Combining Treatment Modalities: Useful or Superfluous?

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First-line Treatments for CLL
Treatment Evolution

1960s 1970s

Alkylating agents
- Chlorambucil
- Cyclophosphamide

1980s

Purine nucleosides
- Fludarabine
- Pentostatin
- Cladribine

1990s

Combination chemotherapy
- FC
- PC

2000s

Monoclonal antibodies
- CD20 mAbs
- Alemtuzumab

Chemoimmunotherapy
- FCR, PCR
- BR

2010s

Targeted therapy - small molecule inhibitors
- BCR pathway
- Bcl-2

Remission depth

Applicability

Myelosuppression

Why eliminate chemotherapy?

- Risk for infection
  - Myelosuppression
  - Immunosuppression (normal T and B cell depletion)
- Trigger autoimmunity

- Selective pressure for clonal evolution, resistance, and transformation events
- Genotoxic, risk for t-MDS/AML

- There are patients who benefit most (*IGHV*-M)

Demonstrating "Useful" – Therapeutic Development Approach – Eliminate Disease

- Fixed duration treatment with combined targeted therapies
- Goals:
  - Increase proportion of CR and U-MRD
    - Deepest remission (U-MRD), for longest treatment-free interval
    - U-MRD4 and U-MRD6 as early indicator of response and outcomes
  - Shorten treatment duration
  - Tolerable treatment for older and comorbid patients
- Cellular immune-based therapy for potential cure
- **Clinical importance of complete remission, U-MRD**
- Unknowns:
  - PFS for U-MRD similar for targeted agents as for CIT?
  - Pattern, timing, and characteristics of therapeutic resistance?
  - Cost reduction or financial toxicity?

Alternative Therapeutic Approach – Sequential Tx

- Continuous or intermittent single-targeted therapy until refractory, then switch targets - therapeutic sequencing
- Long-term disease control by extending “time-on-target”
- Goals:
  - Increase “time-on-target” AND optimize sequencing
  - Minimize toxicity and treatment for all (older and comorbidities)
  - Avoid clonal evolution and resistance
- Major challenge is clinical trial design
- Unknown:
  - Pattern, timing, and characteristics of therapeutic resistance
  - Cost reduction or financial toxicity?

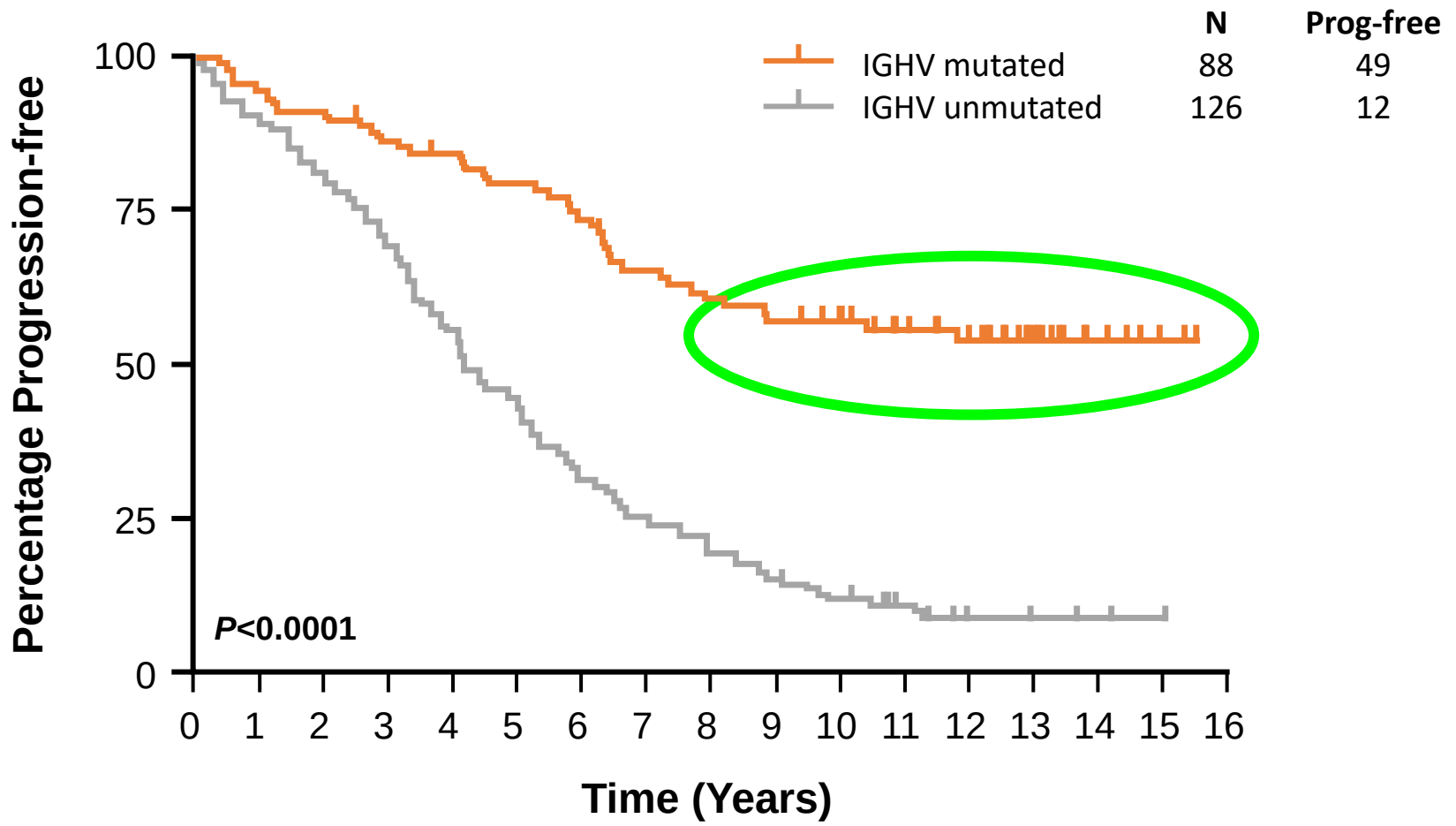
First-line Treatments for CLL by Patient Characteristics and Changing Goals

- **Del(17p) / M-*TP53* – 5% - Durable disease control**
  - BTK-inhibitor-based, no chemo
  - Fixed duration Tx; U-MRD4; no clonal evolution
- **Young, Fit (*IGHV*-M) – 15% - Deep remission, treatment if relapse**
  - CIT – FCR
  - Shorten fixed duration Tx; U-MRD4; no clonal evolution; chemo-free
- **Older, Unfit & Young, Fit (*IGHV*-UM) – 80% - Durable control**
  - BTK-inhibitor-based; chemo-free; (expect VEN+Obin approval)
  - Shorten fixed duration Tx; U-MRD4; no clonal evolution
- **Consider treatments for relapsed CLL - Durable control**
  - Avoid refractory CLL; optimize Tx sequencing; no clonal evolution

Young, fit with *IGHV*-M

Goals: shorten fixed duration Tx; increase U-MRD4; no clonal evolution; chemo-free

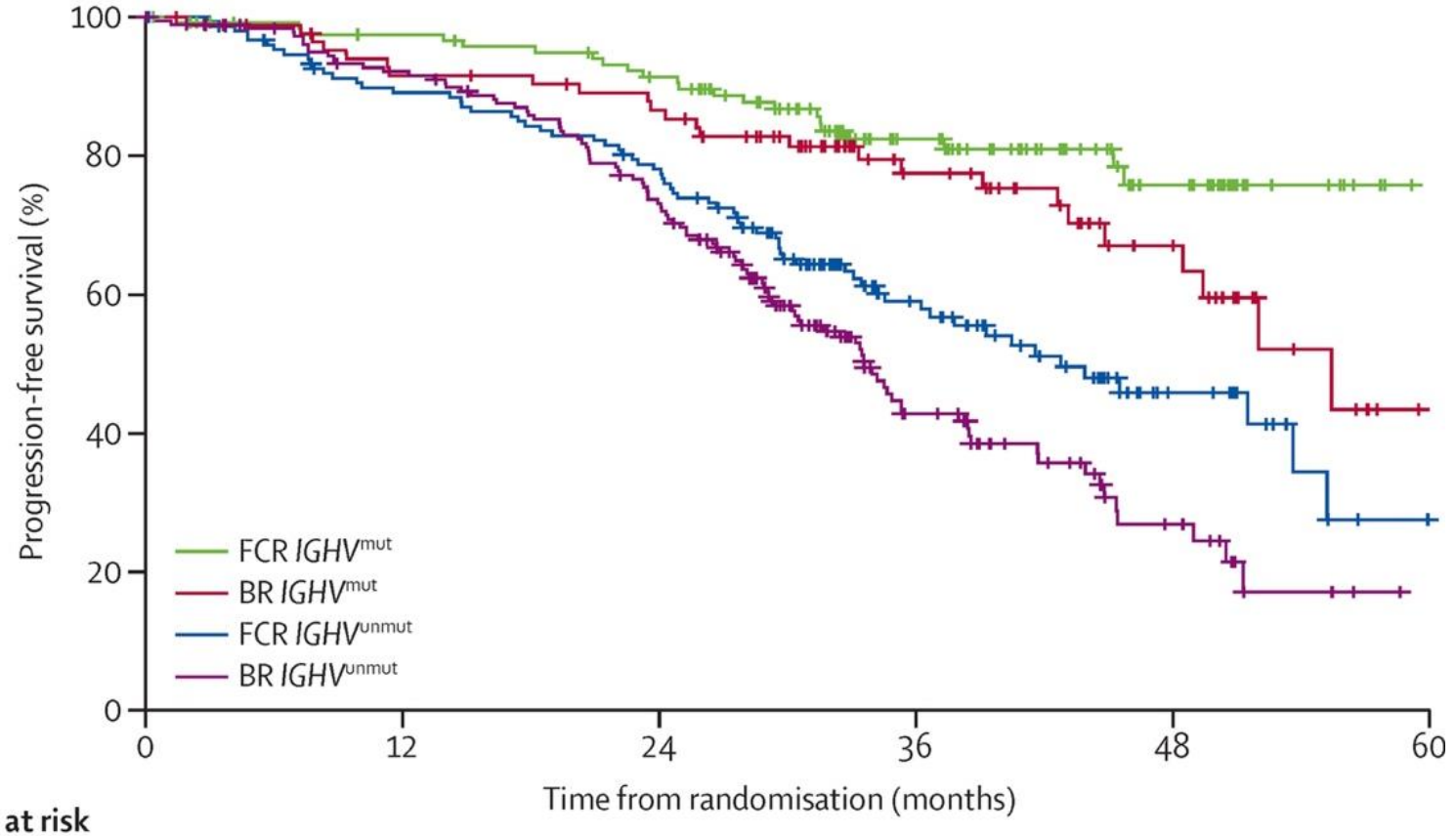
FCR300: PFS by IGHV Mutation Status



Thompson PA, et al. Blood 2016; 127:303–309

CLL10 Study: FCR vs BR in Front-line

Progression-free survival by *IGHV*-MS



Number at risk						
FCR *IGHV*^{mut}	196	112	86	44	13	0
BR *IGHV*^{mut}	86	129	94	37	9	0
FCR *IGHV*^{unmut}	155	74	57	31	12	0
BR *IGHV*^{unmut}	108	161	106	33	8	0

