Hämatologie
Labor Kiel

DEUTSCHE
STUDIENGRUPPE

Clinical Overview: MRD in CLL

Dr. Matthias Ritgen

UKSH, Medizinische Klinik II, Campus Kiel

m.ritgen@med2.uni-kiel.de

Remission in CLL

- Clinical criteria (NCI->WHO)
  - Lymphadenopathy
  - Splenomegaly
  - Hepatomegaly
  - Other manifestations
- Conventional Laboratory criteria
  - WBC, HB, thrombocytes
  - <5000/µl lymphocytes
- No CLL infiltration of bone marrow

iwCLL Remission criteria

Parameter	CR	PR	PD	SD
Lympnodes	None ≥1.5 cm	Decrease ≥50% (from baseline)*	Increase ≥50% from baseline or from response	Change of −49% to +49%
Liver and/or spleen size†	Spleen size <13 cm; liver size normal	Decrease ≥50% (from baseline)	Increase ≥50% from baseline or from response	Change of −49% to +49%
Constitutional symptoms	None	Any	Any	Any
Circulating lymphocyte count	Normal	Decrease ≥50% from baseline	Increase ≥50% over baseline	Change of −49% to +49%
Platelet count	≥100 × 10^9/L	≥100 × 10^9/L or increase ≥50% over baseline	Decrease of ≥50% from baseline secondary to CLL	Change of −49 to +49%
Hemophglobin	≥11.0 g/dL (untransfused and without erythropoietin)	≥11 g/dL or increase ≥50% over baseline	Decrease of ≥2 g/dL from baseline secondary to CLL	Increase <11.0 g/dL or <50% over baseline, or decrease <2 g/dL
Marrow	Normocellular, no CLL cells, no B-lymphoid nodules	Presence of CLL cells, or of B-lymphoid nodules, or not done	Increase of CLL cells by ≥50% on successive biopsies	No change in marrow infiltrate

Hallek et. al. blood 2018

iwCLL Remission criteria

Parameter	CR		SD
Lympnodes	None ≥1.5 cm	Dec	ge of −49% to +49%
Liver and/or spleen size‡	Spleen size <13 cm; liver size normal	Dec	ge of −49% to +49%
Constitutional symptoms	None		Any
Circulating lymphocyte count	Normal	Dec	ge of −49% to +49%
Platelet count	≥100 × 10^9/L	≥100 ≥5(	ge of −49 to +49%
Hemophglobin	≥11.0 g/dL (untransfused and without erythropoietin)	≥11 g/	ease <11.0 g/dL or % over baseline, or ecrease <2 g/dL
Marrow	Normocellular, no CLL cells, no B-lymphoid nodules	Preser B-lyn	change in marrow infiltrate

5.9. Minimal residual disease

The complete eradication of the leukemia is a desired end point. Use of sensitive multicolor flow cytometry, PCR, or next-generation sequencing can detect MRD in many patients who achieved a complete clinical response. Prospective clinical trials have provided substantial evidence that therapies that are able to eradicate MRD usually result in an improved clinical outcome.[97,102-106] The techniques for assessing MRD have undergone a critical evaluation and have become well standardized.[107,108] 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.[108] Refinement and harmonization of these technologies has established that a typical flow cytometry–based assay comprises a core panel of 6 markers (ie, CD19, CD20, CD5, CD43, CD79b, and CD81).[108] As such, 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. The blood generally can be used for making this assessment because the marrow will have detectable CLL when it is also found in the peripheral blood. However, 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. Clinical trials aimed at maximizing the depth of remissions should include at least 1 test to assess for MRD, because the lack of leukemia persistence using these sensitive tests has a strong, positive prognostic impact. The report should be clear as to whether blood and/or marrow have been assessed and should 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).

lood 2018

iwCLL Remission criteria

Parameter	CR		SD
Lympnodes	None ≥1.5 cm	Dec	ge of −49% to +49%
Liver and/or spleen size‡	Spleen size <13 cm; liver size normal	Dec	ge of −49% to +49%
Constitutional symptoms	None		Any
			ge of −49% to +49%
			ge of −49 to +49%
	erythropoietin)		ease <11.0 g/dL or % over baseline, or ecrease <2 g/dL
Marrow	Normocellular, no CLL cells, no B-lymphoid nodules	Preser B-lyn	change in marrow infiltrate

5.1.7. For patients in clinical trials (Table 3). A bone marrow aspirate and biopsy should be performed if clinical and laboratory results listed in sections 5.1.1 to 5.1.5 demonstrate that a CR may have been achieved. To define a CR, the cytological or pathological evaluation of the bone marrow smear or biopsy must be at least normocellular for age, without evidence for typical CLL lymphocytes by morphological criteria. This evaluation is not based on a flow cytometry–based MRD assessment (see section 9).

5.9. Minimal residual disease

The complete eradication of the leukemia is a desired end point. Use of sensitive multicolor flow cytometry, PCR, or next-generation sequencing can detect MRD in many patients who achieved a complete clinical response. Prospective clinical trials have provided substantial evidence that therapies that are able to eradicate MRD usually result in an improved clinical outcome.[97,102-106] The techniques for assessing MRD have undergone a critical evaluation and have become well standardized.[107,108] 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.[108] Refinement and harmonization of these technologies has established that a typical flow cytometry–based assay comprises a core panel of 6 markers (ie, CD19, CD20, CD5, 43, CD79b, and CD81).[108] As such, patients will be defined as ving undetectable MRD (MRD-neg) remission if they have od or marrow with <1 CLL cell per 10 000 leukocytes. The od generally can be used for making this assessment because marrow will have detectable CLL when it is also found in the ripheral blood. However, there are therapies that preferen- ly clear the blood but not the marrow (such as monoclonal tibodies); therefore, it may be important to confirm that the rrow aspirate also is MRD-neg when the blood is found to be RD-neg. Clinical trials aimed at maximizing the depth of re-missions should include at least 1 test to assess for MRD, because the lack of leukemia persistence using these sensitive tests has a strong, positive prognostic impact. The report should be clear as to whether blood and/or marrow have been assessed and should 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).

lood 2018

MRD in clinical use?

- Comparing efficacy of different treatment regimens?
- Which treatments/which patients to perform MRD?
- Which material to test?
- Resistant disease?
- Correlation with pfs or os?
- Prognostification of pfs or os?
- MRD to guide treatment?

The concept of MRD

MRD can indicate depth of remission

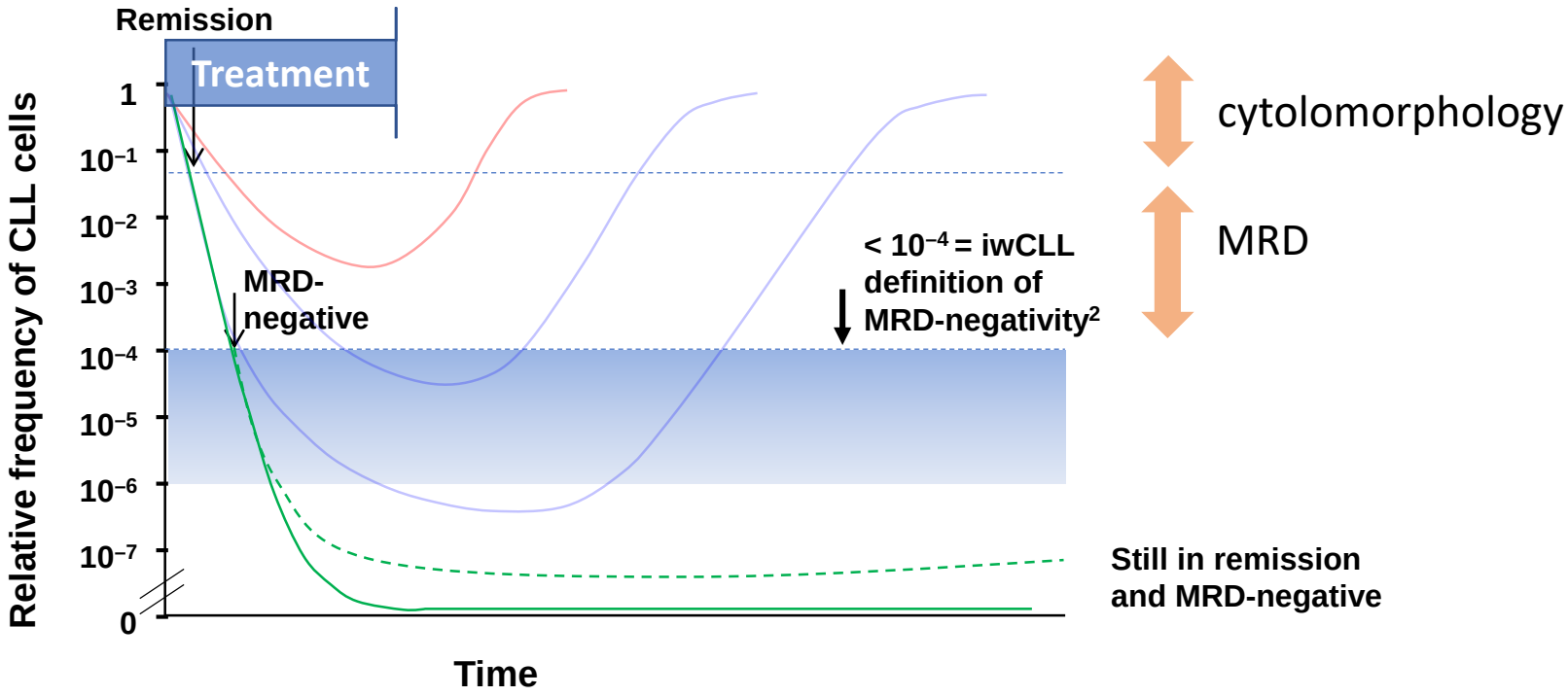
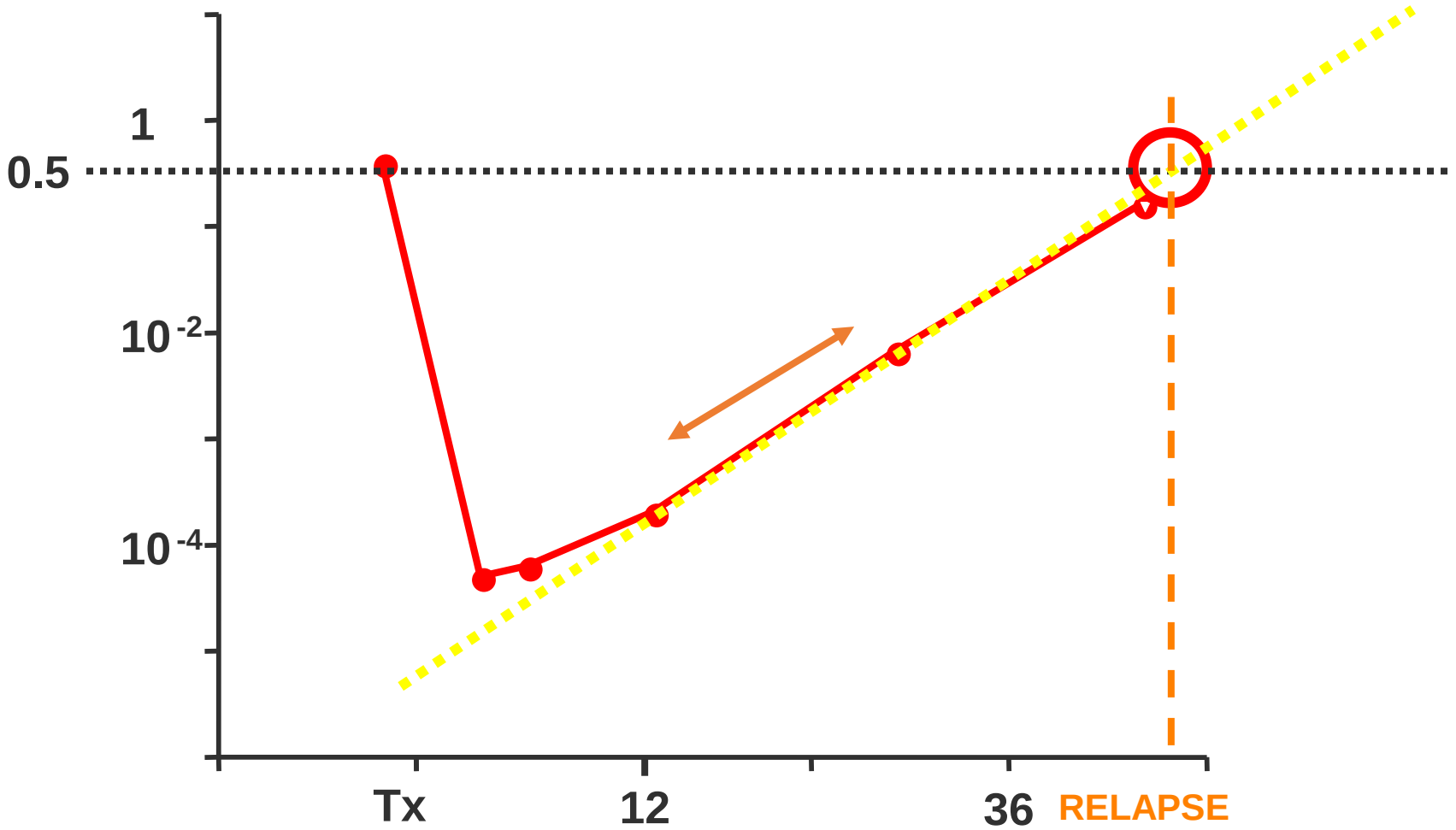


Illustration is conceptual: references contains definitions and descriptions

1 Böttcher S, *et al*. *Hematol Clin N Am* 2013; 27:267–288;
2. Hallek M, *et al. Blood* 2008; 111:5446–5456;
3. Moreno C, *et al. Best Pract Res Clin Haematol* 2010; 23:97–107.

