XVIII IWCLL

International Workshop on CLL
20-23 SEPTEMBER 2019 EDINBURGH

Defining Duration of Therapy: Is there a Role for MRD?

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23/09/2019

Disclosures – Talha Munir

Advisor/Honoraria

- Gilead
- Janssen
- Roche
- Morphosys
- Novartis
- Alexion
- Sunesis
- Acerta

Aims of treatment in CLL?

- Improvement in symptoms/QoL
- Disease control
- Protracted treatment free interval
- Prolonged survival
- Cure

What influences the choice?

Patient age and co-morbidity
→ what is possible?

Patient choice
→ what does the patient want?

Treatment options available/appropriate
→ previous therapy
→ disease biology
→ what therapy is available

Treatment strategy
→ what are the future options

What is possible?

Is continuous targeted therapy desirable?

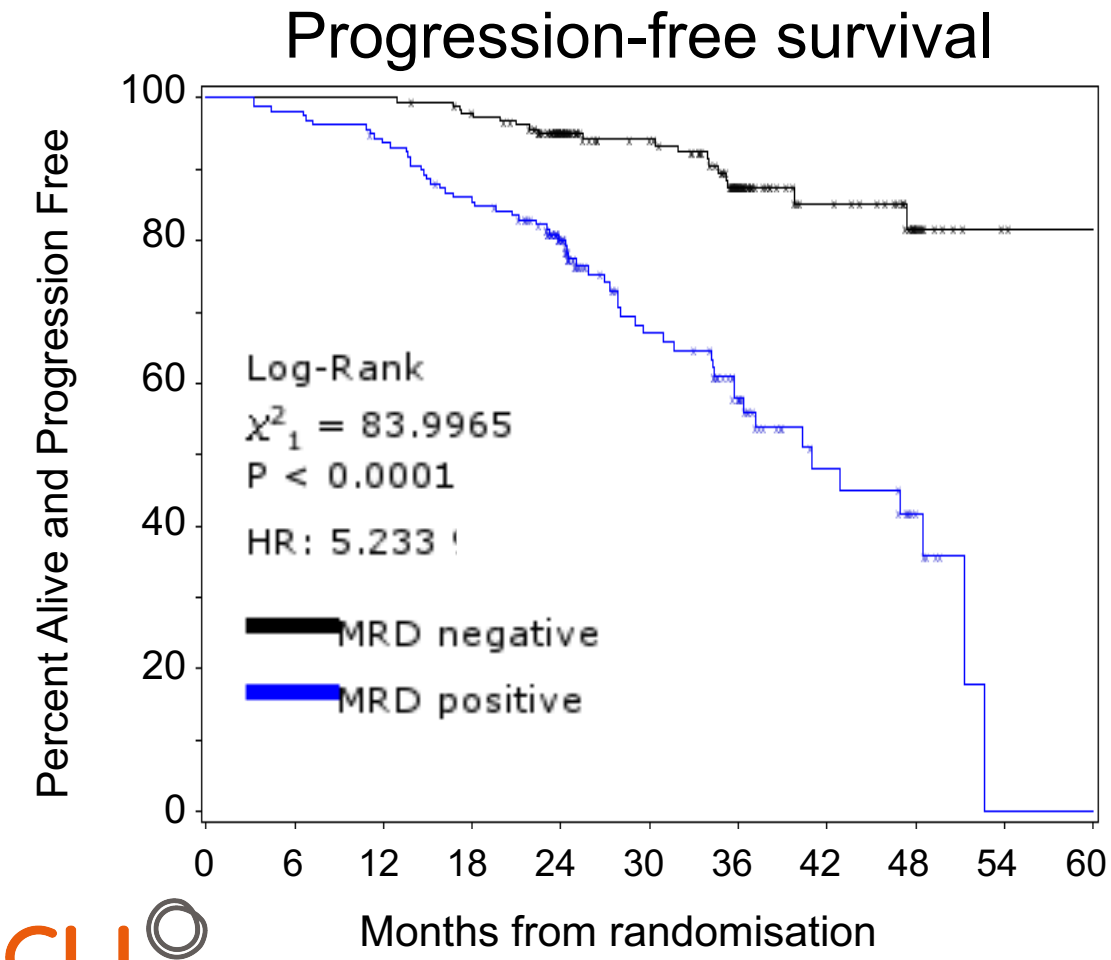
If we are going to stop targeted therapy how should the duration of therapy be defined?

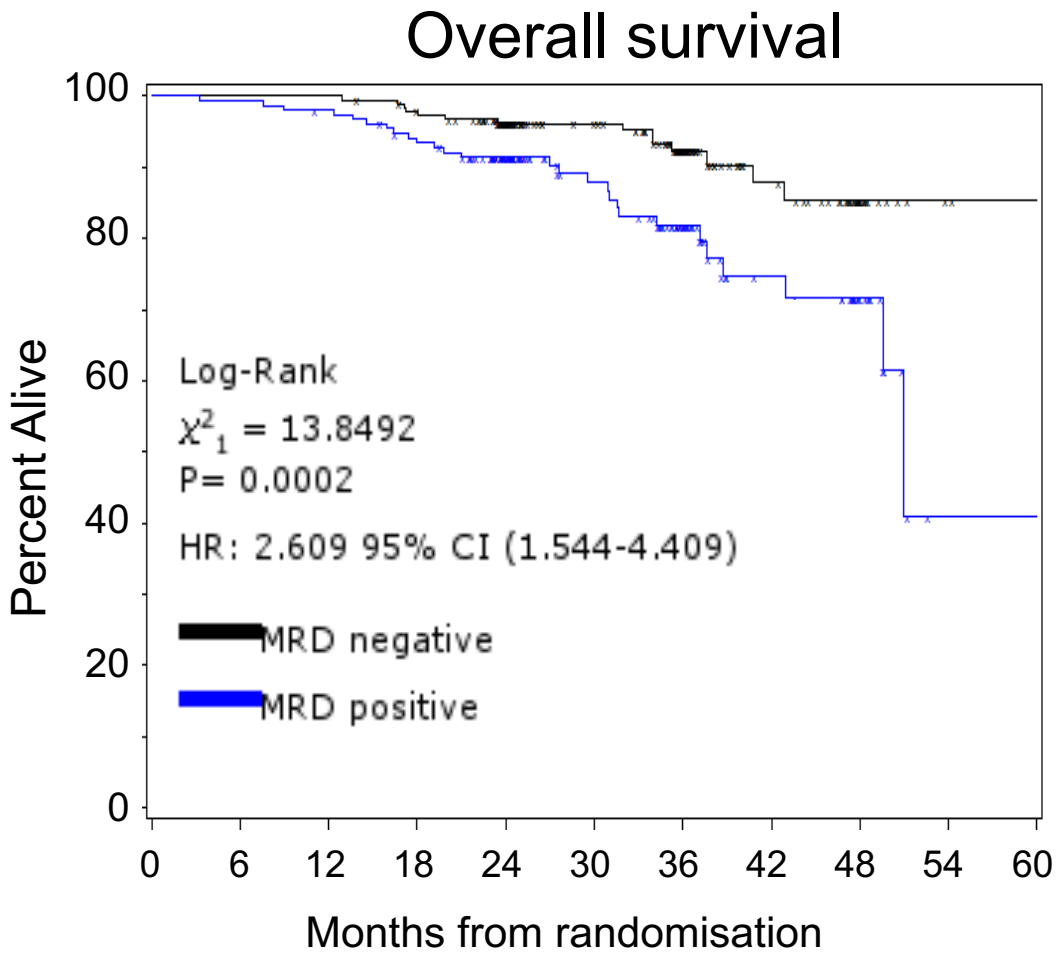
- Fixed duration of therapy for all patients

Or

- Therapy tailored to response in individual patients

UK NCRI ADMIRE and ARCTIC: Chemoimmunotherapy (FCR±M) in 345 patients with previously untreated CLL - marrow MRD at 9 months





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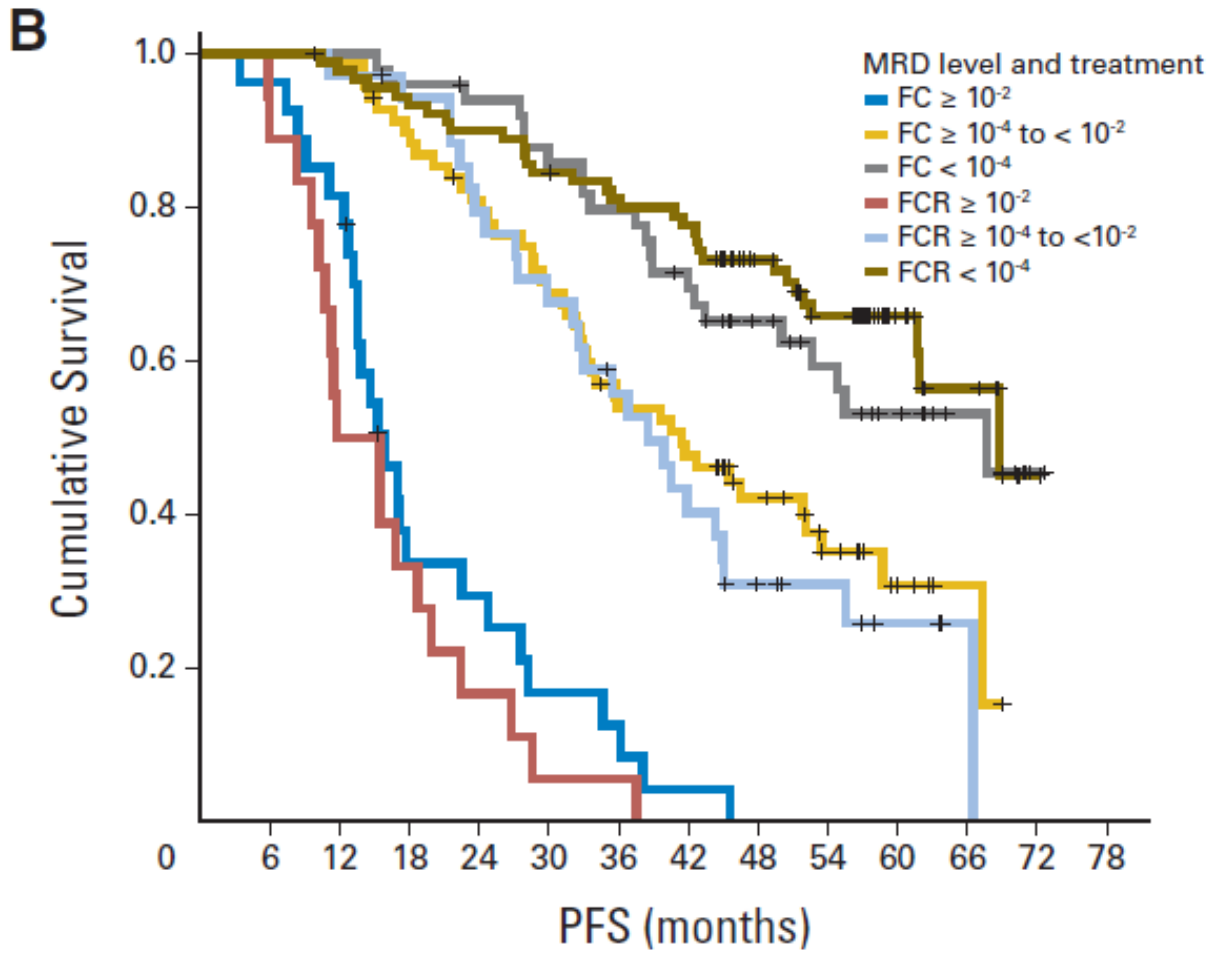
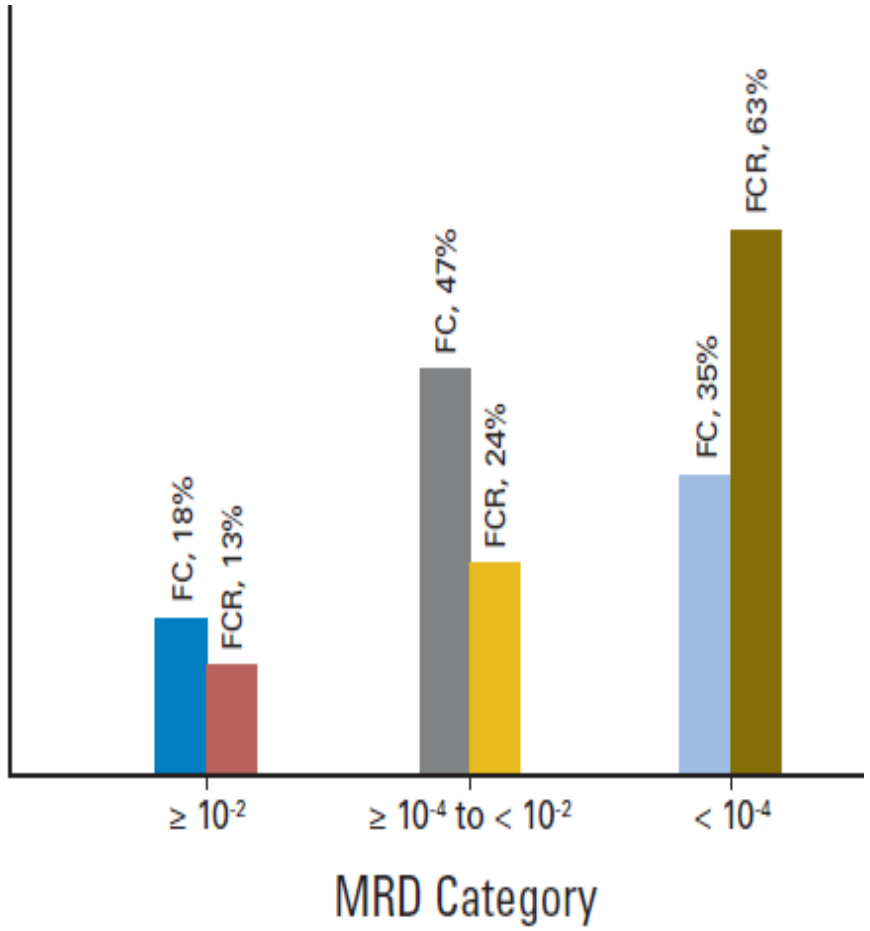
Hillmen *et al.*, unpublished data

