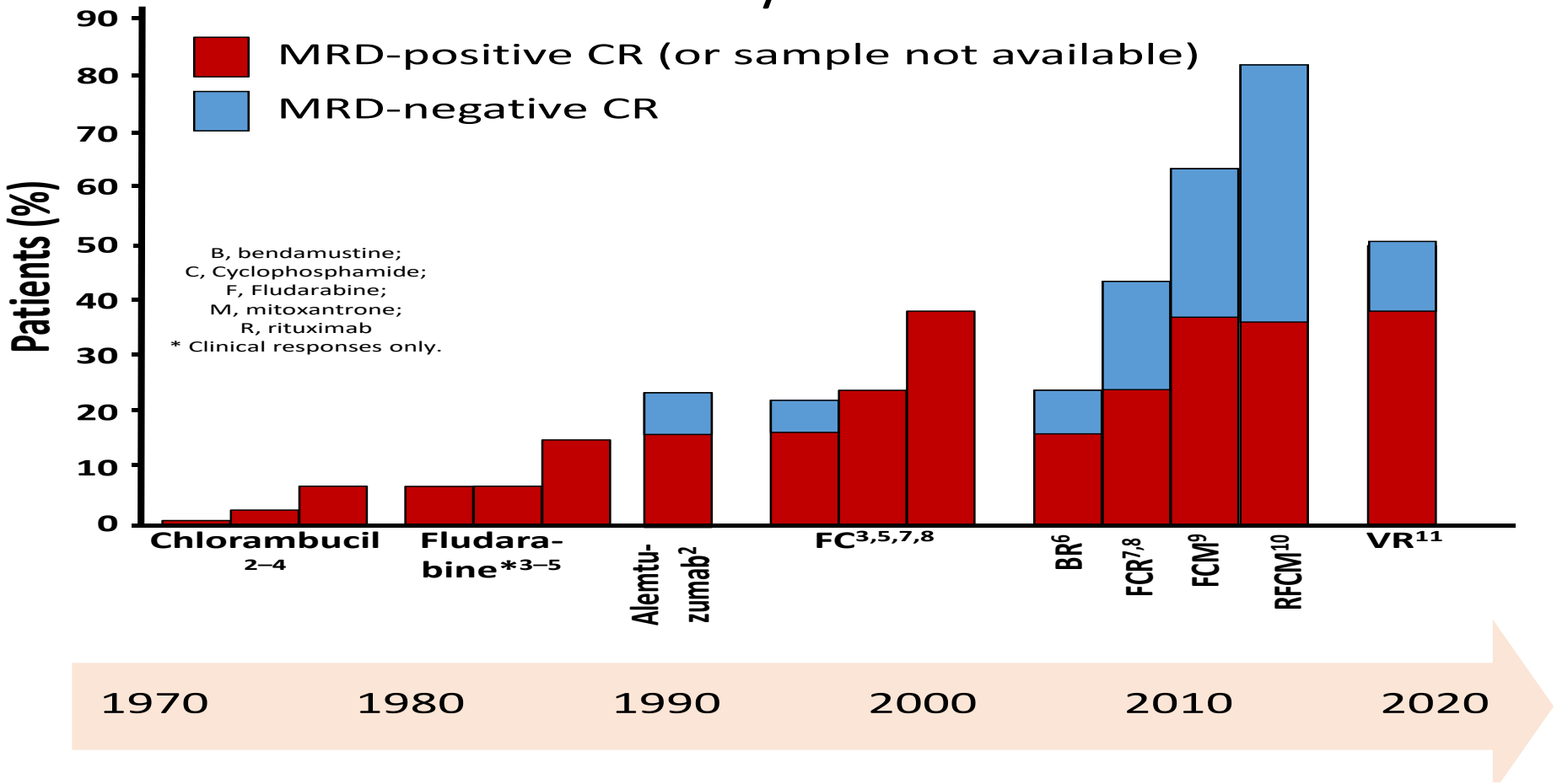
In che misura il raggiungimento della MRD-negatività puo' significare guarigione ?

S. Molica

Brief history of MRD in CLL

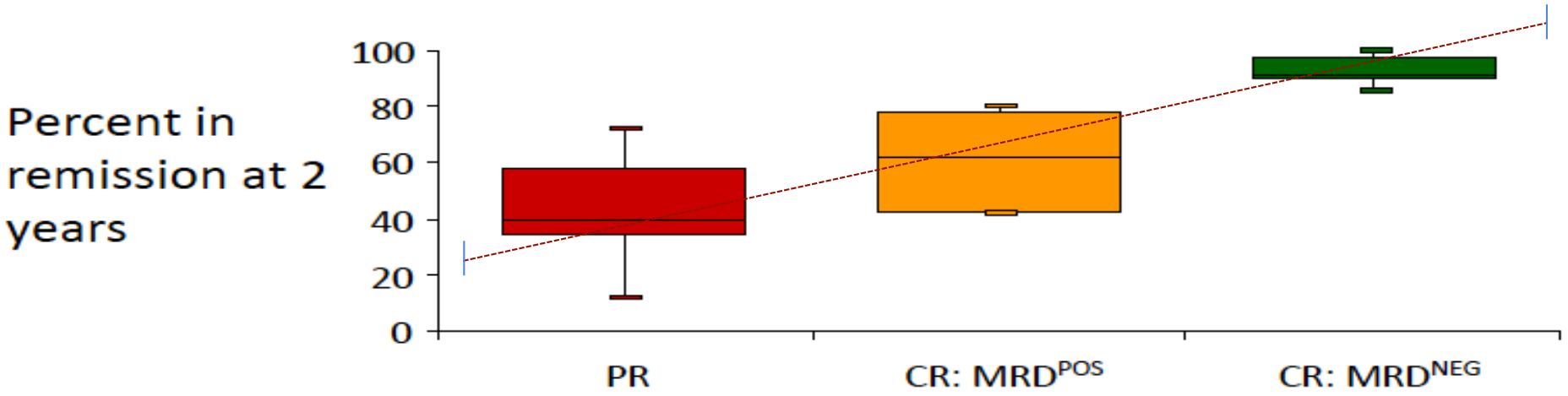


1. Adapted from: Ghia P. *Hematology* 2012; **2012:**97–104; 2. Hillmen P, *et al. J Clin Oncol* 2007; **25:**5616–5623; 3. Catovsky D, *et al. Lancet* 2007; **370:**230–239; 4. Eichhorst BF, *et al. Blood* 2009; **114:**3382–3391; 5. Eichhorst BF, *et al. Blood* 2006; **107:**885–891; 6. Fischer K, *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.

Questions

- Is there any clinical value in reaching MRD-negativity in CLL?
- Is achieving MRD-negativity always necessary?
- Can MRD overcomes the subjectivity of the CR definition regarding pathological lymph node size ?
- Is there any concordance between MRD assessment in PB and BM ?
- Can MRD direct therapy?
- Are patients interested in the attainment of MRD-negativity ?

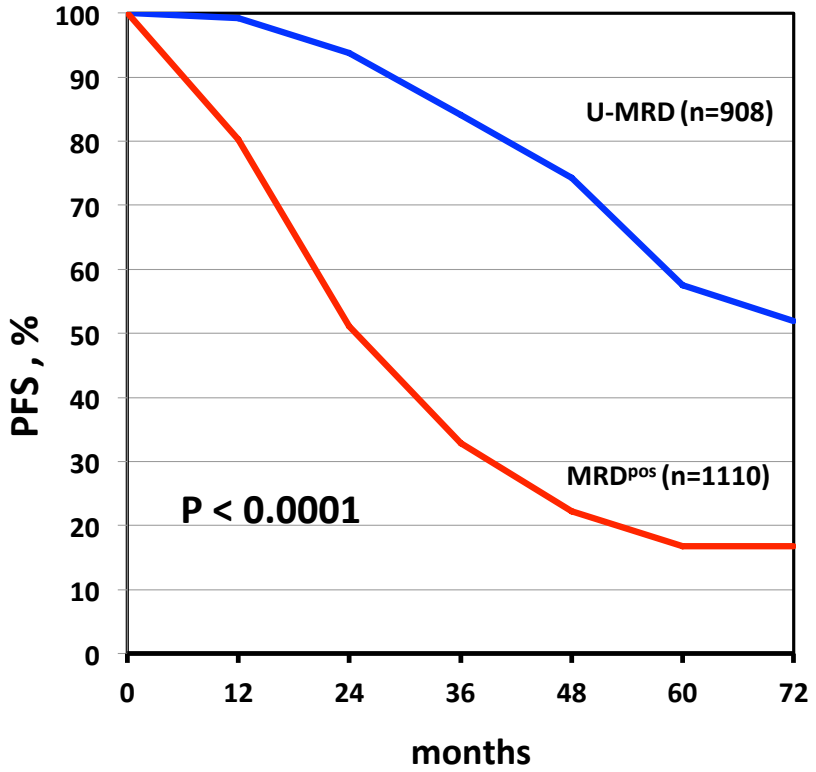
Deepness of response correlates with PFS



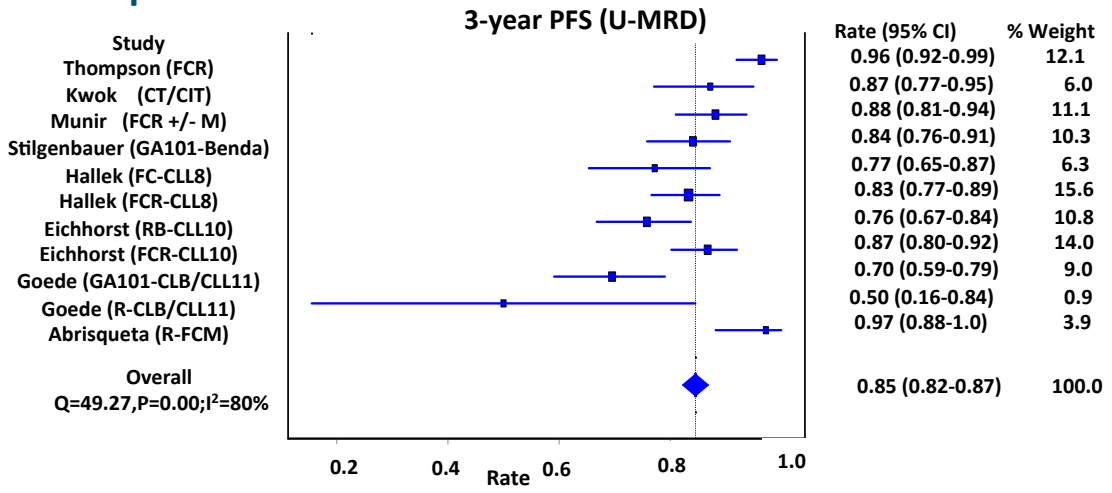
- >20 trials with some form of MRD analysis
- All show improved PFS for MRD^{NEG} response
- Approximately 1-2 years improvement in PFS for CR^{NEG} vs CR^{POS}
- **Wide variety of assays (consensus PCR, ASO-PCR, flow clonality, CD19/CD5, disease-specific MRD flow**

