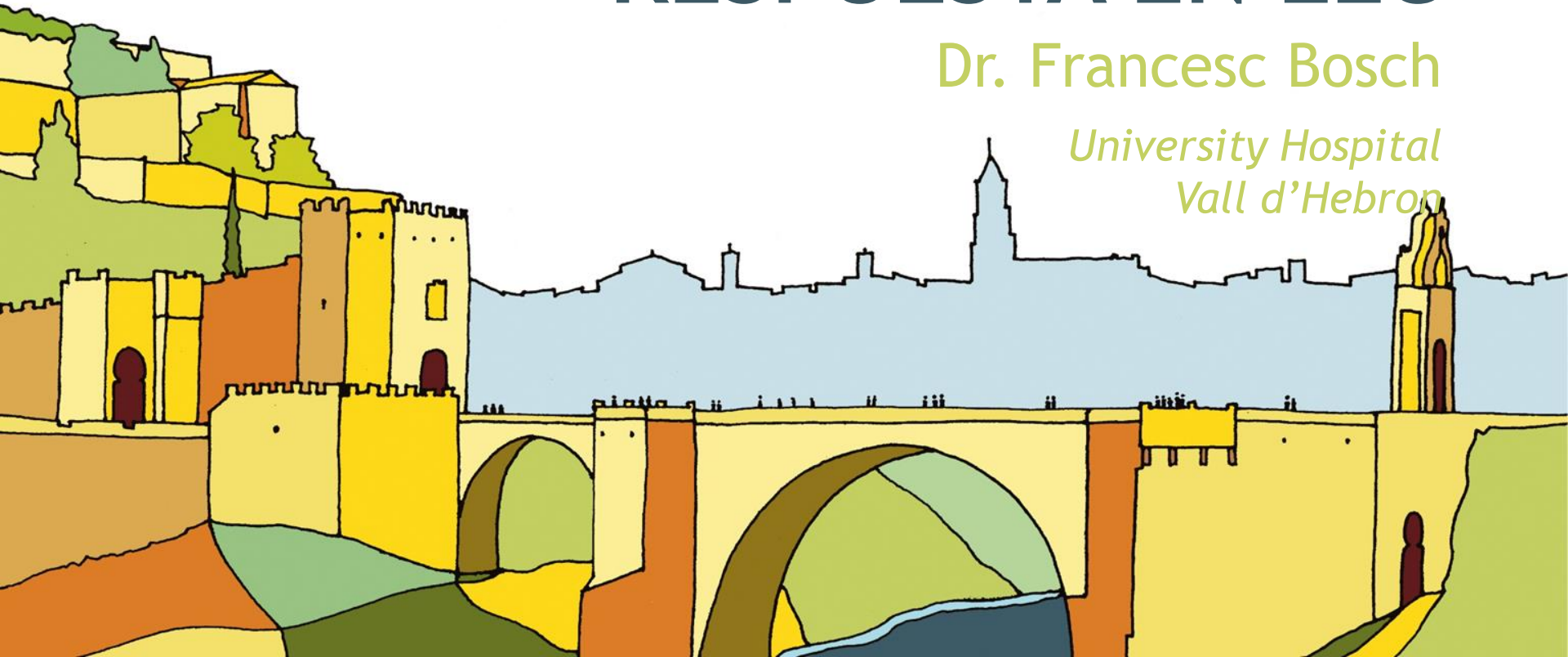


3^{er} CONGRESO
de **Oncología** Médica
y **Farmacía** Oncológica
tendiendo puentes

EVALUACION DE LA RESPUESTA EN LLC

Dr. Francesc Bosch

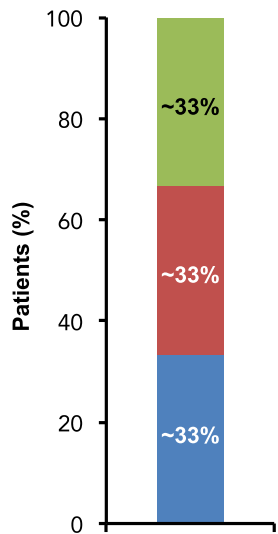
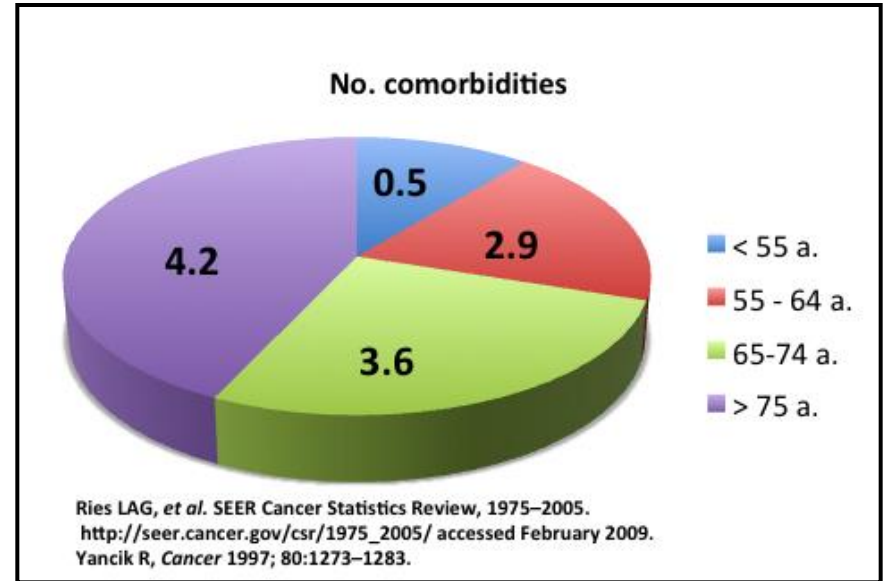
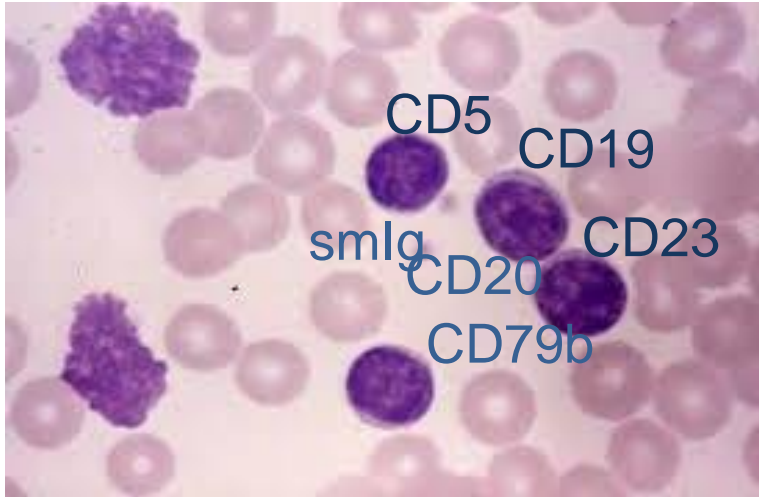
*University Hospital
Vall d'Hebron*



OUTLINE

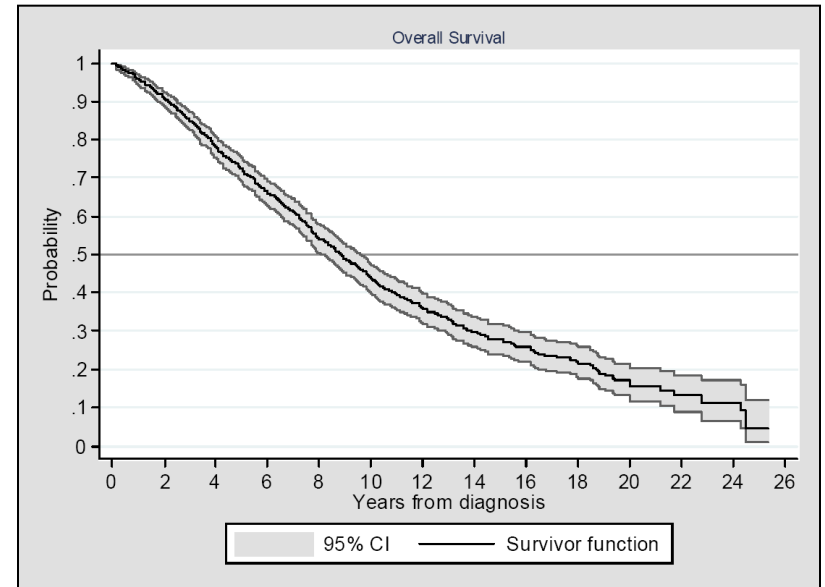
- Métodos de evaluación de la respuesta al tratamiento en LLC
- Impacto en la práctica clínica y en el diseño de ensayos clínicos

