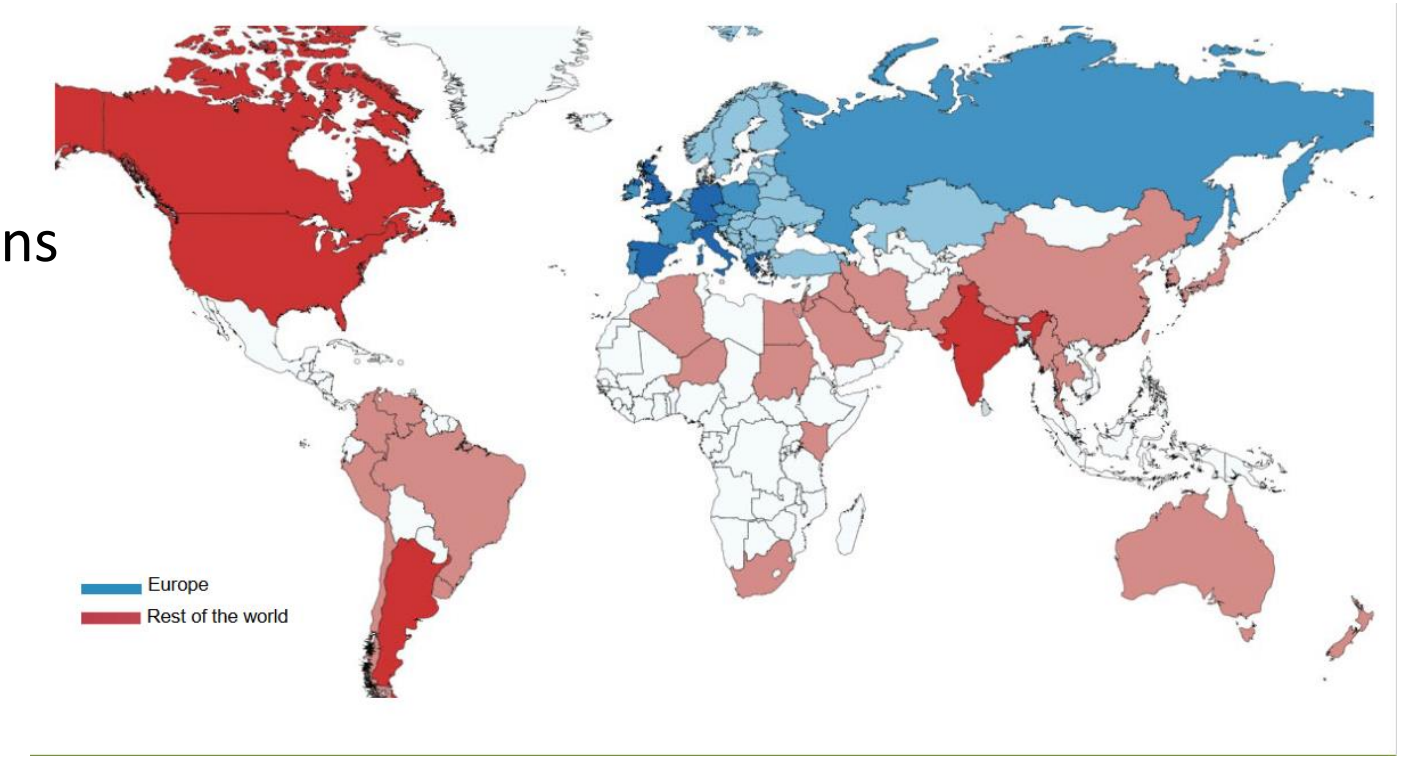
# ERIC guidelines for MRD assessment in CLL 2021

european research initiative on CLL

## Survey to identify key areas to obtain evidence and/or consensus for MRD assessment guidelines

1) Cellular analysis: technical questions
2) Cellular analysis: operational questions
3) MRD assessment: general topics




1475 members from 82 countries

# Development of the ERIC CLL MRD panel

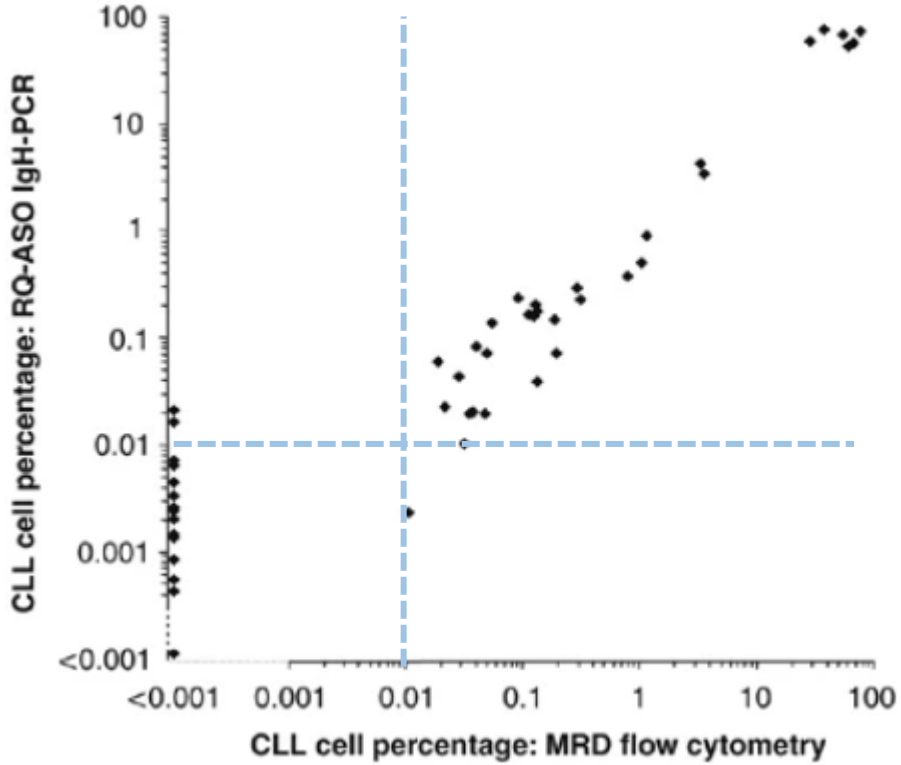
**Tested 35 markers reported to be differentially expressed in CLL vs. normal B-cells in 50 configurations**

**Identified the 3 combinations with the lowest false-positive rate and highest reproducibility**

**Consensus 5-tube 4-marker panel**

| FITC | PE | PerCPCy5.5 | APC | Aim |
|---|---|---|---|---|
| kappa | lambda | CD19 | CD5 | Clonal assessment |
| CD45 | CD14 | CD19 | CD3 | Limit of detection |
| CD20 | CD38 | CD19 | CD5 | CLL quantification |
| CD81 | CD22 | CD19 | CD5 | CLL quantification |
| CD79b | CD43 | CD19 | CD5 | CLL quantification |

**Confirmed concordance and linearity with IGHV qPCR at the 0.01% threshold**




**International standardized approach for flow cytometric residual disease monitoring in chronic lymphocytic leukaemia**

AC Rawstron[1], N Villamor[2,3], M Ritgen[4], S Böttcher[4], P Ghia[5], JL Zehnder[6], G Lozanski[7], D Colomer[2,3], C Moreno[2,3], M Geuna[8], PAS Evans[1], Y Natkunam[6], SE Coutre[6], ED Avery[9], LZ Rassenti[9], TJ Kipps[9], F Caligaris-Cappio[5], M Kneba[4], JC Byrd[7], MJ Hallek[10], E Montserrat[2,3] and P Hillmen[1]

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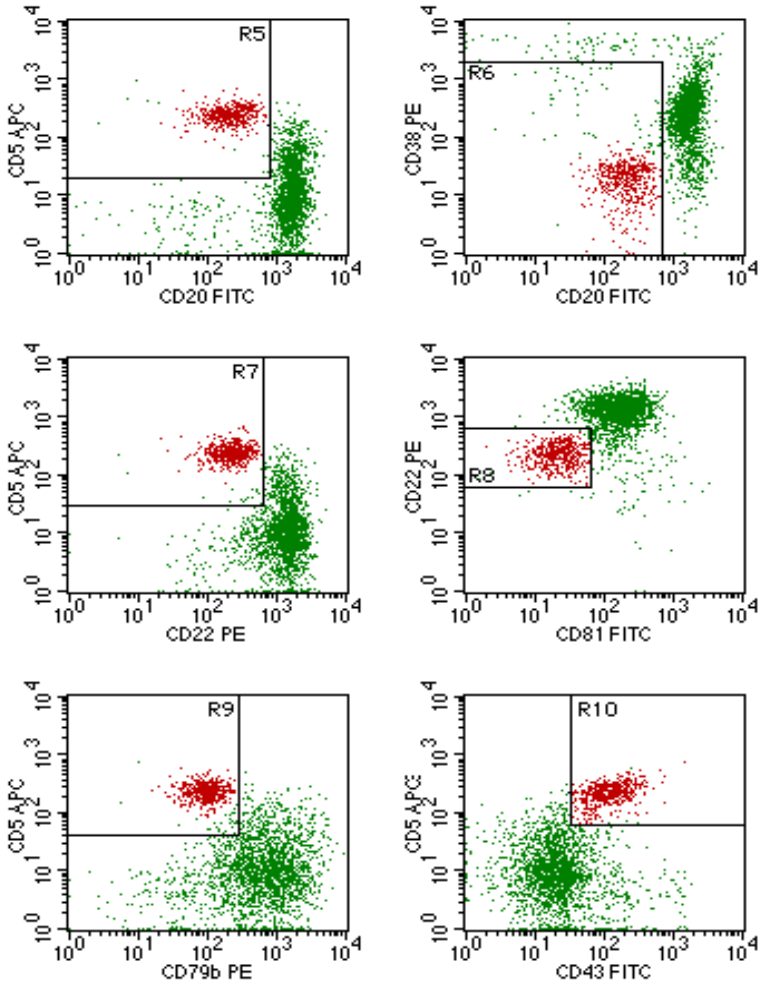
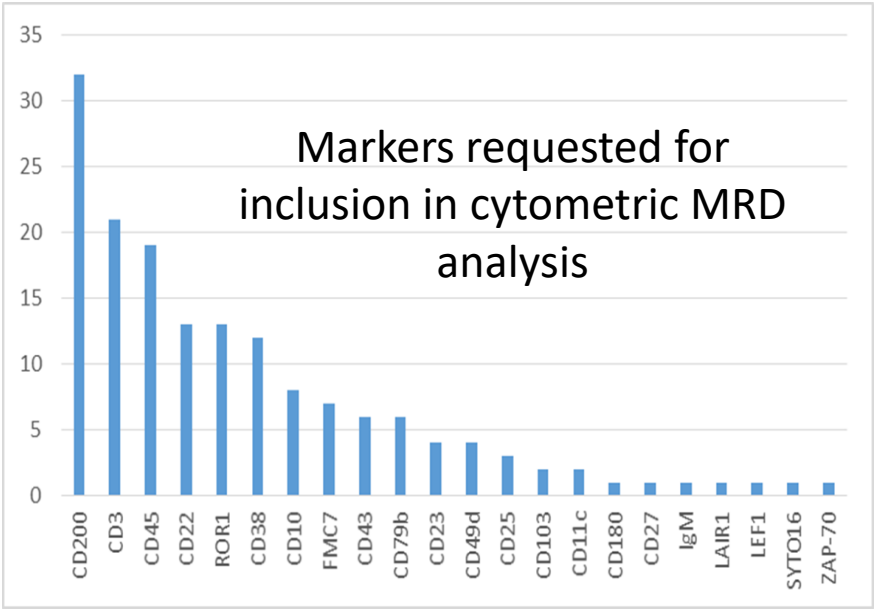
# Development of the ERIC CLL MRD panel




