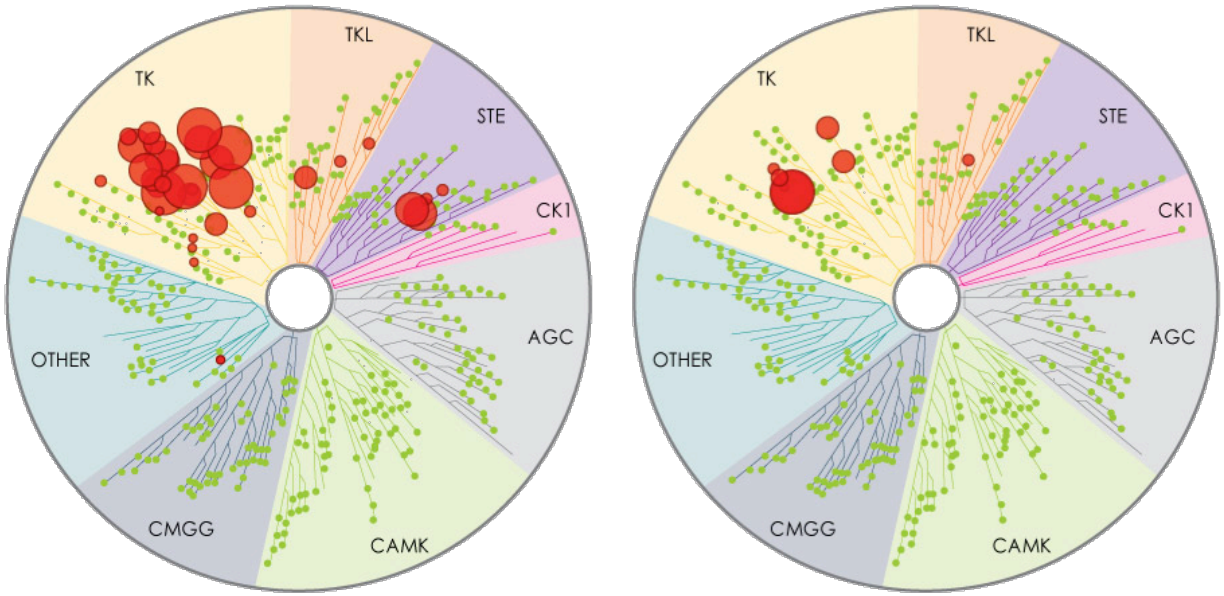


Coutre *et al.*, ASH 2016

Specificity of Btk inhibitors

Kinase selectivity profiling at 1 μM

Ibrutinib **Acalabrutinib**



Kinase Inhibition IC_{50} (nM)

Kinase	Acalabrutinib	Ibrutinib
BTK	5.1	1.5
TEC	93	7.0
BMX	46	0.8
TXK	368	2.0
ERBB2	~1000	6.4
EGFR	>1000	5.3
ITK	>1000	4.9
JAK3	>1000	32
BLK	>1000	0.1

Covey AACR 2015. Abstract 2596.

The size of the red circle is proportional to the degree of inhibition.

Does the off-target irreversible inhibition matter?
Where are the off target kinases expressed?

Kinase inhibition by ibrutinib (RPKM)

Max	50-100%	10-50%	<10%

	Btk	EGFR	ERBB2	ITK	JAK3	BLK	TXK	TEC	BMX
lymph node	25.215	0.96	1.984	23.878	18.238	18.903	5.67	1.401	0.653
spleen	18.354	2.399	3.303	8.016	10.946	13.722	3.293	0.714	0.46
bone marrow	10.689	0.011	0.399	3.903	6.022	1.255	1.151	2.419	2.391
appendix	16.713	2.086	5.688	14.742	19.489	6.903	3.135	1.068	1.054
colon	2.73	6.6	23.463	1.357	1.211	0.614	0.452	0.651	1.609
duodenum	1.996	2.264	25.114	1.192	1.286	0.251	0.38	0.613	1.853
esophagus	1.706	12.244	28.242	1.258	0.539	0.196	0.362	1.448	1.139
small intestine	2.78	2.882	25.254	2.673	1.668	0.558	0.64	0.729	2.083
stomach	2.949	3.675	18.99	2.186	2.055	1.454	0.35	0.522	0.305
gall bladder	4.215	5.19	13.767	4.246	2.691	0.459	0.709	0.578	1.417
urinary bladder	6.332	5.419	18.075	3.533	3.739	1.69	1.284	0.486	1.292
heart	0.536	1.638	13.89	0.247	0.306	0.103	0.097	0.385	1.729
skin	1.161	15.598	30.178	0.303	0.557	0.023	0.651	1.339	0.124
brain	1.391	7.382	3.469	0.166	0.765	0.035	0.038	0.063	0.077
endometrium	1.139	6.099	9.462	0.959	0.907	0.014	0.396	0.512	0.624
fat	0.928	11.438	4.586	0.254	0.509	0.034	0.154	0.203	1.546
kidney	0.347	5.822	34.694	0.212	0.456	0.014	0.335	0.529	0.107
liver	0.897	8.657	8.136	0.508	0.404	0.106	0.229	0.633	0.141
lung	6.878	7.609	19.713	3.135	1.845	0.253	0.749	0.938	0.875
placenta	2.691	36.612	12.284	0.281	2.747	0.087	1.188	0.542	2.234
adrenal	1.428	4.387	2.204	0.549	0.538	0.051	0.236	0.912	0.156
ovary	0.267	7.517	10.64	0.292	3.829	0.027	0.041	0.187	0.255
pancreas	0.134	1.916	3.119	0.099	0.151	0.02	0.031	0.06	0.11
prostate	0.788	6.146	21.356	0.543	0.941	0.198	0.139	0.354	0.274
salivary gland	0.592	4.088	11.97	0.365	0.647	0.24	0.186	0.402	0.086
testis	1.025	2.779	5.871	0.598	1.598	0.117	0.477	0.882	0.162
thyroid	0.47	12.717	18.11	0.463	0.328	0.076	0.186	0.682	0.439

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Kinase inhibition by acalabrutinib (RPKM)

Max	50-100%	10-50%	<10%

	Btk	EGFR	ERBB2	ITK	JAK3	BLK	TXK	TEC	BMX
lymph node	25.215	0.96	1.984	23.878	18.238	18.903	5.67	1.401	0.653
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Integrated Analysis of Resistant Subclones with Ibrutinib in CLL: Study Design and Disposition

Key eligibility criteria
•Patients with CLL treated with ibrutinib

Pooled analysis of 308 patients from The Ohio State University Comprehensive Cancer Center from 4 clinical trials of ibrutinib

Deep sequencing for BTK and PLCG2 using Ion Torrent Personal Genome Machine and covered coding regions of both genes

Preclinical experiments with XLA cell lines infected with lentiviral constructs (empty vector, wild type BTK, or C481S BTK)

- **Explore features associated with discontinuation and disease progression**
- **Analyze biologic phenotype of BTK C481S**

Disposition	(N=308)
Median follow-up, years (range)	3.4 (0.3-5.9)
Remain on study, n (%)	136 (44)
Received transplant or therapy elsewhere, n (%)	14 (5)
Discontinued, n (%) CLL progression Other adverse event Infection Transformation	158 (51) 55 (18) 44 (14) 31 (10) 28 (9)

Woyach et al. ASH 2016. Abstract #55.

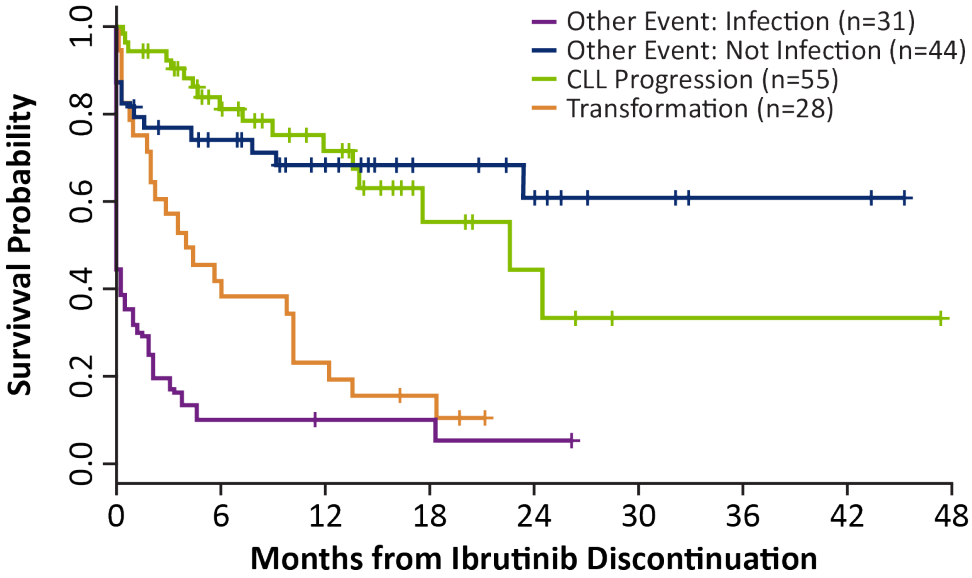
Integrated Analysis of Resistant Subclones with Ibrutinib in CLL: Patient Characteristics

Characteristic	Total (n=308)
Median age, years (range)	65 (26-91)
Male, n (%)	217 (70)
Rai stage, n (%) Low risk (0) Intermediate risk (I/II) High risk (III/IV)	 11 (4) 91 (30) 206 (67)
Median number of prior therapies (range)	3 (0-16)
Median LDH (range)	218 (96-1485)
FISH abnormalities, n (%) Del (17p) Del (11q) Trisomy 12 Del (13q) *MYC* abnormality *BCL6* abnormality	 121 (40) 83 (27) 52 (17) 157 (52) 65 (21) 27 (9)
Complex cytogenetics, n (%)	172 (58)
IGHV unmutated, n (%)	219 (80) 34 unknown

Woyach et al. ASH 2016. Abstract #55.

Integrated Analysis of Resistant Subclones with Ibrutinib in CLL: Key Results

- Multivariable models of baseline risk factors for ibrutinib discontinuation:
  - Due to transformation: complex karyotype (P<0.01) and MYC abnormalities on FISH (*P*=0.051)
  - Due to CLL progression: age <65, del(17p) by FISH, and complex karyotype (all *P*<0.05)

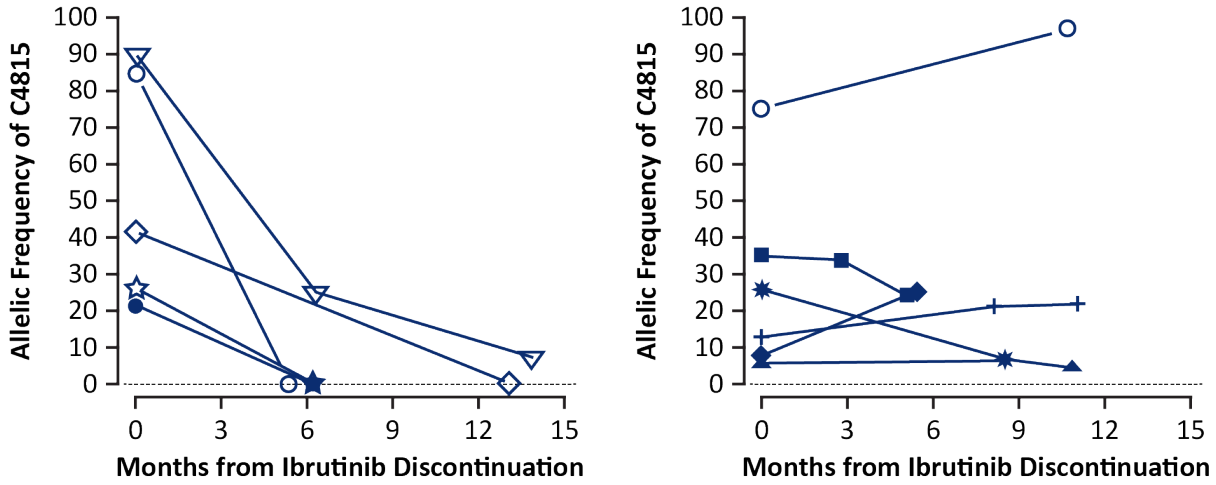


- 46 patients with progressive CLL had blood or marrow samples for deep sequencing
  - 87% had mutations in BTK and/or PLCG2 acquired at relapse
    - Distribution of mutation included patients with BTK C481 only (n=31), mutation in PLCG2 only (n=3), and both BTK/PLCG2 genes (n=6)
- 20 patients with BTK or PLCG2 mutations had serial samples available prior to relapse
  - Clone of resistant cells detected in 18/20 patients prior to clinical relapse

Woyach et al. ASH 2016. Abstract #55.

