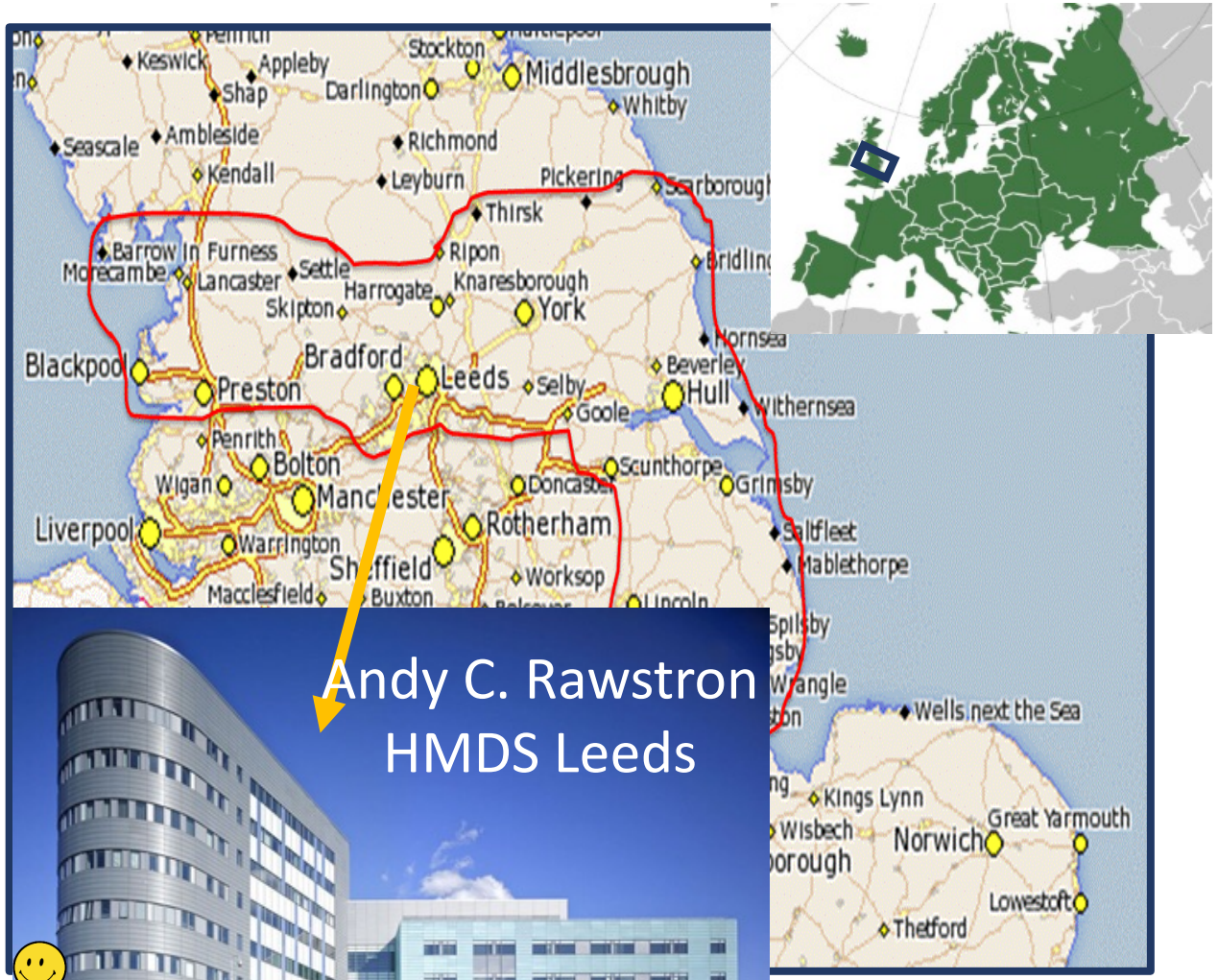
Laboratory assessment of CLL, including MRD as an endpoint



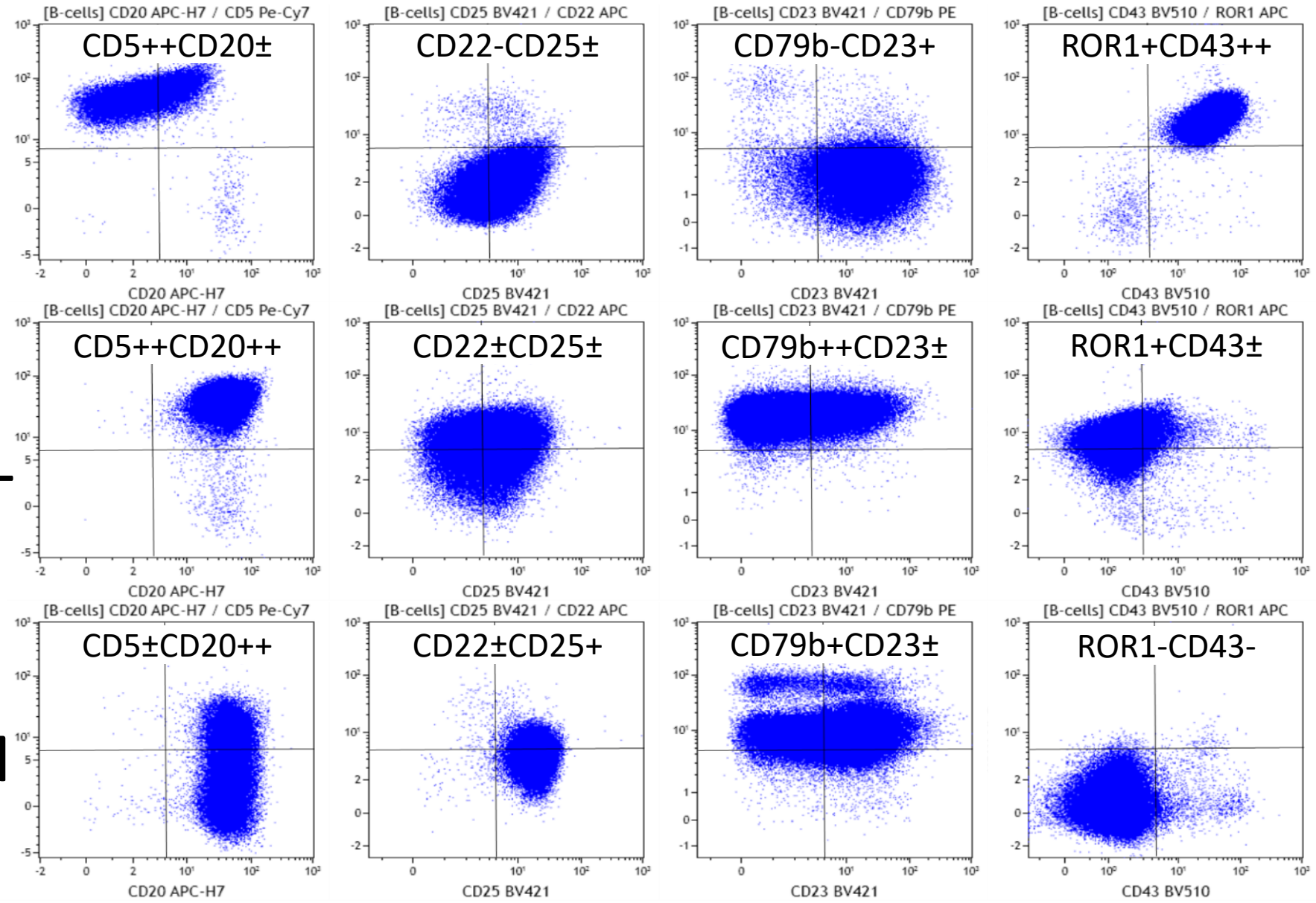
DISCLOSURES

Abbvie: Advisory Board, Research Funding, Honoraria. *BD Bio-sciences:* Research Funding, Honoraria. *Beckman Coulter:* Research Funding, Honoraria *Celgene:* Advisory Board, Consultancy, Research Funding. *Gilead:* Consultancy, Advisory Board, Research Funding. *Janssen:* Advisory Board, Research Funding, Honoraria. *Pharmacyclics:* Consultancy, Research Funding. *Roche:* Advisory Board, Research Funding.

Reproducible diagnosis of CLL by flow cytometry: an ERIC & ESCCA harmonisation project

ERIC european research initiative on CLL

ESCCA European Society for Clinical Cell Analysis



CLL

MCL

WM

Driver

BCR-pathway signalling

CCND1-IGH translocation

MYD88 mutation

"Atypical" CLL: implications for differential diagnosis (vs. mantle cell or WM/LPL/MZL) and disease monitoring

Phenotype	% of total CD5+ B-LPD	Proportion of cases with either CCND1-IGH or MYD88 L265P	Comment
"Typical": CD5^{+} CD23^{+} sIg^{wk} CD20^{wk} CD200^{+} ROR1^{+} CD43^{+} CD81^{wk}	65%	CCND1-IGH <0.1% MYD88 mutation <5%*	Driver = BCR signalling Phenotype suitable for monitoring
CD5+CD23+ ≥1 other marker "atypical"	20%	20-50% **	Disease driver may be unknown Phenotype may not be suitable for monitoring
CD5+CD23-	15%	>50%	

Reproducible diagnosis of CLL by flow cytometry: an ERIC & ESCCA harmonisation project

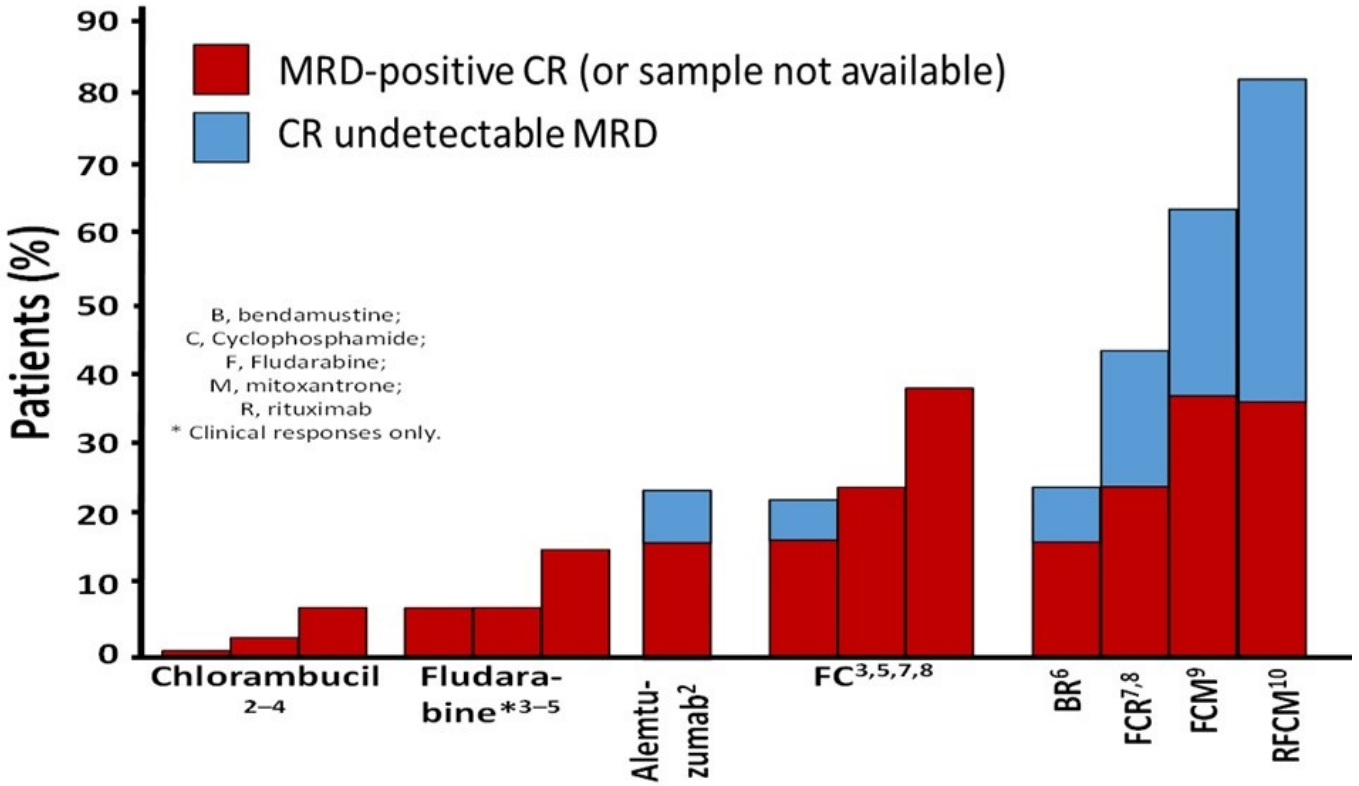
ERIC european research initiative on CLL

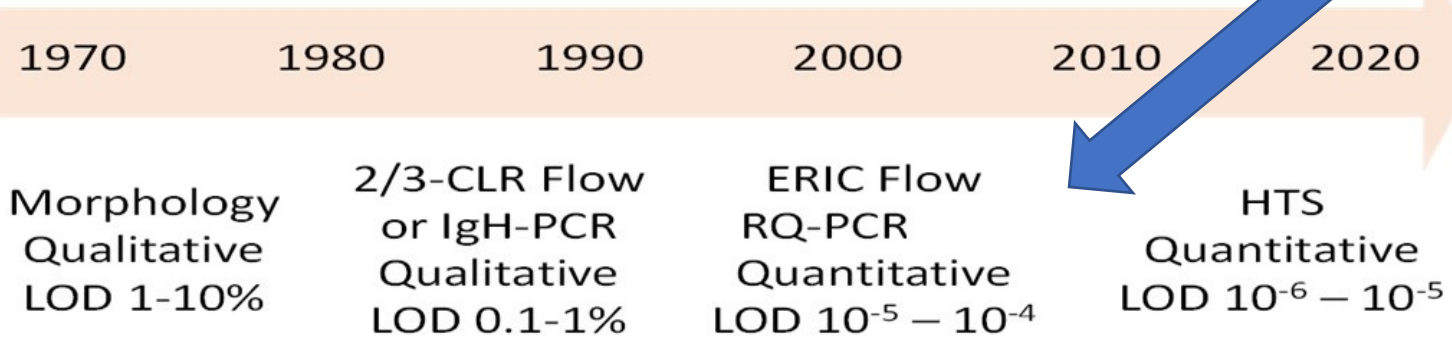
ESCCA European Society for Clinical Cell Analysis