**FDA: development of 'MRD' as a regulatory endpoint:**

- Identify MRD endpoint in clinical trials
- 1995
- Develop assay
- 2002
- Standardisation of assay
- 2007
- Apply standardised assay prospectively
- 2012
- Apply to regulatory action

| Markers | Tubes | Detection limit | Cells required for 0.01% – LoD |
|---|---|---|---|
| 4 | 4 | 0.005% | 4–20 million |
| 6 | 2 | 0.001% | 2–10 million |
| ?8 | 1 | 0.001% | 1–5 million |




LoD, limit of detection.

european research initiative on CLL


Rawstron AC, *et al. Leukemia* 2016; 30:929-936;
Rawstron AC, *et al. Leukemia* 2013; 27:142–149;

# ERIC standard for Flow Cytometry MRD Detection: can be adapted with additional markers

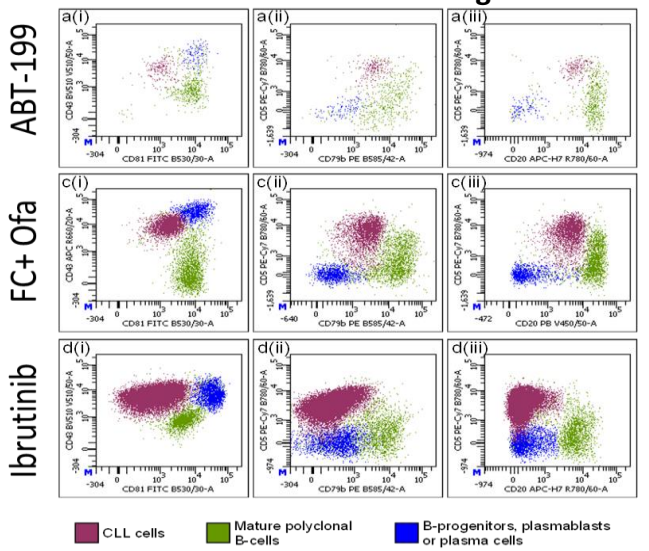
**Requires ≥6 markers to achieve 0.01% – available to most labs Can achieve 0.001%**

**The core panel must meet these 6 specifications, but is flexible thereafter**

**Backwards-compatible and applicable to current treatments**

| Antigen | Typical expression (% positive vs control) | Control population in normal peripheral blood | | Minimum relative fluorescence intensity (preferred) |
|---|---|---|---|---|
| | | Positive | Negative | |
| CD5 | Positive (>20%) | CD3+ T-cells | CD19+ B-cells | >30 (>65) |
| CD20 | Weak | CD19+ B-cells | CD3+ T-cells | >10 (>20) |
| CD43 | Positive (>20%) | CD3+ T-cells | CD20+ B-cells | >15 (>40) |
| CD79b | Weak | CD20+ B-cells | CD3+ T-cells | >15 (>30) |
| CD81 | Weak | CD3+ T-cells | Granulo-cytes | >12 (>20) |

**Examples of MRD analysis in patients treated with non-FCR regimens**





Rawstron AC, *et al. Leukemia* 2016; **30:**929-936;
Rawstron AC, *et al. Leukemia* 2013; **27:**142–149;
Rawstron AC, *et al. Leukemia* 2007; **21:**956–964.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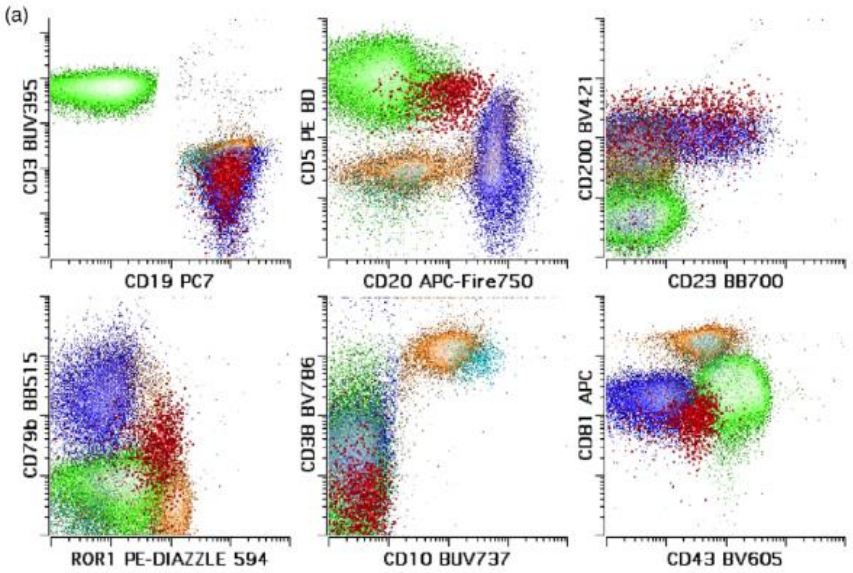
# Building on the ERIC MRD panel for future applications

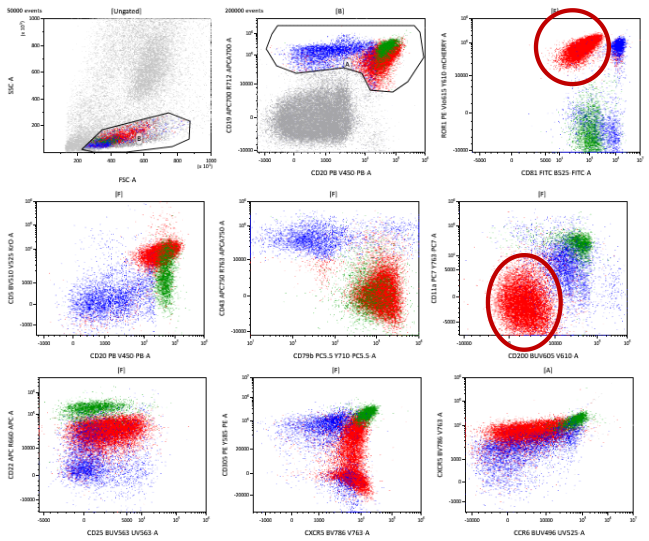
Commercial kits (RUO): ERIC panel + ROR1 and CD45

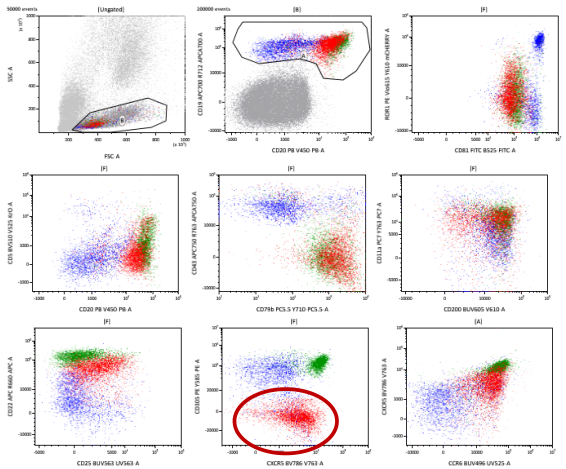

Goshaw JM, Gao Q, Wardrope J, Dogan A, Roshal M. 14-Color single tube for flow cytometric characterization of CD5+ B-LPDs and high sensitivity automated minimal residual disease quantitation of CLL/SLL. Cytometry B Clin Cytom. 2020 Sep 8. doi: 10.1002/cyto.b.21953.

HMDS Leeds approach 16+ marker panel built around the core ERIC marker panel to apply to all CD5+ and post-GC B-cell disorders.

"Atypical" CLL



WM/MZL



B-progenitors

Normal mature B-cells

Neoplastic B-cells

**Should additional markers be added to the core panel?**
**If they are "required", experimental evidence of benefit will be needed**

