Stopping therapy with targeted therapies: will it be possible in the future?

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5th November 2019

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

Is continuous targeted therapy desirable?

Not ideal for all patients – tolerability, resistance and cost

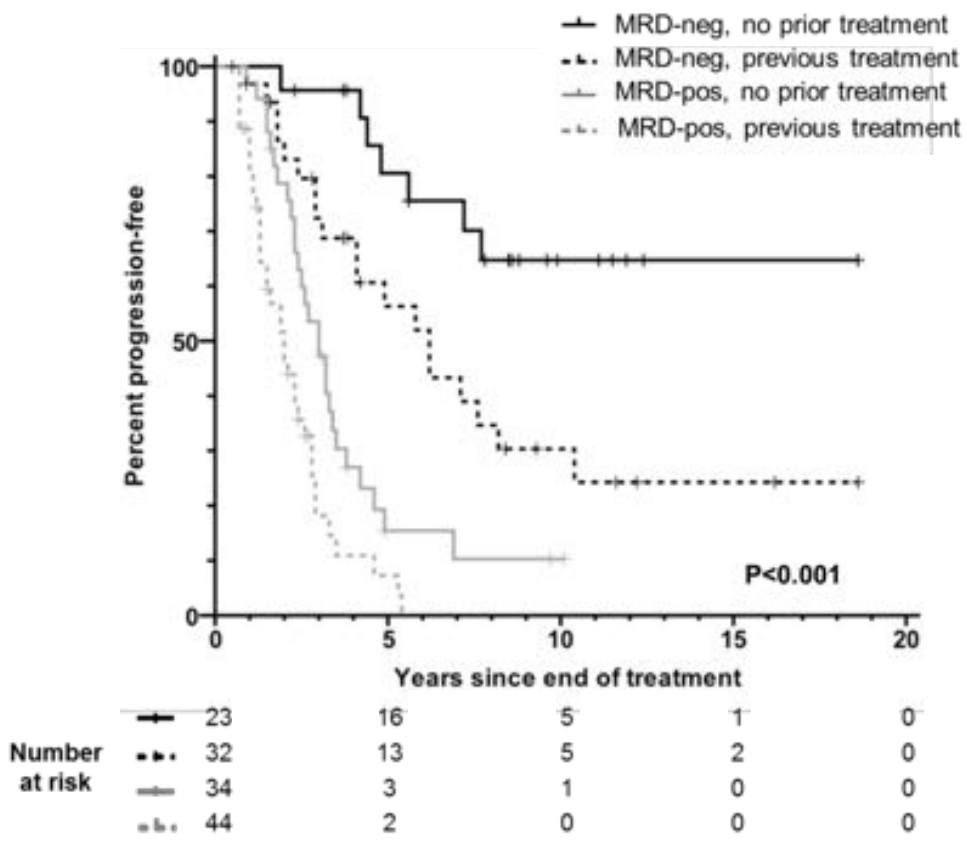
If we are going to stop targeted therapy how should the duration of therapy be defined?

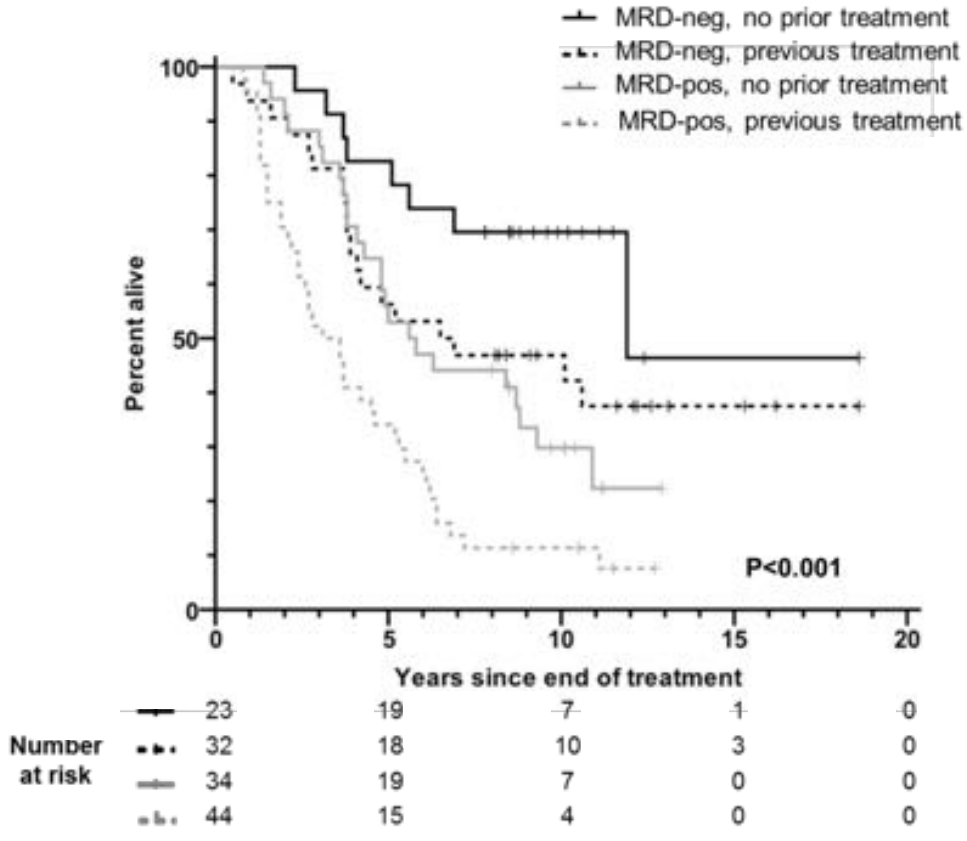
- Fixed duration of therapy for all patients

Or

- Therapy tailored to response in individual patients

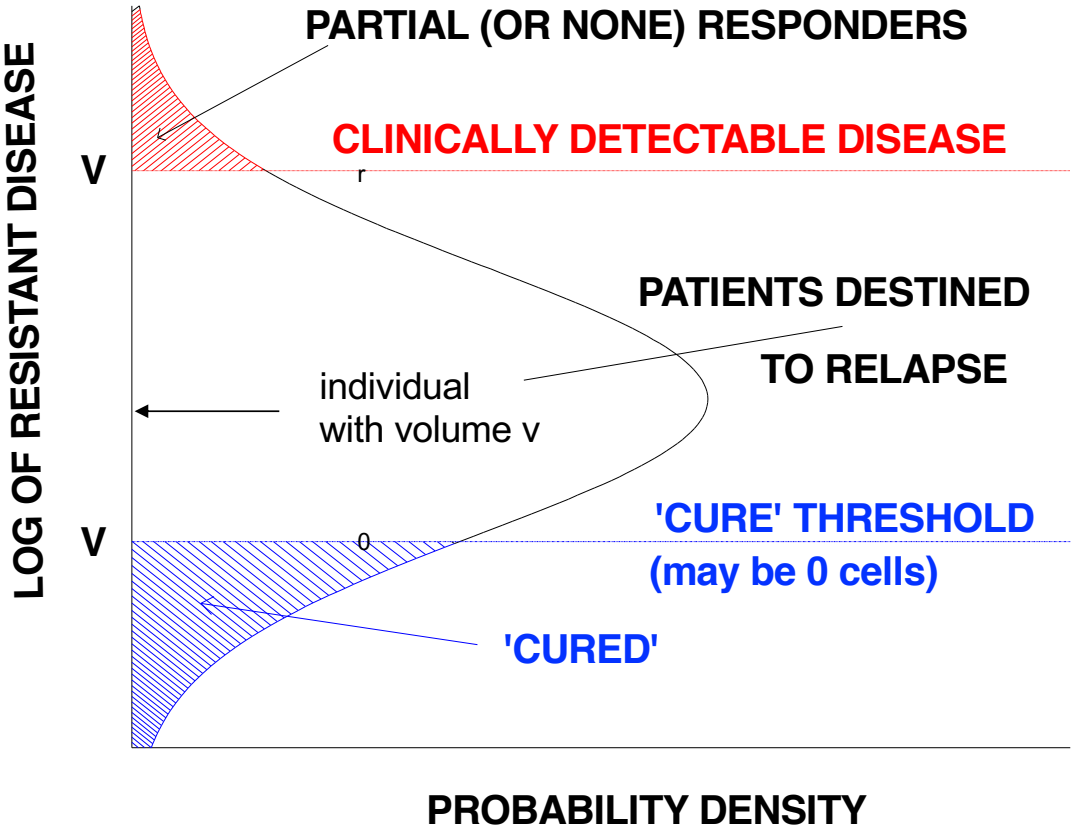
Minimal residual disease eradication predictive in both previously untreated and treated patients





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

Applying mathematical modelling to the treatment of CLL



Full double integral: probability of relapse for the whole population (cdf):

The resistant tumour is log-normally distributed, and not all tumours necessarily achieve CR (v is not always less than V_r). Let the probability of achieving CR be P_c. Then the probability, P, of relapse before a given time t for the whole population is:

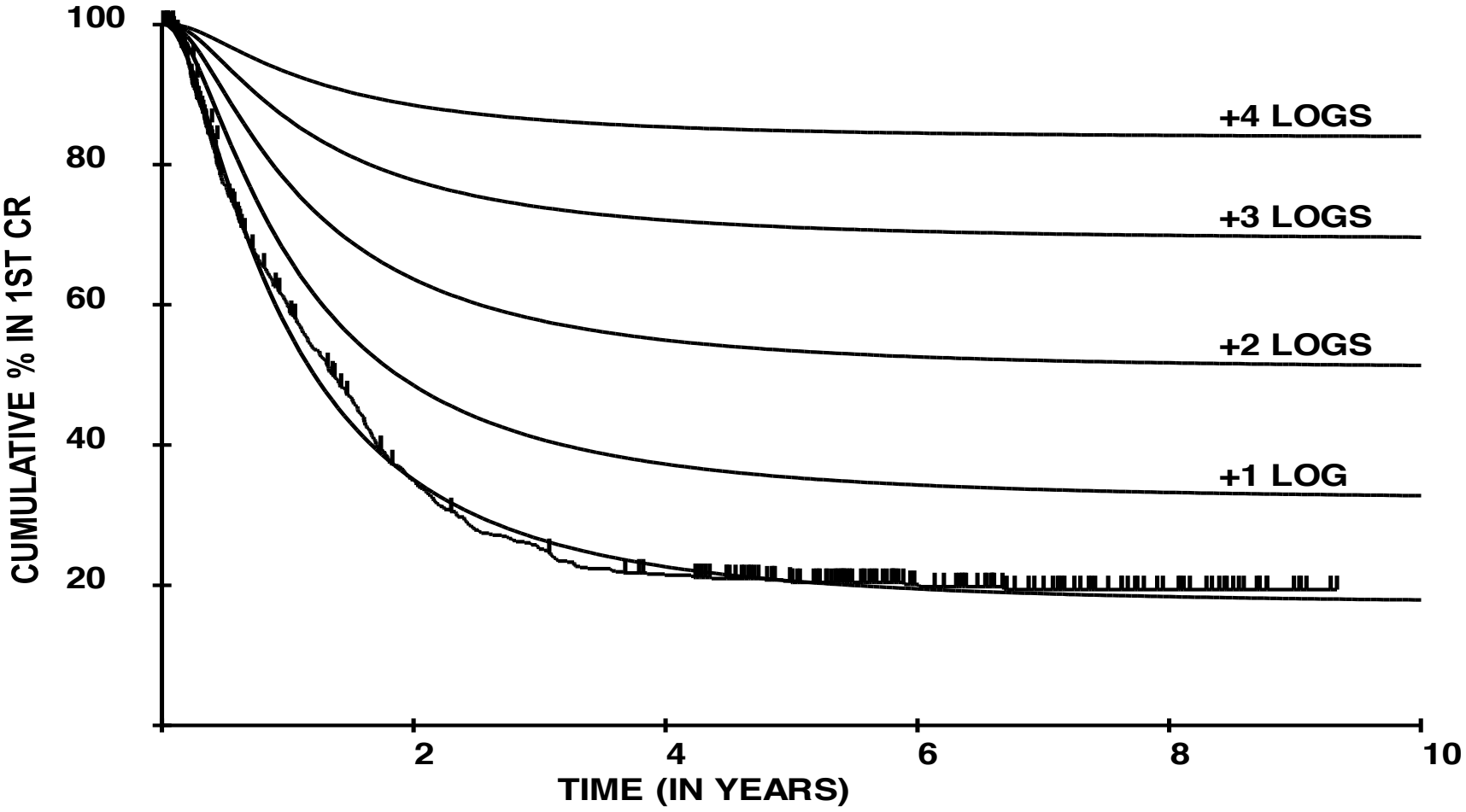
$$P = \frac{\int_{V_0}^{V_r} \left(\frac{1}{\sigma_v\sqrt{2\pi}}\right) exp\left(-\frac{(\mu_v - v)^2}{2\sigma_v{}^2}\right) \int_{-\infty}^{U_t} \left(\frac{1}{\sigma_g\sqrt{2\pi}}\right) exp\left(-\frac{(\mu_g - g)^2}{2\sigma_g{}^2}\right) dg\, dv}{P_c} \qquad (2)$$