Integrated Analysis of Resistant Subclones with Ibrutinib in CLL: Key Results (Cont'd)

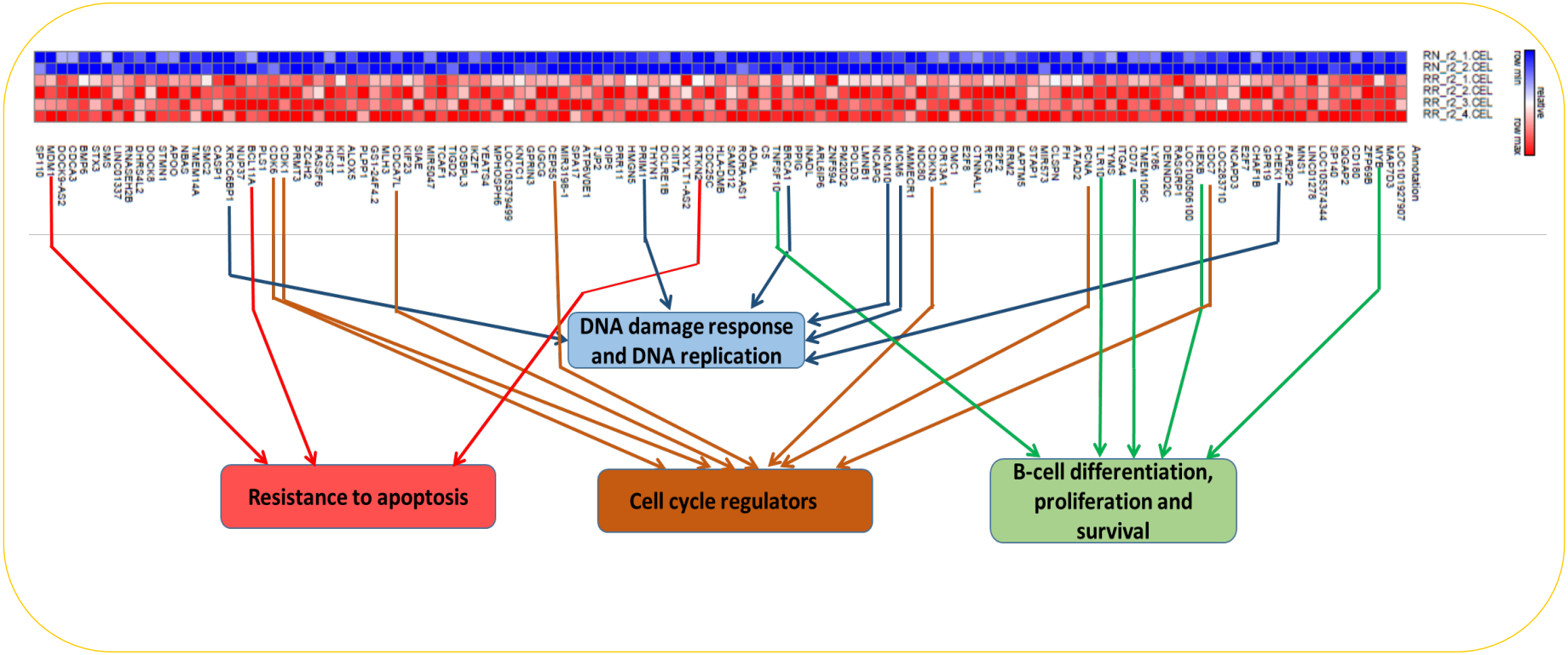
- Mutational analysis of BTK and PLCG2 coding regions on cohort of 112 patients every 3 months
  - 8 patients have clinically relapsed, all with BTK C481S mutations with expansion of clone prior to relapse
- Samples following discontinuation available in 11 patients who relapsed with BTK C481S



- XLA cell lines stably expressing BTK or C481S BTK
  - C481S BTK showed enhanced BCR signaling (pERK and cMYC expression) and enhanced migration vs wild type BTK (P=0.04)
- In a mouse model, BTK C481S reduced survival

Woyach et al. ASH 2016. Abstract #55.

Molecular mechanisms of Ibrutinib resistance: Gene expression in ibrutinib resistant cell lines

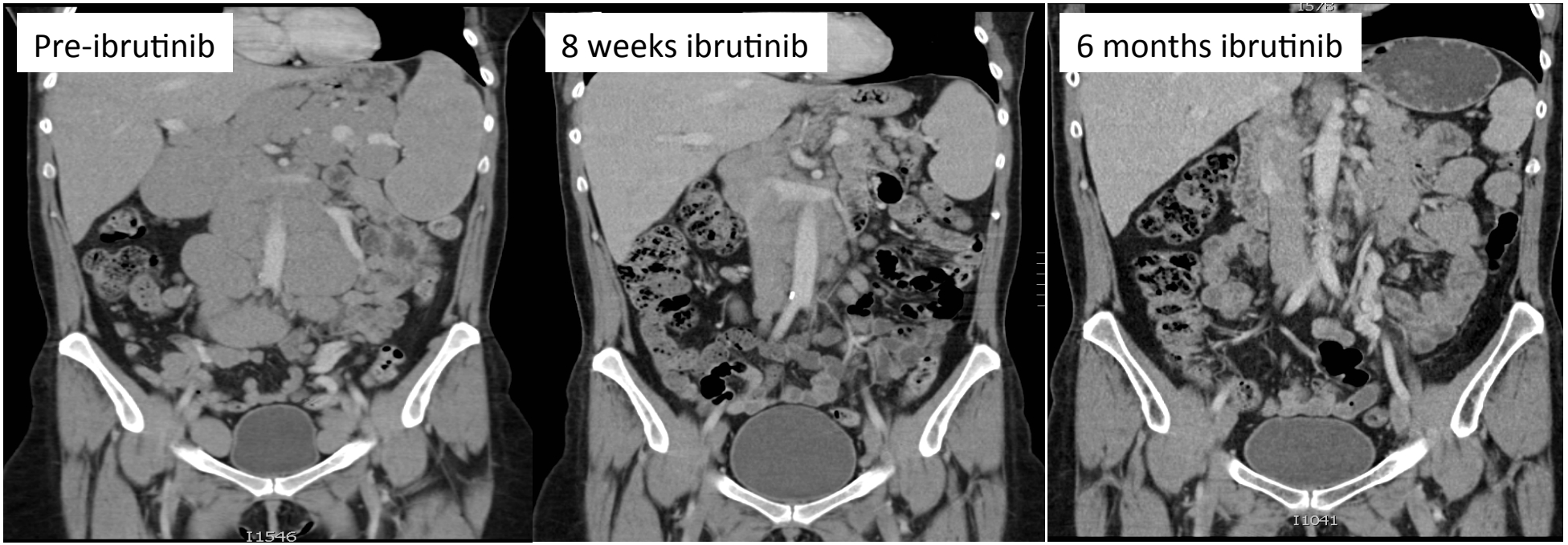


Gene expression profiling (Affymetrix HTA2.0). Resistant Ramos clones (RR) show upregulation of genes responsible for DNA damage response, B cell proliferation and survival transcription factors. In addition, positive regulators of cell cycle and cyclin dependent kinases are upregulated in resistant cells.

Farag *et al.*, ASH 2016

KW, Female, Born 1961

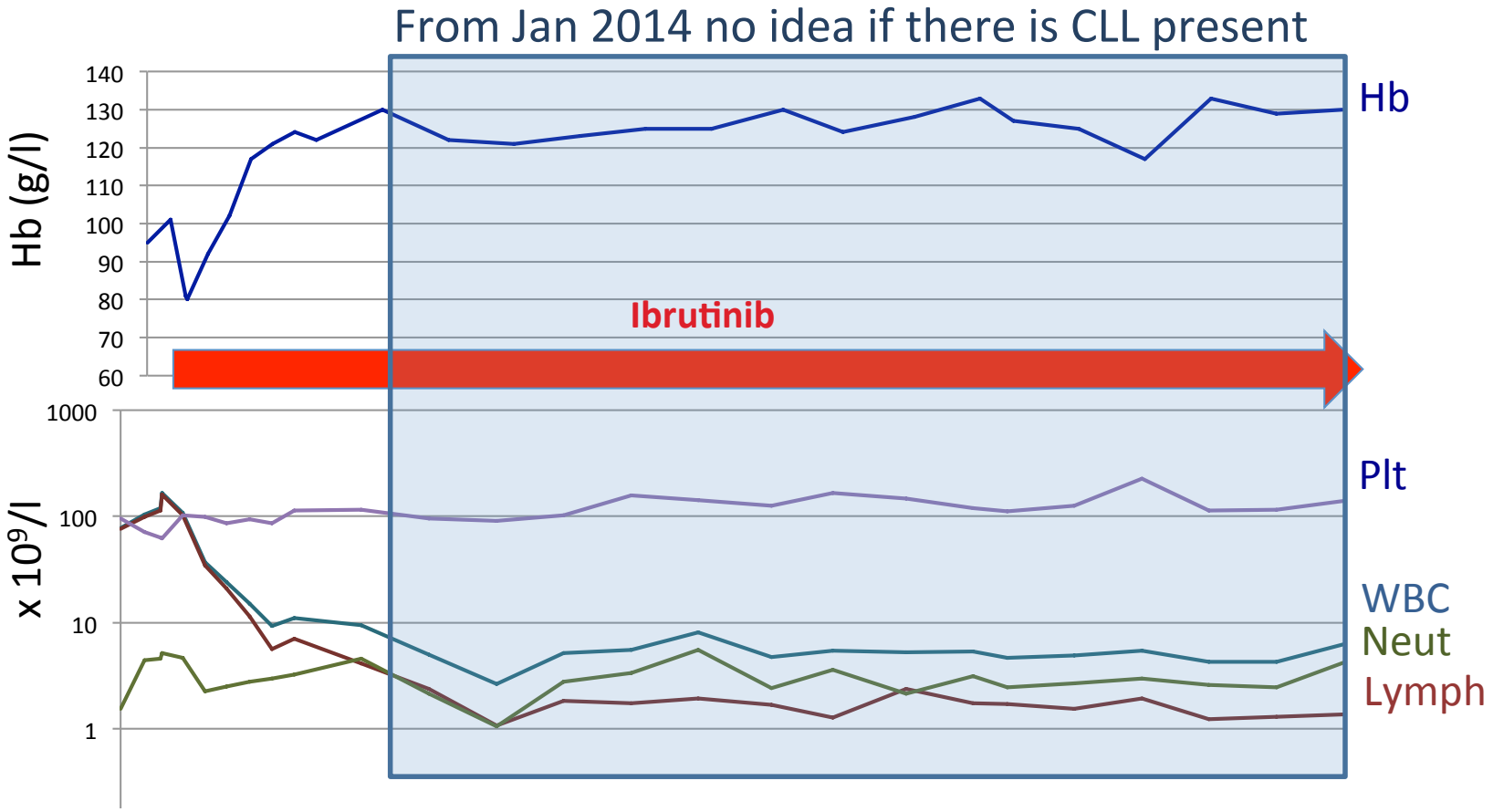
CLL – post FC, BR, alloSCT; 17p and 11q deleted



Pre-ibrutinib	8 weeks ibrutinib	6 months ibrutinib
WBC 104 x 10^9/l	WBC 37.2 x 10^9/l	WBC 5.6 x 10^9/l
Neut 4.4 x 10^9/l	Neut 2.3 x 10^9/l	Neut 3.3 x 10^9/l
Lymph 98.6 x 10^9/l	Lymph 34.3 x 10^9/l	Lymph 1.8 x 10^9/l
Hb 101 g/l	Hb 102 g/l	Hb 125 g/l
Plt 72 x 10^9/l	Plt 99 x 10^9/l	Plt 157 x 10^9/l

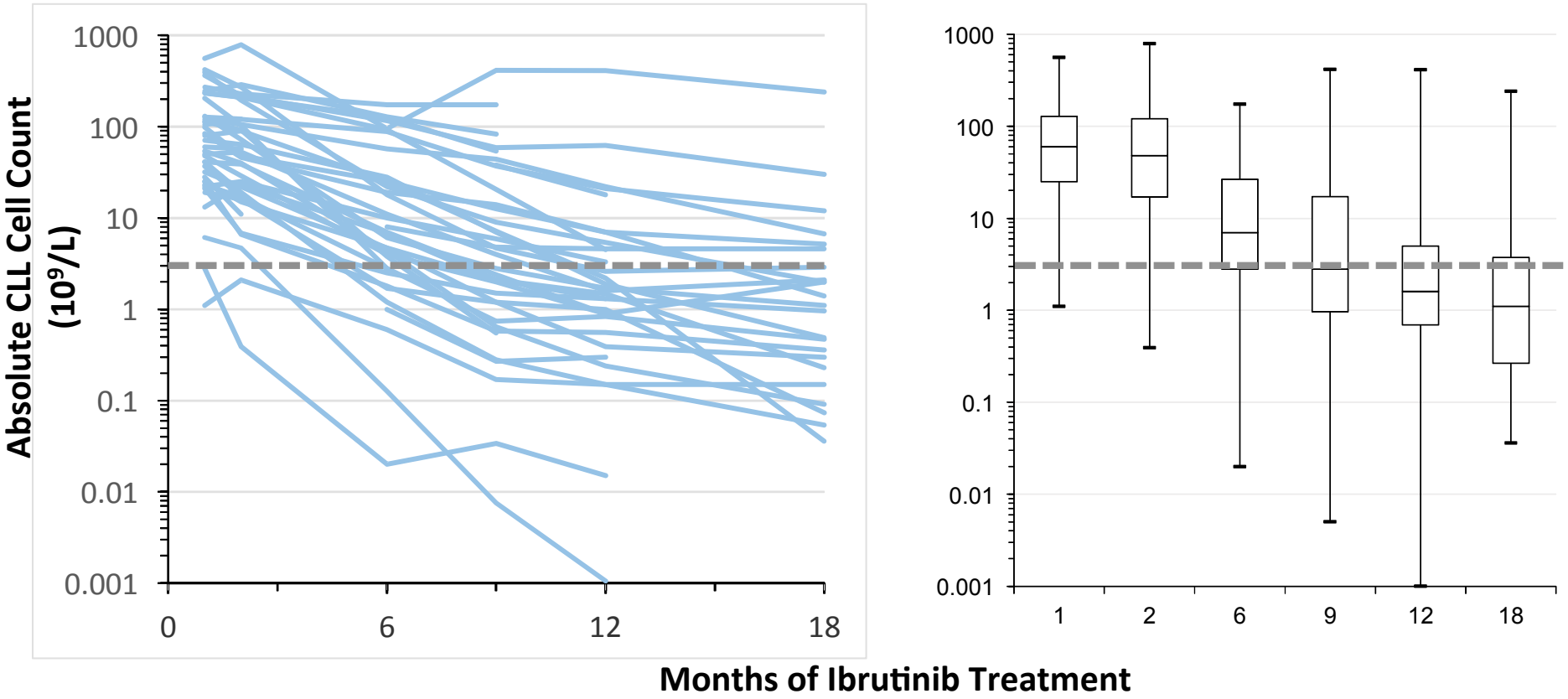
KW, Female, Born 1961

CLL – post FC, BR, alloSCT; 17p and 11q deleted



- WBC 4.0 x 10^9/l, Neut 2.0 x 10^9/l, Lymph 1.5 x 10^9/l, Hb 139g/l, Plt 125 x 10^9/l.
- Flow cytometry (20/2/17) → 0.018 x 10^9/l circulating CLL cells
- CT-scan (16/11/15) → normal
- Bone marrow (16/11/15) → Morphologically normal; 0.3% CLL cells by Flow