LLC: Concepts

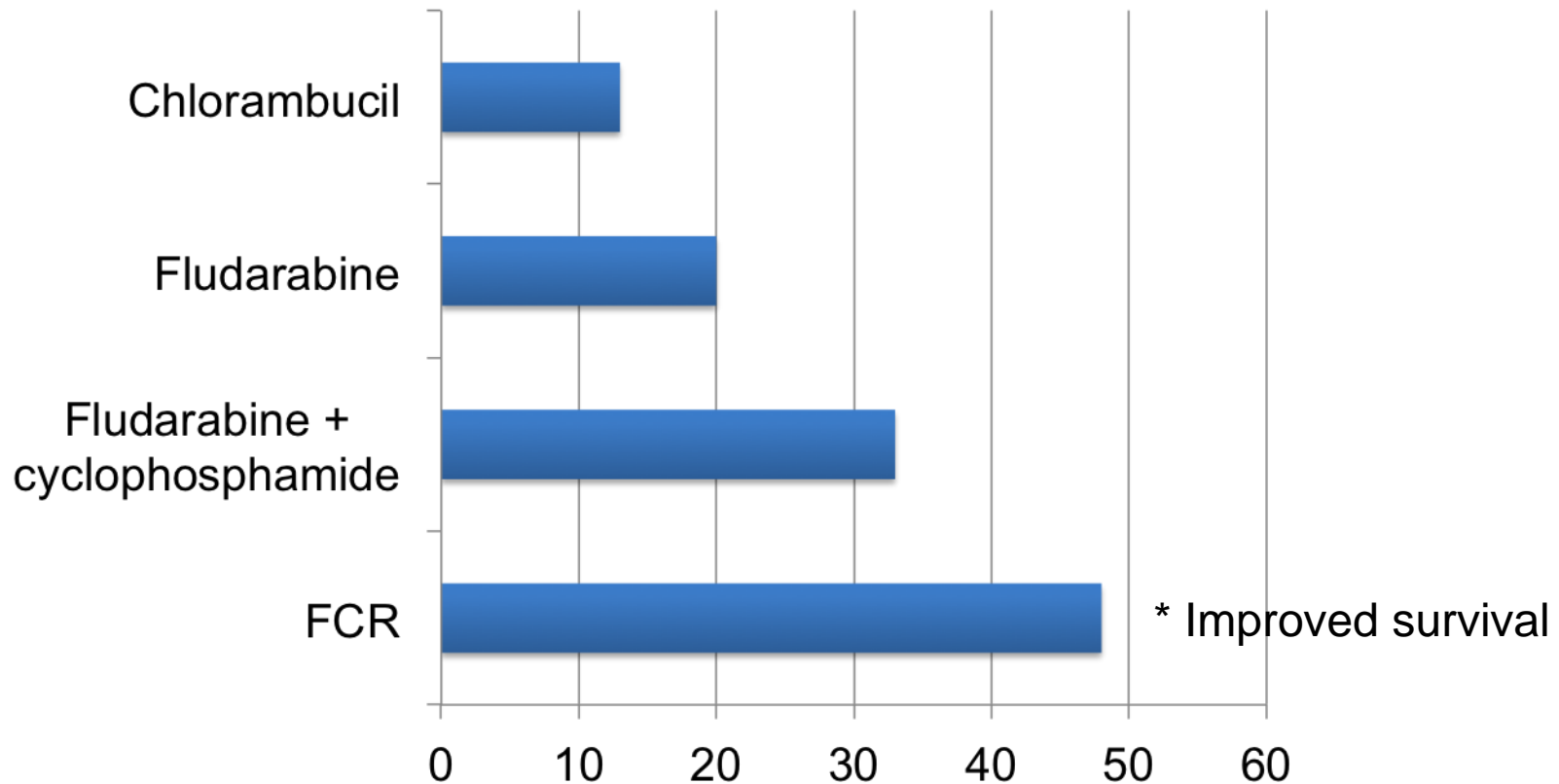


- NEVER REQUIRE TREATMENT → long life expectancy and die of causes unrelated to CLL
- Indolent phase followed by progression of the disease
- AGGRESSIVE DISEASE at diagnosis

Dighiero G. *Leukemia* 2003; 17:2385–2391;
Dighiero G, et al. *N Engl J Med* 1998; 338:1506–1514
Abrisqueta et al, *Blood* 2008
Hallek et al, *Blood* 2008



Advanced Stages: Historic overview of chemoimmunotherapies in CLL (PFS)



Rai et al, NEJM 2000

Eichhorst et al Blood 2005

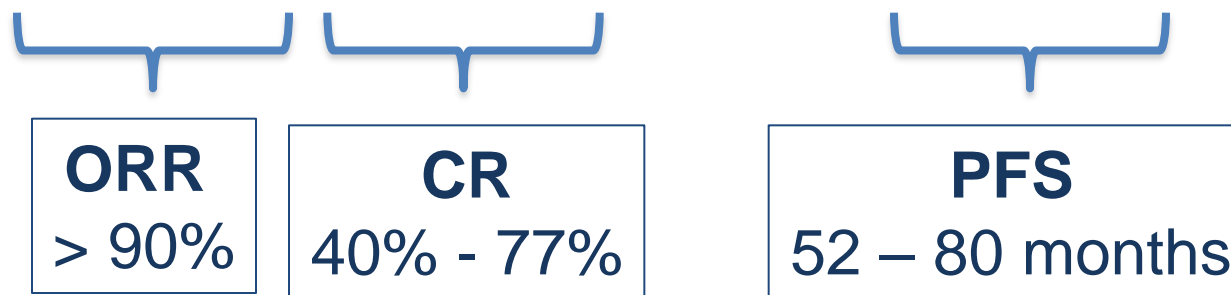
Bosch et al, JCO 2009

Keating et al, Blood 2009

Halleck et al, Lancet 2010

Chemoimmunotherapy combinations based on fludarabine

	n=	ORR	CR rate	MRD(-)	PFS (median)
FCR (MDACC) ¹	300	95%	72%	-	80 months
FCR (CLL8) ²	408	90%	44%	35%	52 months
R-FCM ³	89	90%	77%	47%	60 months
FCR (CLL10 trial) ⁴	282	98%	41%	58%	54 months
FCR "Lite" ⁵	48	100%	77%	-	70 months



¹Tam et al, *J Clin Oncol* 2008; ²Hallek et al, *Lancet* 2010; ³Bosch et al, *J Clin Oncol* 2009

⁴Eichhorst et al, *ASH* 2014; ⁵Foon et al, *J Clin Oncol* 2009

Response evaluation in CLL (IWCLL-2008)

- Clinical assesment
 - Complete response
 - Normal physical examination
 - Normal peripheral blood test
 - Absence of marrow infiltration by cytology
- Minimal residual disease (MRD)
 - Only in clinical trials

Response evaluation in CLL (IWCLL-2008)

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10^{-3}

Response evaluation in CLL (IWCLL-2008)

- Clinical assesment

- Complete response

- Normal physical examination
 - Normal peripheral blood test
 - Absence of marrow infiltration by cytology

10^{-3}

- Minimal residual disease (MRD)