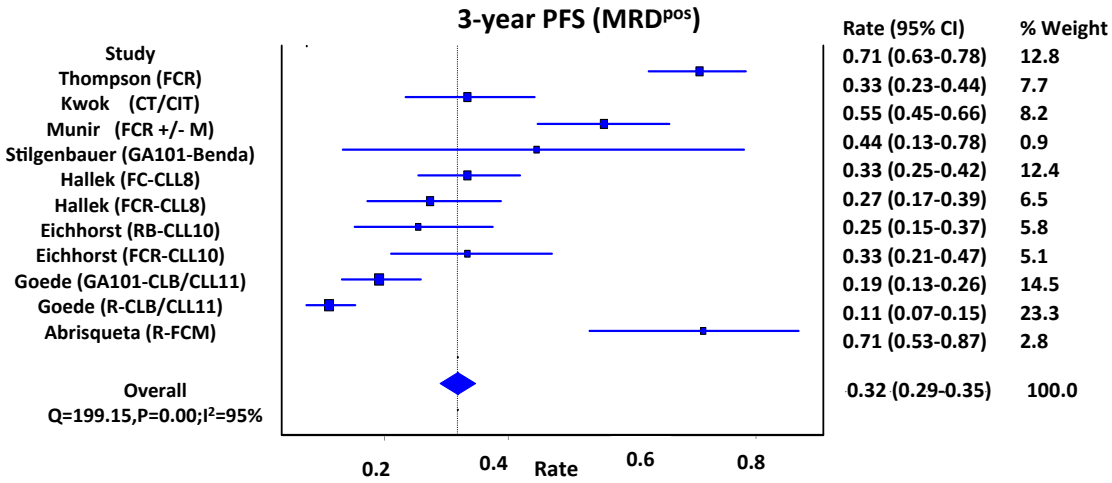
Rawstron, ERIC meeting presentation

Why should we achieve MRD-undetectability and should this be the goal in all patients ?
A meta-analysis of studies in up front of CIT.



U-MRD= Undetectable Minimal Residual Disease



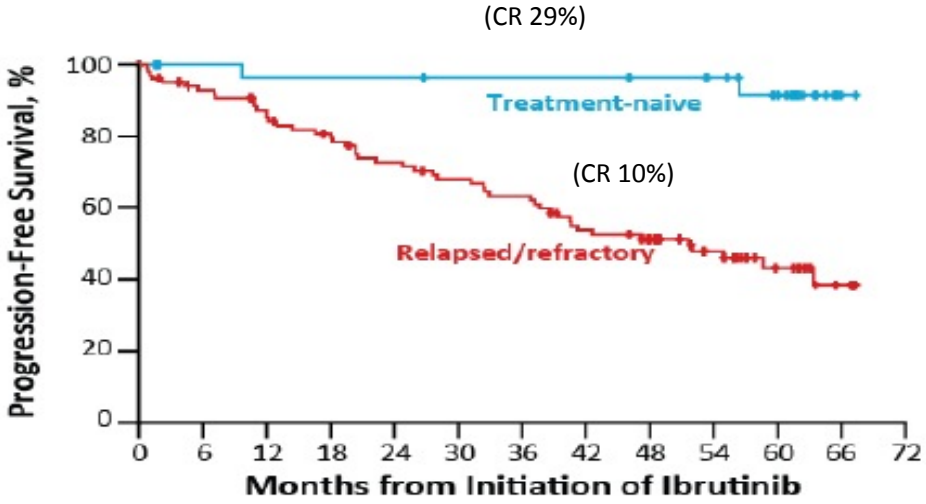


Questions

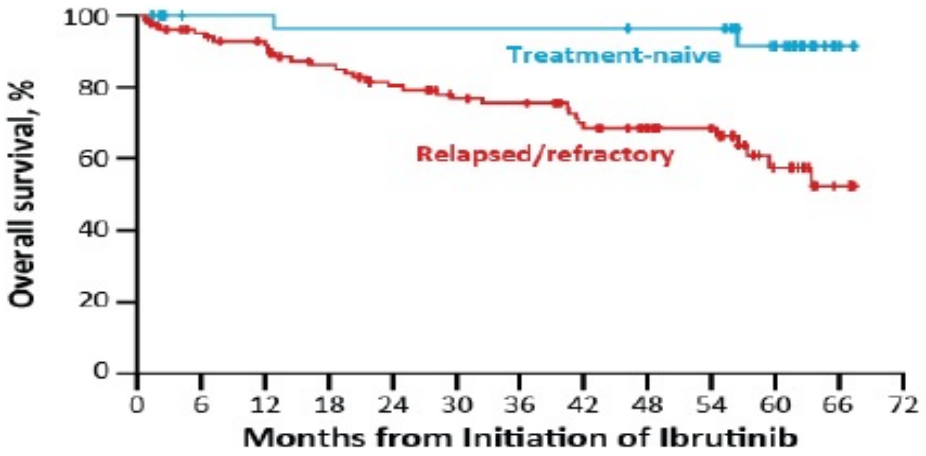
- Is there any clinical value in reaching MRD-negativity in CLL?
- Is achieving MRD-negativity always necessary?
- Is the attainment of MRD^{neg} a desired clinical endpoint due to the subjectivity of the CR definition regarding pathological lymph node size ?
- Is there any concordance between MRD assessment in PB and BM ?
- Can MRD direct therapy?
- Are patients interested in the attainment of MRD-negativity ?

5-Year Experience With Ibrutinib Monotherapy Survival Outcomes: Overall Population

Progression-Free Survival



Overall Survival



	Median PFS	5-year PFS
TN (n=31)	NR	92%
R/R (n=101)	52 mo	43%

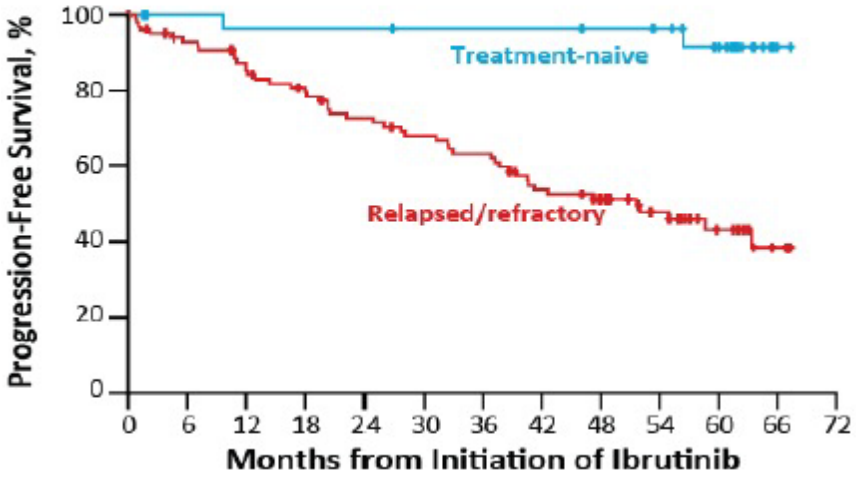
	Median OS	5-year OS
TN (n=31)	NR	92%
R/R (n=101)	NR	57%

O'Brien et al. ASH 2016. Abstract 233

Potential PFS2 in patients with R/R CLL sequentially treated with BCRi and Venetoclax

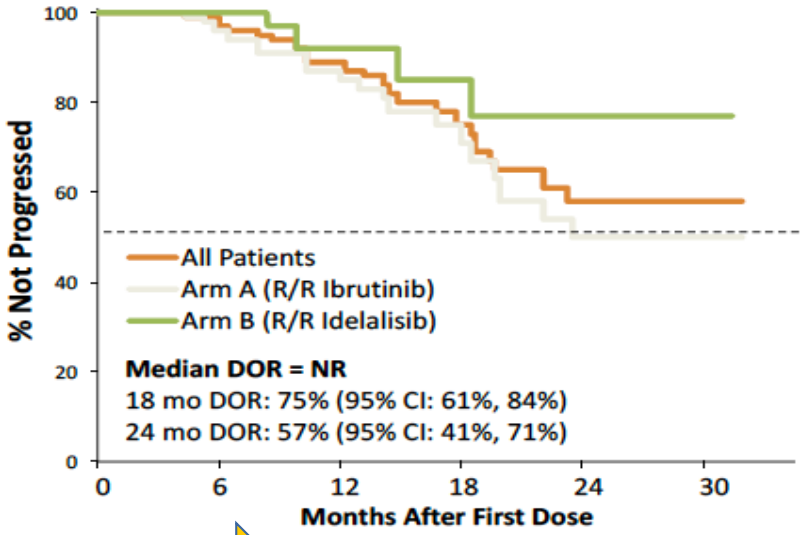
Sequencing of ibrutinib and venetoclax

Median PFS=52 months



O'Brien 2018

Median PFS=24months



Byrd 2018

Median PFS2 = 76 months

Rehabilitation of MRD with venetoclax

(Venetoclax in CLL: PFS by MRD status)

Venetoclax+R MURANO*

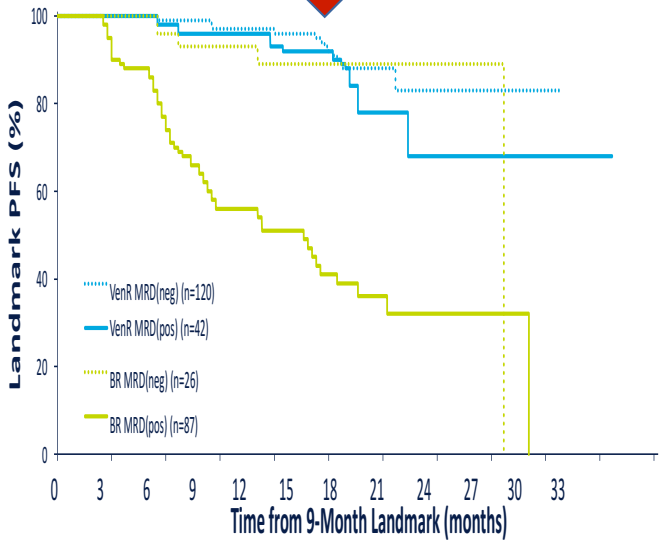
Seymour JF, et al. N Engl J Med. 2018;378(12):1107-1120