where

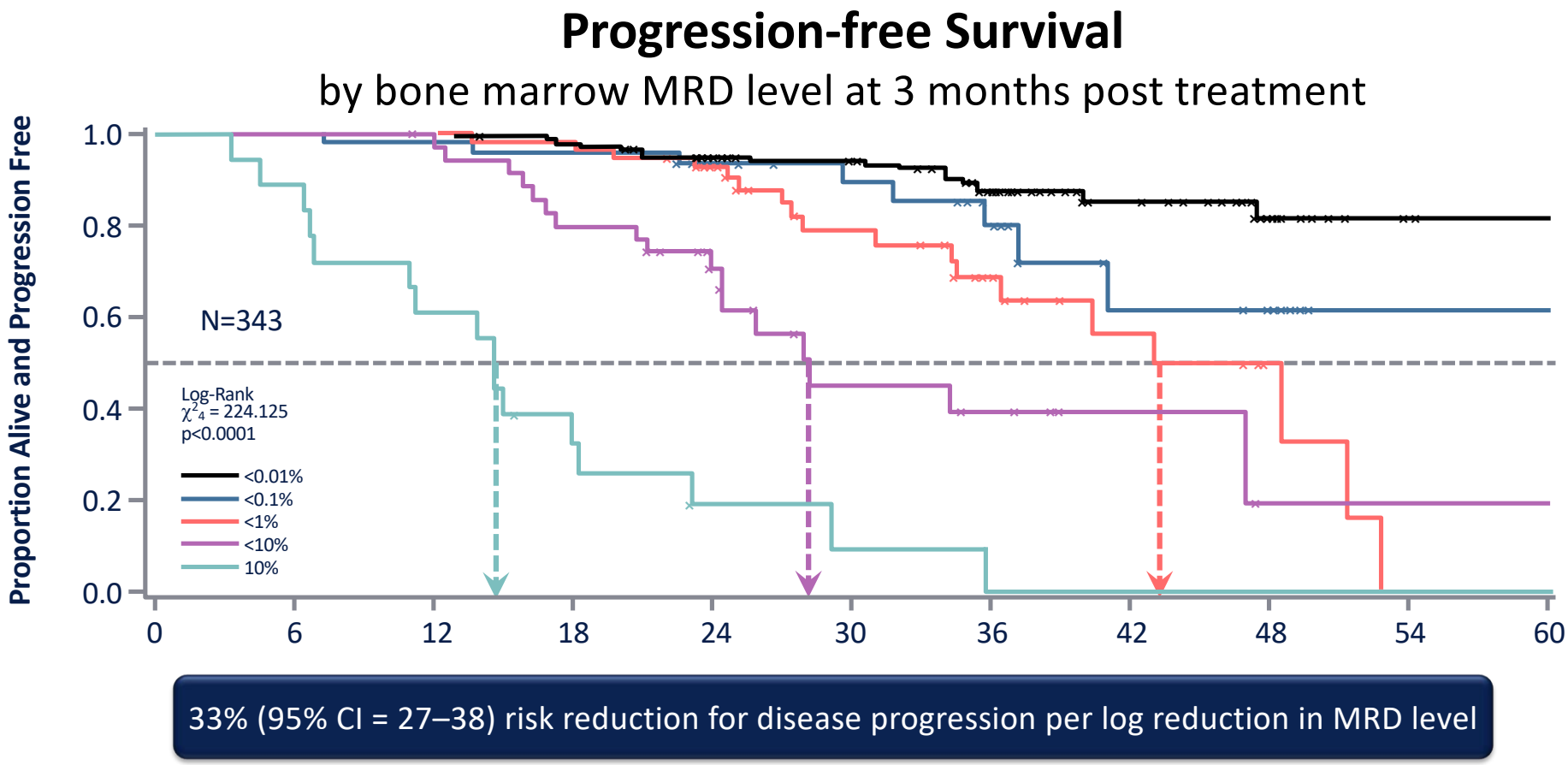
$$P_c = \int_{-\infty}^{V_r} \left(\frac{1}{\sigma_v\sqrt{2\pi}}\right) exp\left(-\frac{(\mu_v - v)^2}{2\sigma_v{}^2}\right) dv \qquad (3)$$

as described.

Hypothesised effect on the duration of 1st CR in AML of reductions in the log of resistant disease (1 log increments)



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

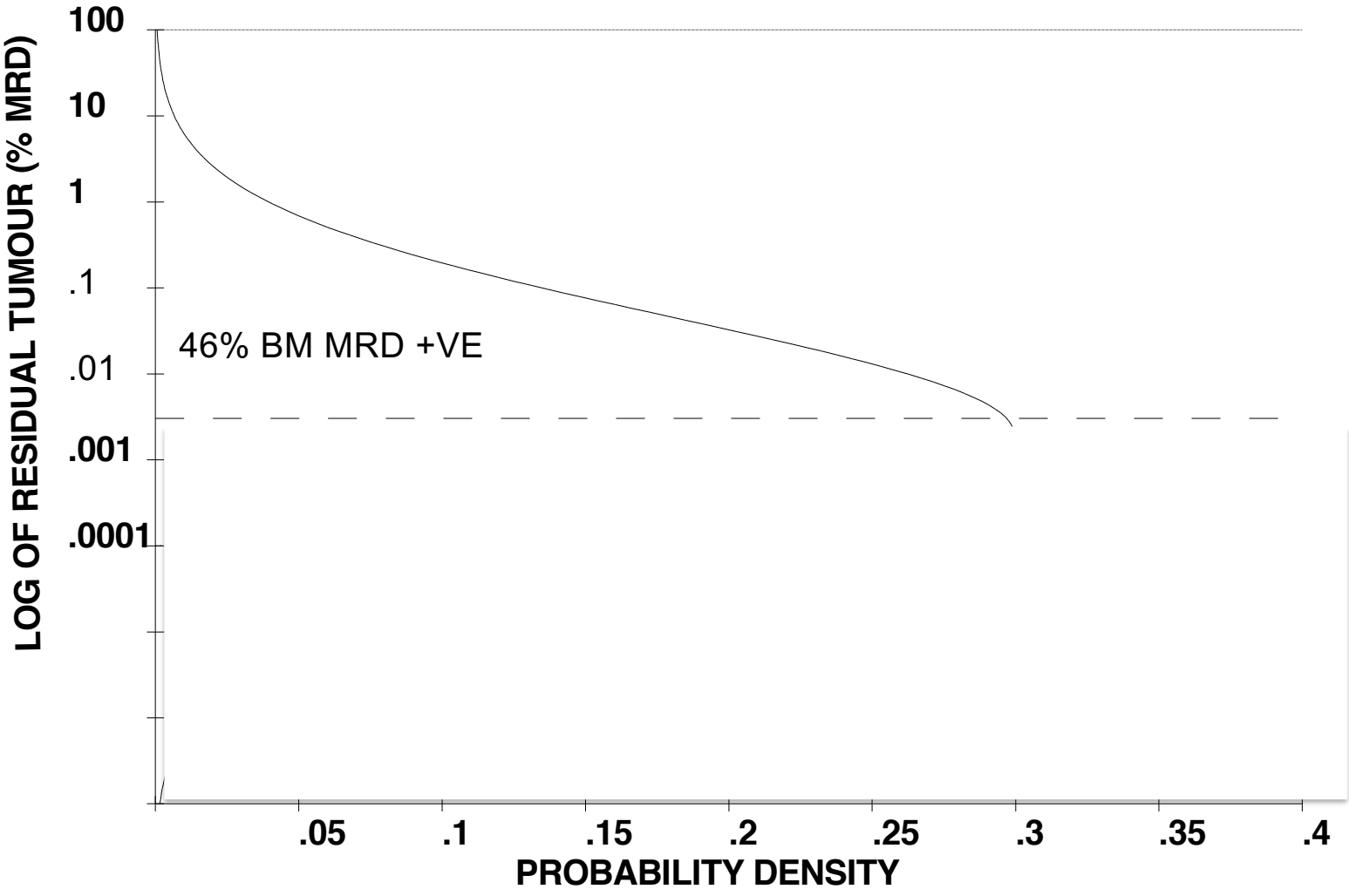


33% (95% CI = 27–38) risk reduction for disease progression per log reduction in MRD level

FCR, fludarabine, cyclophosphamide, rituximab.

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

Normal distribution of MRD identifies a subset of "cured" patients (ADMIRE/ARCTIC)



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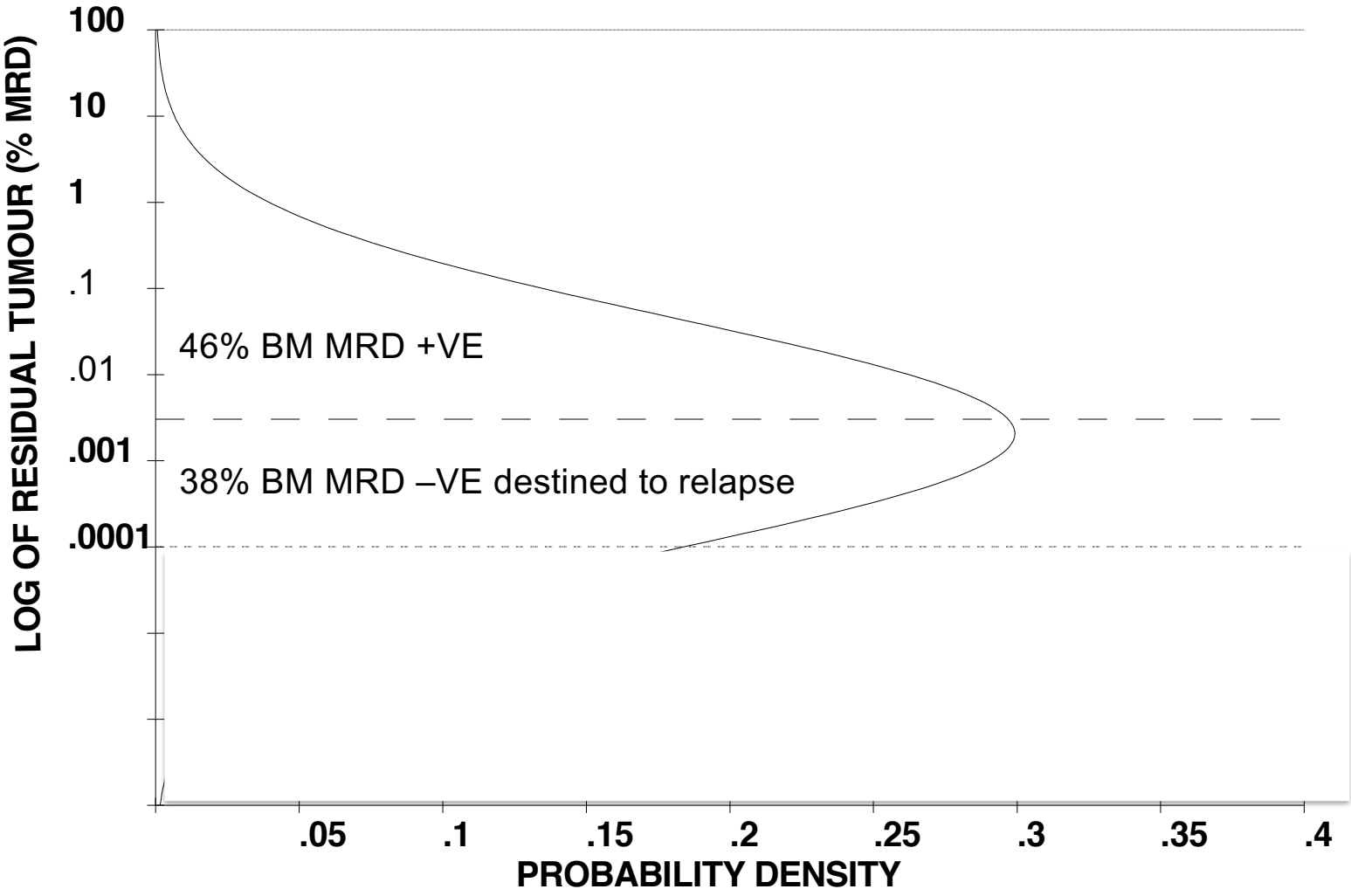