- Only in clinical trials

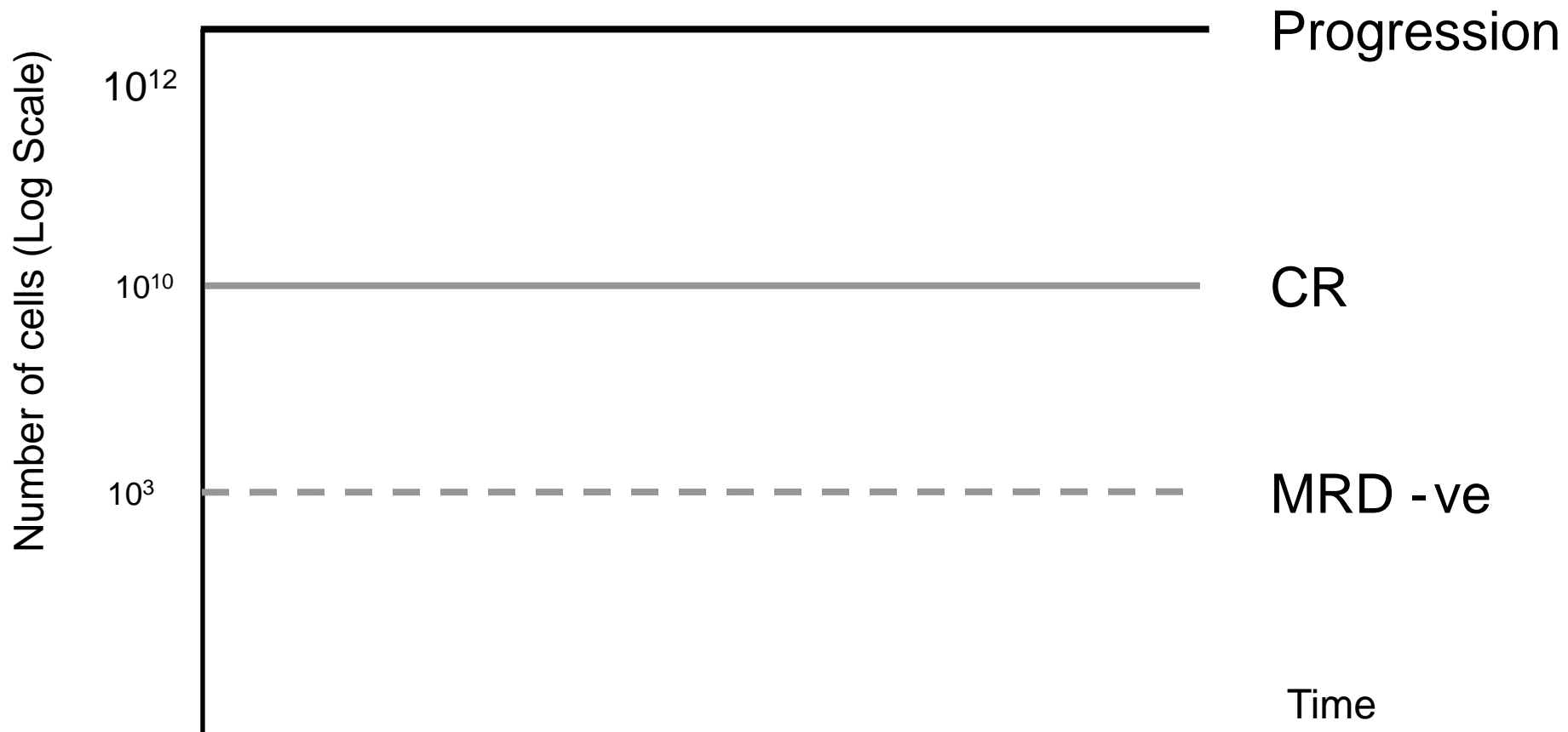
10^{-6}

MRD in CLL

Concept
& Biology

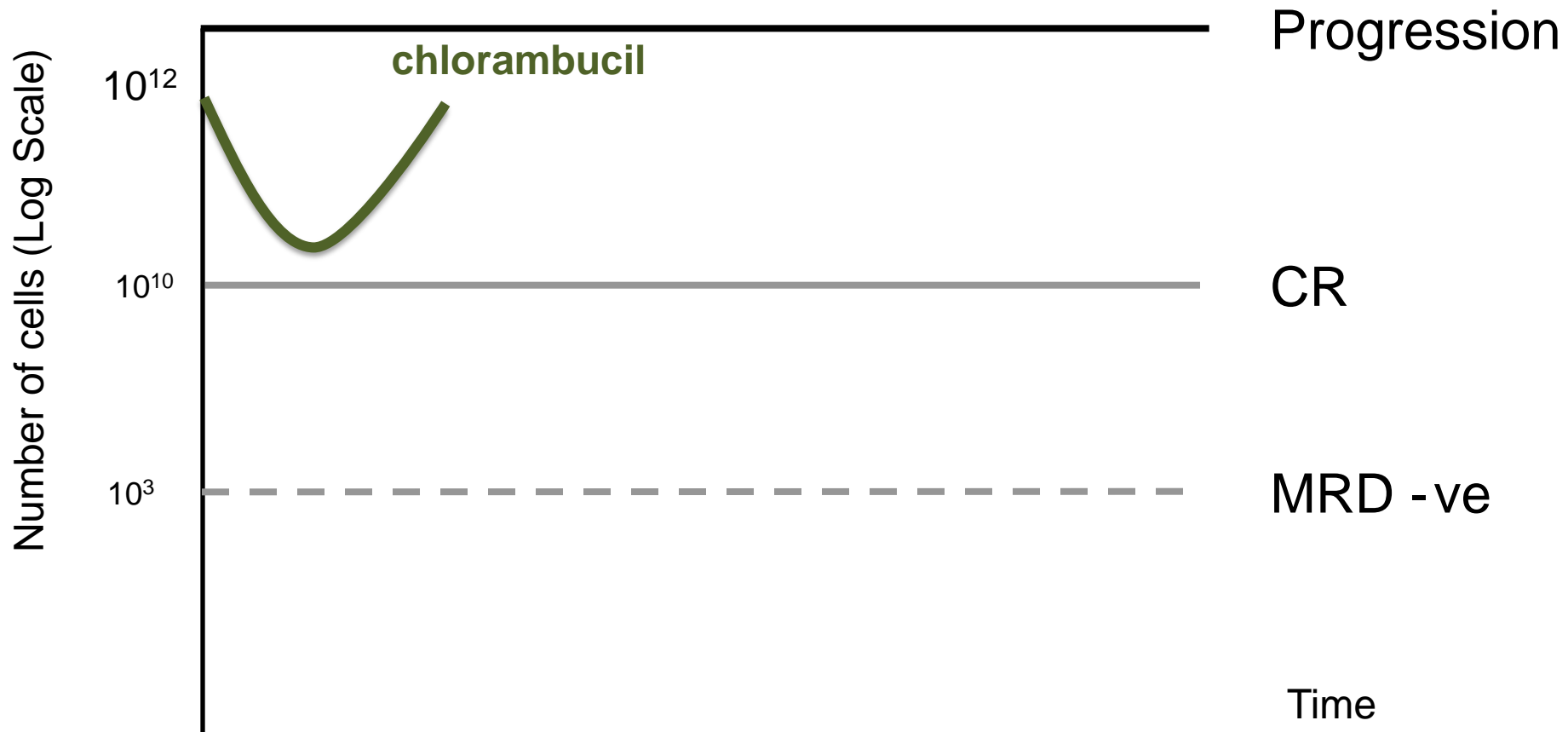
MRD: definition

- MRD is the term used to define the numbers of leukaemic cells remaining in the blood or bone marrow during or after treatment



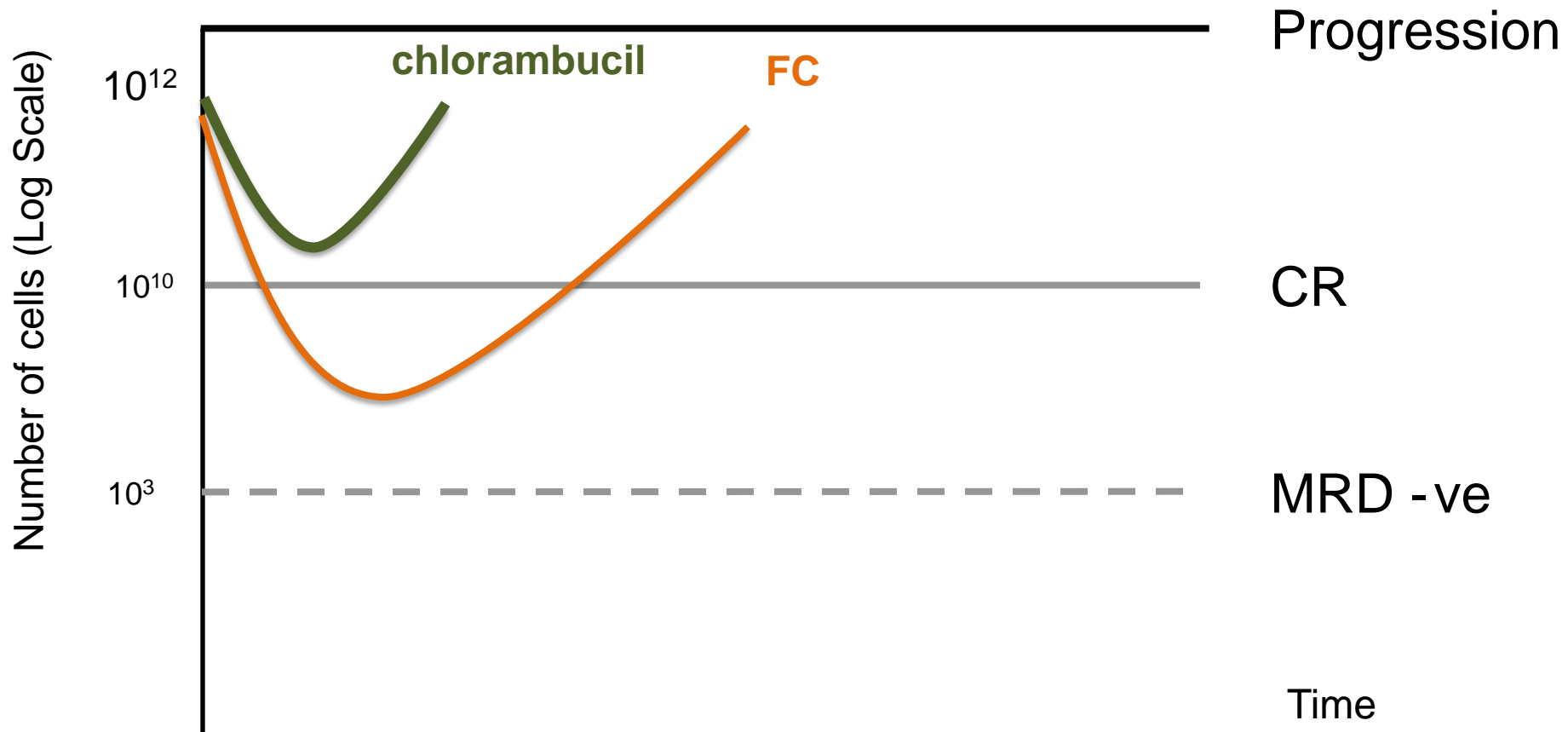
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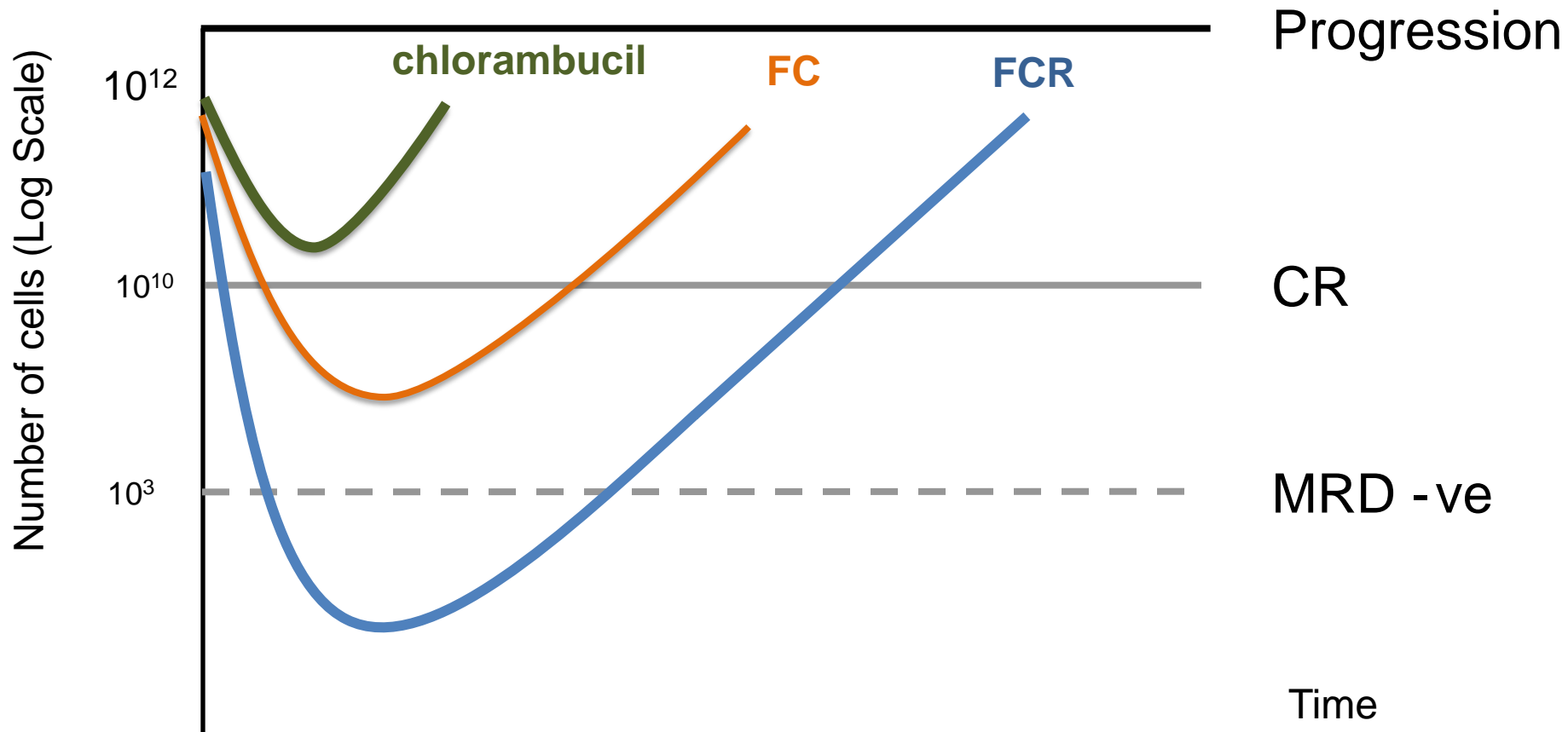
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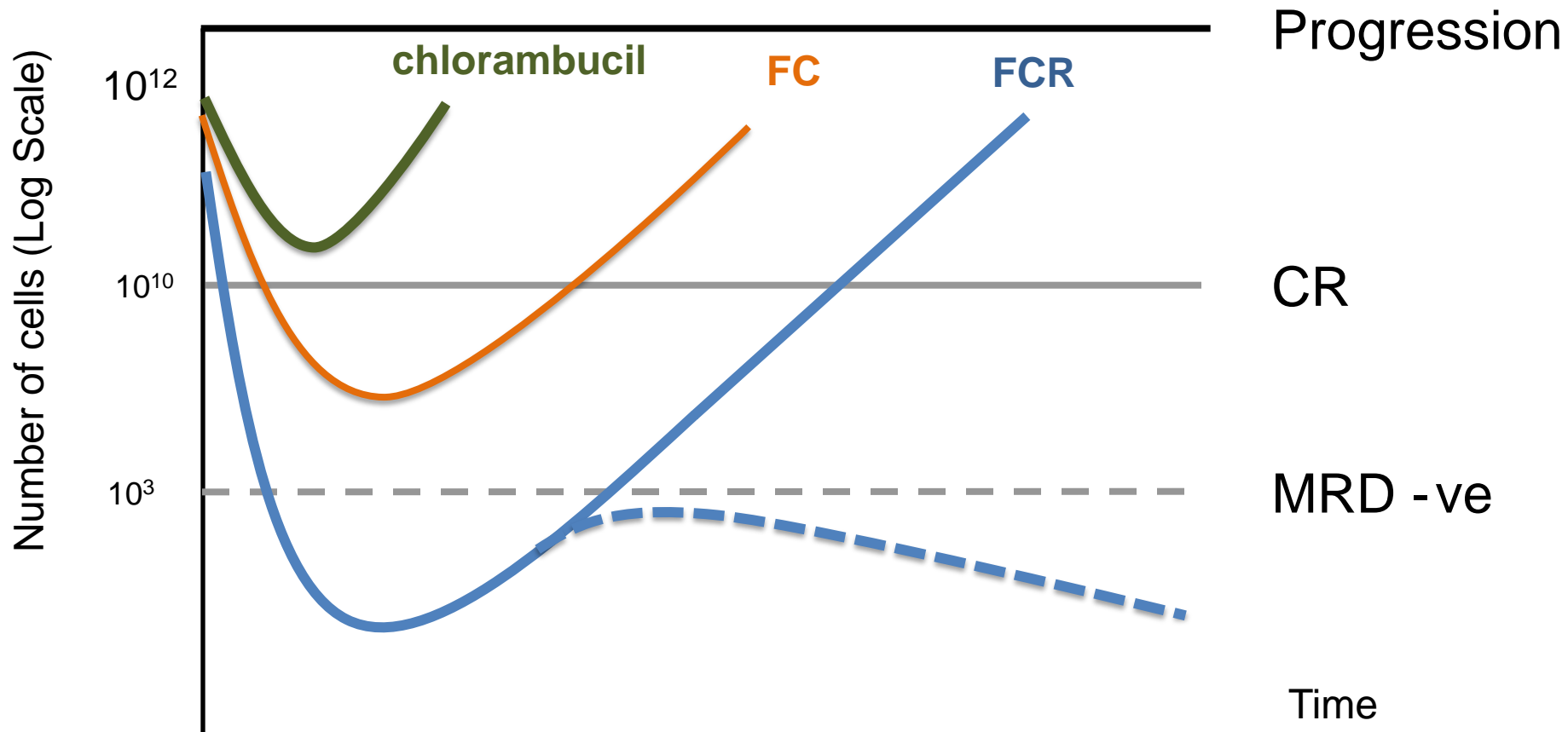
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MRD in CLL