Eichhorst et al., Lancet Oncology 17:928, 2016

t-MDS/AML after FCR

Study	N	Treatment	t-MDS/AML %
MDACC 2004-2012	234	FCR-based	5.1
	131	FCR only	0.7
MDACC 1999-2003	300	FCR	4.6
GCLLSG CLL8	408	FCR	1.5

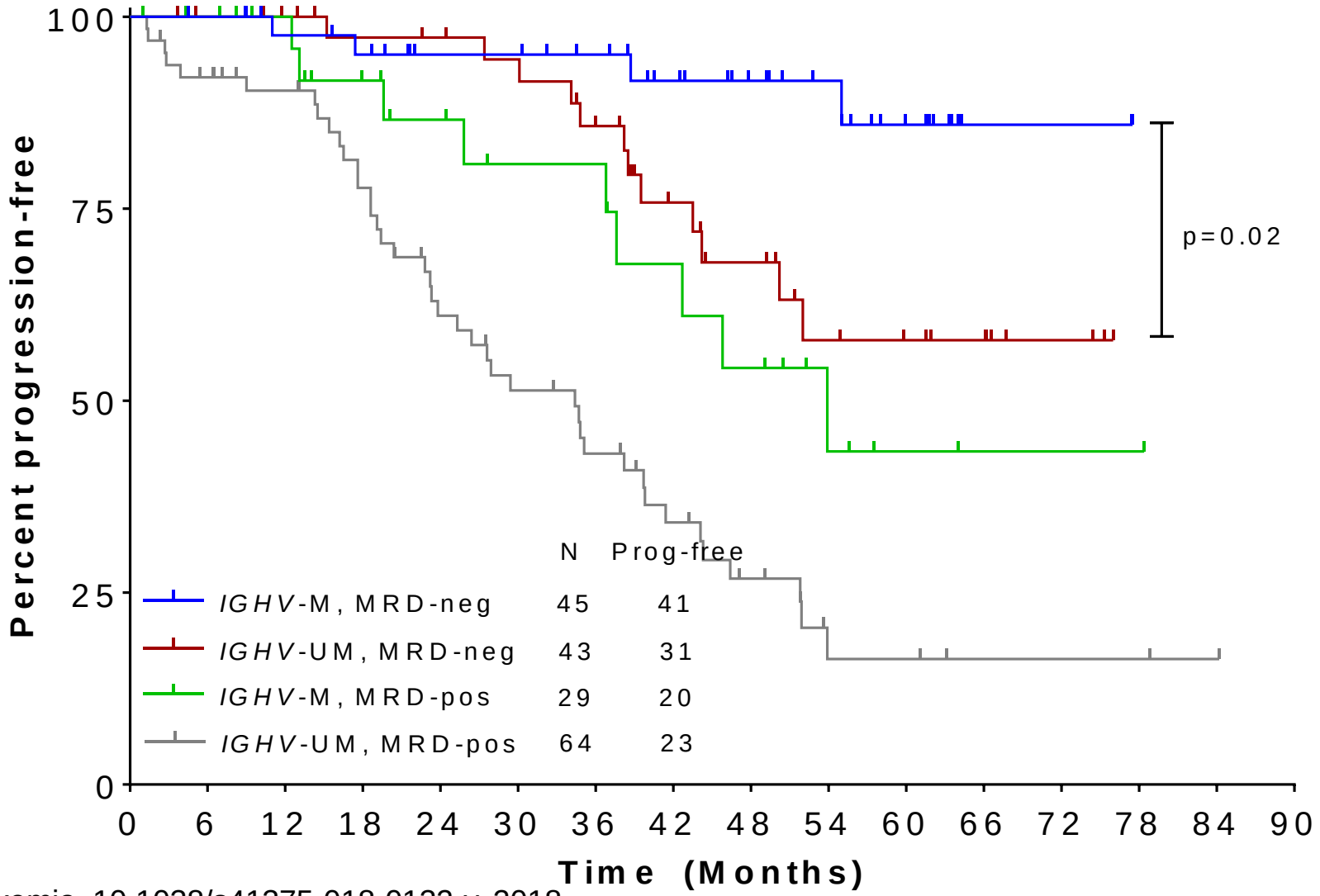
Benjamini, Leuk Lymphoma 2015; Thompson, Blood 2016; Fischer, Blood 2016.

Response with FCR

Study	N	CT scan for response	CR, %	C6 BM U-MRD4, %
MDACC FCR	237	No	65	43
GCLLSG CLL8	408	No	44	45
GCLLSG CLL10	282	Yes	40	58

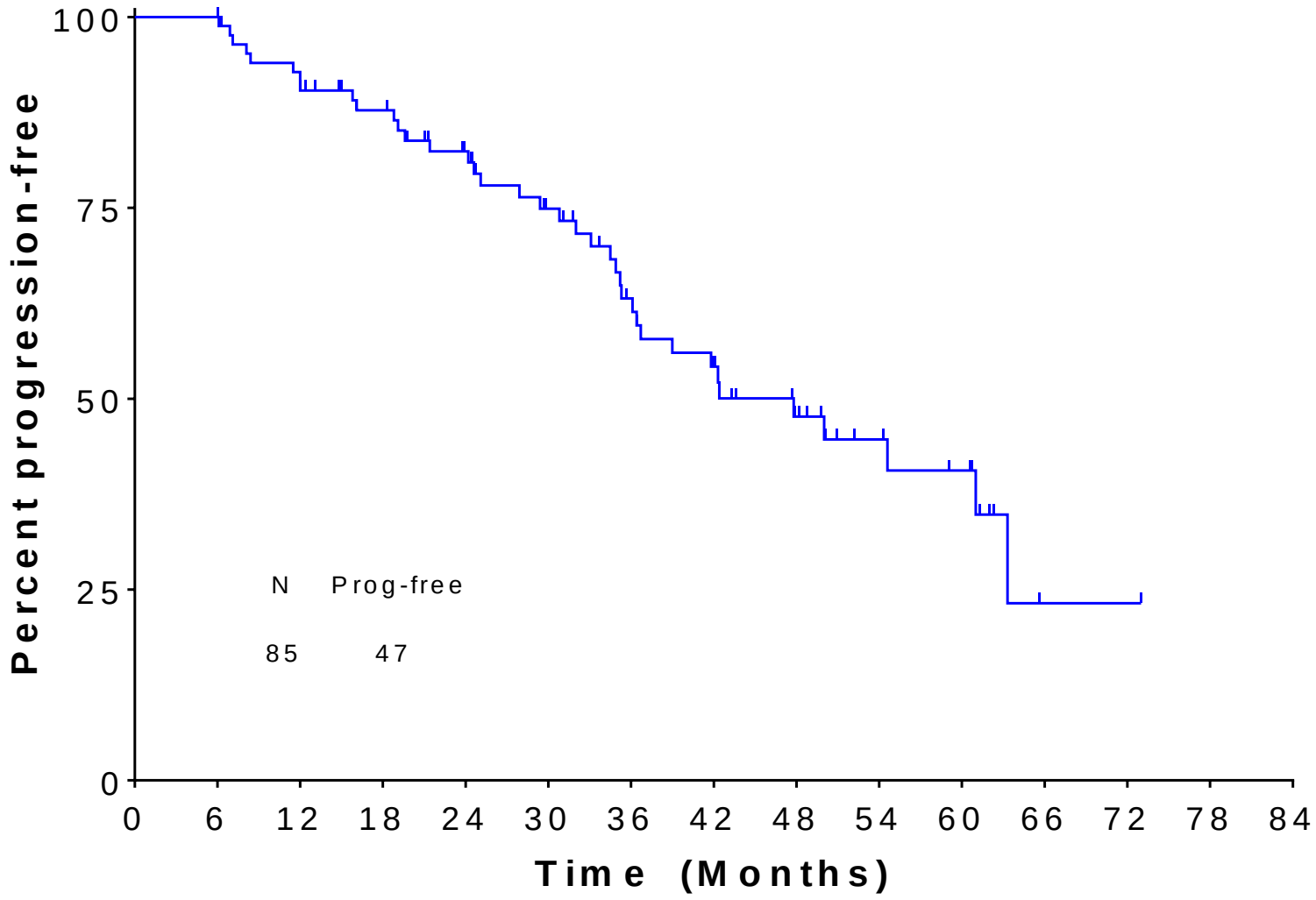
Keating, JCO 2005; Tam, Blood 2008; Thompson, Blood 2016; Strati, Blood 2014;
Hallek, Lancet 2010; Bottcher, JCO 2012; Eichhorst, Lancet Onc 2016.

FCR First-line: 6 mo landmark PFS by MRD at EOT and *IGHV*-MS



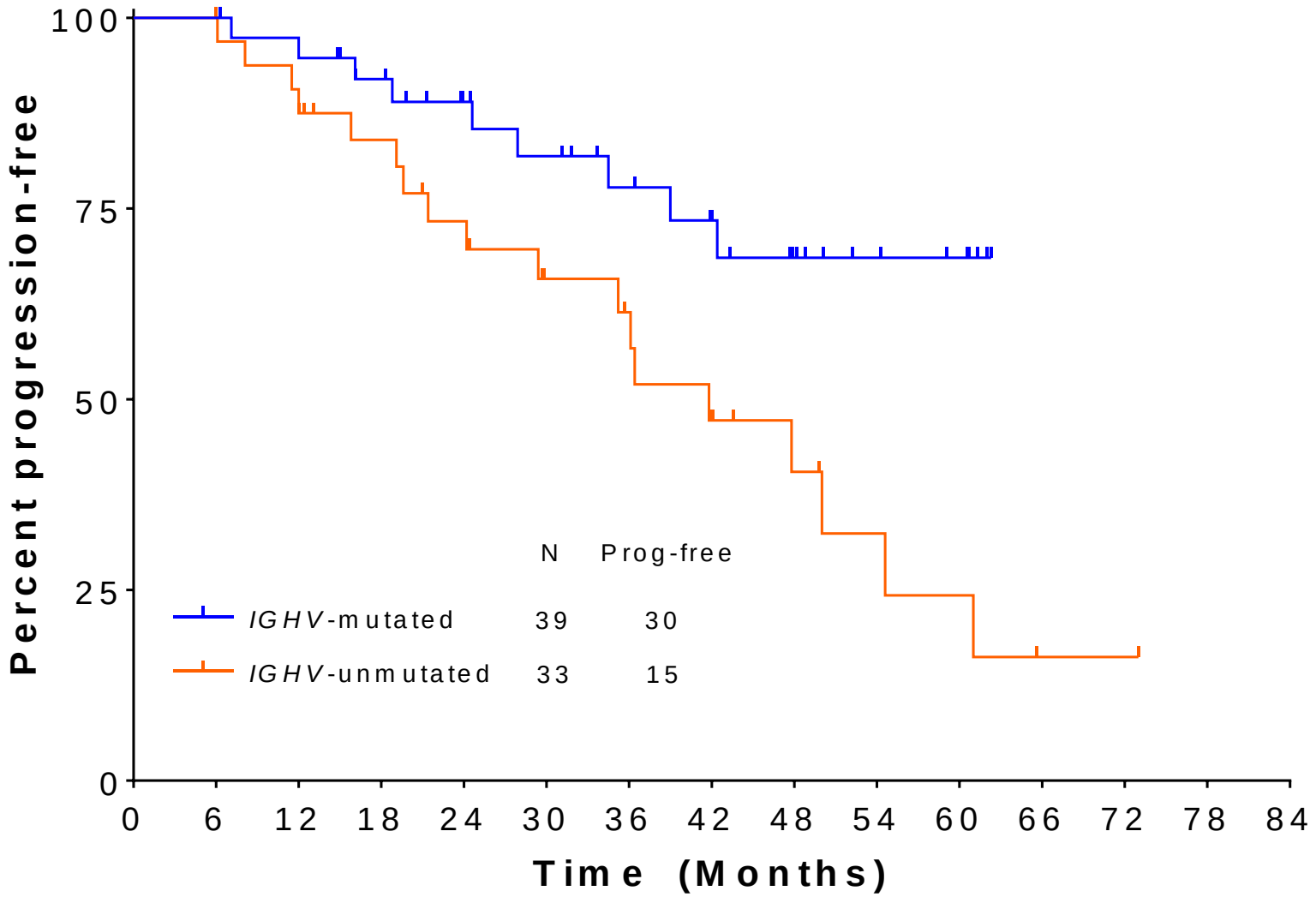
Thompson PA, et al. Leukemia. 10.1038/s41375-018-0132-y, 2018.