DCLLSG CLL 8 trial: improved outcome for FCR vs. FC, MRD is an independent predictor of progression-free and overall survival

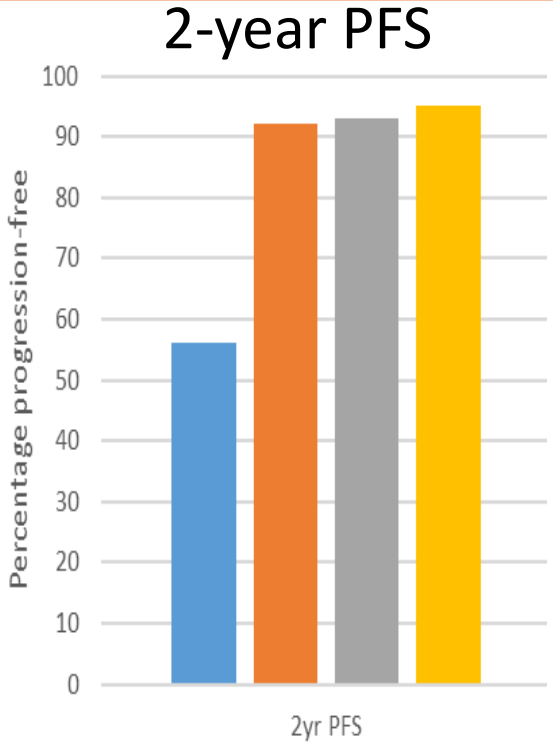




JOURNAL OF CLINICAL ONCOLOGY

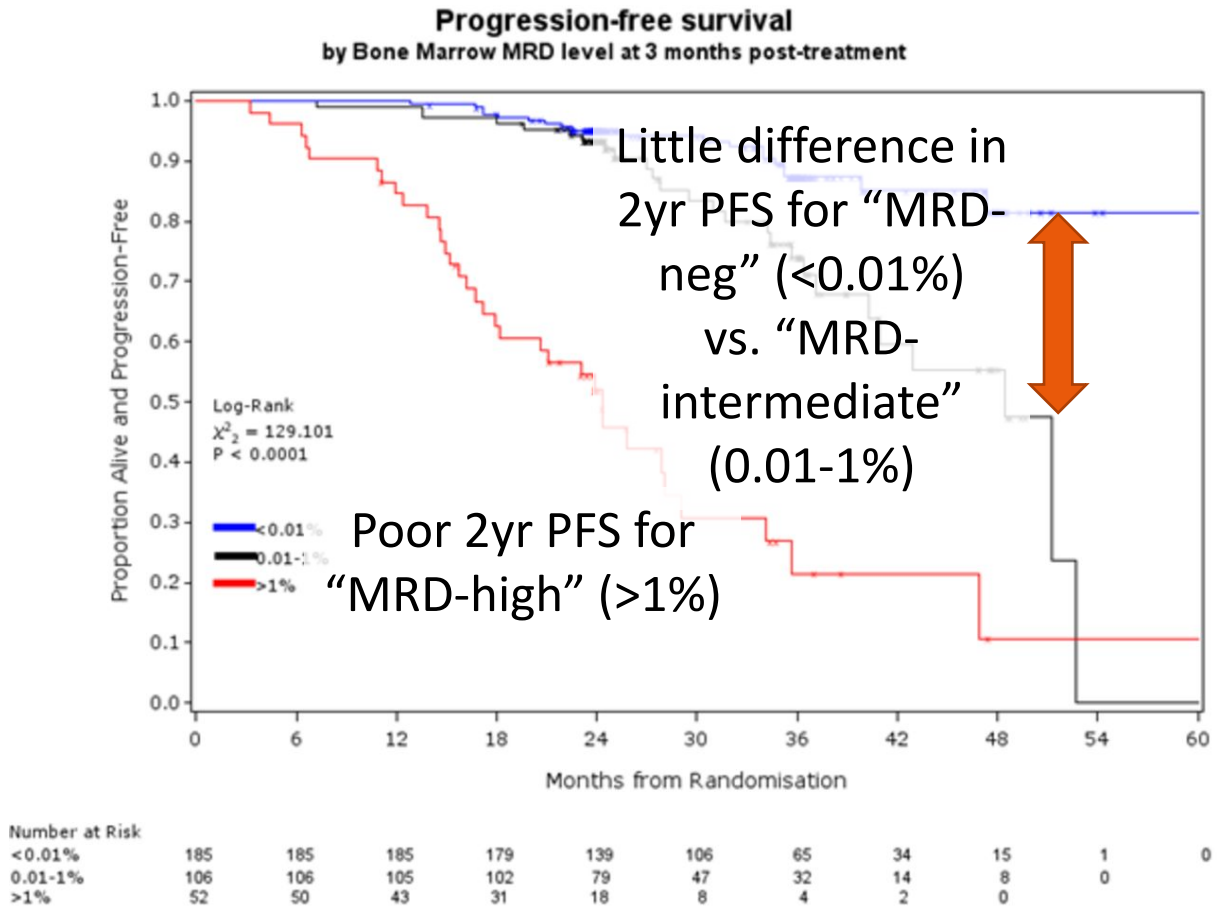
Böttcher, JCO 2012

“High” and “undetectable” MRD levels have different implications



TN CLL
FCR-based Rx
n=343

BM MRD level
- >1%
- 0.1 – 1%
- 0.01 – 0.1%
- <0.01%



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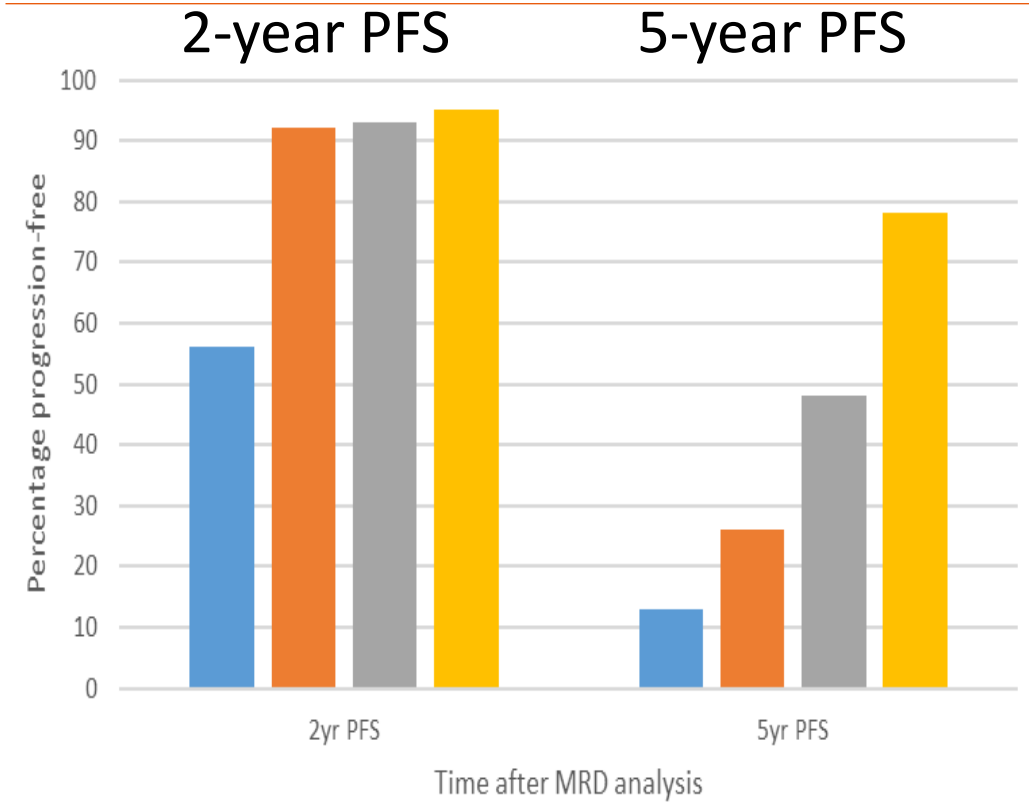
Rawstron et al. Blood 2015 126:1717

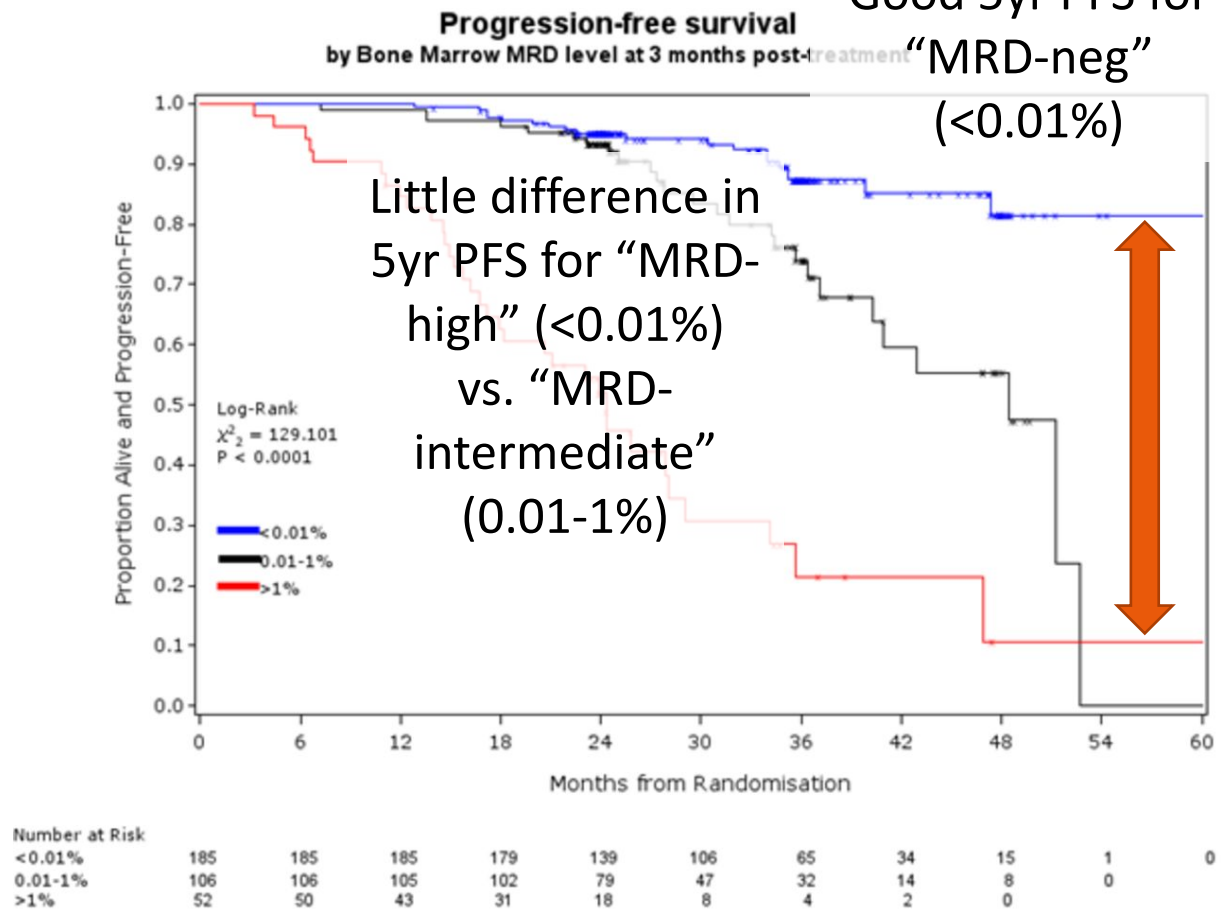
“High” and “undetectable” MRD levels have different implications