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

The Leeds Teaching Hospitals NHS
NHS Trust

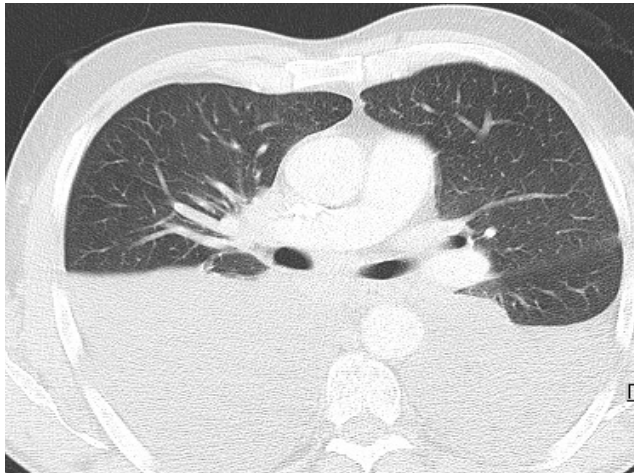
TAP
From Leukaemia & Lymphoma Research

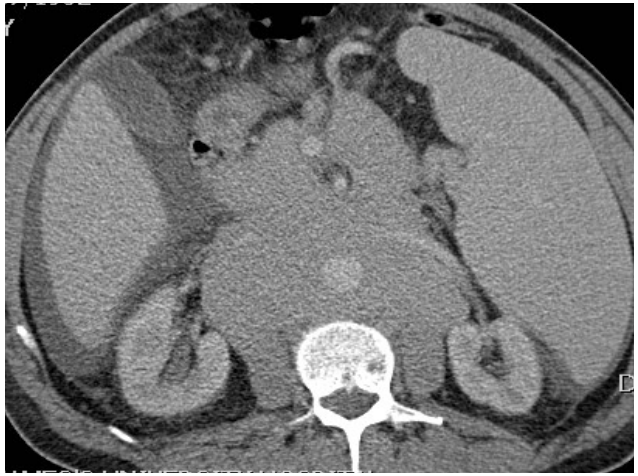
UNIVERSITY OF LEEDS

DF, 62yo, Male

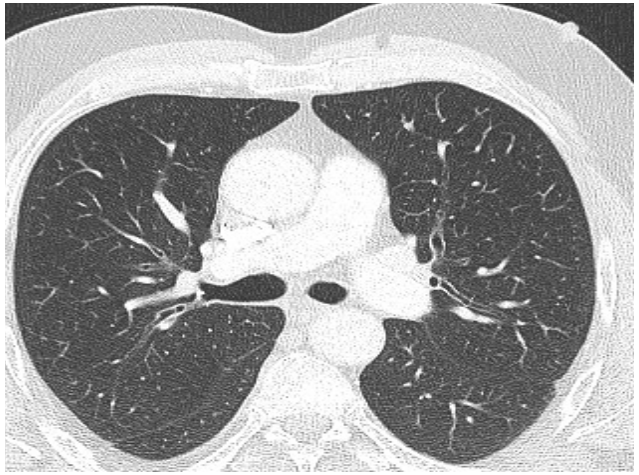
Relapsed after <3 years after FCM-R. Massive LN & 17p deleted.
Commenced venetoclax in March 2014

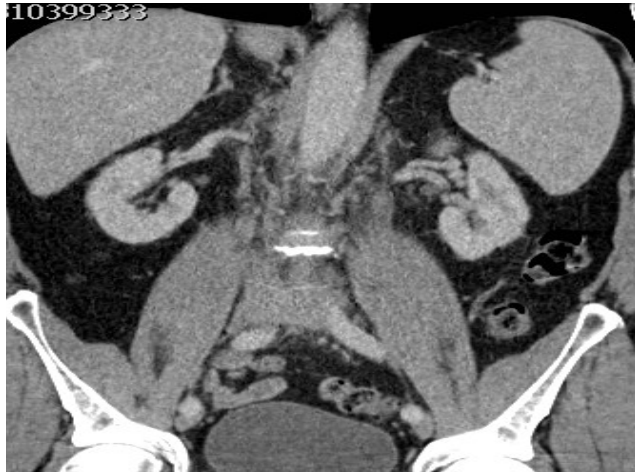
CT scan Pre-treatment





CT scan Week 24

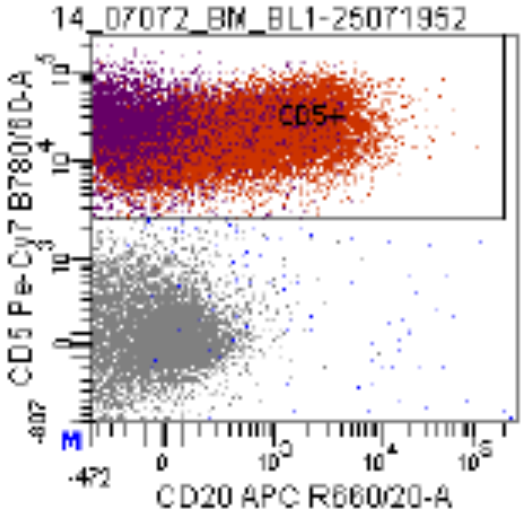


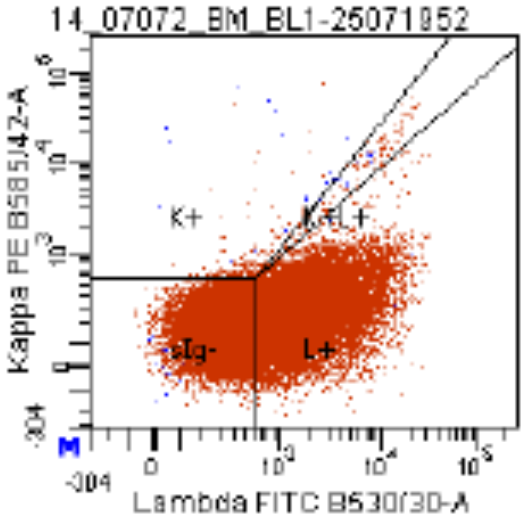


DF, 62yo, Male

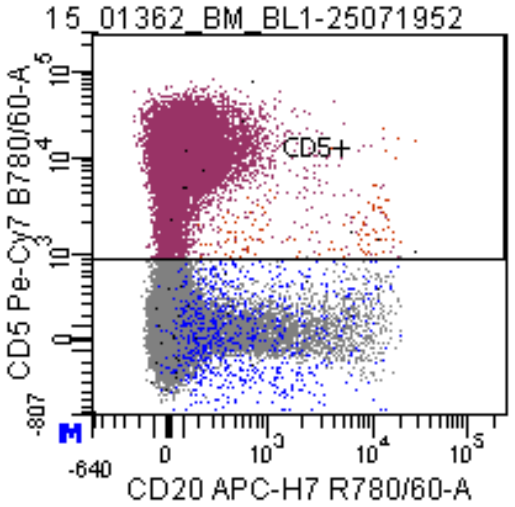
Orange events = CLL cells
Purple events = T-cells

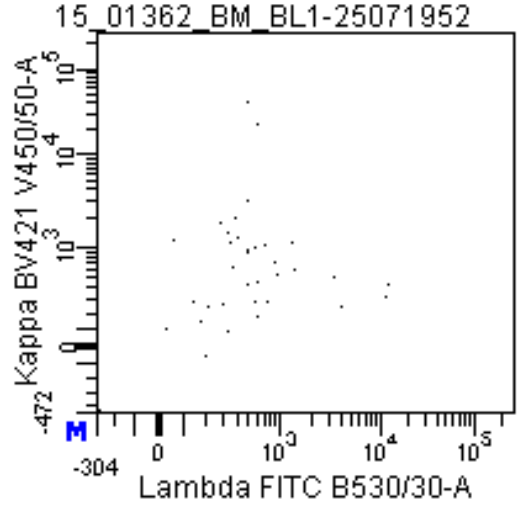
Pre-venetoclax





6 months of venetoclax



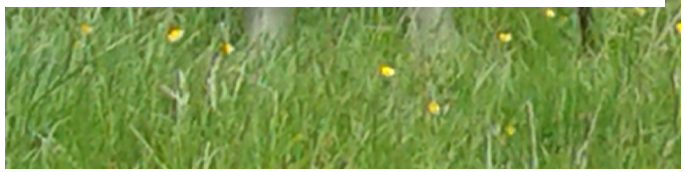


No detectable CLL <0.01%!!

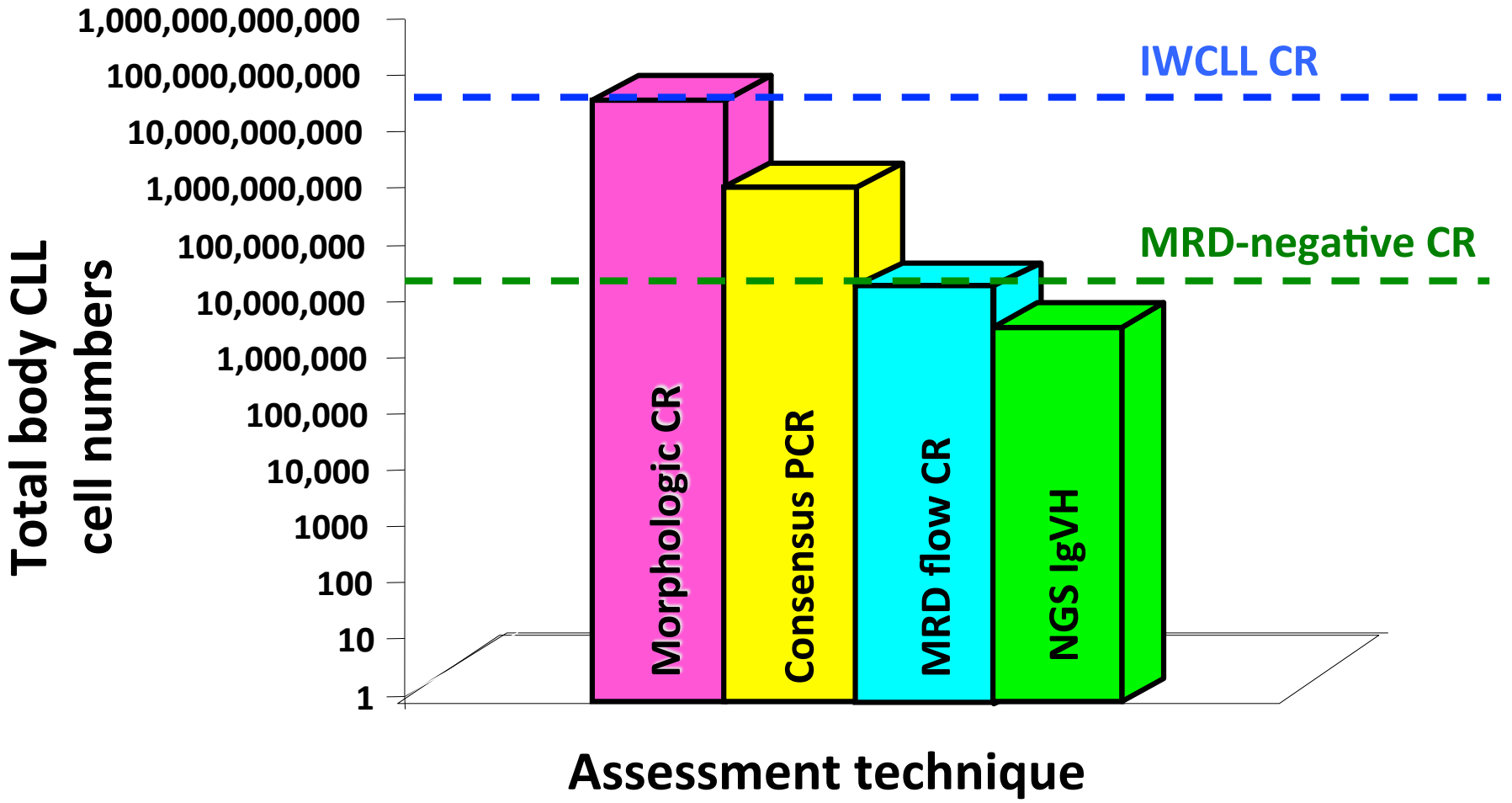
DF, 62yo, Male

- Commenced venetoclax 25/4/14; reviewed 24/08/17 → remains well
- WBC 3.4 x 10^9/l, Neut 2.4 x 10^9/l, Lymph 0.6 x 10^9/l, Hb 150g/l, Plt 143 x 10^9/l
- PB and BM MRD negative (still!)
- 24 weeks CT scan: complete remission