Concept
& Biology

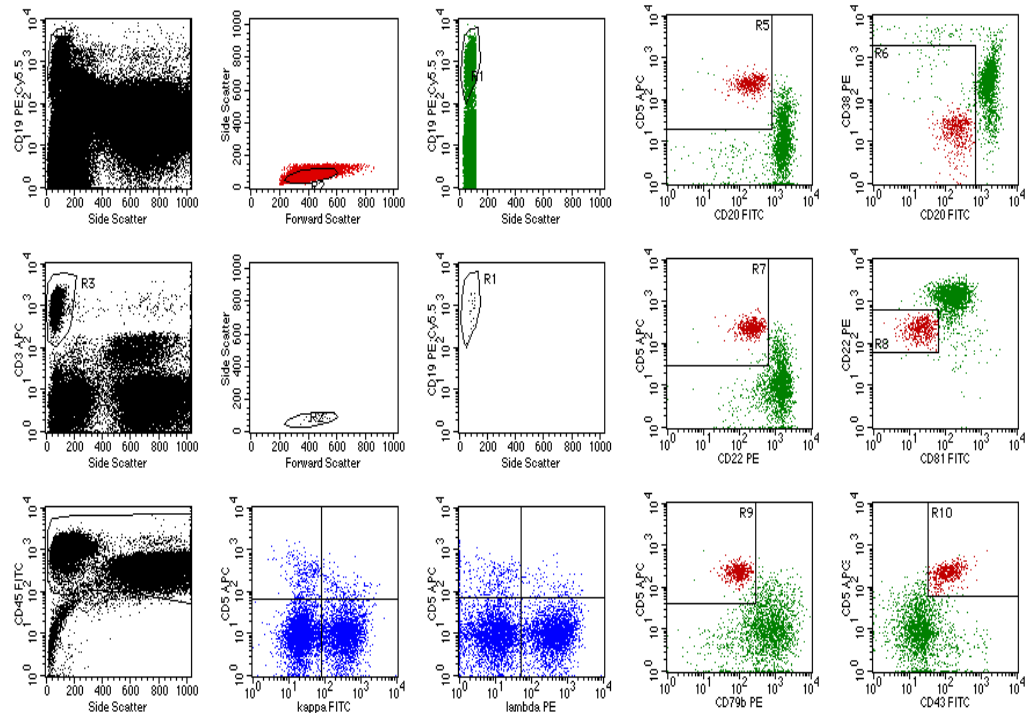
Methods
of analysis

MRD assessment: comparison of high sensitivity approaches

	MRD Flow (8 CLR)	RQ ASO-PCR	NGS
Applicable patients	> 95%	85-95%	> 95%
Sensitivity limit	10^{-5} (0.01%)	10^{-5} (0.001%)	10^{-6}
Cost & complexity	Moderate	Initially high Follow-up low	High
Pre-treatment sample	Preferable	Essential	Essential
Turn-round time	Hours	Weeks	Weeks
Clinical value	High	High	Experimental

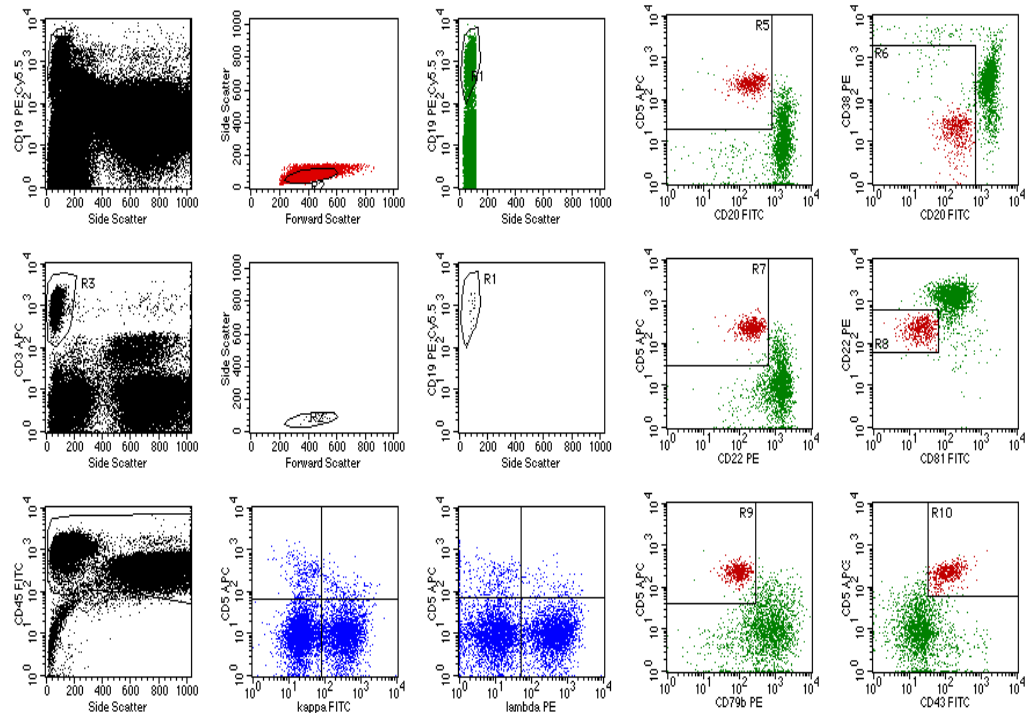
International standardised 4-CLR assay: limitations

- Requires 10 million cells for analysis
 - can be difficult in post-treatment samples
- Slow and difficult to analyse
 - Two pages of analysis, several minutes to update any gate change



International standardised 4-CLR assay: limitations

- Requires 10 million cells for analysis
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ERIC MRD 8-CLR PROJECT