TN CLL
FCR-based Rx
n=343

BM MRD level
- >1%
- 0.1 – 1%
- 0.01 – 0.1%
- <0.01%

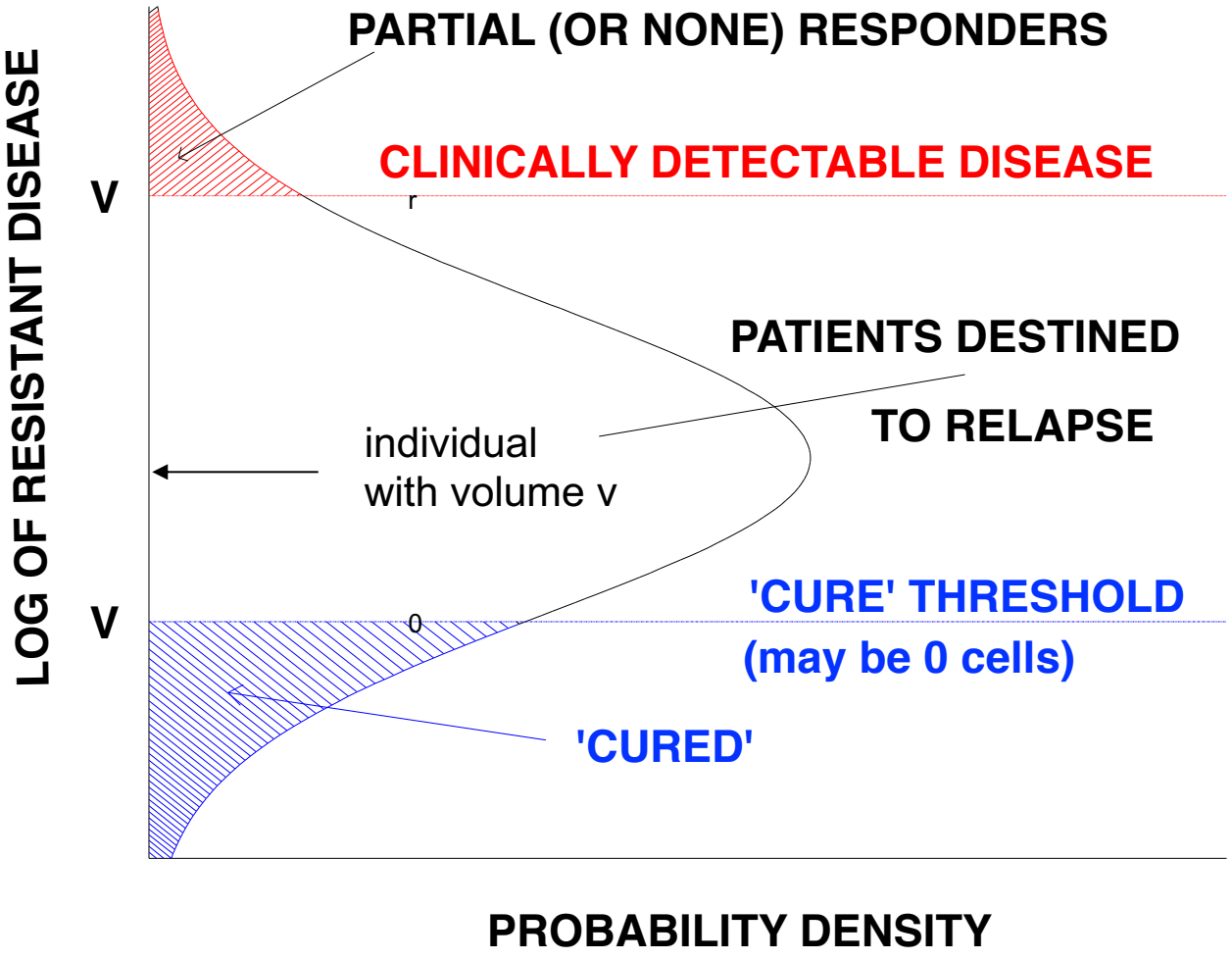
Good 5yr PFS for “MRD-neg” (<0.01%)



Little difference in 5yr PFS for “MRD-high” (<0.01%) vs. “MRD-intermediate” (0.01-1%)

Rawstron et al. Blood 2015 126:1717

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:

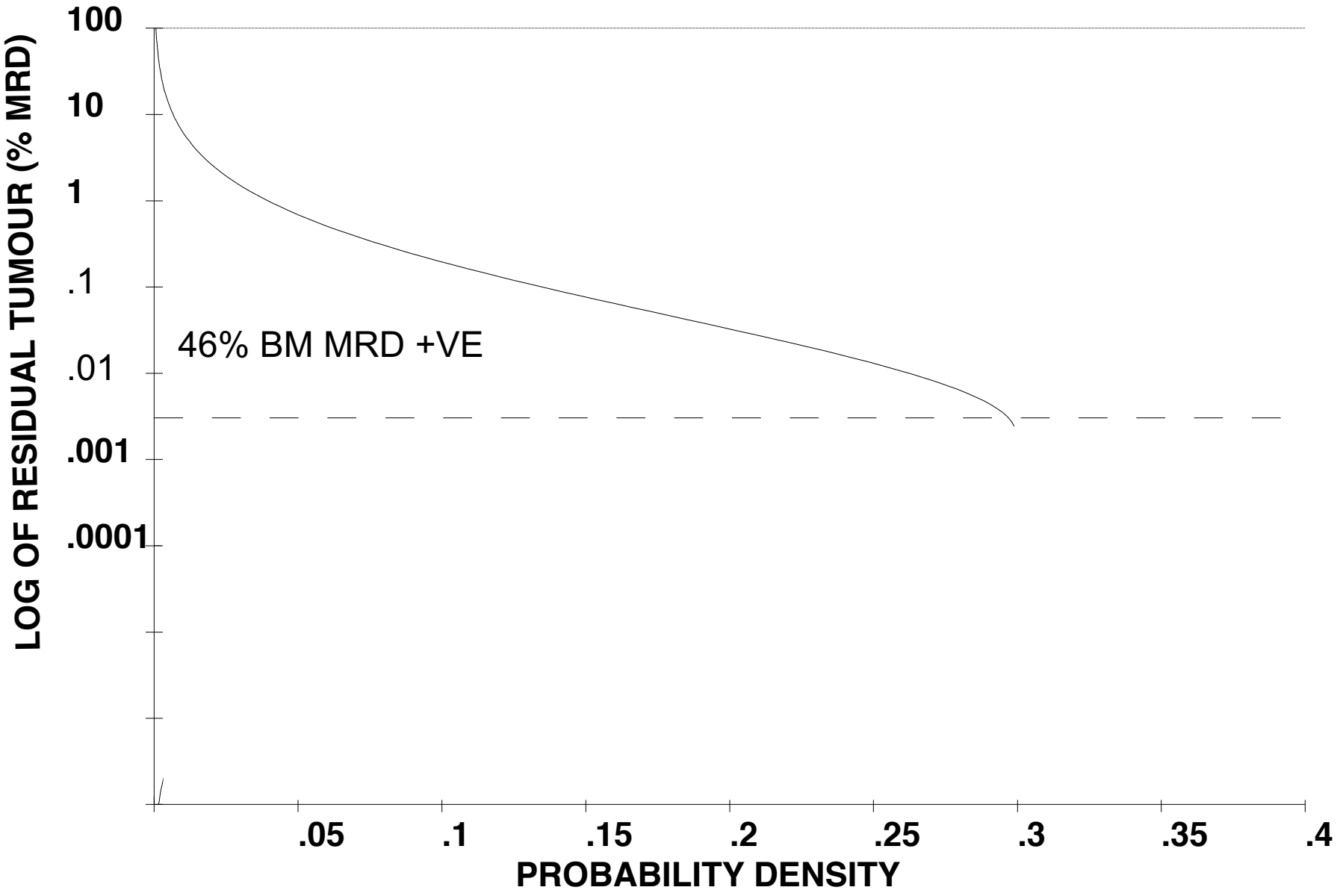
$$P = \frac{\int_{V_0}^{V_r} \left(\frac{1}{\sigma_v\sqrt{2\pi}}\right) exp\left(-\frac{(\mu_v - v)^2}{2\sigma_v{}^2}\right) \int_{-\infty}^{U_t} \left(\frac{1}{\sigma_g\sqrt{2\pi}}\right) exp\left(-\frac{(\mu_g - g)^2}{2\sigma_g{}^2}\right) dg\ dv}{P_c} \qquad (2)$$

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.