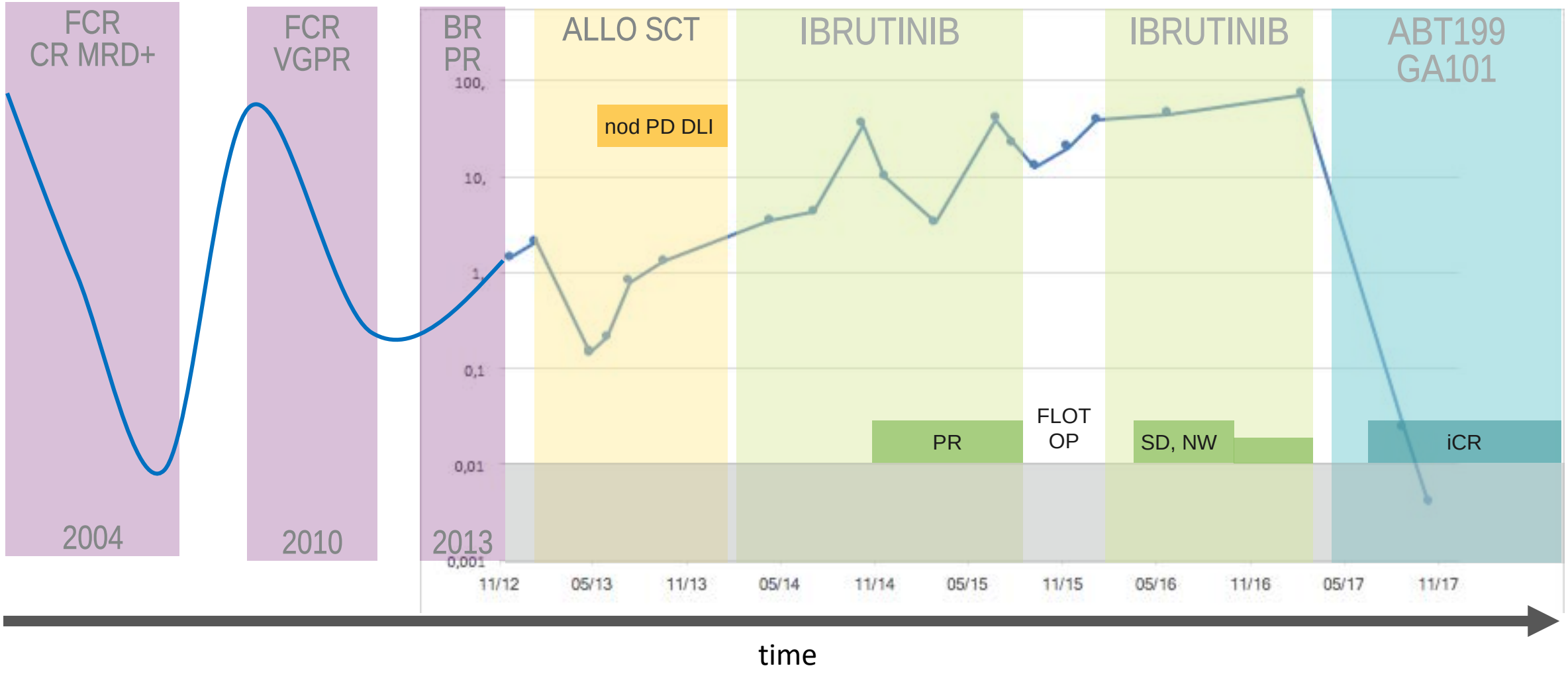
MRD kinetics after treatment



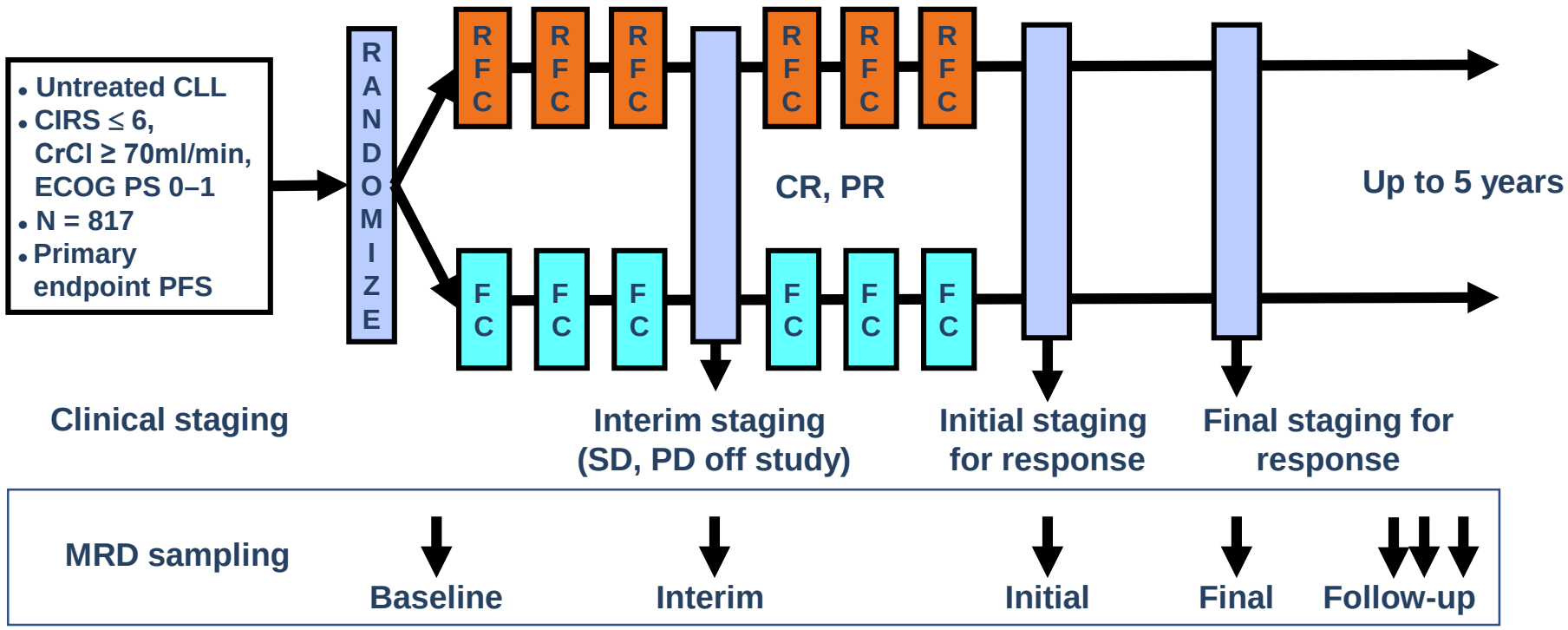
Ritgen ASH 2005

Example of MRD in CLL R/R

2004 ED, 43j, w, no17p, TP53wt, 13q-, IgVH-UM

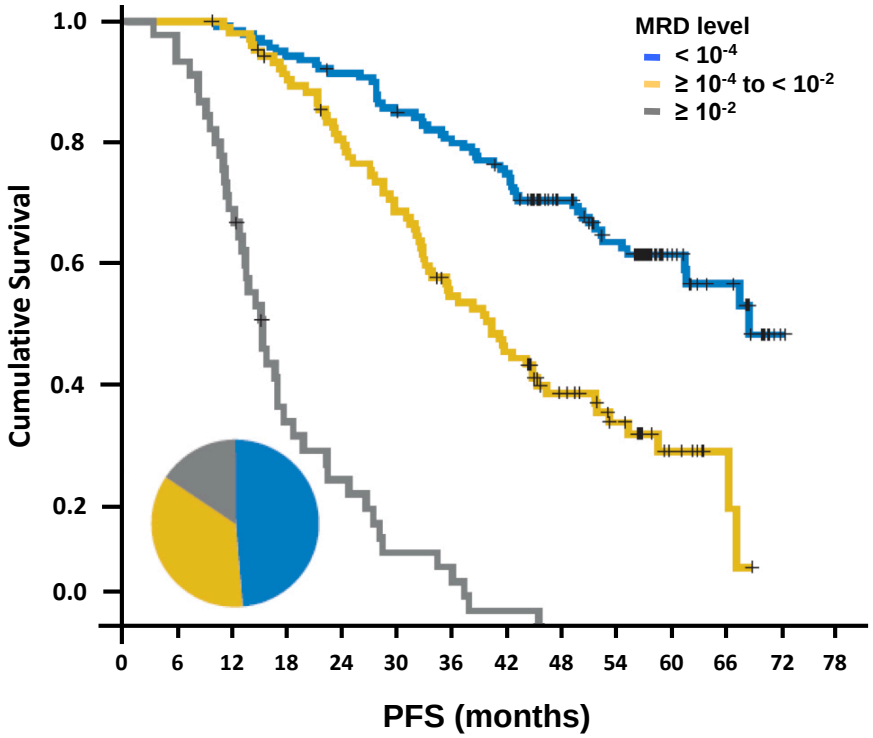


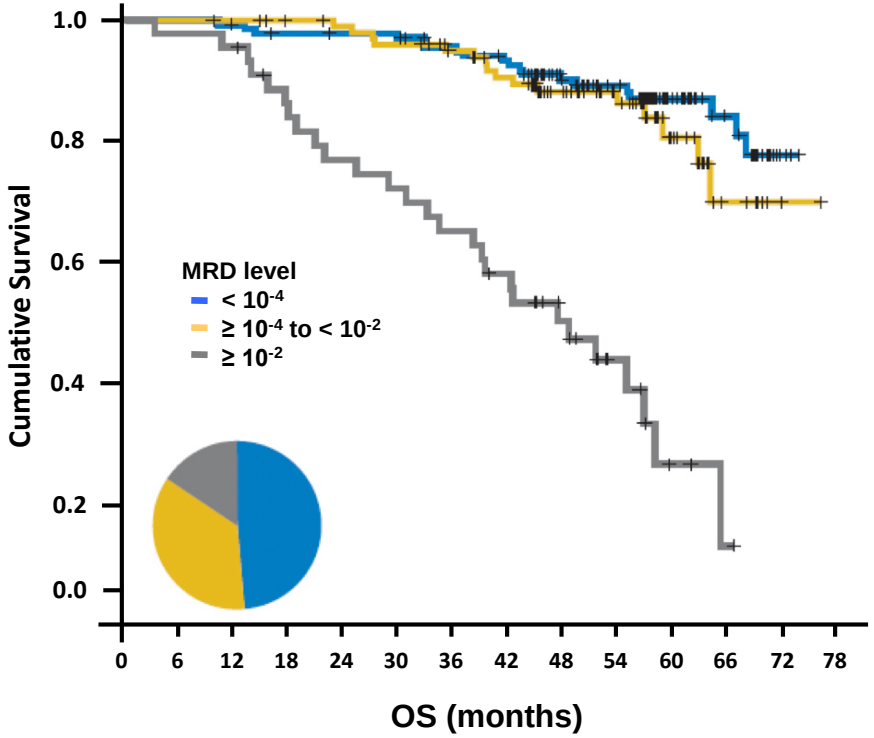
MRD in the CLL8 trial



Hallek M, *et al. Lancet* 2010; 376:1164–1174;
Böttcher S, *et al. J Clin Oncol* 2012; 30:980–988.

Effect of MRD negativity on PFS and OS in CLL8

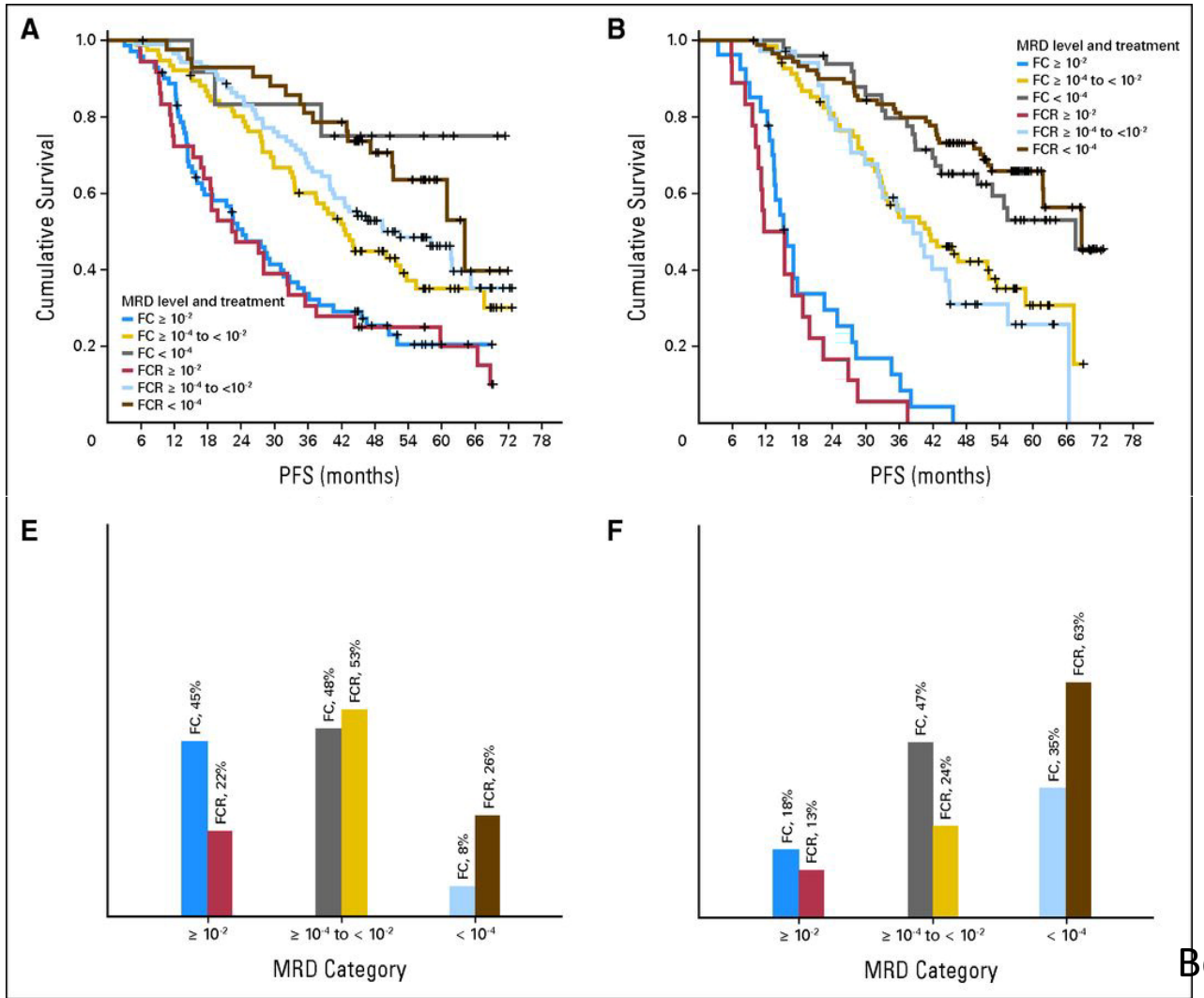




MRD negativity shown on this slide was analysed in peripheral blood at final restaging

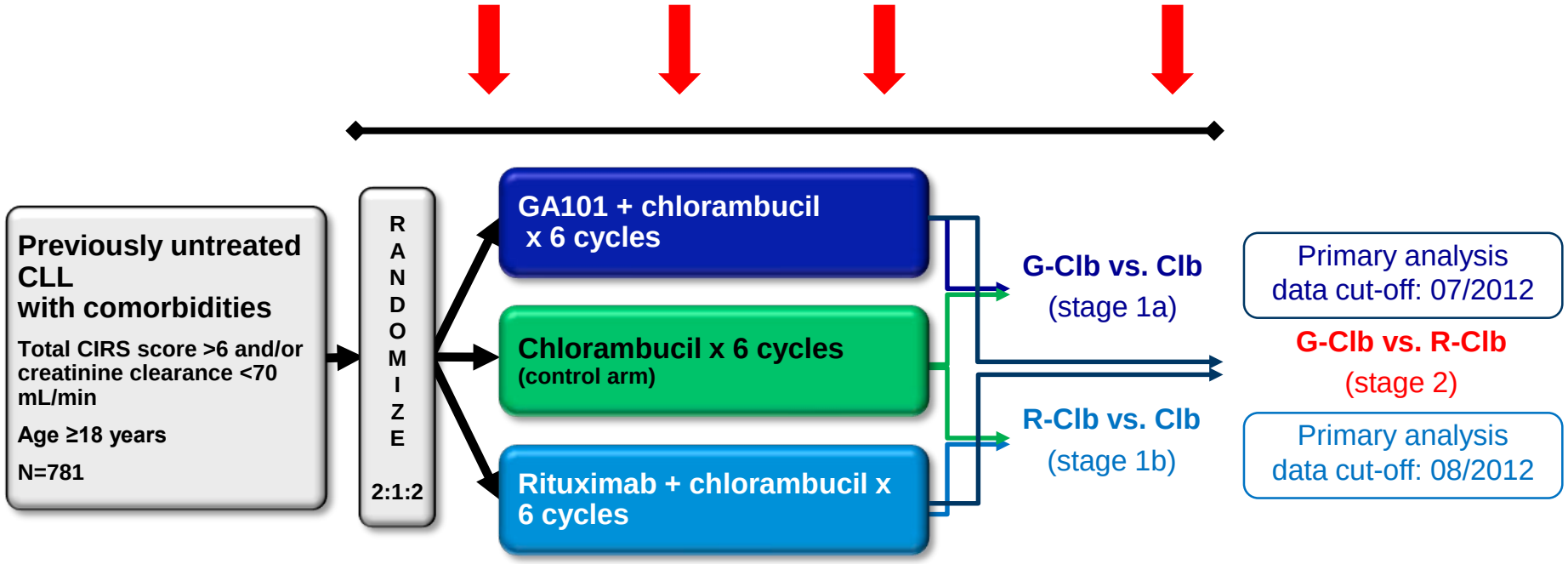
Boettcher S et al. JCO 2012; 30:980-988

MRD and outcome in 1st line treatment CLL8 study (FCR vs. FC)