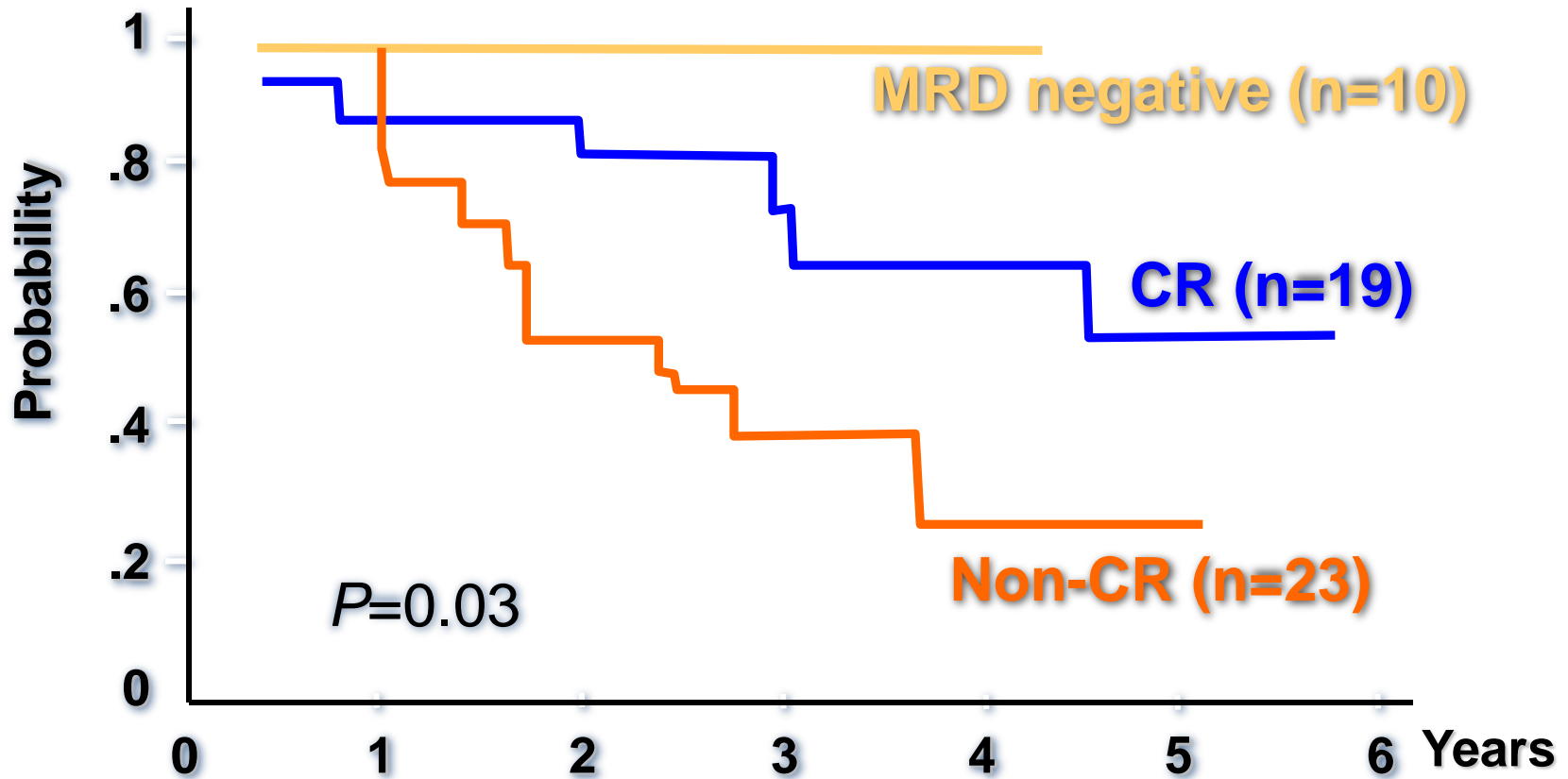
MRD in CLL

Concept &
Biology

Methods of
analysis

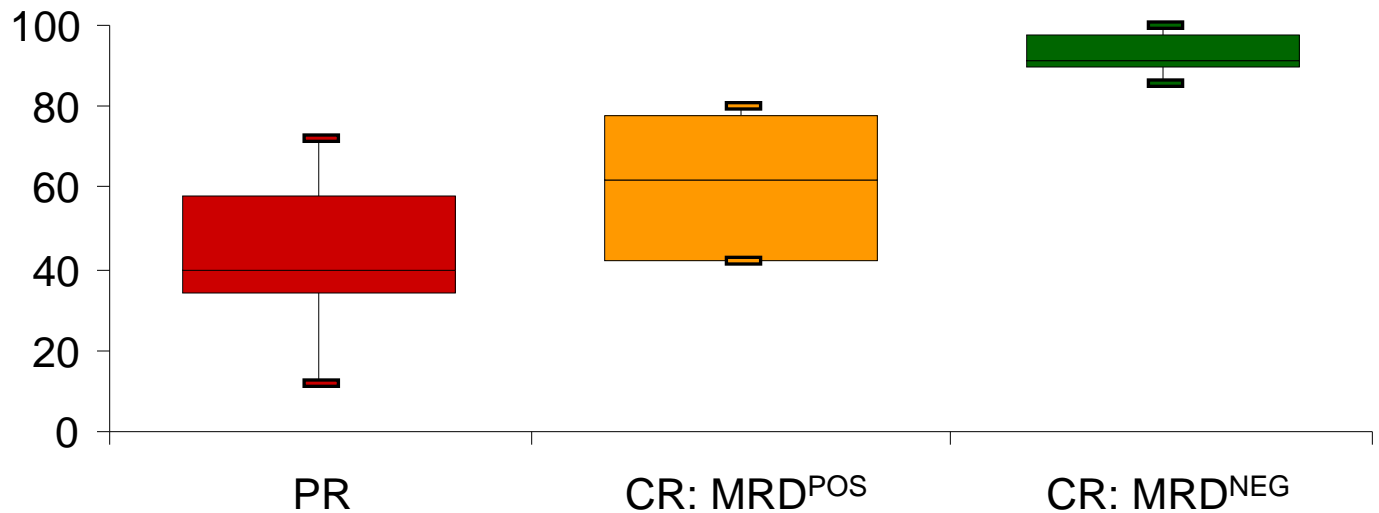
Clinical
Significance

MRD following FCM for Relapsed/Refractory CLL



What is our aim of therapy?