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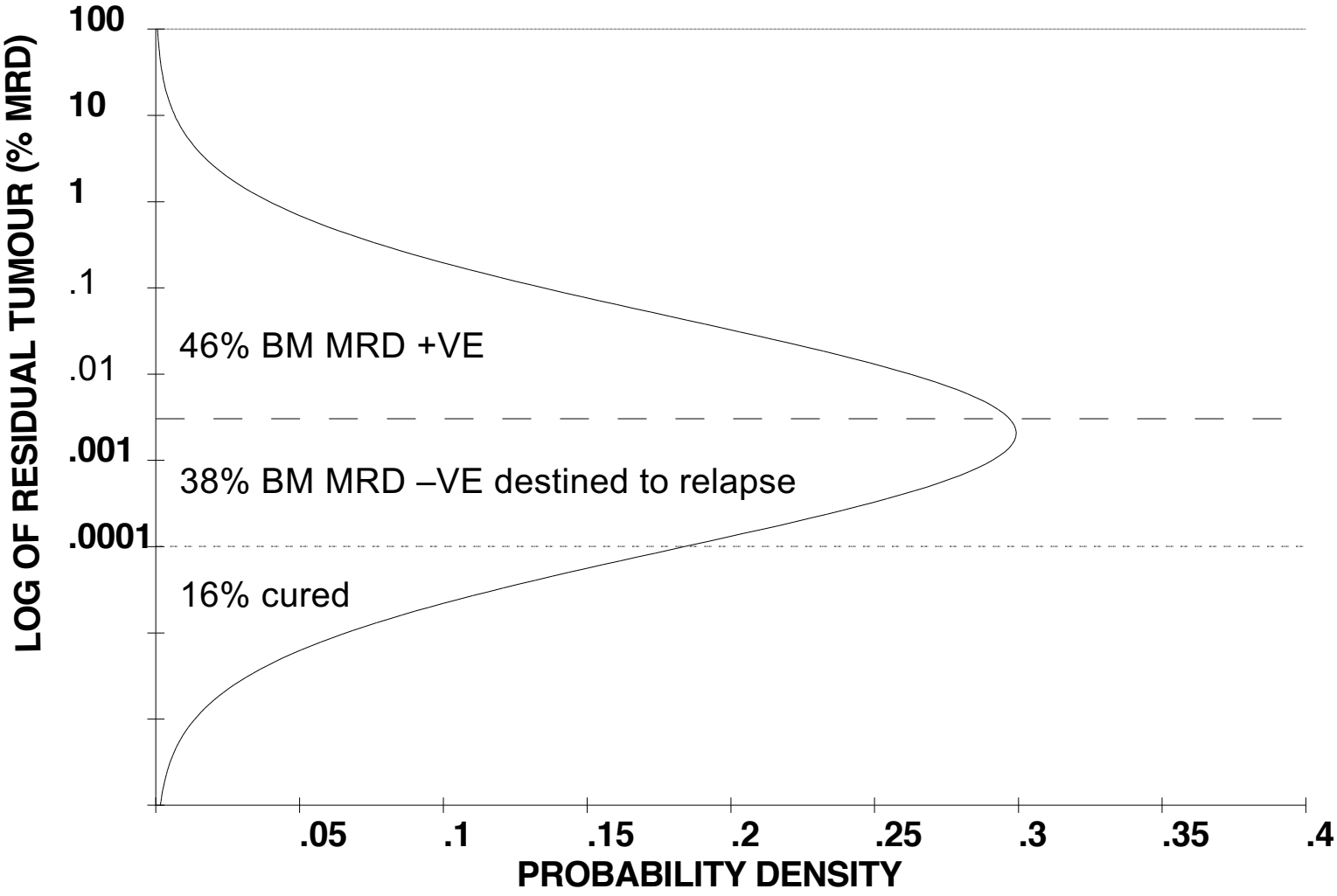
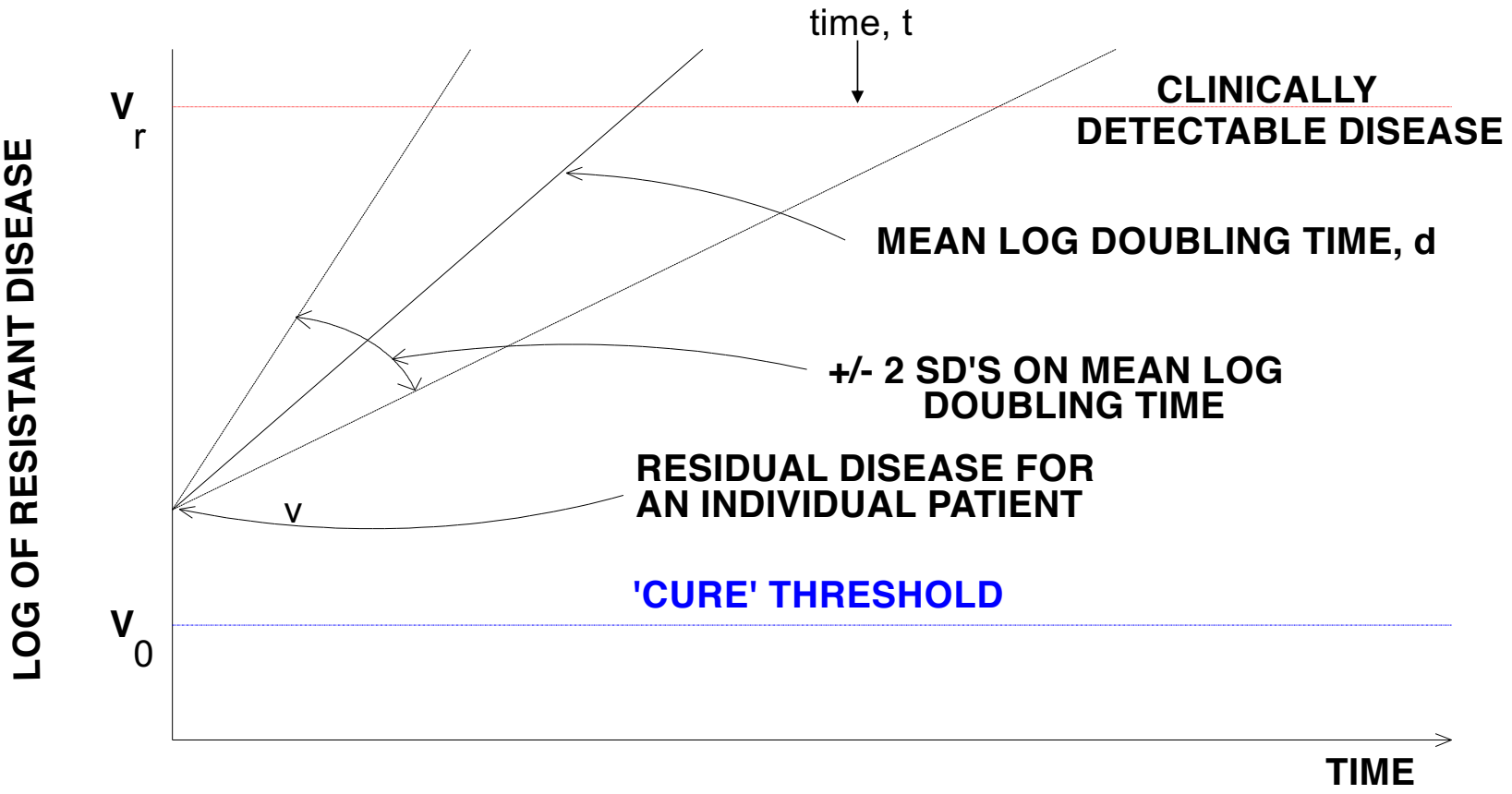
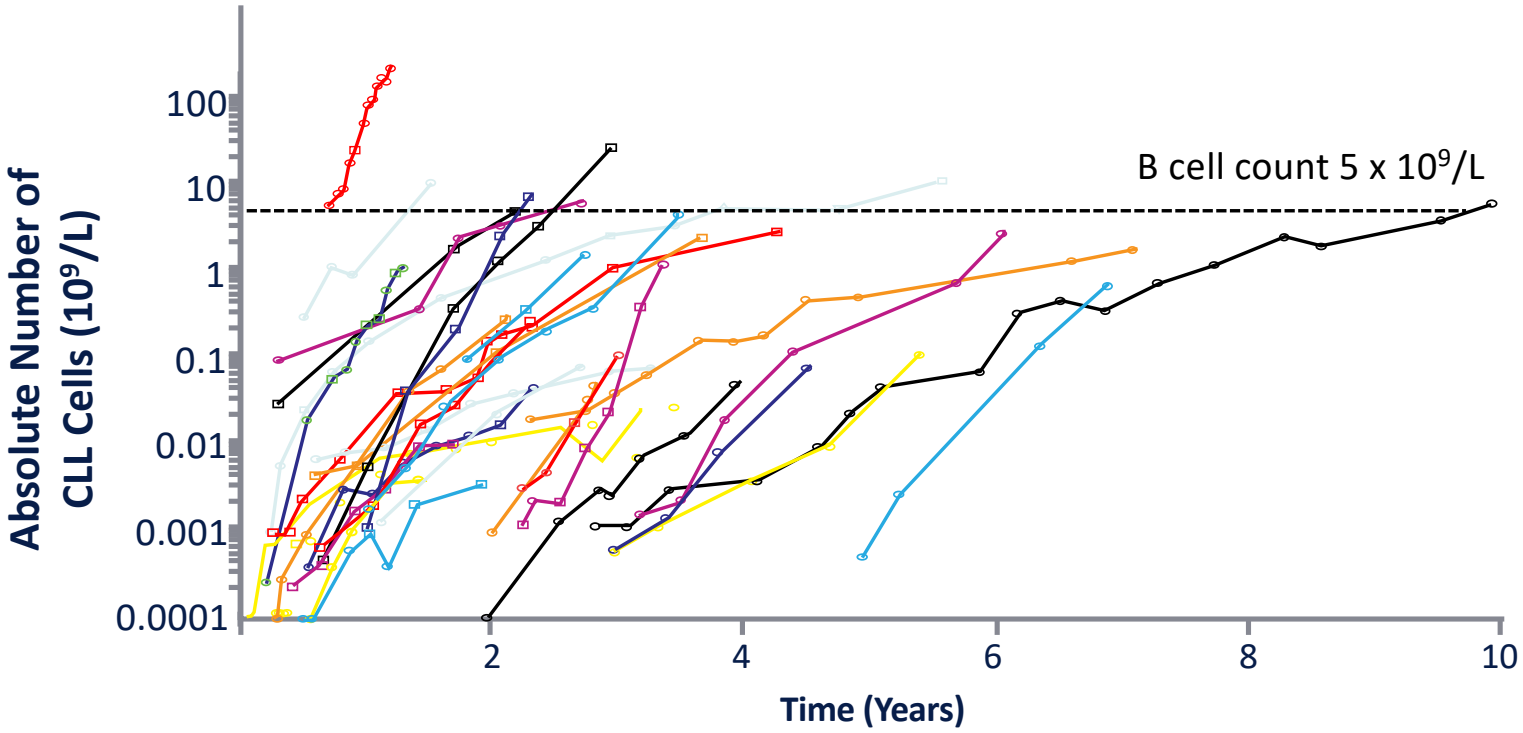