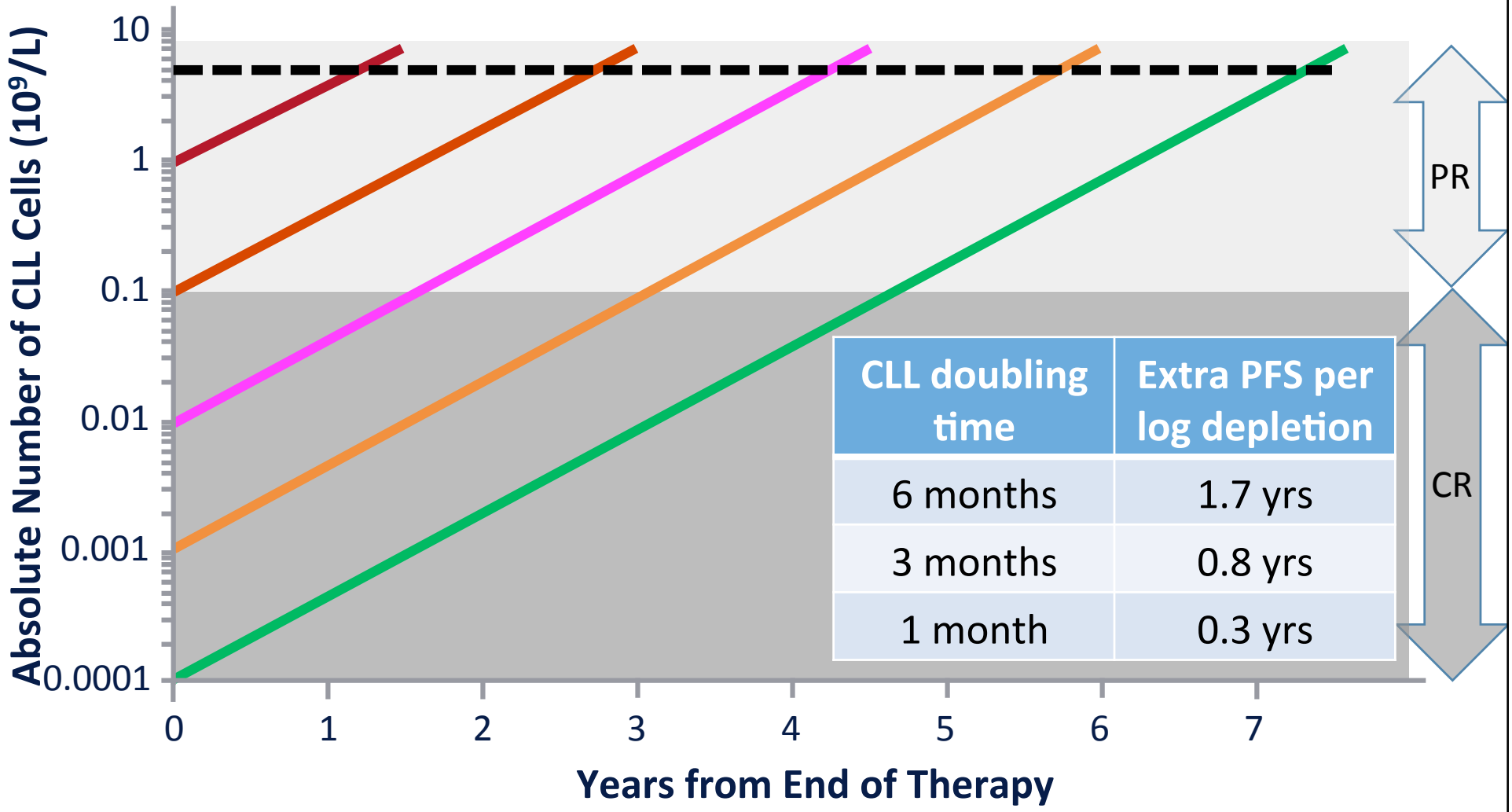
He's been taking venetoclax for 3 years with no evidence of disease ?does he need it



Does eradication of MRD equal eradication of disease?



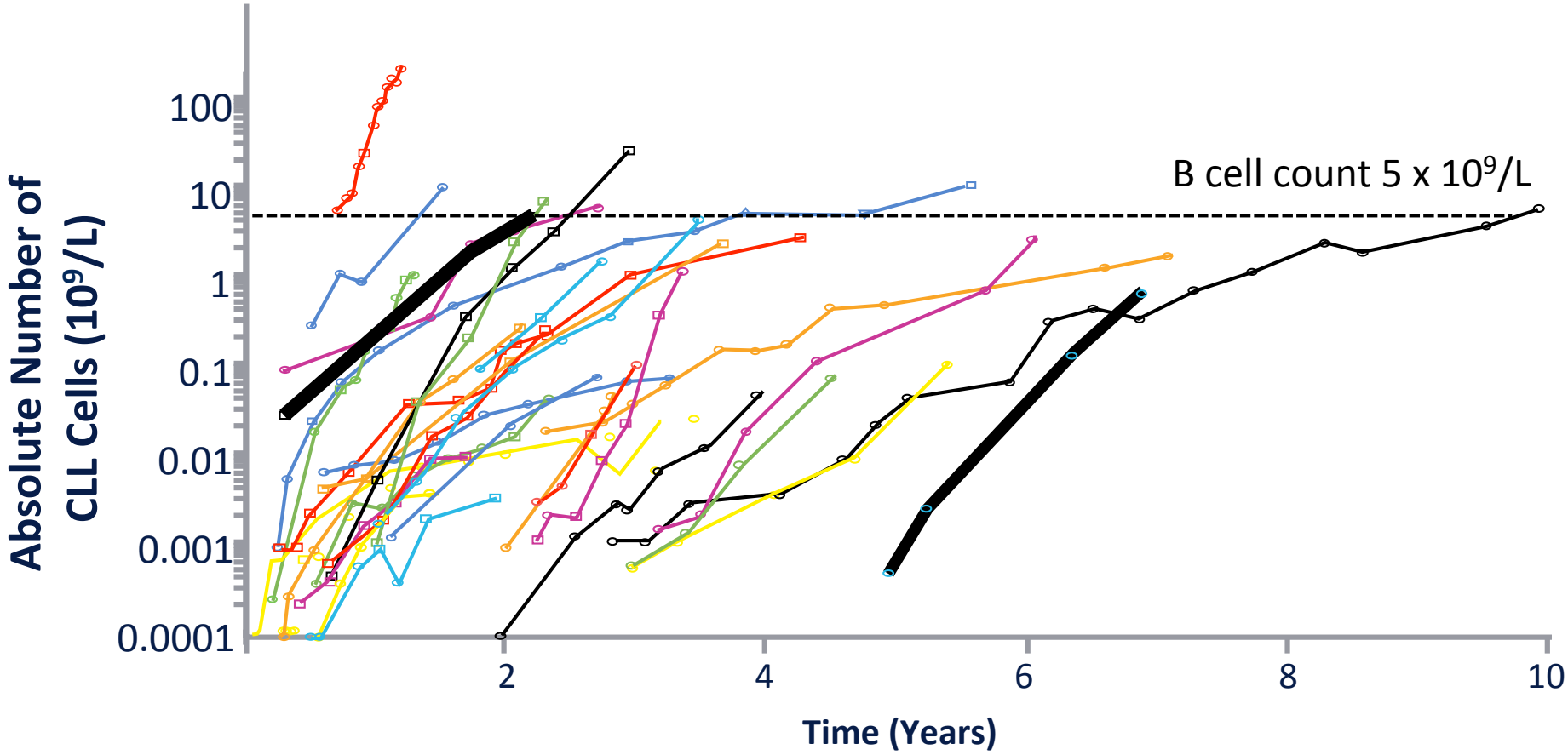
Assuming Exponential Growth at the MRD Level → Linear Increase in PFS per Log Tumour Depletion



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.

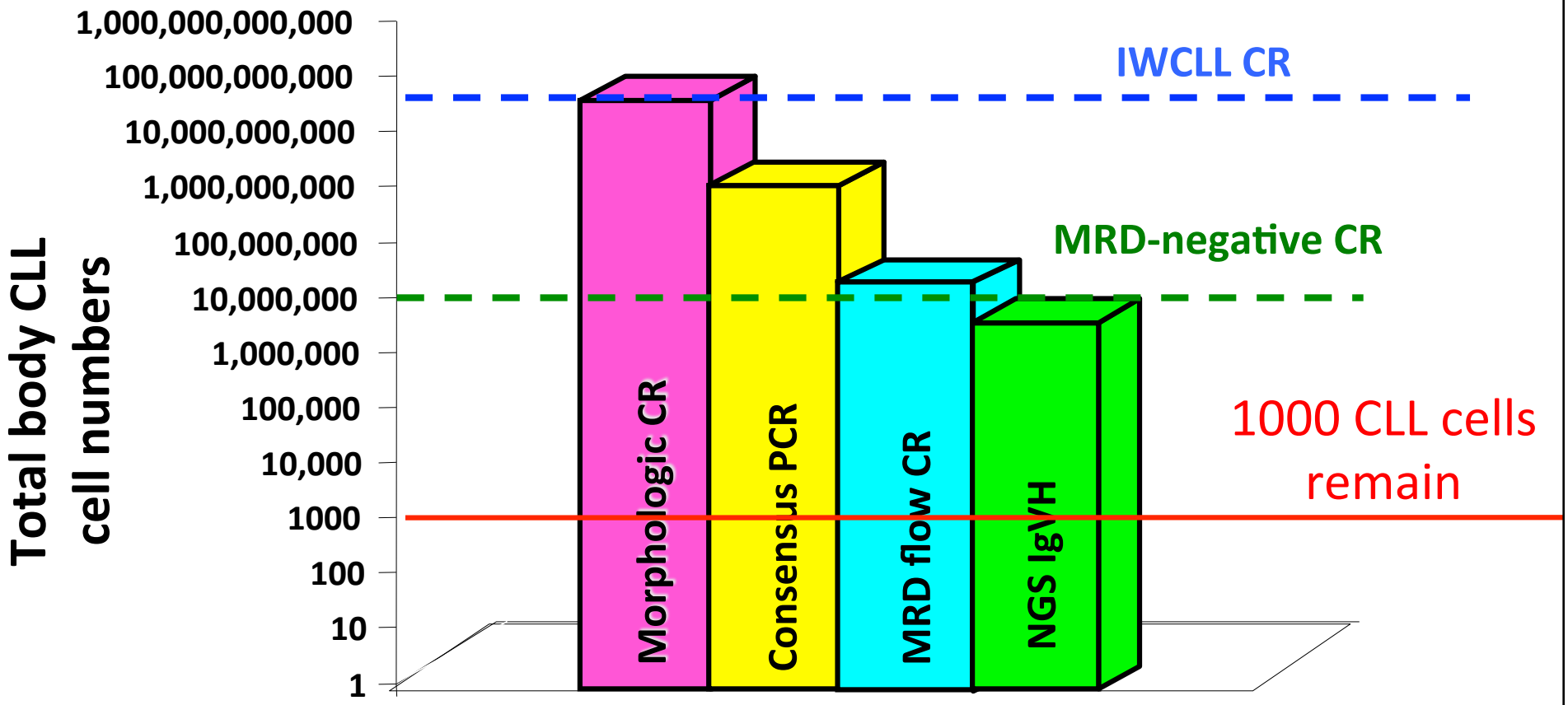
Kinetics of Relapse: Exponential Growth from the Lowest Detectable MRD Level



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

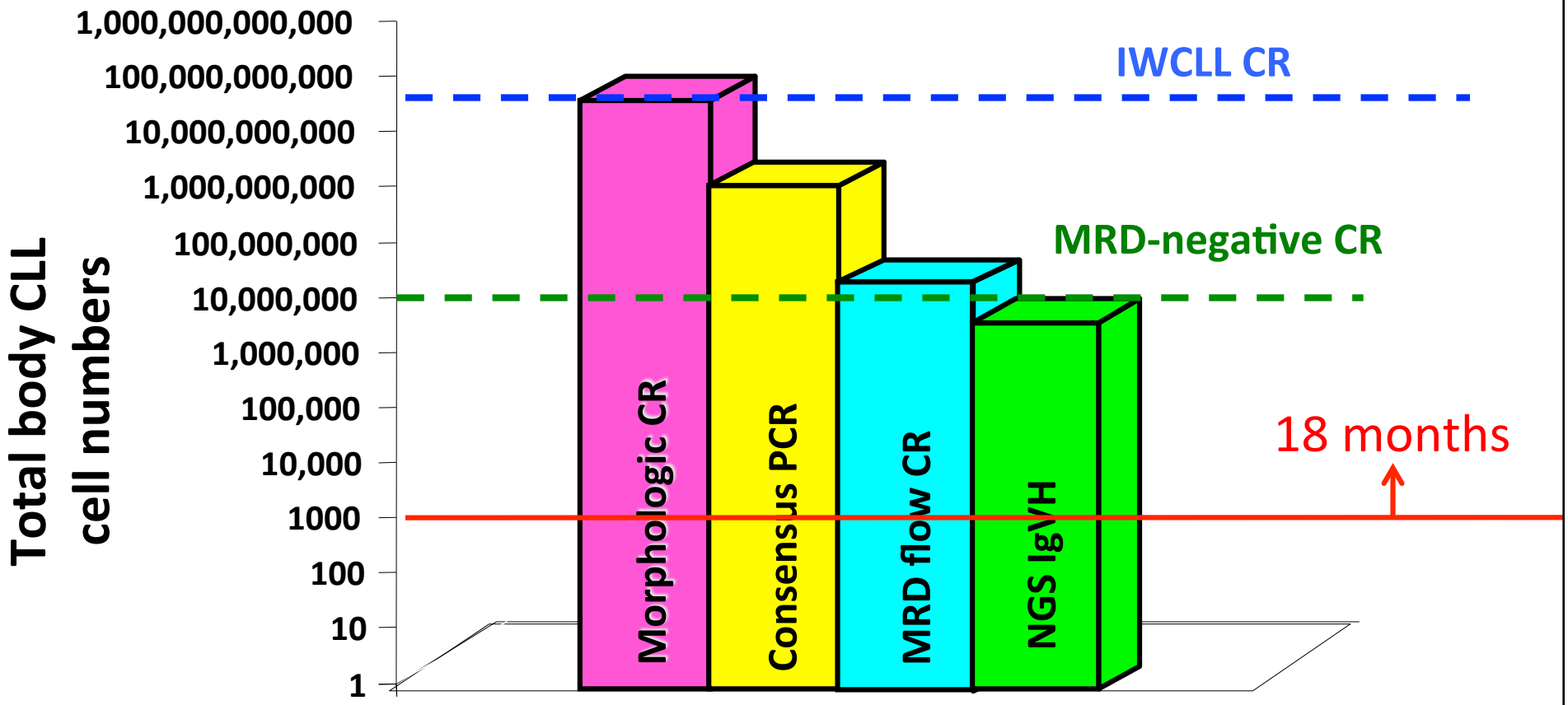
Total 68 patients monitored, 31 persistent MRD <0.01%, 5 insufficient MRD+ timepoints.