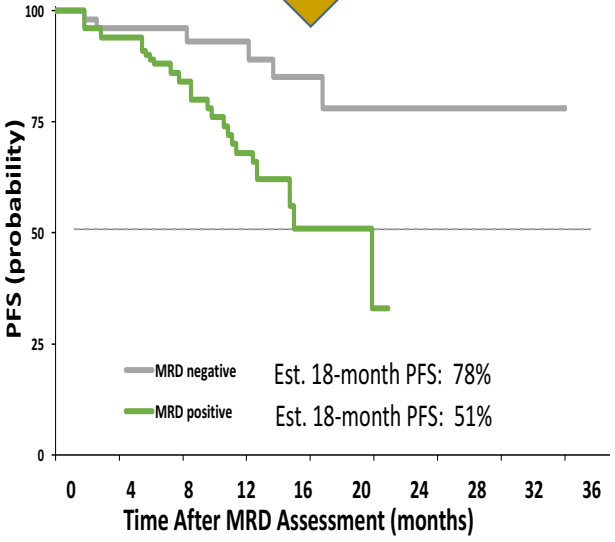
Venetoclax in del17p

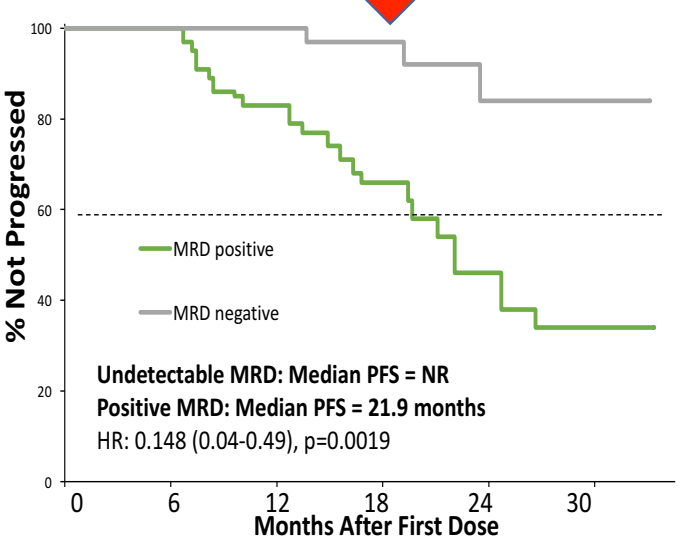
Stilgenbauer S, et al. J Clin Oncol. 2018;36(19):1973-1980

Venetoclax post-BCRi

Byrd JC, et al. Poster #7512. 2018 ASCO Annual Meeting







MRD-negativity achieved with Venetoclax impacts on PFS in patients with High-risk (I) and High-risk (II)

Study	Refractoriness to	TP53 abnormalities (del17p/TP53^{mut})	High-risk (HR) Category
Stilgenbauer (JCO 2018)	CIT only	Yes	**High-Risk (I) – CIT-resistant (BTKi and BCL2i sensitive)**
Jones (Lancet Oncology 2017) Byrd (ASCO 2018)	CIT + BCRi	Yes or No	**High-Risk (II) – CIT and PI-resistant (BCRi and/or BCL2i refractory)**

Partially modified ERIC/EBMT (Blood 2018)

Questions

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- Is there any concordance between MRD assessment in PB and BM ?
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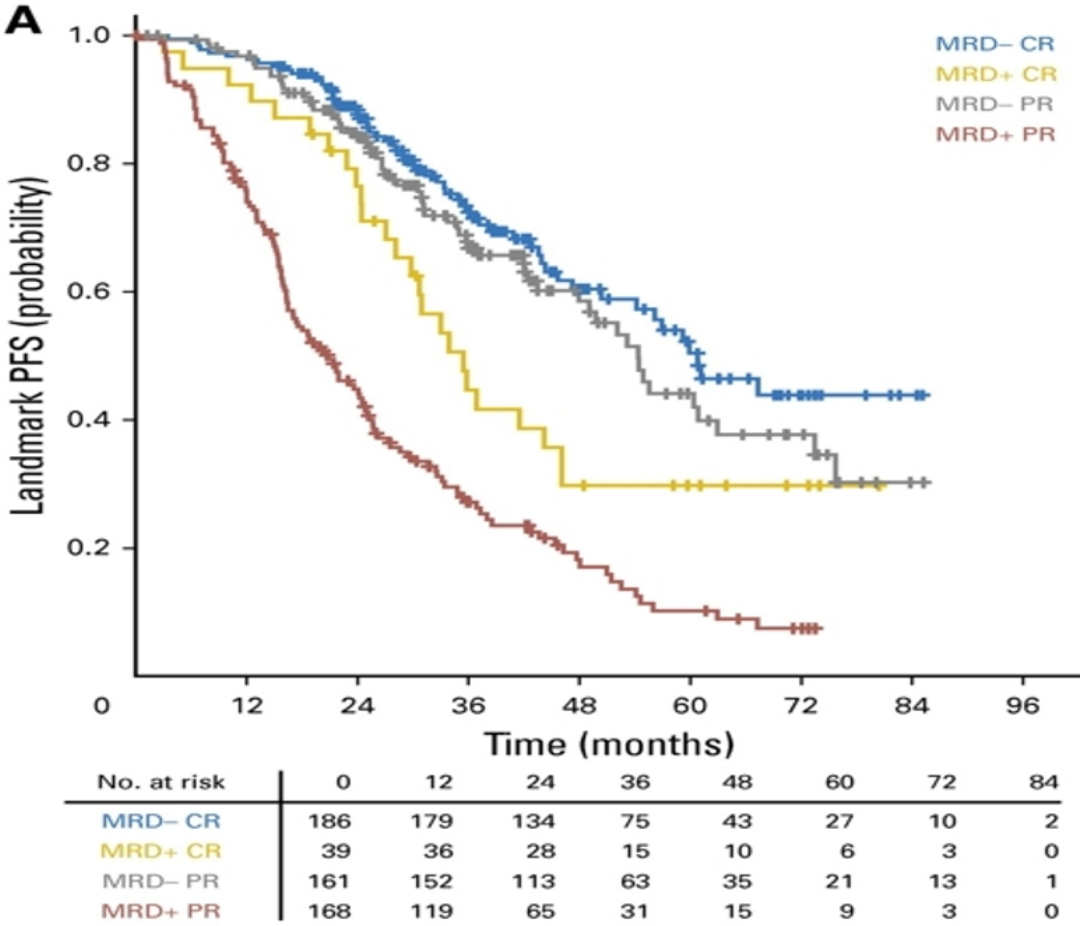
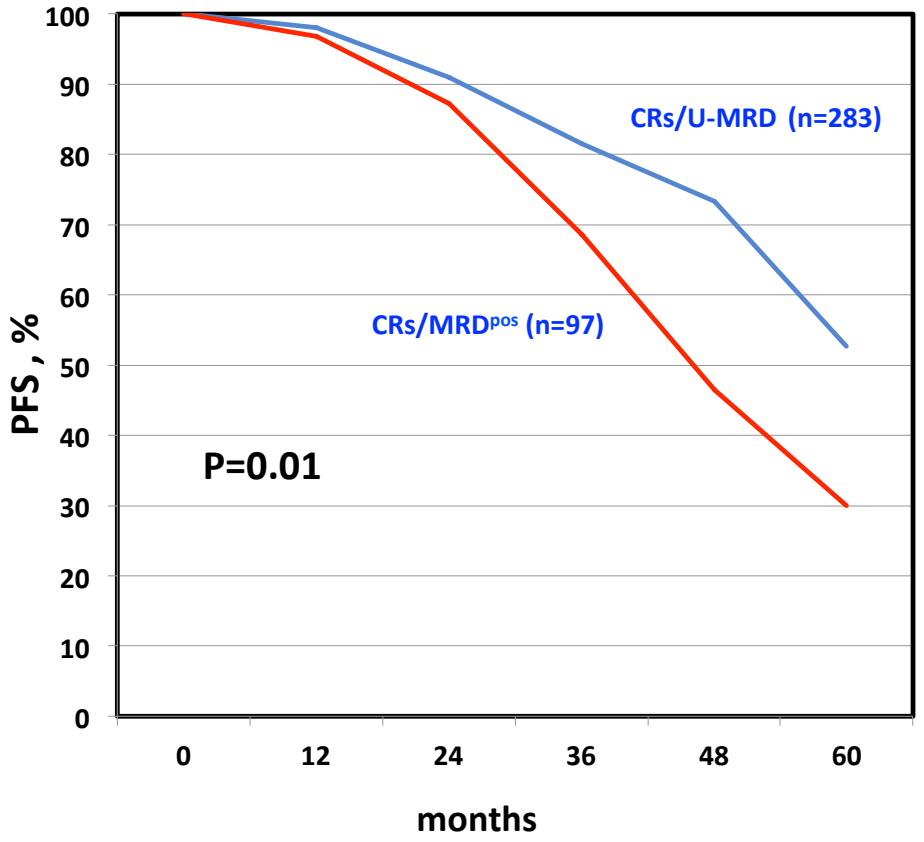
PFS according to MRD status and clinical response in CLL8 and CLL10 trial: No difference between MRD^{neg} CR and MRD^{neg} PR.