Assumed regrowth rates of resistant disease



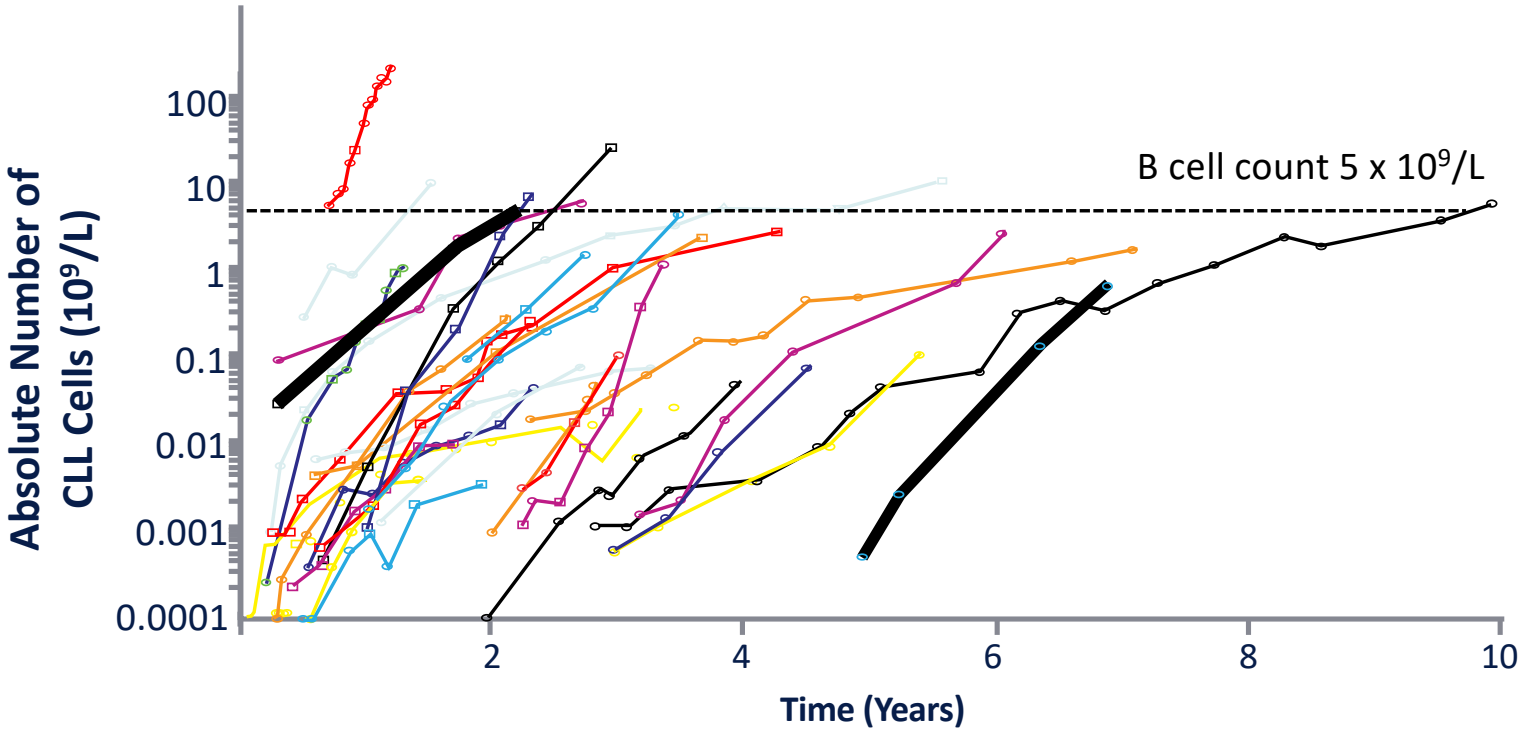
Kinetics of Relapse: Exponential Growth from the Lowest Detectable MRD Level



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.

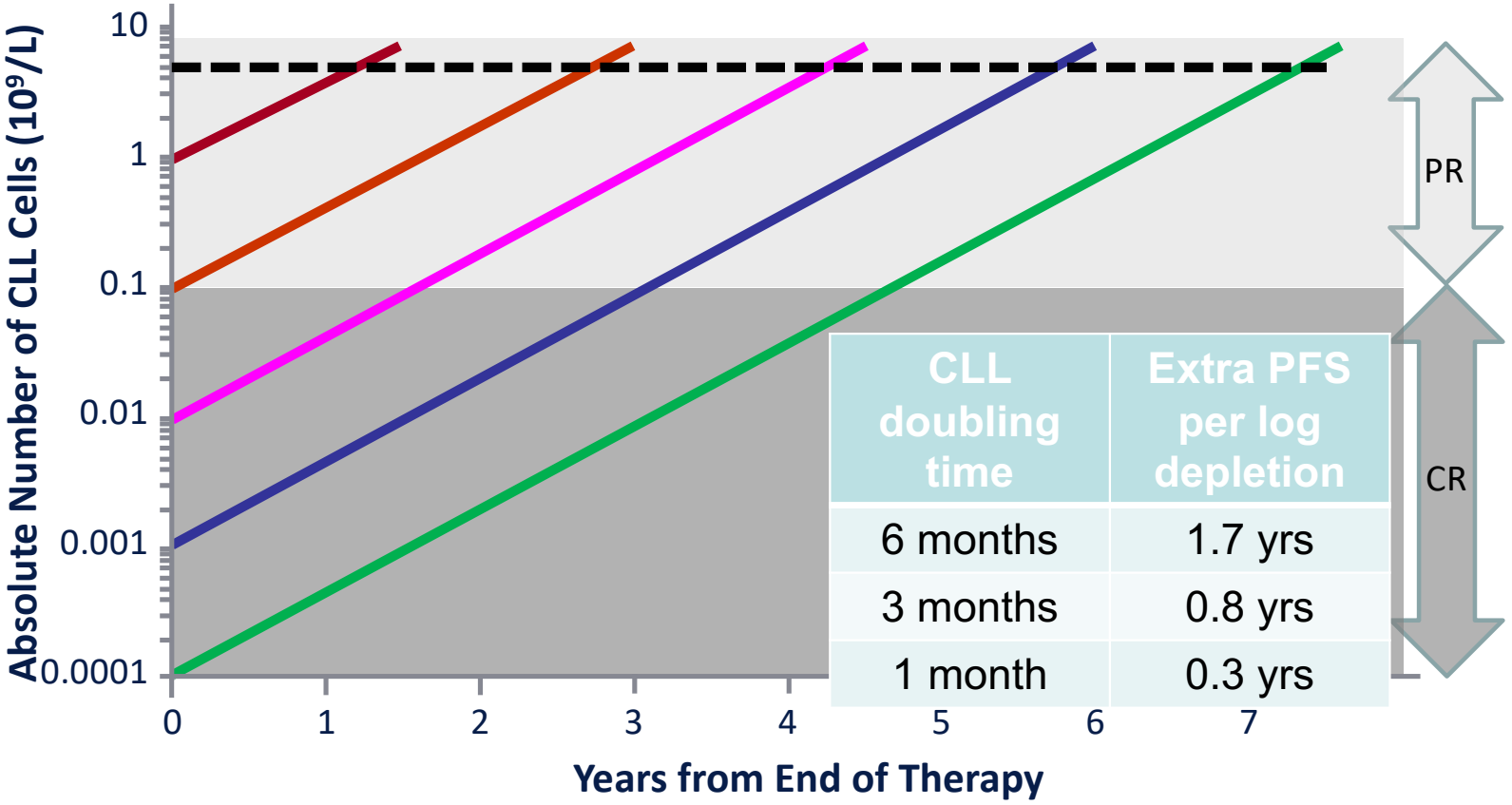
Kinetics of Relapse: Exponential Growth from the Lowest Detectable MRD Level



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.

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.

Regulatory approval of MRD in CLL

October 2014

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 as an endpoint in chronic lymphocytic leukaemia studies

Executive summary

Minimal residual disease (MRD) negativity in patients in clinical complete remission (= MRD response rate) after induction therapy may be used as an intermediate endpoint for licensure in randomised well controlled studies designed to show superiority in terms of PFS. This requires that the benefit/risk of the experimental regimen is well characterised in CLL and that these data would support the superiority of the regimen over established regimens used as induction therapy in CLL.

September 2018

News >

FDA Updates Venetoclax CLL Label With MRD Data

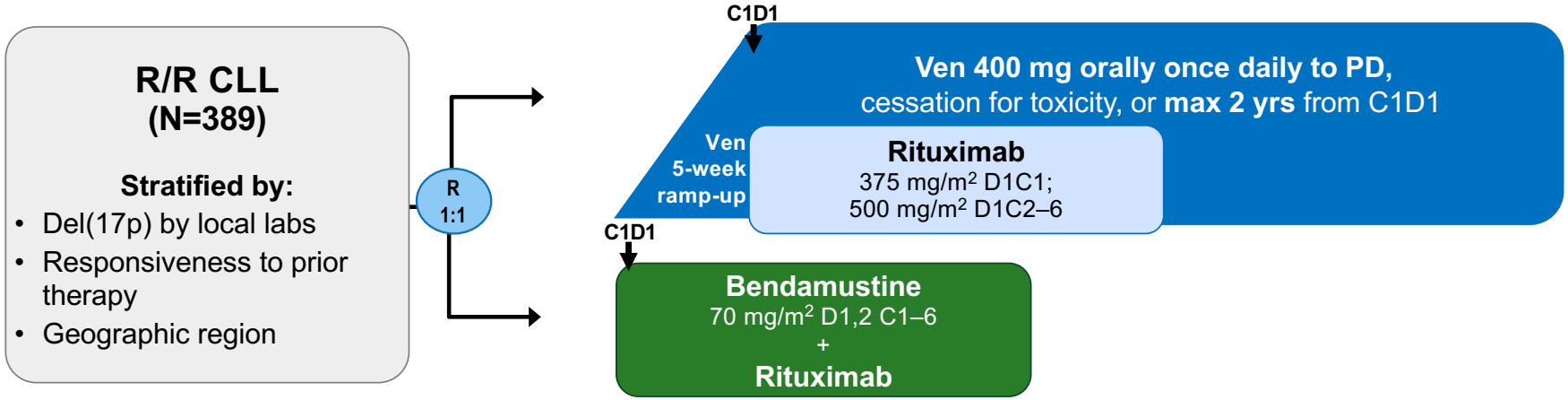
Jason M. Broderick @jasoncology
Published: Tuesday, Sep 11, 2018

MURANO trial establishes feasibility of time-limited venetoclax-rituximab combination therapy in relapsed/refractory chronic lymphocytic leukemia

John F Seymour,[1] Thomas J Kipps,[2] Barbara Eichhorst,[3] Peter Hillmen,[4] James D'Rozario,[5] Sarit Assouline,[6] Carolyn Owen,[7] Tadeusz Robak,[8] Javier de la Serna,[9] Ulrich Jaeger,[10] Guillaume Cartron,[11] Marco Montillo,[12] Nicole Lamanna,[13] Maria Verdugo,[14] Elizabeth A Punnoose,[15] Yanwen Jiang,[15] Jue Wang,[15] Michelle Boyer,[16] Kathryn Humphrey,[16] Mehrdad Mobasher,[15] Arnon P Kater[17]

[1]Peter MacCallum Cancer Centre, Royal Melbourne Hospital, and University of Melbourne, Melbourne, Australia; [2]University of California School of Medicine, San Diego, CA, USA; [3]University of Cologne, Cologne, Germany; [4]St. James' University Hospital, Leeds, United Kingdom; [5]The John Curtin School of Medical Research, Australian National University, Canberra, Australia; [6]Segal Cancer Center, Lady Davis Institute, Jewish General Hospital, Montreal, Canada; [7]University of Calgary, Calgary, Canada; [8]Medical University of Lodz, Copernicus Memorial Hospital, Lodz, Poland; [9]Hospital Universitario 12 de Octubre, Madrid, Spain; [10]Medical University of Vienna, Vienna, Austria; [11]University Hospital Montpellier, Montpellier, France; [12]Niguarda Cancer Center, ASST Grande Ospedale Metropolitano Niguarda, Milan, Italy; [13]Columbia University Medical Center, New York, NY, USA; [14]AbbVie, North Chicago, IL, USA; [15]Genentech Inc, South San Francisco, CA, USA; [16]Roche Products Limited, Welwyn Garden City, United Kingdom; [17]Amsterdam UMC, University of Amsterdam, Hovon CLL working group, The Netherlands

MURANO study: Venetoclax+rituximab in relapsed CLL

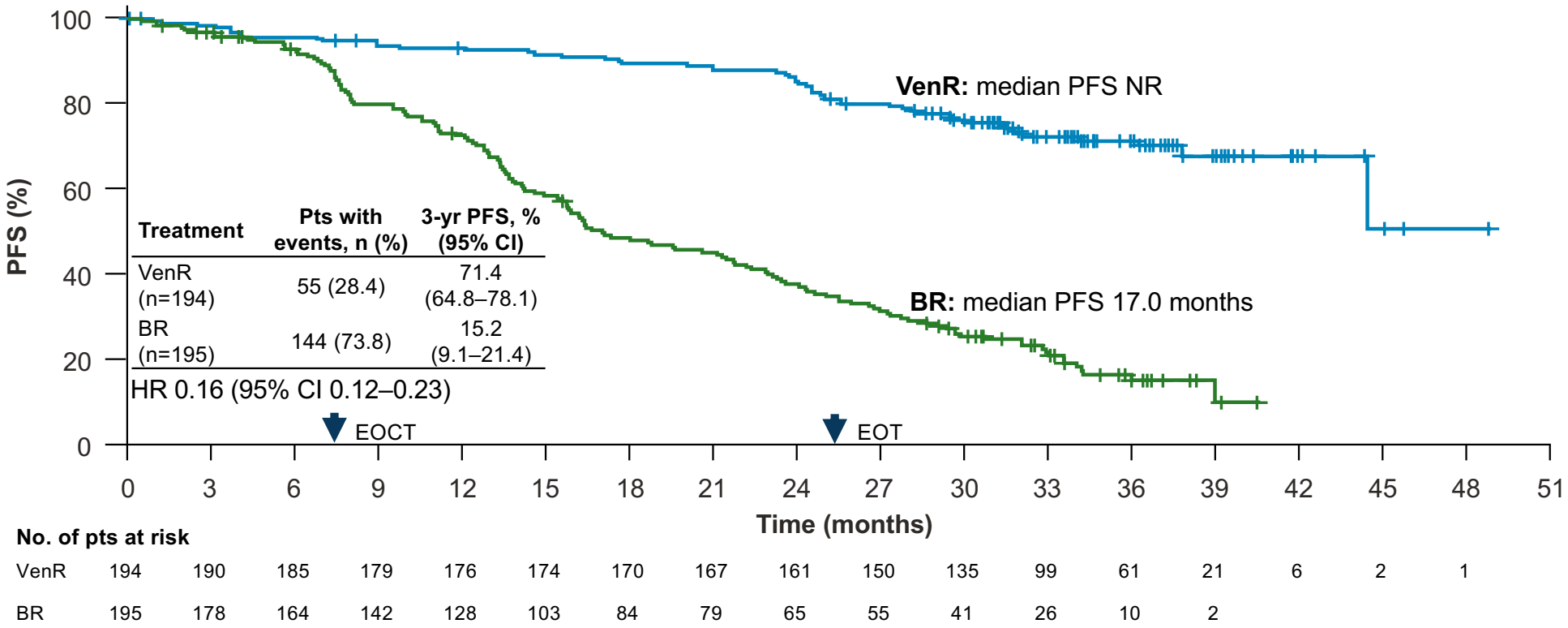


- Primary endpoint: investigator-assessed PFS; secondary endpoints include rate of undetectable MRD (uMRD)
- Clinical response and MRD in PB/BM during Ven single-agent and at follow-up visits were assessed every 3 mo for 3 yrs, then every 6 mo thereafter or until PD
- Primary analysis was pre-planned at 140 PFS events; this follow-up analysis was conducted 1 yr later

BM, bone marrow; C, cycle; D, day; PB, peripheral blood; R, randomized.