Time-to-Blood MRD4 Re-emergence Among BM U-MRD4 at EOT



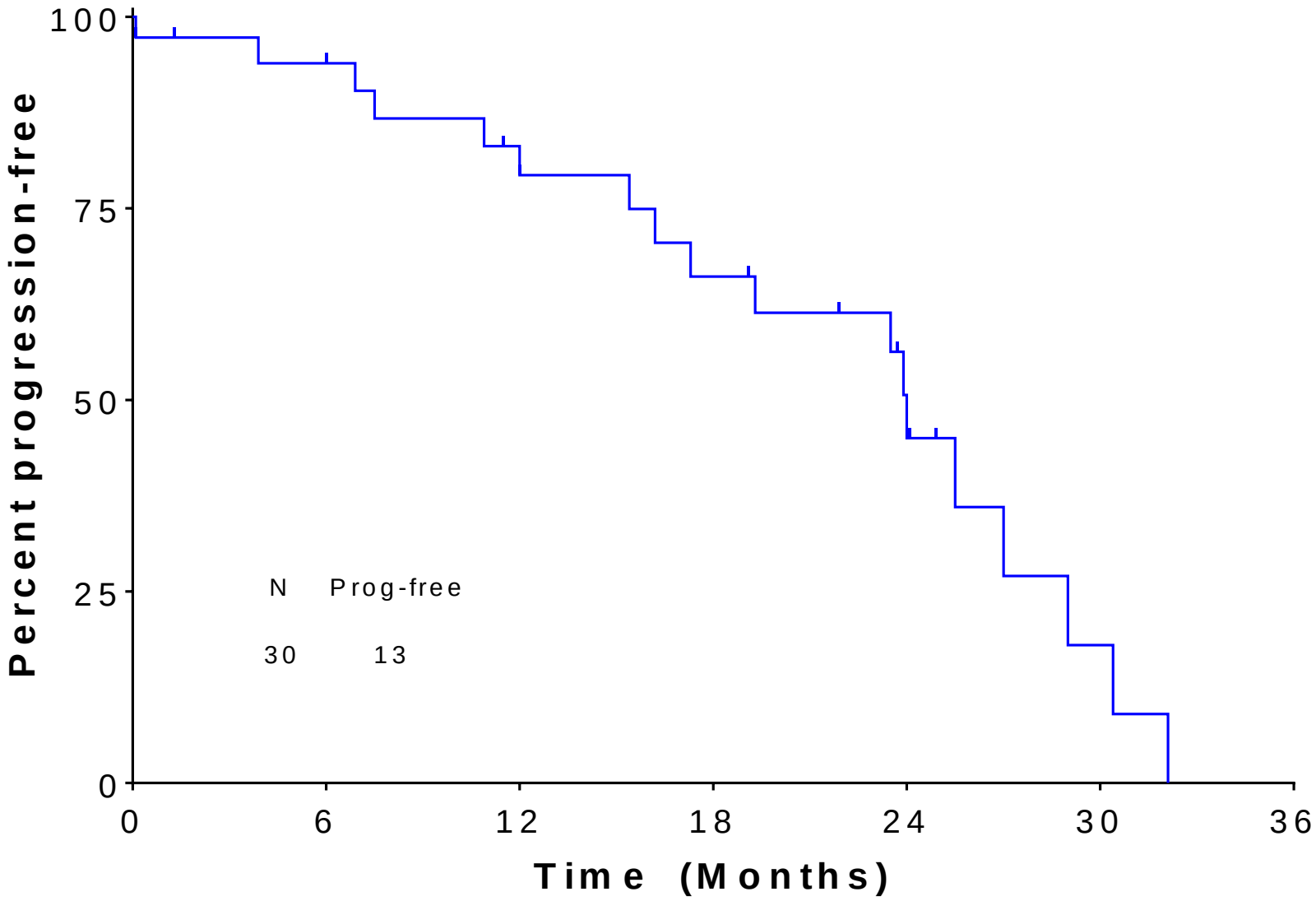
Thompson PA, et al. Leukemia. 10.1038/s41375-018-0132-y, 2018.

Time-to-Blood MRD4 Re-emergence by *IGHV*-mutation Status



Thompson PA, et al. Leukemia. 10.1038/s41375-018-0132-y, 2018.

Time-to-Progression After Blood MRD4 Re-emergence

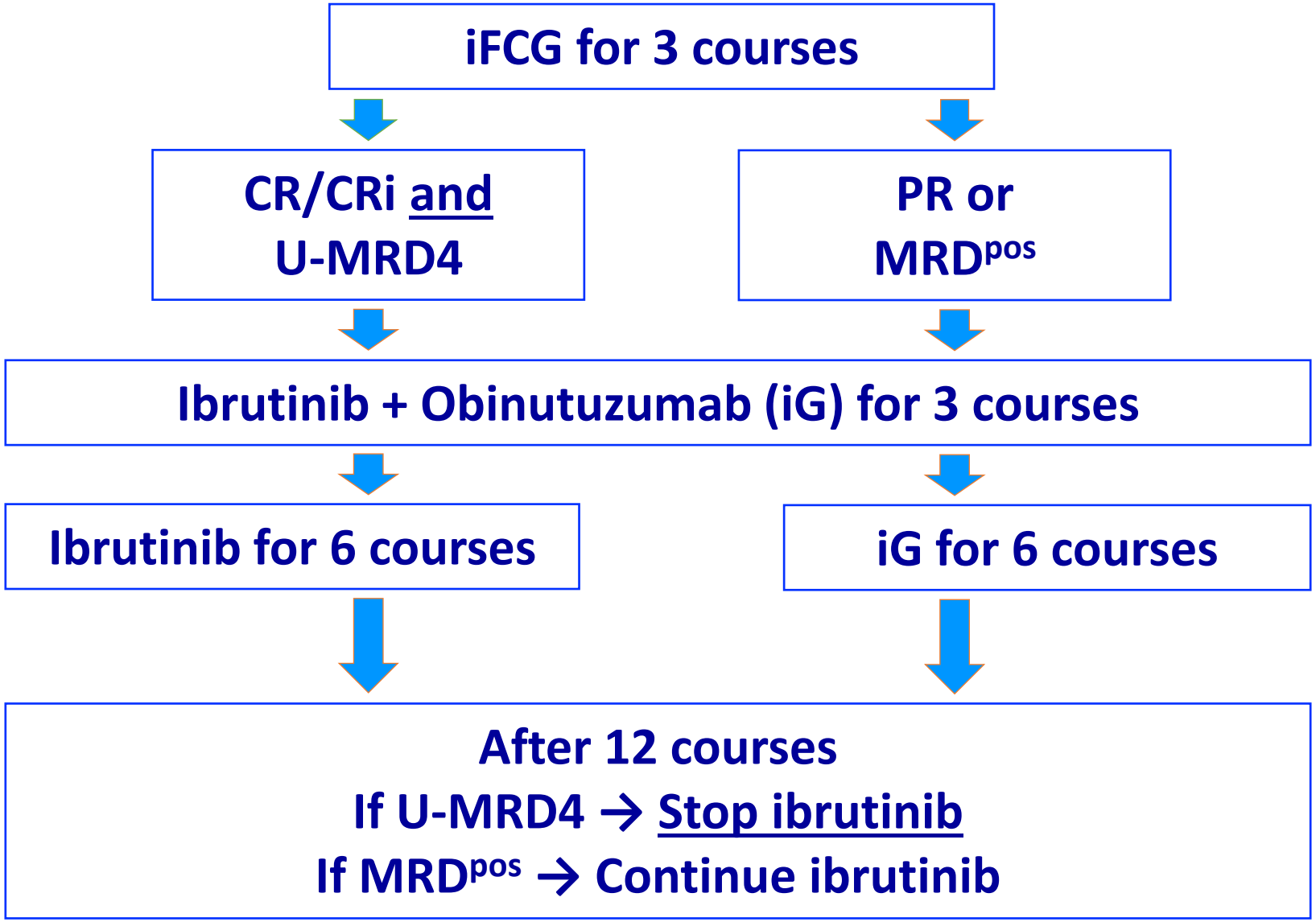


Thompson PA, et al. Leukemia. 10.1038/s41375-018-0132-y, 2018.

iFCG Clinical Trial (Protocol 2015-0281)

- Investigator-initiated Phase II trial
- iFCG regimen
  - **I**brutinib
  - **F**ludarabine
  - **C**yclophosphamide
  - Obinutuzumab (**G**A101)
- First-line treatment
- *IGHV*-M CLL; no del(17p) / m-*TP53*
- Primary endpoint
  - CR/CRi and BM U-MRD4 after C3 iFCG

iFCG: Study Design



iFCG: Baseline Characteristics

		N (%) or median [range] N=43
Age		60 [25-71]
Gender, M		33 (77)
ALC, K/µL		49.3 [1.5-208]
Platelets, K/µL		120 [62-292]
Hb, g/dL		11.8 [8.5-15.6]
B2M, mg/L		2.6 [1.3-8.1]
FISH	Del(13q)	29 (68)
	Trisomy 12	7 (16)
	Negative	6 (14)
	Del(11q)	1 (2)
Cytogenetics (n=37)	Diploid	25 (68)
Mutations (n=37)	MYD88	5 (14)
	SF3B1	3 (8)
	NOTCH1	1 (3)

Jain, N et al. ASH 2017, Abstract #495

iFCG: Responses after Course 3 (n=42)