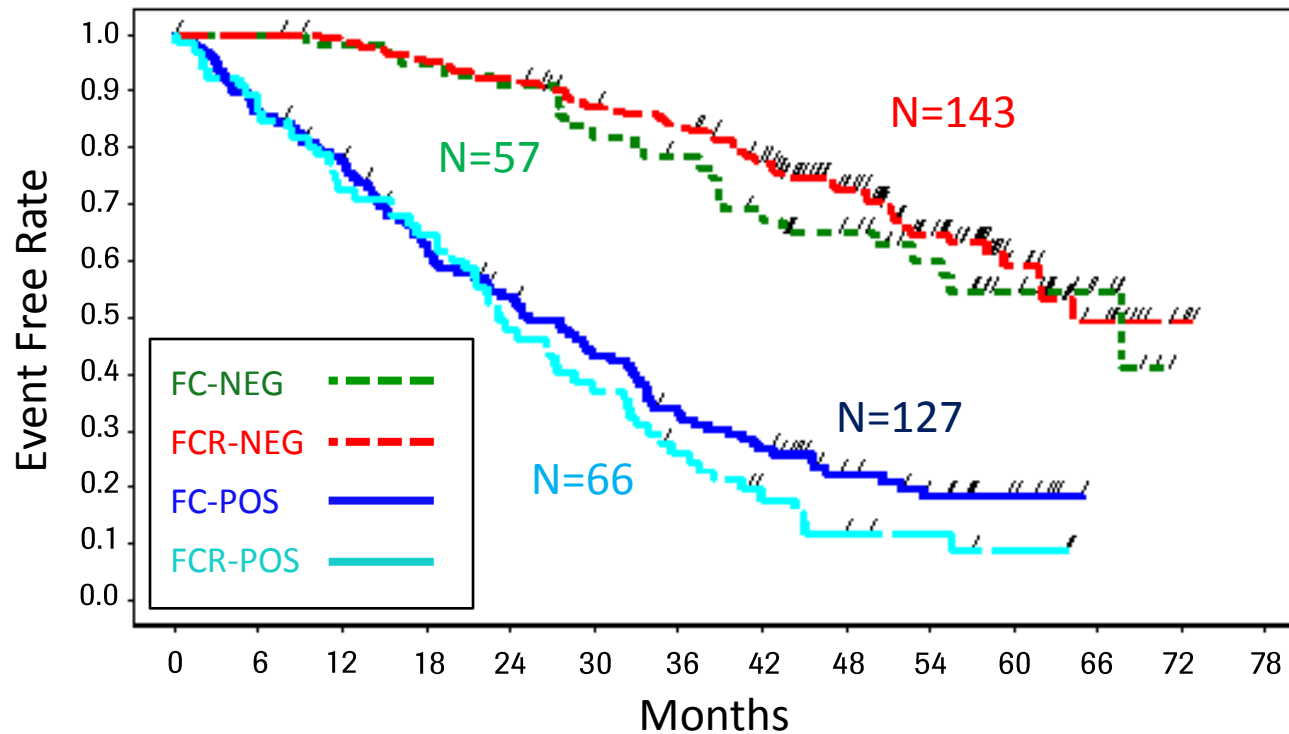
Percent in remission at 2 years



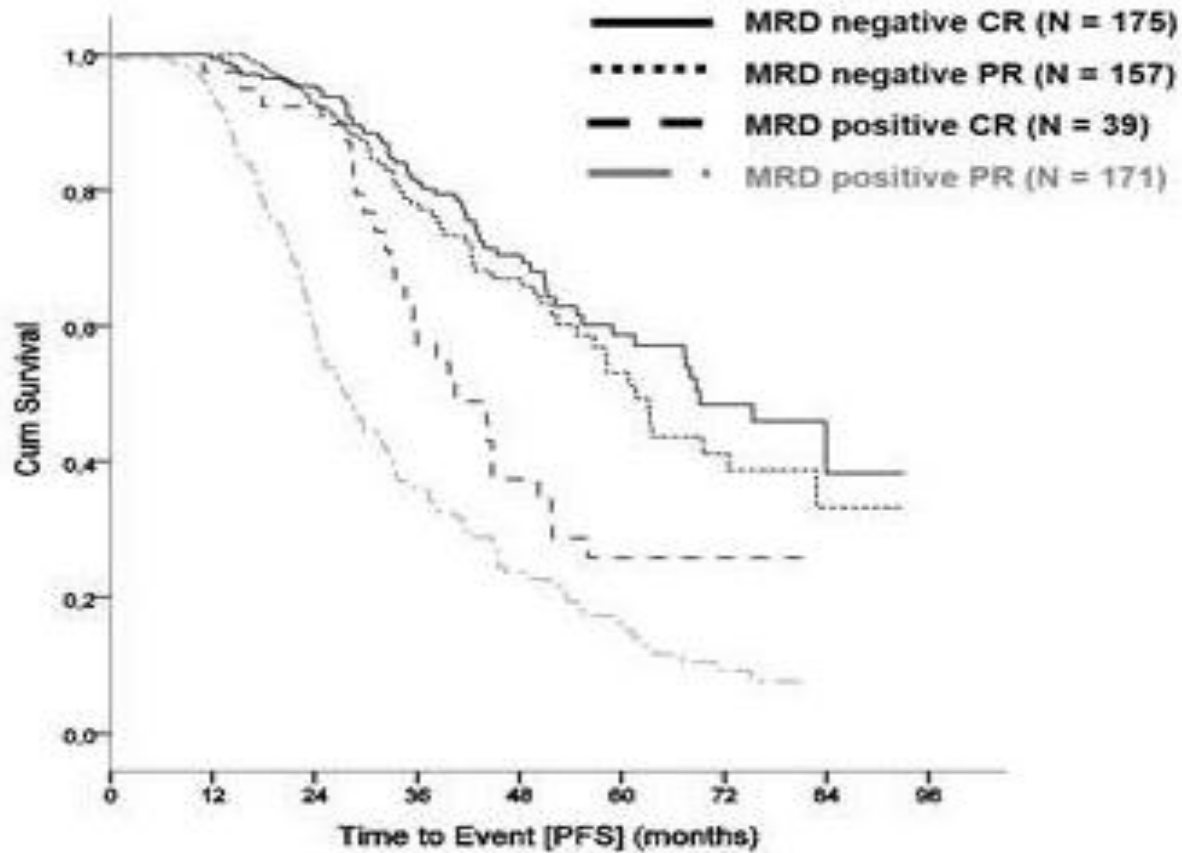
- ~25 trials with MRD analysis
- All show improved PFS for MRD^{NEG} response
- Approximately 1-2 years improvement in PFS for CR^{NEG} vs CR^{POS}

MRD in CLL: Influence of treatment

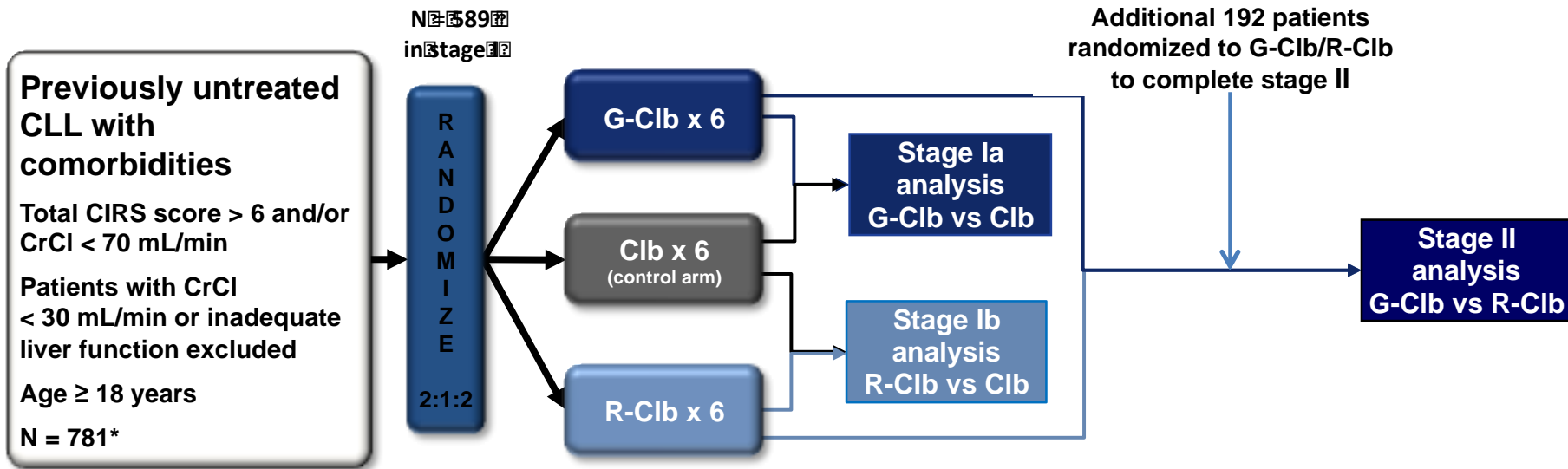
MRD-negative status predicts longer PFS irrespective of treatment



MRD in CLL: CR. vs PR.



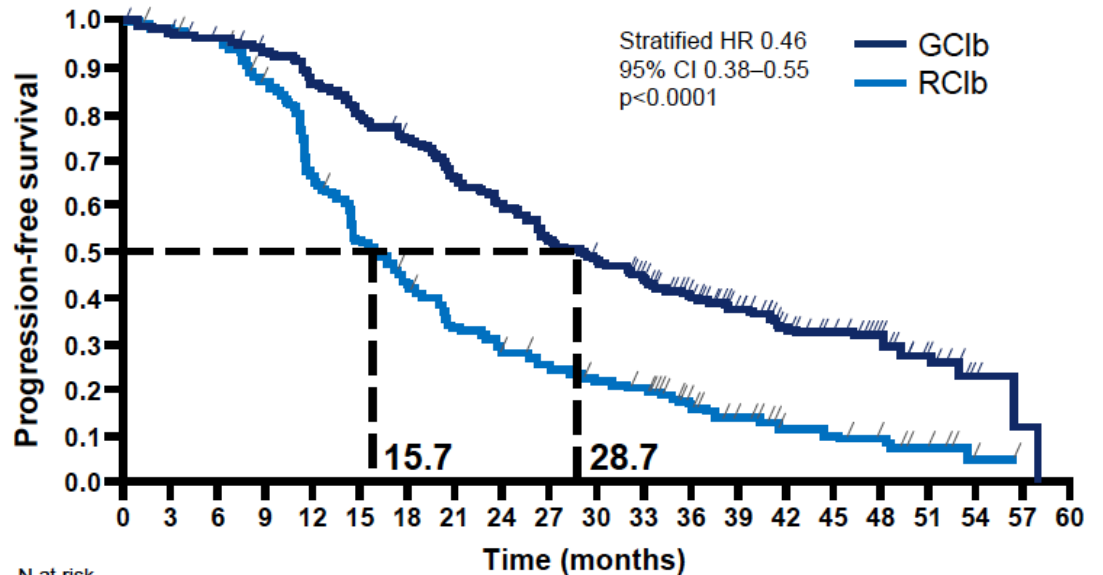
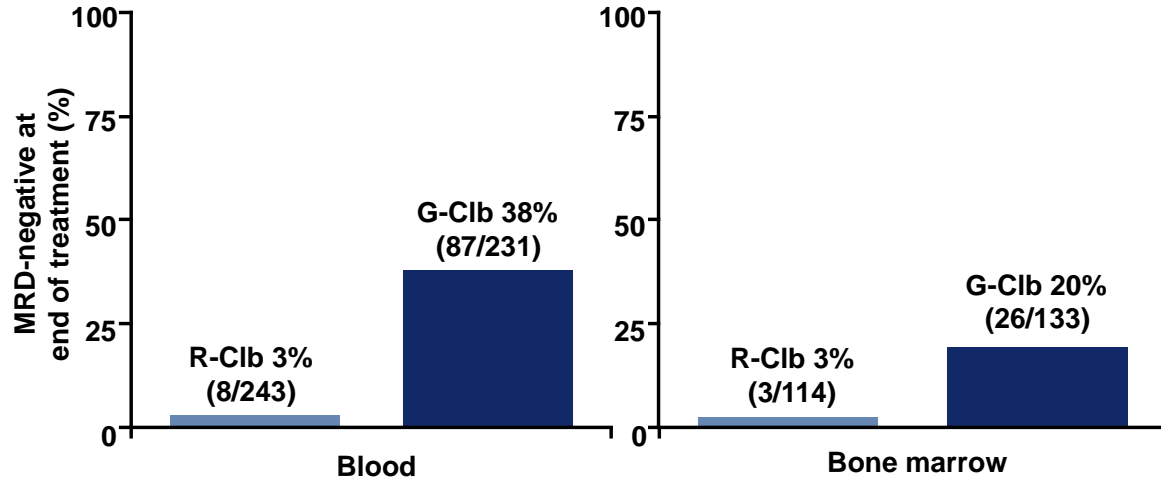
CLL11 Phase III: Study design 1



Primary endpoint	Investigator-assessed PFS
Secondary endpoints	ORR, CR rate, PR rate, IRC-assessed PFS, overall survival, EFS, time to next treatment, MRD, safety, patient-reported outcomes and symptom burden by EORTC questionnaire

GAZYVA: 1,000 mg Days 1, 8, and 15 Cycle 1; Day 1 Cycles 2–6, every 28 days
 MabThera: 375 mg/m² Day 1 Cycle 1; 500 mg/m² Day 1 Cycles 2–6, every 28 days
 Clb: 0.5 mg/kg Day 1 and Day 15 Cycle 1–6, every 28 days
 Patients with PD in the Clb arm were allowed to crossover to the G-Clb arm