Seymour JF, et al. N Engl J Med 2018;378:1107–20.

“Protracted” treatment free interval & prolonged survival:
Venetoclax (2 years) + rituximab in relapsed CLL (MURANO Trial)

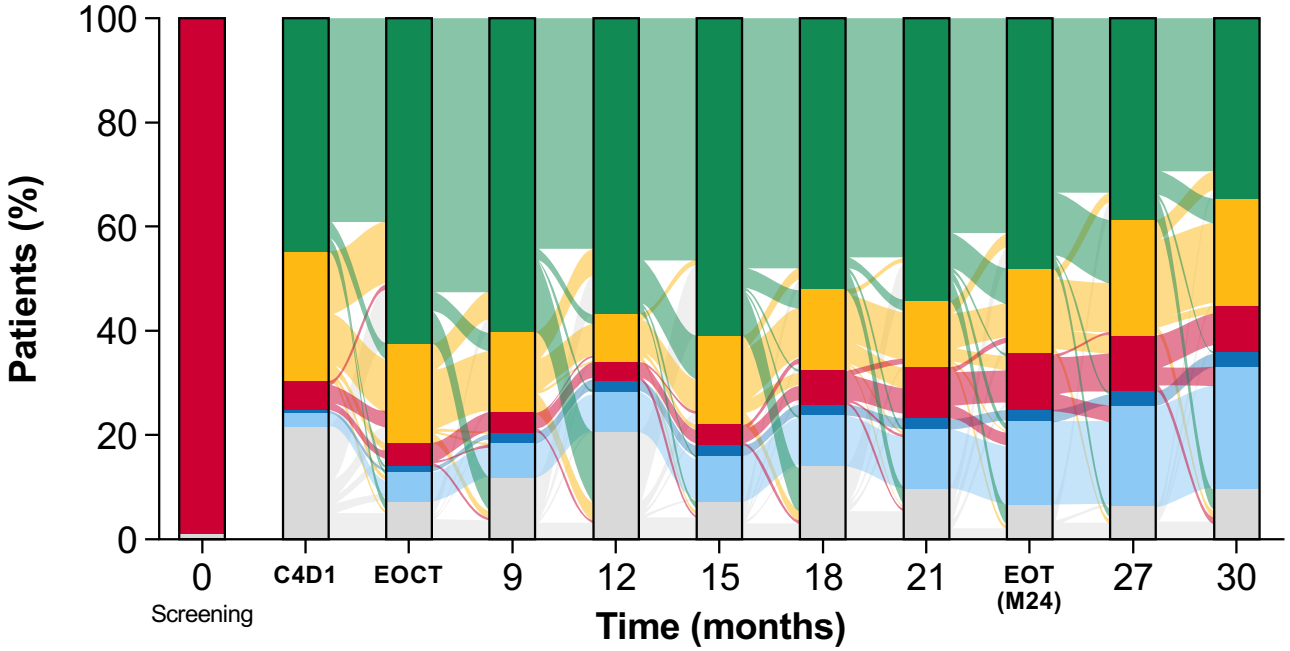


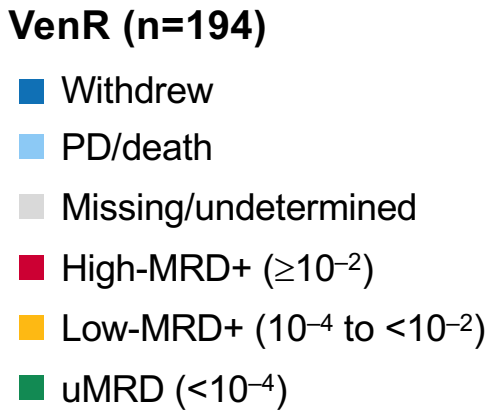
- Median follow-up 36.0 mo (range 0.0–48.6); VenR 36.1 mo, BR 35.9 mo

Data cut-off date: May 8, 2018

Seymour J *et al,* ASH, 2018

MRD status over time in VenR arm: high uMRD rate is sustained



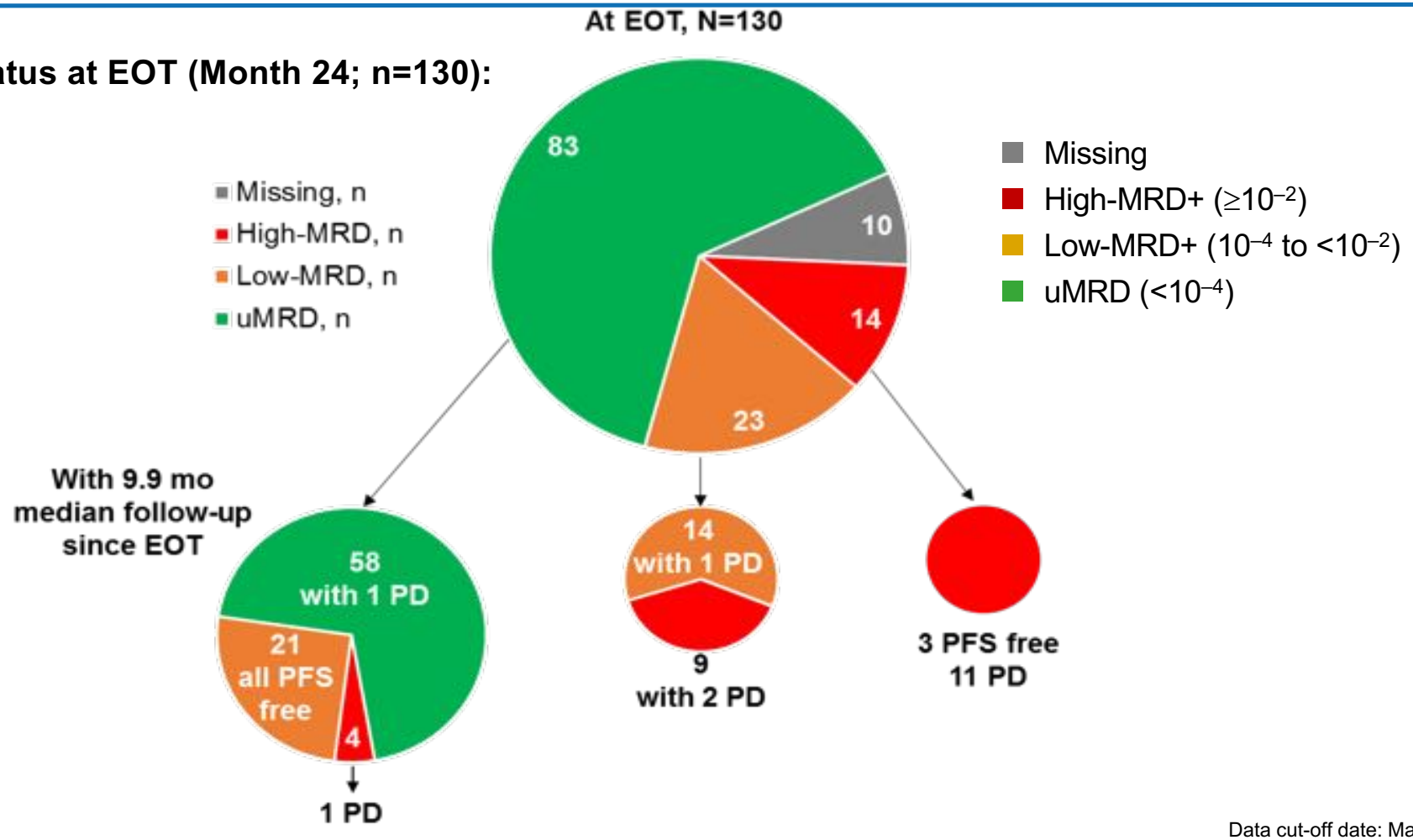


- Few low-MRD+ pts progressed
- Pts who did progress had mainly converted to high-MRD+ first

Data cut-off May 8, 2018; median follow-up: 36.0 months. Missing values also include pts who have not yet reached the time point

After cessation of Ven monotherapy at EOT most patients did not progress

MRD status at EOT (Month 24; n=130):



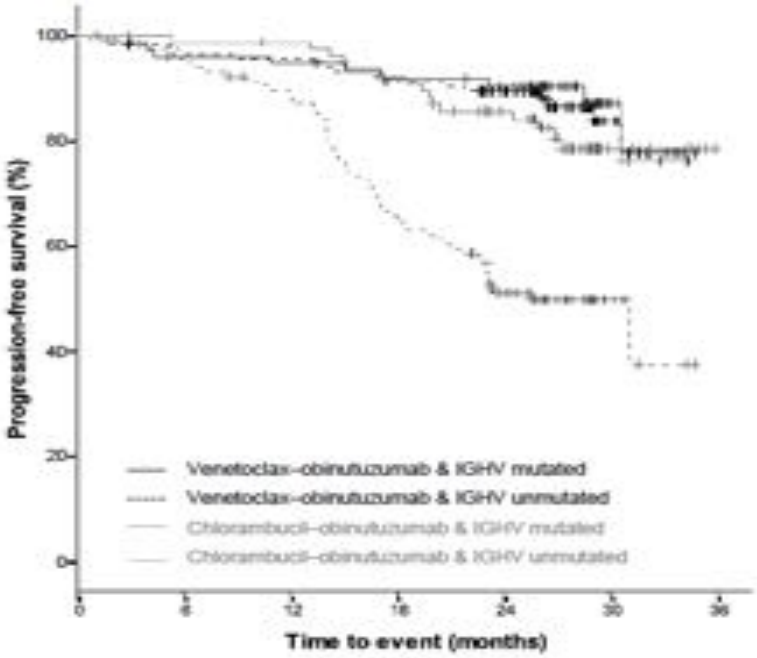
Data cut-off date: May 8, 2018

GCLLSG CLL14 Trial:

Venetoclax+obinutuzumab vs Chlorambucil+obinutuzumab

12 month fixed duration of therapy in both arms

PFS by V_H mutation status



Fischer *et al.*, N Engl J Med 2019;380:2225-32.