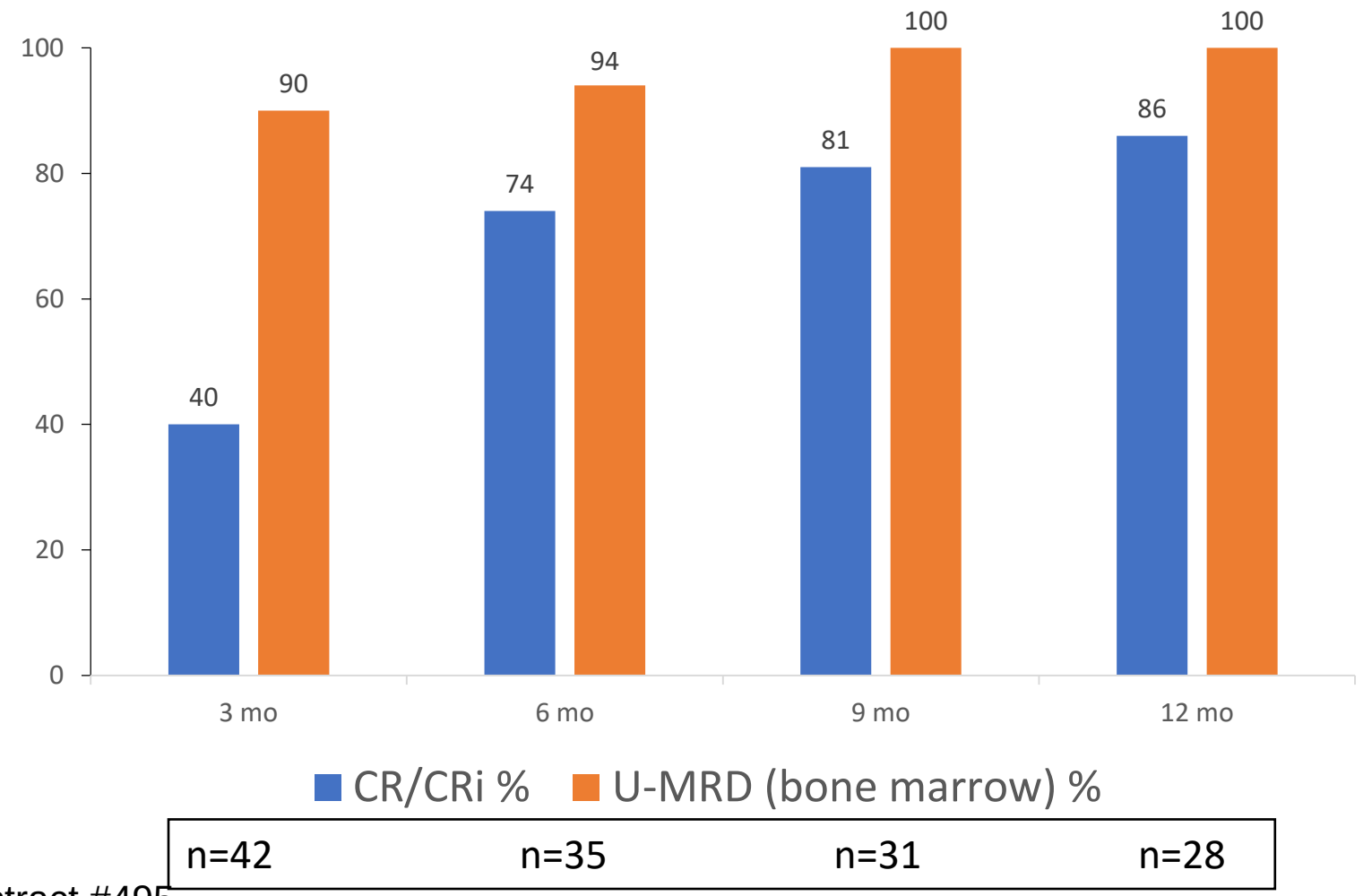
	After 3 courses of iFCG	
	n=42 (%)	BM U-MRD4 (%)
ORR	42 (100)	38/42 (90)
CR/CRi	17 (40)	17/17 (100)
PR	25 (60)	21/25 (84)

BM U-MRD4 after 3 courses: iFCG 90% *vs.* FCR 26%

Jain, N et al. ASH 2017, Abstract #495

iFCG: Responses Improve with Time

iFCG ➡ Ibrutinib + obinutuzumab ➡ Ibrutinib +/- obinutuzumab

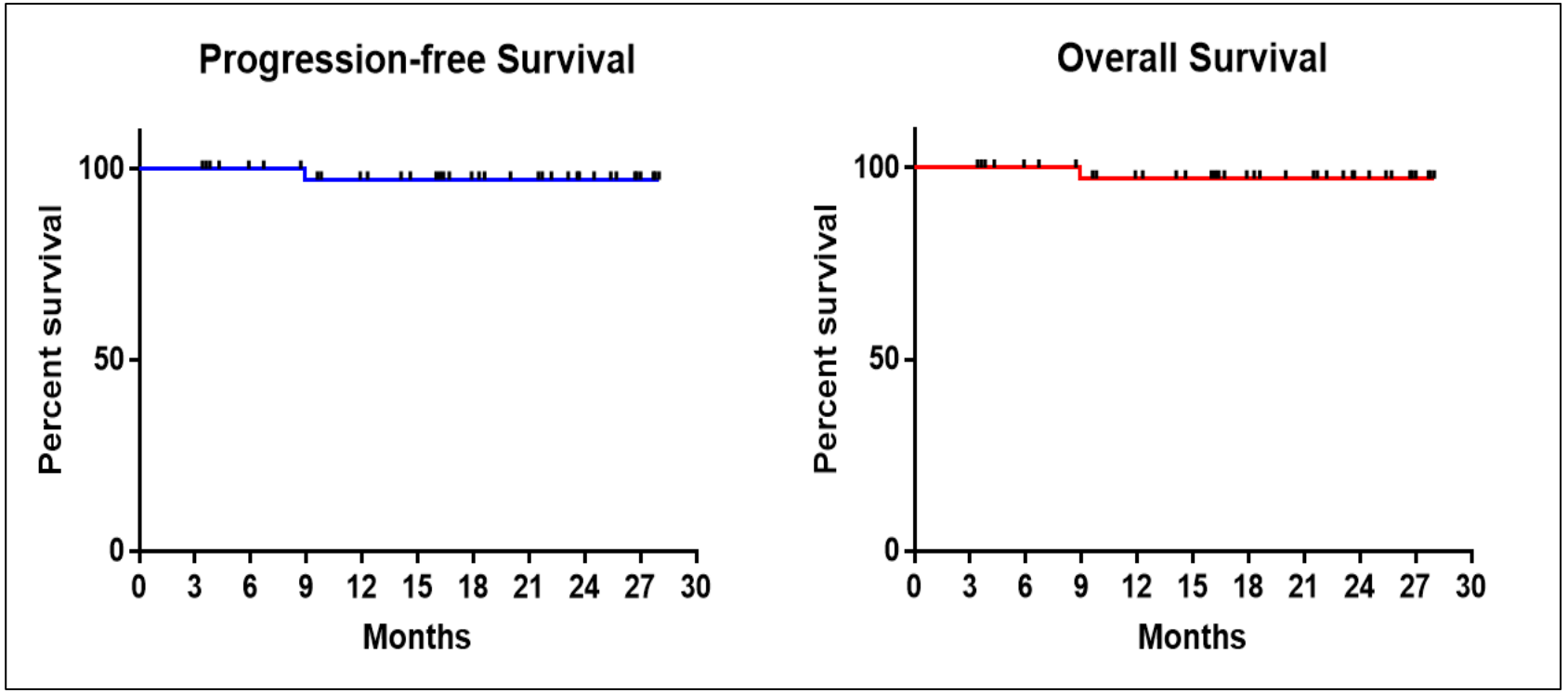


Jain, N et al. ASH 2017, Abstract #495

iFCG: Treatment Discontinuation at 1 Year

- 28 pts reached 1-yr
- All 28 with BM U-MRD4 (24 CR/CRi, 4 PR) and discontinued ibrutinib
- All remain blood U-MRD4
- Median follow-up after d/c ibrutinib 10.1 mos (range 1.9-16.7)
- BM and blood MRD6 data ASH 2018

iFCG: PFS and OS (N=43)

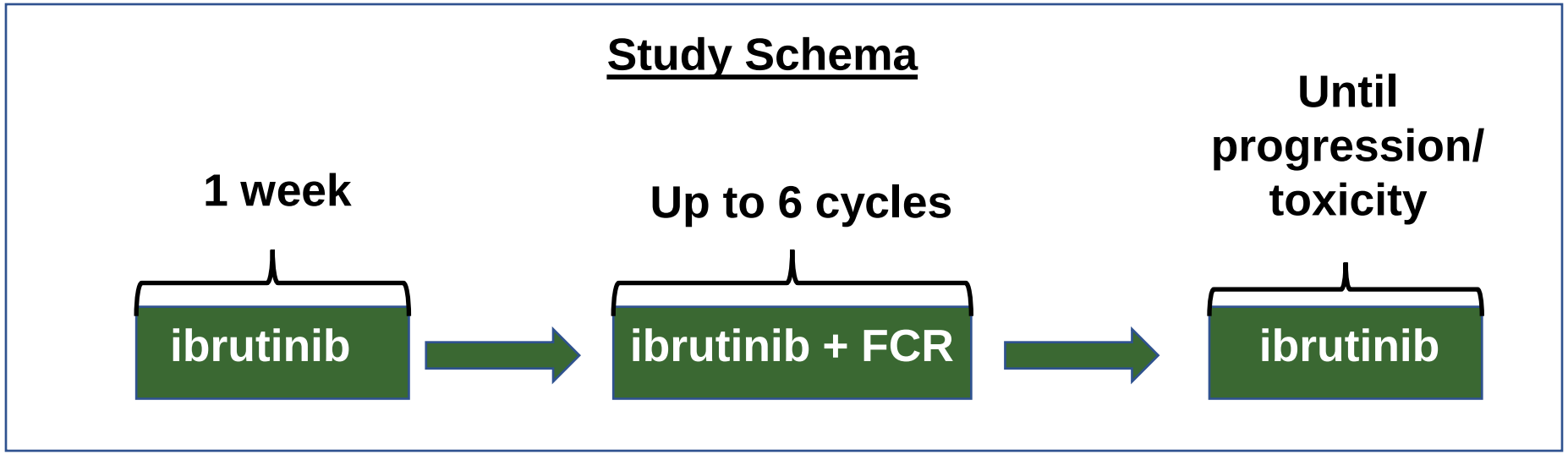


No patient had disease progression or MRD relapse

iFCG: Pertinent Adverse Events

- G3-4 neutropenia 46%
- G3-4 thrombocytopenia 40%
- Neutropenic fever 10%
- Atrial fibrillation 7%

A phase II investigator-initiated study of ibrutinib + FCR for younger, previously untreated patients with CLL (iFCR)



G-CSF and PCP/HSV/VZV prophylaxis mandatory for all patients

- Ibrutinib dosed at 420 mg daily
- FCR dosed as per standard of care
- Toxicity assessments by CTCAE v4.03 and IW-CLL hematologic criteria
- Response evaluations: after 3 cycles, 2 mo. after final FCR, then q6 mo.