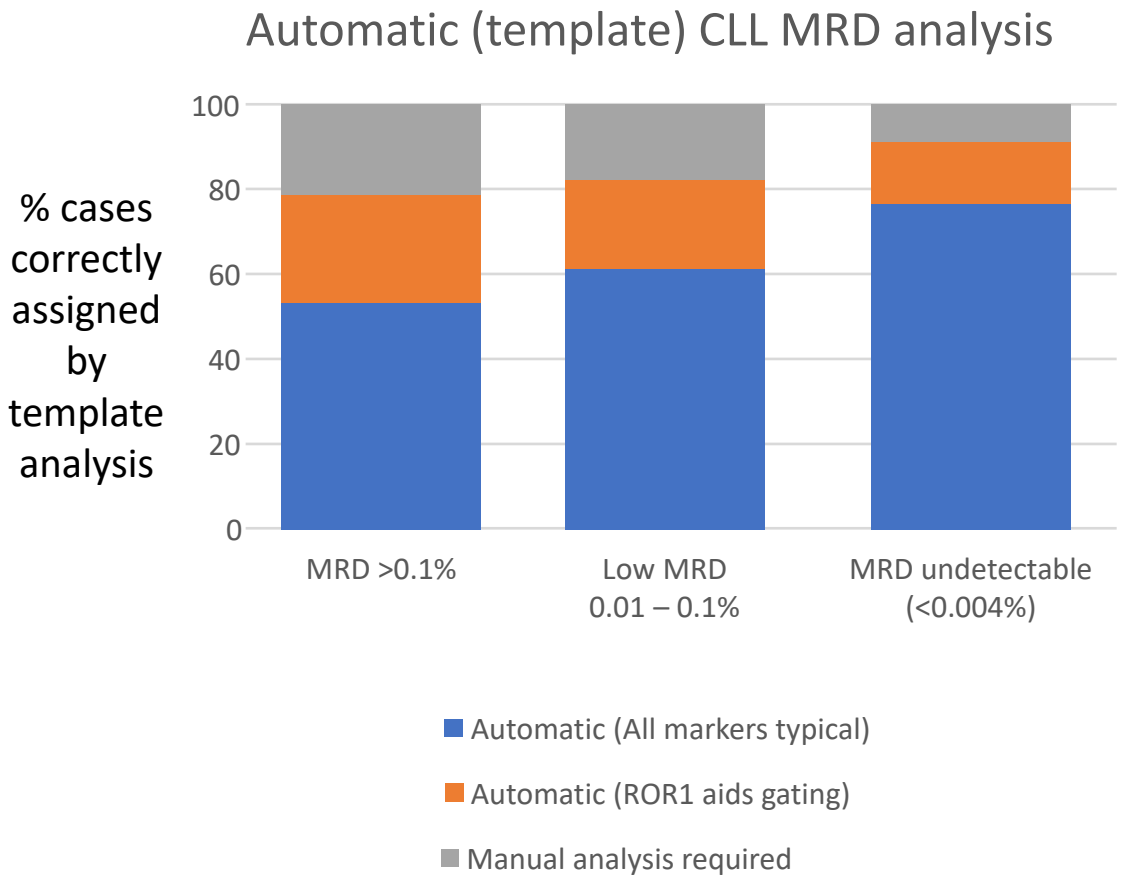
# 1) Cellular analysis: technical questions

| | Yes | No | Not sure |
|---|---|---|---|
| 1A) The core marker panel should be updated | | | |

Free text comment:

# 1B) ROR1

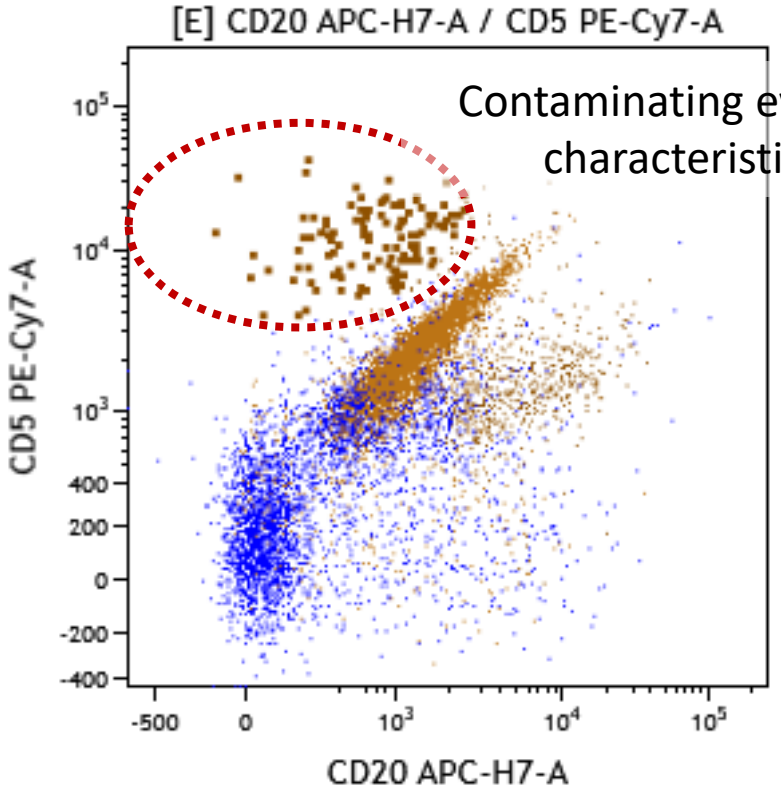
- ROR1
  - Expressed in nearly all CLL and Burkitt lymphoma, some mantle cell and B-ALL. No expression on normal circulating leucocytes, but is detectable on a subset of B-progenitors.
- ? Required or recommended
  - Facilitates analysis for less experienced operators
  - Improves automated analysis
  - Increases proportion of “atypical” cases that can be monitored



# 1C) CD3

- CD3
  - Low level CD3+CD19+ events can affect MRD analysis of disease near the assay detection limit
  - Less informative in assays incorporating CD81, CD200, or ROR1
- ? Required or recommended
  - Currently recommended in cases with disease levels near the assay detection limit

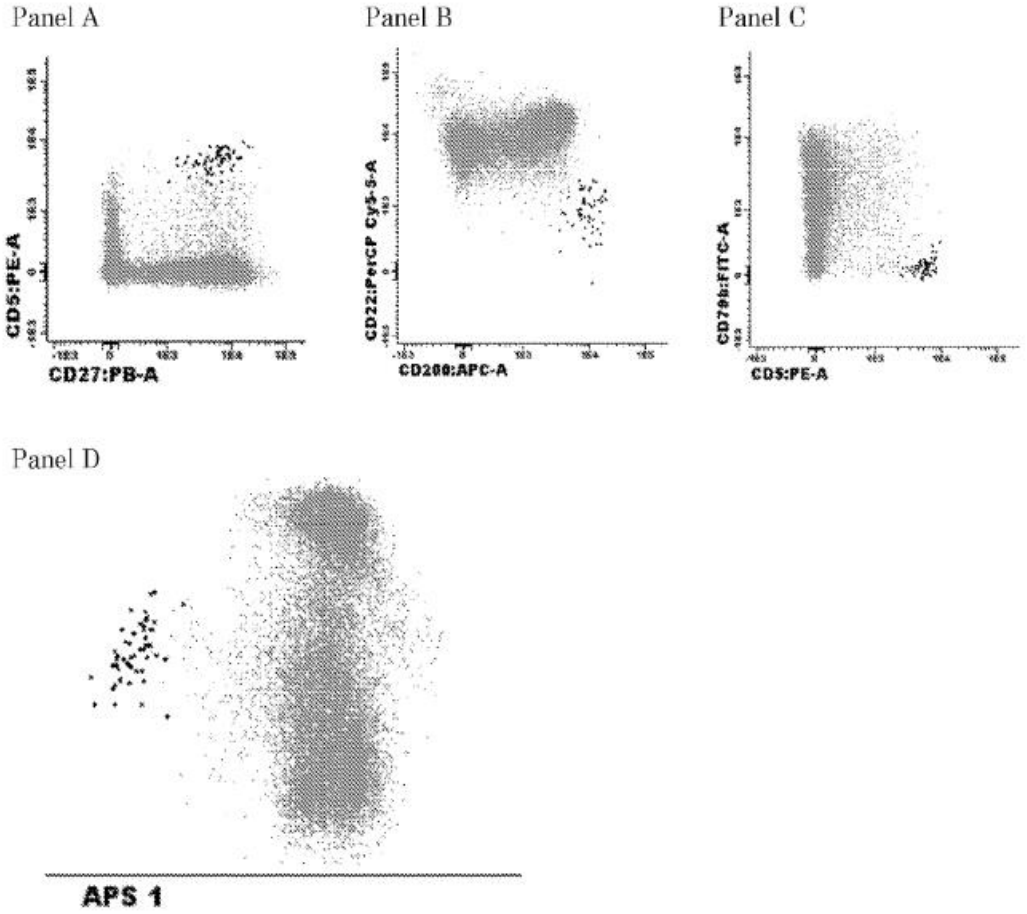
CD19+SSClo events (no additional gating) with **CD19+SSCloCD3+ events highlighted in brown**



# 1D) CD27

- CD27
  - Expressed on most CLL cases (variable level) and memory B-cells
  - In the Euroflow patent for CLL MRD
  - One of the markers tested in the 2007 ERIC consensus
- ? Required or recommended

Figure 4




US 20210177936A1

(19) **United States**

(12) **Patent Application Publication** (10) **Pub. No.: US 2021/0177936 A1**

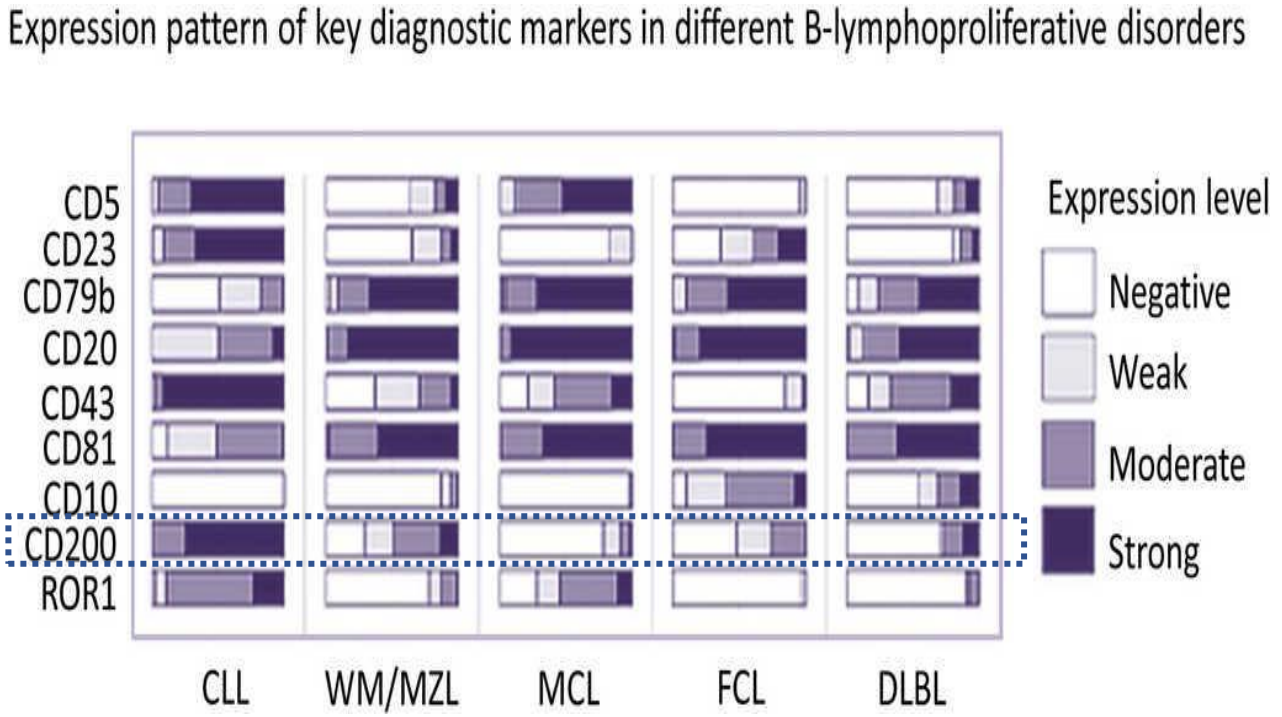
**van Dongen et al.** (43) **Pub. Date: Jun. 17, 2021**

(54) **METHODS, REAGENTS AND KITS FOR DETECTING MINIMAL RESIDUAL DISEASE**

(60) Provisional application No. 61/659,524, filed on Jun. 14, 2012.