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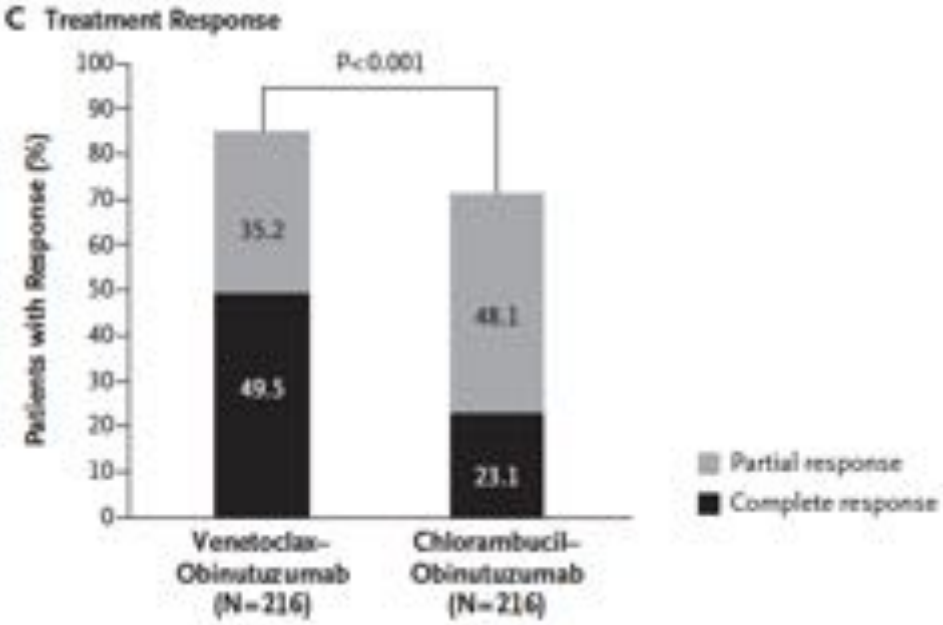


Minimal residual disease status by ASO-PCR in marrow

	Venetoclax + obinutuzumab (N=216)	Chlorambucil + obinutuzumab (N=216)
Negative	123 (56.9%)	37 (17.1%)
Non-negative including	93 (43.1%)	179 (82.9%)
Positive	25 (11.6%)	109 (50.5%)
Non-response	18 (8.3%)	21 (9.7%)
Progression, relapse, death	5 (2.3%)	13 (6%)
Withdrawal from trial	5 (2.3%)	3 (1.4%)
Non-evaluable sample	8 (3.7%)	3 (1.4%)
Missing sample	32 (14.8%)	30 (13.9%)

Fischer *et al.*, N Engl J Med 2019;380:2225-32.

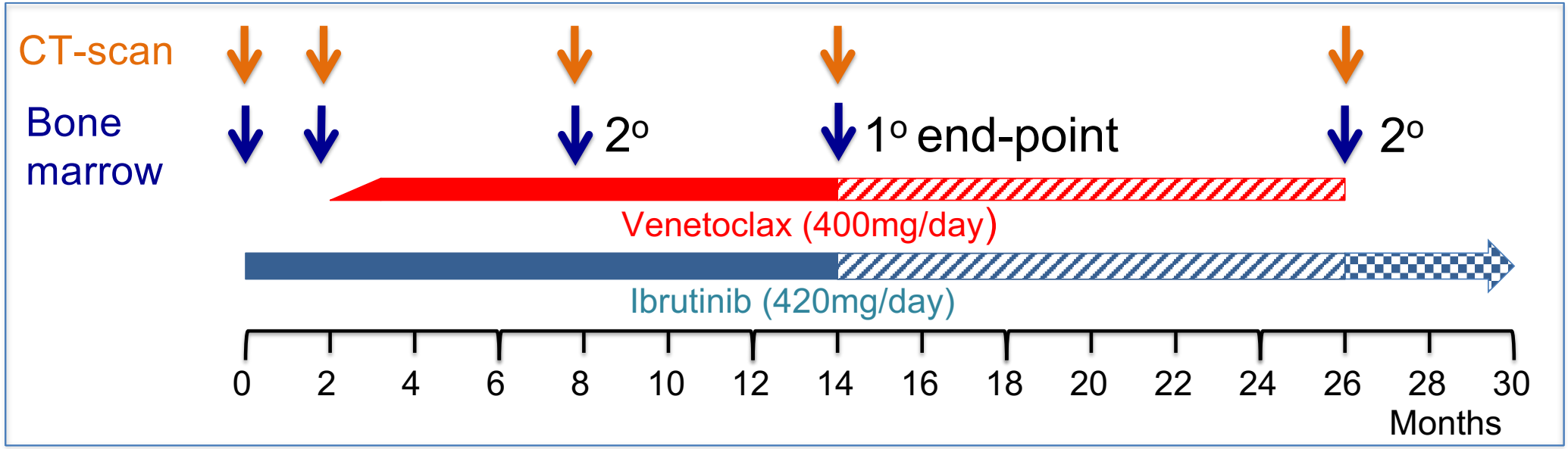
Ibrutinib Plus Venetoclax in Relapsed, Refractory CLL: Results of the Bloodwise TAP CLARITY Study

Peter Hillmen, Andy Rawstron, Kristian Brock, Samuel Muñoz-Vicente, Francesca Yates, Rebecca Bishop, Donald MacDonald, Christopher Fegan, Alison McCaig, Anna Schuh, Andrew Pettitt, John G. Gribben, Piers Patten, Stephen Devereux, Adrian Bloor, Christopher P. Fox, Francesco Forconi, Talha Munir

Abstract: 182

Saturday, December 1, 2018: 2:15 PM

Treatment Schedule and Stopping Rules



Stopping rules: Duration of therapy is double time to MRD4 negative

1) MRD negative (<0.01%) at M8 stop I+V at M14
2) MRD negative (<0.01%) at M14 or M26 stop I+V at M26
3) MRD positive (≥0.01%) at M26 continue ibrutinib monotherapy

Hillmen *et al.* ASH 2018; Abst 182

IWCLL Responses in rel/refr CLL Month 14 (12 months I+V)

	No.	CR	CRi	PR	ORR
All patients*	**49**	**22 (44%)**	**5 (10%)**	**20 (40%)**	**47 (94%)**
FCR/BR relapsed <36 months[1]	20	8 (40%)	2 (10%)	9 (45%)	19 (95%)
Prior idelalisib[2]	9	3 (33%)	1 (11%)	4 (44%)	8 (89%)

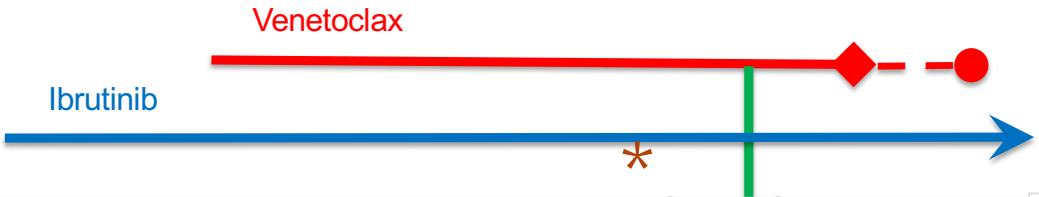
[1] Percentages calculated over the total number of patients who had FCR/BR and relapsed <36 months and have been assessed for response
[2] Percentages calculated over the total number of patients who had Idelalisib before joining the study and have been assessed for response

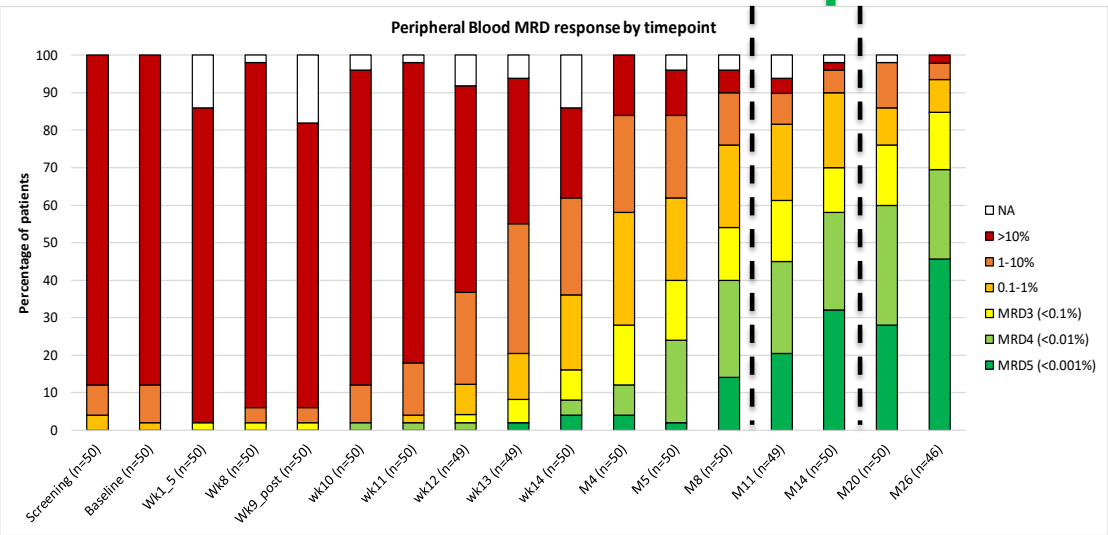
Date of data lock: 05 November 2018

Hillmen *et al.* ASH 2018; Abst 182

MRD level by time-point (up to Month 26)

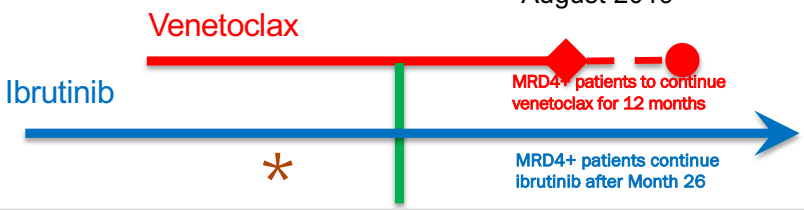
Peripheral Blood

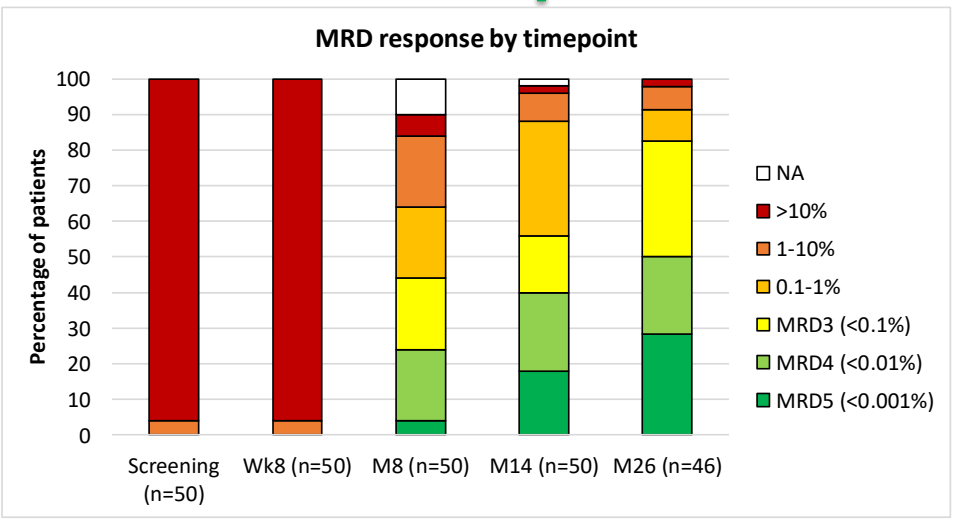




Bone Marrow

Date of data lock: 2nd August 2019

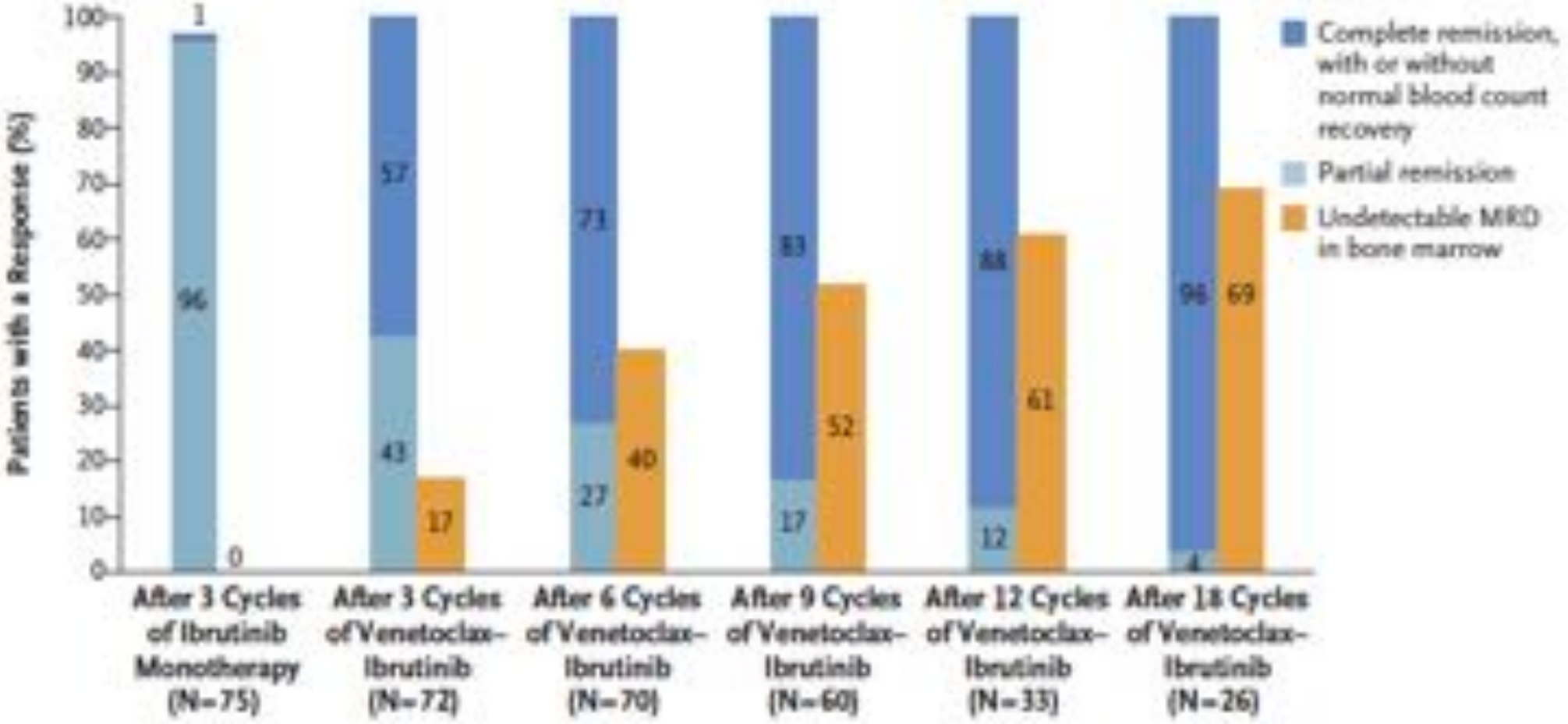




*PB & BM MRD negative pts at Month 8 & 14 stop I+V → All 16/17 reaching M26 remain MRD negative to date