CLL11 stage II: MRD at the end of treatment



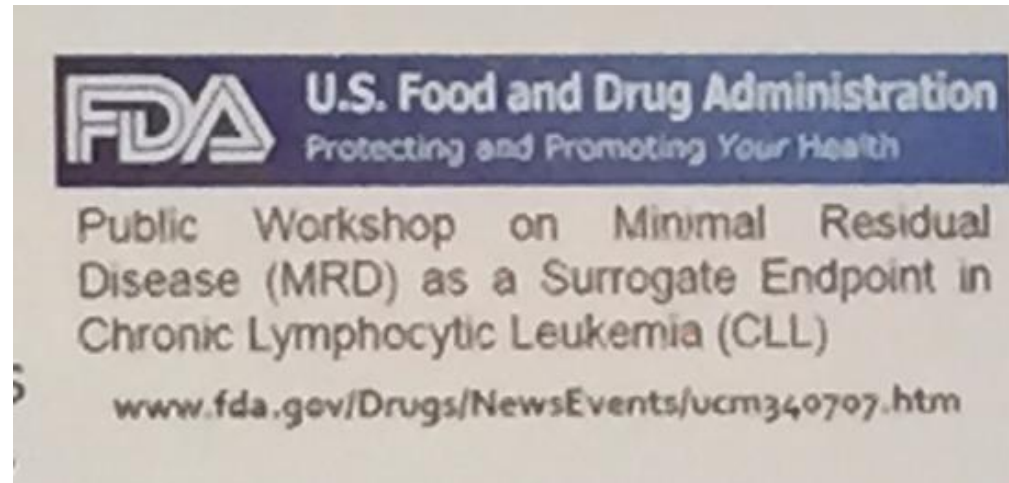
N at risk

	0	3	6	9	12	15	18	21	24	27	30	33	36	39	42	45	48	51	54	57	60
G-C1b	333	307	302	290	269	245	227	204	183	161	146	129	99	76	54	43	24	15	3	1	0
R-C1b	330	317	309	274	207	164	133	103	86	74	64	57	38	24	15	12	10	6	1	0	0

MRD and Regulatory Agencies



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

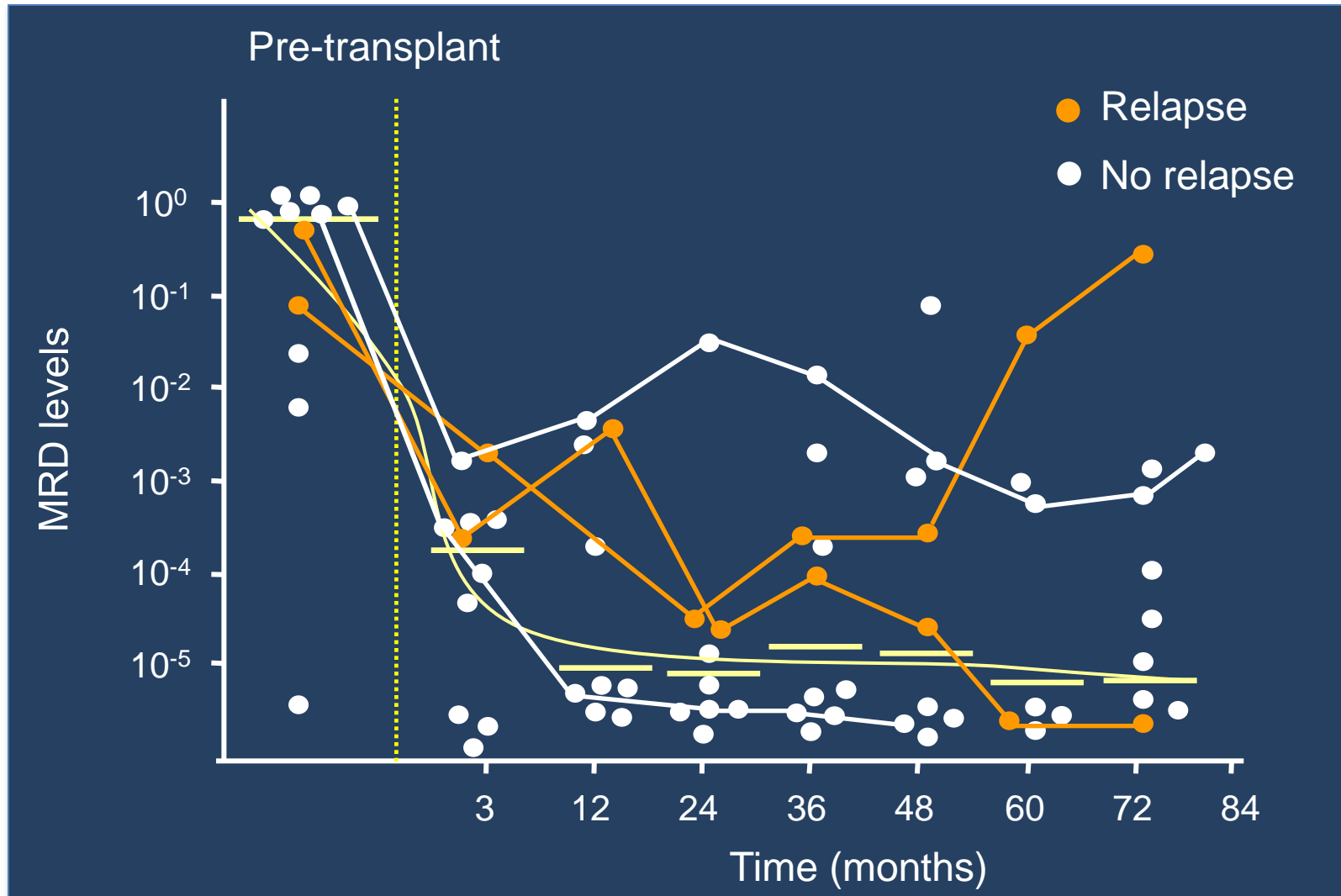


- 1 23 October 2014
- 2 EMA/629967/2014
- 3 Committee for Medicinal Products for Human Use (CHMP)

- 4 **Guideline on the use of minimal residue disease as an**
- 5 **endpoint in chronic lymphocytic leukaemia studies**
- 6 **Draft**

Draft agreed by Oncology Working Party	June 2014
Adopted 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

MRD kinetics after AlloSCT (ASO-PCR)