Patient with a CLL doubling time of 6 months - MRD negative remission with 1000 residual CLL cells



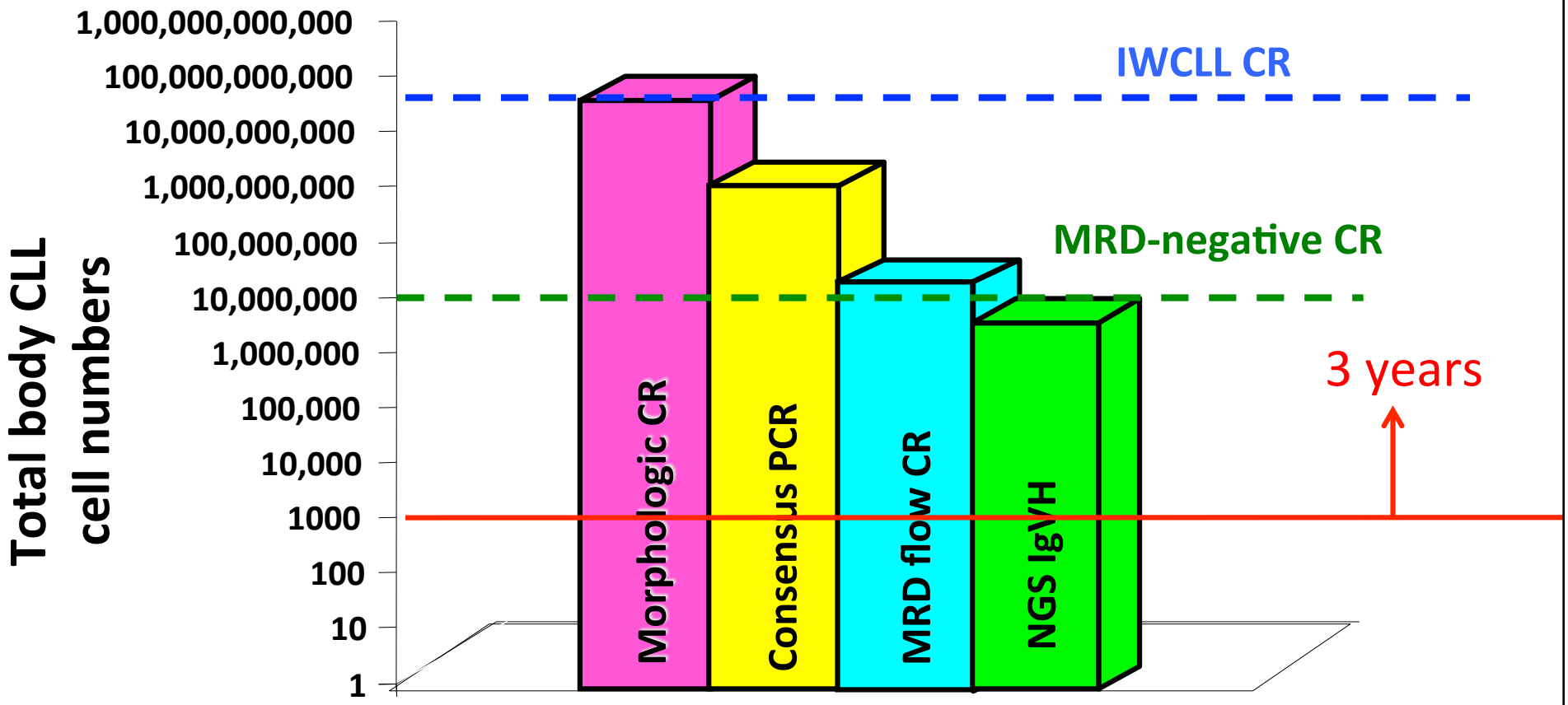
3 CLL doubling times = 8-fold increase in MRD

Patient with a CLL doubling time of 6 months - still MRD negative at 18 months



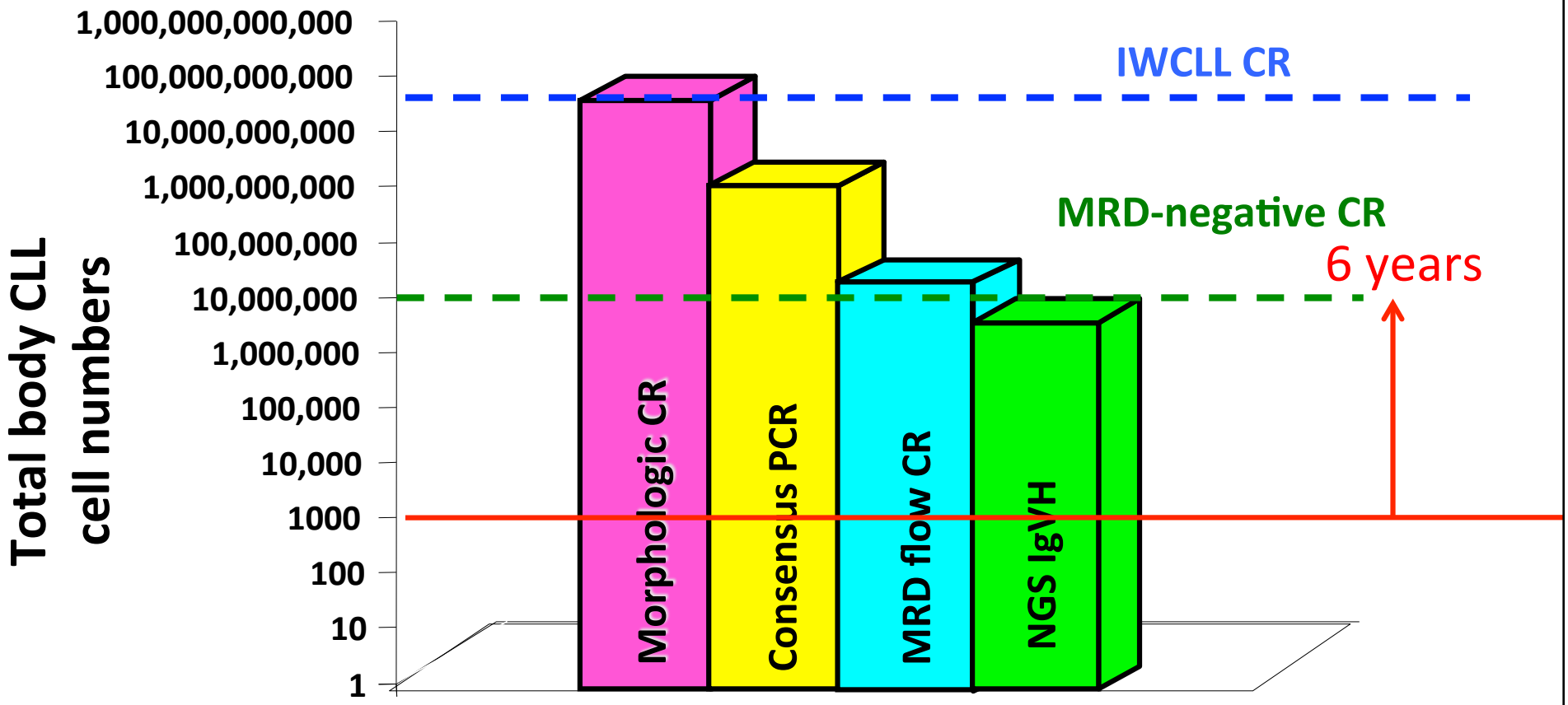
3 CLL doubling times = 8-fold increase in MRD

Patient with a CLL doubling time of 6 months - still MRD negative at 3 years



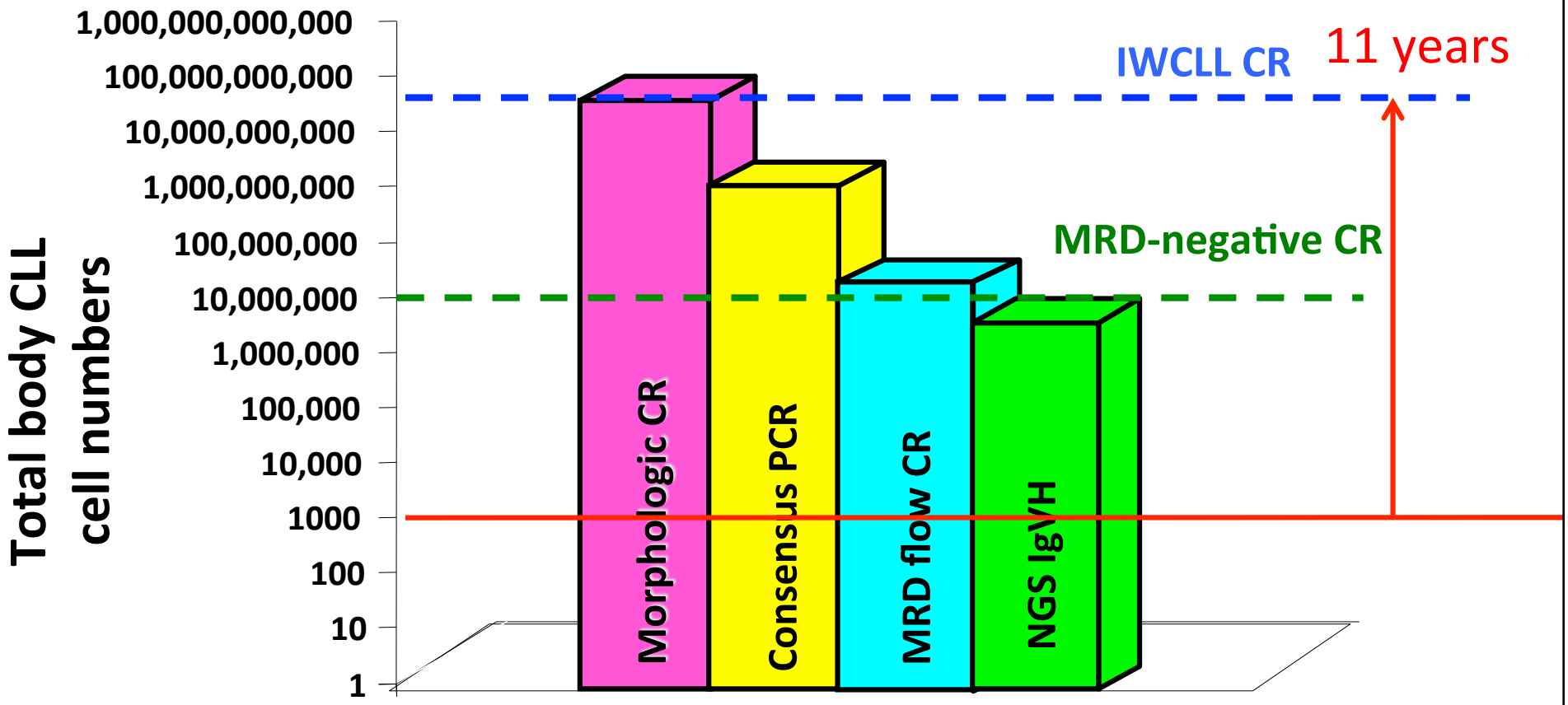
3 CLL doubling times = 8-fold increase in MRD

Patient with a CLL doubling time of 6 months - MRD positive at 6 years



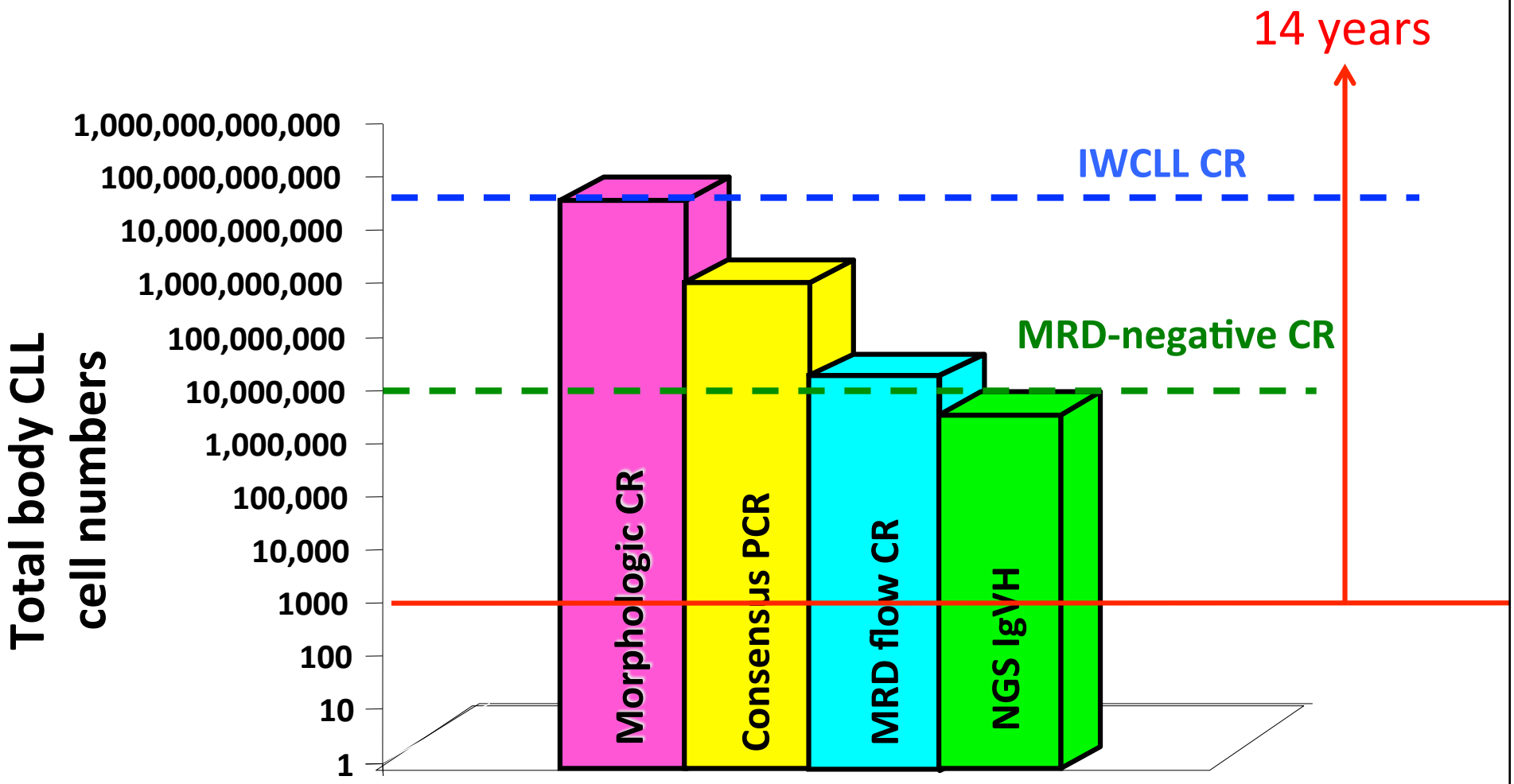
3 CLL doubling times = 8-fold increase in MRD