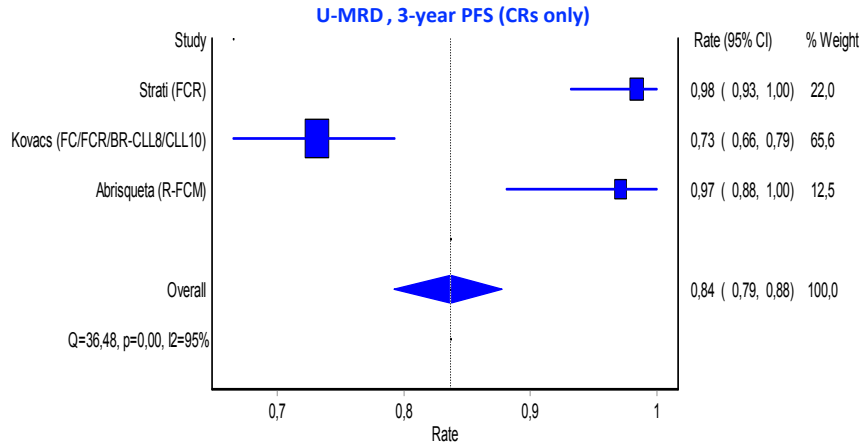


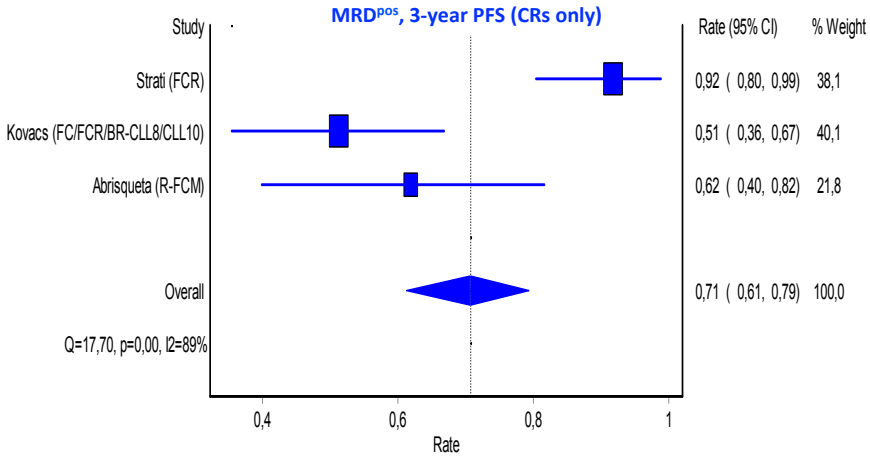
MRD status and response	Median PFS
MRD- CR (n = 186)	68.9 mo
MRD- PR (n = 161)	61.7 mo
MRD+ CR (n = 39)	44.4 mo
MRD+ PR (n = 169)	28.1 mo

Kovacs et al, *J Clin Oncol*, 2016



U-MRD= Undetectable Minimal Residual Disease





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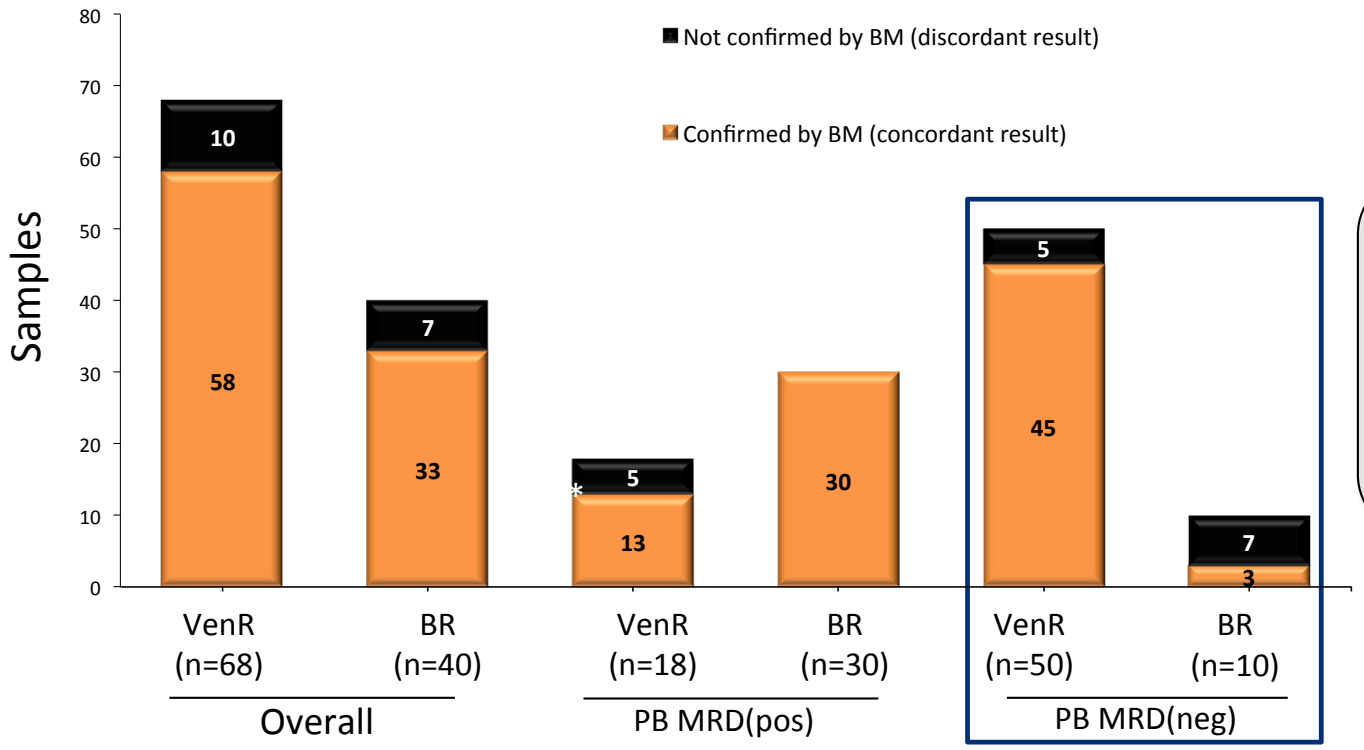
MURANO* – 90% concordance between PB and BM in VenR.



Compartment effect in relation to treatment

- ***Alemtuzumab (BM ^{pos}/PB ^{neg})*** **52%**
- ***FCR (BM^{pos}/PB ^{neg})*** **22%**
- ***VenR (BM ^{pos}/PB ^{neg})*** **10%**

*Hillmen P, et al. Oral #7508. ASCO Annual Meeting; June 1-5, 2018; Chicago, IL.

Questions

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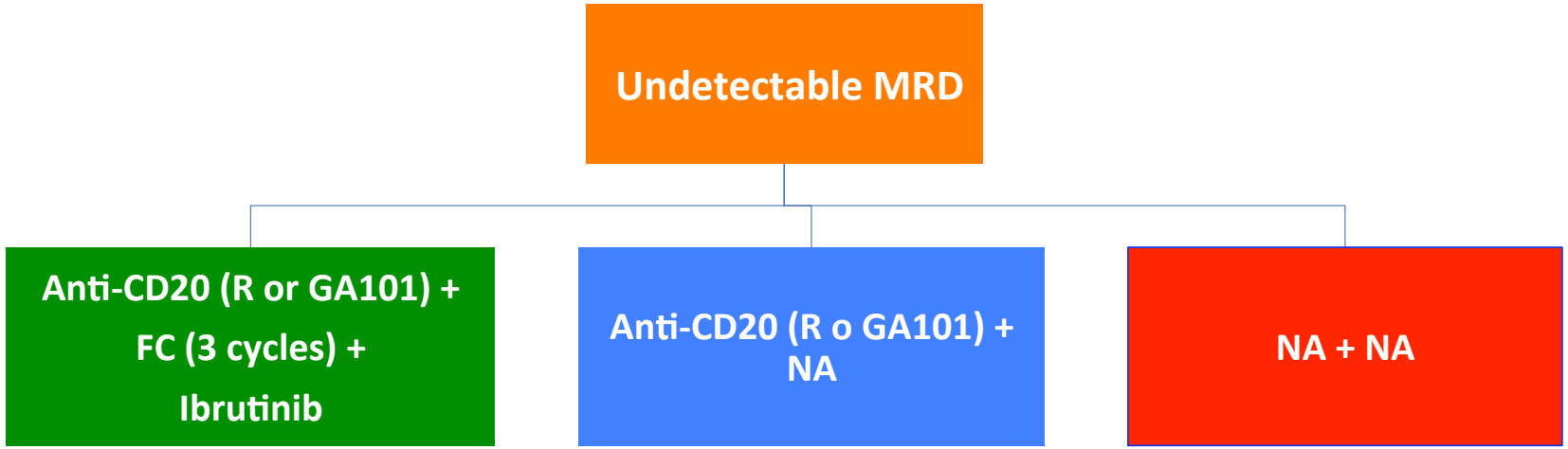
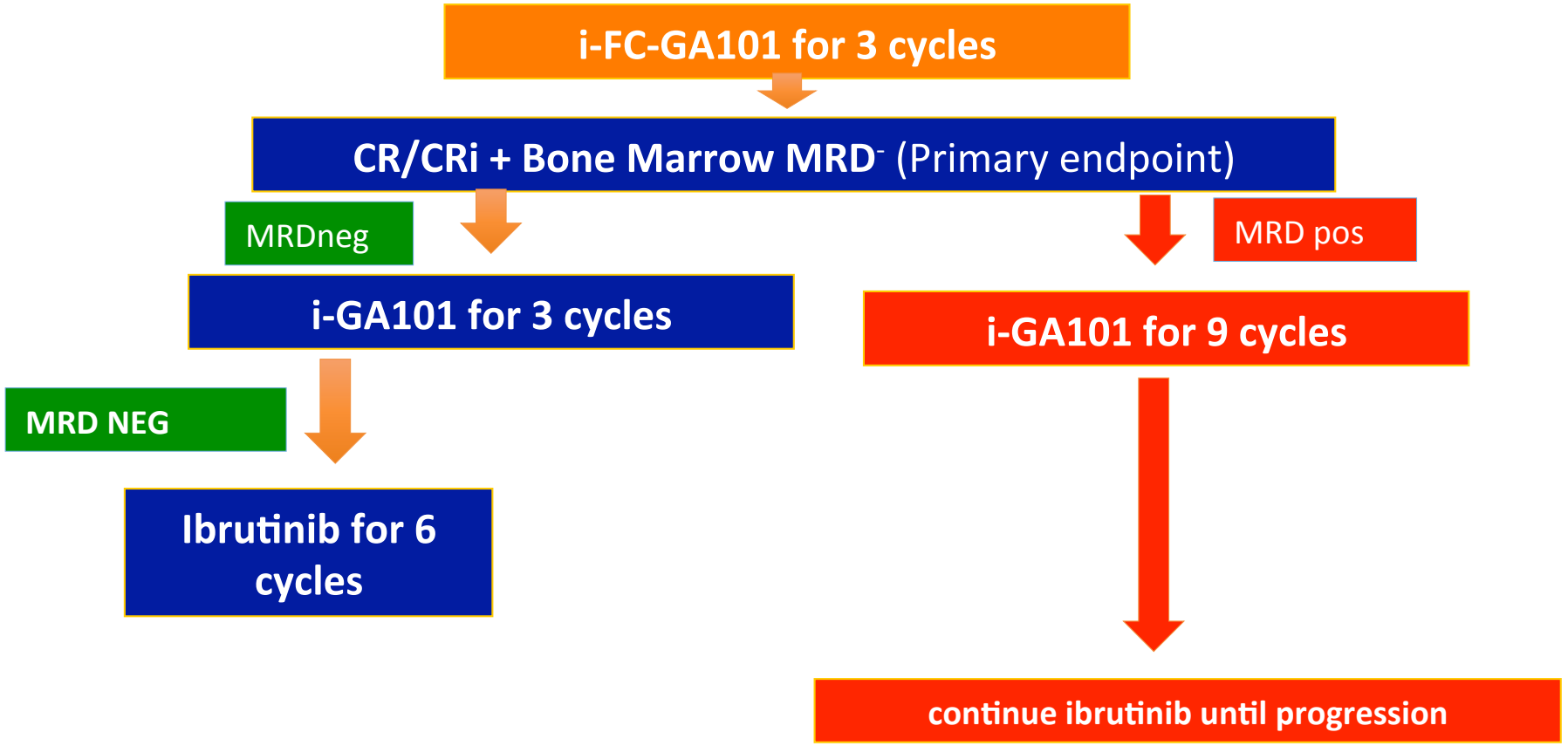
Mission:U-MRD