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



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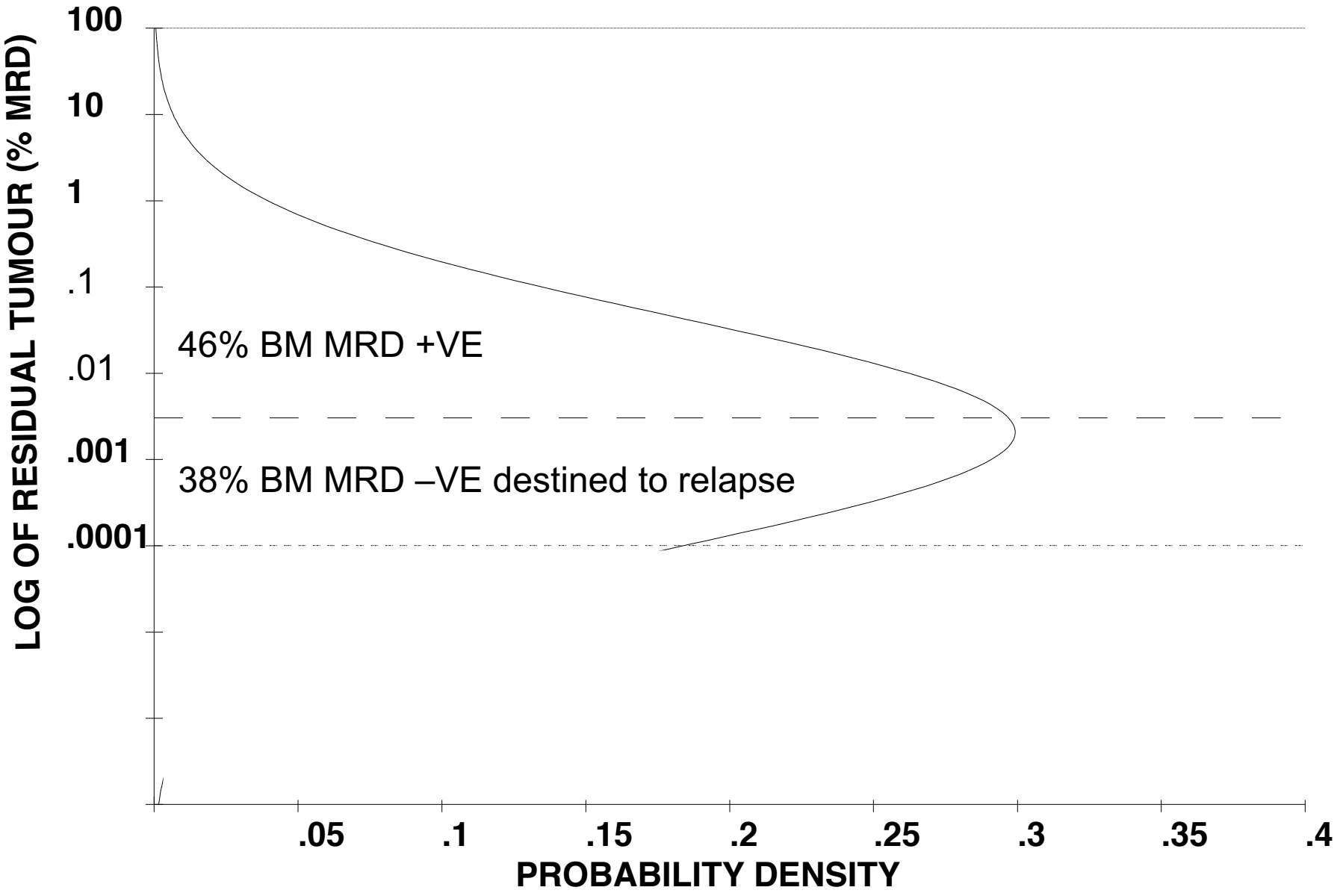
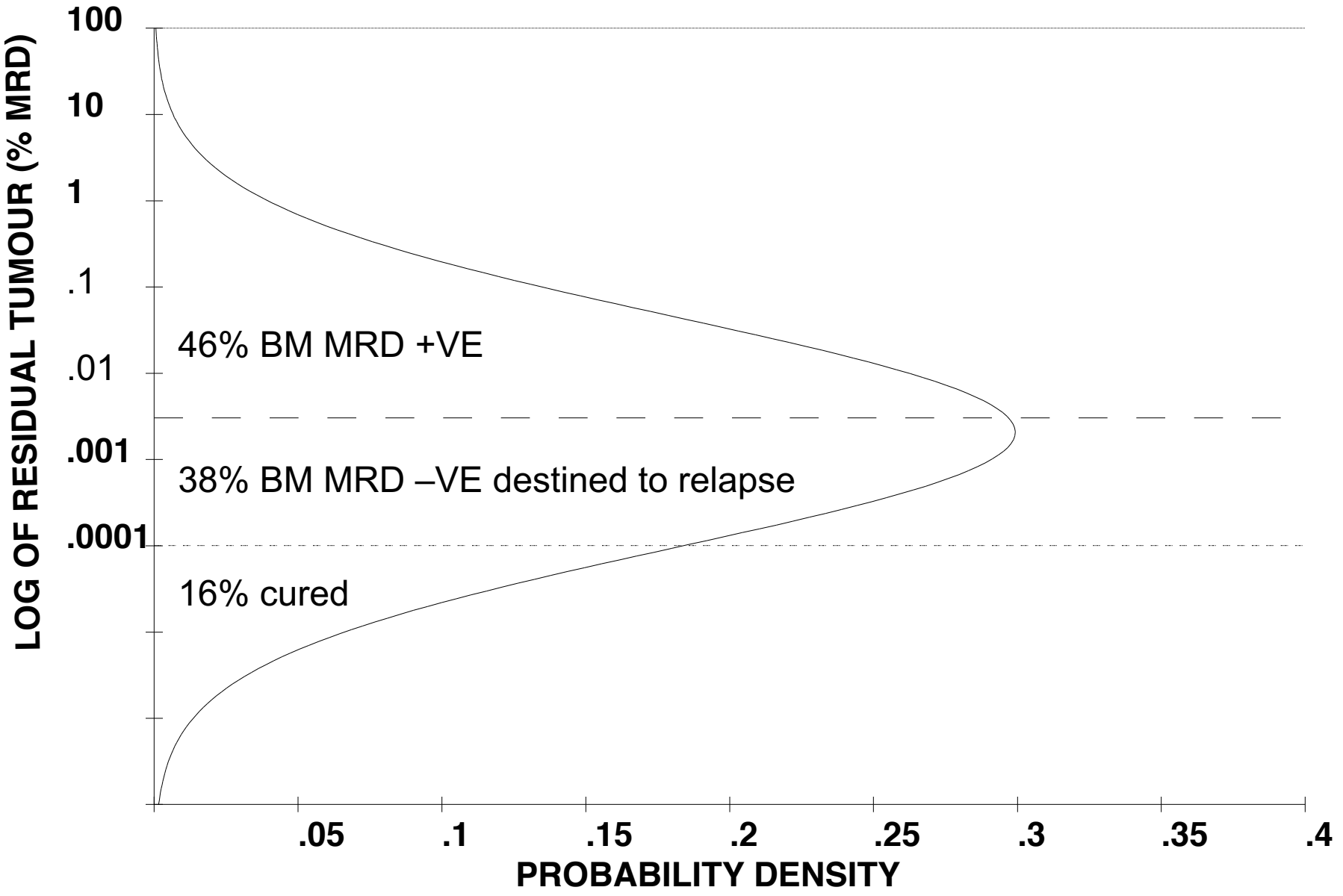
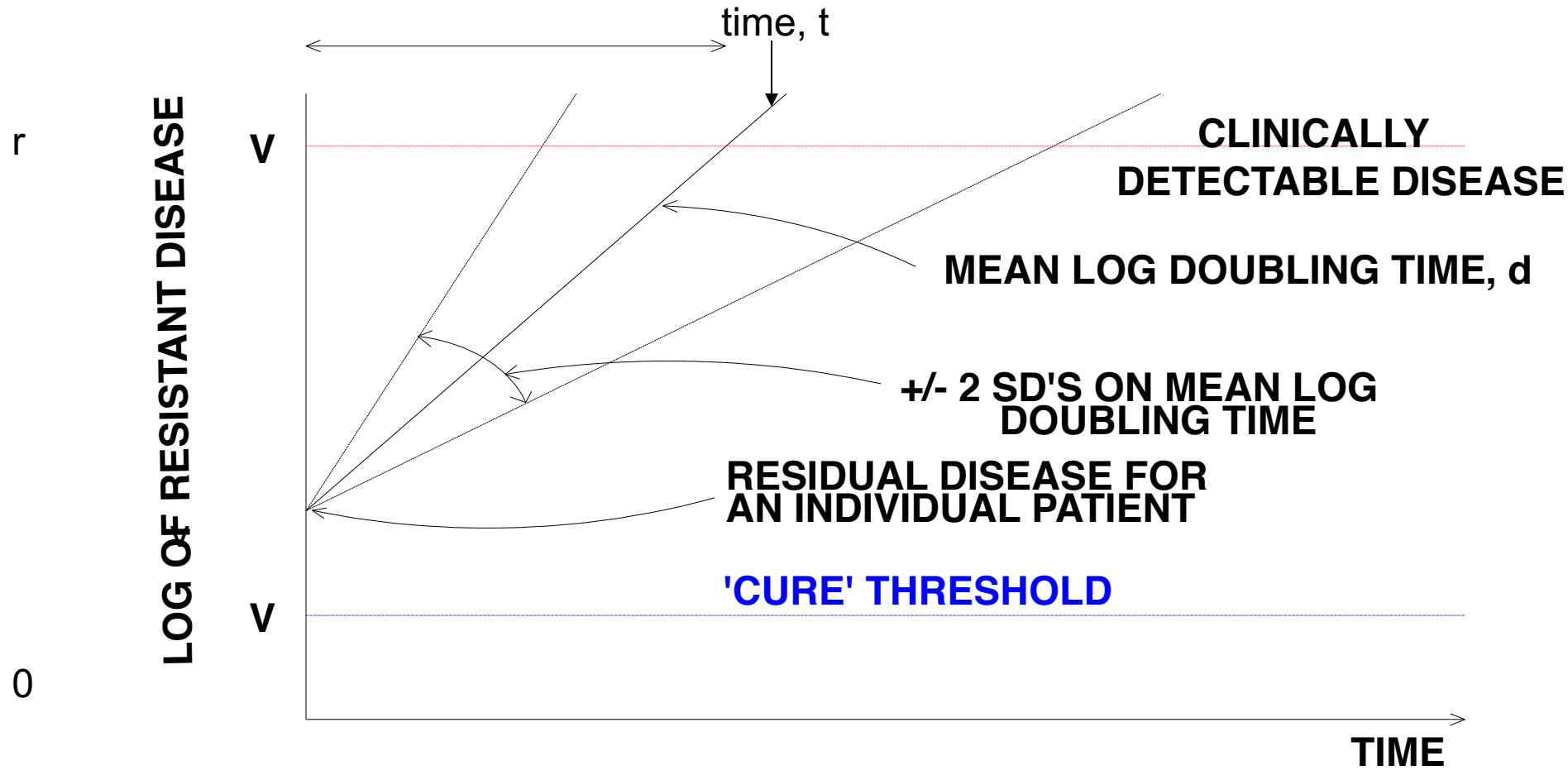


Normal distribution of MRD identifies a subset of "cured" patients (ADMIRE/ARCTIC)



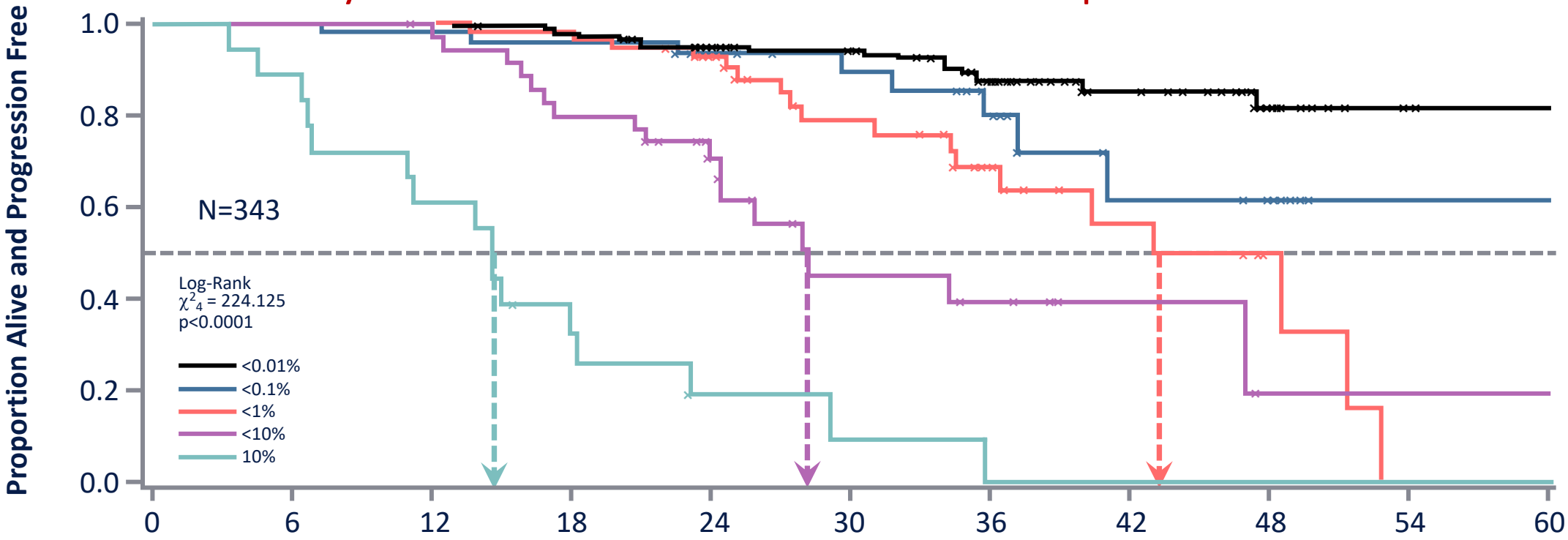
Assumed regrowth rates of resistant disease



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

Progression-free Survival

by bone marrow MRD level at 3 months post treatment



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.

iLLUMINATE: Ibrutinib + Obinutuzumab

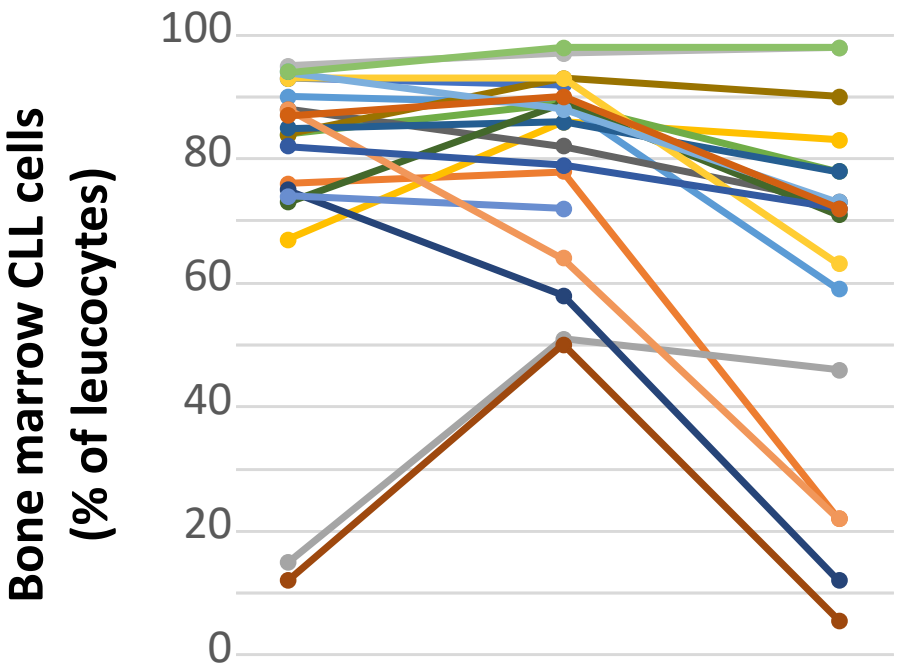
	All Patients		High-Risk Patients	
Outcome	Ibrutinib + Obinutuzumab (n = 113)	Chlorambucil + Obinutuzumab (n = 116)	Ibrutinib + Obinutuzumab (n = 73)	Chlorambucil + Obinutuzumab (n = 75)
ORR (per IRC), % ▪ CR/CRi	88 19	73 8	90 14	68 4
Median DoR, mos	NR (29.7-NE)	18.1 (15.2-NE)	NR (NE-NE)	11.8 (10.4-15.9)
MRD undetectable in BM or PB, % ▪ BM ▪ PB	35 20 30	25 17 20	27 -- --	15 -- --

- At follow-up of 31.3 mos, median OS not reached in either arm; HR: 0.92 (95% CI: 0.48-1.77)
  - 30-mo OS: 86% (95% CI: 77-91) for ibrutinib arm, 85% (95% CI: 77-90) for chlorambucil arm
- 4/113 (4%) in the ibrutinib arm vs 51/116 (44%) in the chlorambucil arm initiated subsequent therapy, with median time to next treatment not reached in either arm
  - Need for second-line therapy reduced with ibrutinib (HR: 0.06; 95% CI: 0.02-0.18)

Moreno. Lancet Oncol. 2018;[Epub].