* usually 2nd CD5neg monoclonal B-cell pop^{n}

** ~ ⅓ MCL cases in this category also CD200±

Measurable Residual Disease in CLL

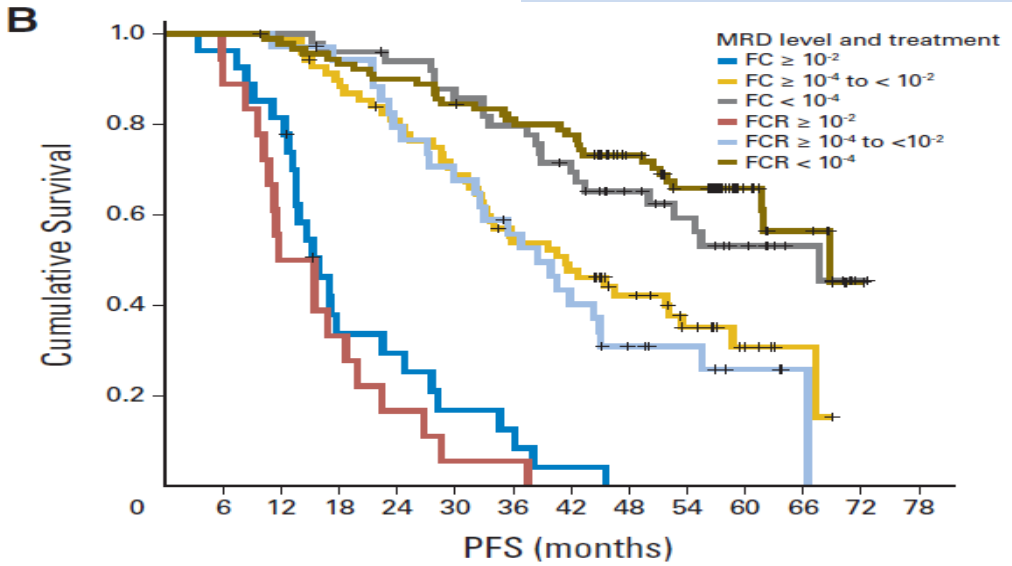




Graph is composed of data from multiple independent studies.

Böttcher S et al

VOLUME 30 · NUMBER 9 · MARCH 20 2012
JOURNAL OF CLINICAL ONCOLOGY

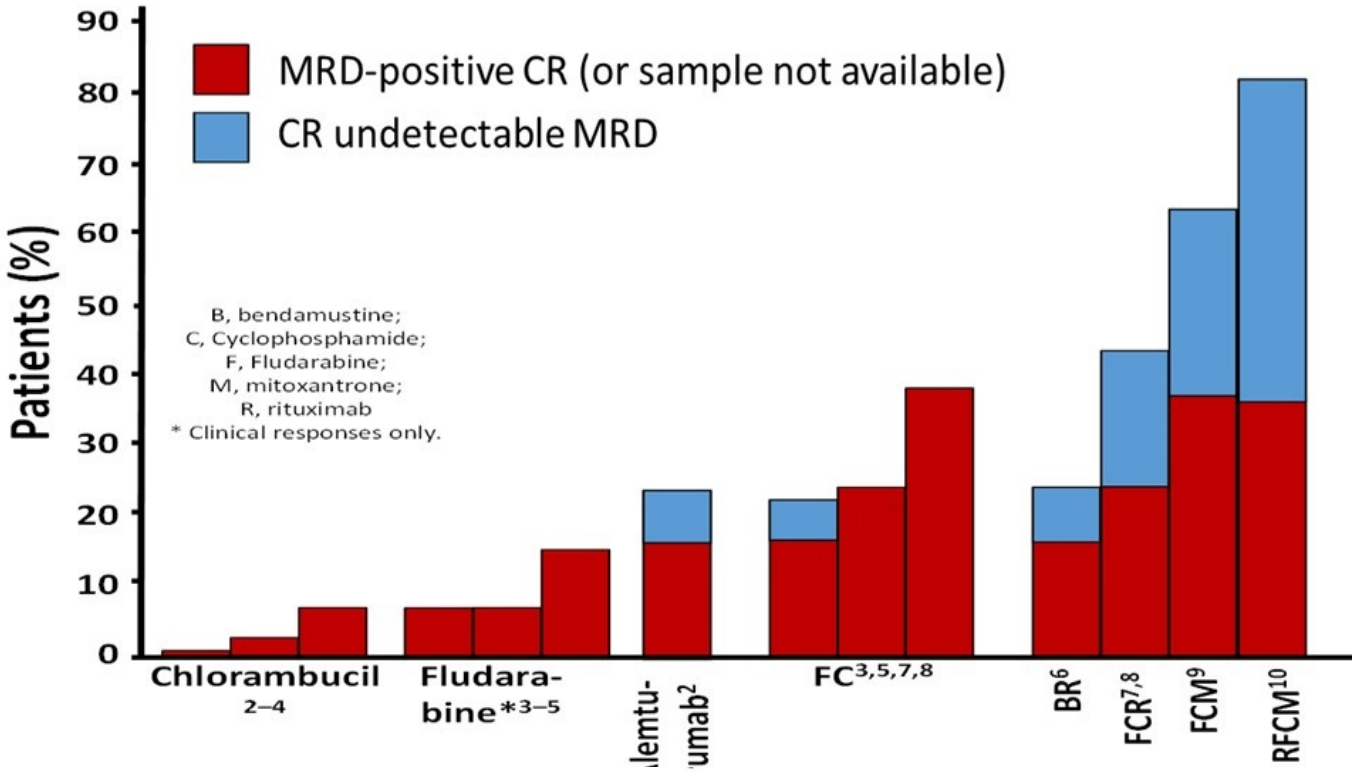


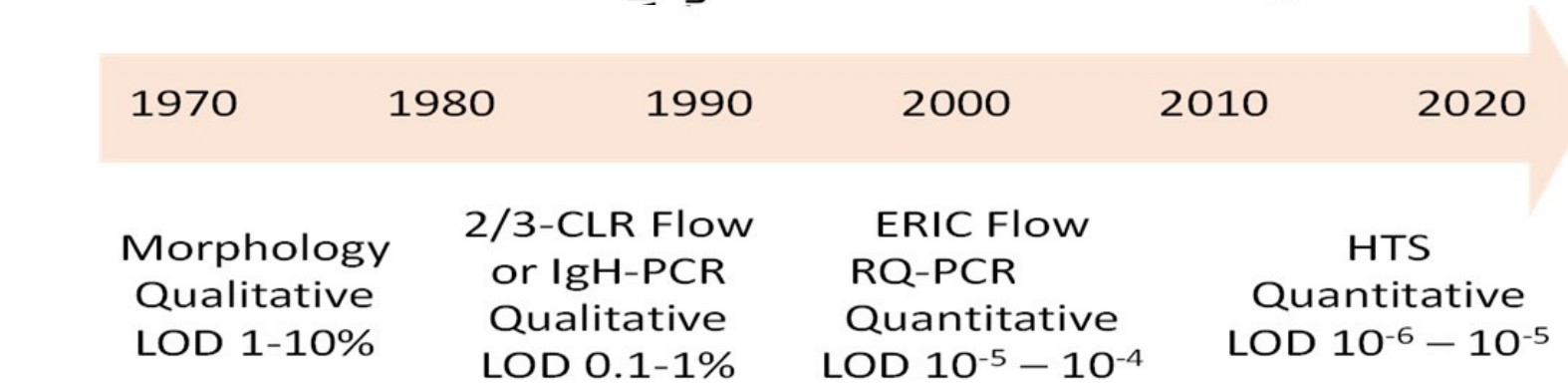
MRD becomes relevant:

1) >50% of patients achieve CR
2) Assay is directly quantitative
3) Randomised trial → MRD prediction is Rx-independent

1. Adapted from: Ghia P. *Hematology* 2012; **2012:**97–104; 2. Hillmen P, *et al. J Clin Oncol* 2007; **25:**5616–5623; 3. Catovsky D, *et al. Lancet* 2007; **370:**230–239; 4. Eichhorst BF, *et al. Blood* 2009; **114:**3382–3391; 5. Eichhorst BF, *et al. Blood* 2006; **107:**885–891; 6. Fischer K, *et al. J Clin Oncol* 2012; **30:**3209–3216; 7. Hallek M, *et al. Lancet* 2010; **376:**1164–1174; 8. Böttcher S, *et al. J Clin Oncol* 2012; **30:**980–988; 9. Bosch F, *et al. Clin Cancer Res* 2008; **14:**155–161; 10. Bosch F, *et al. J Clin Oncol* 2009; **27:**4578–4584; 11. Seymour J, *et al. Lancet Oncol* 2017; **18**:230-240.

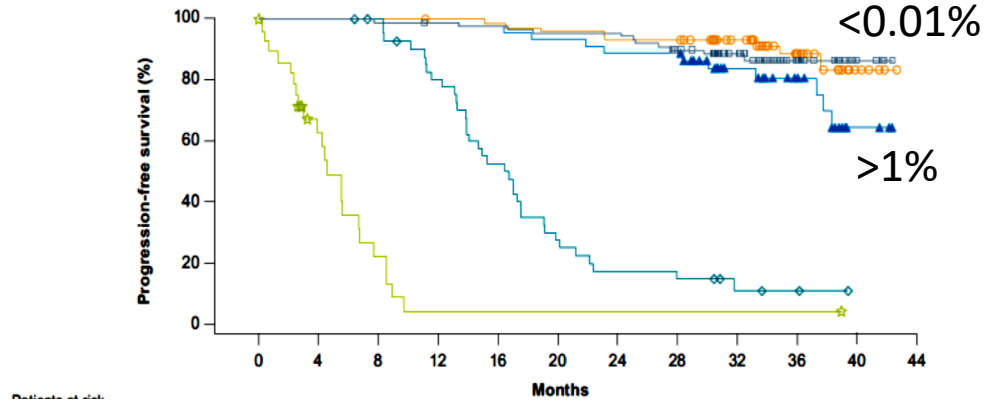
Measurable Residual Disease in CLL



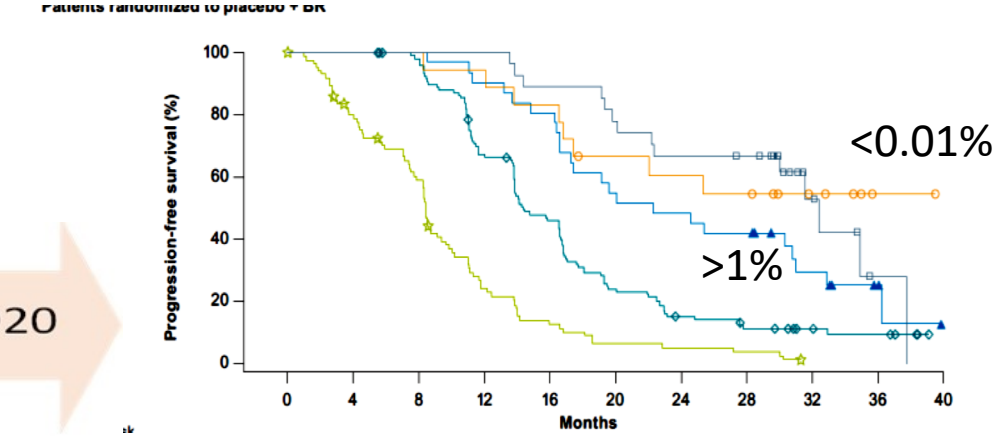


Gr

HELIOS R/R CLL n=578 Bendumastine rituximab 6 cycles followed by ibrutinib monotherapy or placebo
https://www.ncbi.nlm.nih.gov/pubmed/30315239