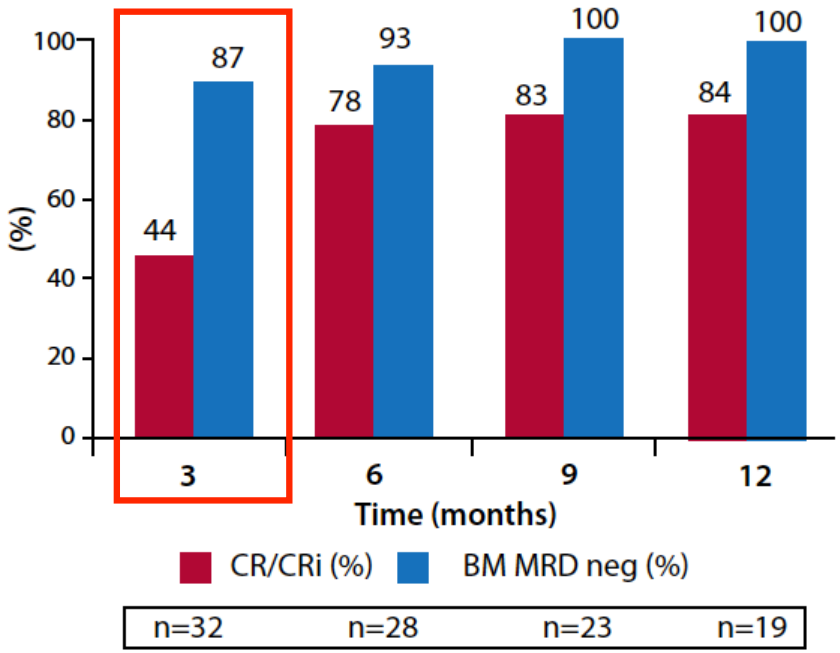
iFCG: Study Design

(CLL with Mutated *IGHV* and without *TP53* Aberrations)



Jain et al, oral presentation, abstr 495 (ASH 2017)

iFCG in *IGHV*-M CLL: Responses improve with time



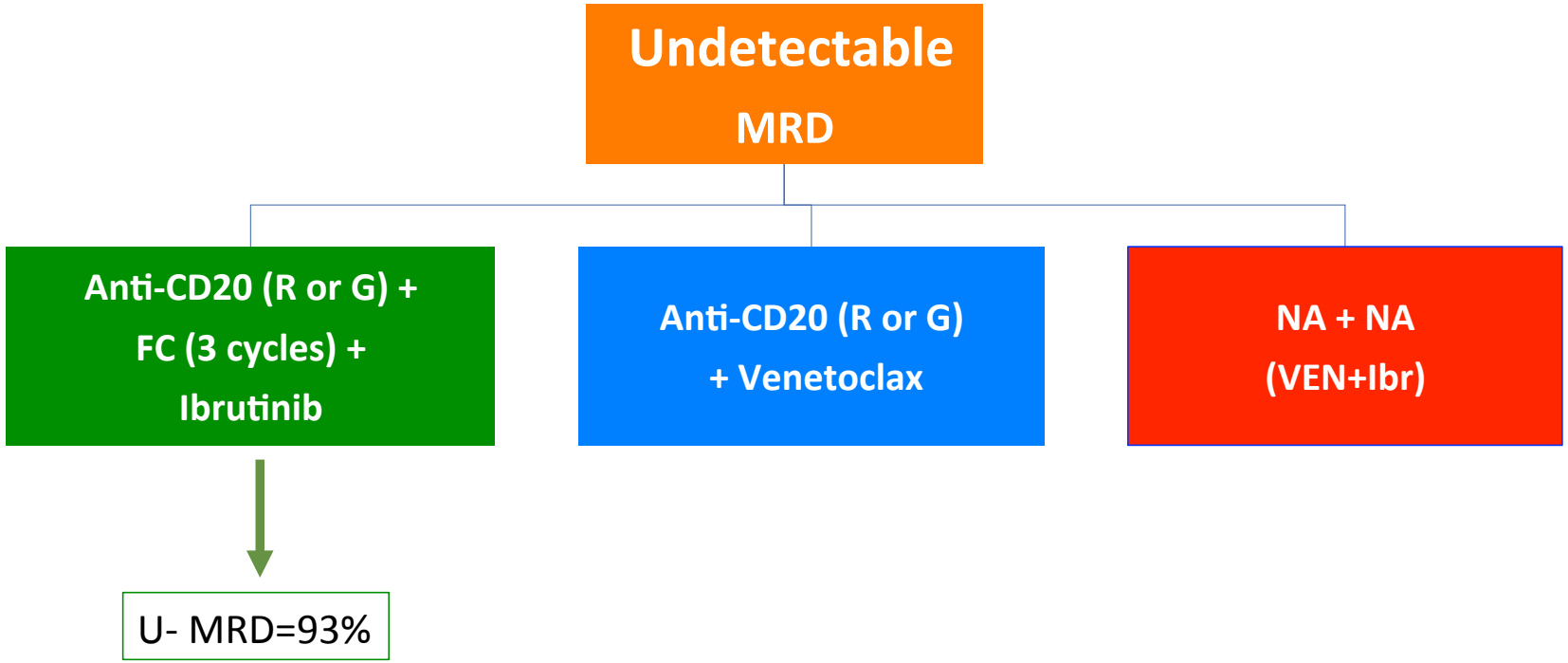
Jain et al, oral presentation, abstr 495

iFCG in *IGHV*-M CLL: Responses in *IGHV*-M after cycle 6.

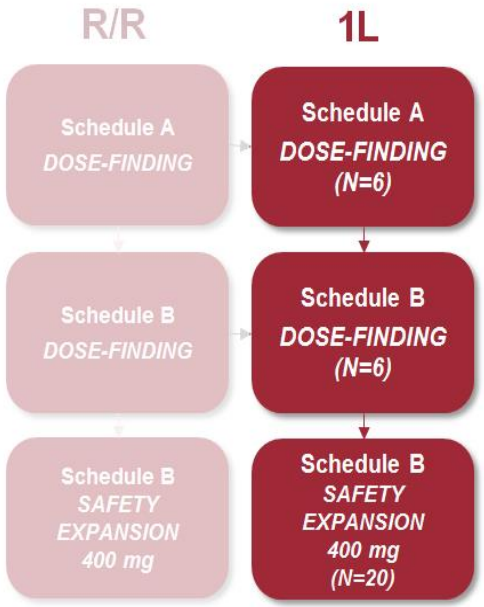
Trial	Regimen	N. pts	CT scan	CR/CRi (%)	BM MRD^{neg} (%)
MDACC	FCR x 6	88	No	83	51
MDACC	FCR x 6	82	No	66	56
CLL8	FCR x 6	113	No	50	50
CLL10	FCR x 6	123	Yes	39	62
MDACC	iFCG x3 → iG x3	28	Yes	78	93

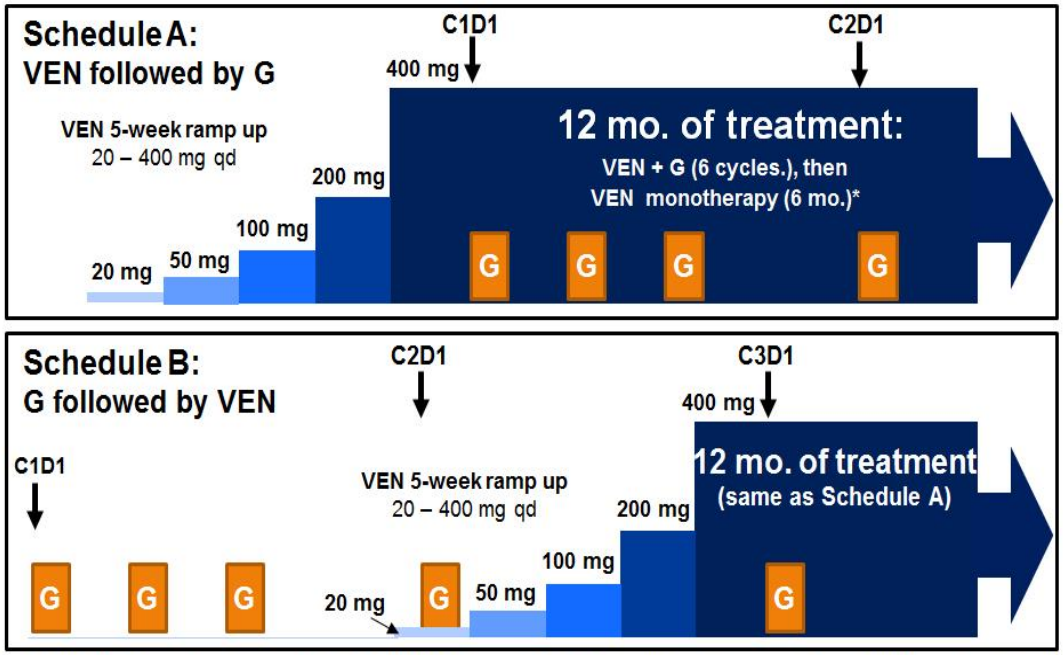
Jain et al, oral presentation, abstr 495

Mission:U-MRD



GP28331 Study Design and Treatment Dosing





***Potential VEN extension if BM MRD+ or PR; G=obinutuzumab; VEN=venetoclax.**

- MTD not reached. Safety monitoring team recommended Schedule B (G followed by VEN) and the 400 mg dose for expansion cohorts after reviewing the study and program-wide data

G dosing schedule: C1D1: 100 mg, C1D2: 900 mg, C1D8 and 15:1000 mg, C2–6D1: 1000 mg.