Davids, M et al. ASH 2017, Abstract #496

iFCR: Primary Efficacy Analysis (all 35 patients evaluable for 1º endpoint)

	C4D1	Primary Endpoint (2 mo. post-FCR)	Best Response
ORR	100% (35/35)	100% (35/35)	100% (35/35)
PR	74% (26/35)	60% (21/35)	37% (13/35)
CR/CRi	26% (9/35)	40% (14/35)	63% (22/35)
CR with BM U-MRD4	21% (7/34)	37% (13/35)*	57% (20/35)
BM U-MRD4	44% (15/34)	77% (28/35)	83% (29/35)

- Median time to best response: 95 days (range 85-452)
- 91% (20/22) of CR patients are BM U-MRD4
- 69% (9/13) of PR patients are BM U-MRD4, most w/ residual LN <2.5 cm

Davids, M et al. ASH 2017, Abstract #496

***primary endpoint**

Responses in *IGHV*-M after C6

Trial	Regimen	N	CT scan	CR / CRi %	BM U-MRD4, %
MDACC	FCR x6	88	No	83	51
MDACC	FCR x6	82	No	66	56
CLL8	FCR x6	113	No	50	50
CLL10	FCR x6	123	Yes	39	62
DFCI	iFCR x6	12	Yes	58	92
MDACC	iFCG x3 → iG x3	35	Yes	74	94

Keating, JCO 2005; Tam, Blood 2008; Thompson, Blood 2016; Strati, Blood 2014; Hallek, Lancet 2010; Eichhorst, Lancet Onc 2016; Personal communication Barbara Eichhorst, GCLLSG; Davids, ASH 2017

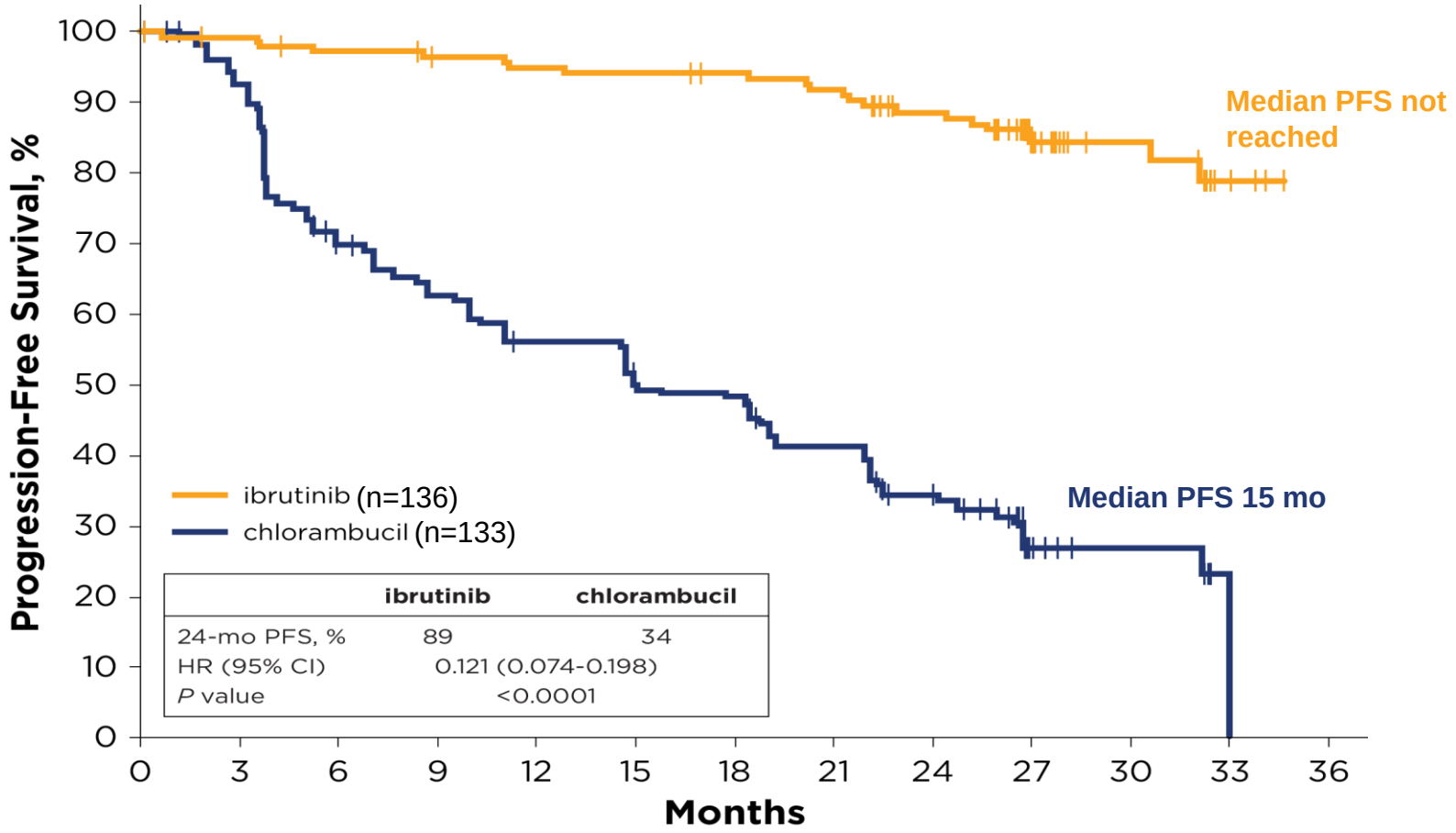
Can combined targeted therapy achieve the same for *IGHV*-M, including “older”?

Possibly ……. but need more follow up with new treatments

Del(17p) / M-*TP53*
&
Older, unfit
&
Young, fit with *IGHV*-UM

Goals: shorten fixed duration Tx;
increase U-MRD4; no clonal evolution

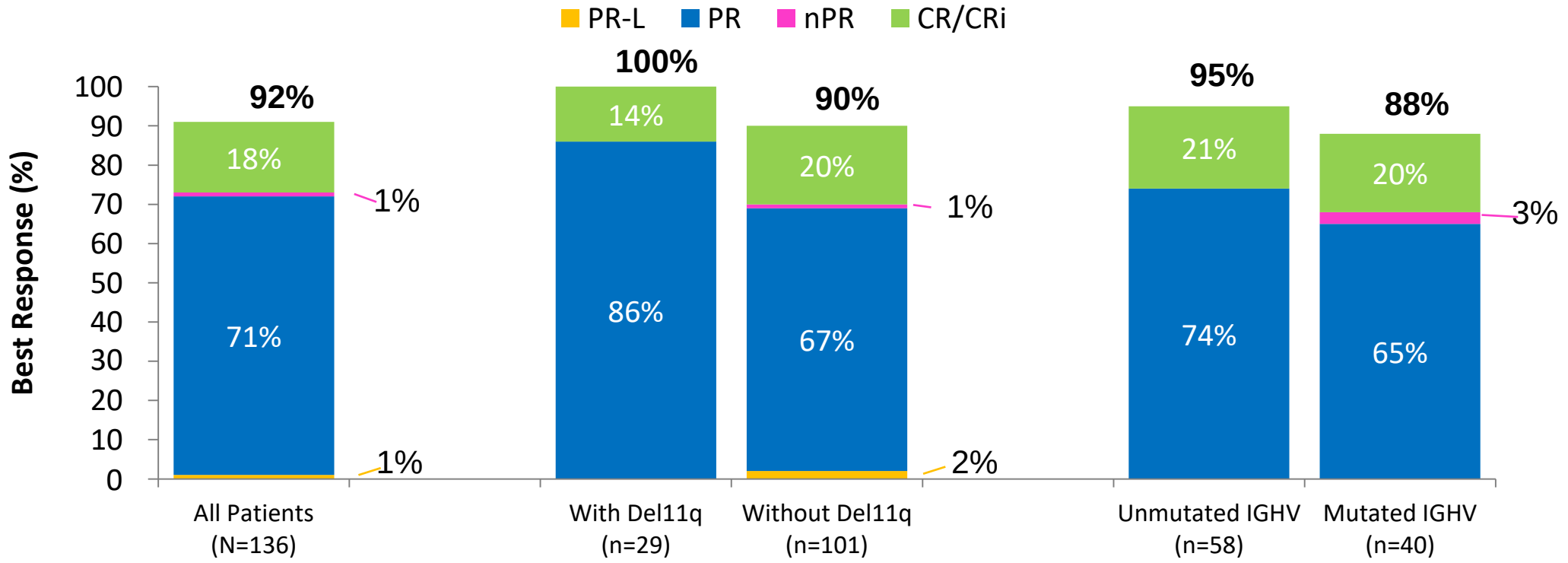
RESONATE-2: First-line, Age >65yrs
Ibrutinib Prolonged PFS Over Chlorambucil



- 88% reduction in the risk of progression or death for patients randomized to ibrutinib
- Subgroup analysis of PFS revealed benefit was observed across all sub-groups

Barr et al. ASH 2016, Abstract 234

RESONATE-2: ORR in the Ibrutinib* Arm



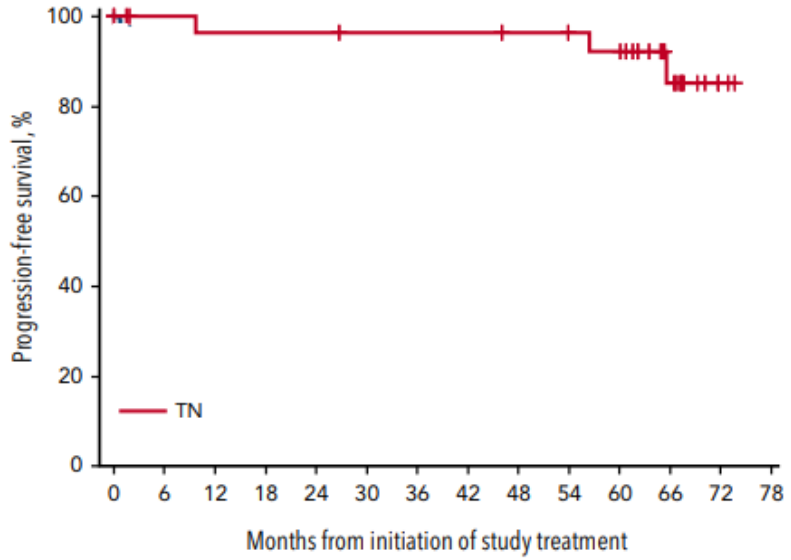
- Ibrutinib CR rates continue to improve over time: increasing from 7% at 12 months to 15% at 24 months to 18% with median follow-up of 29 months.

**Response rates with chlorambucil are the same as in the original report (Burger NEJM 2015)*

CR, complete response; CRi, CR with incomplete blood count recovery.