Böttcher S et al *J. Clin. Oncol.* 2012

R-Clb, G-Clb in first line CLL (CLL11)



ORIGINAL ARTICLE

Obinutuzumab plus Chlorambucil in Patients with CLL and Coexisting Conditions

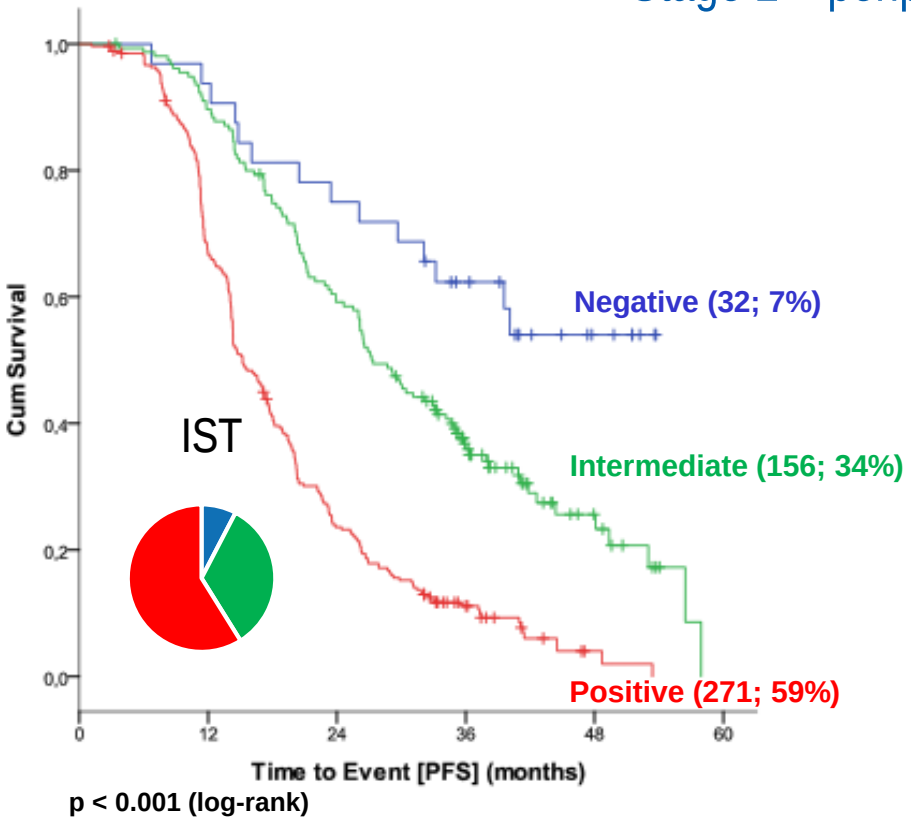
Valentin Goede, M.D., Kirsten Fischer, M.D., Raymonde Busch, Ph.D.,

- GA101: 1000 mg days 1, 8, and 15 cycle 1; day 1 cycles 2–6, every 28 days
- Rituximab: 375 mg/m^2 day 1 cycle 1, 500 mg/m^2 day 1 cycles 2–6, every 28 days
- Chlorambucil: 0.5 mg/kg day 1 and day 15 cycle 1–6, every 28 days
- Patients with progressive disease in the Clb arm were allowed to cross over to G-Clb

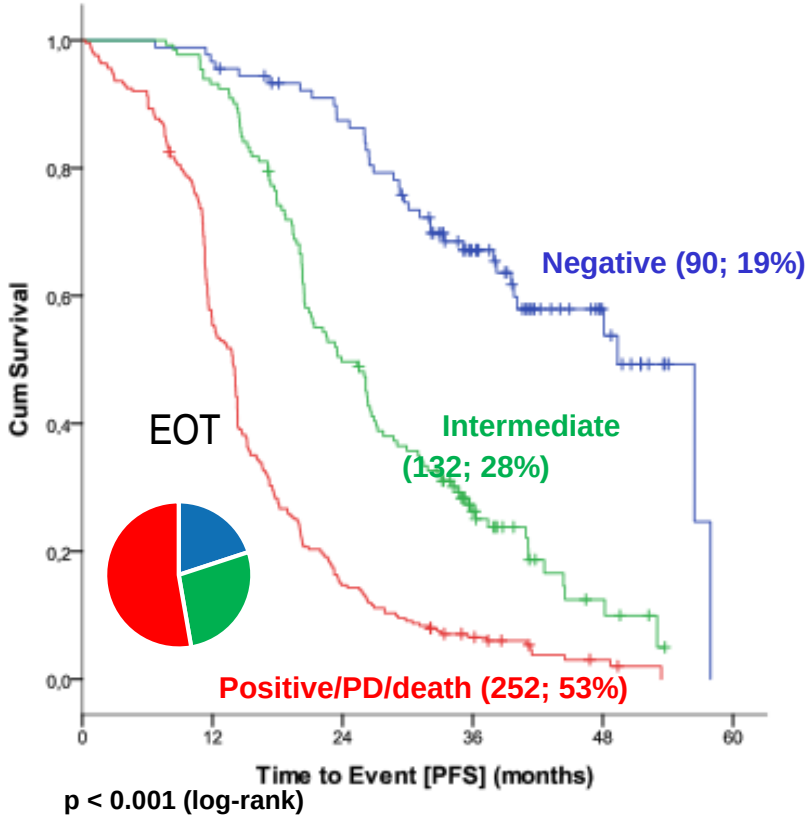
R-Clb, G-Clb in first line CLL (CLL11)
MRD during treatment

CLL11

Stage 2 – peripheral blood



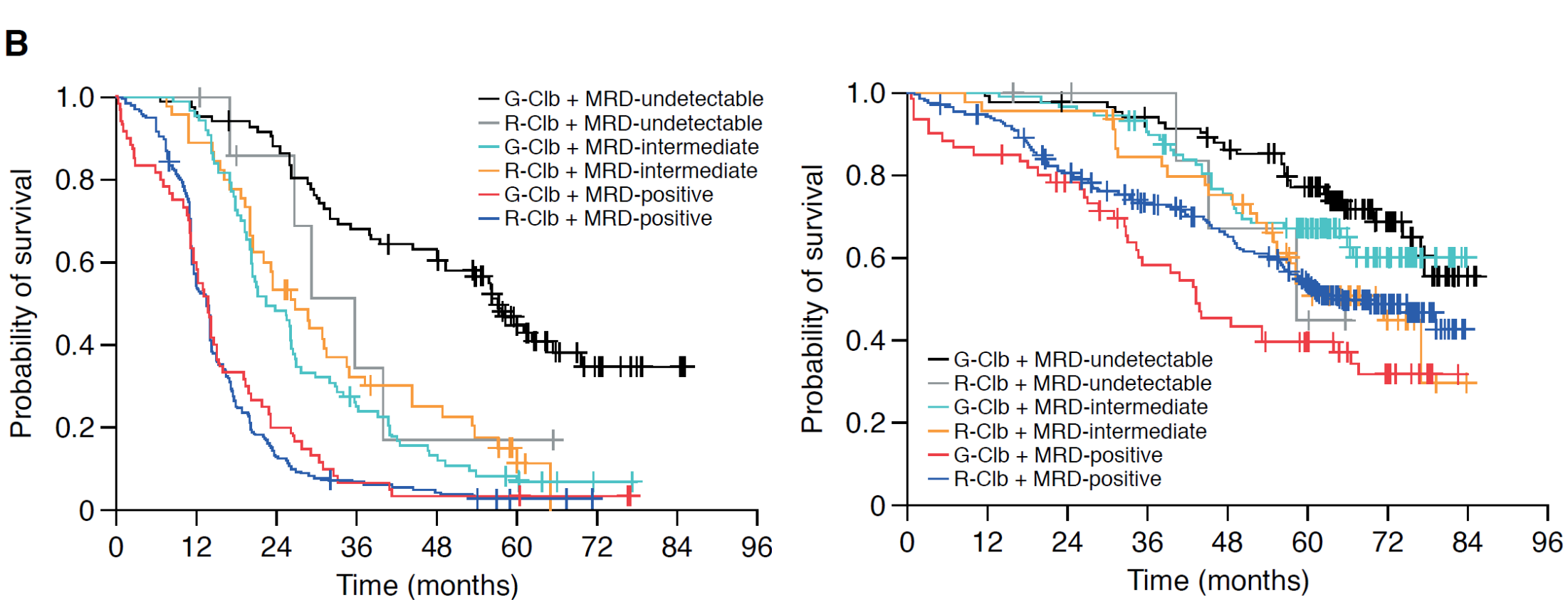
p < 0.001 (log-rank)



p < 0.001 (log-rank)

Langerak & Ritgen blood accepted

MRD in older patients – CLL11



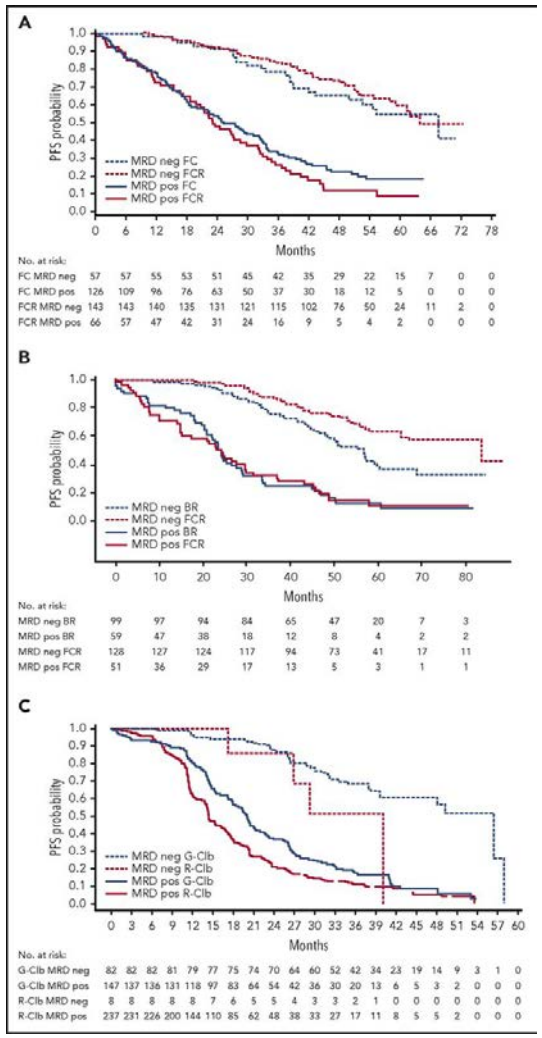
Langerak & Ritgen accepted

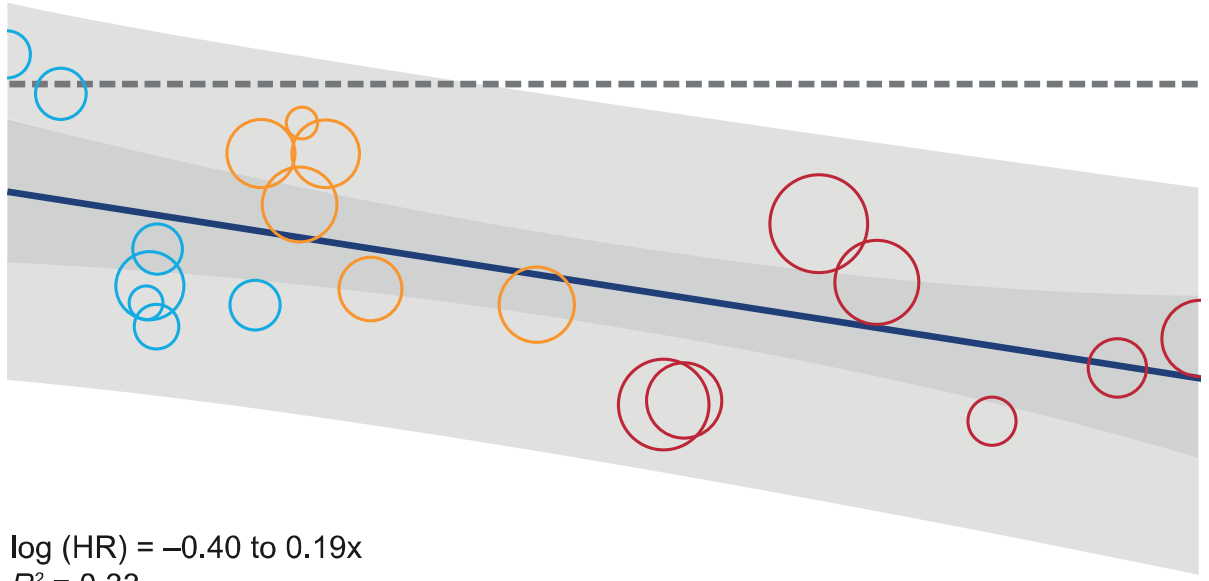
MRD in conventional (chemo +/- anti-CD20) treated CLL