# 1E) CD200

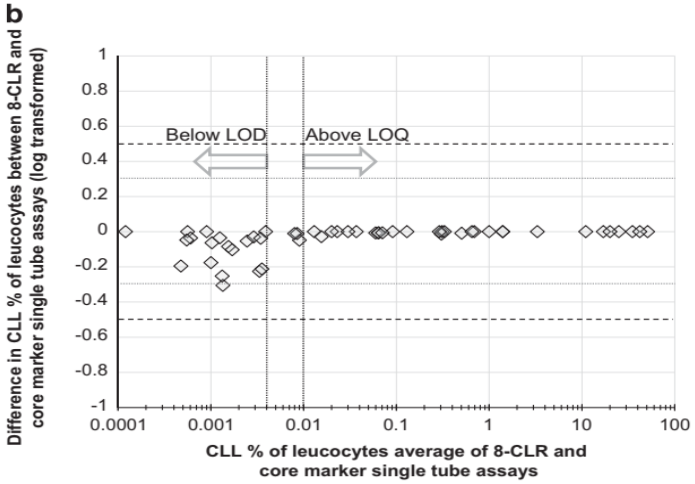
- CD200
  - Expressed by normal B-cells and most cases of CLL
  - One of the key markers for differentiating CLL vs. MCL
  - Not expressed by T-cells → if included in the MRD panel, CD3 might not be required
- ? Required or recommended



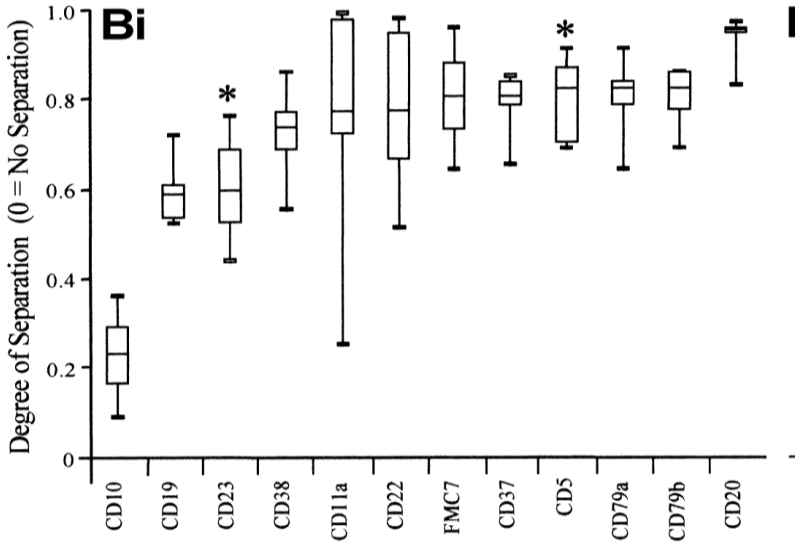
# 1F) CD20 or CD22…or both?

- CD20 vs. CD22
  - Expression level is highly correlated and using both markers together is probably not required
  - CD20 is not detectable during treatment with anti-CD20 therapeutic antibodies…but normal mature B-cells are also absent
  - Discrimination between normal B-cells and CLL cells is (much) better with CD20
- ? Required or recommended

Inclusion of CD22 (or CD3) is not required if the ERIC 6 core markers are used




CD20 is the best marker for discriminating CLL vs. normal mature B-cells



# 1) Cellular analysis: technical questions

| | Yes | No | Not sure |
|---|---|---|---|
| Q1) The core marker panel should be updated (slides 2-5) | | | |

Free text comment:

| Additional markers which should be considered for the core panel | Required | Recommended | Not informative | Not sure |
|---|---|---|---|---|
| Q2) ROR1 (slide 7) | | | | |
| Q3) CD3 (slide 8) | | | | |
| Q4) CD27 (slide 9) | | | | |
| Q5) CD200 (slide 10) | | | | |

Free text comment (especially other markers for which evidence should be considered)

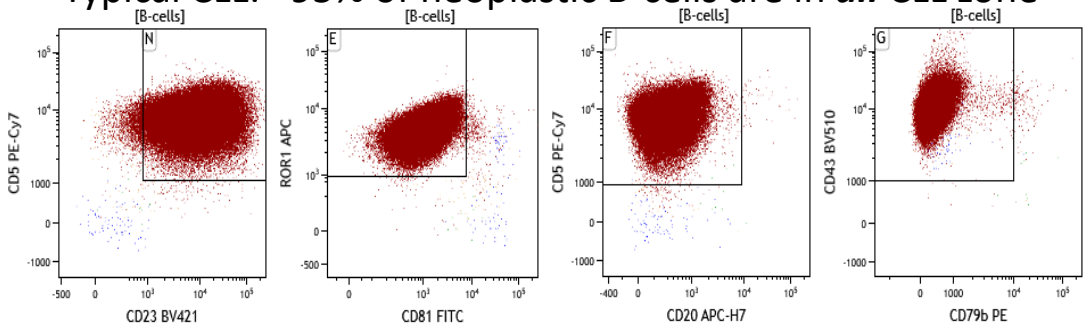
| CD20 vs. CD22 | CD20 is more informative | CD22 is more informative | Both CD22 & CD20 are required | Either CD22 or CD20 is suitable | Not sure |
|---|---|---|---|---|---|
| Q6) CD20 vs. CD22 (slide 11) | | | | | |

Free text comment:

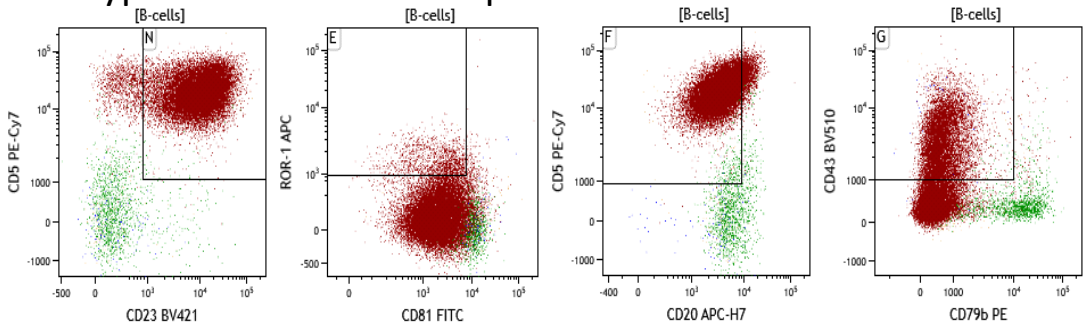
# 2A/B) Analysis of atypical cases and CD19+CD5+ B-cell clonality assessment

- MRD analysis strategies with fixed/stringent gates may exclude a (high) proportion of neoplastic cells in atypical cases
- CD19/CD5/κ/λ thresholds that have >99% positive predictive value (PPV) for the presence of residual disease have been identified
- Cross-checking the MRD results against CD19/CD5 clonality assessment can improve detection in atypical cases, which can be particularly helpful if the pre-treatment phenotype is not known.
- If clonality is performed separately to MRD analysis it can also identify sample-switch errors
- **? Should CD19/CD5 clonality assessment be required as part of the MRD assessment, or recommended ?**
- **? Should pre-treatment analysis be required for clinical trials, or recommended ?**

Typical CLL: >95% of neoplastic B-cells are in ***all*** CLL zone




Atypical CLL: <5% of neoplastic B-cells are in ***all*** CLL zone




Referred "atypical" CLL cases usually have mod/strong CD5 – otherwise they would be classed as a different type of B-LPD

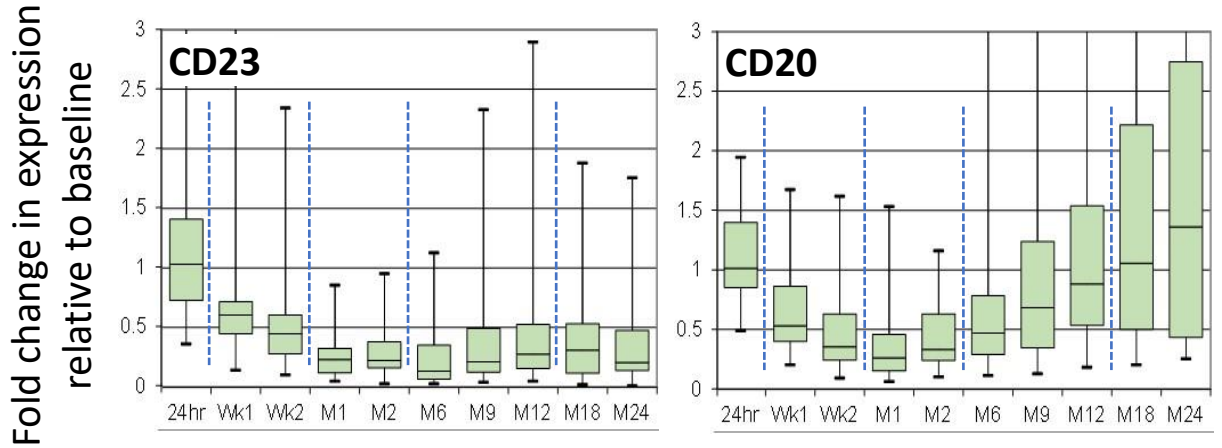
| Parameter | Training set (n=392): 100% PPV threshold | PPV in validation set (n=392) |
|---|---|---|
| CD19+ K:L ratio | <0.04:1 or >61:1 | 98.8% (n=85) |
| CD5+ % of B-cells | >82% | 100% (n=144) |
| CD19+CD5+ K:L ratio | <0.05:1 or >32:1 | 100% (n=128) |
| %sIg- of CD19+CD5+ | >54% | 100% (n=40) |

Leukemia. 2013 Jan;27(1):142-9. doi: 10.1038/leu.2012.216.