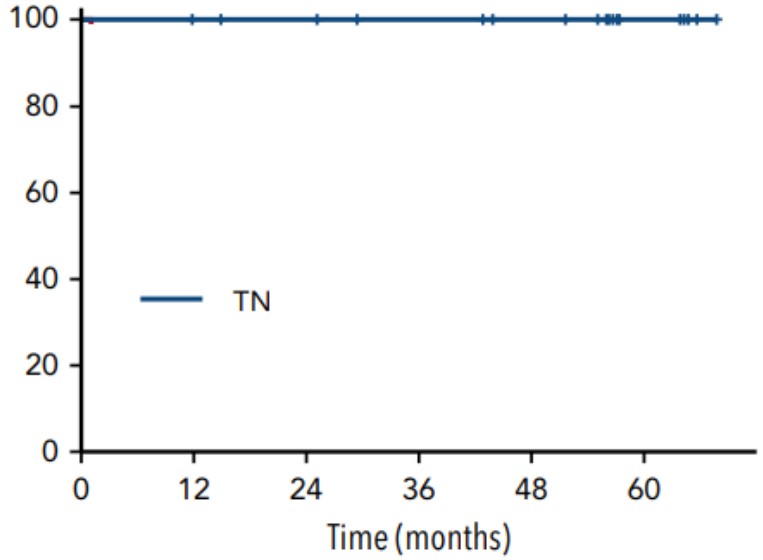
Barr et al. ASH 2016, Abstract 234

First-line Ibrutinib
PFS 5-yr



- N=31
- ≥65 yr (median age 71)
- 6% del(17p)

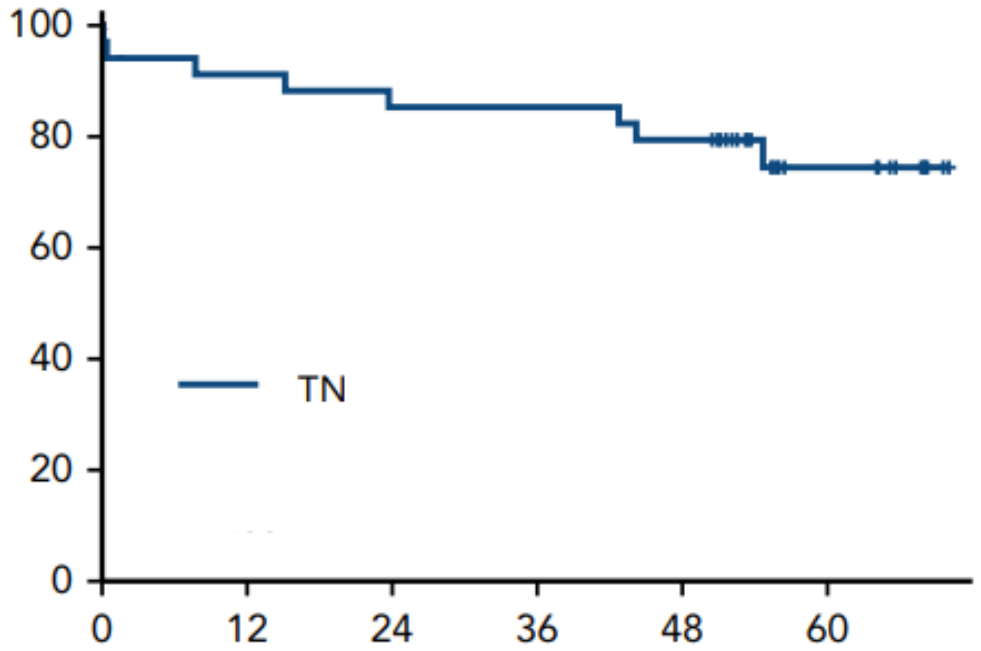
O'Brien, Blood. 2018;131(17):1910-1919.



- N=18
- ≥65 yr (median age 69)
- No del(17p)

Ahn, Blood. 2018;131(21):2357-2366.

First-line Ibrutinib
PFS 5-yr, del(17p)



- N=35
- 100% del(17p) or *TP53* mut

Ahn, Blood. 2018;131(21):2357-2366.

Ibrutinib has impressive PFS in first-line setting….with continuous treatment

Indefinite Therapy

Low CR (10% 1-yr, 29% 5-yr)

U-MRD4: EXTREMELY RARE

Rationale for Combination of Ibrutinib and Venetoclax

- Non-overlapping mechanism of action
- Non-overlapping toxicity profile
- Act on CLL cells in different compartments
- Synergy in preclinical studies

Cervantes-Gomez, Clin Cancer Res. 2015; Deng, Leukemia 2017; Slinger, ASH 2017.

Ibrutinib + Venetoclax
Clinical Trial (2015-0860)

- Investigator-initiated phase II trial
- Patients with a diagnosis of CLL/SLL
  - **Cohort 1**: Relapsed/refractory CLL (n=40→80 pts)
  - **Cohort 2**: Untreated with at least one high-risk feature (n=40→80→120 pts)
    - del(17p) or M-*TP53*
    - del(11q)
    - *IGHV*-UM
    - ≥65 yrs

IBR + VEN
Treatment Schema (2015-0860)

	C1	C2	C3	C4 ---> C27
Ibrutinib	420mg daily	420mg daily	420mg daily	420mg daily
Venetoclax	-	-	-	20mg daily x1 wk then; 50mg daily x1 wk then; 100mg daily x1 wk then; 200mg daily x1 wk then; 400mg daily continuous

Duration of Therapy

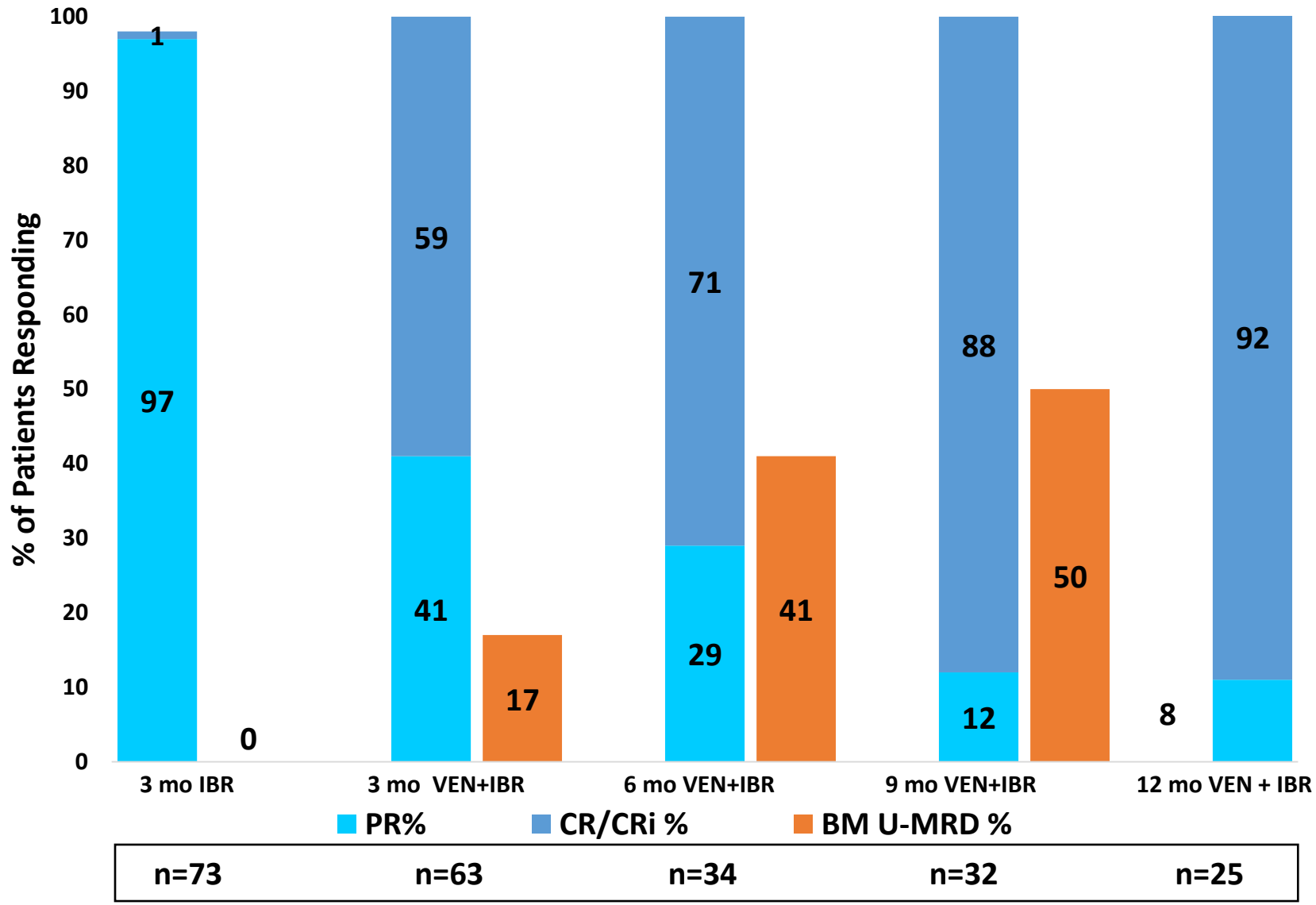
- VEN: 24 cycles of combination
- IBR: 24 cycles of combination (U-MRD4)
  (For MRD-positive: IBR continues until PD)

Primary endpoint: CR/CRi

Baseline Characteristics, First-line Cohort (N=80)

		Number (%) or median [range]
Age, years		65 [26-83]
≥65		43 (54)
≥70		24 (30)
Gender, Male		57 (71)
Labs at start of study	ALC, x 10^9/L	75.6 [1.14-338]
	Hemoglobin, g/dL	11.6 [7.7-15.8]
	Platelet count, x 10^9/L	130 [28-334]
	Serum B2M, mg/L	3.5 [1.7-13.7]
FISH	Del(17p)	14 (18)
	Del(11q)	20 (25)
	Trisomy 12	17 (21)
	Neg	10 (12)
	Del(13q)	19 (24)
IGHV status	Unmutated	63/76 (83)
	Mutated	13/76 (17)
Cytogenetics	Complex	12/78 (15)
	Diploid	32/78 (41)
Gene mutation	*TP53*	11/79 (14)
	NOTCH1	22/79 (28)
	SF3B1	18/79 (23)
	BIRC3	5/79 (6)
ZAP-70 positive		60/79 (76)
CD38 positive		42/80 (53)