CLL8

CLL10

CLL11





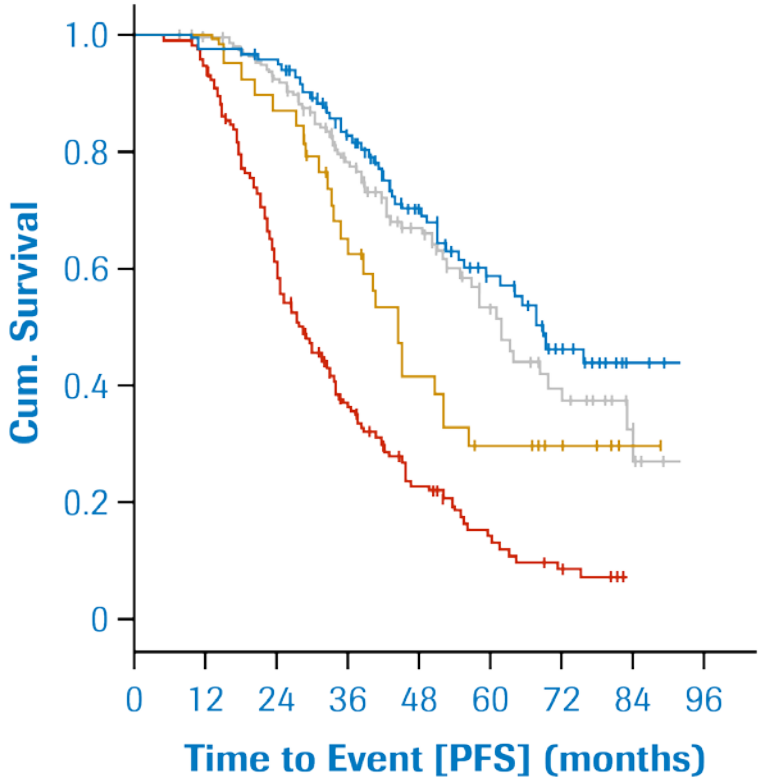
log (HR) = –0.40 to 0.19x
R^2 = 0.33

g Relative Risk

Natalie Dimier et al. Blood 2018;131:955-962

MRD and clinical stage

PFS grouped by MRD and clinical response at EOT



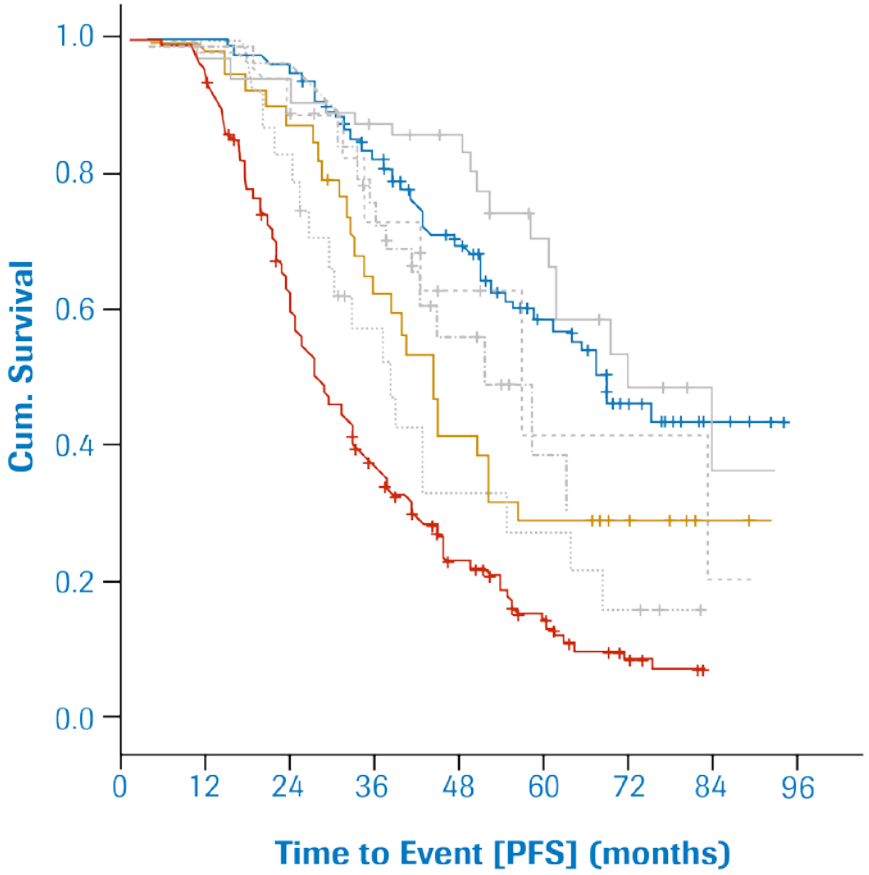
	Median PFS	p value (compared to MRD-CRs)
MRD- CRs	68.9 mo	-
MRD+ CRs	44.4 mo	**p=0.004**
MRD- PRs	61.7 mo	p=0.227
MRD+ PRs	28.1 mo	**p<0.001**

MRD- PRs	**vs.**	MRD+ CRs	**p=0.047**

Mod. Kovacs G et al, ASH 2014,

MRD and clinical stage and manifestations

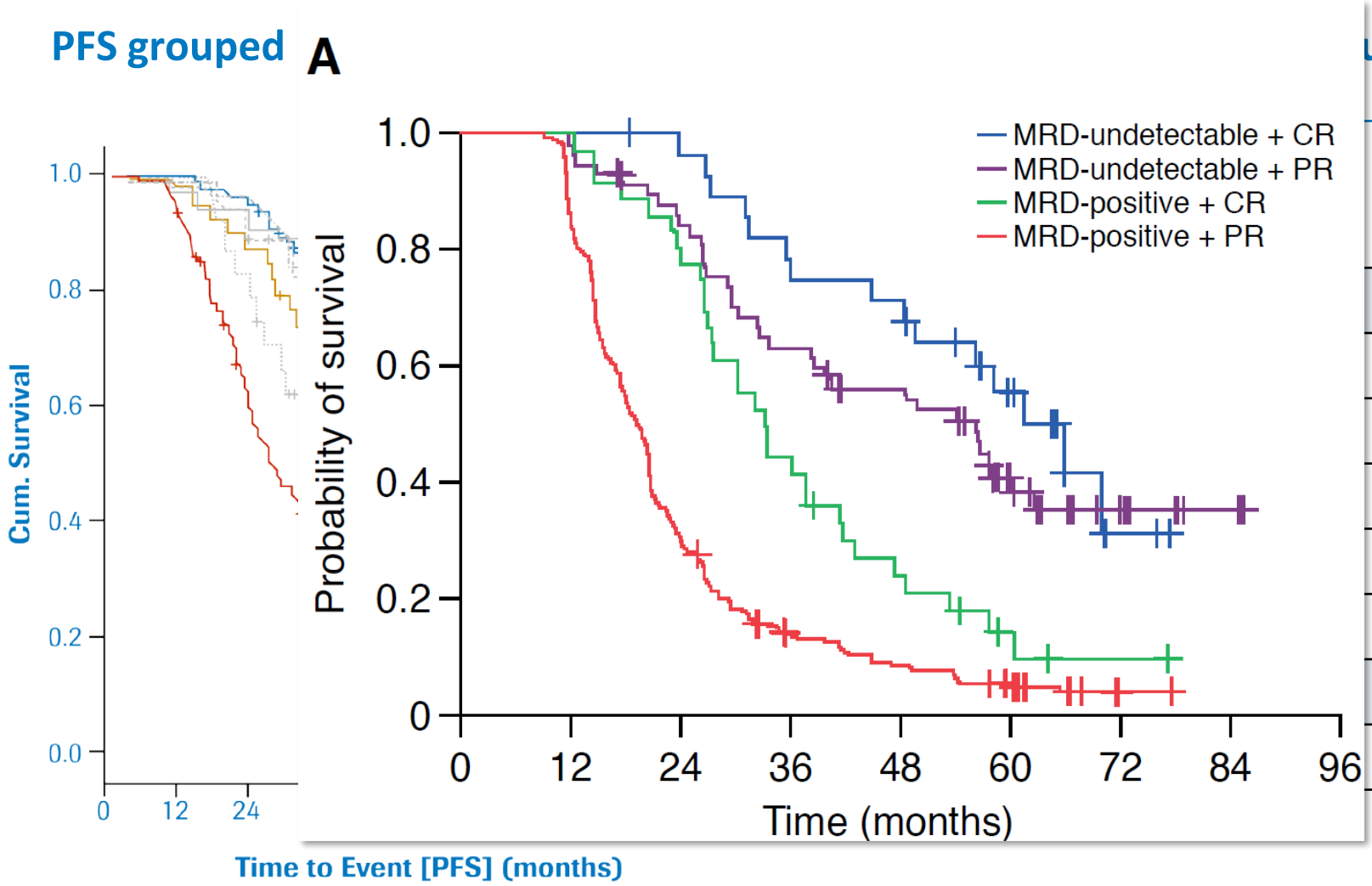
PFS grouped by MRD and clinical response (including MRD- PR subgroups) at EOT



	Median PFS	p value (compared to MRD-CRs)
MRD- CRs	68.9 mo	-
MRD- PRs:		
with splenom.	72.0 mo	p=0.331
with ly. node	38.7 mo	**p<0.001**
with BM	56.8 mo	p=0.420
>1 above	51.8 mo	p=0.202
MRD+ CRs	44.4 mo	**p=0.004**
MRD+ PRs	28.1 mo	**p<0.001**

Mod. Kovacs G et al, ASH 2014, Oral Abstract Session,

MRD and clinical stage and manifestations



ups) at EOT

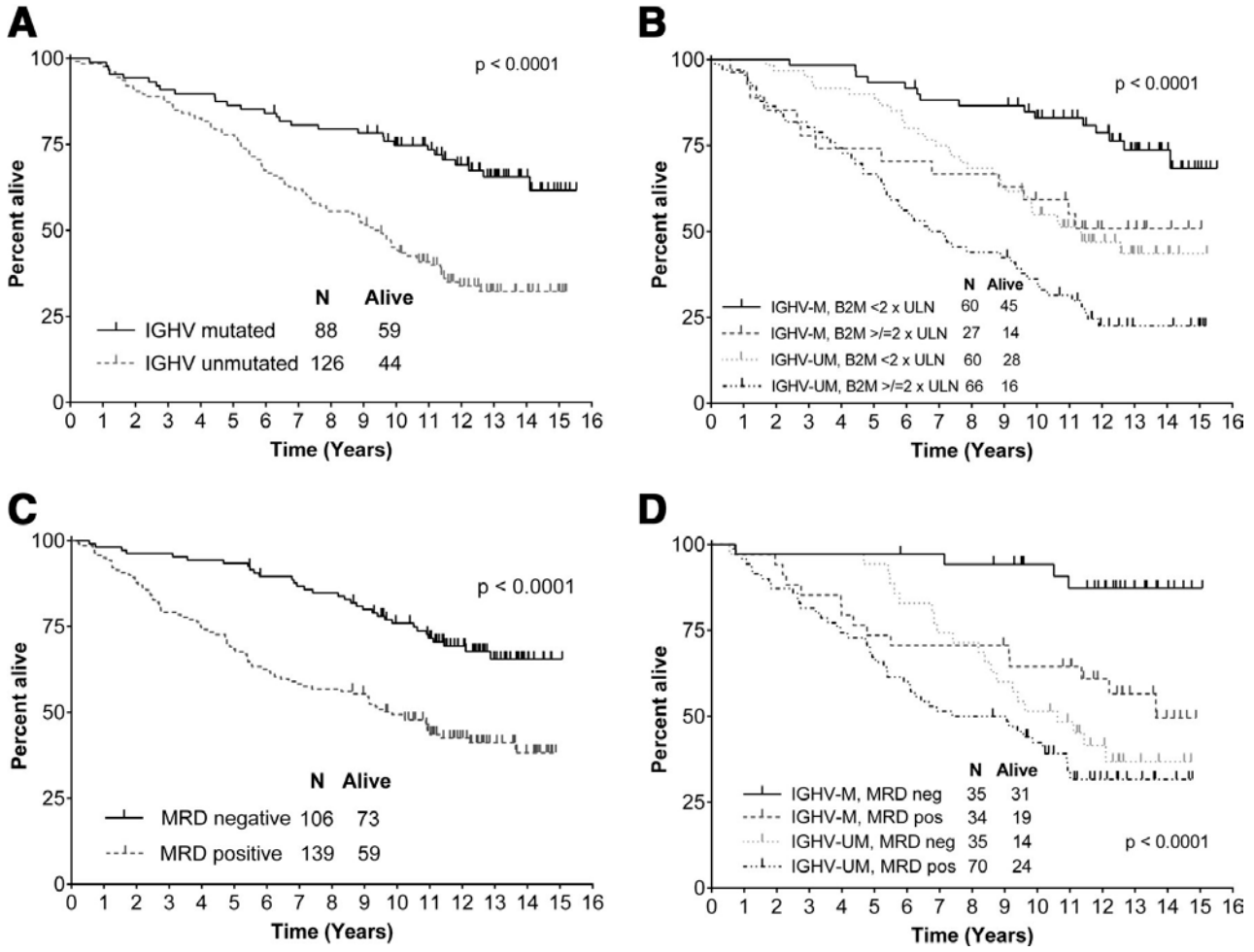
p value (compared to **MRD-CRs**)
-
p=0.331
p<0.001
p=0.420
p=0.202
p=0.004
p<0.001

Mod. Kovacs G et al, ASH 2014, Oral Abstract Session,

MRD in specific clinical situations

CLL – individualised treatment?

FCR 1stL CLL (MDA)

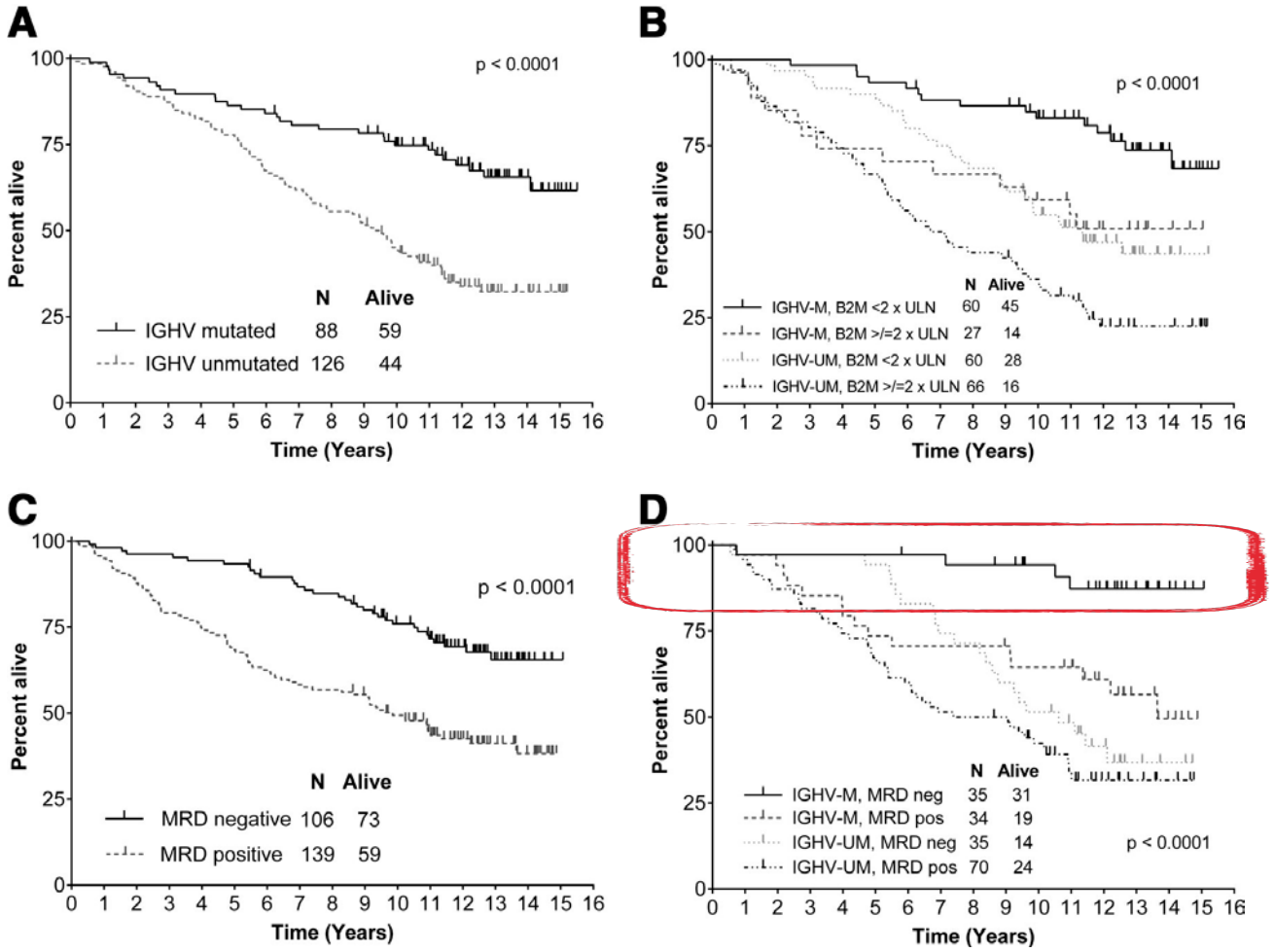


©2016 by American Society of Hematology

Philip A. Thompson et al. Blood 2016;127:303-309

CLL – individualised treatment?