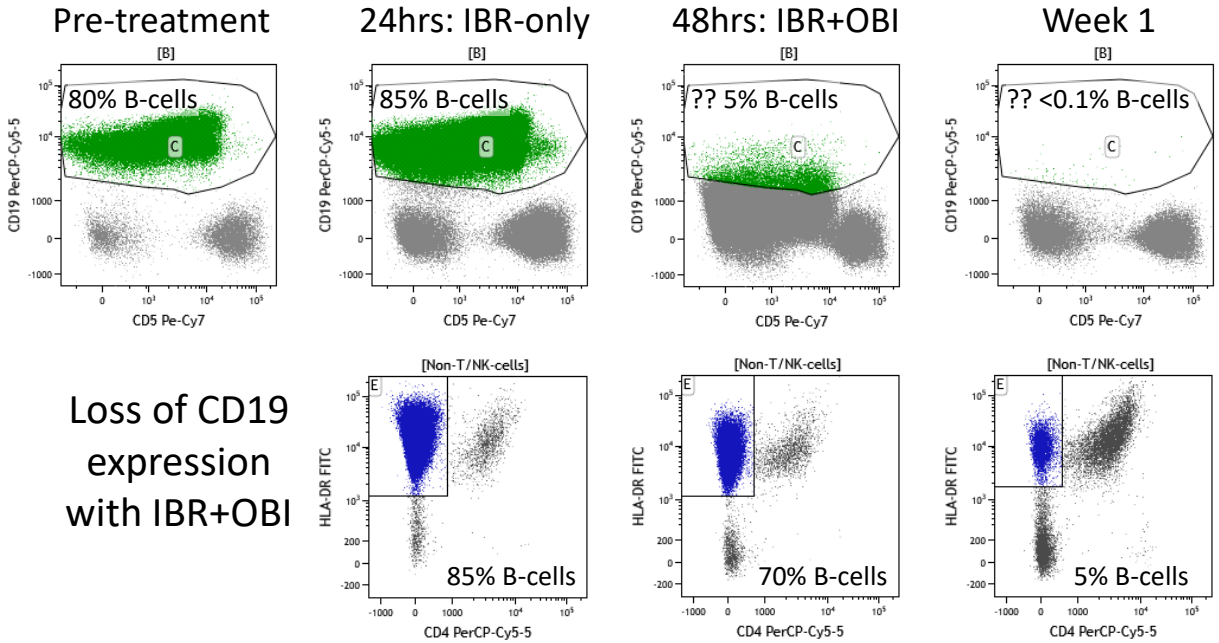
# 2C) Phenotype change with inhibitor Rx

- BCR-pathway inhibitors affect expression of a number of molecules
  - CD23 expression is substantially decreased for the duration of treatment
  - CD20 expression is decreased for the first 6-12 months of treatment
- Occasionally there is a substantial change in expression profile
- **? Should an early assessment be recommended to check for phenotype shift (in clinical trials) ?**

**Inhibitor treatment usually changes are mild**




**Inhibitor treatment occasionally causes substantial phenotype shift**



# 2) ERIC should seek evidence and/or consensus on the following topics to include in any update on updated cellular MRD guidance:

| | Required | Recommended | Not informative | Not sure |
|---|---|---|---|---|
| 2A) CD19/CD5 clonality assessment in addition to any MRD panel (slide 13) | | | | |
| 2B) Pre-treatment immunophenotyping (slide 13) | | | | |
| 2C) Early evaluation during novel treatment to check for phenotype shift (slide 14) | | | | |

Free text comment (for each):

# ERIC 2020: application of MRD


**1. Q1. I would like to use MRD to:**

| | | |
|---|---|---|
| a. | a) Assess response and predict outcome for clinic patients | 65% |
| b. | b) Determine duration of treatment for clinic patients | 44% |
| c. | c) Monitor patients in remission after treatment | 62% |
| d. | d) Improve drug development in clinical trials | 31% |
| e. | e) Other application | 3% |
| f. | f) None of the above | 0% |

**10. Q10. Which technologies are appropriate for monitoring MRD in clinical trials?**

| | | |
|---|---|---|
| a. | a) Morphology | 0% |
| b. | b) 4-colour flow cytometry | 12% |
| c. | c) 6 or more colour flow cytometry | 80% |
| d. | d) RQ-PCR or digital droplet PCR | 25% |
| e. | e) NGS/high-throughput sequencing | 83% |
| f. | f) Other | 0% |
| g. | g) None of the above | 0% |

Mul

Nur

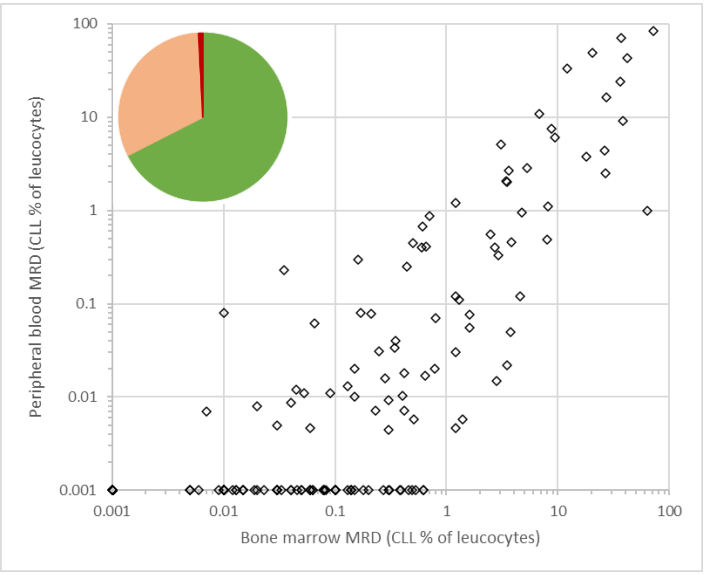
% o

**4. Q4. Which technologies are appropriate for monitoring MRD in the clinic?**

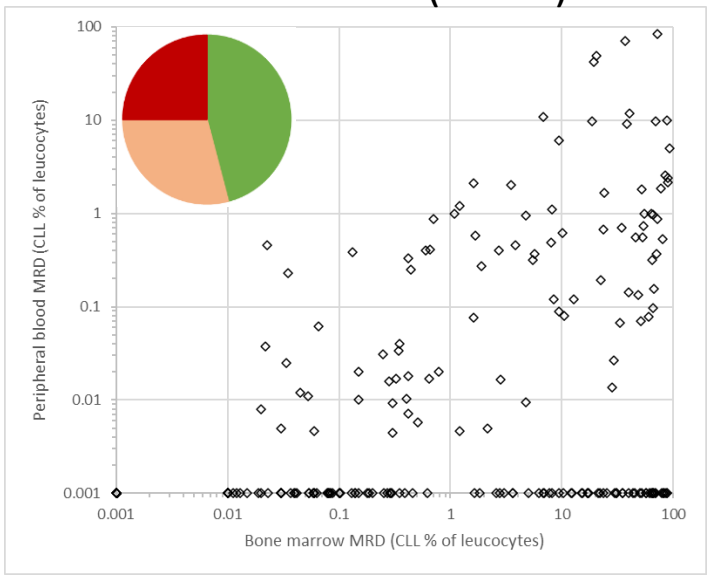
| | | |
|---|---|---|
| a. | a) Morphology | 3% |
| b. | b) 4-colour flow cytometry | 7% |
| c. | c) 6 or more colour flow cytometry | 96% |
| d. | d) RQ-PCR or digital droplet PCR | 21% |
| e. | e) NGS/high-throughput sequencing | 3% |
| f. | f) Other | 0% |
| g. | g) None of the above | 0% |

# PB vs. BM MRD: impact of different treatments

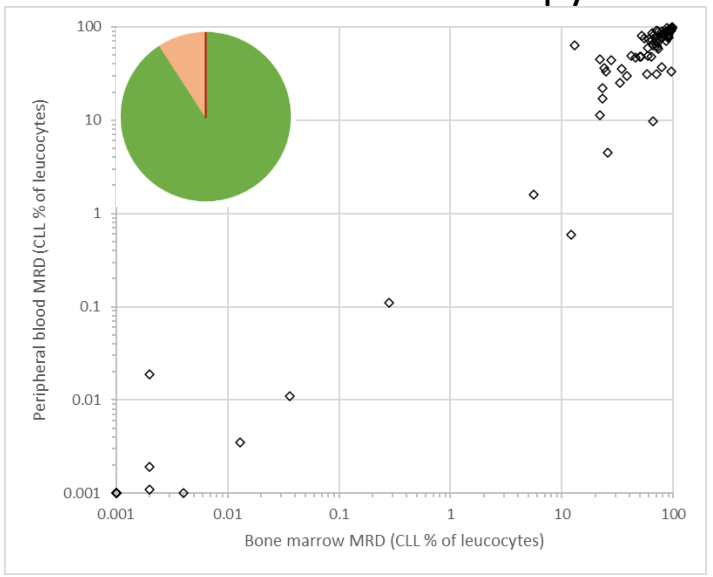
FC + rituximab (3M post)




Alemtuzumab (≤12M)



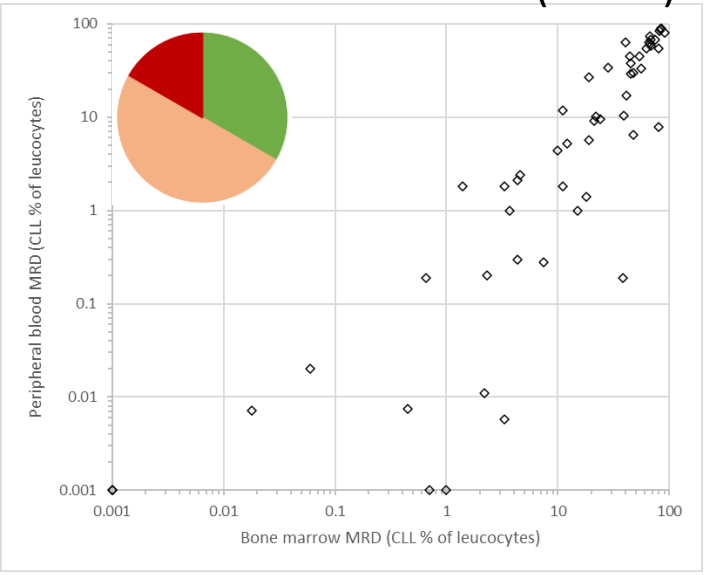

Ibrutinib monotherapy



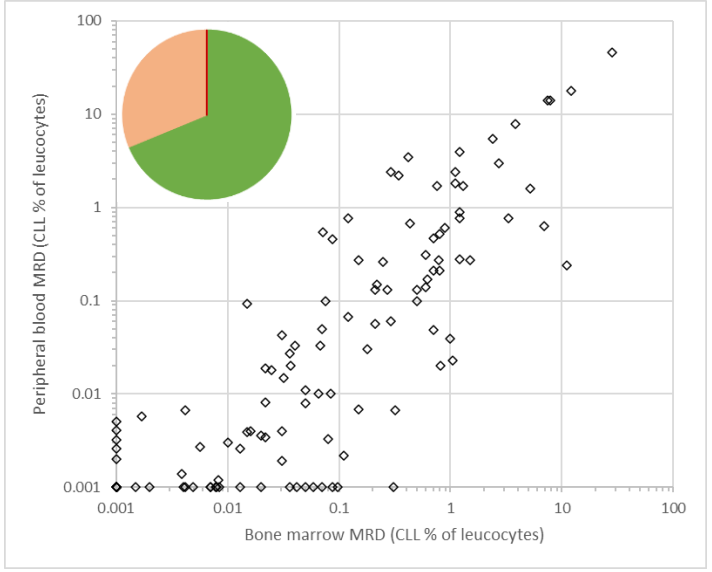

Proportion of cases with PB MRD <0.01% and BM MRD

- <0.01%
- 0.01-1%
- >1%

Ibrutinib + obinutuzumab (≤12M)