Flinn et al ASH 2017, abt 430

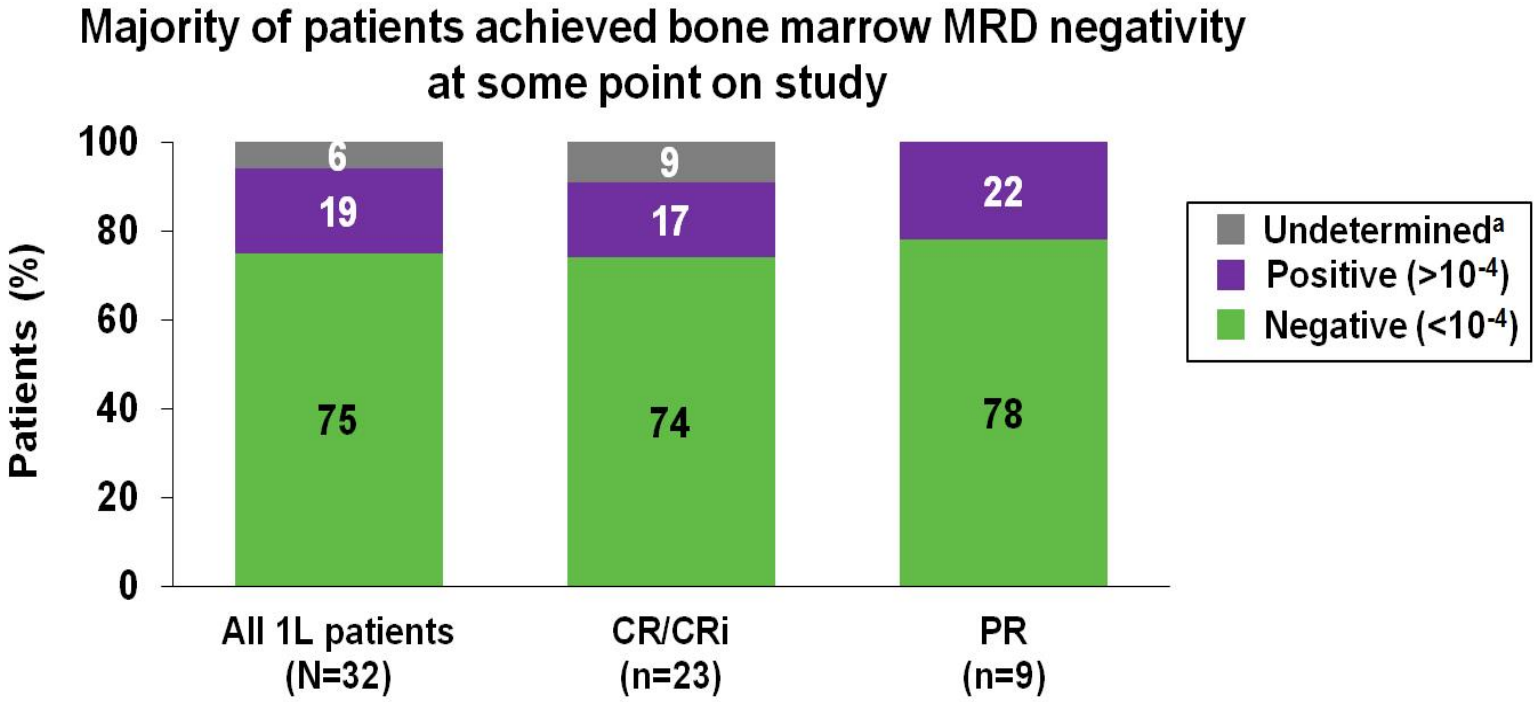
Efficacy of VEN + G: Response in All Patients and High CR Rates in All CLL Subgroups

Response n (%)	All 1L patients (N=32)	By cytogenetic abnormalities[b] (n=29)					By IGHV gene mutational status (n=27)	
		del(17p) n=5	del(11q) n=6	Trisomy 12 n=6	No abnormalities n=1	del(13q) n=11	Mut n=11	Unmut n=16
ORR	32 (100)	5 (100)	6 (100)	6 (100)	1 (100)	11 (100)	11 (100)	16 (100)
CR/CRi	23 (72)	3 (60)	5 (83)	5 (83)	1 (100)	7 (64)	9 (82)	11 (69)
PR	9 (28)[a]	2 (40)	1 (17)	1 (17)	--	4 (36)	2 (18)	5 (31)

[a]One patient downgraded to PR due to a mild splenomegaly 16cm (by imaging) and hypocellular BM (by histology); all other components consistent with CR.
[b]Responses by cytogenetic abnormalities according to the hierarchical model.

Flinn et al ASH 2017, abt 430

High Bone Marrow MRD Negativity Rates



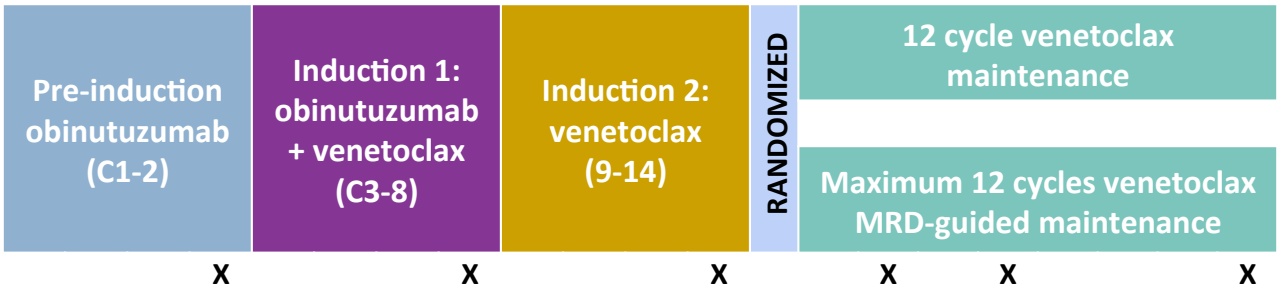
- 4 of 7 PR patients with BM MRD negativity were classified as PR (2008 iwCLL criteria) due to presence of residual lymphadenopathy (between 16–34 mm)
  - All other parameters were consistent with CR

[a]<10^{-4}, but <200,000 leukocytes analyzed.

Flinn et al ASH 2017, abt 430

Phase 2 GIVE Study* - Sequential Obinutuzumab + Venetoclax in Patients With Treatment Naïve, FCR-unfit CLL

Key eligibility criteria
- Age ≥18 years
- Treatment-naïve CLL, not fit for FCR-like regimens
- WHO PS 0-2



Primary endpoint: MRD after 24 cycles of Ven
Secondary endpoints: ORR, PFS, EFS, OS, MRD in blood, Toxicity, QoL

X=MRD measurement

Levin MD, et al. EHA 2018. Abstract PF348.
http://www.hovon.nl/studies/studies-per-ziektebeeld/cll.html?action=showstudie&studie_id=128&categorie_id=8.

Phase 2 GIVE Study *- Sequential Obinutuzumab + Venetoclax in Patients With Treatment Naïve, FCR-unfit CLL

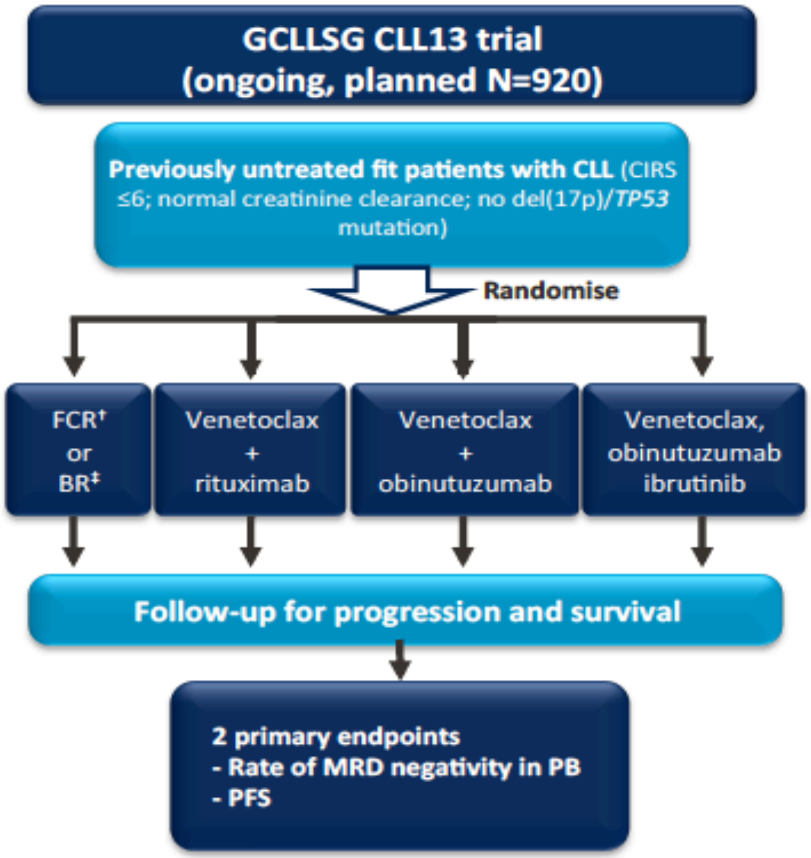
Until the January 29, 2018, 46 patients were included in this trial and the 30 patients who were followed for ≥3 cycles are included in this report

PB MRD, %	After 6 Cycles Induction (n=25)[a]	After 12 Cycles Induction (n=4)[b]
$<10^{-4}$	21 (84)	4 (100)
10^{-4} - $<10^{-2}$	3 (12)	0
$\geq 10^{-2}$	1 (4)	0