FCR 1stL CLL (MDA)

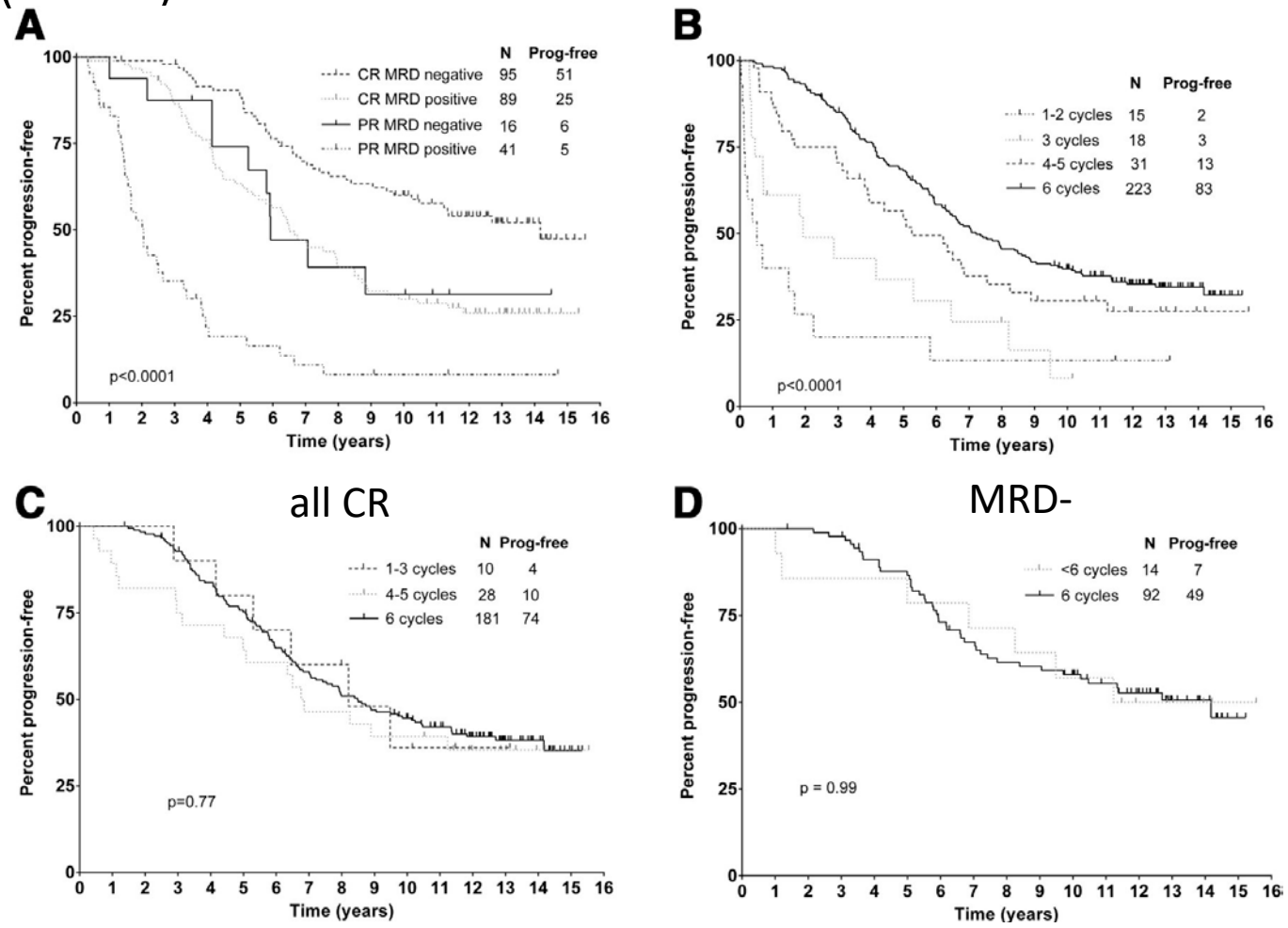


©2016 by American Society of Hematology

Philip A. Thompson et al. Blood 2016;127:303-309

CLL – individualised treatment?

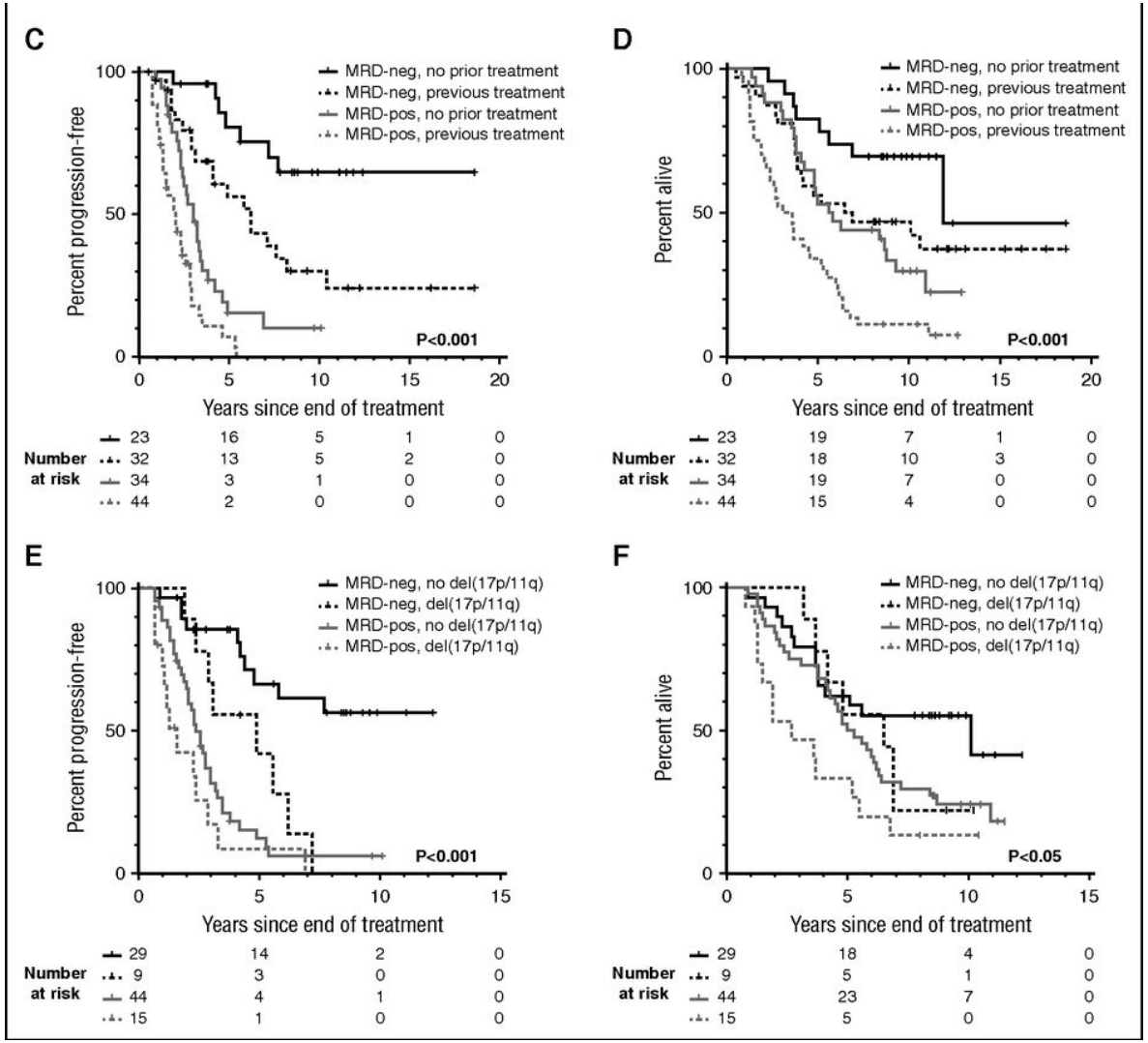
FCR 1stL CLL (MDA)



Philip A. Thompson et al. Blood 2016;127:303-309

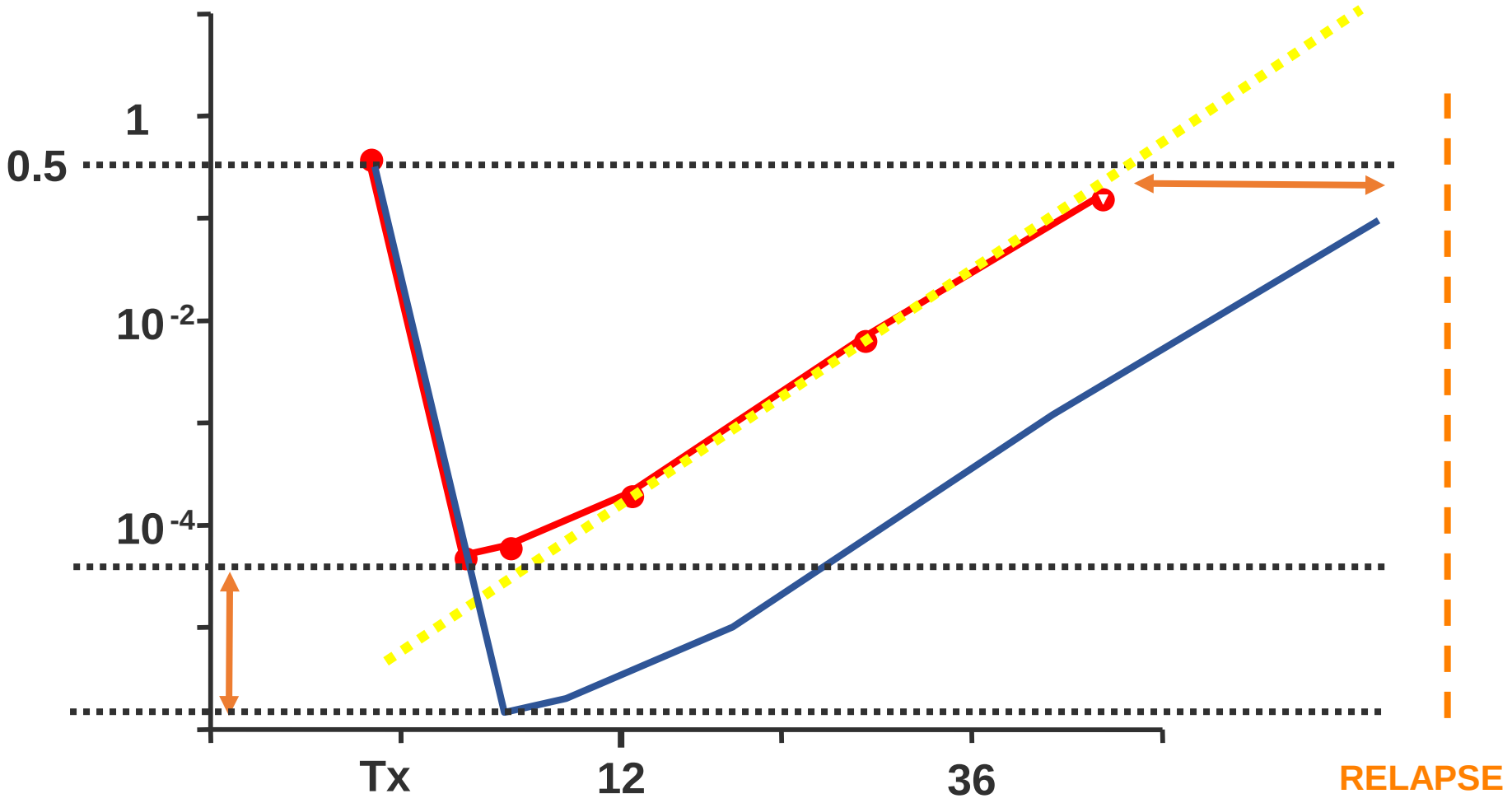
MRD desireable in 1st-line?

FCR 1st and 2nd line, Leeds retrospective analysis



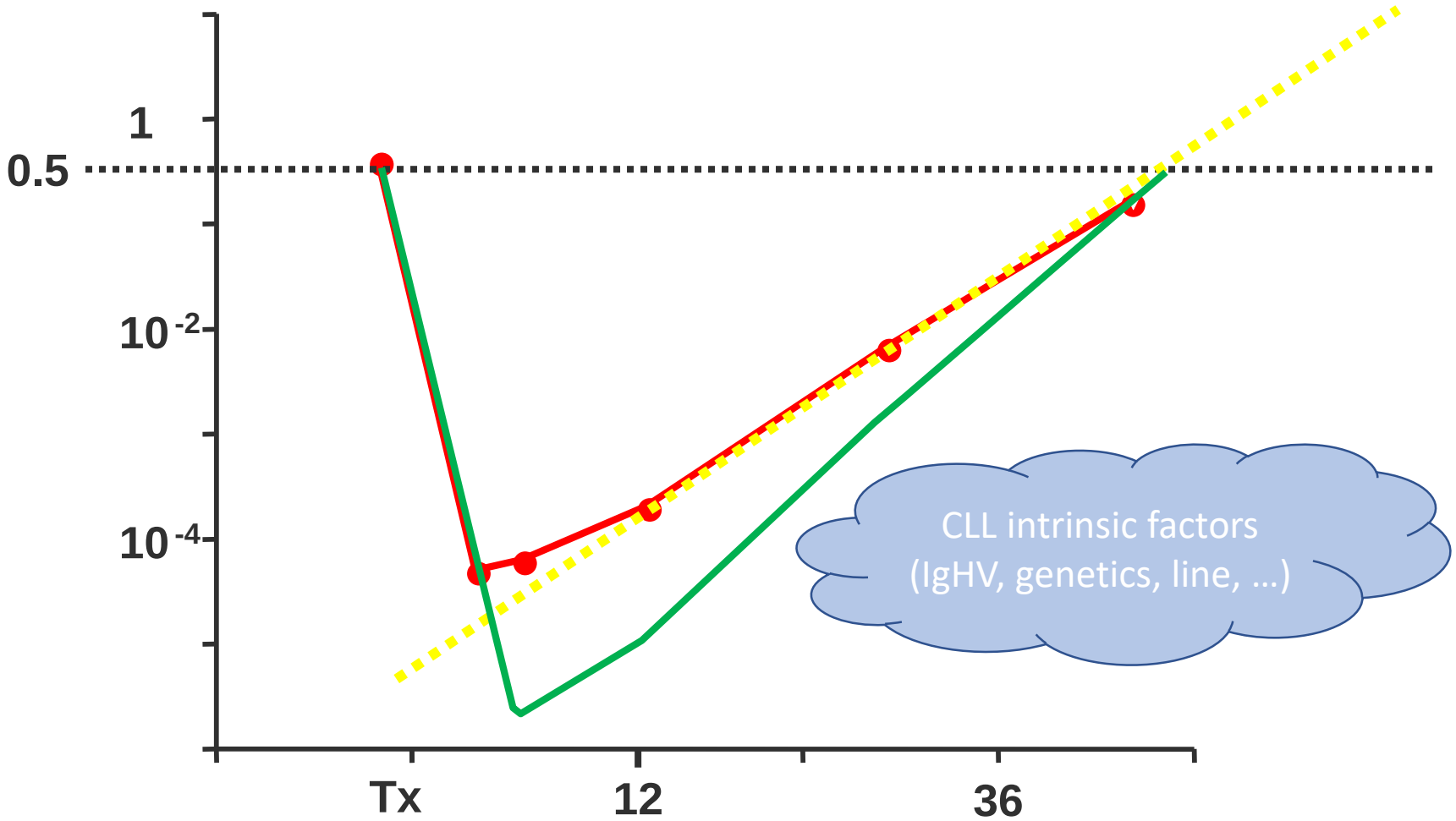
Marwan Kwok et al. Blood 2016;128:2770-2773