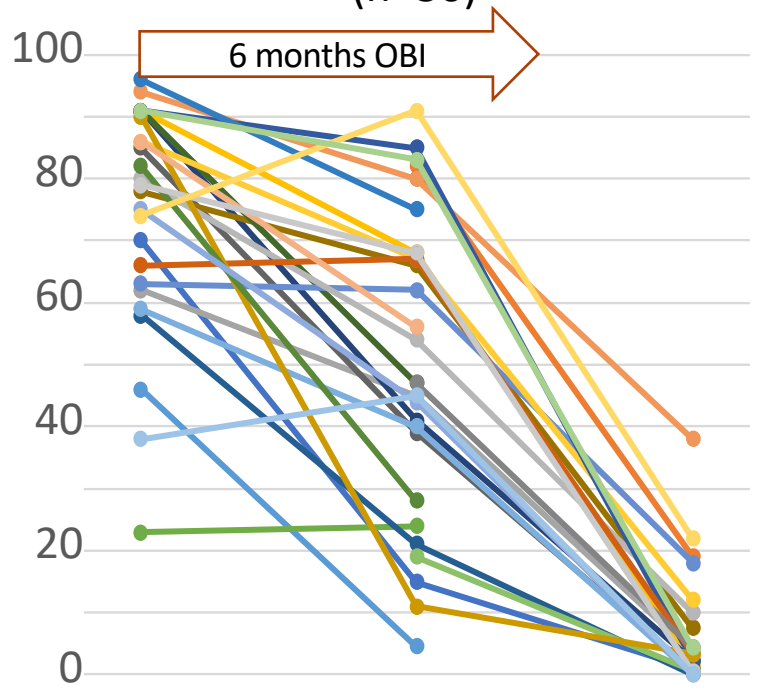
IciCLLe extension: Ibrutinib (IBR) +/- obinutuzumab (OBI) for R/R CLL- bone marrow MRD responses

IBR monotherapy for IBR-naïve R/R CLL (n=20)



IBR dur^{n}	Baseline	1 month	6 months
Median:	85%	87%	72%
Range:	12-95%	50-98%	6-98%
P-value:	-	0.27	0.028
Log dep^{n}:	-	0.0	0.1

IBR + OBI for IBR-naïve R/R CLL (n=30)



Baseline	1 month	9 months
79%	51%	3.3%
23-96%	5-95%	<0.001-38%
-	<0.001	<0.001
-	0.1	1.5

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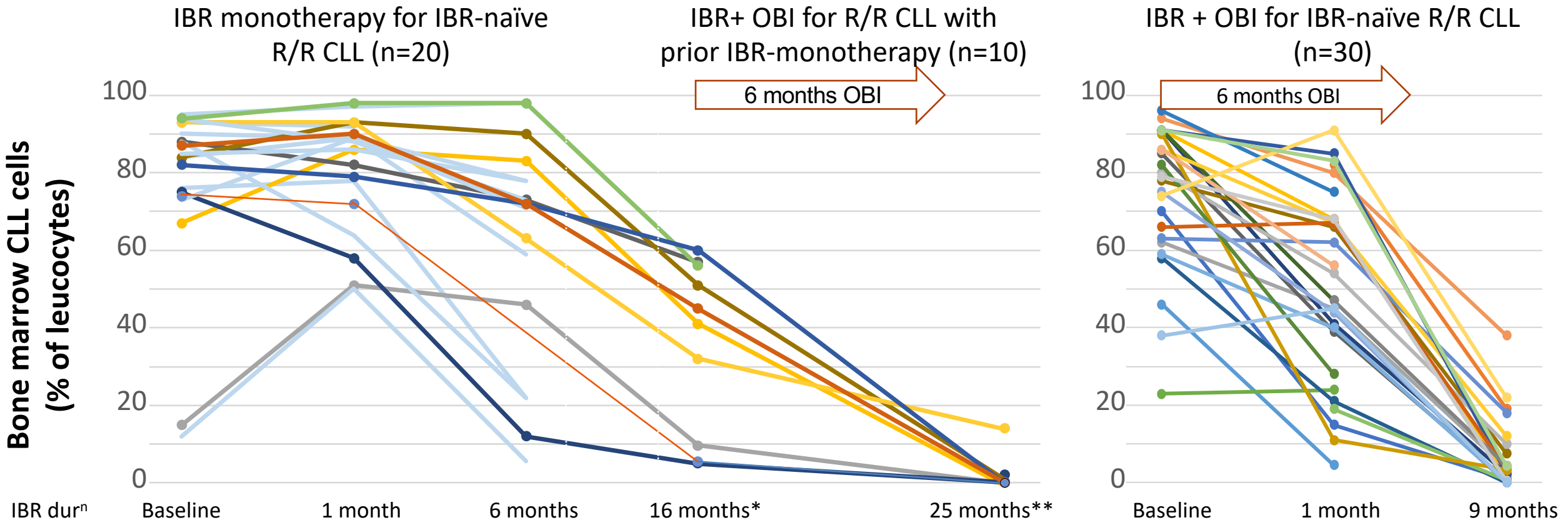
Date of data lock: 26 October 2018

Rawstron *et al.* ASH 2018; Abst 181

Timing of Obinutuzumab addition: Deeper MRD responses



IBR durⁿ	Baseline	1 month	6 months	16 months*	25 months**	Baseline	1 month	9 months
Median:	85%	87%	72%	43%	0.003%	79%	51%	3.3%
Range:	12-95%	50-98%	6-98%	5-60%	<0.001-14%	23-96%	5-95%	<0.001-38%
P-value:	-	0.27	0.028	<0.001	<0.001	-	<0.001	<0.001
Log depⁿ:	-	0.0	0.1	**0.2**	**4.0**	-	0.1	**1.5**

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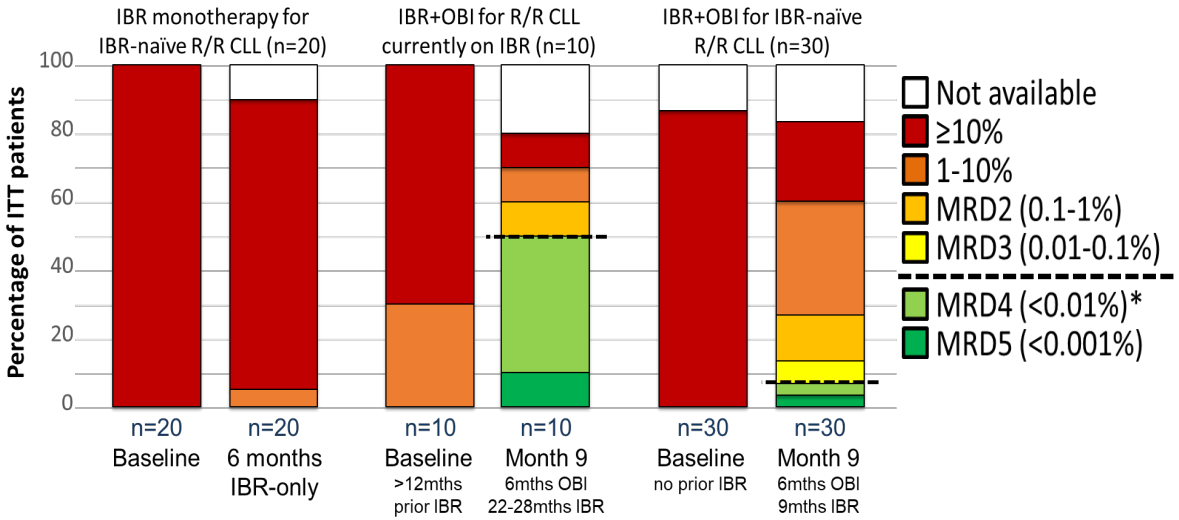
Date of data lock: 26 October 2018

*median 16 months, range 13-19 months
** median 25 months, range 22-28 months

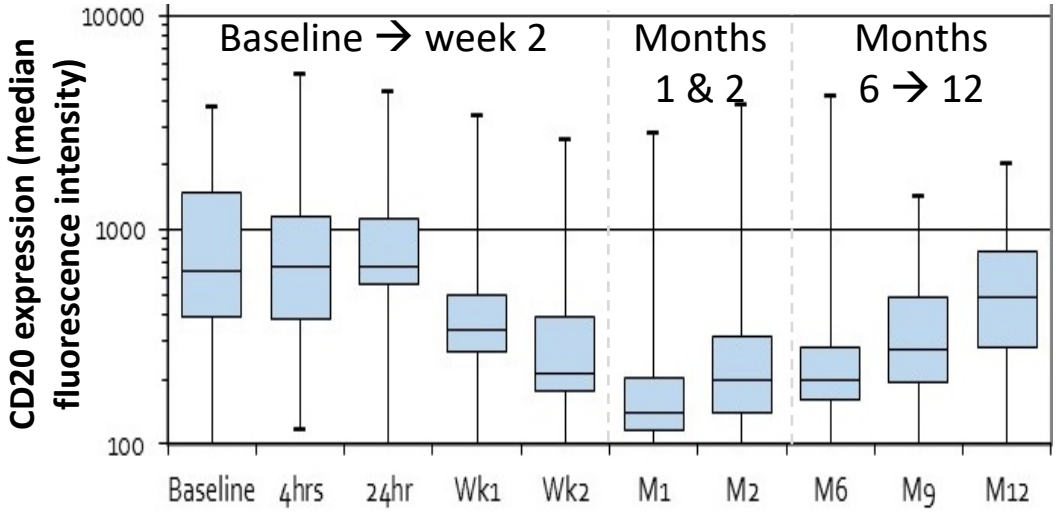
Rawstron *et al.* ASH 2018; Abst 181

Ibrutinib (IBR) +/- obinutuzumab (OBI) for R/R CLL: factors affecting obinutuzumab efficacy

- **Disease bulk pre-obinituzumab is lower in the ibrutinib-exposed cohort vs. IBR-naïve:**
- Lymphadenopathy: 0% vs. 87%
- BM CLL involvement: 43% vs 80%



- **CD20 expression decreases during first 6 months of ibrutinib exposure**
- Nadir at month 1 with expression increasing after month 9