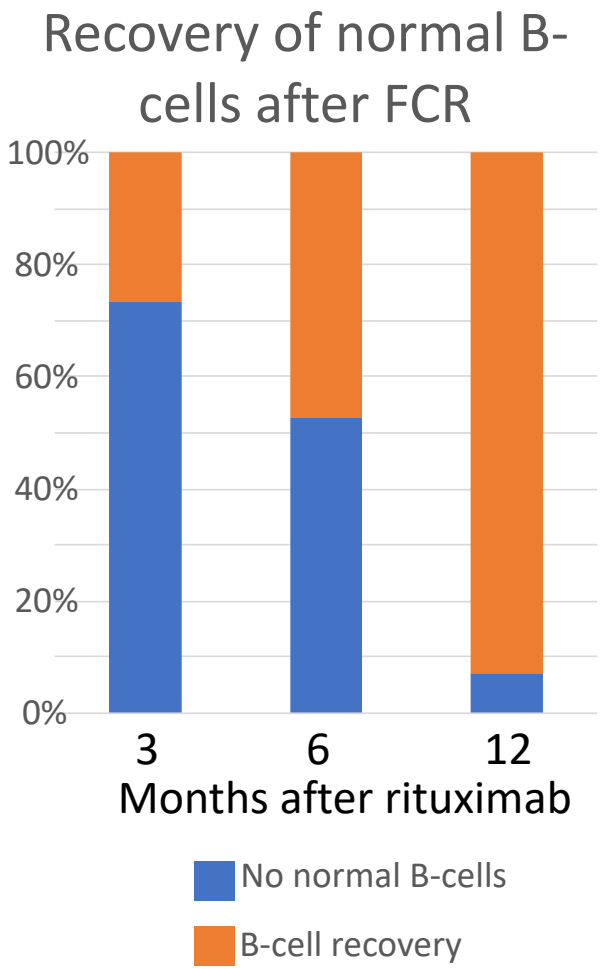

Ibrutinib + venetoclax

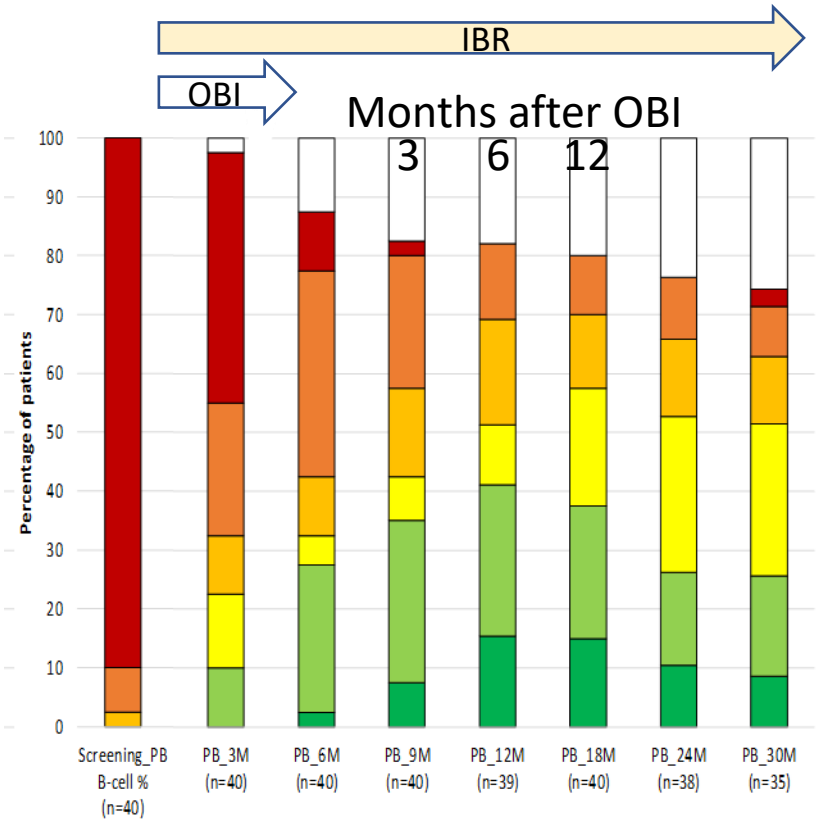



| Treatment | Median log difference (range) |
|---|---|
| Ibrutinib | 0.0 (-0.9 to 1.3) |
| Ibrutinib + venetoclax | 0.2 (-0.9 to 1.7) |
| Ibrutinib + obinutuzumab | 0.3 (-0.2 to 2.8) |
| FCR | 0.7 (-0.9 to 2.4) |
| Alemtuzumab | 1.2 (-1.3 to 3.3) |

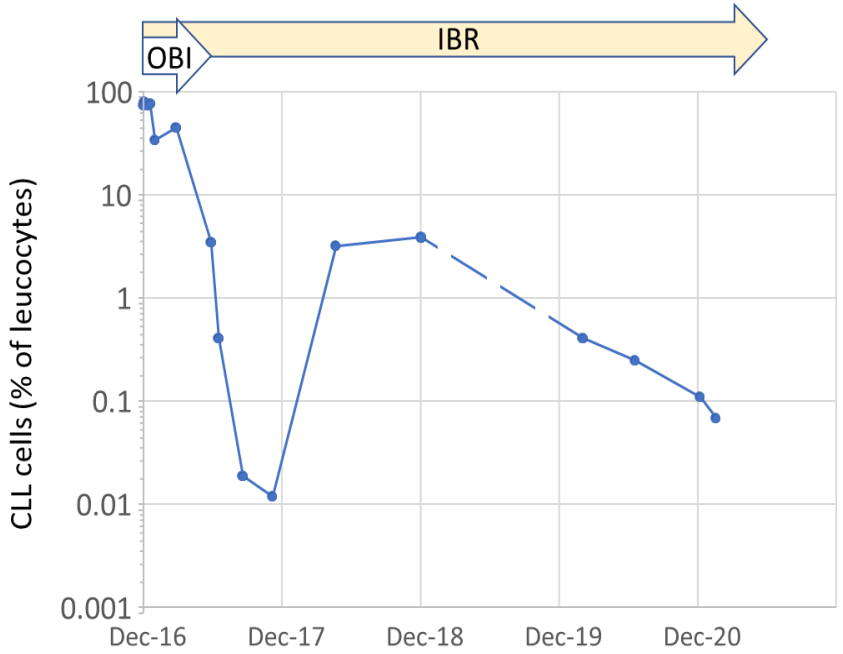
# PB vs. BM: anti-CD20 therapeutic antibodies

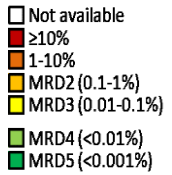
- CLL14 Venetoclax-obinutuzumab PB 76% vs. BM 57%
- Chlorambucil-obinutuzumab PB 35% vs. BM 17%