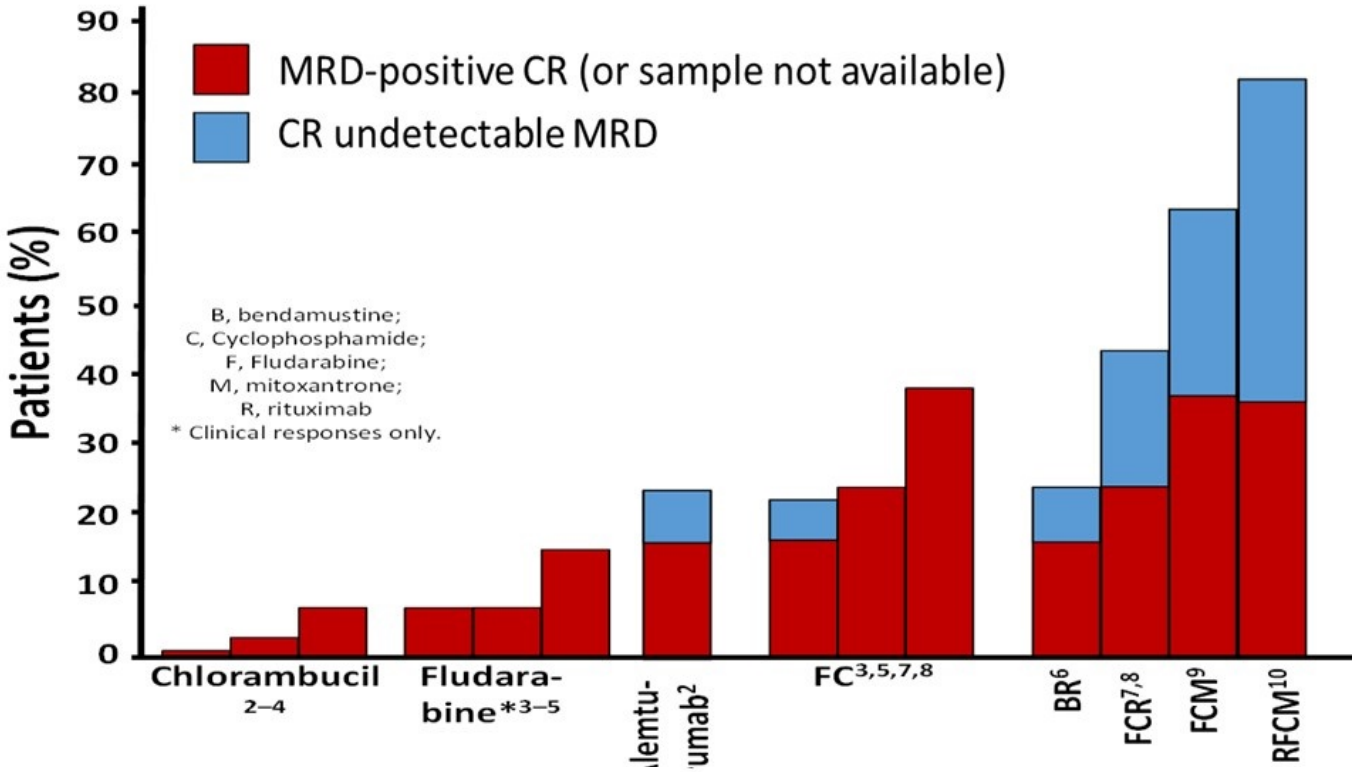


BR+IBR → Similar PFS for >1% vs <0.01% MRD



BR only → improved PFS for MRD <0.01% vs. >1%

Measurable Residual Disease in CLL



1970 1980 1990 2000 2010 202

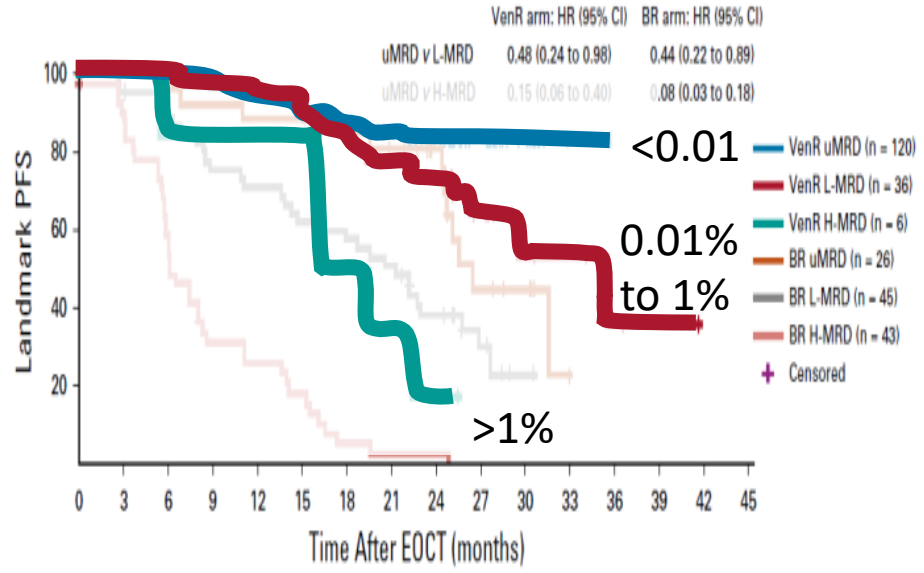
Morphology
Qualitative
LOD 1-10%

2/3-CLR Flow
or IgH-PCR
Qualitative
LOD 0.1-1%

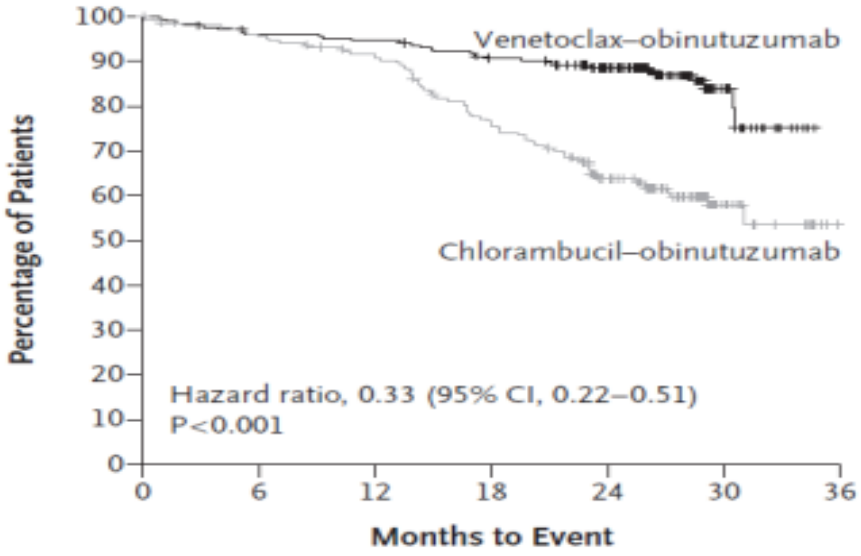
ERIC Flow
RQ-PCR
Quantitative
LOD $10^{-5} - 10^{-4}$

HTS
Quantitativ
LOD $10^{-6} - 10^{-5}$

Gr

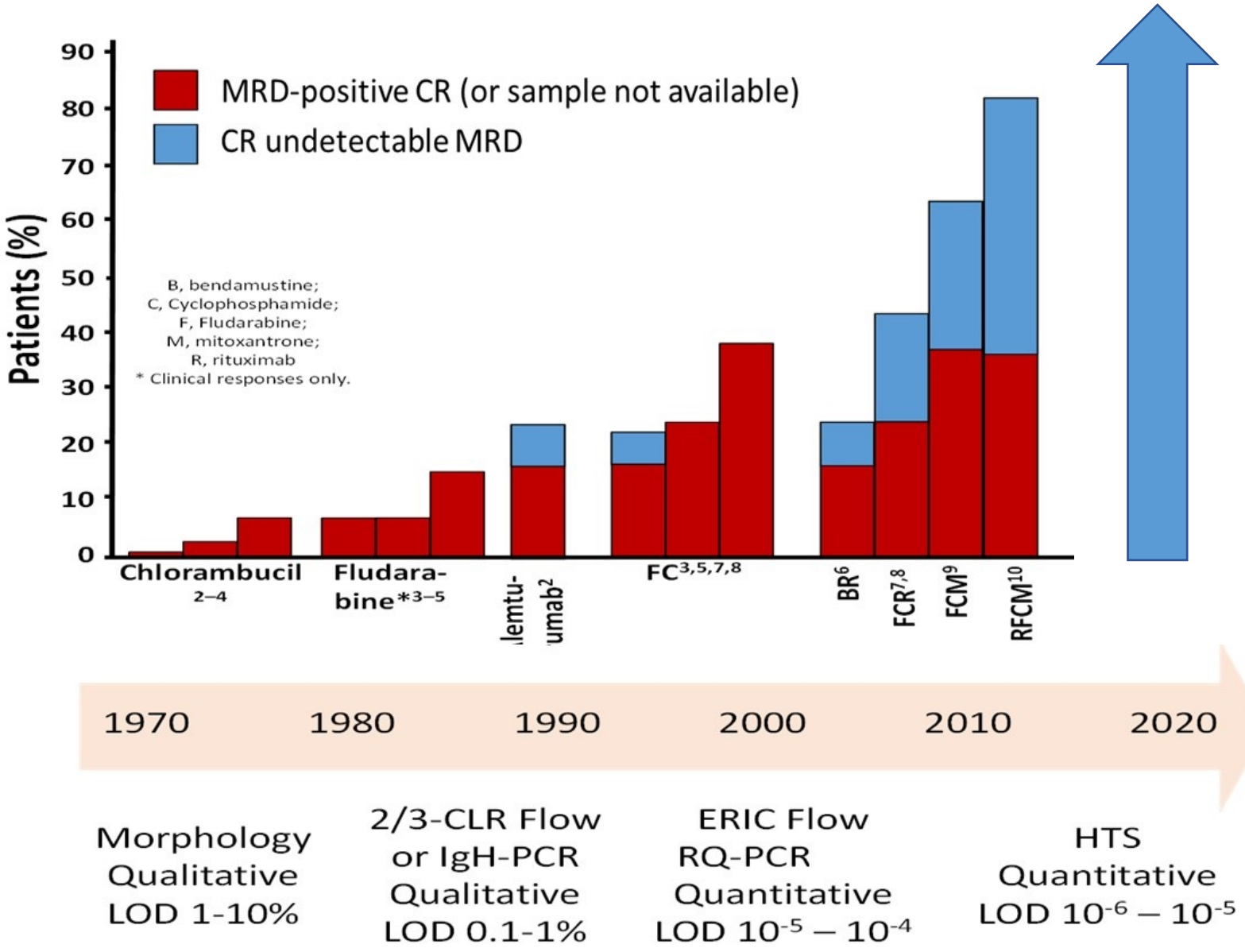


https://www.ncbi.nlm.nih.gov/pubmed/30523712



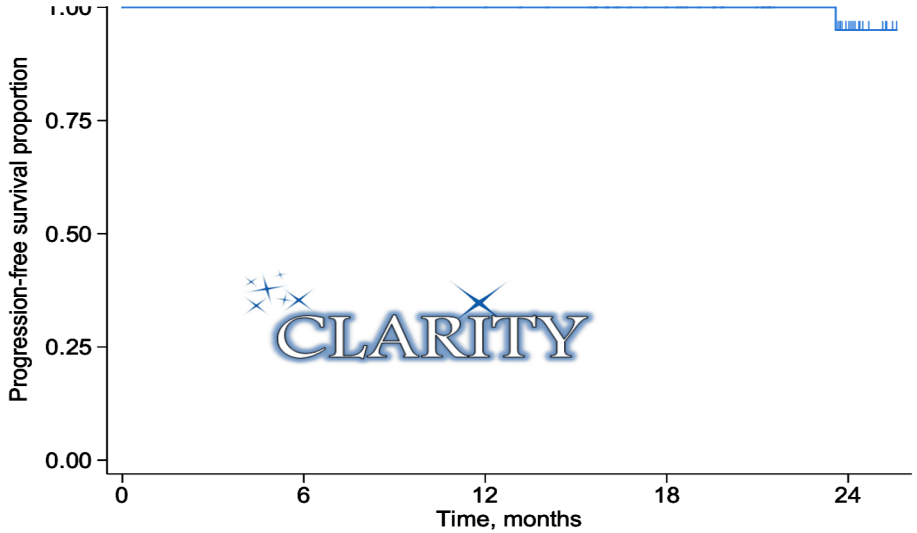
https://www.nejm.org/doi/full/10.1056/NEJMoa1815281

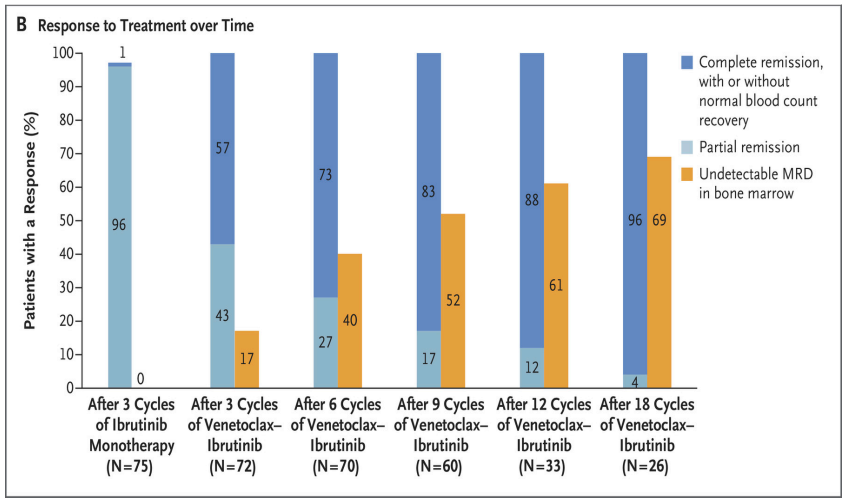
Measurable Residual Disease in CLL



Graph is composed of data from multiple independent studies.

ASH Dec' 2018 **Measurable Residual Disease in CLL: Moving Towards a Cure**





Jain et al, NEJM May 2019

96% CR with

69% BM MRD <0.01%

https://www.ncbi.nlm.nih.gov/pubmed/31141631

MRD as an intermediate endpoint for licensing

Appendix 4 to the guideline on the evaluation of anticancer medicinal products in man

Condition Specific Guidance

Agreed by Oncology Working Party	June 2014
Agreed by CHMP for release for consultation	23 October 2014
Start of public consultation	15 December 2014
End of consultation (deadline for comments)	30 June 2015
Agreed by Oncology Working Party	November 2015
Adoption by CHMP for publication	17 December 2015
Date for coming into effect	1 July 2016

7. Minimal residual disease as an endpoint in chronic lymphocytic leukaemia studies NEW 16

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Hematologic Malignancies: Regulatory Considerations for Use of Minimal Residual Disease in Development of Drug and Biological Products for Treatment

Guidance for Industry

OCTOBER 2018

Download the Draft Guidance Document | Read the Federal Register Notice

Draft

Not for implementation. Contains non-binding recommendations.