Munir *et al.* IWCLL 2019

Responses Improve with Ongoing Ibrutinib + Venetoclax Therapy in previously untreated CLL

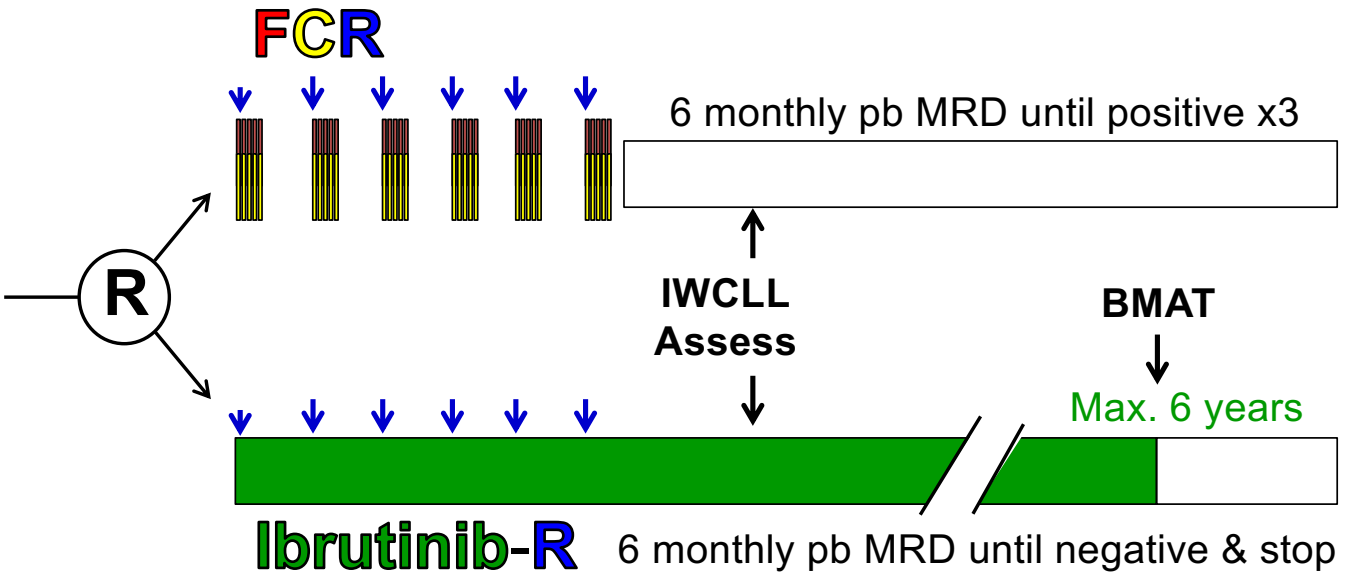


Jain *et al.*, N Engl J Med 2019;380:2095-103.

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

Front Line therapy in CLL: Assessment of Ibrutinib plus Rituximab

Patients with CLL requiring therapy by IWCLL Criteria (n=754)