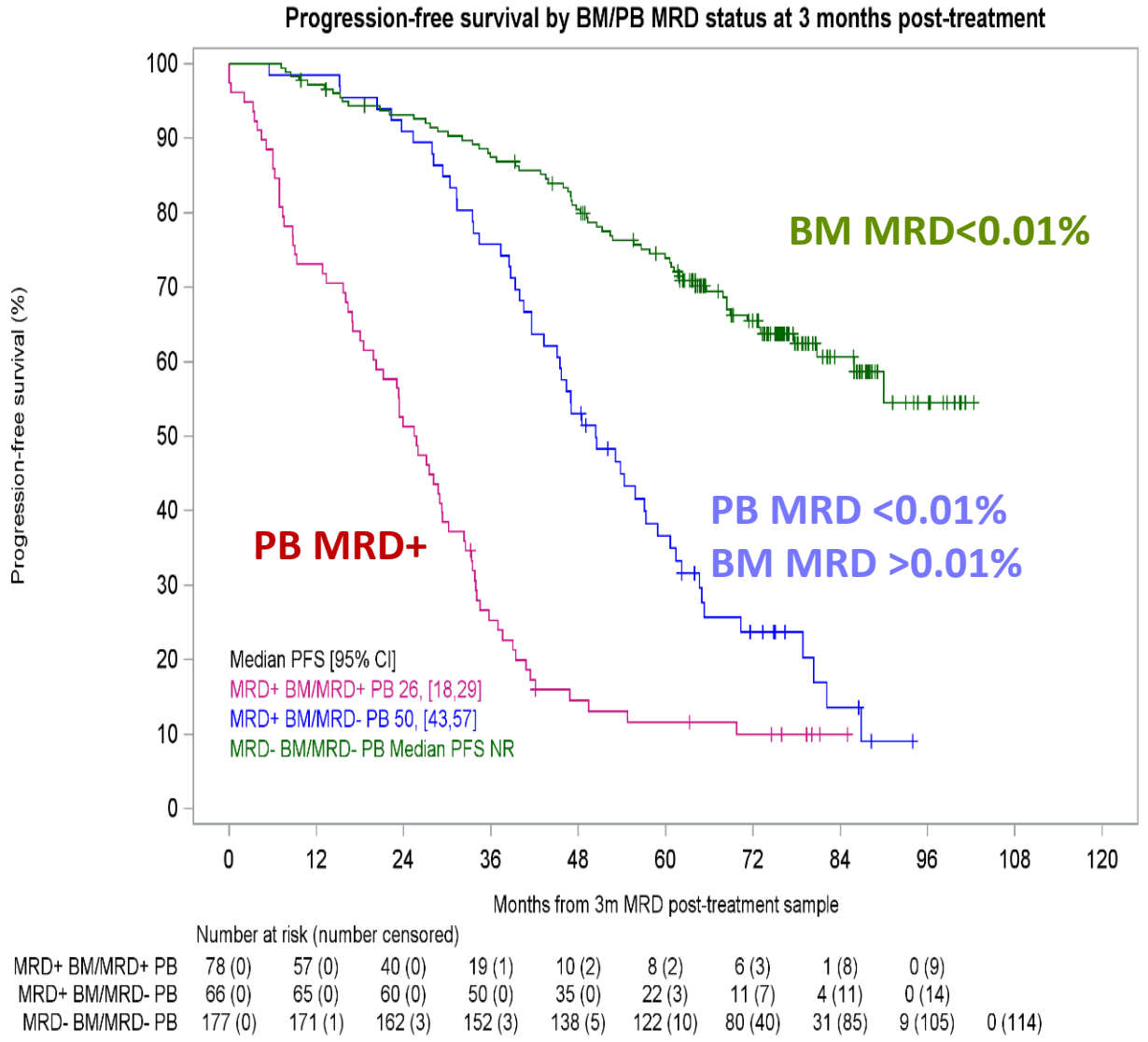

IcICLLe R/R Ibrutinib+Obinutuzumab



# 3A) PB vs. BM MRD assessment

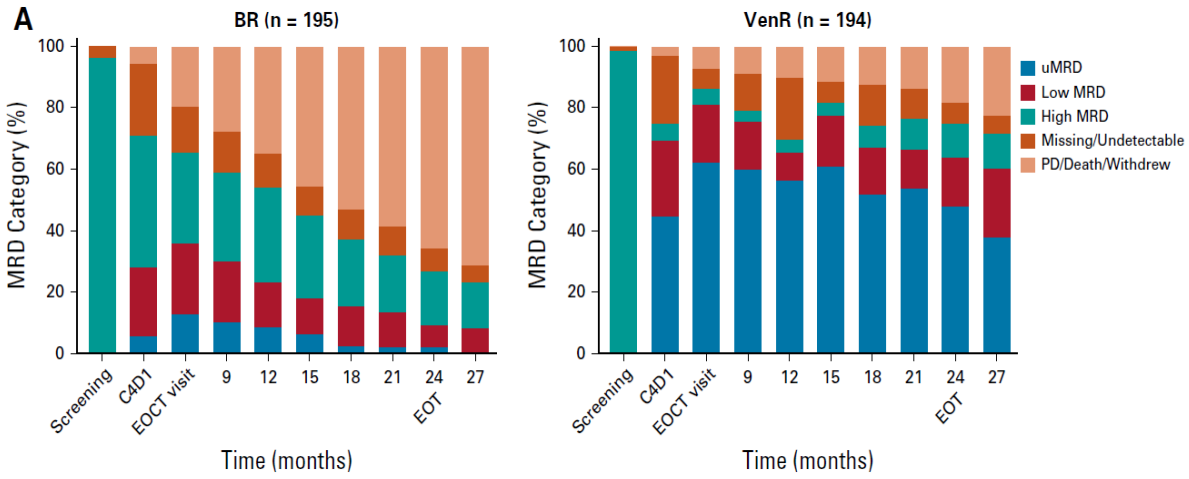
- Bone marrow may be the most informative compartment for MRD analysis but is not appropriate for many applications.
- Treatment-related differences between PB and BM MRD are largely known:
  - Steady state: PB MRD ~0.2log lower than BM
  - Therapeutic antibody: PB MRD **0.5-2 log** lower than BM up to 1 year after last dose
  - BCRi: PB MRD levels **equivalent** to BM
  - BCL2i: PB MRD **~0.5log** lower than BM
- **? Should the updated guidance seek consensus on which applications can be achieved using PB analysis only and which applications require bone marrow MRD assessment**




ADMIRE/ARCTIC trials: FCR for treatment-naïve CLL patients

# 3B) Appropriate timepoints for MRD assessment

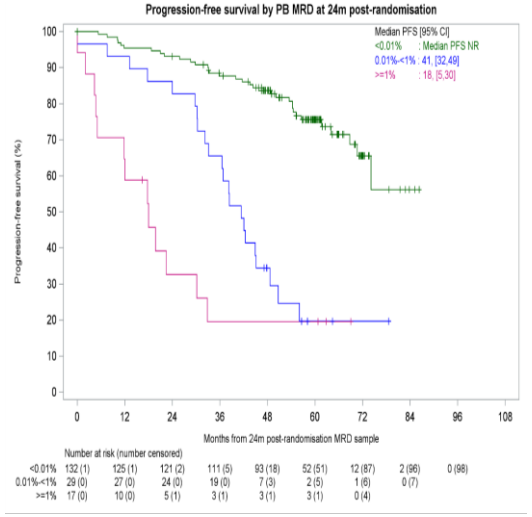
- After end of duration treatment, PFS follows as similar pattern for high (>1%) vs. intermediate (0.01 – 1%) vs <0.01% MRD independent of treatment type or time since end of treatment. Patients with <1% PB disease or highly unlikely to show disease progression in the subsequent year.
- BCRi shows ongoing stable or gradually depleting disease unless resistant disease develops
- BCL2i assessment at 6 – 12 months may be informative to guide treatment
- **? Is there sufficient evidence / consensus to recommend optimal timepoints for MRD assessment ?**

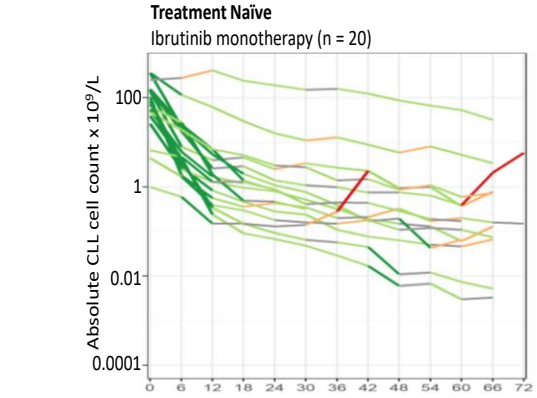




- 1. Seymour JF, *et al. N Engl J Med* 2018; **378:**1107–1120 (incl. suppl.);
2. Kater AP and Seymour JF, *et al. J Clin Oncol* 2018; DOI: 10.1200/JCO.18.01580.


PB MRD 18 months after end of FCR




| Log depletion relative to baseline (# evaluable) | 1.5 (17) | 1.9 (16) | 1.9 (14) | 2.2 (13) | 2.6 (12) |
|---|---|---|---|---|---|

1-2 log reduction in first year with gradual depletion (~0.2log/year) after

# 3) ERIC should seek evidence and/or consensus on the following topics to include in any update on updated general MRD guidance:

| The updated guidance should include: | Yes | No | Not sure |
|---|---|---|---|
| 3A) Guidance on when to use peripheral blood vs. bone marrow (slide 19) | | | |
| 3B) Guidance on MRD timepoints should be included (slide 20) | | | |

Free text comment (for each):

# 3C) Reporting MRD results: individual laboratory results (current guidance)

- **Current guidance**: the report should indicate the **limit of quantification**, (defined as 100* 50 / total number of cells analysed) for cases with detectable residual disease, and the **limit of detection** for cases with no detectable disease (defined as 100* 20/ total number of cells analysed, assuming the laboratory has demonstrated an appropriate limit of blank).

Examples

- If there are 80 CLL events detected in a total of 1 million total cells, the report would state “CLL cells = 0.0080% (limit of quantitation 0.0050%)”.
- If CLL cells are not detectable the report should state “CLL cells not detected (limit of detection 0.0020%).
- If CLL cells are detected at a level intermediate to the limit of detection and quantitation, e.g. 40 CLL events in 1 million total cells, the report should state “CLL cells detected below the quantitative range (0.0020 – 0.0050%).

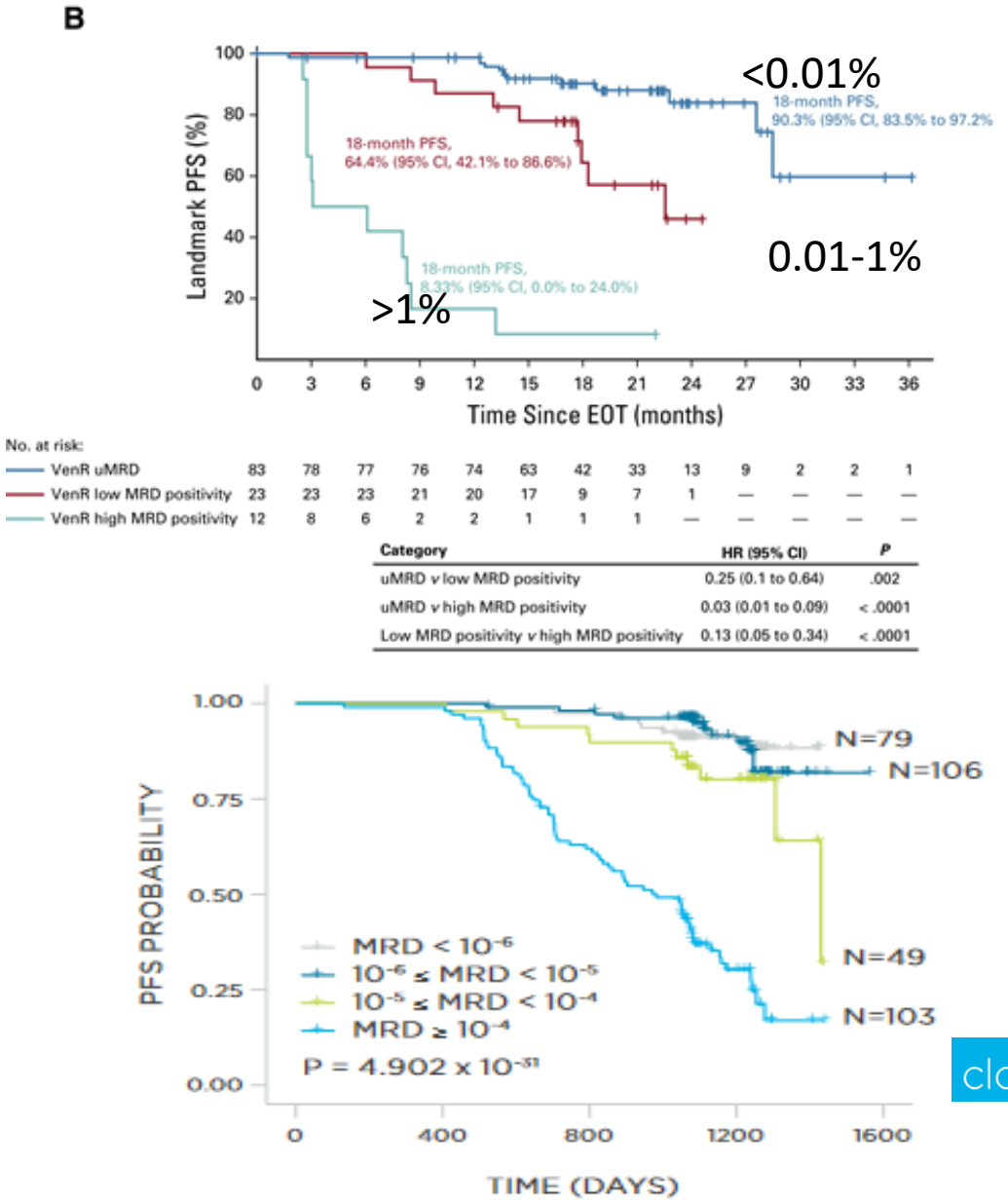
- **New proposal:** the quantitative point estimate, LoD and LoQ should be reported in all cases.
- **Additional questions:**
  - Should other parameters be provided, e.g. confidence interval, total #cells or leucocytes?
  - Can we generalise the approach (?? to all disorders)