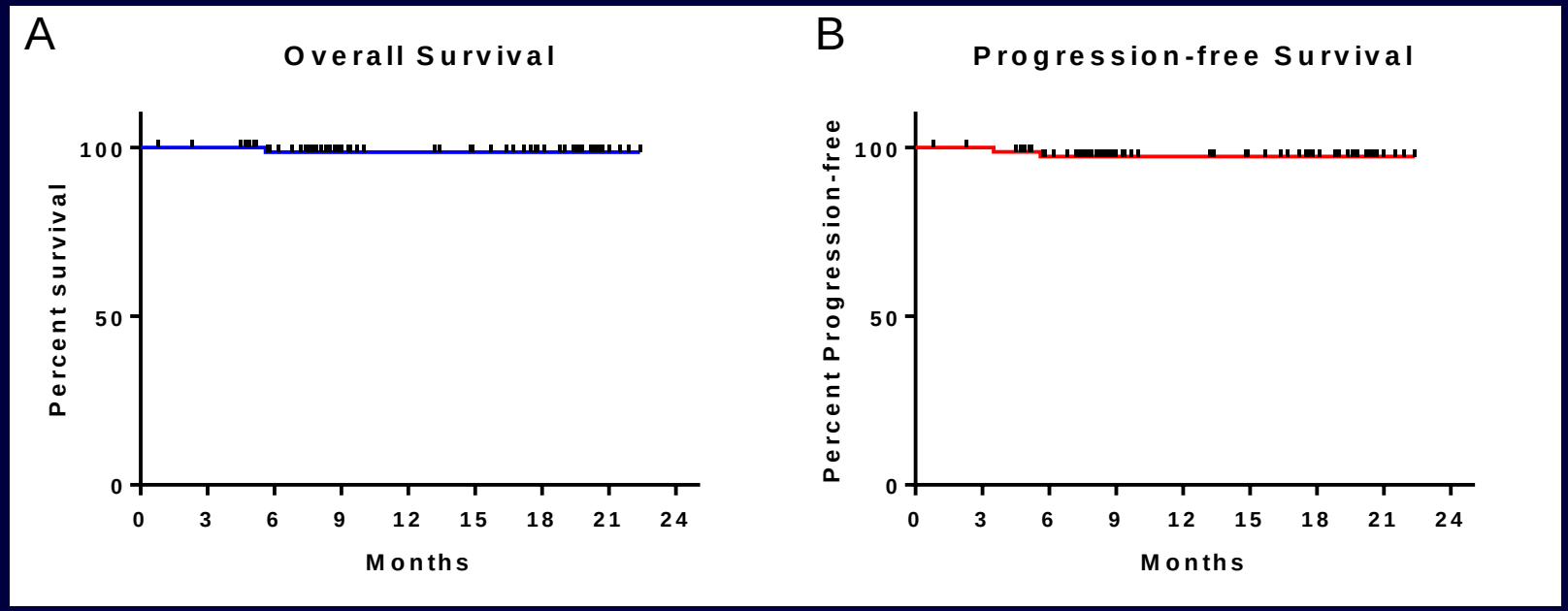
IBR + VEN: Response: First-line Cohort



IBR + VEN: Bone Marrow U-MRD4 by Baseline Characteristics First-line Cohort

		BM U-MRD4 Remission, n (%)			
		Venetoclax + Ibrutinib Combination			
		3 months	6 months	9 months	12 months
All Patients		11/63 (17)	14/34 (41)	16/32 (50)	17/25 (68)
Age, years	<65	3/28 (11)	5/18 (28)	6/16 (38)	7/12 (58)
	≥65	8/35 (23)	9/16 (56)	10/16 (63)	10/13 (77)
	≥70	4/19 (21)	3/5 (60)	4/5 (80)	4/5 (80)
Sex	Female	1/18 (6)	3/8 (38)	3/8 (38)	4/5 (80)
	Male	10/45 (22)	11/26 (42)	13/24 (54)	13/20 (65)
FISH	del(17p)	1/12 (8)	2/6 (33)	4/6 (67)	4/5 (80)
	del(11q)	4/14 (29)	5/7 (71)	5/7 (71)	5/7 (71)
	Trisomy 12	2/13 (15)	1/4 (25)	1/4 (25)	1/2 (50)
	Negative	0/8 (0)	2/5 (40)	2/4 (50)	2/3 (67)
	del(13q)	4/16 (25)	4/11 (36)	4/10 (40)	4/7 (57)
Cytogenetics	Complex	2/11 (18)	2/4 (50)	3/4 (75)	2/2 (100)
IGHV status	Unmutated	10/52 (19)	12/25 (48)	12/23 (52)	13/18 (72)
	Mutated	1/8 (13)	2/6 (33)	2/6 (33)	2/5 (40)
Gene mutation	*TP53*	0/9 (0)	1/4 (25)	2/4 (50)	3/4 (75)
	NOTCH1	2/16 (13)	4/12 (33)	4/11 (36)	6/9 (67)
	SF3B1	3/12 (25)	4/9 (44)	3/8 (38)	3/6 (50)

PFS and OS
First-line Cohort (2015-0860)

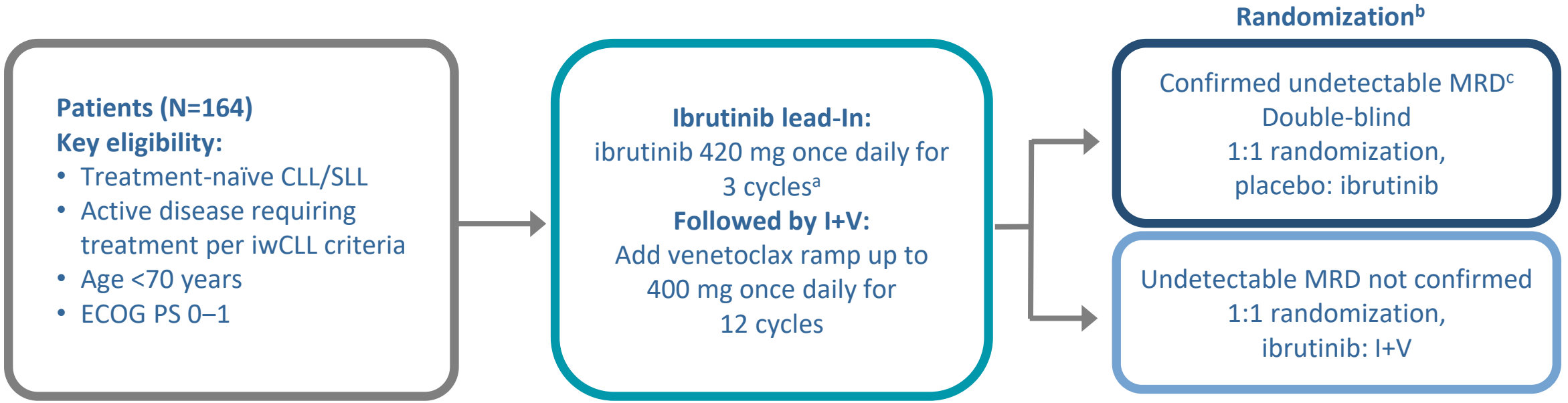


- One pt (UM-*IGHV*, *NOTCH1* mutation) developed DLBCL transformation
- No pt with CLL progression

Adverse Event Profile (2015-0860)

- Easy bruising, arthralgia and diarrhea were the most common non-hematological AEs
- Grade 3-4 neutropenia 48%
- Grade 3-4 thrombocytopenia 2%
- Neutropenic fever 5%
- Atrial fibrillation 14%

Phase 2 CAPTIVATE Study Design (NCT02910583)

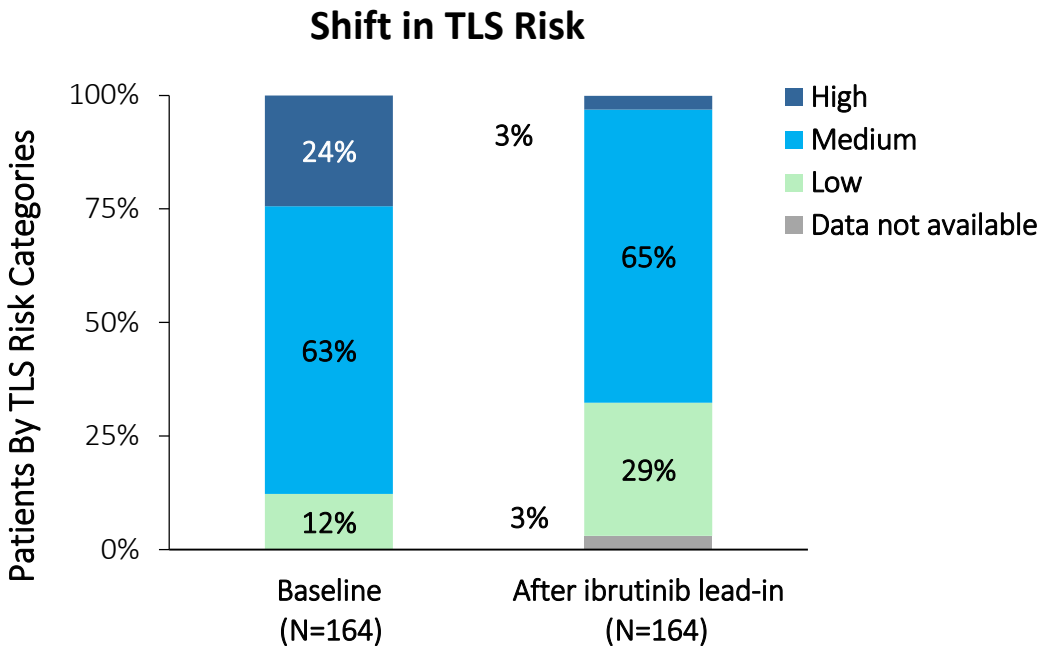


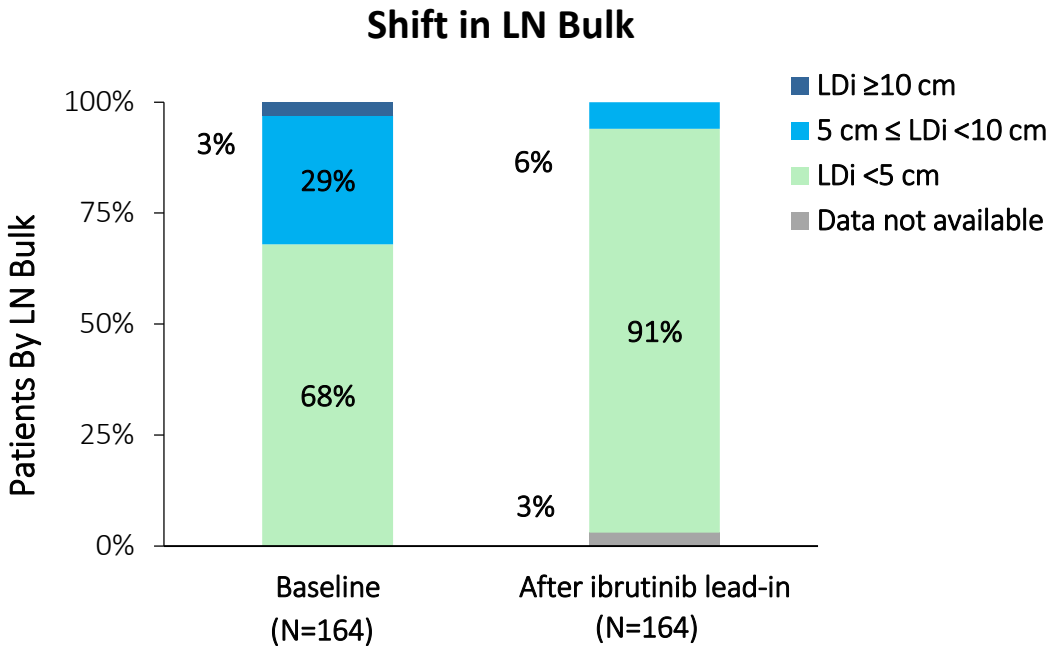
[a]1 cycle = 28 days.
[b]Stratified by *IGHV* mutation status.
[c]Confirmed undetectable MRD for randomization defined as undetectable MRD serially over at least 3 cycles in peripheral blood (PB), and undetectable MRD in both PB and BM.