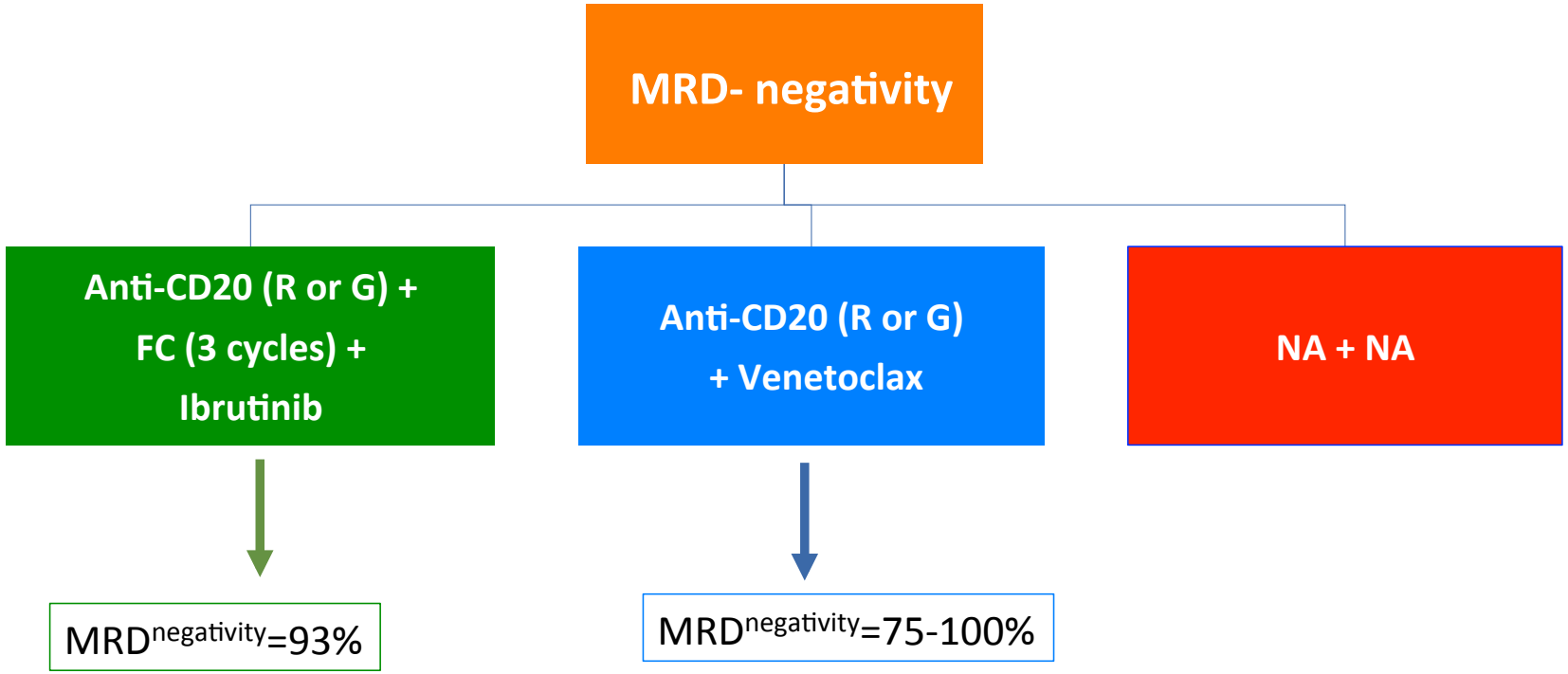
[a]In 5 patients, MRD assessment after 6 cycles have not yet been done.
[b]Only 4 patients have completed 12 cycles.

Levin MD, et al. EHA 2018. Abstract PF348.

Ongoing trials with obinotuzumab, venetoclax and Ibrutinib (GIVE).



Mission: U-MRD

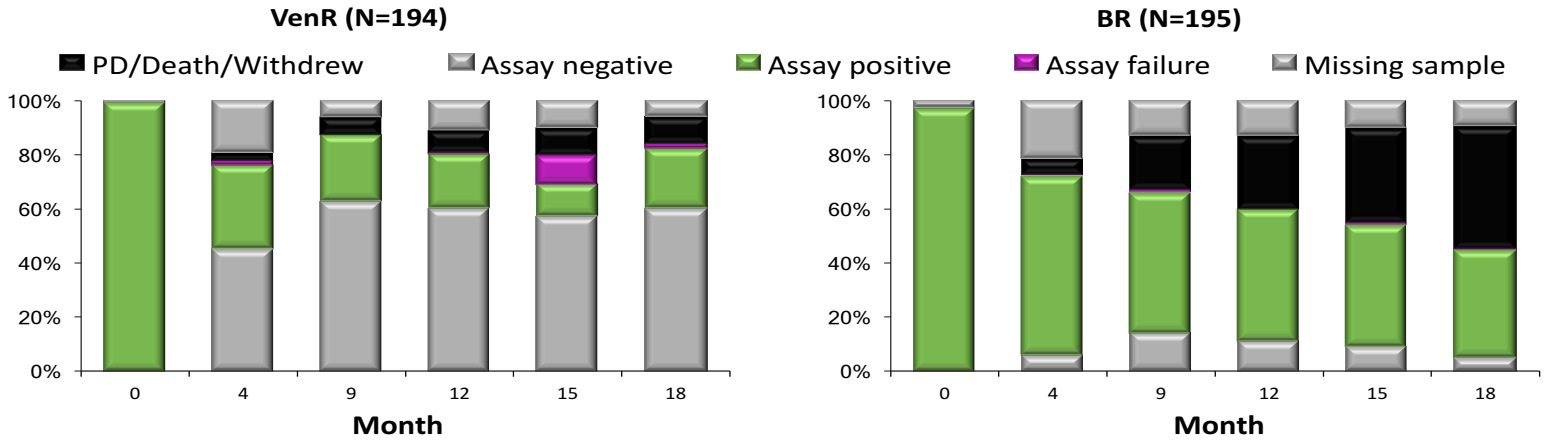


Towards a time-limited treatment also with pathway inhibitors: MRD-negativity as a surrogate to stop therapy

CAPTIVATE
(Treatment Naïve)

Preliminary Results

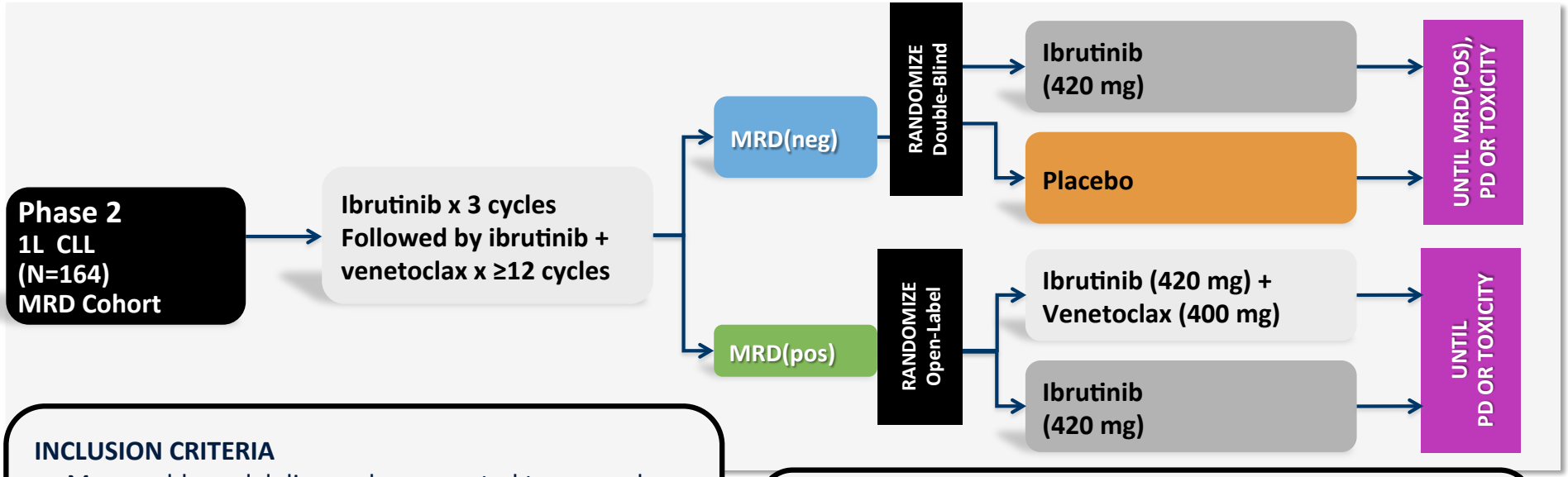
MRD kinetics in the MURANO Study*



Seymour JF, et al. N Engl J Med. 2018;378(12):1107-1120.

CAPTIVATE* – Phase 2 Study of Ibrutinib + Venetoclax

A phase 2 study of the combination of ibrutinib plus venetoclax in subjects with previously untreated CLL/SLL.[1]



INCLUSION CRITERIA

- Measurable nodal disease by computed tomography
- Adequate hepatic, renal and hematologic function

EXCLUSION CRITERIA

- Any prior therapy for CLL

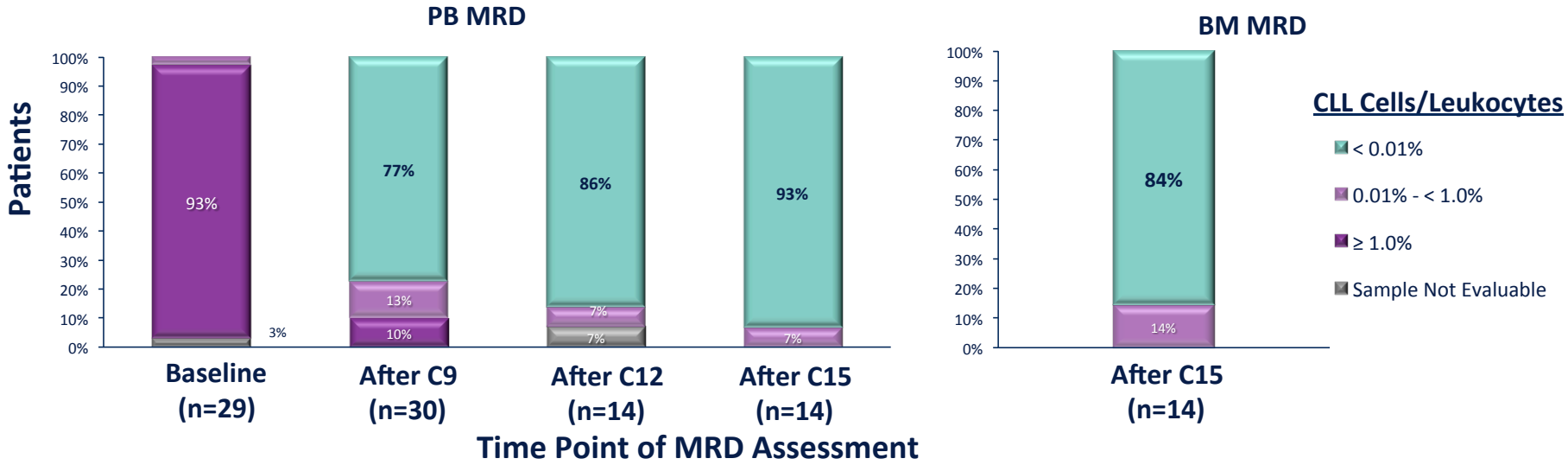
PRIMARY ENDPOINTS (MRD COHORT)[2]