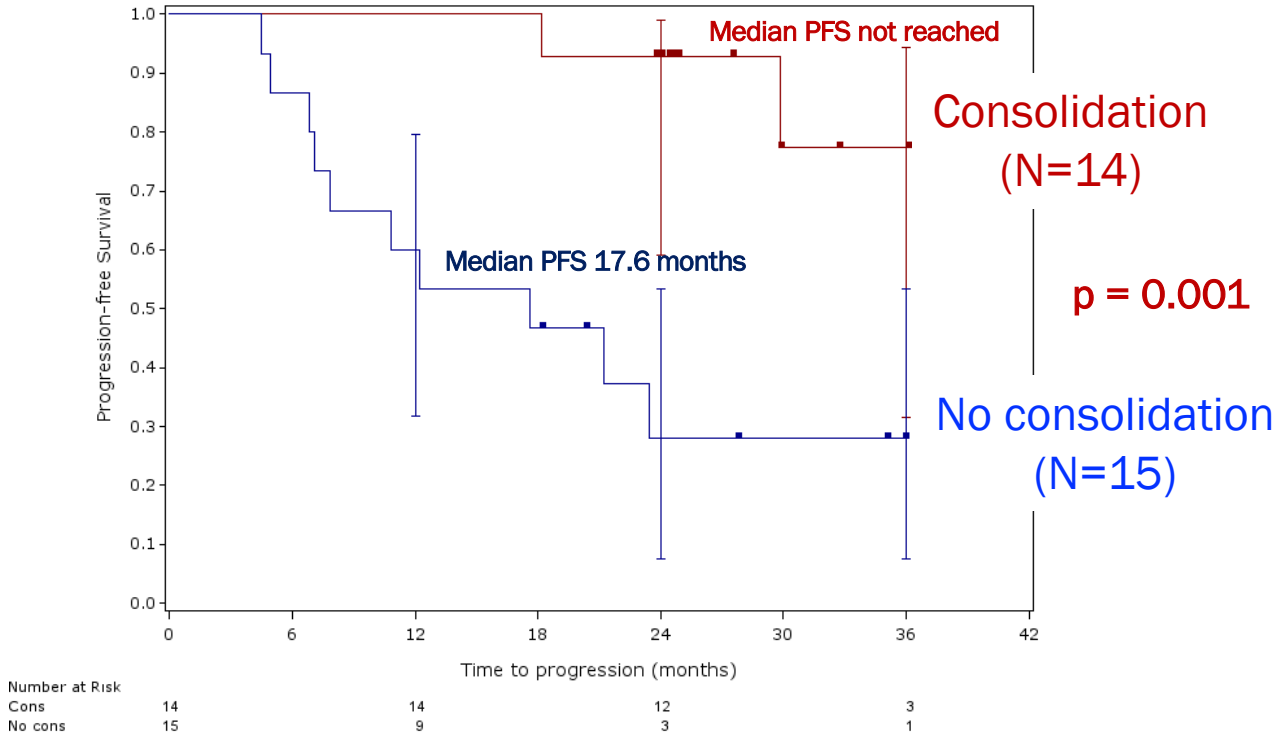


Date of data lock: 26 October 2018

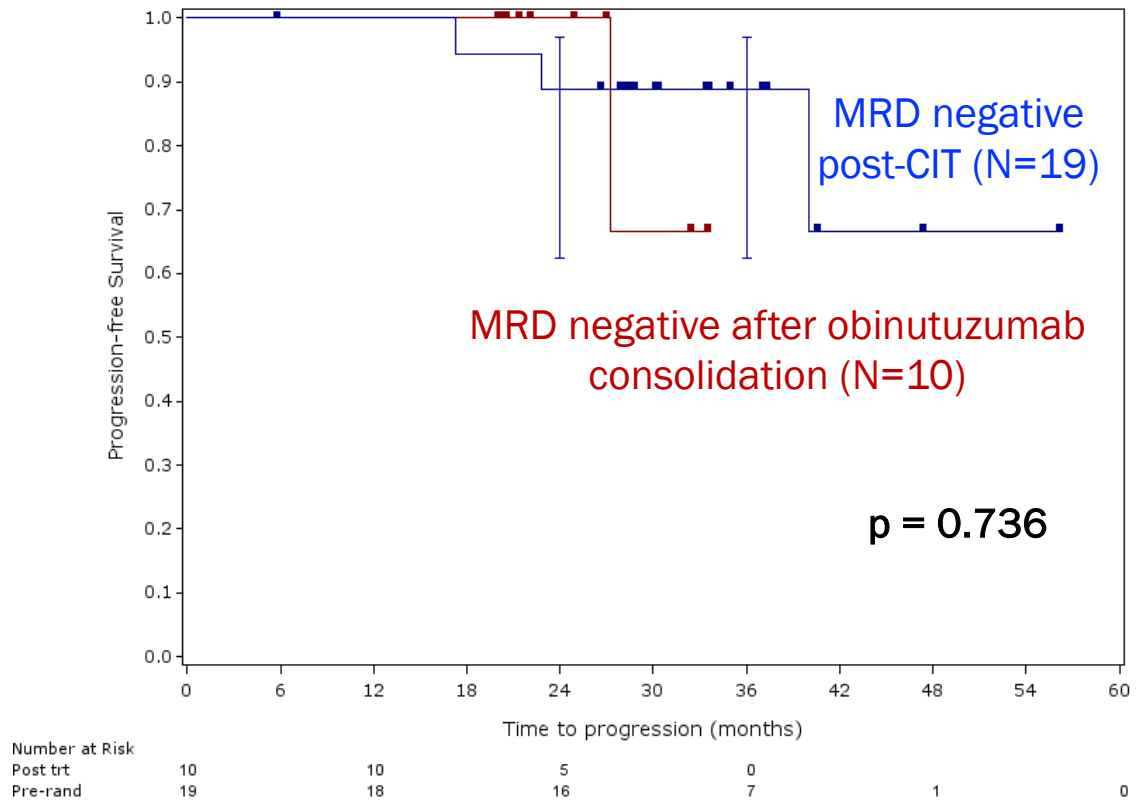
Rawstron *et al.* ASH 2018; Abst 181

Consolidation with Obinutuzumab results in PFS improvement and MRD negativity post CIT

Progression-Free Survival (PFS)



Progression-Free Survival (PFS)



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PFS- Progression-free survival, OS- Overall survival

GALACTIC

HELIOS (3-year follow-up): Increased depth of response with continuous ibrutinib therapy

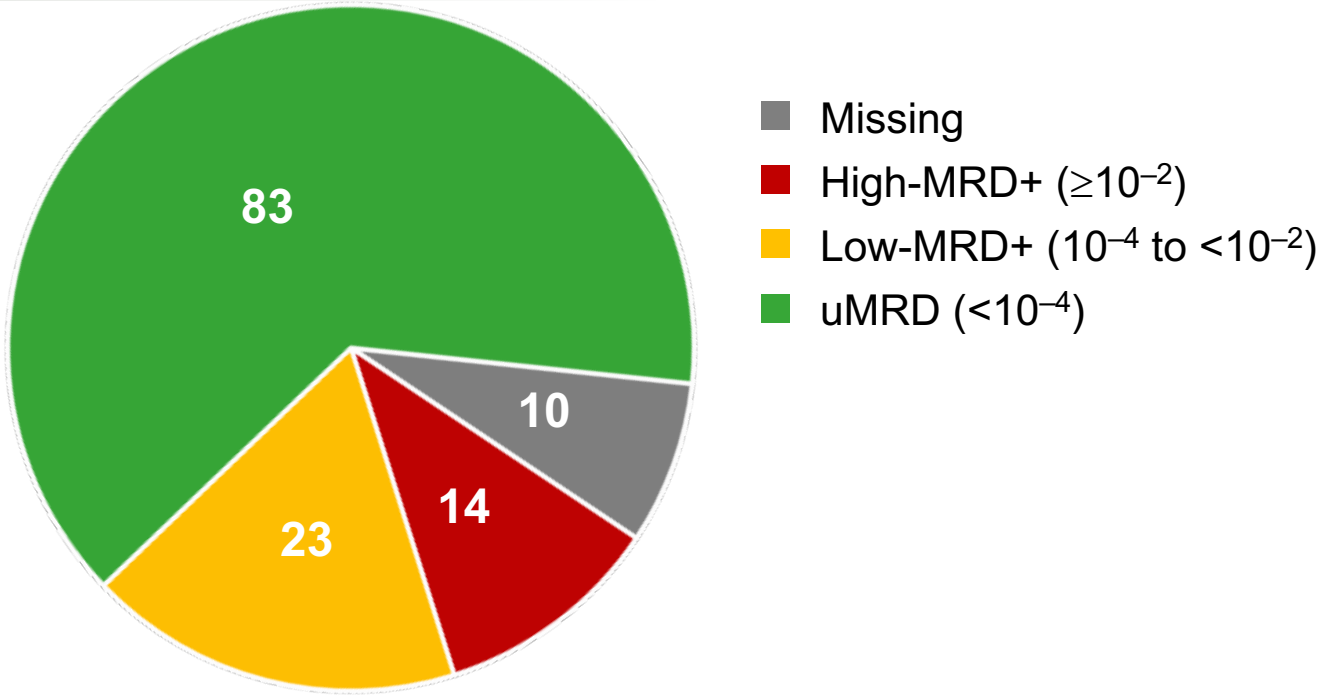
	CR/CRi (Investigator-Assessed)		MRD-Negative (Central Laboratory)	
	Ibrutinib + BR	Placebo + BR	Ibrutinib + BR	Placebo + BR
Median follow-up, 17 months	21.4%	5.9%	12.8% (n = 37)	4.8% (n = 14)
Median follow-up, 34.8 months	38.1%	8.0%	26.3% (n = 76/289)	6.2% (n = 18/289)

- Median time to CR/CRi was 11.14 months for ibrutinib + BR and 11.07 months for placebo + BR
- Median time to MRD-negative response was 12.91 months for ibrutinib + BR and 10.63 months for placebo + BR
- MRD-negative response continues to increase over time for patients treated with ibrutinib + BR

Fraser et al. Leukemia. 2019 Apr;33(4):969-980

MURANO study- After cessation of Ven monotherapy at EOT most patients did not progress (fixed duration venetoclax)

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

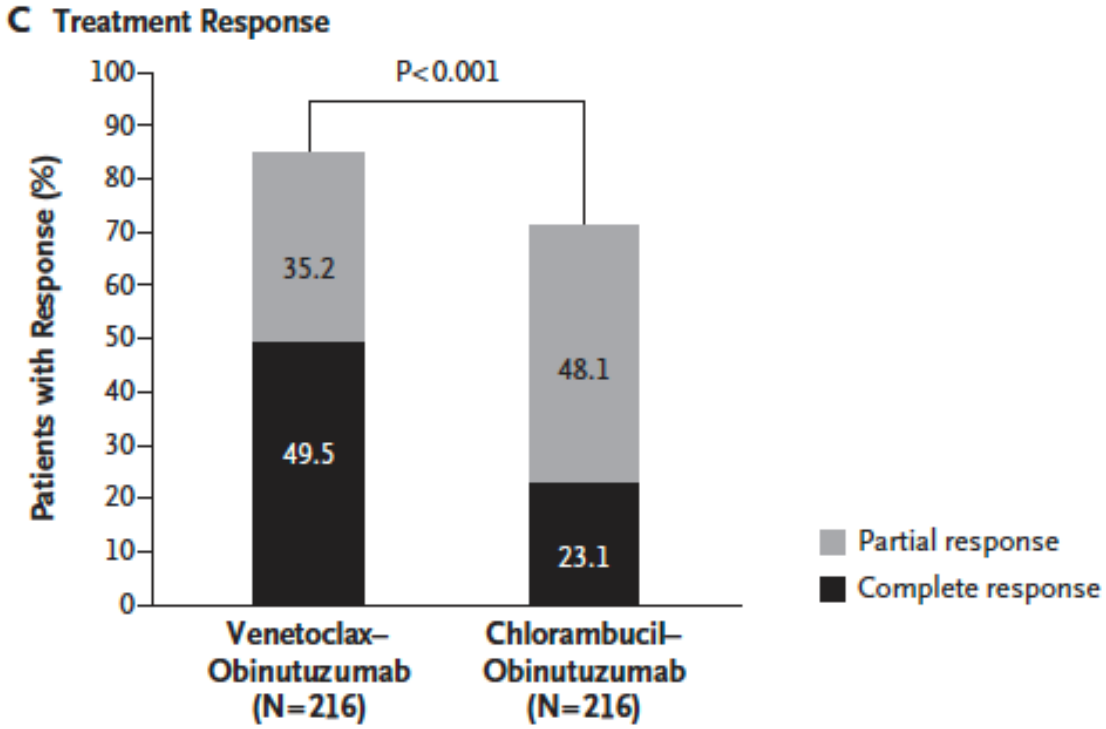


Status off-therapy (median follow up: 9.9 mo)	uMRD (n=83)	Low-MRD+ (n=23)	High-MRD+ (n=14)	Missing (n=10)
Progression-free, n (%)	81 (97.6%)	20 (87.0%)	3 (21.4%)	10 (100%)
PD, n (%)	2 (2.4%)	3 (13.0%)	11 (78.6%)	0 (0%)

Seymour J.F. et al. Oral Abstract #184: ASH December 2018, San Diego, CA.

GCLLSG CLL14 Trial:
Venetoclax+obinutuzumab vs Chlorambucil+obinutuzumab

12 month fixed duration of therapy in both arms

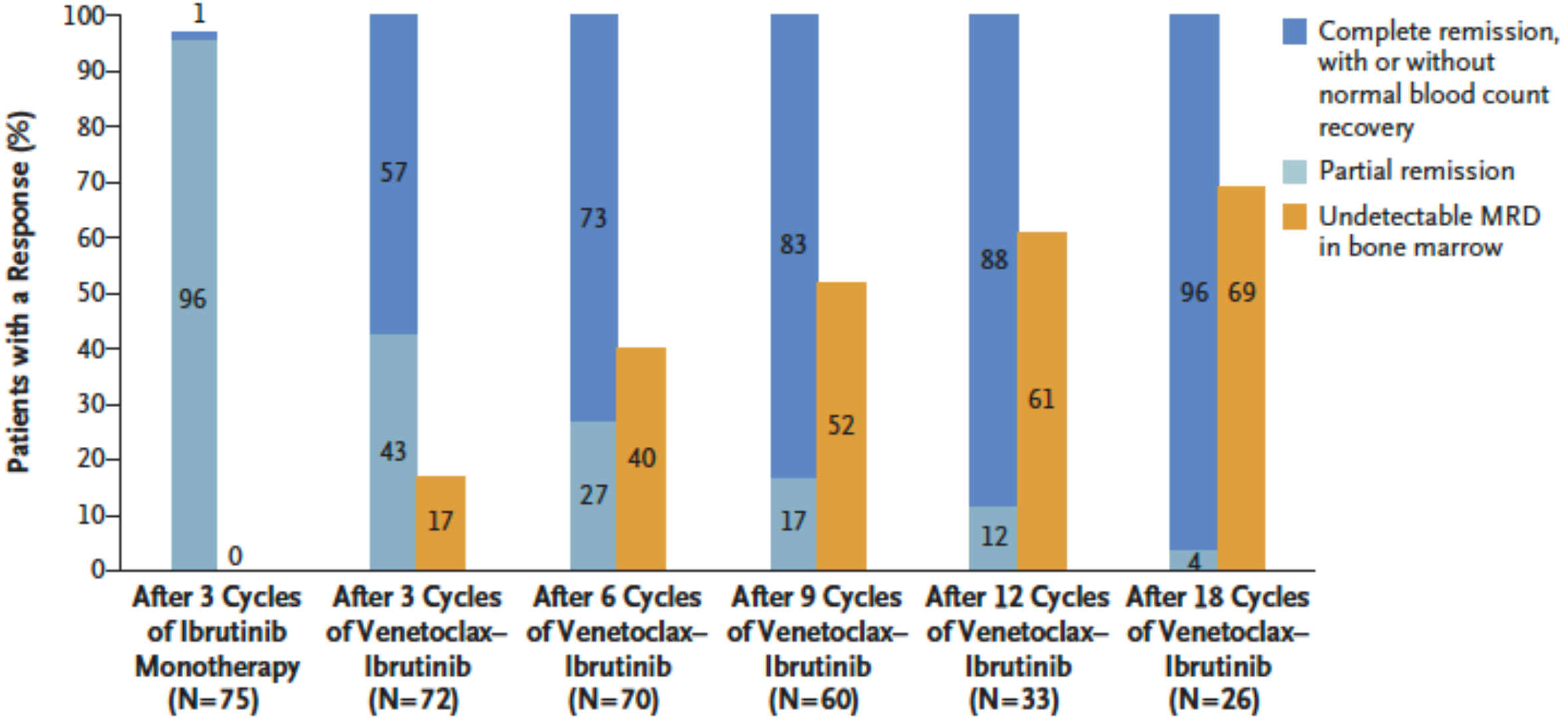


Minimal residual disease status by ASO-PCR in marrow

	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%)