Patient with a CLL doubling time of 6 months - still in remission at 11 years



3 CLL doubling times = 8-fold increase in MRD

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



3 CLL doubling times = 8-fold increase in MRD

GCLLSG Cologne, Sept 2012

There is an elephant in the room

The cost!

Can we create a model?

Assumptions (mine)!!

1)Treatment will be life-long (let's say 5 years)

2)All patients survive 5 years

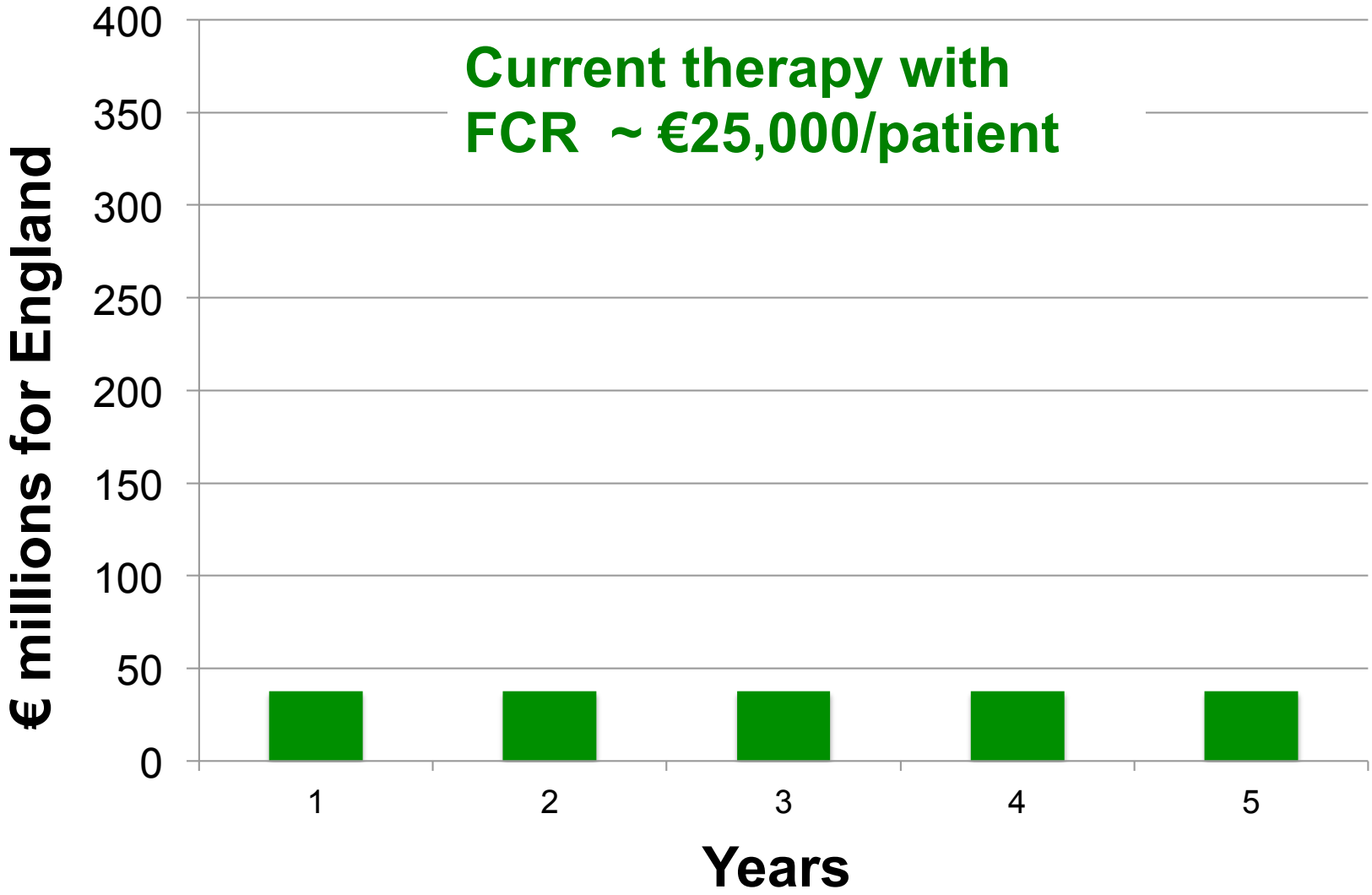
3)30 patients/million/year need therapy

4)Assume (for the sake of the model only!):

→ €50,000/patient/year

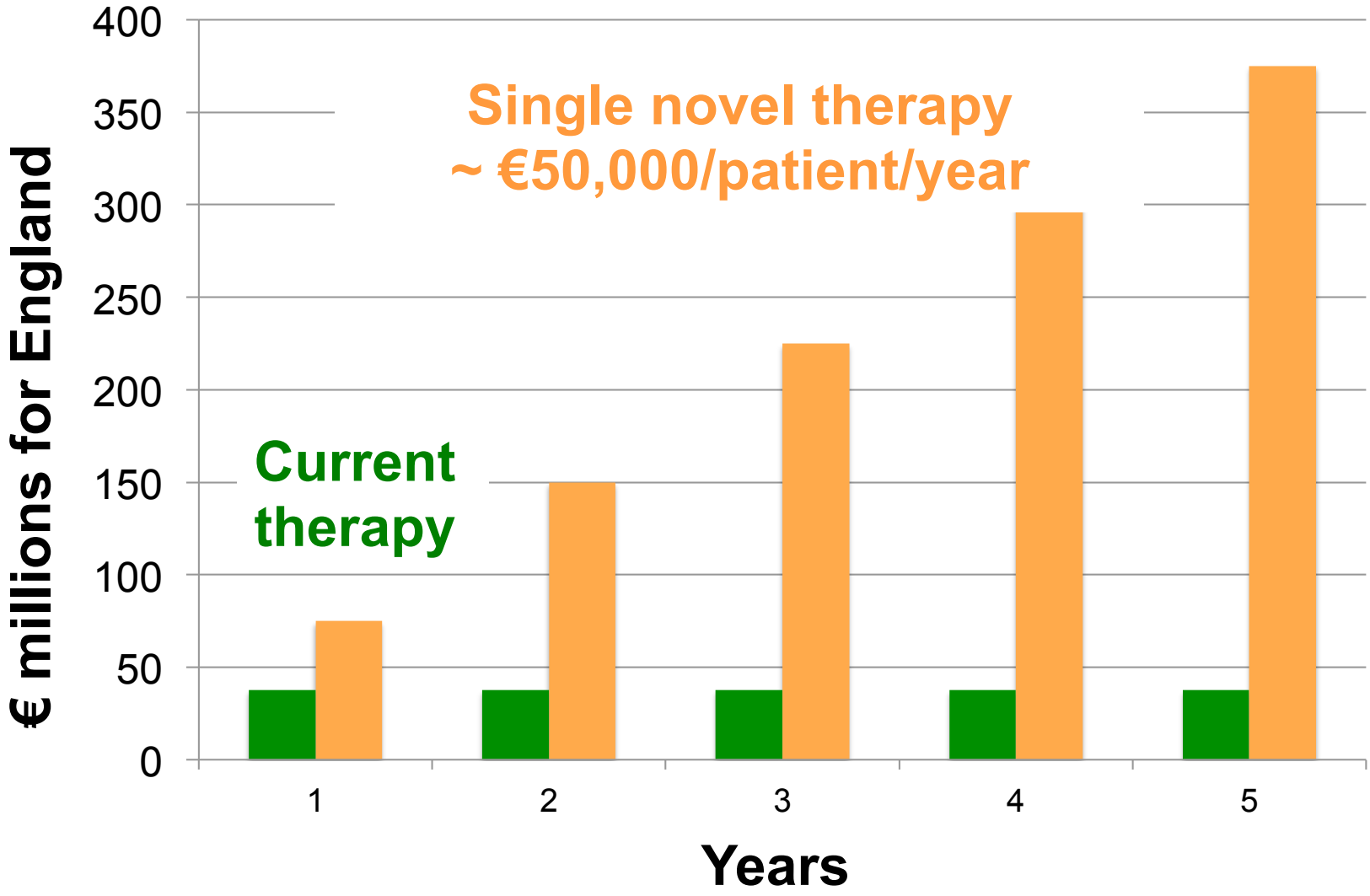
5)We will probably combine therapies

Predicted Annual Cost in England (population ~ 50 million)



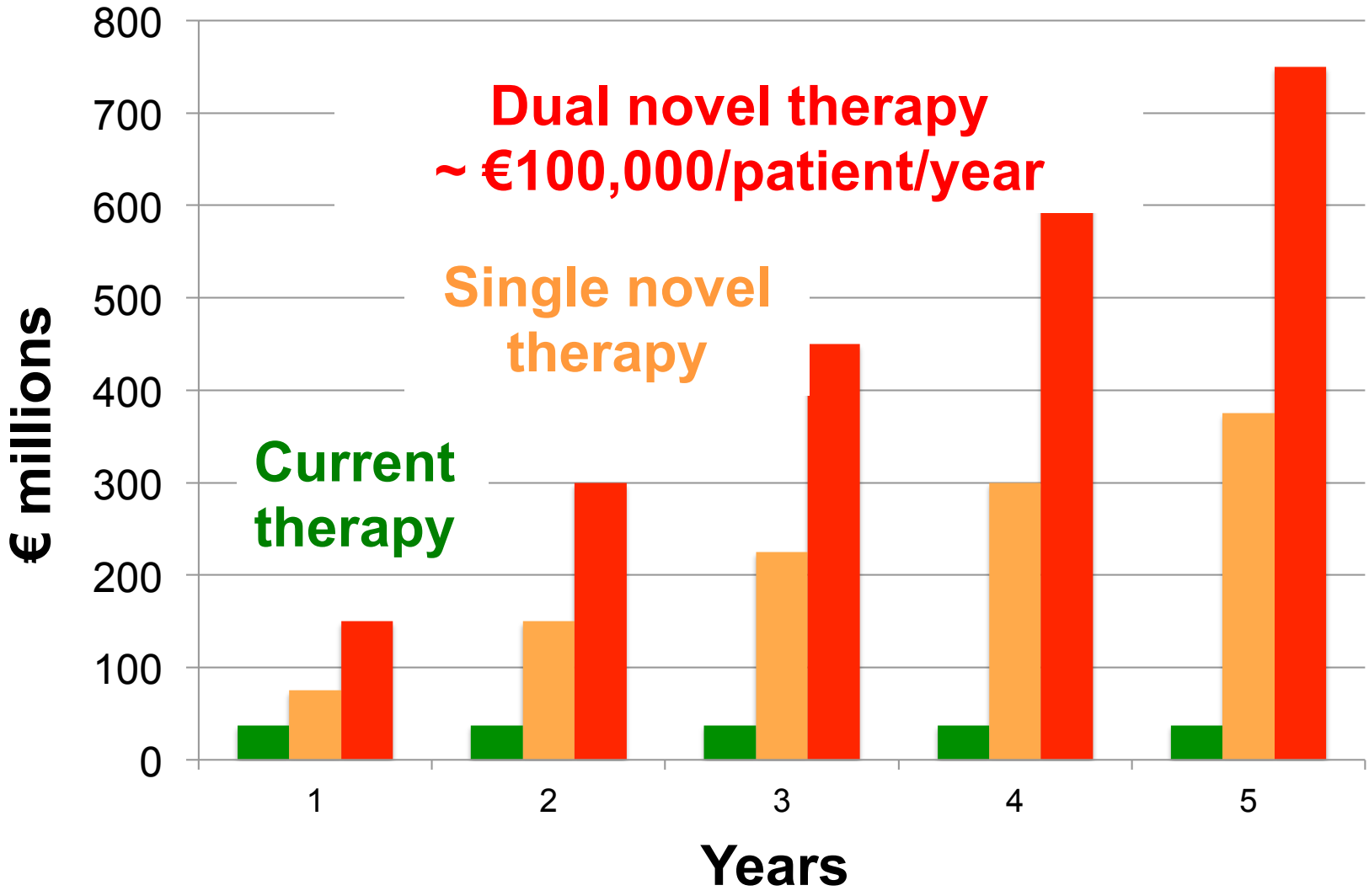
GCLLSG Cologne, Sept 2012

Predicted Annual Cost in England (population ~ 50 million)



GCLLSG Cologne, Sept 2012

Predicted Annual Cost in England (population ~ 50 million)



GCLLSG Cologne, Sept 2012

Why should we stop targeted therapy in CLL?