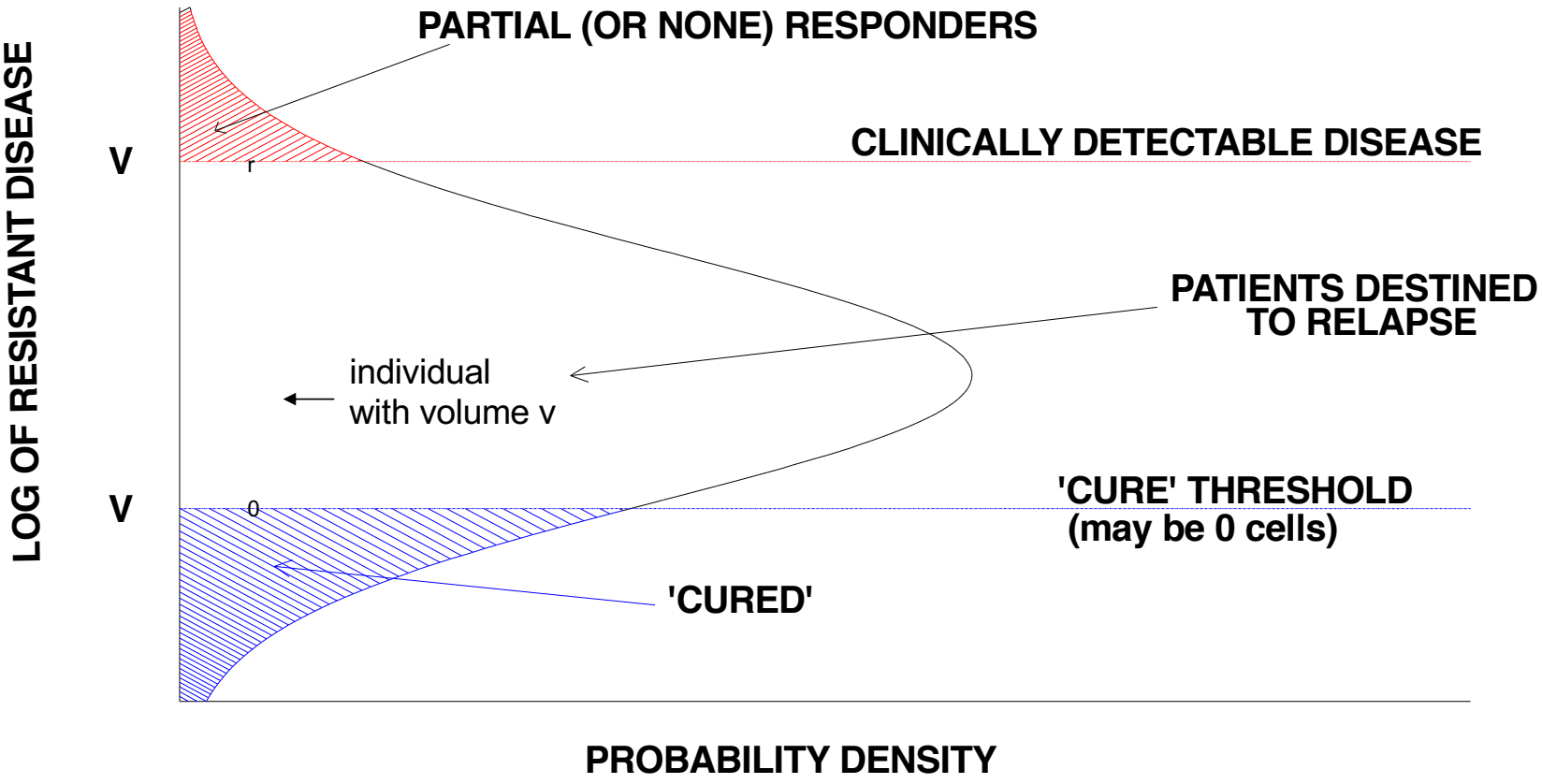


NCRI National Cancer Research Institute
Partners in cancer research

CANCER RESEARCH UK

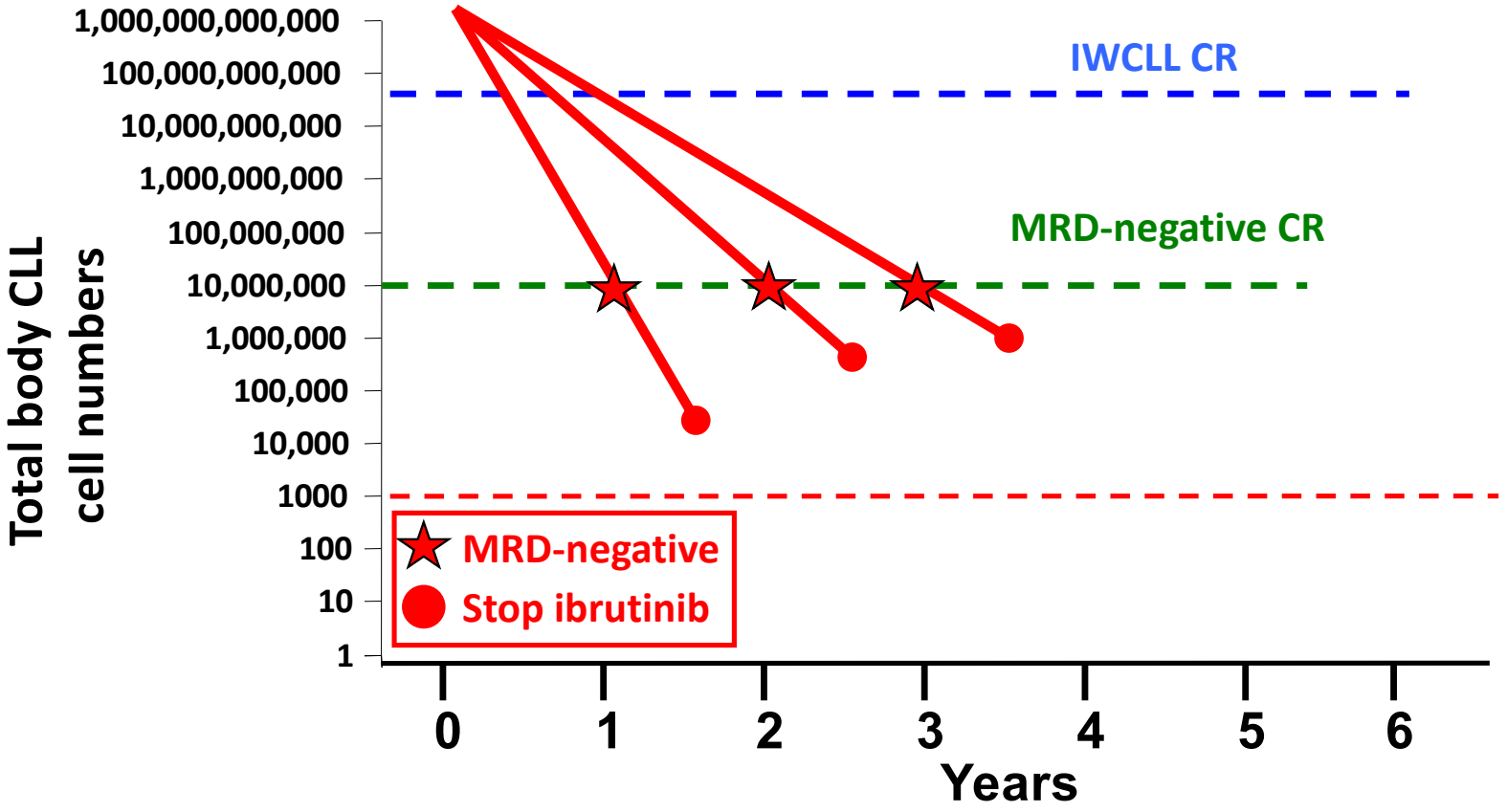
ctru University of Leeds

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



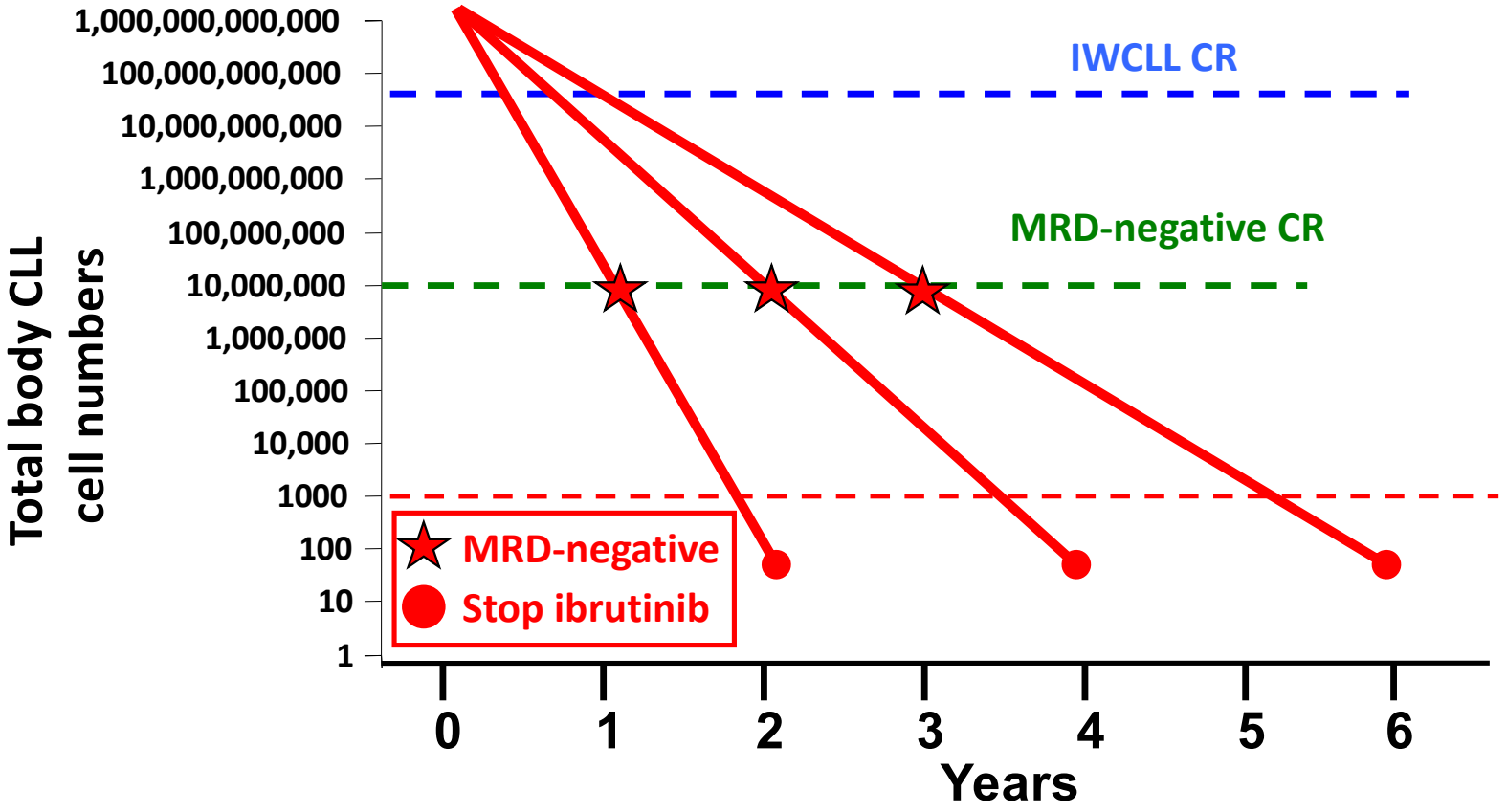
When to stop targeted therapy in CLL?

Original stopping rule in FLAIR – 6 months post MRD negativity

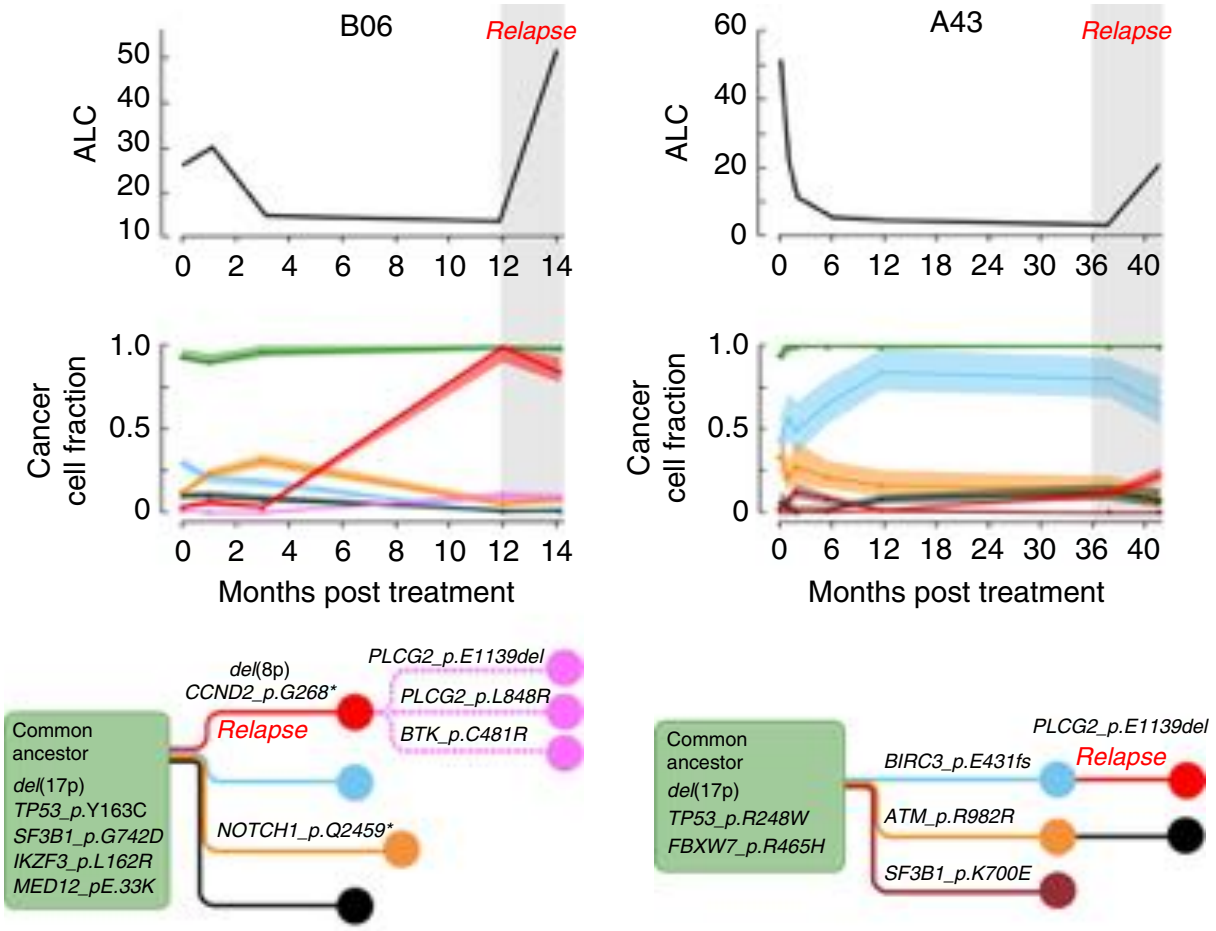


When to stop targeted therapy in CLL?

Modified stopping rule in FLAIR
- double time to MRD negativity



The evolutionary landscape of chronic lymphocytic leukemia treated with ibrutinib targeted therapy



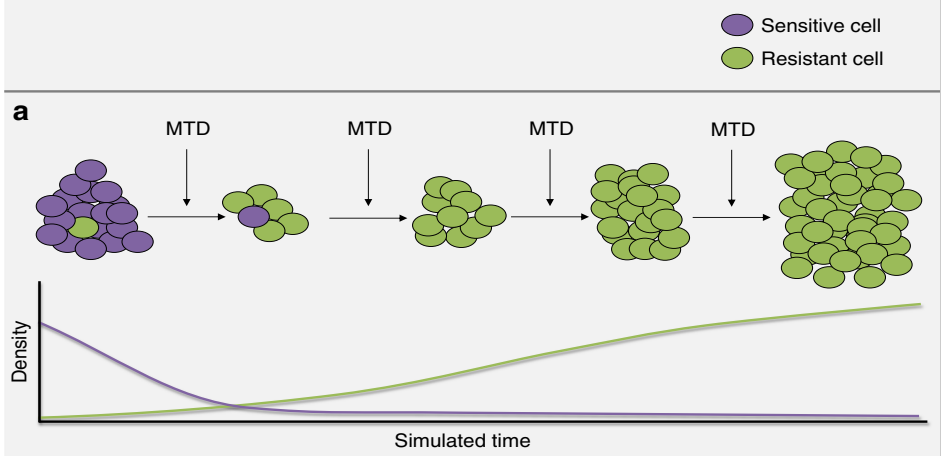
Landau *et al.,* Nature Comm, 2018; 8: 2185

NATURE COMMUNICATIONS | 8: 1816 | DOI: 10.1038/s41467-017-01968-5 | www.nature.com/naturecommunications

Integrating evolutionary dynamics into treatment of metastatic castrate-resistant prostate cancer

Jingsong Zhang[1], Jessica J. Cunningham[2], Joel S. Brown[2,3] & Robert A. Gatenby[2,4]

Evolution of resistance to therapy → intra-tumoral Darwinian dynamics



Continuous therapy at maximal tolerated dose (MTD)

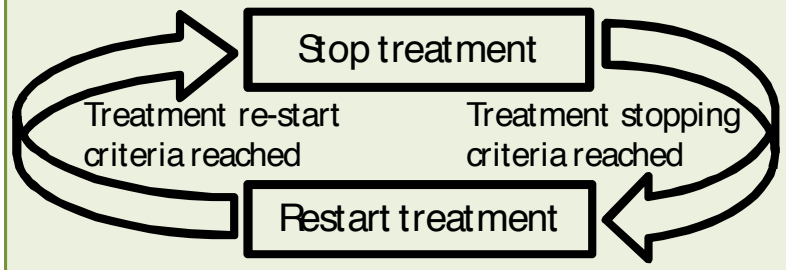
- Sensitive cells are rapidly eliminated and the resistant cells have a selective advantage leading to treatment failure

STATIC: Stopping Therapy to Avoid Treatment-resistance In CLL

RANDOMISATION (1:1). N = 800
Stratification factors: no of prior therapies, time on current therapy, MRD, VH status, BTKinhibitor

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)

HTA (NIHR) funded
Awaiting Janssen agreement

Set-up to start Sept 2019

Will open Sept 2020

FLAIR patients eligible but including relapsed patients

Primary end-point = treatment strategy failure

STATIC: Stopping Therapy to Avoid Treatment-resistance In CLL

Patient eligibility

Previously untreated patients on ibrutinib in FLAIR (n=360)

From IR, I or I+V arms; Will have been on ibrutinib for 6 years;
MRD positive (can be MRD negative)

Previously treated or 17p deleted front-line (n=440)

On ibrutinib (or alternative Btk inhibitor) for at least 2 years (no maximum)
Normal lymphocyte count for at least 12 months;
MRD positive (can be MRD negative)

Key exclusion criteria

· Treatment break for toxicity/patient choice for >28 days in last 12 months

STATIC: Stopping Therapy to Avoid Treatment-resistance In CLL

Treatment strategies:

Continuous treatment

Ibrutinib (oral) 420mg per day (or other BTK inhibitor at licenced dose) until disease progression (strategy failure) as per iwCLL criteria, death or withdrawal.

Intermittent treatment strategy

Initial stopping criteria (defined within the eligibility criteria; all to be met and maintained continuously for preceding 12 months): no palpable lymph nodes (<2cm), no palpable spleen, absolute lymphocyte count (ALC) $<5x10^9/L$.

Treatment restart criteria: Any one of palpable lymph nodes (≥2cm), palpable spleen, or ALC $>5\ x10^9/L$.

Treatment stop criteria: Received at least a further 12 months of ibrutinib, no palpable lymph nodes or spleen, and $<5\ x10^9/L$ ALC for at least 6 months.

Conclusions: Stopping targeted therapy in CLL

1. It is desirable to stop targeted therapy in CLL to:
   a) Reduce the impact of toxicity
   b) Reduce the emergence of resistance
   c) Define and limit cost

2. How should we stop targeted therapy?
   a) Fixed duration for all patients → some patients will not have achieved their maximal response
   b) Fixed duration tailored to individual patient response → attractive but requires sophisticated approach
   c) In good MRD positive remission with planned re-treatment?