MRD kinetics after treatment



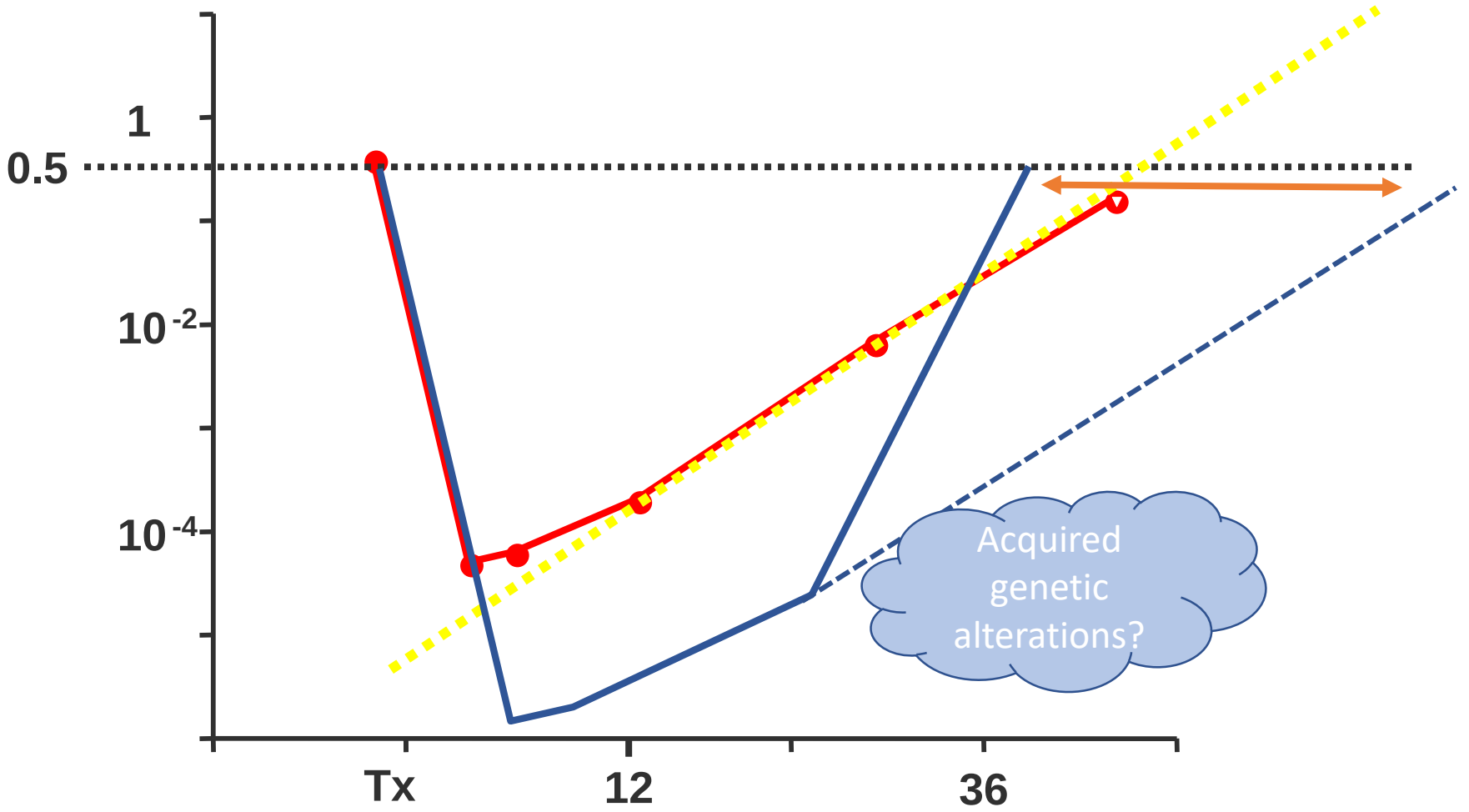
Ritgen ASH 2005

MRD kinetics after treatment



Ritgen ASH 2005

MRD kinetics after treatment



Ritgen ASH 2005

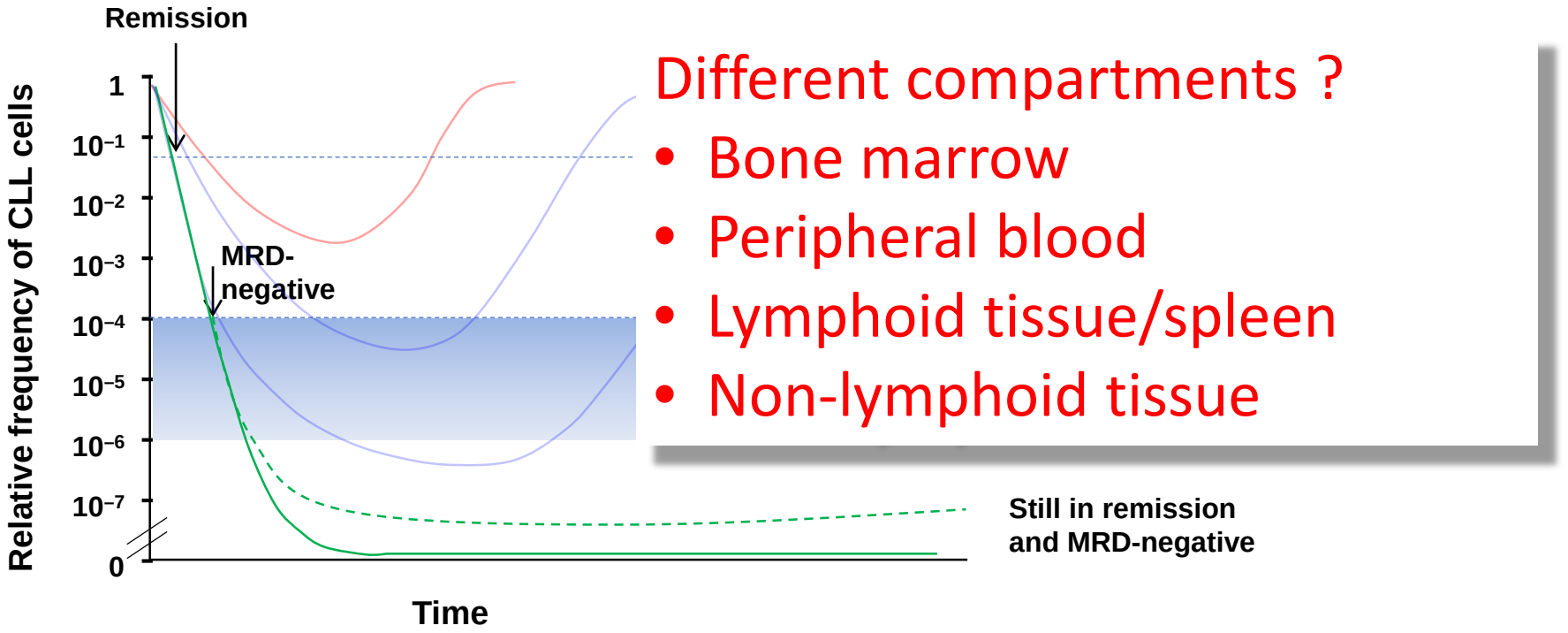
MRD in conventional treatment

- MRD independent prognostic factor for outcome
  - MRD risk stratification in 3 groups of >1E-1, between 1E-2 and 1E-4 and below 1E-4
  - MRD risk groups established in slow-go and go-go patients
- MRD level is related to PFS
- Risk stratification independent from treatment regimen
  - with or without antibody
  - But not comparable across studies
- MRD may improve clinical remission criteria
- Bone marrow probably more appropriate than blood (not shown)

Targeted treatment and MRD

The concept of MRD

MRD can indicate depth of remission and predict relapse



Different compartments ?

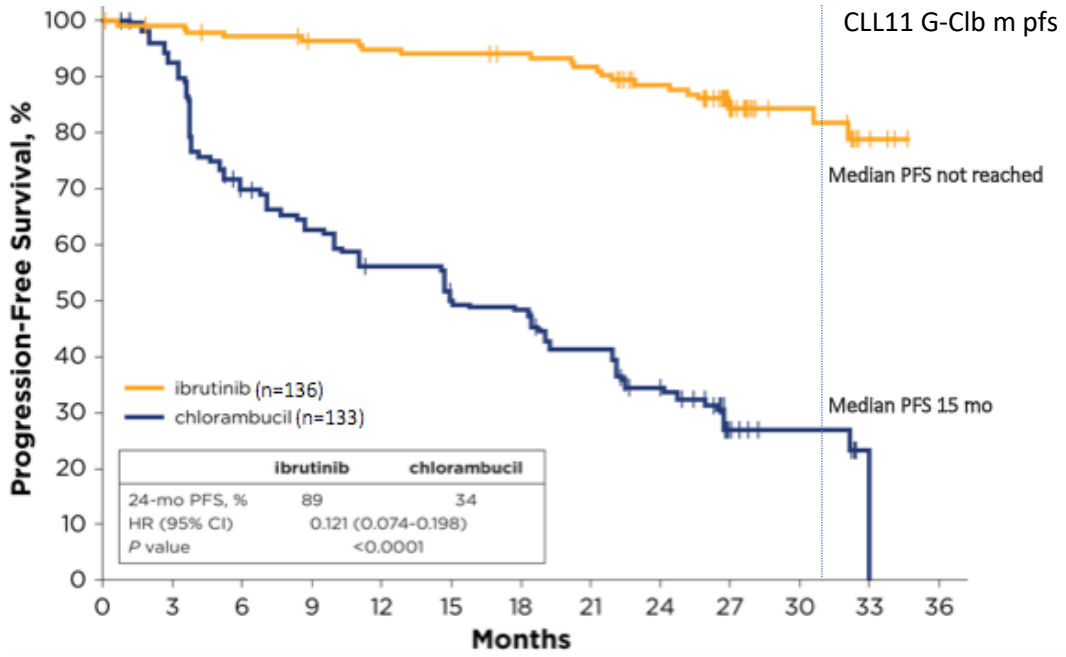
- Bone marrow
- Peripheral blood
- Lymphoid tissue/spleen
- Non-lymphoid tissue

Illustration is conceptual: references contains definitions and descriptions

1 Böttcher S, *et al*. *Hematol Clin N Am* 2013; 27:267–288;
2. Hallek M, *et al. Blood* 2008; 111:5446–5456;
3. Moreno C, *et al. Best Pract Res Clin Haematol* 2010; 23:97–107.

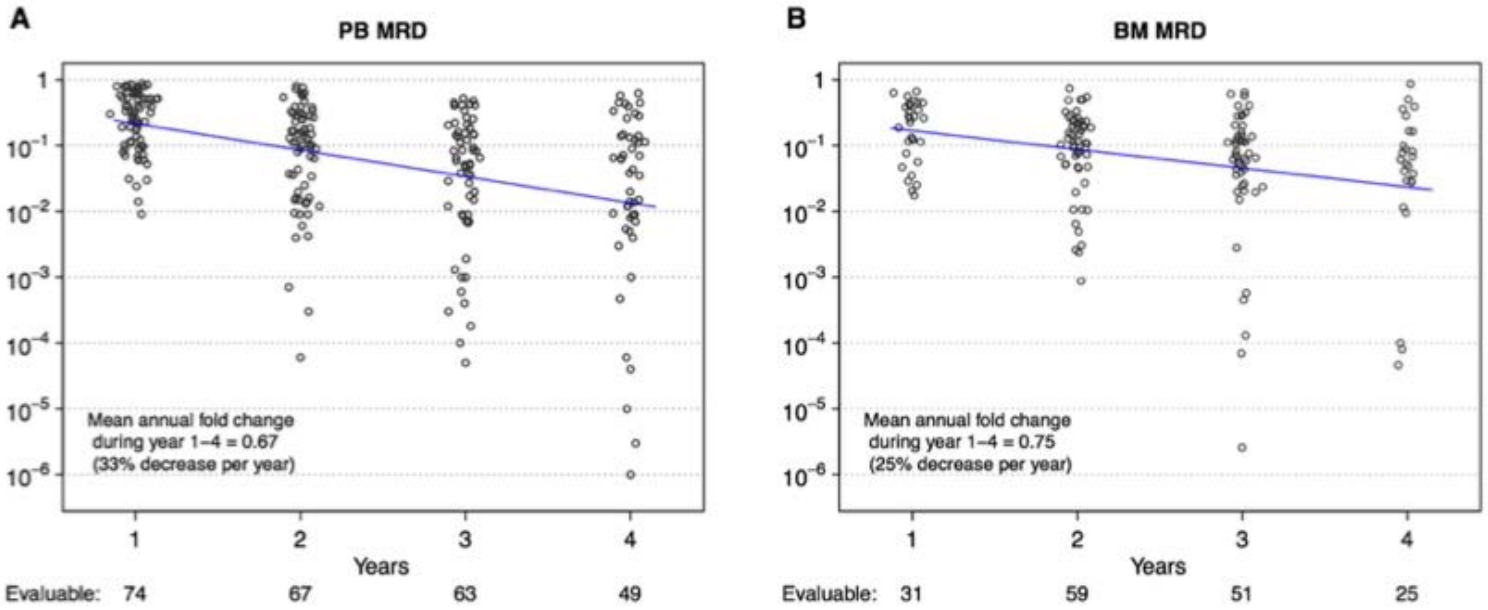
MRD in BTK treatment – what is different?

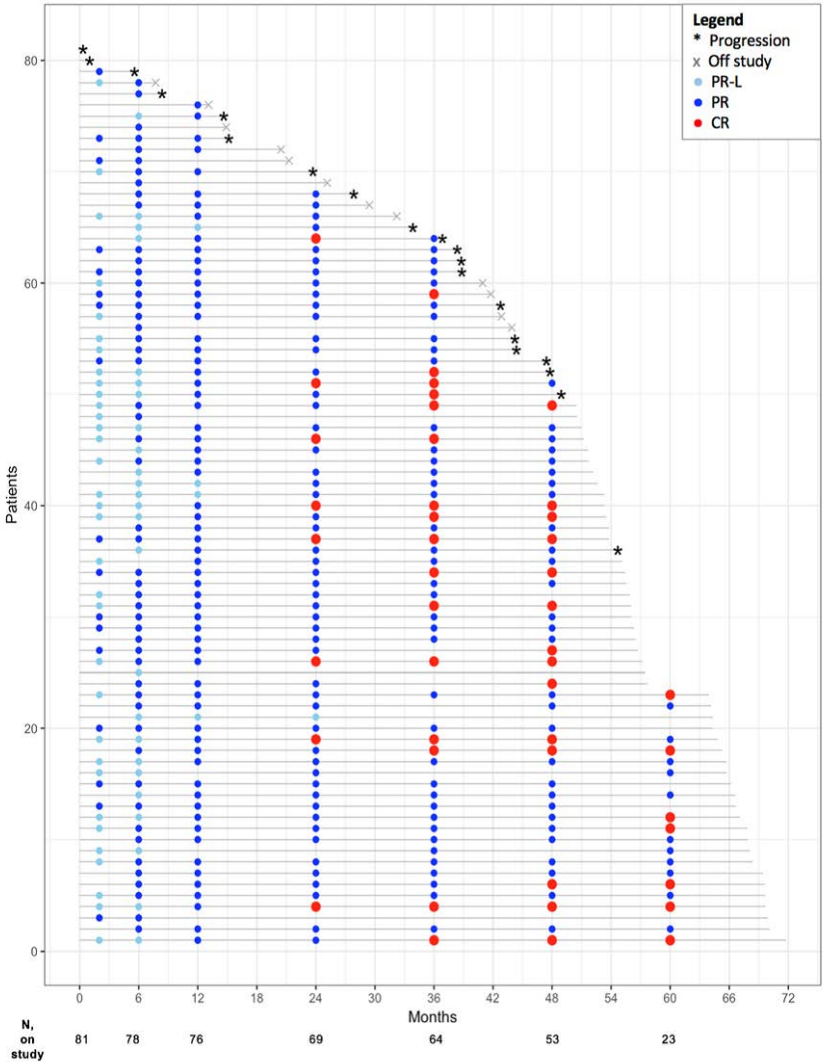
- Ongoing lymphocytosis
- Continuous treatment