1. Potential for toxicity
2. Resistance
3. “Functional” cure
4. Patient preference
5. Cost

What is the aim of stopping therapy?

1. Actual or “functional” cure
2. Avoidance of resistance
3. Drug holidays?

How should we stop targeted therapy in CLL?

Understanding MRD – the maths!

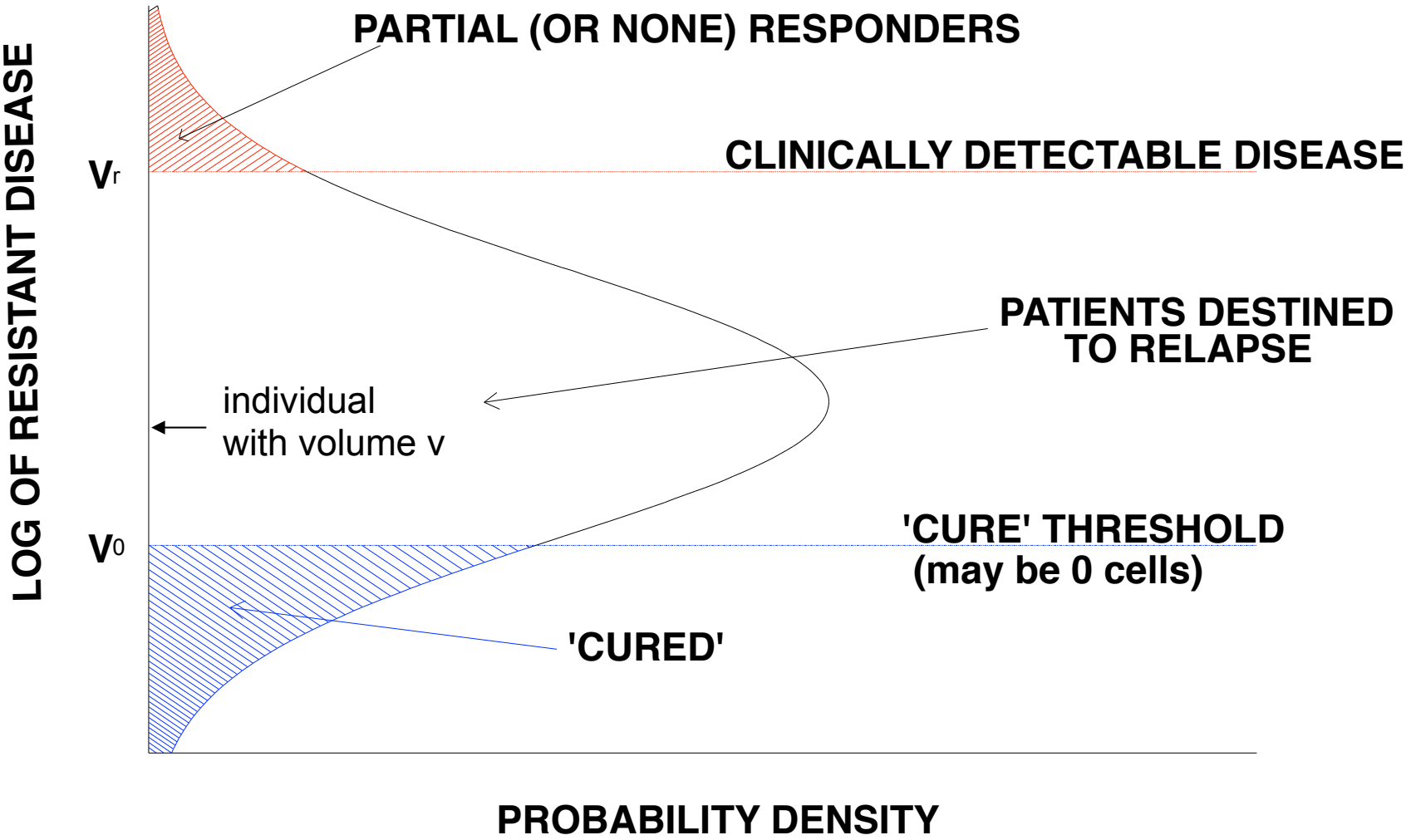
Walter Gregory *et al.* Characterizing and quantifying the effects of breast cancer therapy using mathematical modelling.

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

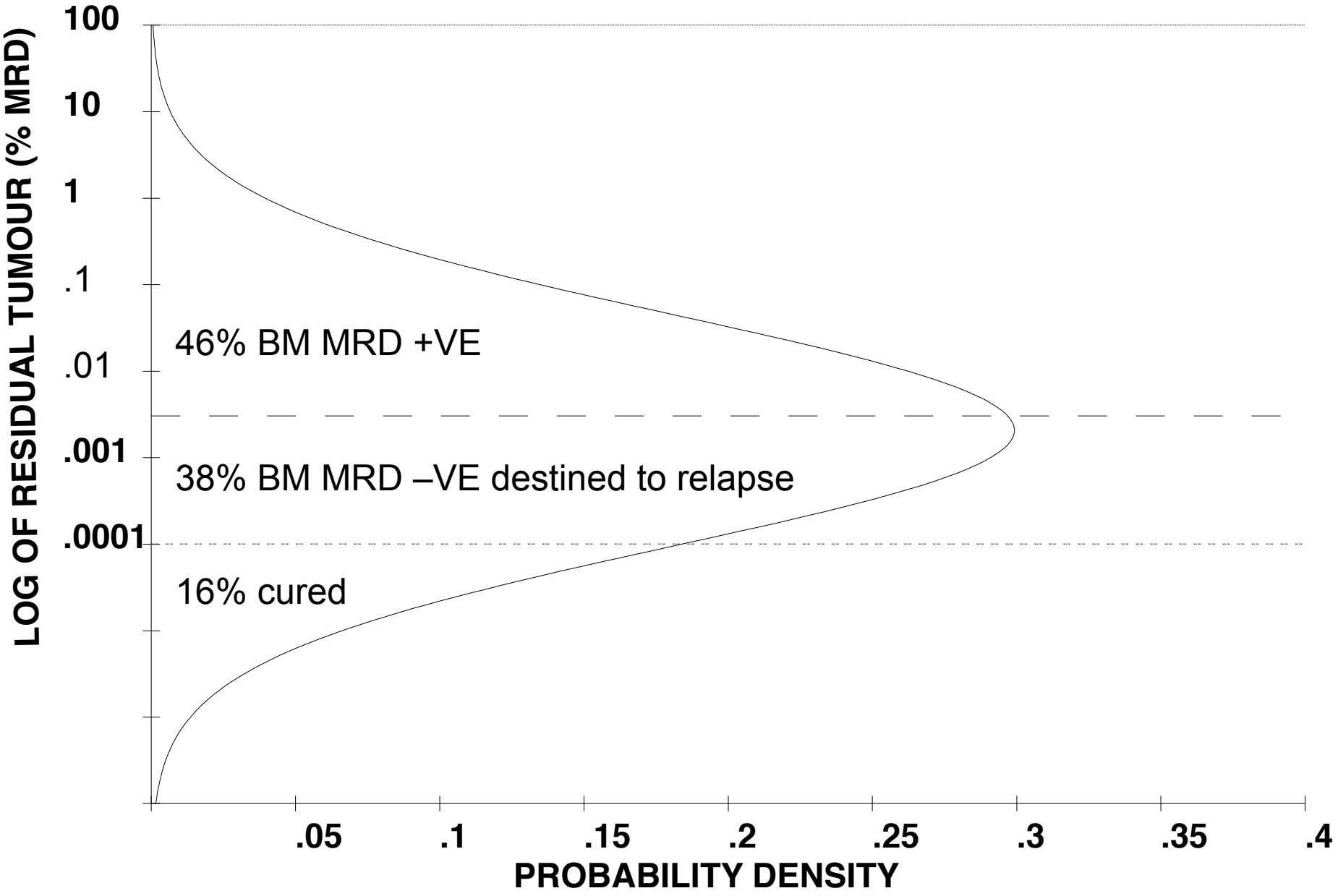
Walter M. Gregory → w.m.gregory@leeds.ac.uk

- "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)



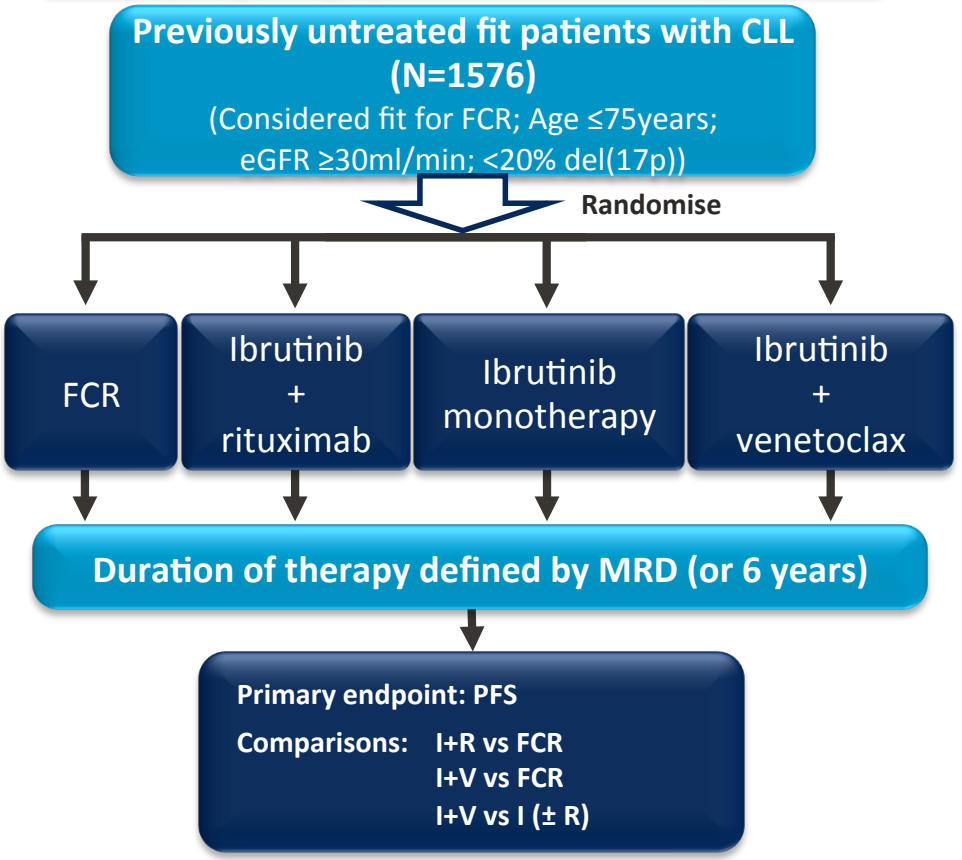
Modified the NCRI *Flair* Trial –opened July 2017

Bloodwise TAP CLARITY trial: Peripheral blood CLL responses[1]

Time point	Median, × 10^9/L (range)
Pre-treatment	50 (0–330)
End of 8 weeks' ibrutinib monotherapy	55 (0–237)
After 8 weeks' venetoclax + ibrutinib	0.017 (0–3.1)

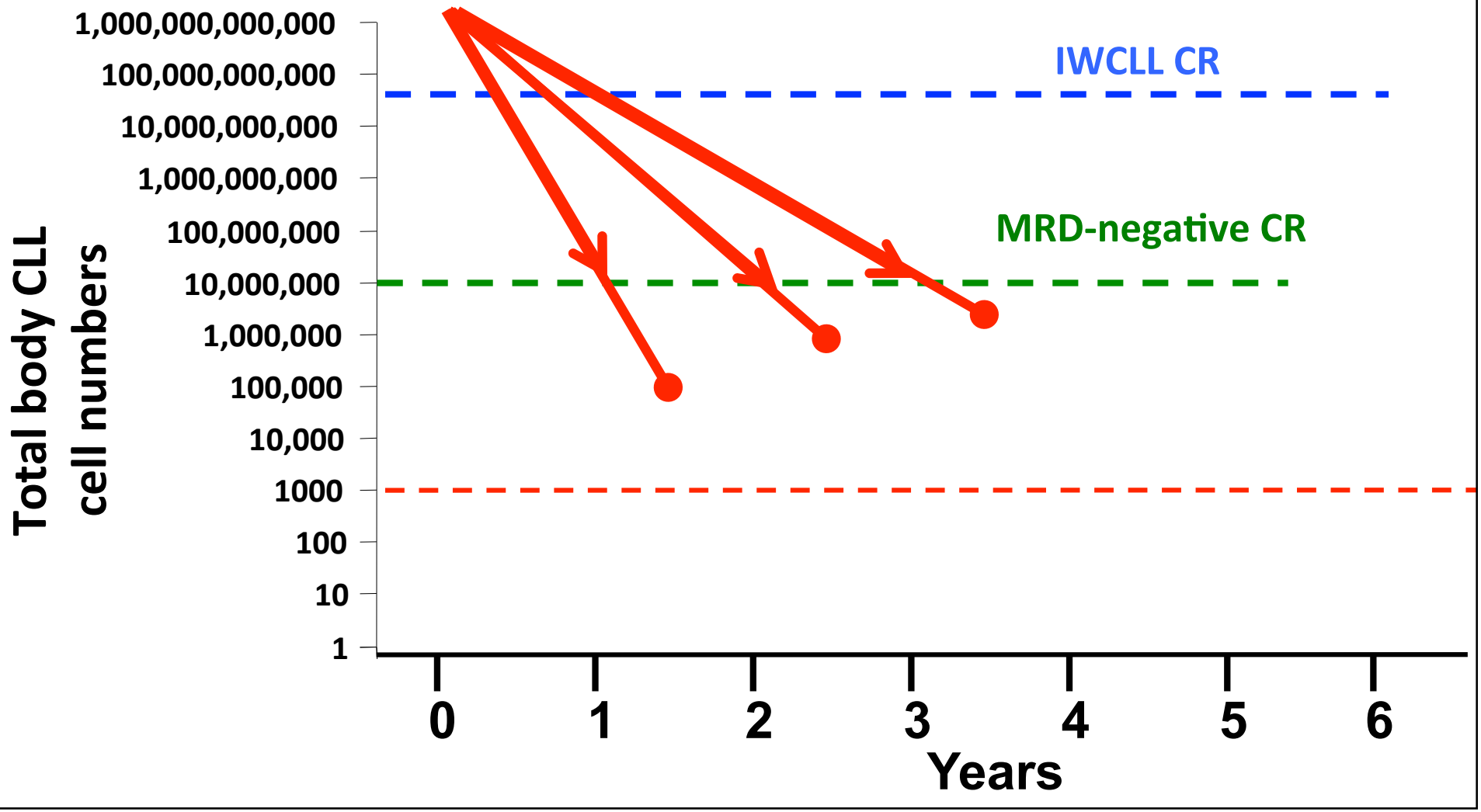
- One case of laboratory TLS observed
  - Resolved with venetoclax + ibrutinib dose interruption
- To date, 5 SAEs and 22 AEs of special interest have been observed, including:
  - Lung infection (n=3)
  - Neutropenia (n=11)