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Docket Number: FDA-2018-D-3090

Issued by: Center for Drug Evaluation and Research
Center for Biologics Evaluation and Research

FDA U.S. FOOD & DRUG ADMINISTRATION

IWCLL, EMA and FDA - concordance

- “patients will be defined as having undetectable MRD (MRD-neg) remission if they have blood or marrow with <1 CLL cell per 10 000 leukocytes.”
- “report the proportion of MRD-neg patients on an intent-to-treat basis using the total number of patients in that treatment arm as the denominator (not those assessed or those who responded to treatment).”
- “Six-color flow cytometry (MRD flow), allele-specific oligonucleotide PCR, or high-throughput sequencing using the ClonoSEQ assay are reliably sensitive down to a level of <1 CLL cell in 10 000 leukocytes” or “FDA is agnostic to which technology platform is used in clinical trials assessing MRD”

IWCLL guidelines https://www.ncbi.nlm.nih.gov/pubmed/29540348
https://www.fda.gov/media/117035/download

https://www.ema.europa.eu/en/documents/scientific-guideline/evaluation-anticancer-medicinal-products-man-appendix-4-condition-specific-guidance-rev2_en.pdf

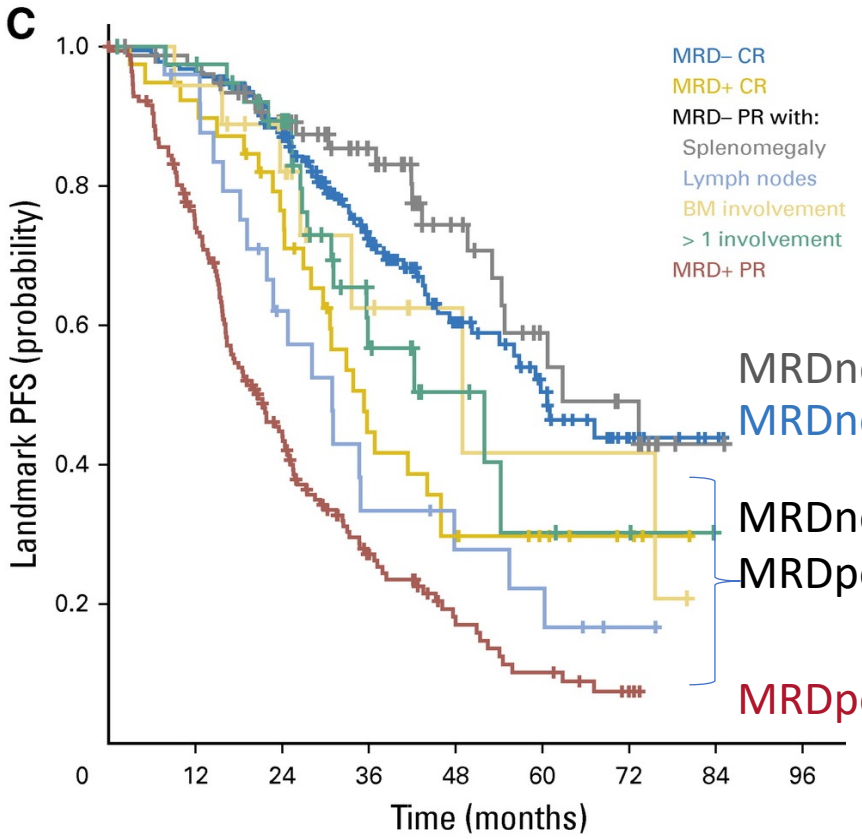
IWCLL, EMA and FDA - variations

- EMA: MRD response rate is defined as the proportion of patients in the ITT population in whom a clinical complete response (CR) and undetectable MRD status in bone marrow is achieved following induction treatment in CLL.
- FDA: MRD should be assessed in patients that are in CR. If MRD assessments are to be made in patients in other response categories (e.g., partial response (PR)), the sponsors should include data to justify the plan.
- IWCLL: not specifically stated

IWCLL guidelines https://www.ncbi.nlm.nih.gov/pubmed/29540348
https://www.fda.gov/media/117035/download

https://www.ema.europa.eu/en/documents/scientific-guideline/evaluation-anticancer-medicinal-products-man-appendix-4-condition-specific-guidance-rev2_en.pdf

Relationship between MRD and response status varies with treatment



MRDneg PR (splenomegaly)

MRDneg CR

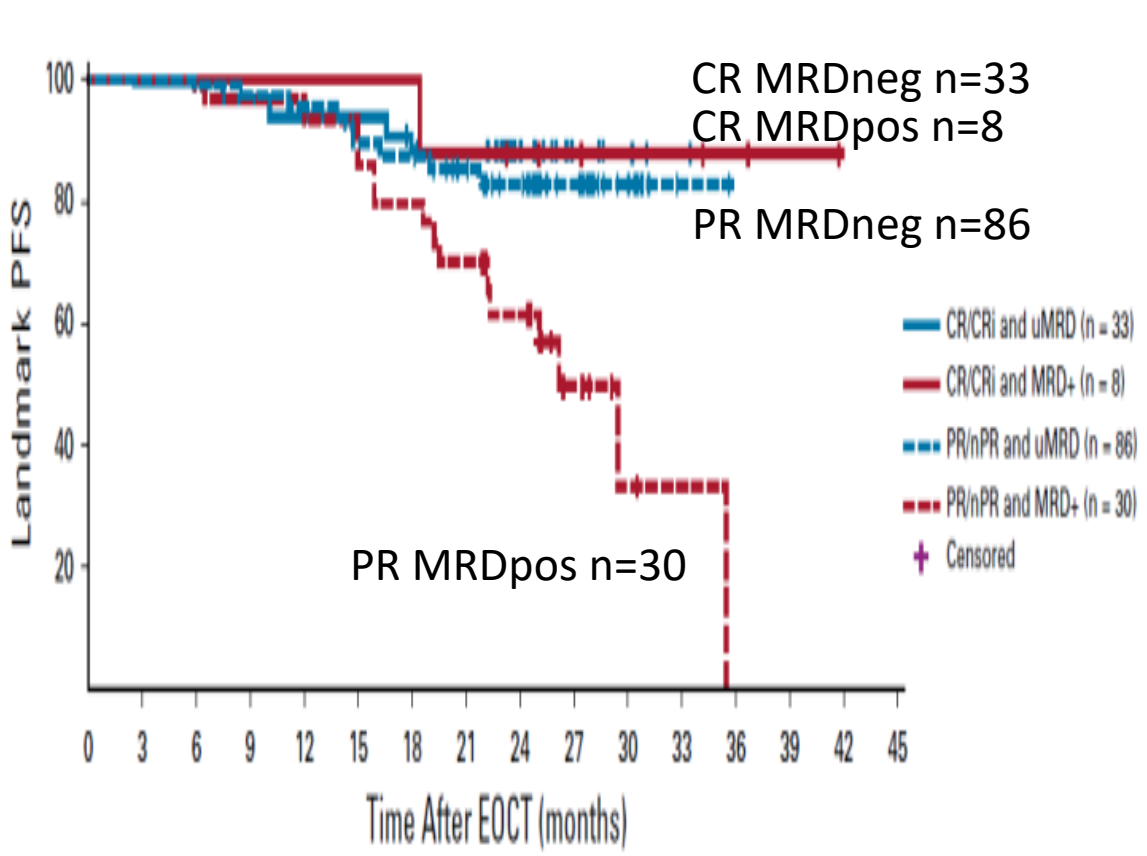
MRDneg PR (LN/BM) or MRDpos CR

MRDpos PR

No. at risk	0	12	24	36	48	60	72	84
MRD– CR	186	179	134	75	43	27	10	2
MRD+ CR	39	36	28	15	10	6	3	0
MRD– PR with								
Splenomegaly	78	74	58	37	21	12	8	1
Lymph nodes	25	23	13	7	5	4	1	0
BM involvement	18	17	12	6	3	2	2	0
> 1 involvement	40	38	30	13	6	3	2	0
MRD+ PR	168	119	65	31	15	9	3	0

Kovacs et al
CLL8 & CLL10

https://www.ncbi.nlm.nih.gov/pubmed/27573660



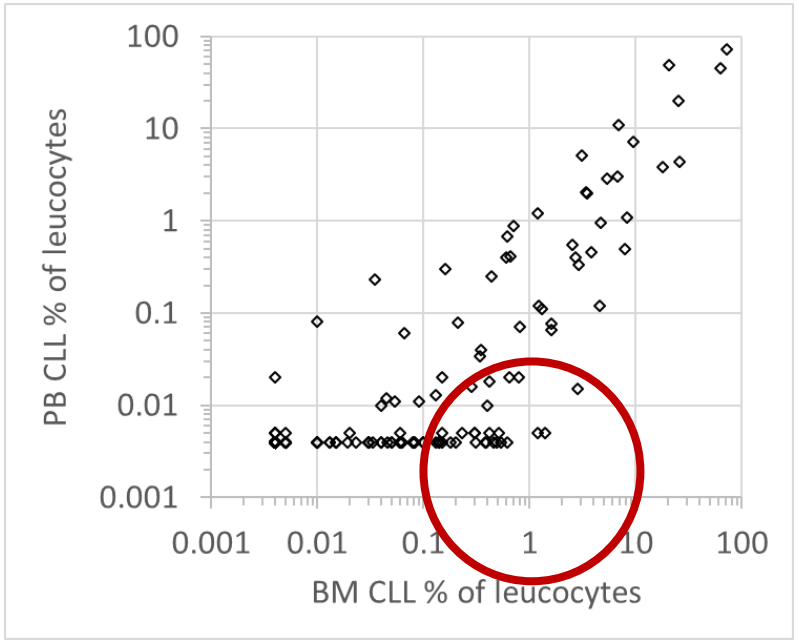
Fixed Duration of Venetoclax-Rituximab in Relapsed/Refractory Chronic Lymphocytic Leukemia Eradicates Minimal Residual Disease and Prolongs Survival: Post-Treatment Follow-Up of the MURANO Phase III Study

https://www.ncbi.nlm.nih.gov/pubmed/30523712

IWCLL, EMA and FDA - variations

- EMA: all patients with clinical response (CR or PR) should be assessed for MRD in PB first. Only patients with undetectable MRD in PB should have confirmation of MRD status in BM
- FDA: it may be acceptable to use the PB as a screening assessment with confirmation in the BM if the PB suggests MRD negativity,
- IWCLL: there are therapies that preferentially clear the blood but not the marrow (such as monoclonal antibodies); therefore, it may be important to confirm that the marrow aspirate also is MRD-neg when the blood is found to be MRD-neg.

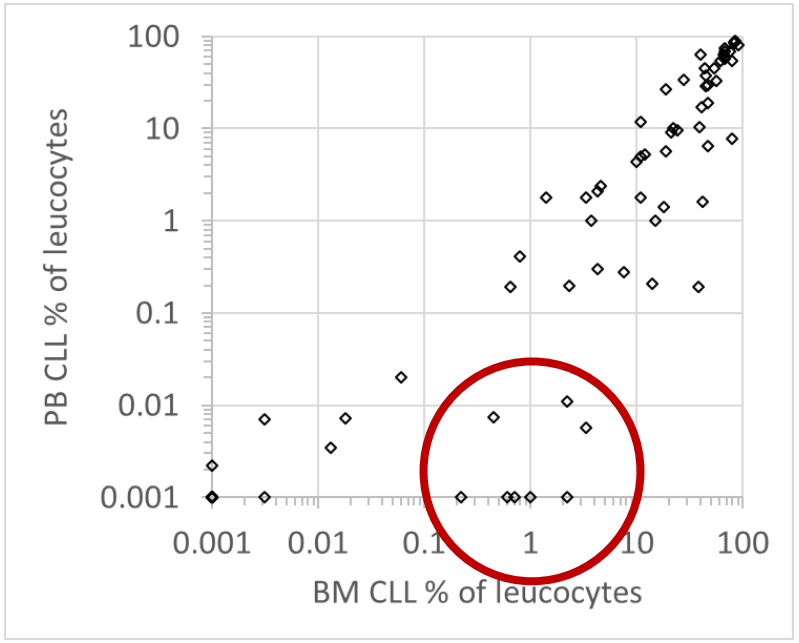
Discrepancies between peripheral blood and bone marrow MRD



FCR-based TN

Median >0.88 log

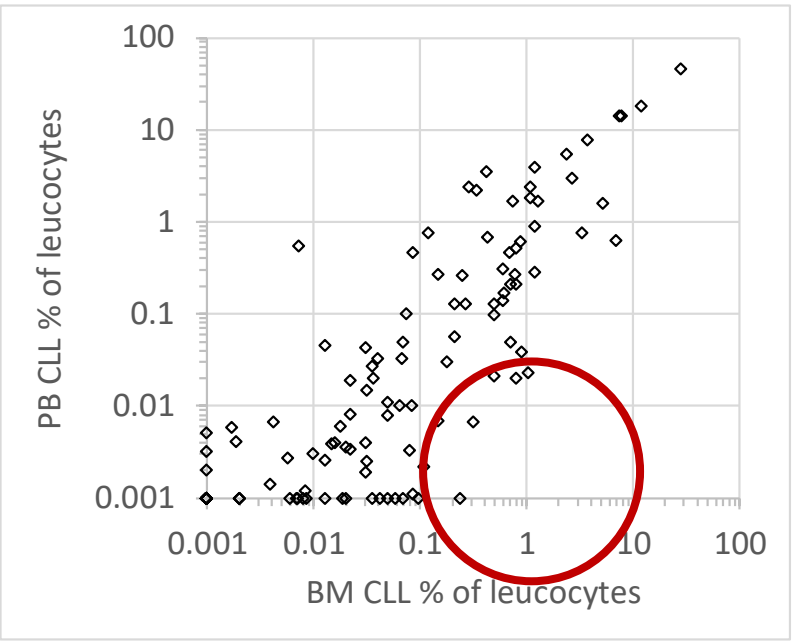
>2log 8/272 (3%)



IBR+OBI R/R

Median >0.36 log

>2log 8/76 (11%)