RESONATE-2, Byrd JC *N. Engl. J. Med.* 2013, updated

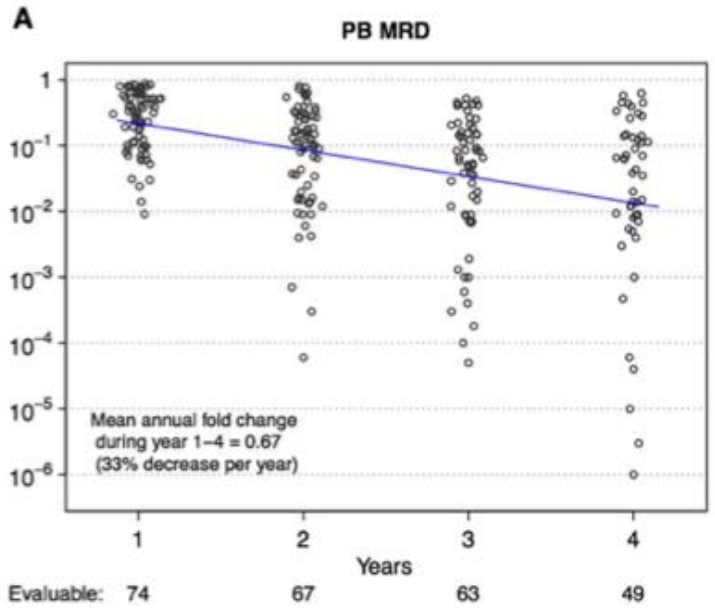
MRD and BTK directed treatment

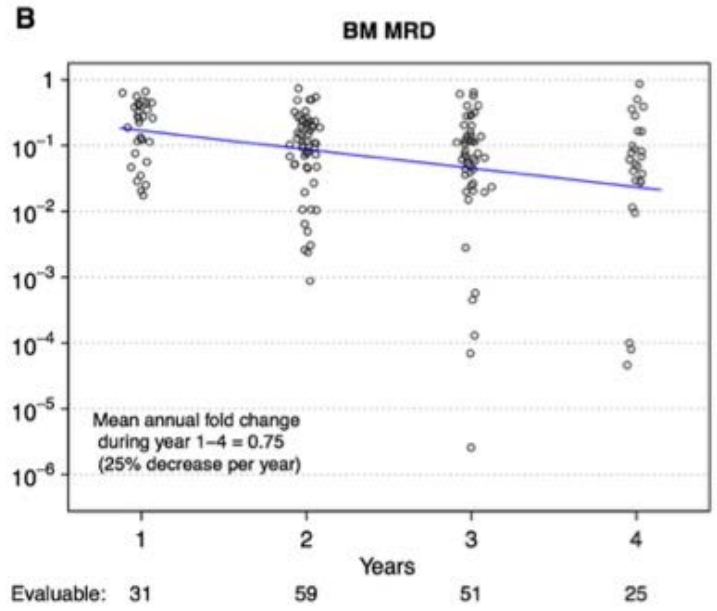


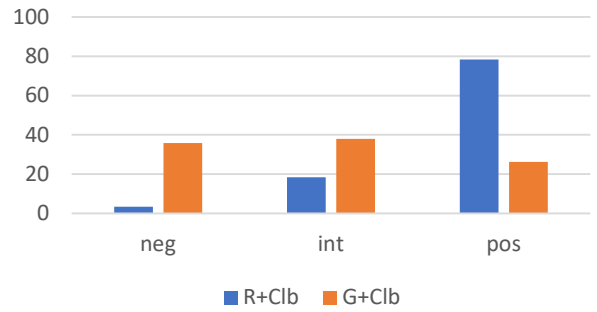


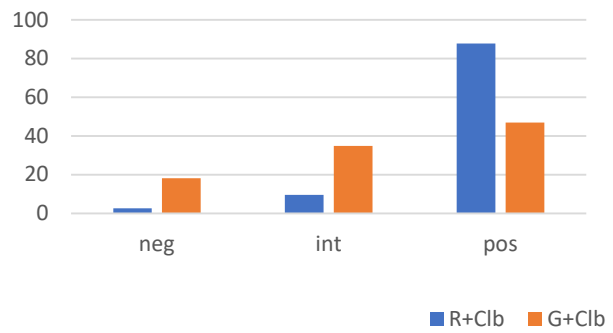
Ahn IE et al. *Blood*. 2018

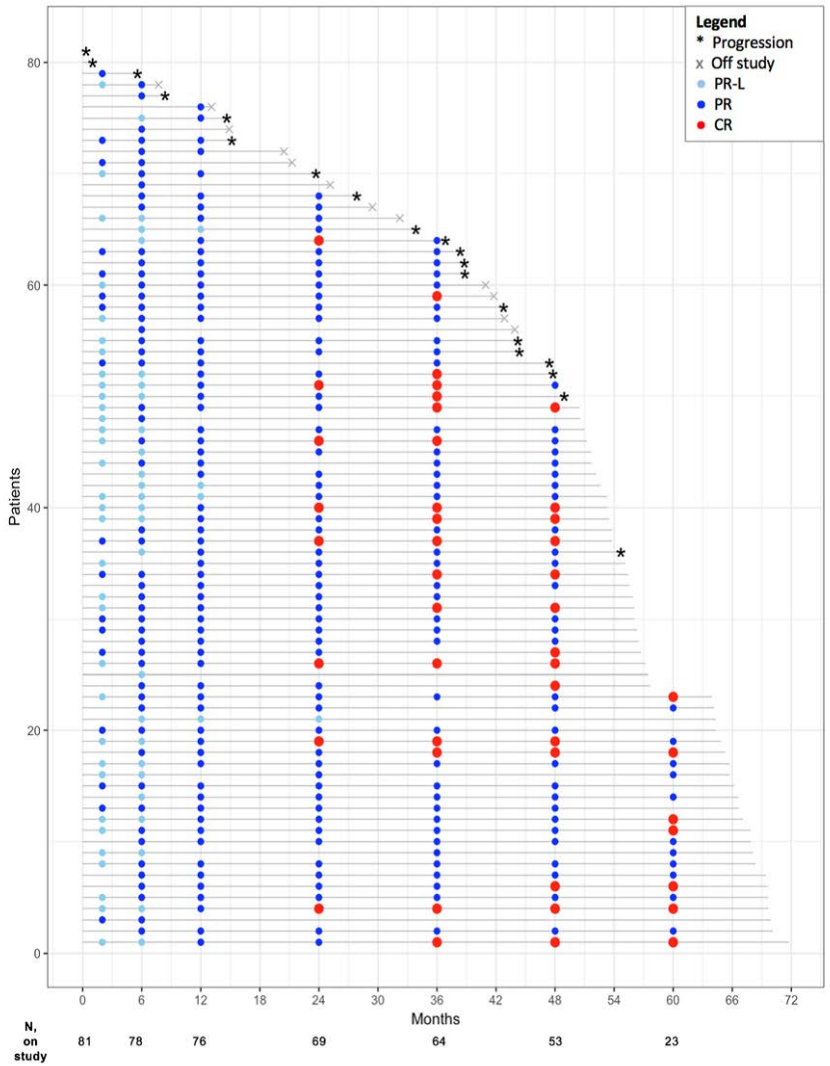
MRD and BTK directed treatment











Ahn IE et al. *Blood*. 2018

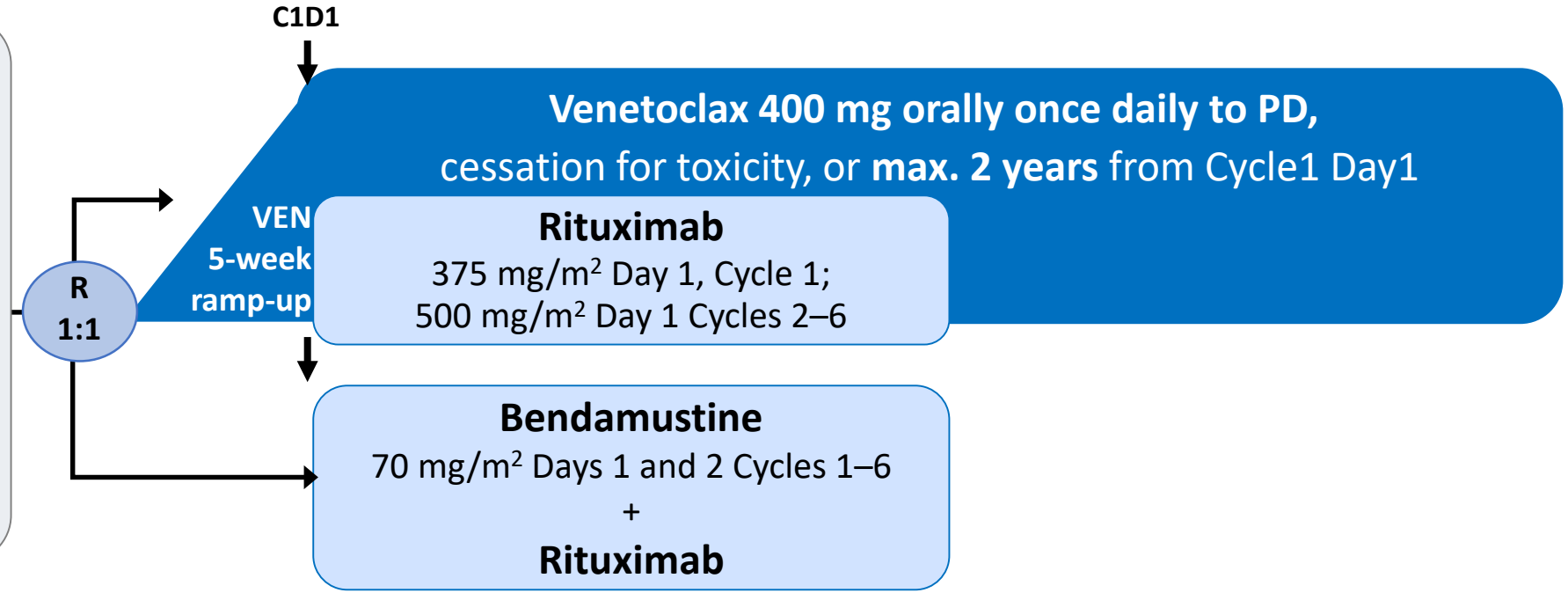
Bcl2-treatment: MURANO Study Design

Relapsed/refractory CLL (N=389)

- ≥18 years of age
- Prior 1–3 lines of therapy, including ≥1 chemo-containing regimen
- Prior bendamustine only if DoR ≥24 months

Stratified by:

- Del(17p) by local labs
- Responsiveness to prior therapy*
- Geographic region



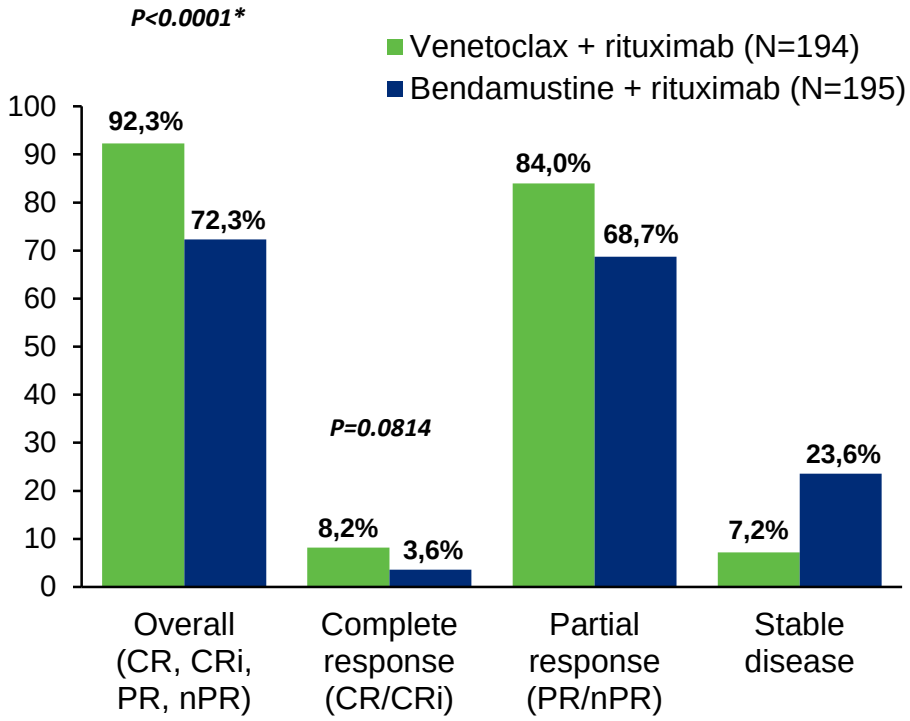
Primary Endpoint	INV-assessed PFS
Major Secondary Endpoints	• IRC-CR ⇒ IRC-ORR ⇒ OS (hierarchical testing) • IRC-assessed PFS and MRD-negativity
Key Safety Endpoints	Overall safety profile, focusing on serious adverse events and Grade ≥3 adverse events
Interim Analysis	Approximately 140 INV-assessed PFS events (75% of total information)

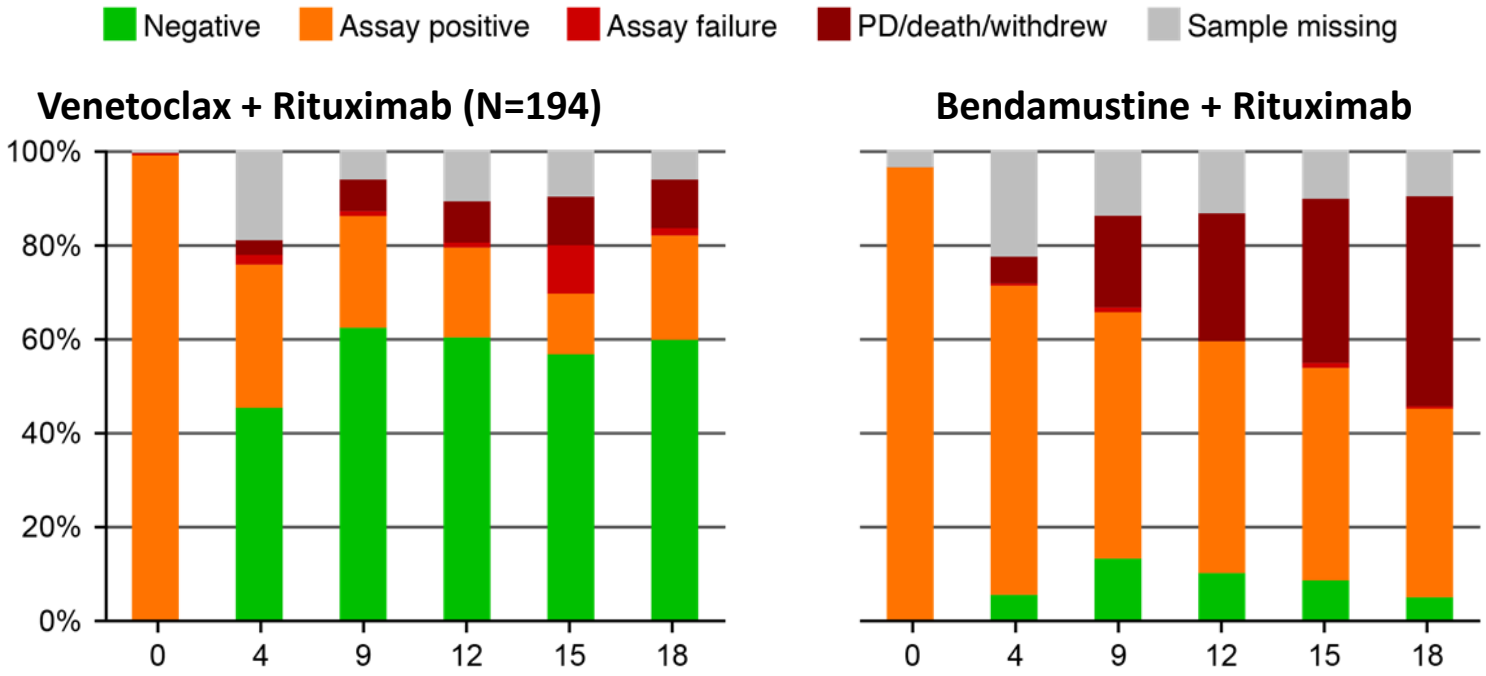
NCT02005471

*High-risk CLL – any of following features: del(17p) or no response to front-line chemotherapy-containing regimen or relapsed ≤12 months after chemotherapy or within ≤24 months after chemoimmunotherapy.