UK NCRI FLAIR trial (ongoing, planned N=1576)[2,3]

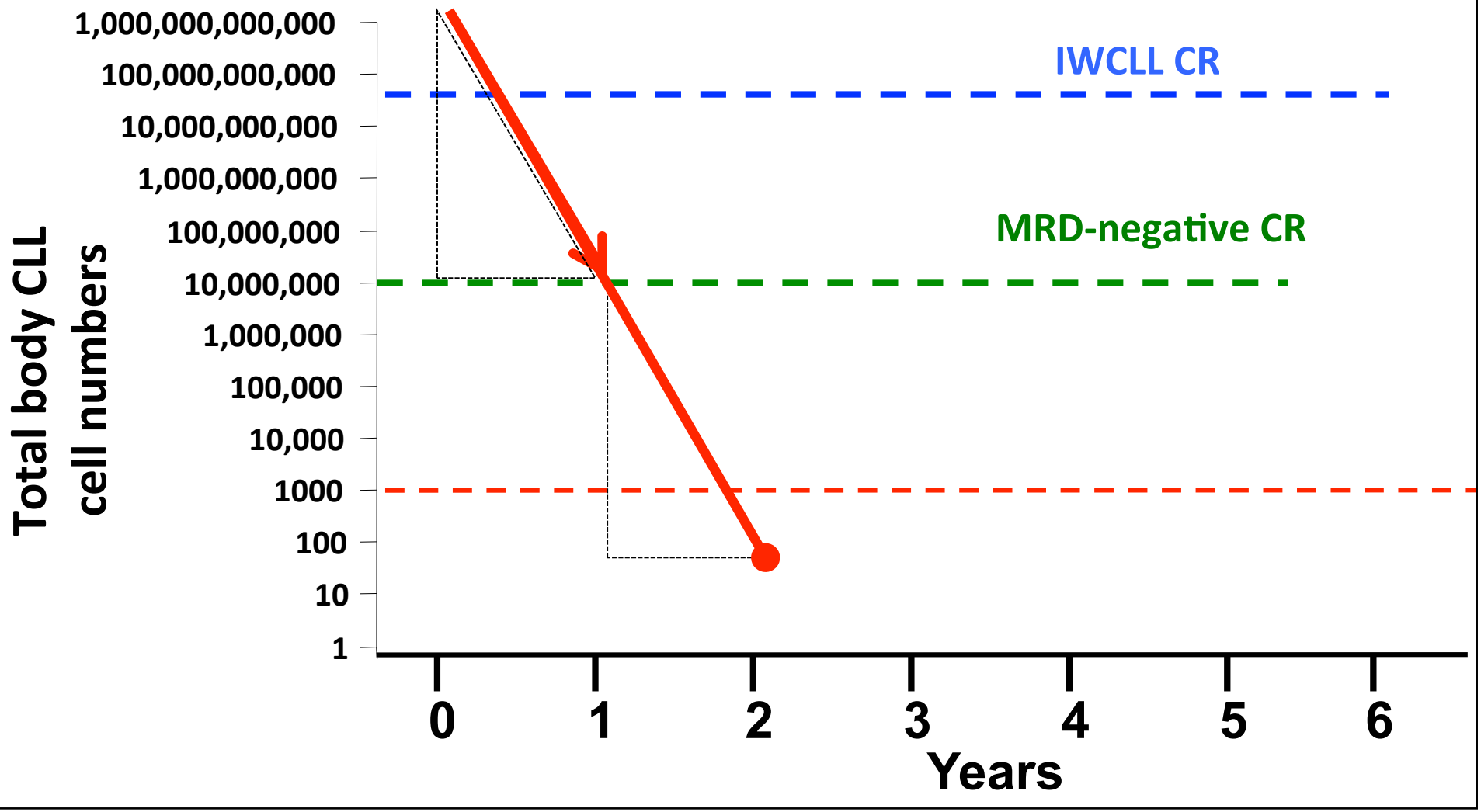


1. Hillmen P, *et al. Haematologica* 2017; Abstract 2810;
2. EudraCT. Available at: https://www.clinicaltrialsregister.eu/ctr-search/trial/2013-001944-76/GB (accessed June 2017);
3. Derby-Burton Local Cancer Network. Available at: http://www.derbyhospitals.nhs.uk/EasysiteWeb/getresource.axd?AssetID=288688&type=full&servicetype=Attachment (accessed June 2017).

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
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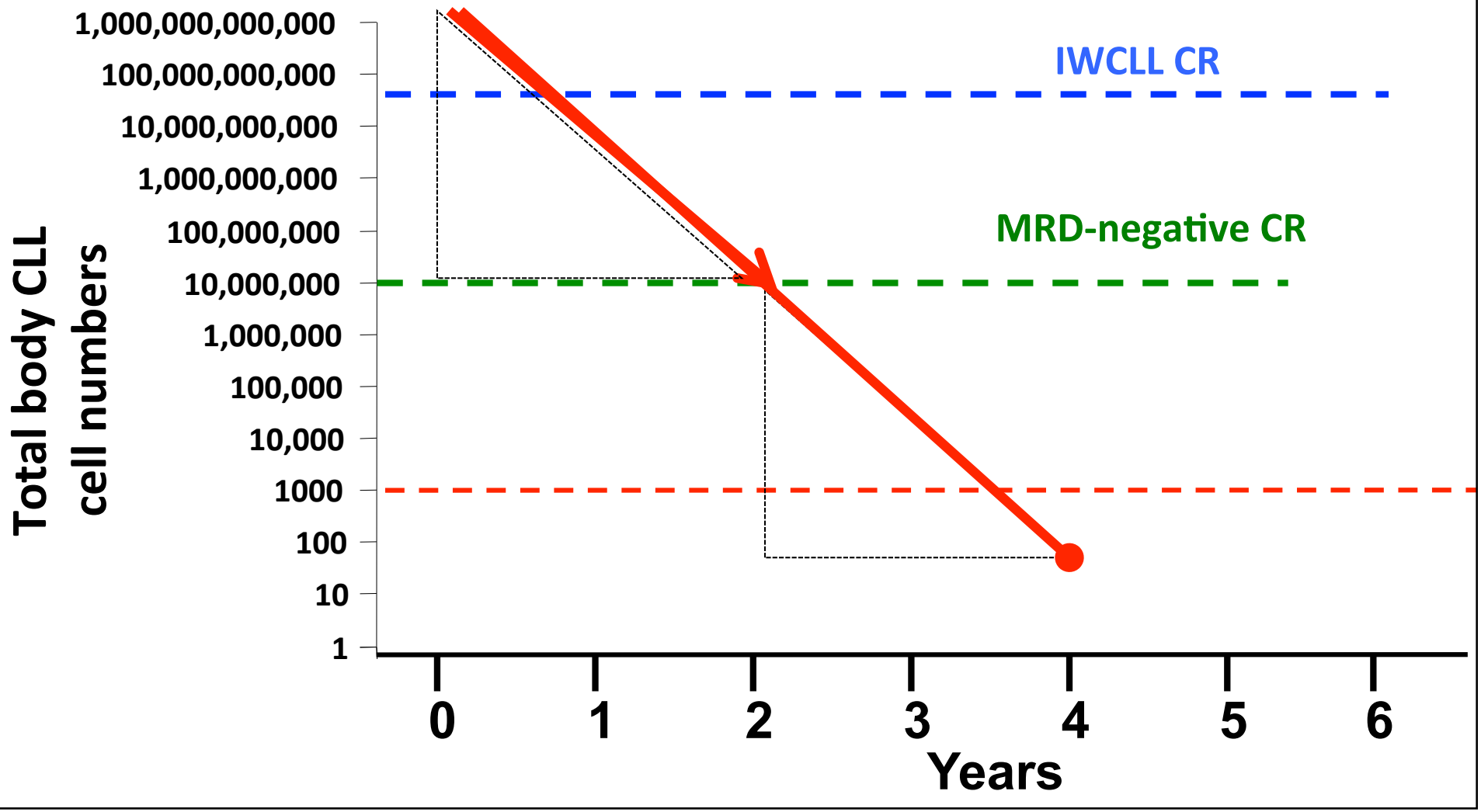

Modified treatment stopping rule in FLAIR
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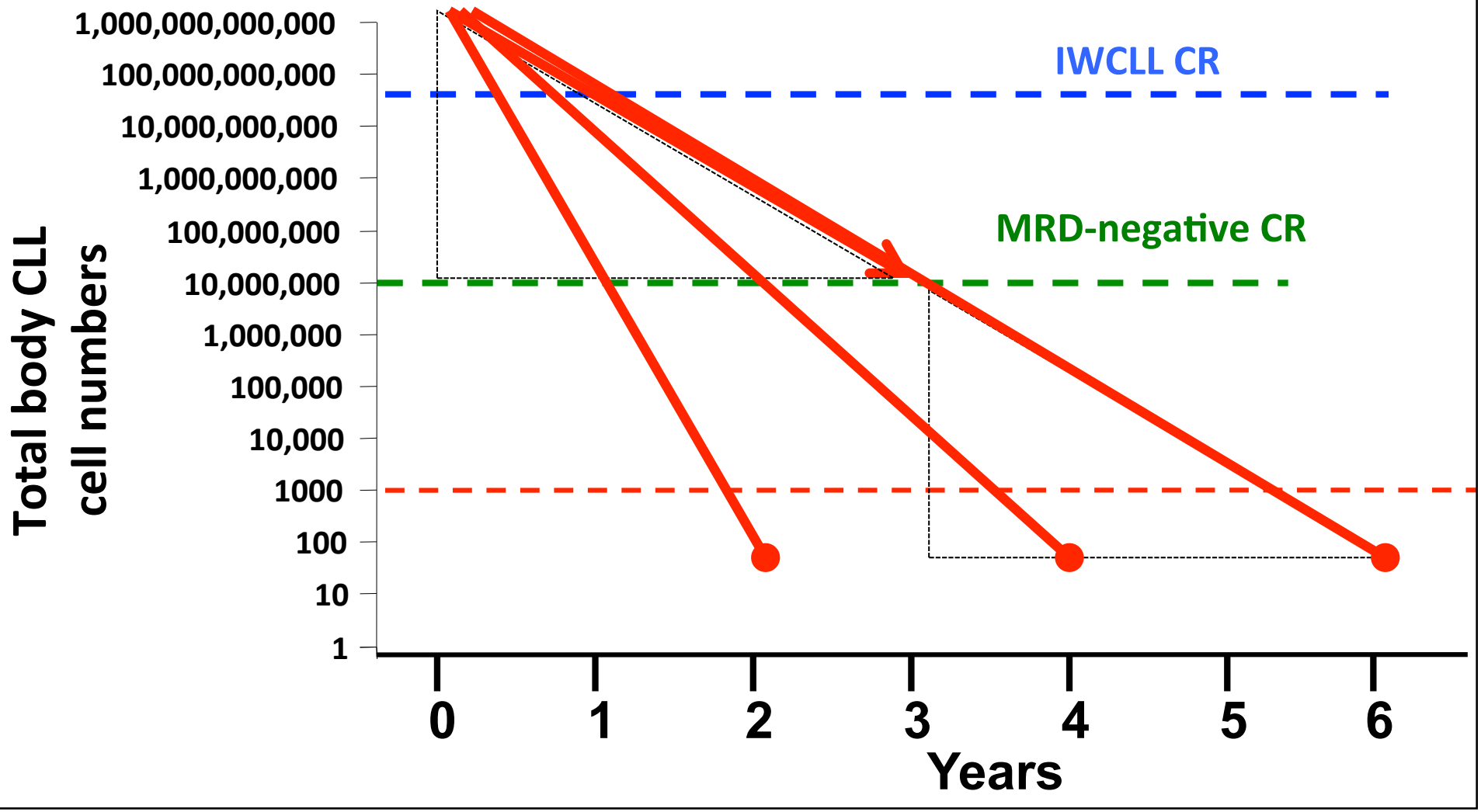

Conclusion: Stopping targeted therapy in CLL

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

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Bloodwise
Beating blood cancer since 1960

Pharmacyclics
Abbvie
Janssen
Roche

Bloodwise TAP Programme

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