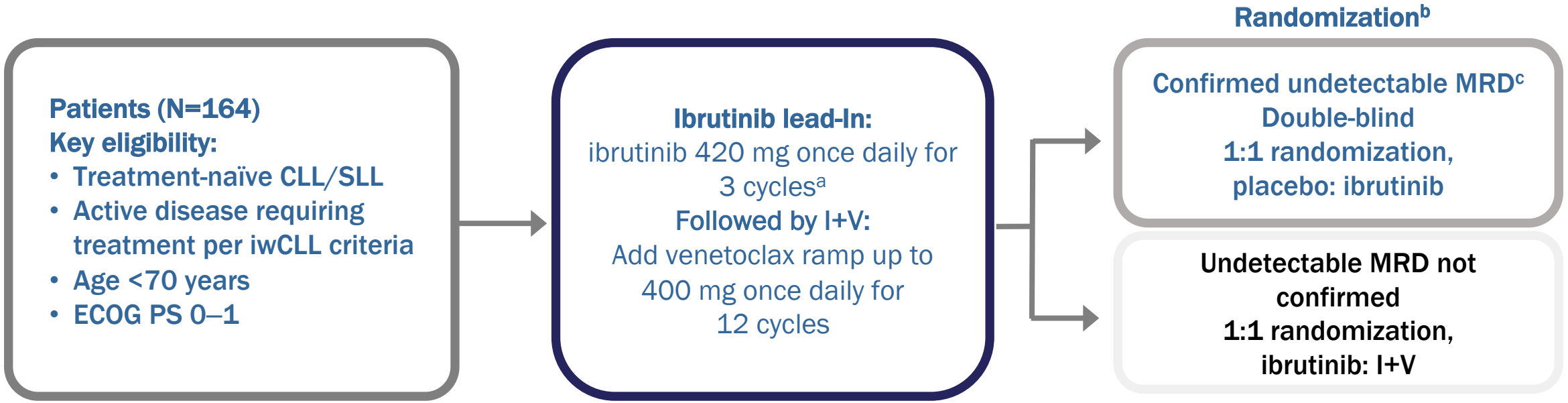
Fischer *et al.*, N Engl J Med 2019;380:2225-32.

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



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

Phase 2 CAPTIVATE Study Design (NCT02910583)- MRD adaptive approach



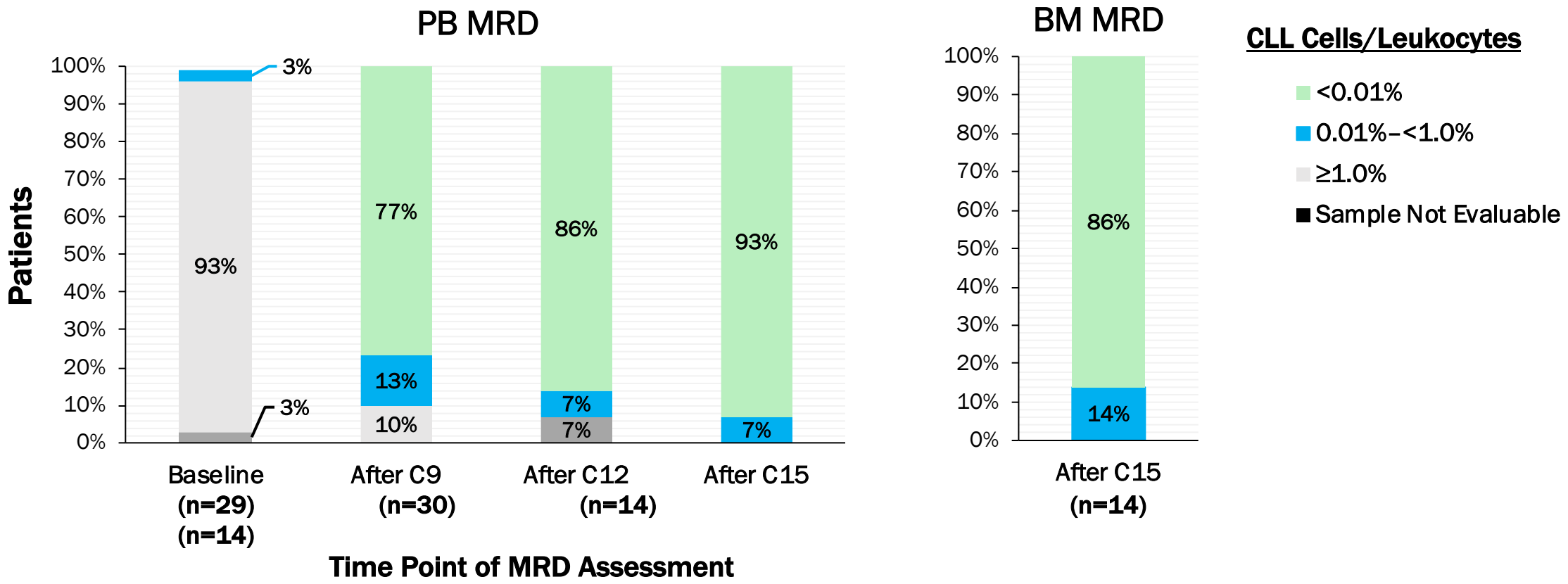
[a]**1 cycle = 28 days.**
[b]Stratified by *IGHV* mutation status.
[c]Confirmed undetectable MRD for randomization defined as undetectable MRD serially over at least 3 cycles in peripheral blood (PB), and undetectable MRD in both PB and BM.

Study Populations:

- MRD cohort (N=164): exposure and safety analysis
  - Safety Run-in: first 14 patients completed C15 treatment (12 cycles of I+V); no dose-limiting toxicities (DLT) or clinical TLS during first 6 weeks of I+V combination
  - Prespecified analysis of the first 30 patients who completed C9 treatment (6 cycles of I+V) for MRD evaluation
- Fixed Duration cohort (N=159): separate cohort; analysis not shown

ASCO 2018, 1142 Wierda et al.

CAPTIVATE Early Undetectable MRD Responses Sustained Over Time

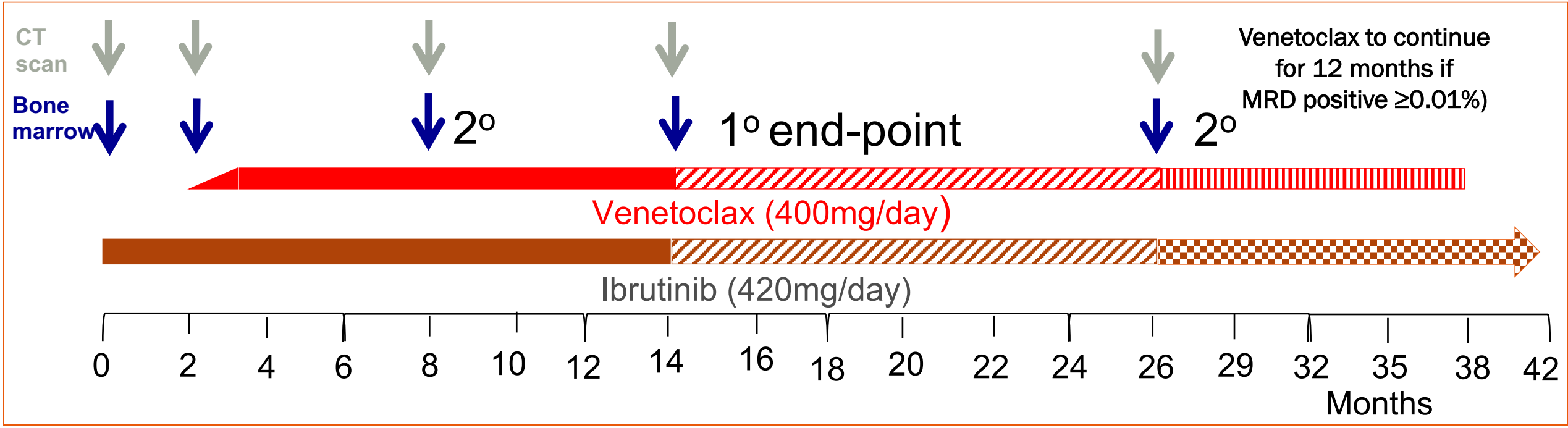


- High rates of undetectable MRD (77%) in PB after 6 cycles of I+V
- Confirmed undetectable MRD* in 11 of 14 patients (79%) after 12 cycles of I+V

*Confirmed undetectable MRD defined as undetectable MRD serially over at least 3 cycles in PB, and undetectable MRD in both PB and BM. BM MRD was assessed per protocol after C15 for all patients who reached this time point as of the data extract.

ASCO 2018, 1142 Wierda et al.

CLARITY: Treatment Schedule and Stopping Rules

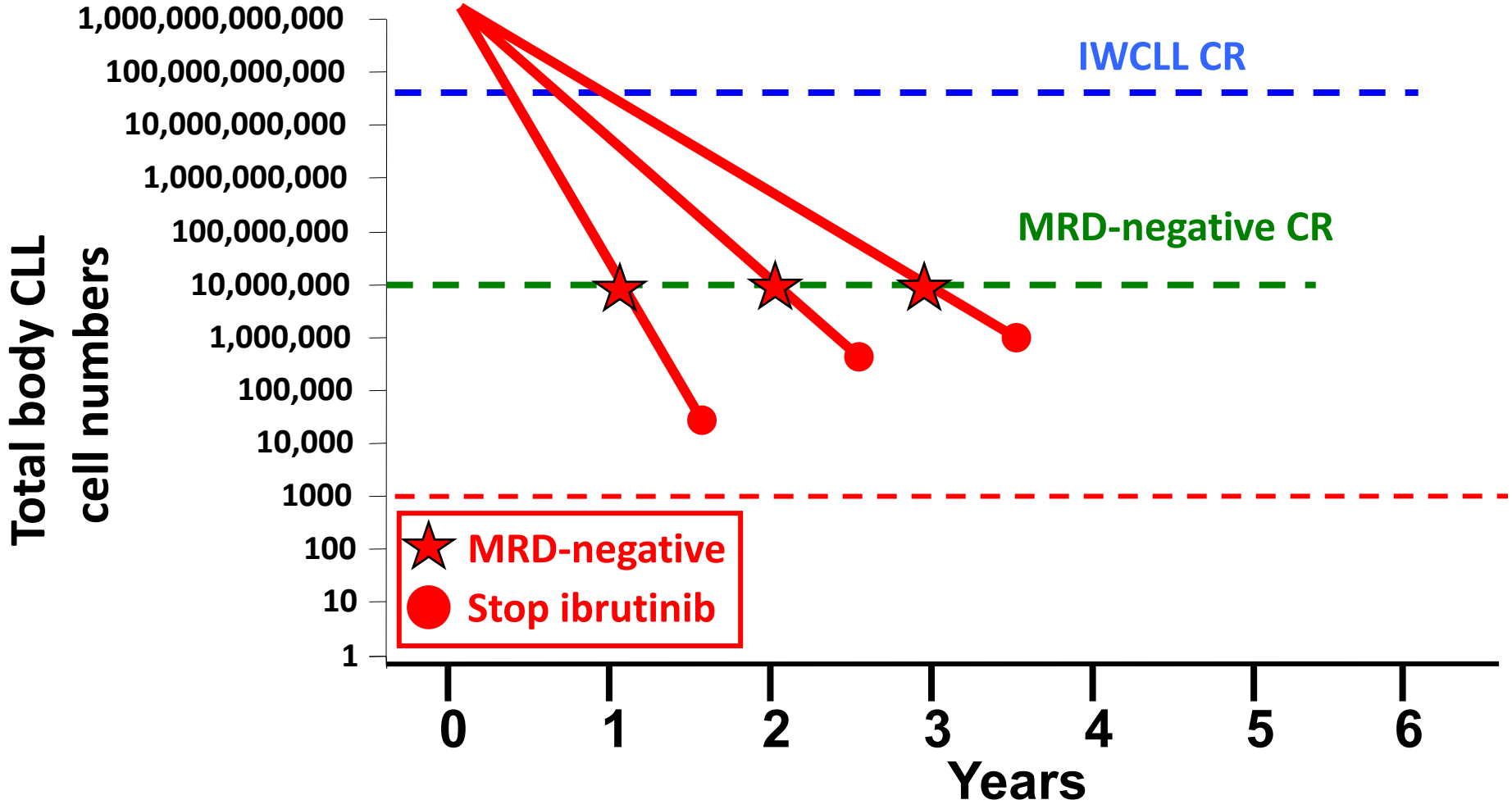


Stopping rules: Duration of therapy is double time to MRD4 negative

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
4) MRD positive (≥0.01%) at M26 can continue venetoclax for 12 months (Amendment)