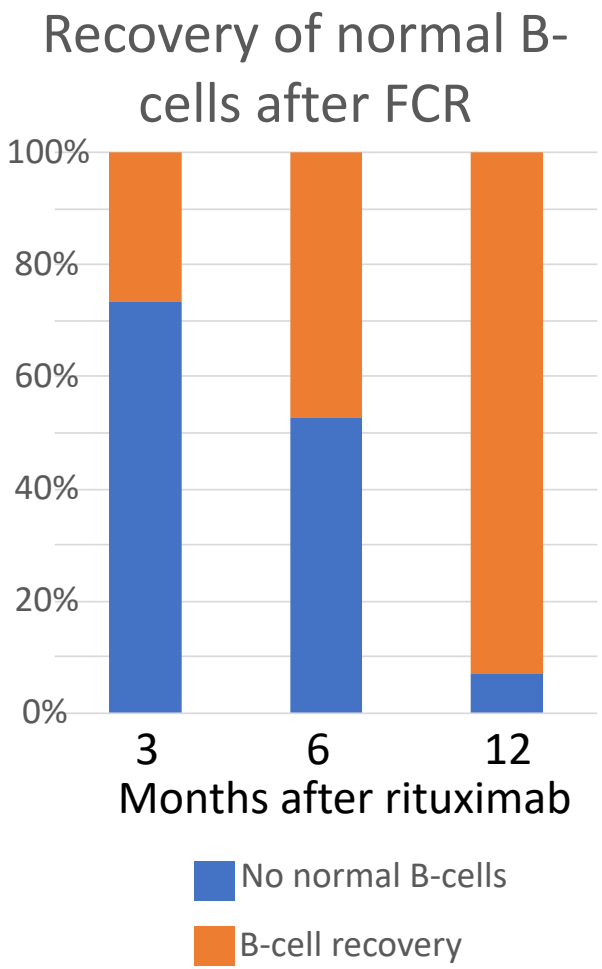
IBR+VEN R/R

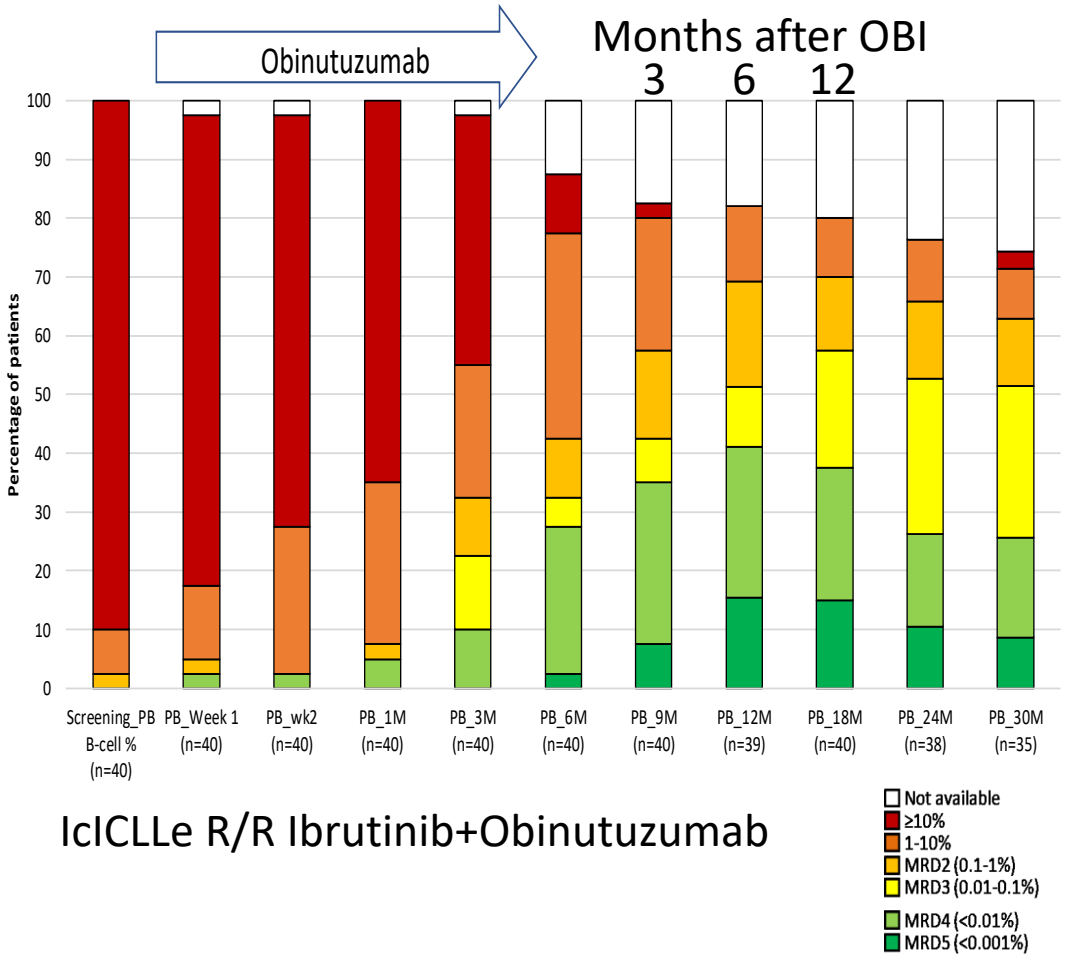
Median >0.48 log

>2log 1/142 (<1%)

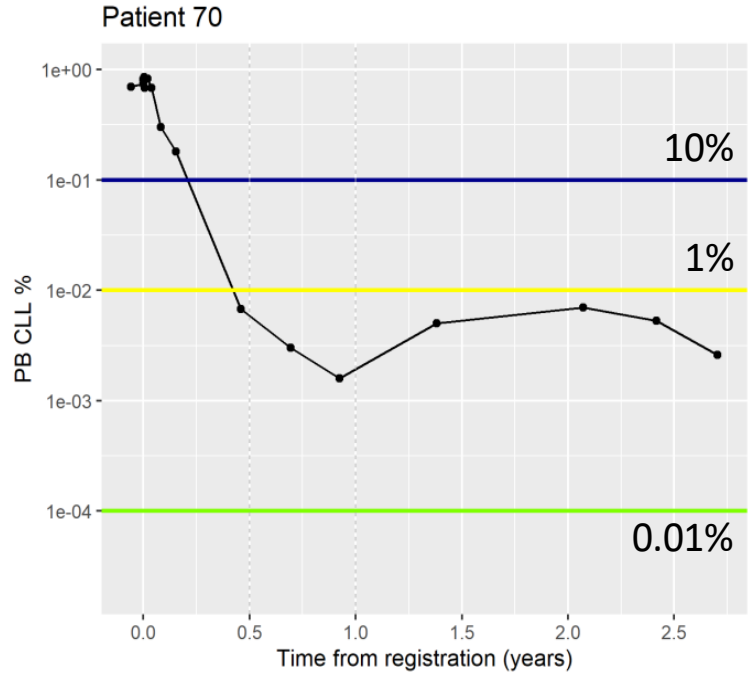
PB vs. BM: anti-CD20 therapeutic antibodies

- CLL14 Venetoclax-obinutuzumab PB 76% vs. BM 57%
- Chlorambucil-obinutuzumab PB 35% vs. BM 17%





IcICLLe R/R Ibrutinib+Obinutuzumab



PB vs. BM: Venetoclax

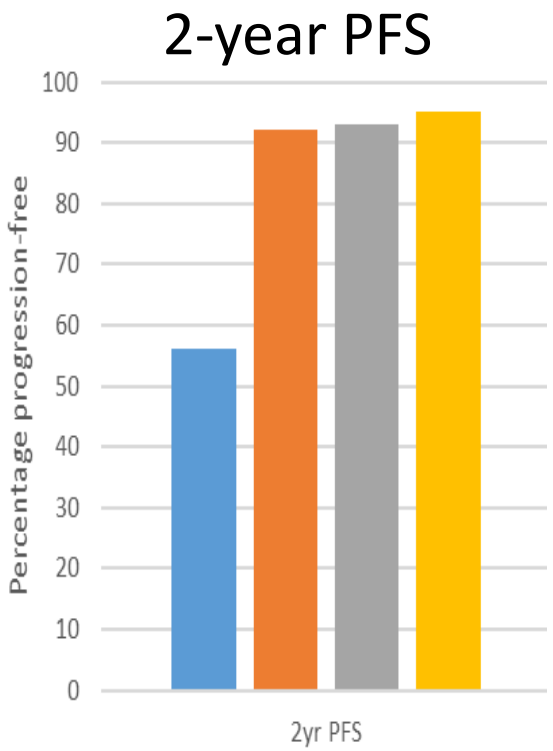
# with Bone Marrow MRD4 <0.01% CLL (% of patients per PB MRD level)			
Months on VEN	**PB MRD ≥0.01%**	**PB MRD 0.001-0.01%**	**PB MRD <0.001%**
6	1/28 (4%)	4/9 **(44%)**	8/11 **(73%)**
12	0/20 (0%)	5/12 **(42%)**	15/17 **(88%)**

IWCLL, EMA and FDA - variations

- the sensitivity of the MRD assay should be at least 10-fold below the clinical decision-making threshold (the definition of MRD). For example, if MRD positive or negative is defined as detection of greater or less than 1x10-5 cells, respectively, then the assay should be optimized and validated to have an analytical sensitivity of at least 1x10-6.

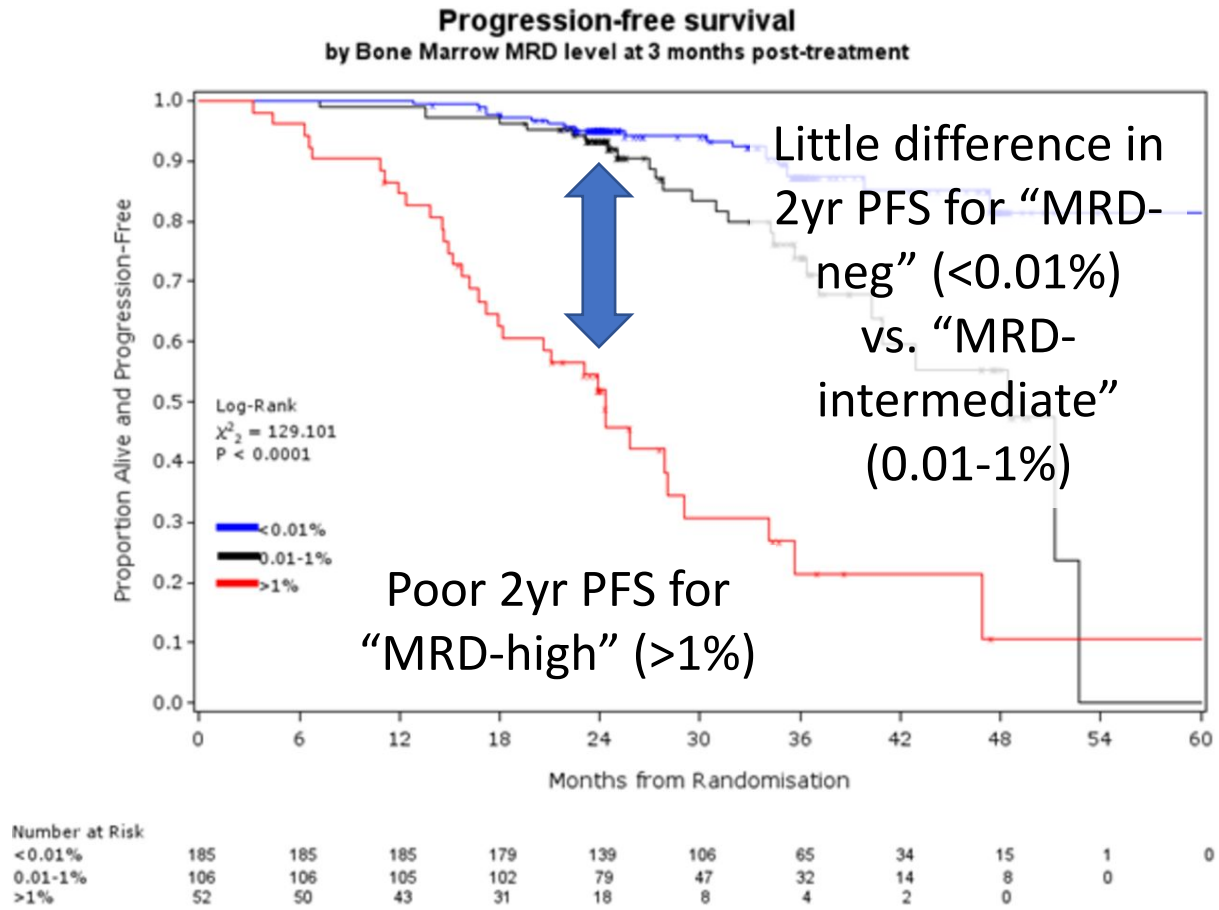
https://www.fda.gov/media/117035/download