John F. Seymour ASH 2017

Murano Trial – Response rates (IRC)



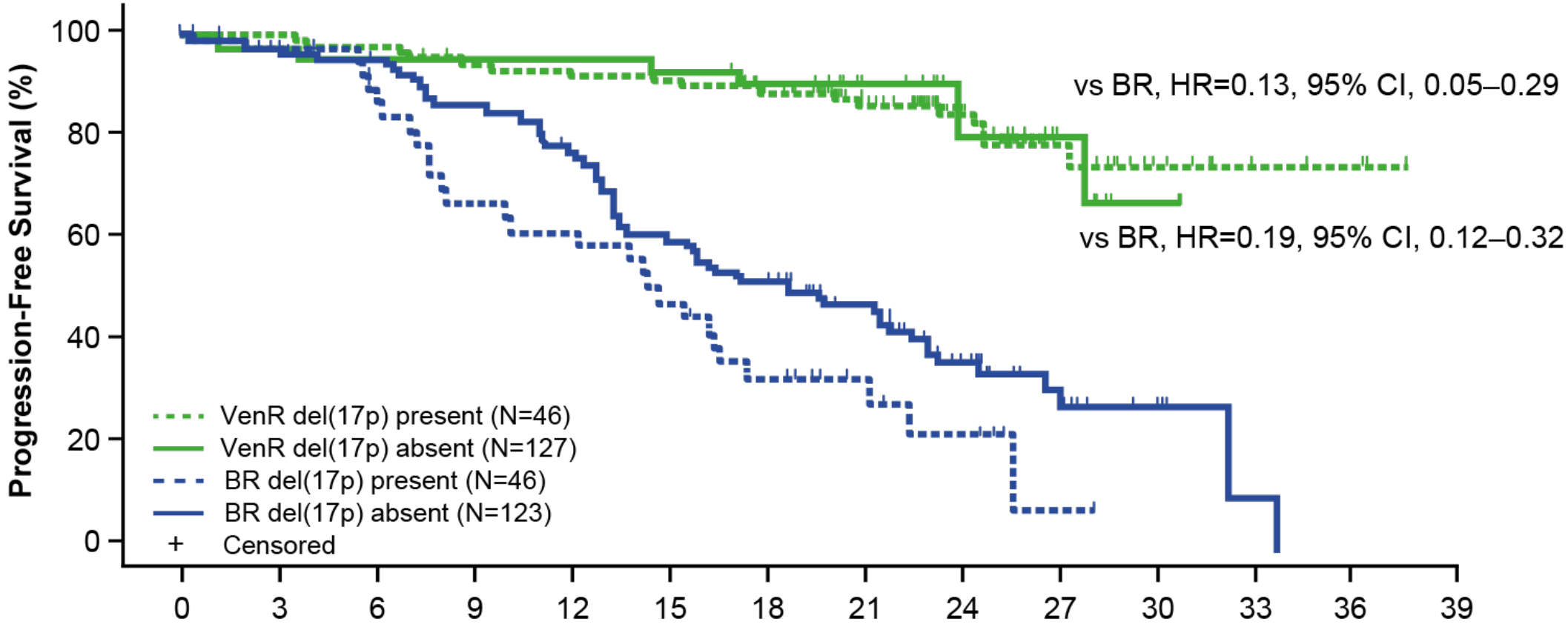


John F. Seymour ASH 2017

Hämatologie Labor Kiel

DEUTSCHE STUDIENGRUPPE

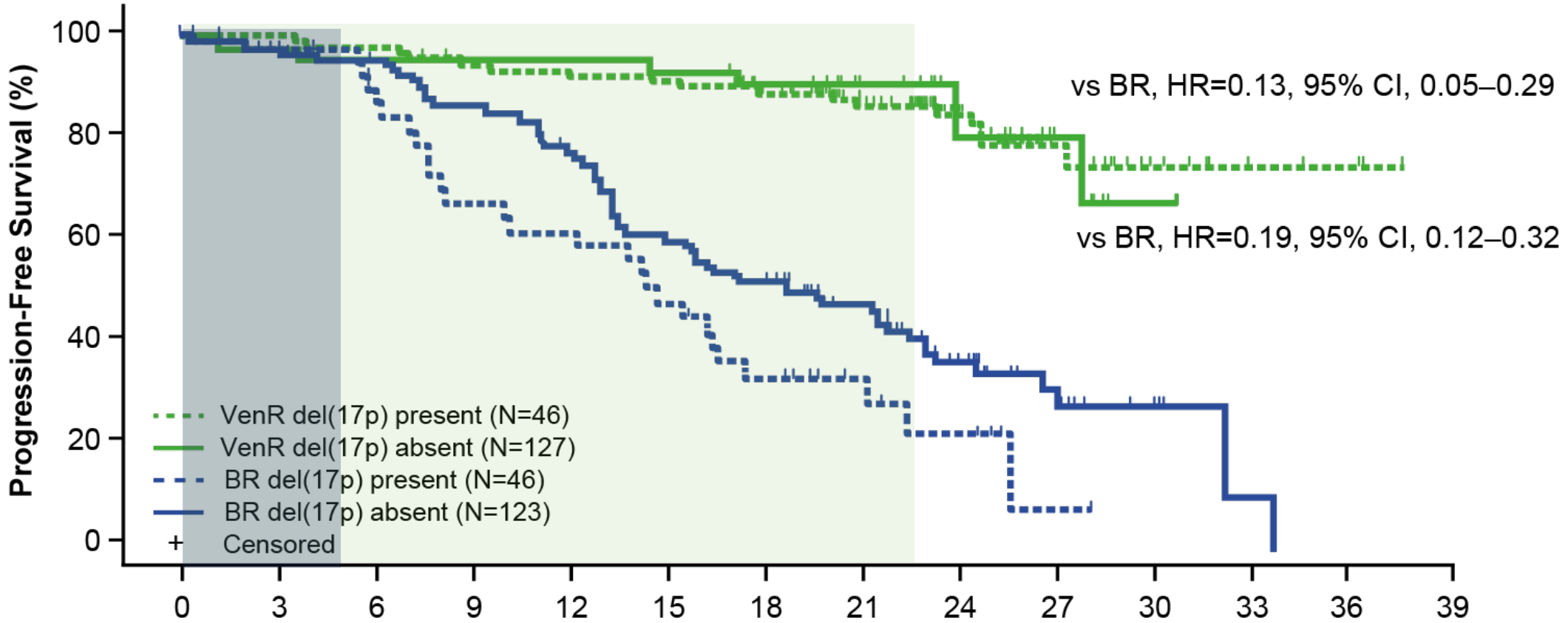
Investigator-assessed PFS Superior for VenR vs. BR Among Patients With and Without del(17p)



No. of patients at risk:													
VenR del(17p) present	46	44	43	43	43	42	36	25	17	7	2		
VenR del(17p) absent	127	127	124	118	116	114	105	76	48	20	10	4	3
BR del(17p) present	46	40	34	27	25	20	14	8	5	1			
BR del(17p) absent	123	114	108	99	88	70	60	44	26	10	3	1	

John F. Seymour ASH 2017

Investigator-assessed PFS Superior for VenR vs. BR Among Patients With and Without del(17p)



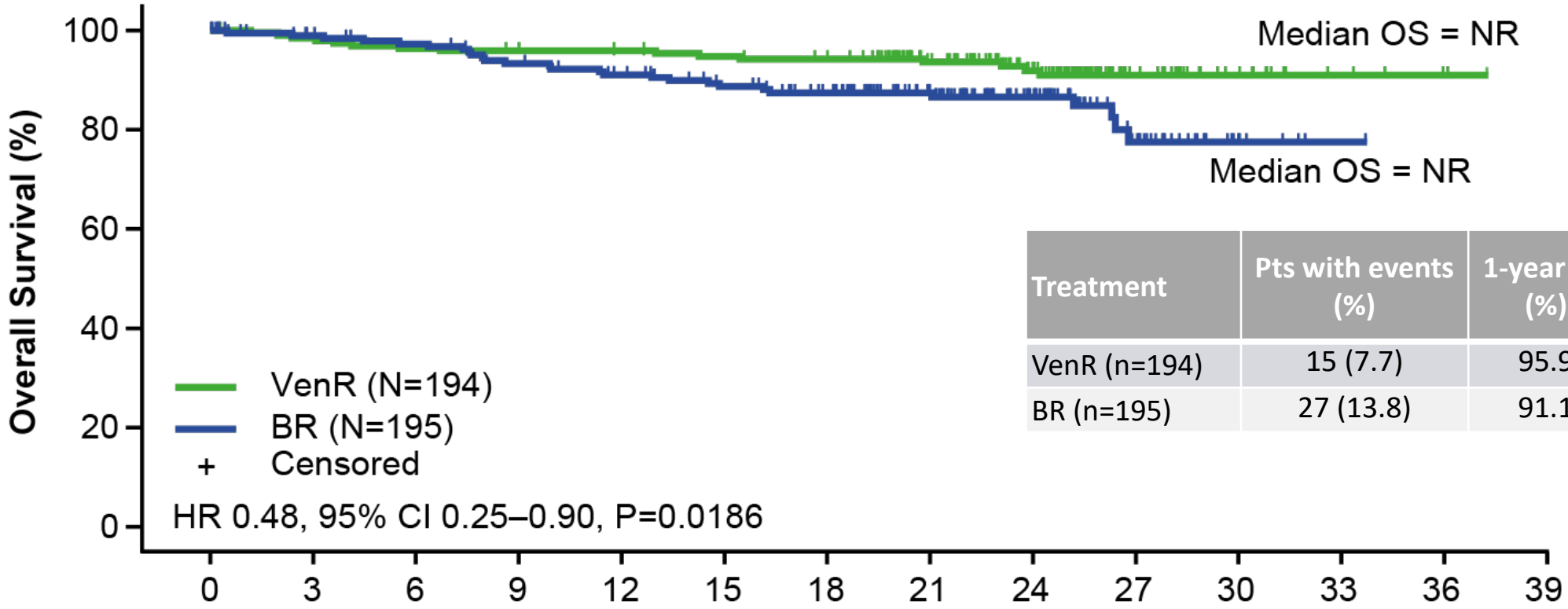
No. of patients at risk:													
VenR del(17p) present	46	44	43	43	43	42	36	25	17	7	2		
VenR del(17p) absent	127	127	124	118	116	114	105	76	48	20	10	4	3
BR del(17p) present	46	40	34	27	25	20	14	8	5	1			
BR del(17p) absent	123	114	108	99	88	70	60	44	26	10	3	1	

John F. Seymour ASH 2017

Hämatologie Labor Kiel

DEUTSCHE STUDIENGRUPPE

Clinically Meaningful Improvement in Overall Survival for VenR vs. BR



Treatment	Pts with events (%)	1-year OS (%)	2-year OS (%)
VenR (n=194)	15 (7.7)	95.9	91.9
BR (n=195)	27 (13.8)	91.1	86.6

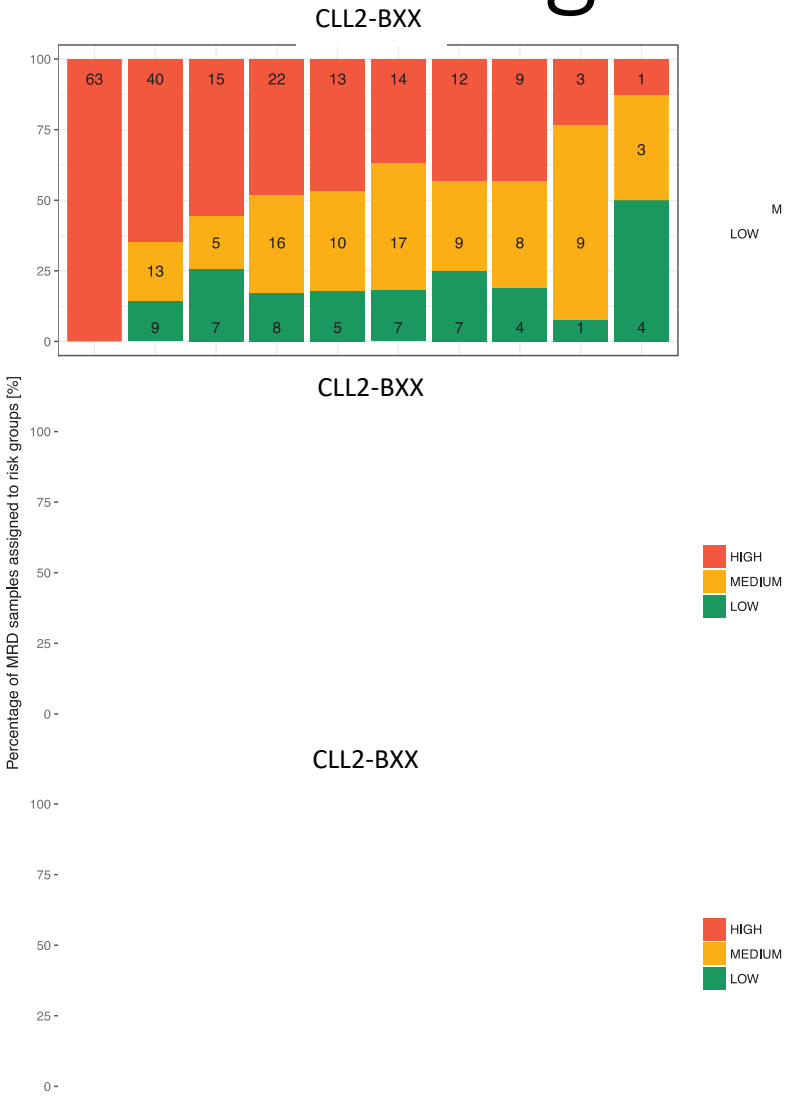
No. of patients at risk:

VenR	194	190	185	183	181	178	175	142	102	36	15	5	3
BR	195	181	175	166	158	146	134	102	66	29	8	2	

Descriptive p-values
Pre-specified boundary, P=0.0001.

John F. Seymour ASH 2017

MRD in targeted treatment CLL2-BXX concept



- 3 individual phase II trials
- Bendamustin debuliking followed by consolidation and maintenance phases
- Ibrutinib + Anti-CD20
- Ibrutinib + bcl2

Ritgen/Schilhabel unpublished data

Conclusion

- Clinical significance of MRD risk groups are confirmed in several trials and clinical conditions (R/R, GoGo, SlowGo, genetic risk groups)
- MRD can be used to compare treatment efficacy
- MRD may be used as surrogate marker (conventional treatment)
- Up to now no convincing data on how to guide treatment by MRD
- BTK-inhibition alone is not able to achieve high rates of MRD negativity but achieves convincing clinical data
- Role of MRD in BTK-treatment not clear
- Relevance of MRD in maintenance treatment not proven

Thank You!