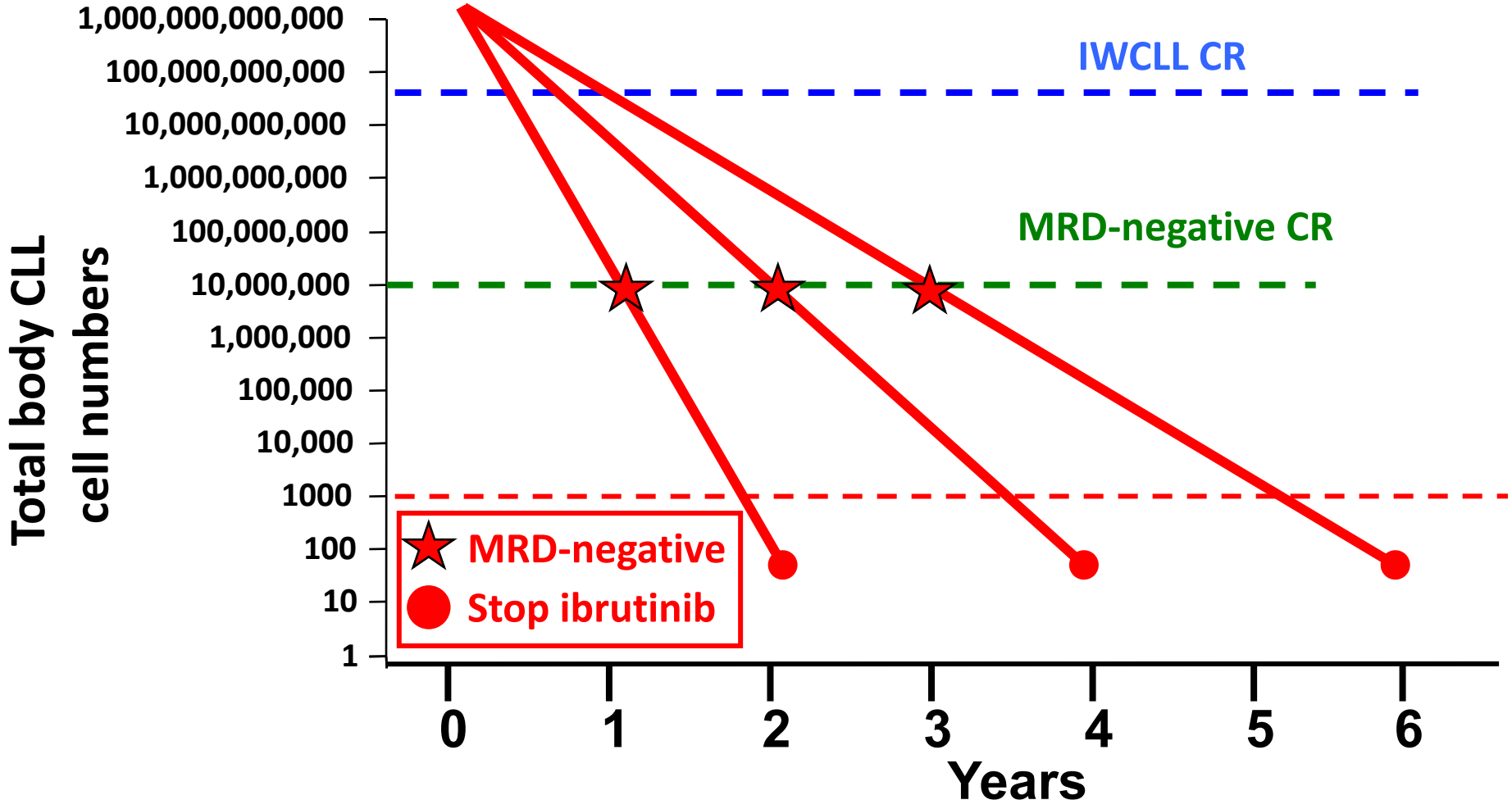
When to stop targeted therapy in CLL?

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



Patient selection: MRD now used in most (all) trials

Table 3. Recommendations regarding the response assessment in CLL patients

Diagnostic test	General practice	Clinical trial
History, physical examination	Always	Always
CBC and differential count	Always	Always
Marrow aspirate and biopsy	At cytopenia of uncertain cause	At CR or cytopenia of uncertain cause
Assessment for minimal residual disease	NGI	Desirable
Ultrasound of the abdomen*	Possible, if previously abnormal	NGI
CT scans of chest, abdomen, and pelvis	NGI	Recommended if previously abnormal and otherwise with a CR and PR

For a detailed description of these parameters, see section 5. General practice is defined as the use of accepted treatment options for a CLL patient not enrolled on a clinical trial.

*Used in some countries to monitor lymphadenopathy and organomegaly.

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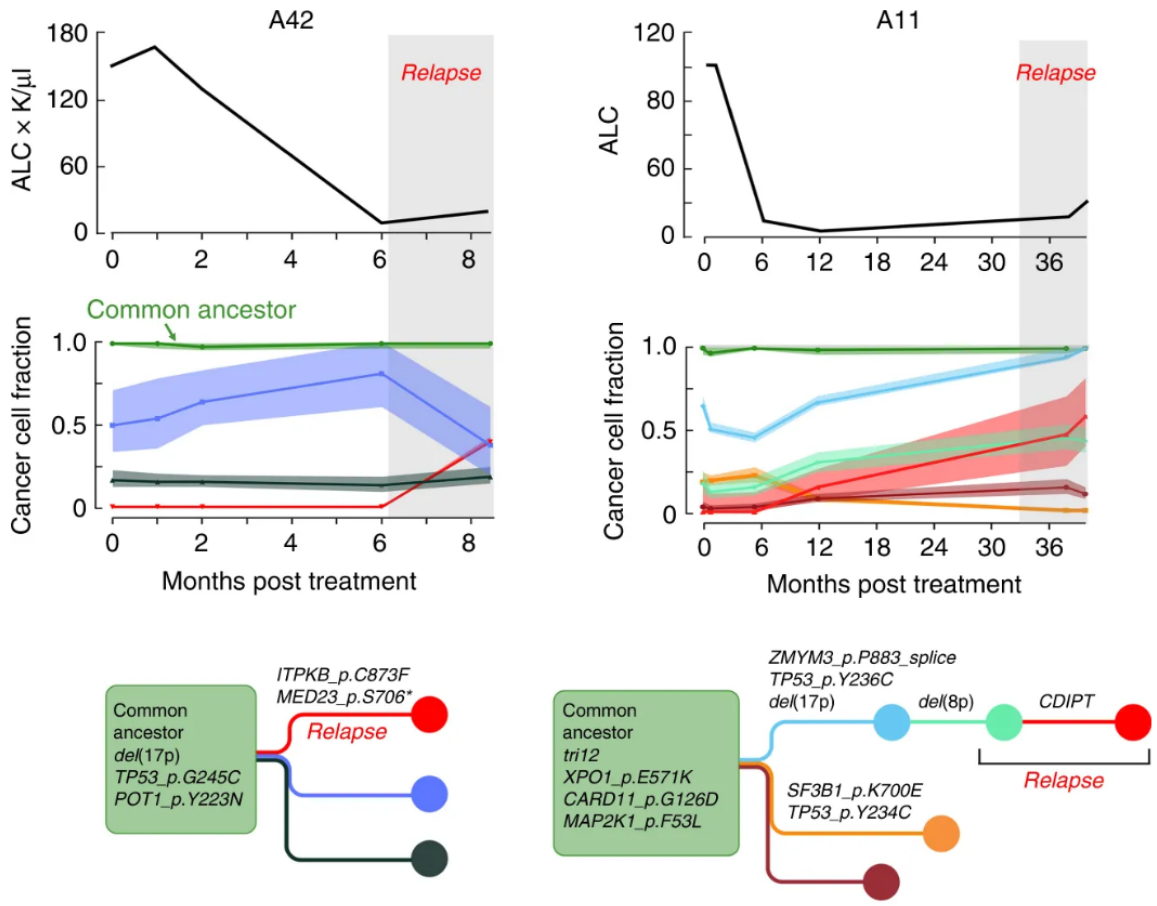
Blood. 2018 Jun 21;131(25):2745-2760. doi: 10.1182/blood-2017-09-806398. Epub 2018 Mar 14.
iwCLL guidelines for diagnosis, indications for treatment, response assessment, and supportive management of CLL

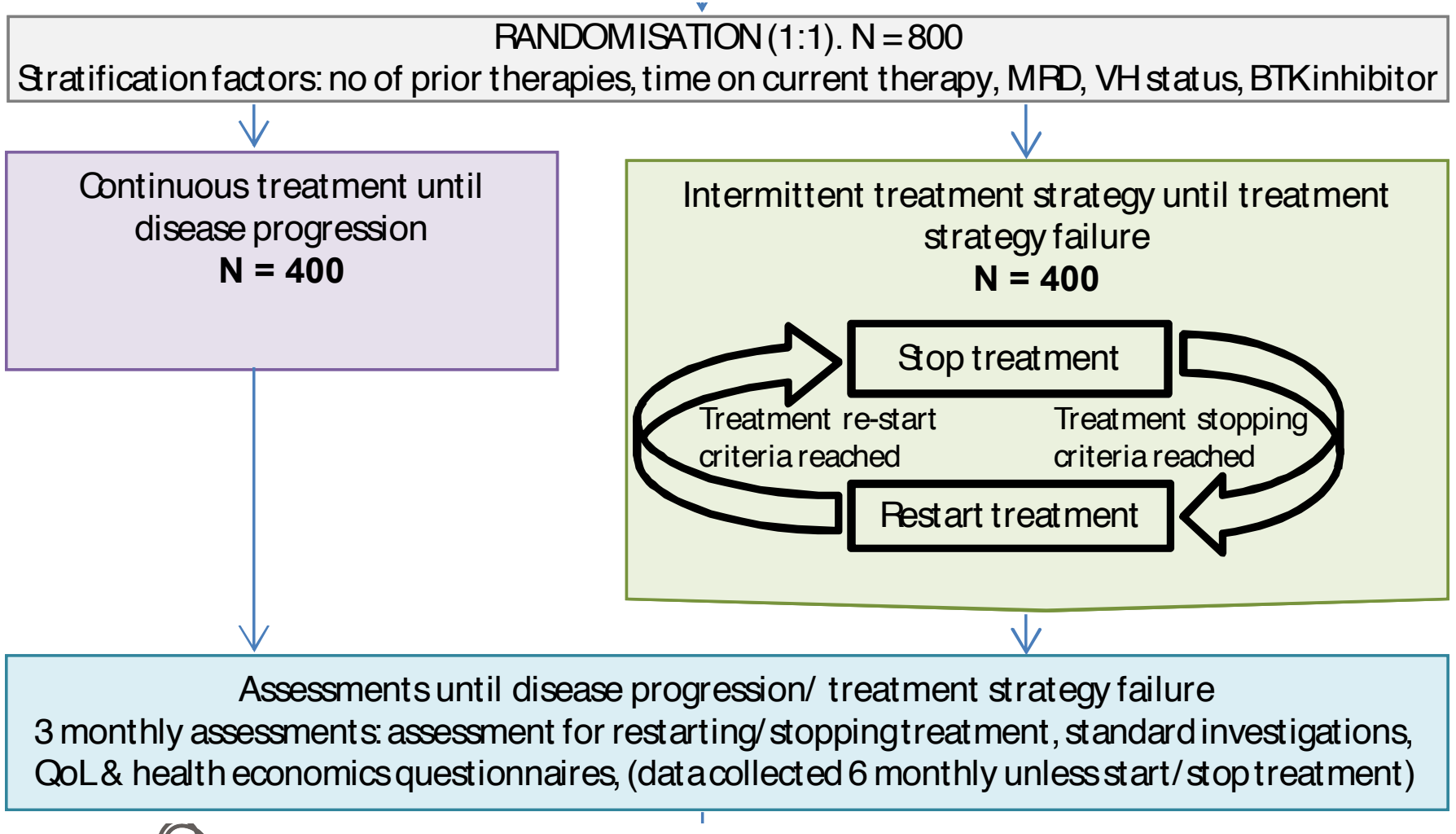
Measurable Residual Disease in CLL: back in the headlines

- Development of resistance mutations after 3-4years of continuous treatment.
- High cost of continuous treatment.
- Increased efficacy of combination approaches (ASH Dec' 2018 Session 642. "Measurable Residual Disease in CLL: Moving Towards a Cure") → time-limited treatments
- Biological rationale for treatment windows to avoid resistance



Dan Landau et al. *Nature Communications* **volume 8**, 2185 (2017)

STATIC: Stopping Therapy to Avoid Treatment-resistance In CLL



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

Can MRD be used to determine subsequent treatment strategy?

- Optimise combinations
  - BCL2i / BCRi / Antibodies / Chemotherapy
- Optimise duration of component treatment
  - BCL2i → 12 months
  - BCRi → ongoing
  - Antibodies → ? ongoing ? Low disease bulk

Conclusions: MRD in Chronic Lymphocytic Leukaemia (CLL)

- Clinical relevance
  - MRD level is relevant for most (if not all) trials and can be used to identify optimal combinations and duration of treatment components.
- Regulatory considerations
  - In most settings, MRD is a better predictor of PFS and OS than response status. PFS is the key endpoint for licensure, MRD may be an intermediate/accelerated endpoint as long as PFS benefit is confirmed.
- Funding/logistical challenges
- Technical issues

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