>1% or “high” and “undetectable” MRD levels have different implications



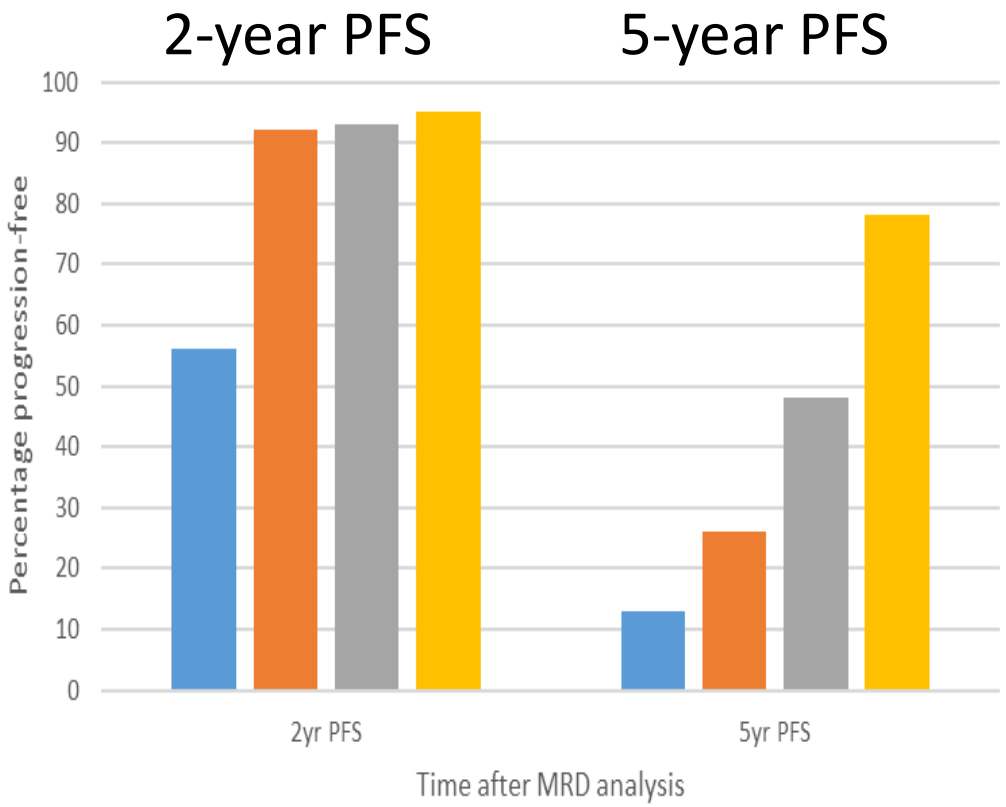
TN CLL
FCR-based Rx
n=343

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



http://www.bloodjournal.org/content/126/23/1717

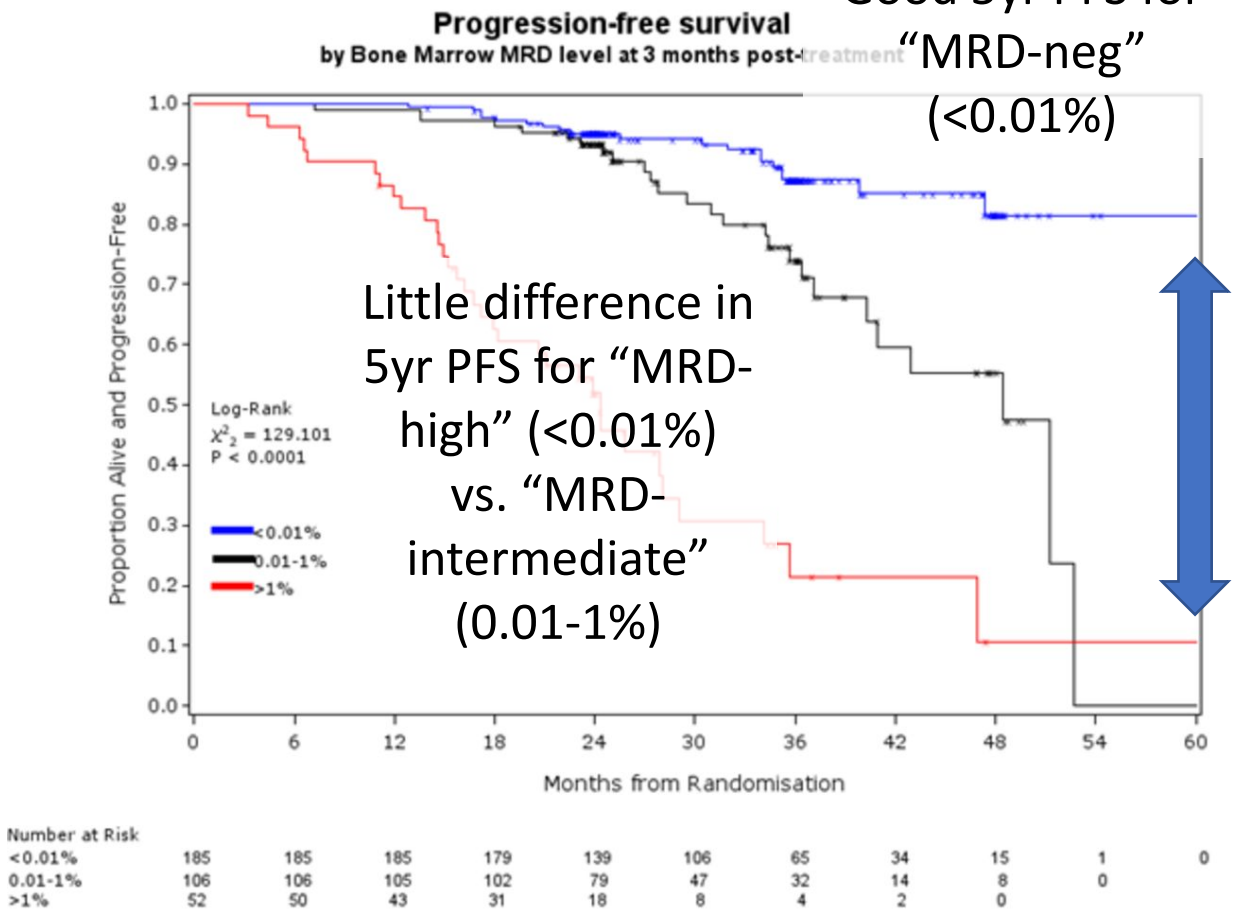
“High” and “undetectable” MRD levels have different implications



TN CLL
FCR-based Rx
n=343

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

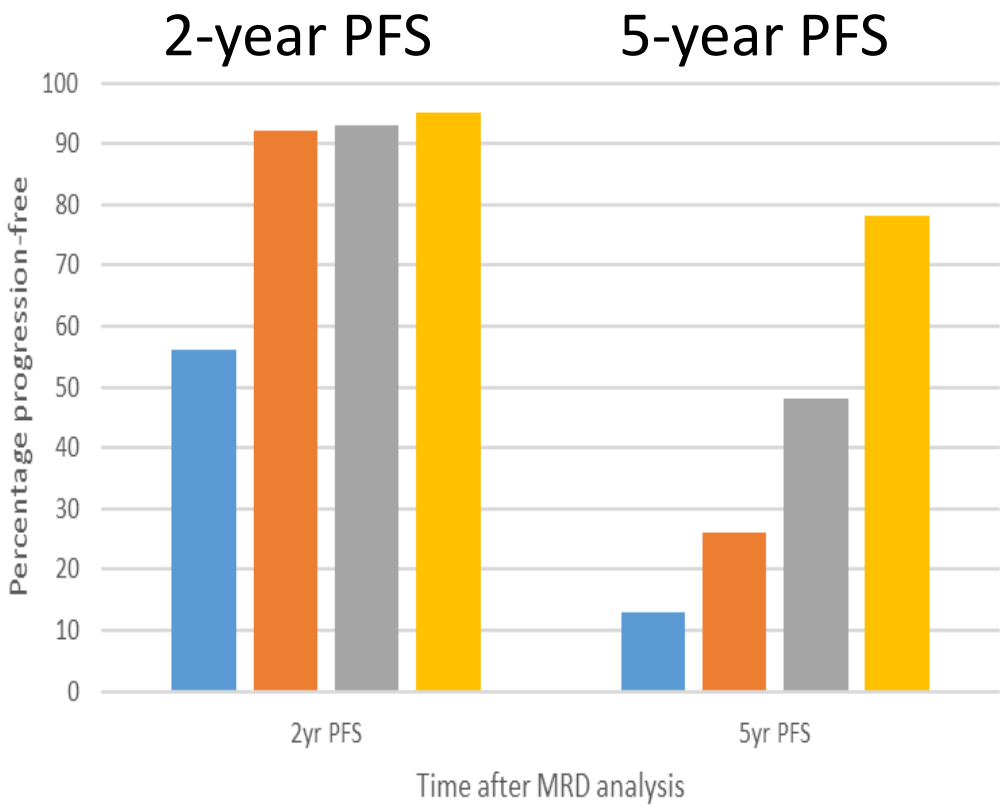
Good 5yr PFS for “MRD-neg” (<0.01%)



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

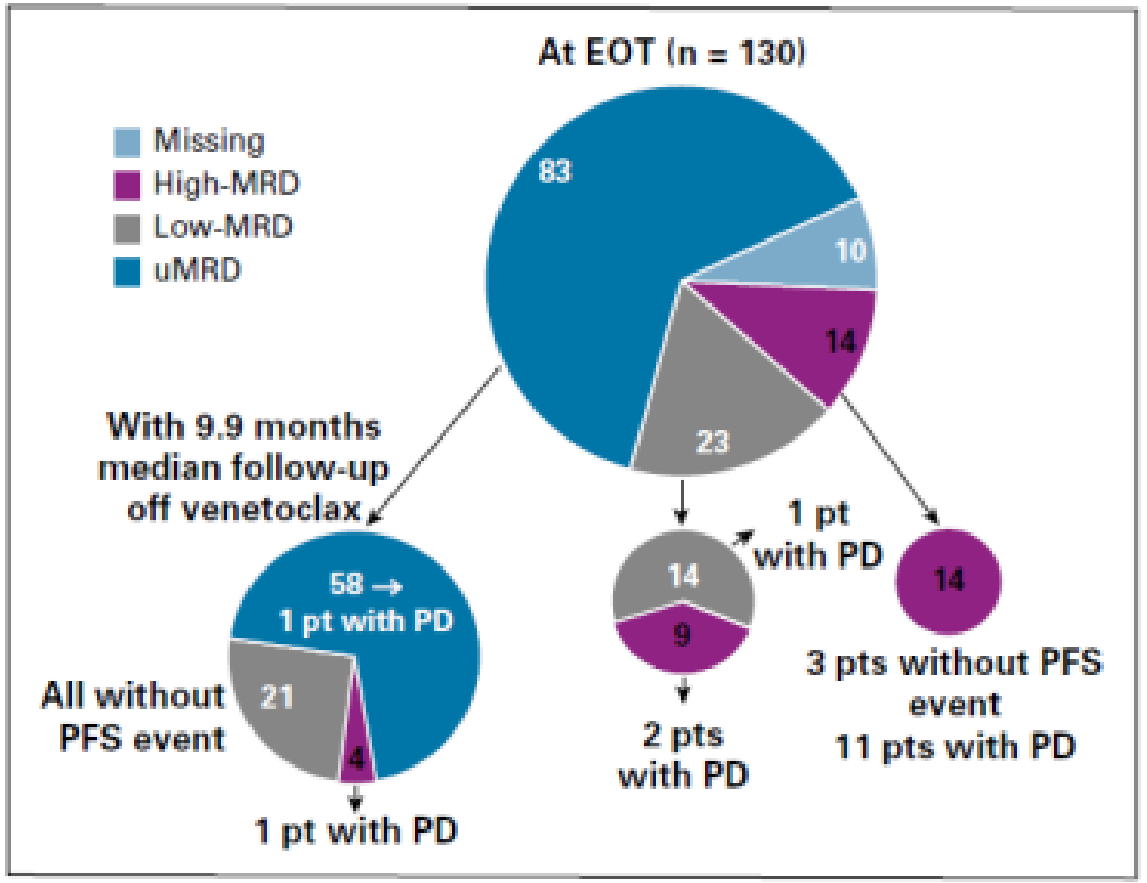
http://www.bloodjournal.org/content/126/23/1717

“High” MRD and “undetectable” MRD have different applications



TN CLL
FCR-based Rx
n=343

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



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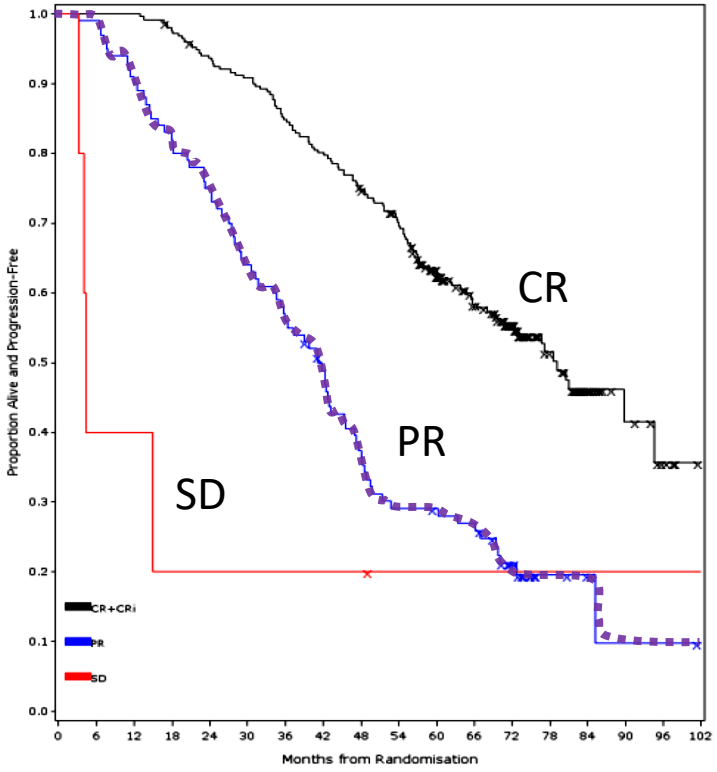
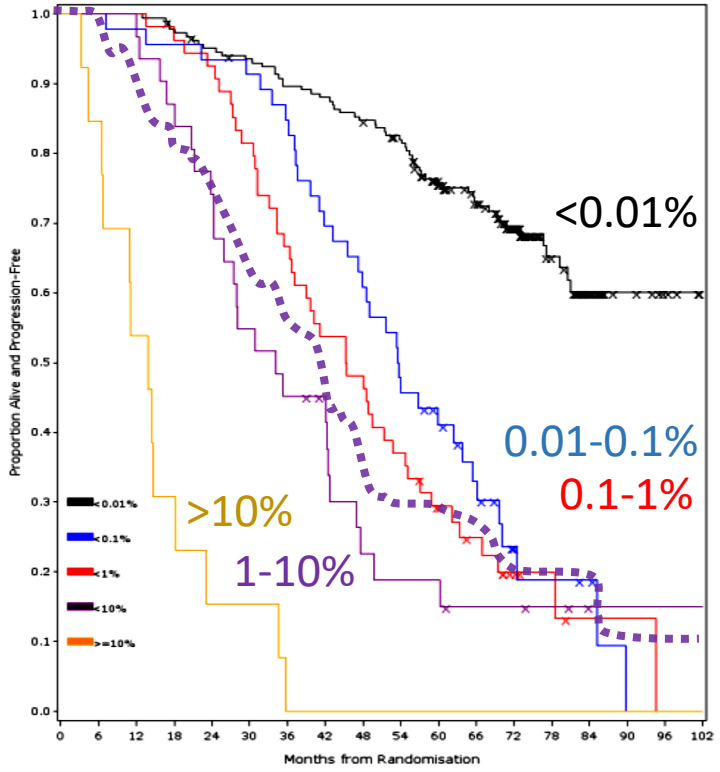
https://www.ncbi.nlm.nih.gov/pubmed/30523712