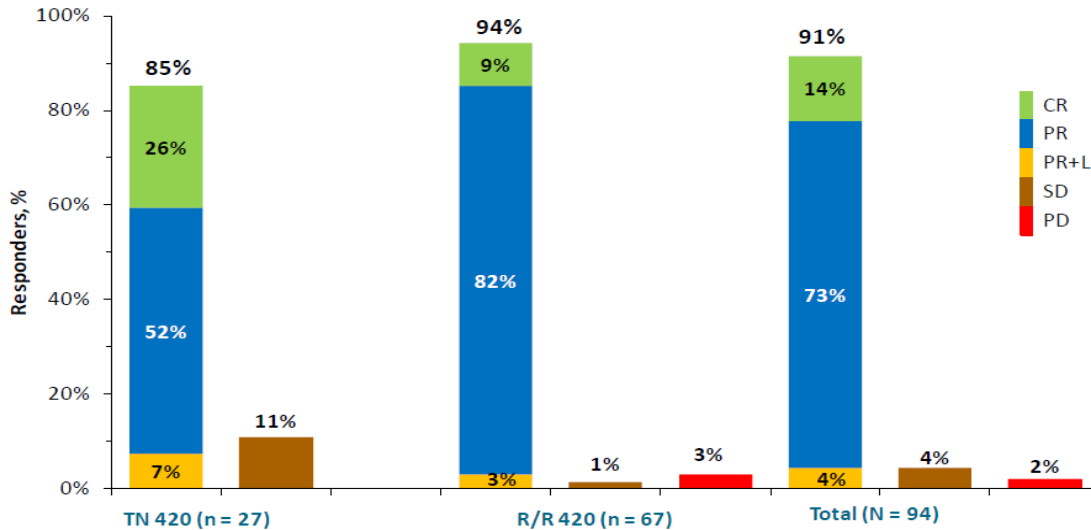
MRD & NEW TARGETED DRUGS

IBRUTINIB

IDELALISIB

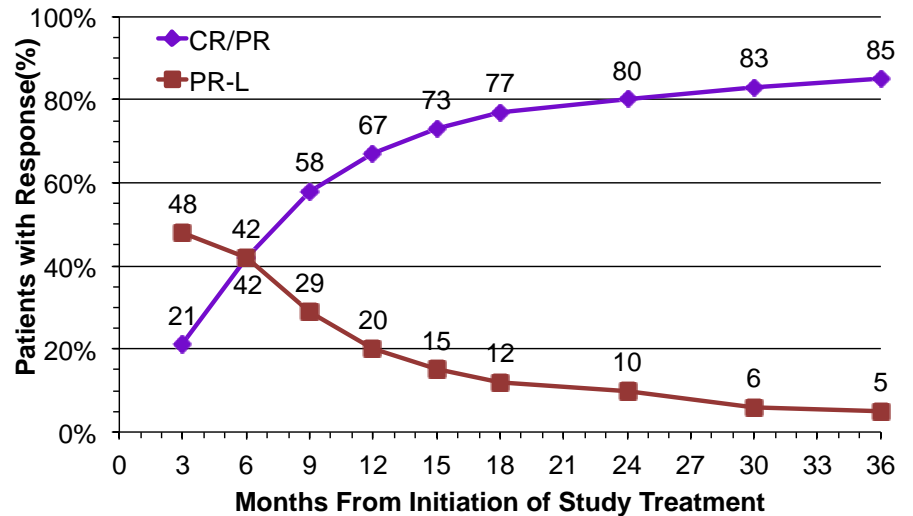
ABT-199

CLL 1102: Responses

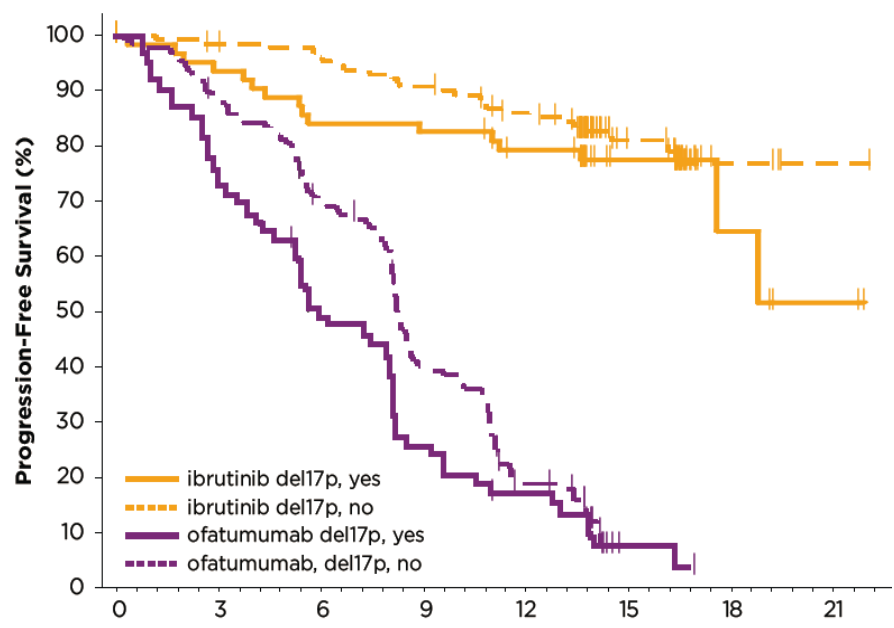
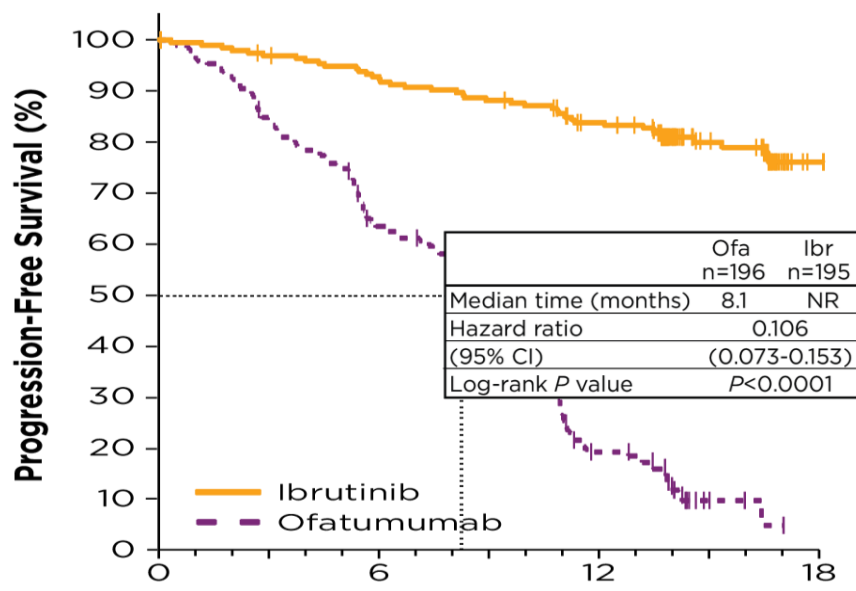


Median time to best response was 7.4 months for both TN and R/R cohorts

AACR 2015, PCYC-1102-1103, Coutre S, et al.



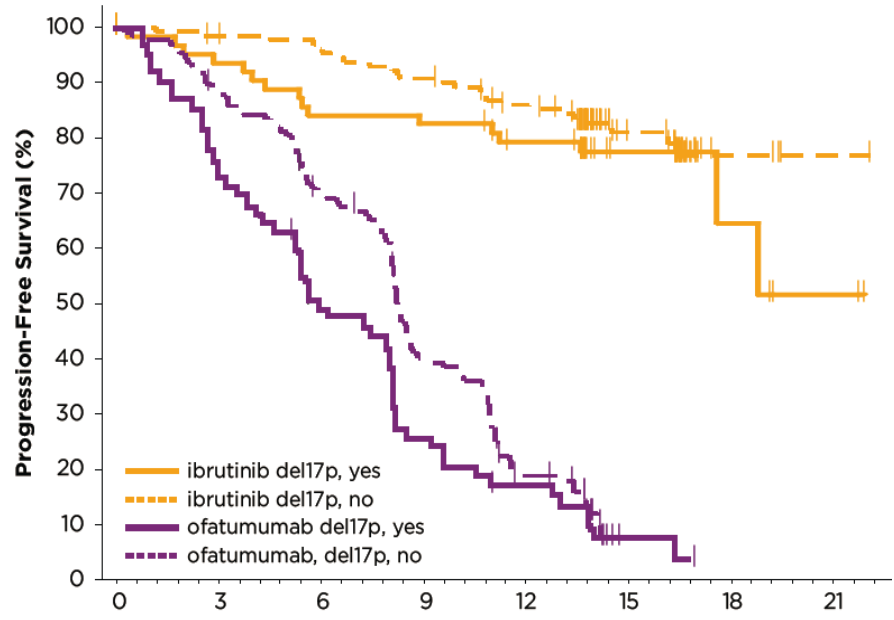
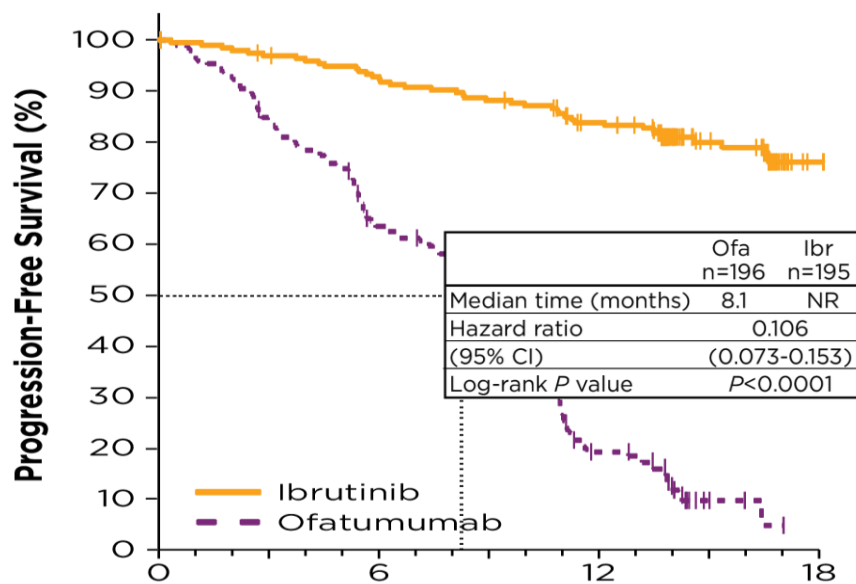
Brown et al. RESONATE (PCYC-1112) Update



Byrd JC, et al. *N Engl J Med.* 2014; ePub 31May2014.

Brown et al ASH 2014 Poster 3331

Brown et al. RESONATE (PCYC-1112) Update



Do we need MRD neg?

VS

Long-term side effects?
Clonal selection?
Cost?

Byrd JC, et al. *N Engl J Med.* 2014; ePub 31May2014.

Venetoclax (ABT-199 / GDC-0199) Combined with Rituximab Induces Deep Responses in Patients with Relapsed/Refractory Chronic Lymphocytic Leukemia

Andrew W. Roberts¹, Shuo Ma², Danielle Brander³, Thomas J. Kipps⁴, Jacqueline C. Barrientos⁵, Matthew S. Davids⁶, Mary Ann Anderson¹, Michael Choi⁴, Constantine Tam⁷, Lisa Magee¹, Jennifer Kreutzer², Ranju Singh³, Jennifer Kim⁴, Belinda Dimovski⁷, Tanita Mason-Bright⁸, Betty Prine⁸, Ming Zhu⁸, Rod A. Humerickhouse⁸, John F. Seymour⁷

¹Royal Melbourne Hospital and Walter and Eliza Hall Institute of Medical Research, Australia;

²Northwestern University, USA; ³Duke University Medical Center, USA; ⁴University of California San Diego, USA; ⁵Hofstra North Shore-LIJ School of Medicine, USA; ⁶Dana-Farber Cancer Institute, USA; ⁷Peter MacCallum Cancer Centre, Australia; ⁸AbbVie, USA

Responses by Subgroup

Best Response, n (%)	All n=49	del17p n=9	Fludarabine- refractory n=9	IGVH unmutated n=19
Overall Response	41 (84)	7 (78)	5 (56)	16 (84)
CR/CRi	20 (41)	3 (33)	4 (44)	7 (37)
PR/nodular PR	21 (43)	4 (44)	1 (11)	9 (47)
SD	5 (10)	1 (11)	2 (22)	1 (5)
Disease progression	2 (4)	0	1 (11)	1 (5)
Death (TLS) ^a	1 (2)	1 (11)	1 (11)	1 (5)

^a Fatal TLS event previously reported; no other fatal TLS events occurred after May 2013 protocol amendment

30 % CR MRD neg

Responses by Subgroup

Best Response, n (%)	All	del17p	Fludarabine-refractory n=9	IGVH unmutated n=19
Overall Response	30% CR MRD neg		(56)	16 (84)
CR/CRi	20 (41)	3 (33)	4 (44)	7 (37)
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30 % CR MRD neg


MRD in CLL: Conclusions

- MRD eradication is associated with improved outcome and longer duration of PFS and OS
- Rapid indicator of treatment efficacy
- Potential to greatly reduce the time taken for clinical trials (years for PFS & OS)
- To discontinue therapies we need MRD eradication → To cure is cheap!





Pau Abrisqueta
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Marta Crespo
Neus Villamor
María J Terol
Eva González-Barca
Marcos González
Christelle Ferrà
Eugenia Abella
Julio Delgado
Jose A García-Marco
Yolanda González
Félix Carbonell
Secundino Ferrer
Isidro Jarque
Ana Muntañola
Mireia Constants
Lourdes Escoda
Bruno Montoro



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John Seymour, Melbourne, Australia

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