# 3D) Summarising MRD results



- **0.01% / $10^{-4}$** is the IWCLL threshold for reporting **detectable vs. undetectable** disease but
  - Current technologies can detect disease below this level
  - MRD is a continuous variable: both lower and higher thresholds are also informative

- LoD is dependent both on the assay and sample characteristics
  - Example: sample with 0.005% CLL (5 CLL cells per 100 thousand leucocytes) tested using IGH-HTS.
  - Assay detection limit is 1/million (10^6) but there was only sufficient DNA to report at the 1/100 thousand (10^5) level
  - How to report? MRD negative (or undetectable) at iwCLL 0.01% threshold, detectable at MRD5, not assessable at MRD6?




clonoSEQ®

https://www.clonoseq.com/wp-content/uploads/PM-US-cSEQ-0353_clonoSEQ_ClinicalData_Branded_CLL.pdf

# 3D) Summarising MRD results: lessons from CML



- Use of binary terms such as positive vs. negative or detectable vs. undetectable are only meaningful in the context of a stated threshold or detection limit.
- A readily-identifiable abbreviation for the threshold is helpful

**REVIEW**

Laboratory recommendations for scoring deep molecular responses following treatment for chronic myeloid leukemia

NCP Cross[1,2], HE White[1,2], D Colomer[3], H Ehrencrona[4], L Foroni[5], E Gottardi[6], T Lange[7], T Lion[8], K Machova Polakova[9], S Dulucq[10], G Martinelli[11], E Oppliger Leibundgut[12], N Pallisgaard[13], G Barbany[14], T Sacha[15], R Talmaci[16], B Izzo[17], G Saglio[6], F Pane[17,18], MC Müller[19] and A Hochhaus[20]

- $MR^4$ ($\geqslant$4-log reduction from IRIS baseline) = either (i) detectable disease $\leqslant$0.01% BCR-$ABL^{IS}$ or (ii) undetectable disease in cDNA with 10 000–31 999 *ABL1* transcripts or 24 000–76 999 *GUSB* transcripts.
- $MR^{4.5}$ ($\geqslant$4.5-log reduction from IRIS baseline) = either (i) detectable disease $\leqslant$0.0032% BCR-$ABL^{IS}$ or (ii) undetectable disease in cDNA with 32 000–99 999 *ABL1* transcripts or 77 000–239 999 *GUSB* transcripts.
- $MR^5$ ($\geqslant$5-log reduction from IRIS baseline) = either (i) detectable disease $\leqslant$0.001% BCR-$ABL^{IS}$ or (ii) undetectable disease in cDNA with $\geqslant$100 000 *ABL1* transcripts $\geqslant$240 000 *GUSB* transcripts.

# 3D) Reporting MRD results: summarising 3/3

- Use of binary terms such as positive vs. negative or **detectable vs. undetectable** should only ever be used in the context of a stated **threshold or detection limit**.
- Detection limit depends on both the **assay and the individual sample**: if the sample is insufficiently cellular the assay detection limit may be different to the assay sensitivity.
- Expert consensus review propose to use the terminology **"MRD3", "MRD4", "MRD5"** etc to denote a sample containing less than 1 neoplastic cells per thousand, ten thousand, or hundred thousand normal cells respectively (Wierda et al, Leukemia. 2021 Jun 24. doi: 10.1038/s41375-021-01241-1)
- **Sub-classifying** as detectable or undetectable will depend on the assay and sample characteristics and is **secondary to the MRD threshold**.
  - A sample classified as MRD4 using an assay with a detection limit of 10-4 may have 0.005% MRD, or a much lower level of residual disease, e.g. less than 1 in a million or even no disease.
  - A sample classified as MRD4 using an assay with a detection limit of $10^{-6}$ would have a level of residual disease between 0.001-0.01% by definition if sample quality criteria were met.
- This approach could be used with any **directly quantitative validated method** that has a defined limit of detection (sensitivity) and limit of quantification. Any directly quantitative approach, including assays using patient-specific probes such as RQ-ASO-IG-PCR, must determine these values during the evaluation of each probe-set.

# Summarising MRD results: appropriate for any validated quantitative method and potentially applicable to many quasi-quantitative assays

| MRD classification | Neoplastic cells / total normal cells | Neoplastic cells % of total cells | Scientific notation | Cell required for flow cytometry | Cells (DNA) required for molecular analysis |
|---|---|---|---|---|---|
| **MRD3** | <1/ thousand | <0.1% | 10E-3 ($10^{-3}$) | >20 thousand | >3 thousand (0.02µg DNA) |
| **MRD4** | <1/ 10 thousand | <0.01% | 10E-4 ($10^{-4}$) | >200 thousand | >30 thousand (0.2µg DNA) |
| **MRD5** | <1/ 100 thousand | <0.001% | 10E-5 ($10^{-5}$) | >2 million | >300 thousand (2µg DNA) |
| **MRD6** | <1/ million | <0.0001% | 10E-6 ($10^{-6}$) | >20 million | >3 million (20µg DNA) |
| **MRD7** | <1/ 10 million | <0.00001% | 10E-7 ($10^{-7}$) | >200 million | >30 million (120µg DNA) |

# Criteria for reporting individual samples and summarising MRD status independent of assay type (? also independent of disease type)

| | Yes | No | Not sure |
|---|---|---|---|
| 3C) The proposed criteria for reporting individual samples are acceptable (slide 22) | | | |
| 3D) The proposed criteria for reporting categorical MRD status are acceptable (slide 23-26) | | | |

Free text comment (for each):

# Acknowledgements

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ORIGINAL ARTICLE

## International standardized approach for flow cytometric residual disease monitoring in chronic lymphocytic leukaemia

AC Rawstron[1], N Villamor[2,3], M Ritgen[4], S Böttcher[4], P Ghia[5], JL Zehnder[6], G Lozanski[7], D Colomer[2,3], C Moreno[2,3], M Geuna[8], PAS Evans[1], Y Natkunam[6], SE Coutre[6], ED Avery[9], LZ Rassenti[9], TJ Kipps[9], F Caligaris-Cappio[5], M Kneba[4], JC Byrd[7], MJ Hallek[10], E Montserrat[2,3] and P Hillmen[1]

Leukemia (2013) 27, 142–149
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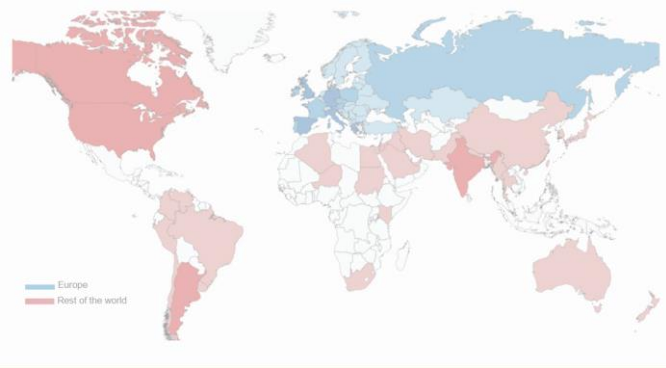
www.nature.com/leu

ORIGINAL ARTICLE

## Improving efficiency and sensitivity: European Research Initiative in CLL (ERIC) update on the international harmonised approach for flow cytometric residual disease monitoring in CLL

AC Rawstron[1,2], S Böttcher[3], R Letestu[4,5], N Villamor[6], C Fazi[7], H Kartsios[1], RM de Tute[1], J Shingles[1], M Ritgen[3], C Moreno[8], K Lin[9], AR Pettitt[9], M Kneba[3], E Montserrat[6], F Cymbalista[4,5], M Hallek[10], P Hillmen[11] and P Ghia[7] on behalf of the European Research Initiative in CLL (ERIC)

ERIC
european research initiative on CLL




Leukemia (2016) 30, 929–936
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www.nature.com/leu

ORIGINAL ARTICLE

## A complementary role of multiparameter flow cytometry and high-throughput sequencing for minimal residual disease detection in chronic lymphocytic leukemia: an European Research Initiative on CLL study

AC Rawstron[1], C Fazi[2], A Agathangelidis[2], N Villamor[3], R Letestu[4], J Nomdedeu[5], C Palacio[6], O Stehlikova[7], K-A Kreuzer[8], S Liptrot[9], D O'Brien[9], RM de Tute[1], I Marinov[10], M Hauwel[11], M Spacek[12], J Dobber[13], AP Kater[13], P Gambell[14], A Soosapilla[15], G Lozanski[16], G Brachtl[17,18], K Lin[19], J Boysen[20], C Hanson[20], JL Jorgensen[21], M Stetler-Stevenson[22], C Yuan[22], HE Broome[23], L Rassenti[23], F Craig[24], J Delgado[3], C Moreno[5], F Bosch[6], A Egle[17], M Doubek[7], S Pospisilova[7], S Mulligan[25], D Westerman[14], CM Sanders[26], R Emerson[26], HS Robins[26], I Kirsch[26], T Shanafelt[20], A Pettitt[19], TJ Kipps[23], WG Wierda[21], F Cymbalista[4], M Hallek[8], P Hillmen[27], E Montserrat[3], and P Ghia[2,28] on behalf of ERIC (European Research Initiative on CLL)