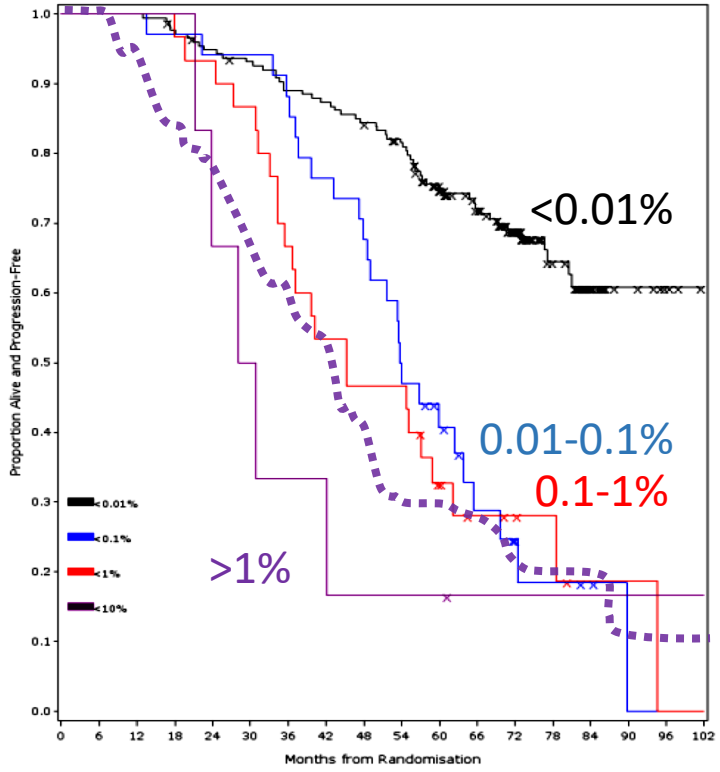
>1% “high” MRD = PR

Partial response

Proportion progression-free







Number at Risk

CR+CRi	253	253	253	246	235	228	213	201	187	172	138	109	74	40	19	9	4	0
PR	100	99	90	82	75	64	56	47	36	28	27	25	15	5	3	1	1	0
SD	5	2	2	1	1	1	1	1	1	0								

Number at Risk

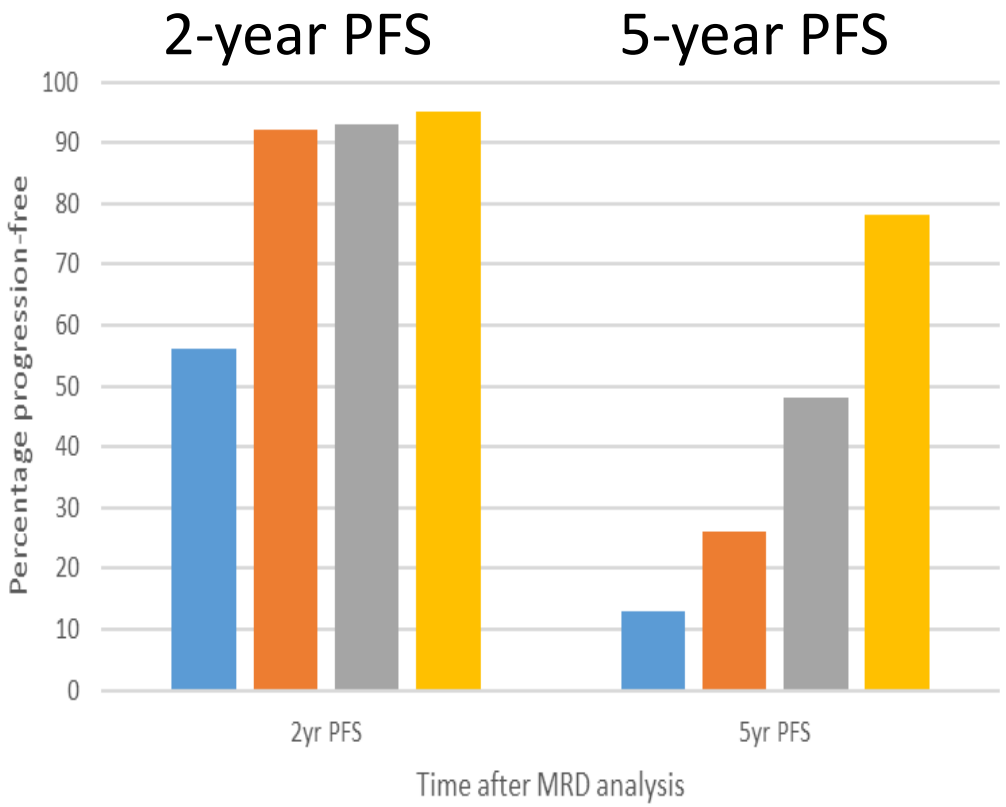
<0.01%	186	186	186	181	175	171	164	161	155	147	124	107	75	39	19	8	4	0
<0.1%	46	46	45	44	43	42	39	32	28	22	17	12	5	4	3	0		
<1%	54	54	54	52	50	44	36	29	26	20	14	10	5	3	1	1	0	
<10%	31	31	30	27	23	17	14	12	6	5	5	3	3	2	0			
>=10%	13	11	7	4	2	2	0											

Number at Risk

<0.01%	176	176	176	171	165	161	154	151	146	138	116	99	68	36	17	7	3	0
<0.1%	34	34	34	33	32	32	30	26	23	17	12	7	4	3	2	0		
<1%	30	30	30	29	28	26	20	16	14	14	8	5	4	3	1	1	0	
<10%	6	6	6	6	4	3	2	2	1	1	1	0						

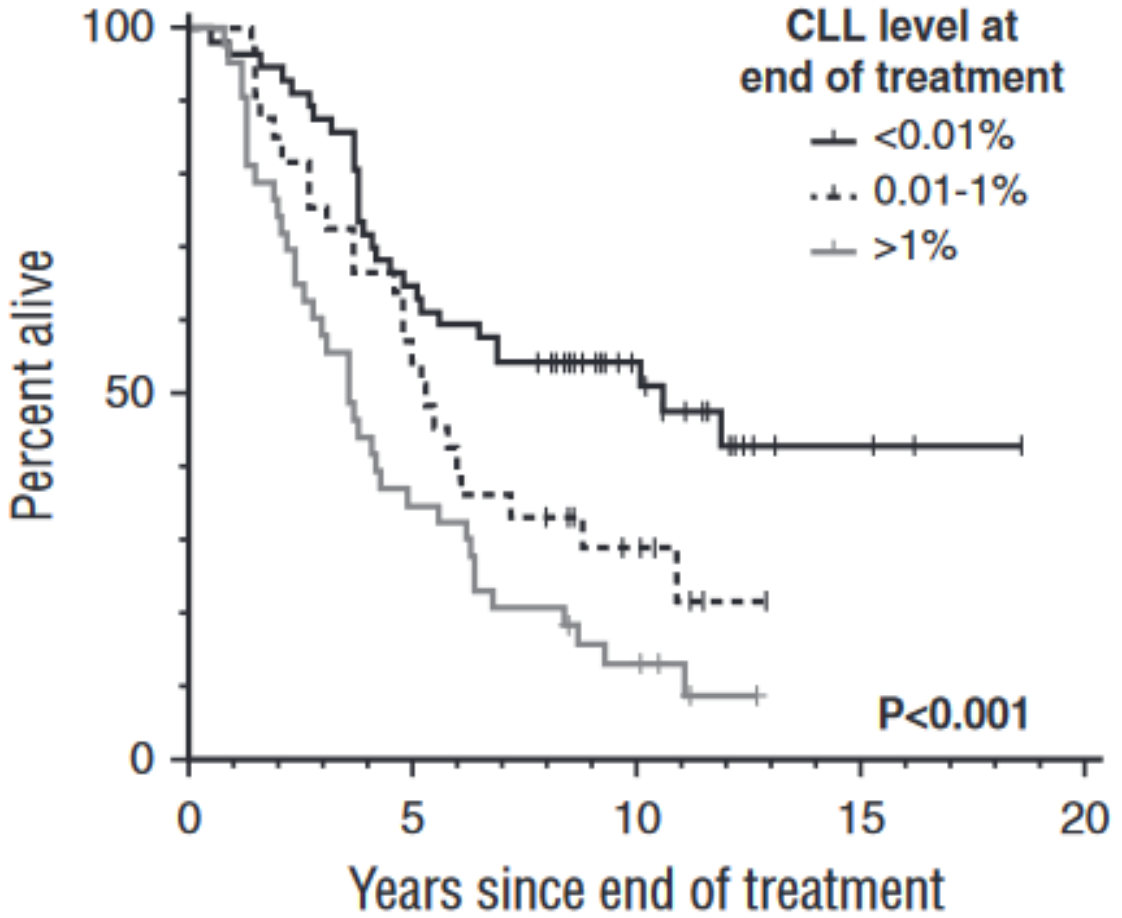
ADMIRE/ARCTIC TN FCR-based therapy

“High” MRD and “undetectable” MRD have different applications



TN CLL
FCR-based Rx
n=343

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

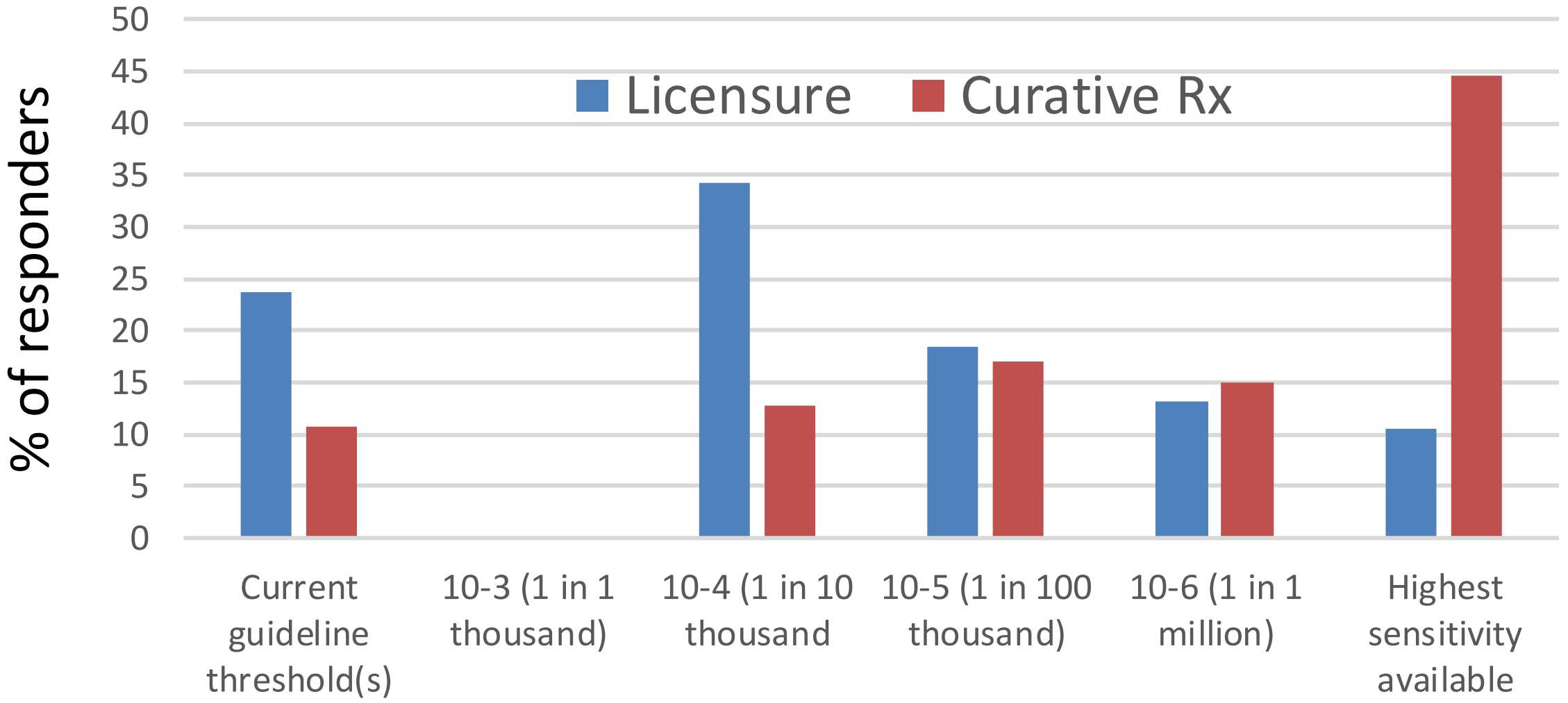


Blood. 2016 Dec 15;128(24):2770-2773. Epub 2016 Oct 3.

Minimal residual disease is an independent predictor for 10-year survival in CLL.

Kwok M[1,2], Rawstron AC[1], Varghese A[1], Evans PA[1], O'Connor SJ[1], Doughty C[1], Newton DJ[3], Moreton P[1], Hillmen P[3].

What is the appropriate MRD threshold for licensure vs. developing a curative treatment strategy?