Primary for pre-randomization phase:
MRD(neg) response rate

Primary for randomization phase:
1-year MRD(neg) DFS rate*

1. ClinicalTrials.gov. NCT02910583. https://clinicaltrials.gov/ct2/show/NCT02910583. Accessed June 2017. 2. Wierda WG, et al. Oral #7502. ASCO Annual Meeting. June 1-5, 2018. Chicago, IL

CAPTIVATE* – Undetectable MRD Responses Over Time



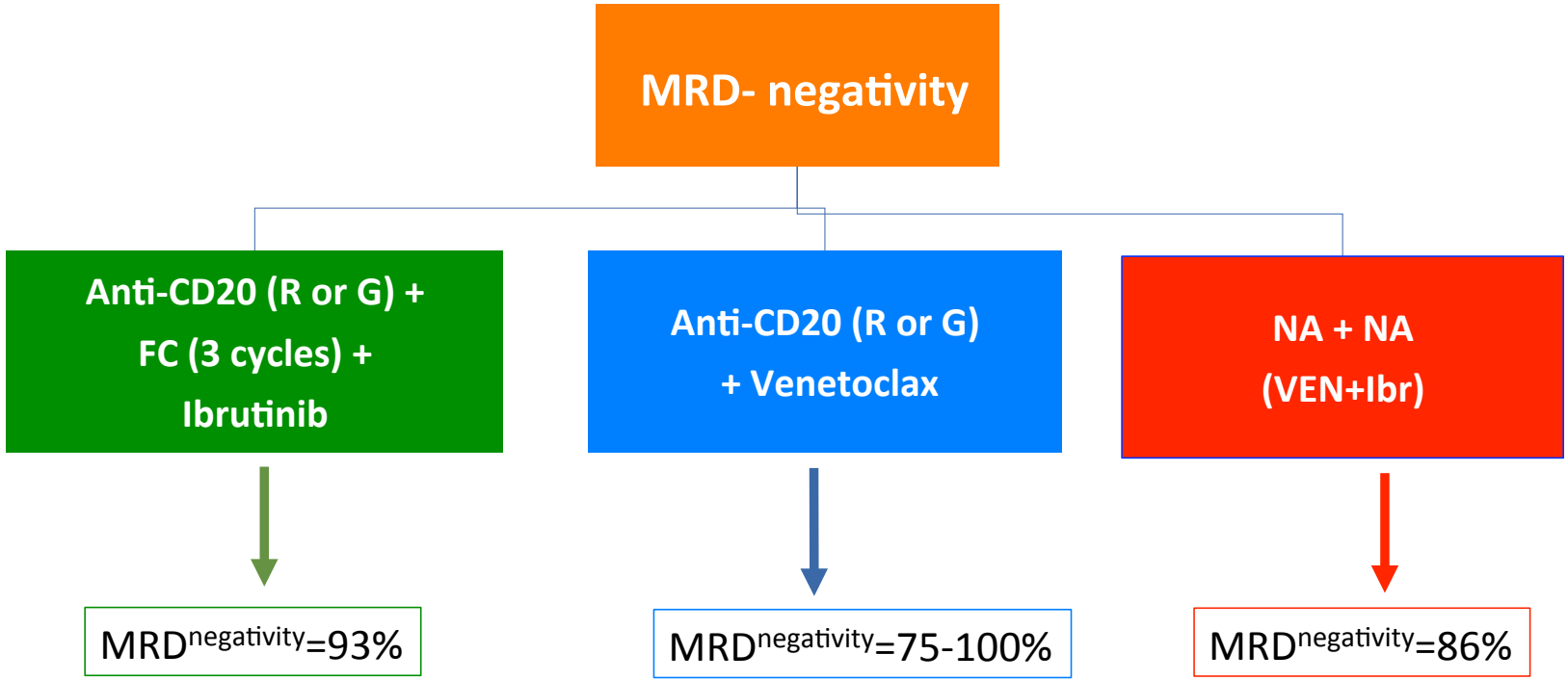
BM was assessed per protocol after C15 for all patients who reached this time point as of the data extract

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

*Confirmed undetectable MRD defined as undetectable MRD serially over at least 3 cycles in PB and undetectable MRD in both PB and BM

Wierda WG, et al. Oral #7502. ASCO Annual Meeting. June 1-5, 2018. Chicago, IL.

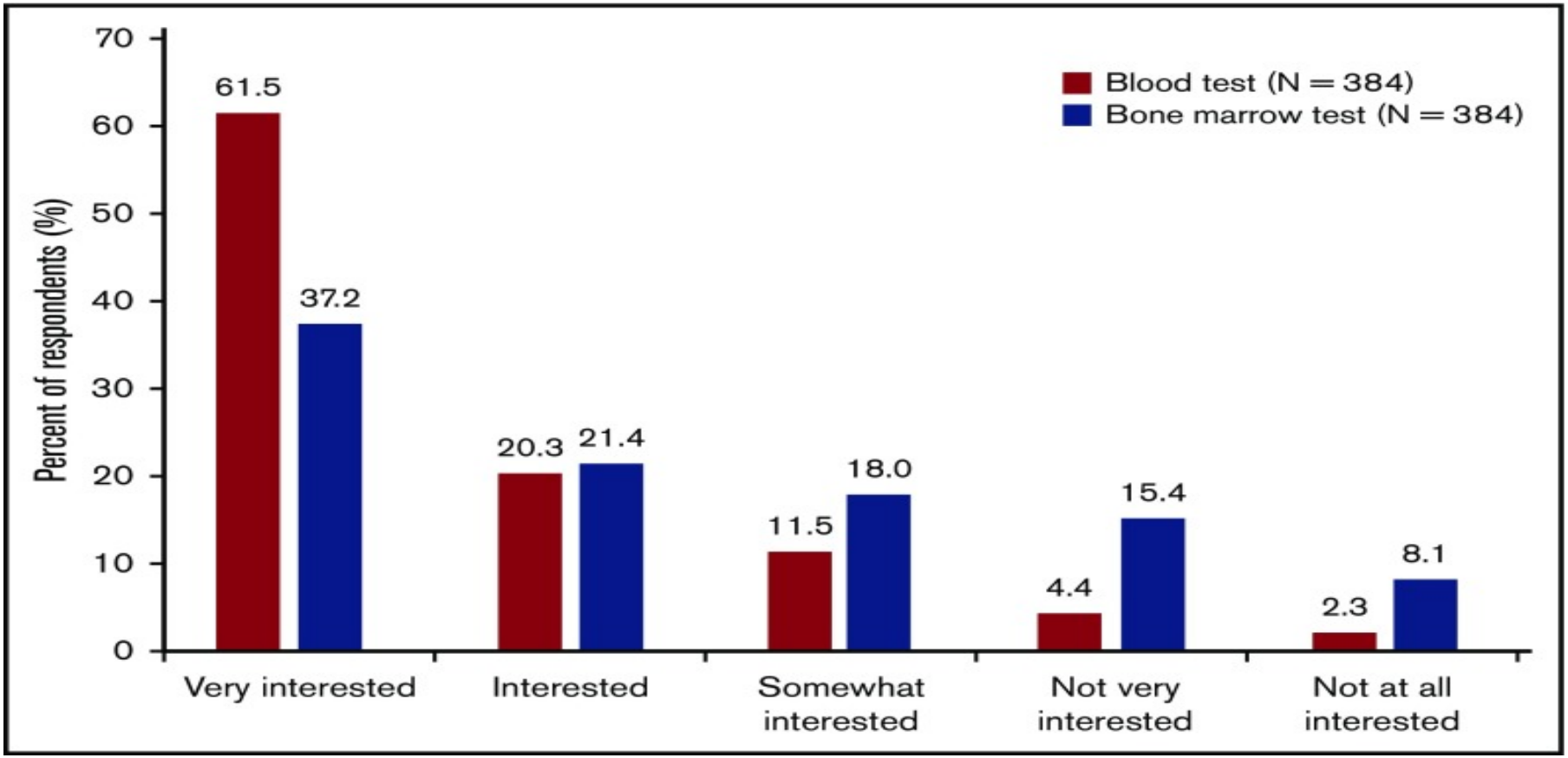
Mission: MRD-negativity



Questions

- Is there any clinical value in reaching MRD-negativity in CLL?
- Is achieving MRD-negativity always necessary?
- Can MRD overcomes the subjectivity of the CR definition regarding pathological lymph node size ?
- Is there any concordance between MRD assessment in PB and BM ?
- Can MRD direct therapy?
- Are patients interested in the attainment of MRD-negativity ?

Discrete-choice experiment (DCE) study to investigate the patient interest in knowing their MRD status



Mansfield et al Blood Adv. 2017 Nov 14; 1(24): 2176–2185

Questions/Answers

- Is there a clinical value in reaching MRD-negativity in CLL ? /**Yes**
- Is achieving MRD-negativity always necessary ? /**No**
- Can MRD overcomes the subjectivity of the CR definition regarding pathological lymph node size ? / **It seems so with CIT.**
- Is there any concordance between MRD assessment in PB and BM ? / **No with CIT. It seems so with venetoclax, more data are needed.**
- Can MRD direct therapy? / **This is an endpoint of modern trials based on the association of novel agents.**
- Are patients interested in the attainment of MRD-negativity ?/**Yes**

CT		mAB		Targeted			Study	Line	n	CR(%)	MRD(%)
FC	B	R	Ob	Ibru	Idela	V					
*		*		*			Davids et al.	TN	35	21	20
	*	*		*			Helios	R/R	289	40	25
*			*	*				TN	32		87*
	*	*			*		Barrientos	R/R	207	*PFS 23 months*	
		*				*	Murano	R/R	194	60	60
		*		*			ILLUMINATE	TN	212		
		*		*			Burger et al.	TN	104	28	5 pts
		*		*			Bosch et al.	TN	83		
			*			*	G-CLL14	TN	13	58%	100%
			*			*	Flinn et al	TN	32	72	78
		*	*	*		*	G-CLL13	TN			
				*		*	Jain et al	TN R/R	40 37	100 80	100 40
				*		*	Hillmen et al	R/R	38	49	30
				*		*	Rogers et al	TN	24	20	46
30 pts		reported		*		*	CAPTIVATE	TN	164	36	100