Survey of participants at the European Society for Clinical Cell Analysis 2018 (n=47/~150)

Uniform reporting criteria for MRD

- Binary classification: MRD positive vs. negative at guideline threshold.
  - MRD-positive and MRD-negative is sub-optimal because it is usually used without reference to the assay sensitivity, and may imply <0.1%, <0.01% or <0.001%. However, this terminology is in frequent use and embedded in many trial/regulatory documents.
- Semi-Quantitative classification: MRD4, MRD5, MRD6
  - The assay detection limit is 10^{-n} (1 neoplastic cell in 10^{n} normal cells) or better
  - Sample/reagents of sufficient quality to achieve a detection limit 10^{-n}
  - Residual disease is not detected or measurable below 10^{-n} but above 10^{n-1}
- Detectable vs. Undetectable
  - MRD4 detectable disease → between 0.001% (10-5) and 0.01% (10-4)
  - MRD4 undetectable → between zero and 0.01% (10-4)

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

Table 3. Recommendations regarding the response assessment in CLL patients

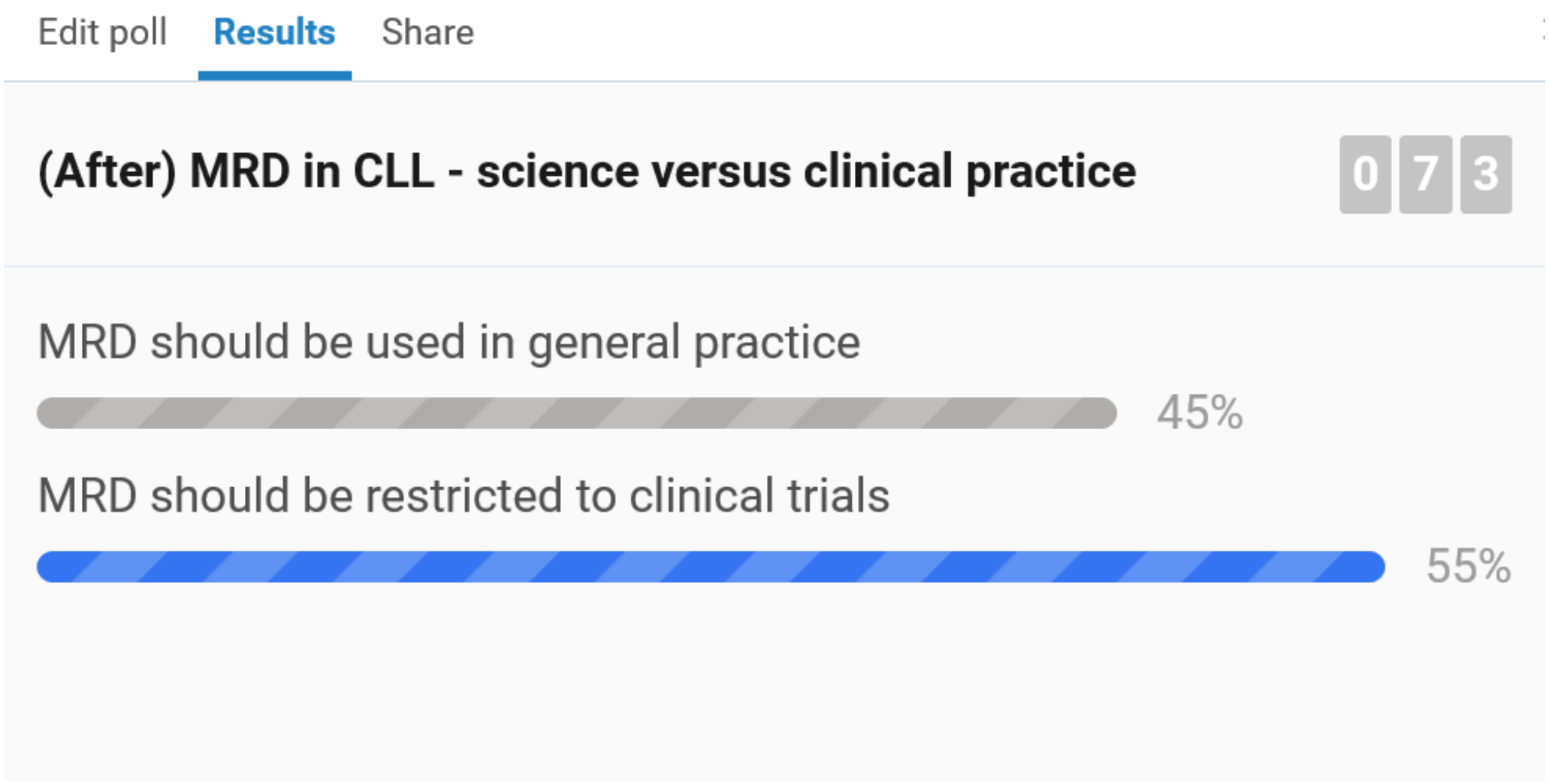
Diagnostic test	General practice	Clinical trial
History, physical examination	Always	Always
CBC and differential count	Always	Always
Marrow aspirate and biopsy	At cytopenia of uncertain cause	At CR or cytopenia of uncertain cause
Assessment for minimal residual disease	NGI	Desirable
Ultrasound of the 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.

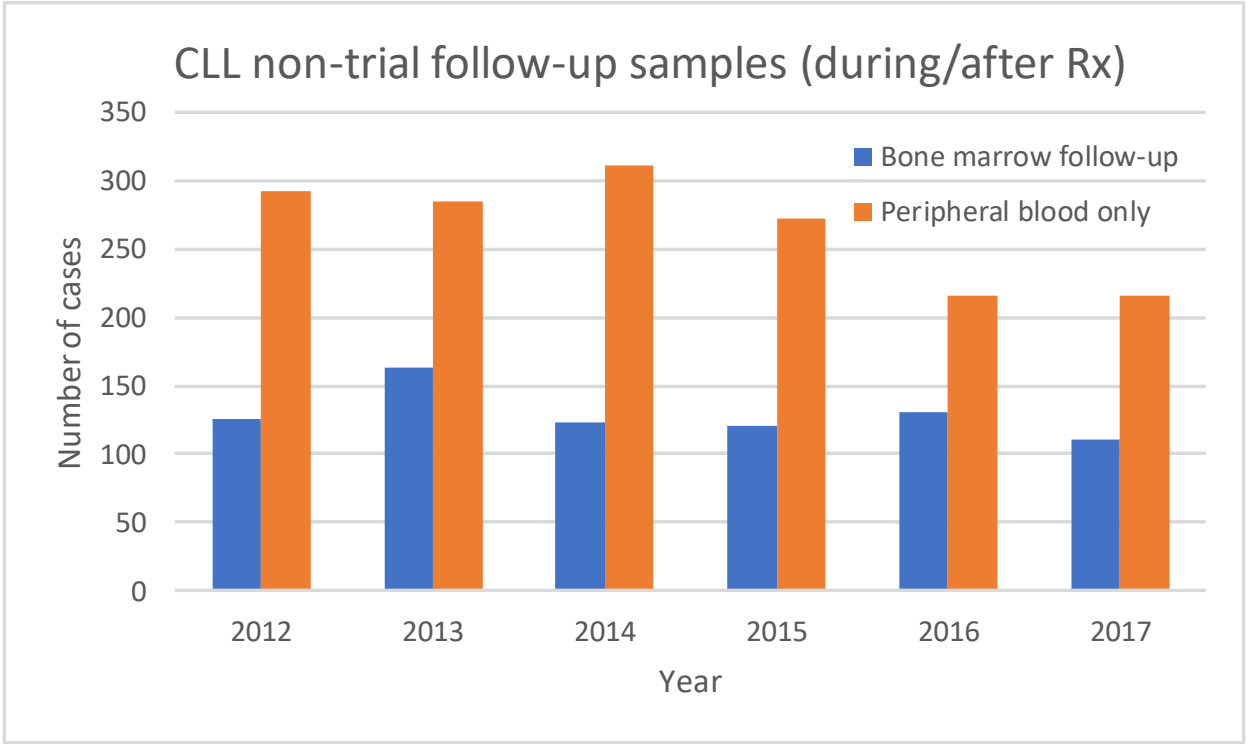
Blood. 2018 Jun 21;131(25):2745-2760. doi: 10.1182/blood-2017-09-806398. Epub 2018 Mar 14.
iwCLL guidelines for diagnosis, indications for treatment, response assessment, and supportive management of CLL

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



Application of MRD analysis in a routine diagnostic laboratory

- **Not "MRD testing" but "response / remission assessment"**
  - **Cytopenia during/after treatment: ? CLL vs. CRi vs. MDS**
  - **After allogeneic transplant: ? still in remission ? DLI**
- UK access currently limited by hospital budget and clinical need
  - Trials are designed for future implementation of MRD to determine Rx duration
  - Specific request for "MRD" in routine practice is still infrequent

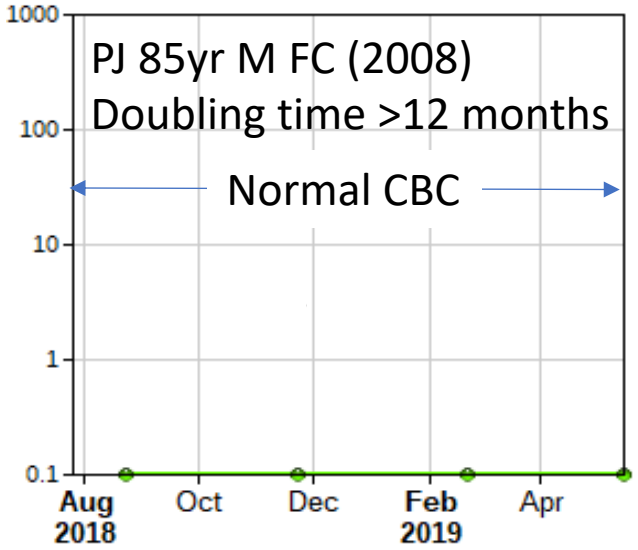


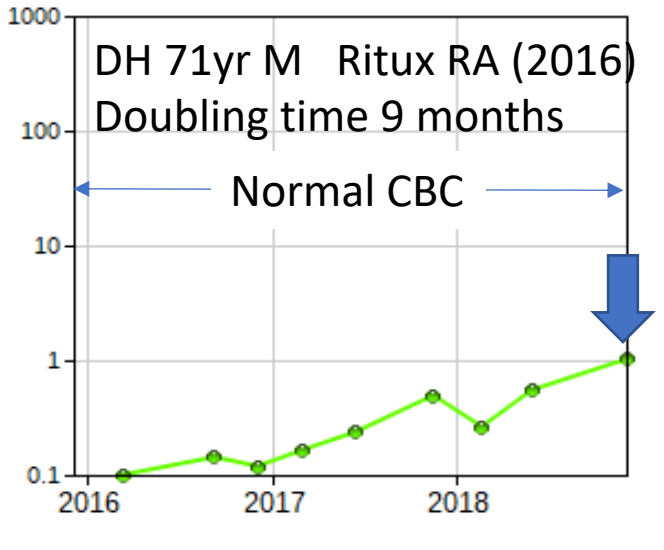
- Bone-marrow follow-up samples:
  - 55 – 75% have no disease or minimal CLL
- Peripheral blood follow-up samples:
  - ~half from Leeds, mostly R/R on newer agents/combinations

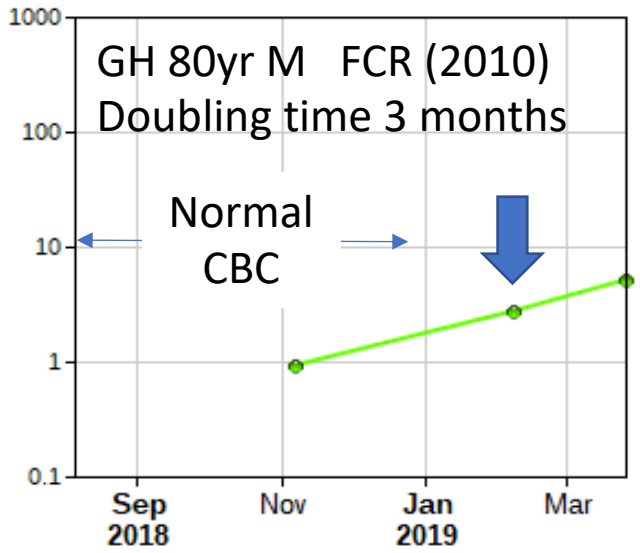
Using MRD in a postal service to reduce need for clinic attendance

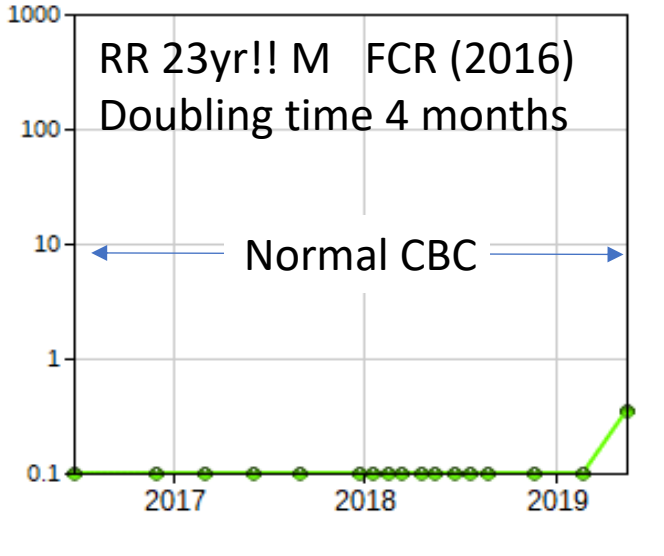
Outreach postal service: 10 years' experience in ~3000 patients

Patients have blood samples taken in primary care and complete a self-assessment symptom questionnaire









- Many patients have MRD <0.01% for several years after Rx
- Typically no progression within 1 year if <0.1% MRD
- Pilot service for patients in remission post-treatment (n>20)
- Most remain with undetectable residual disease
- Tailor clinic appointments to likelihood of progression

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european research initiative on CLL

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Bloodwise
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UNIVERSITY OF BIRMINGHAM
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HMDS
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NHS Trust

PB & BM MRD to understand kinetics of disease and identify response timepoints

PB: CLL % of cells	Predicted BM MRD status	During treatment &/or <12M after antibody Rx	Key trial response assessment timepoint	MRD guided treatment	Steady state (after Rx): BM not informative
>1%	>1% BM disease (? PR)	BM may be informative: 1) Cytopenia 2) Log depletion in trials 3) Supporting treatment decisions	BM not informative		PFS may be <2 years.
0.01-1%	MRD+ (>0.01%)		MRD level varies by Rx → BM essential.	BM not informative	Expected PFS ~2-6 years.
MRD4 (0.001%-0.01%)	Potential MRD4 (0.001-0.01%)			MRD level varies by Rx → reasonable to schedule BM	Probable BM MRD <0.01% Expected PFS > 5 years
MRD5 <0.001%	Probable MRD4 Potential MRD5				