Study Populations:

- MRD cohort (N=164): exposure and safety analysis
  - Safety Run-in: first 14 patients completed C15 treatment (12 cycles of I+V); no dose-limiting toxicities (DLT) or clinical TLS during first 6 weeks of I+V combination
  - First 30 patients completed C9 treatment (6 cycles of I+V) for MRD evaluation
- Fixed Duration cohort (N=159): separate cohort; analysis not shown

3 Cycles of Ibrutinib Lead-in Reduces TLS Risk and Bulky Disease

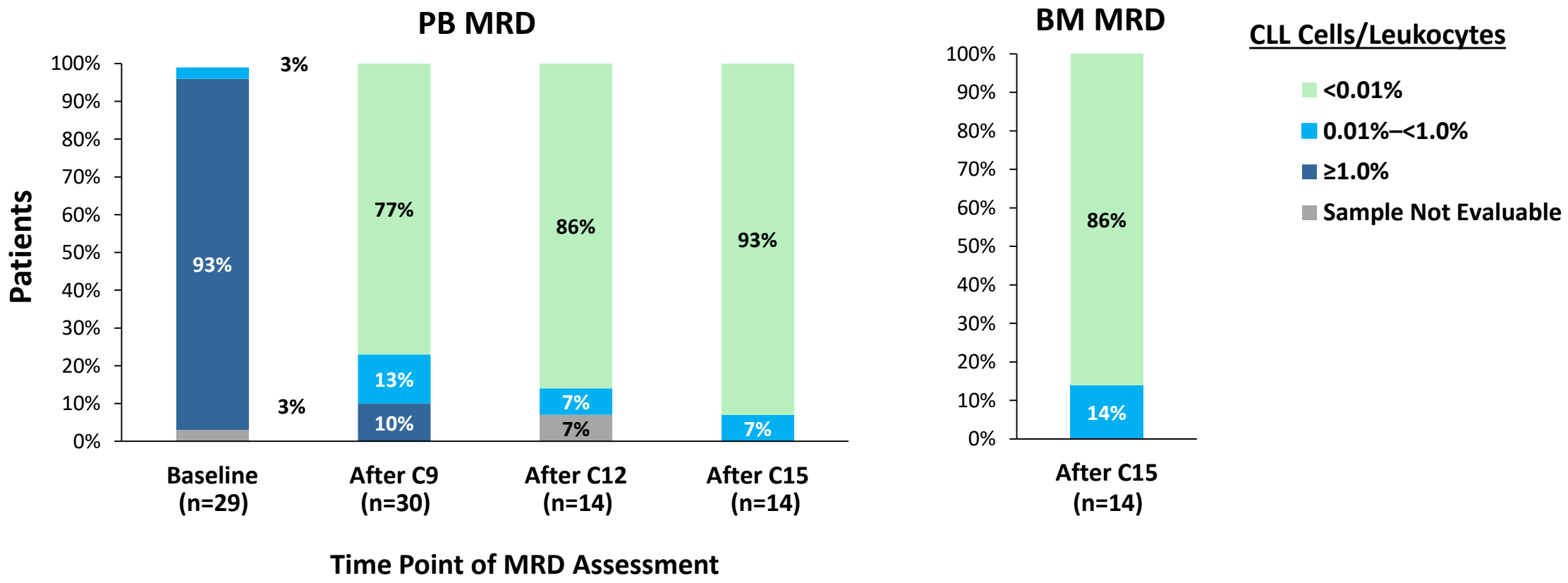




- After 3 cycles of ibrutinib lead-in:
  - 36 of 40 patients (90%) with high baseline TLS risk shifted to medium or low risk; hospitalization avoided in 30 patients
  - 7 of 37 patients (19%) with medium baseline TLS risk plus CrCl <80 mL/min shifted to low risk; no hospitalization in 29 patients
- No patients developed clinical TLS; laboratory TLS reported as AEs in 2 patients (neither met Howard criteria)
  - 1 additional lab TLS not reported as AE but met Howard criteria

ASCO 2018, 1142 Wierda et al.

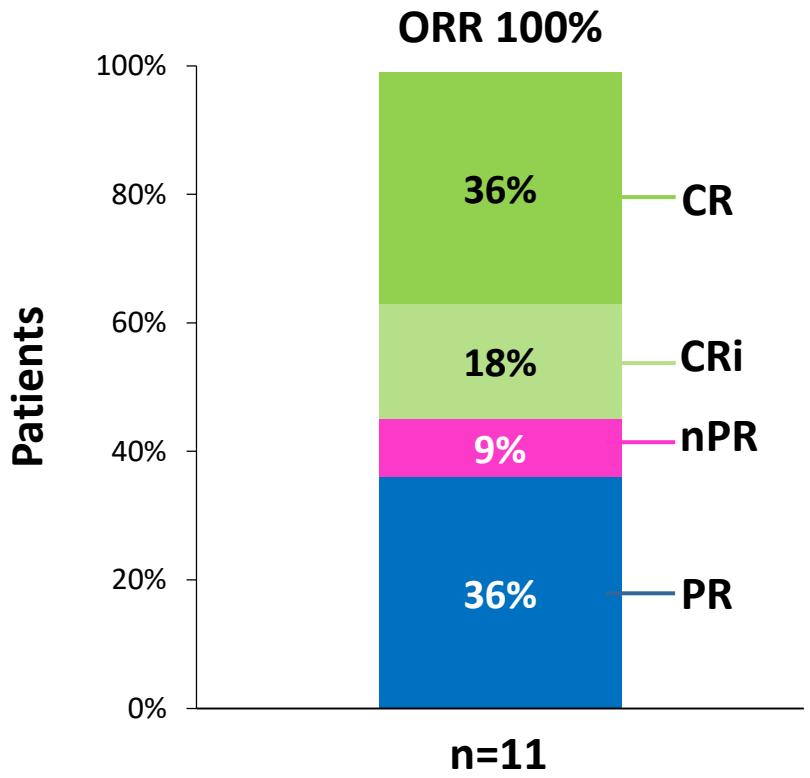
Early Undetectable MRD Responses Sustained Over Time



- High rates of undetectable MRD (77%) in PB after 6 cycles of I+V
- Confirmed undetectable MRD in 11 of 14 patients (79%) after cycle 15

ASCO 2018, 1142 Wierda et al.

Deep Responses Achieved With 12 Cycles I+V With Undetectable MRD in PB and BM



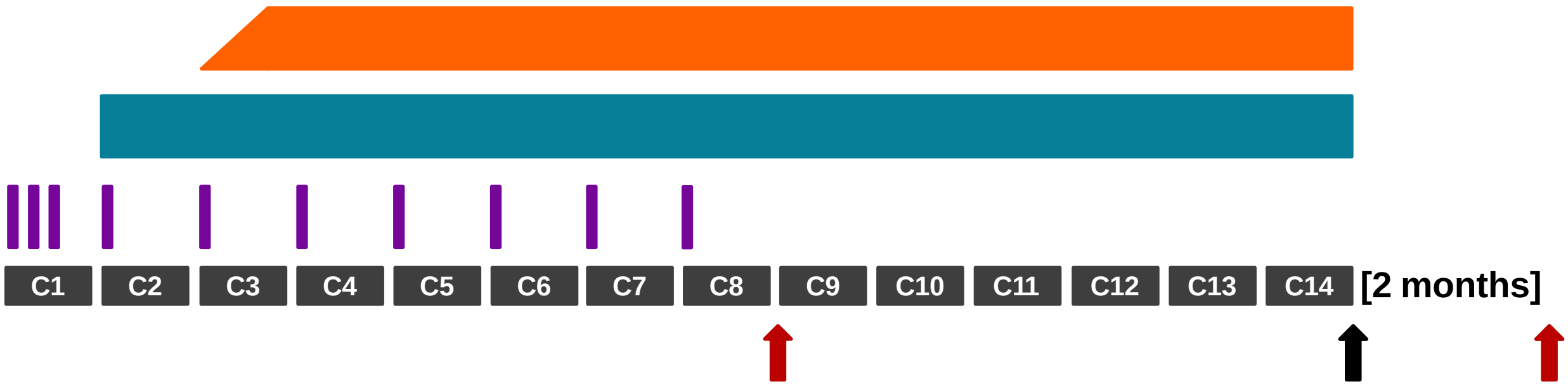
MRD and Full ORR Assessments to Date (n=11)	CR/CRi (n=6)	PR/nPR (n=5) [a]
Confirmed undetectable MRD (n=9)	6/6[b]	3/5
Detectable MRD (n=2)[c]	0/6	2/5

[a]4/5 patients had LN >1.5 cm, but ≤2.5 cm.
[b]Includes 1 patient with variant CLL.
[c]CLL cells <1% in these 2 patients.

- Clinical response assessment in 11/14 patients who completed 12 cycles of I+V
  - 6/11 (55%) CR/CRi and 5/11 (45%) nPR/PR
- Confirmed undetectable MRD ($<10^{-4}$) in all patients with CR/CRi
- CR/CRi in 2/2 patients with del17p and 4/9 patients without del17p

ASCO 2018, 1142 Wierda et al.

IBR + VEN + Obin: Study Diagram



Obinutuzumab 1000 mg IV

Ibrutinib 420 mg daily PO*

Venetoclax 400 mg daily PO

End of Treatment

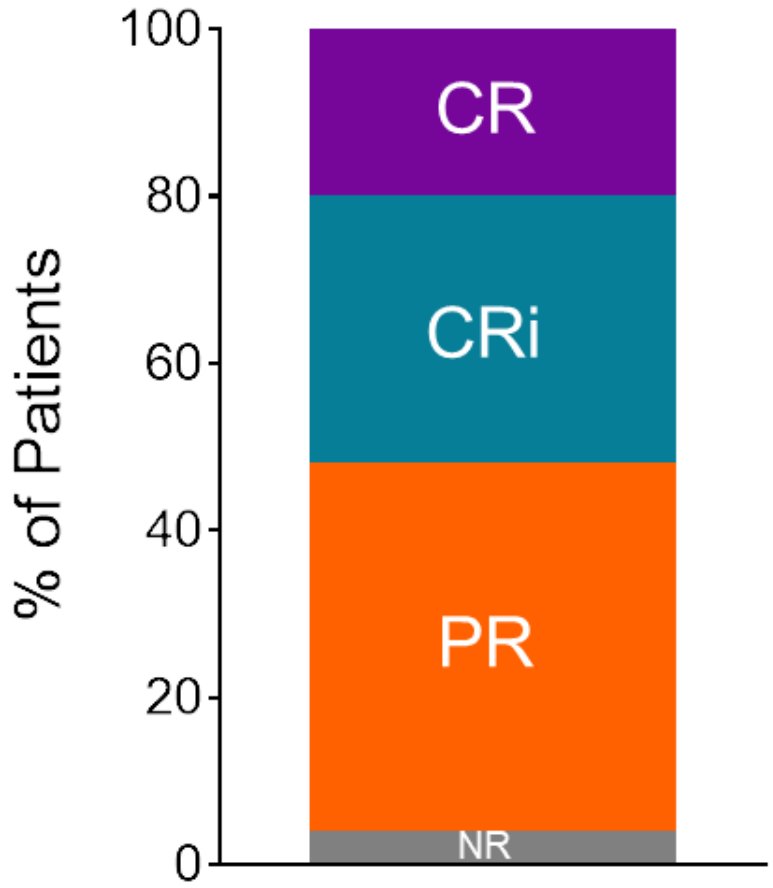
Response assessed
(CT + Bone Marrow Biopsy)

*Patients may continue ibrutinib past C14 at the discretion of the treating investigator

Rogers, K et al. ASH 2017, Abstract #431

Cycle length = 28 days

IBR + VEN + Obin: Mid-point (post-Cycle 8) Responses (n=25)



- **ORR= 96%** (95% CI: 80-100%)

CR	5 (20%)
CRi	8 (32%)
PR	11 (44%)
NR	1 (4%)

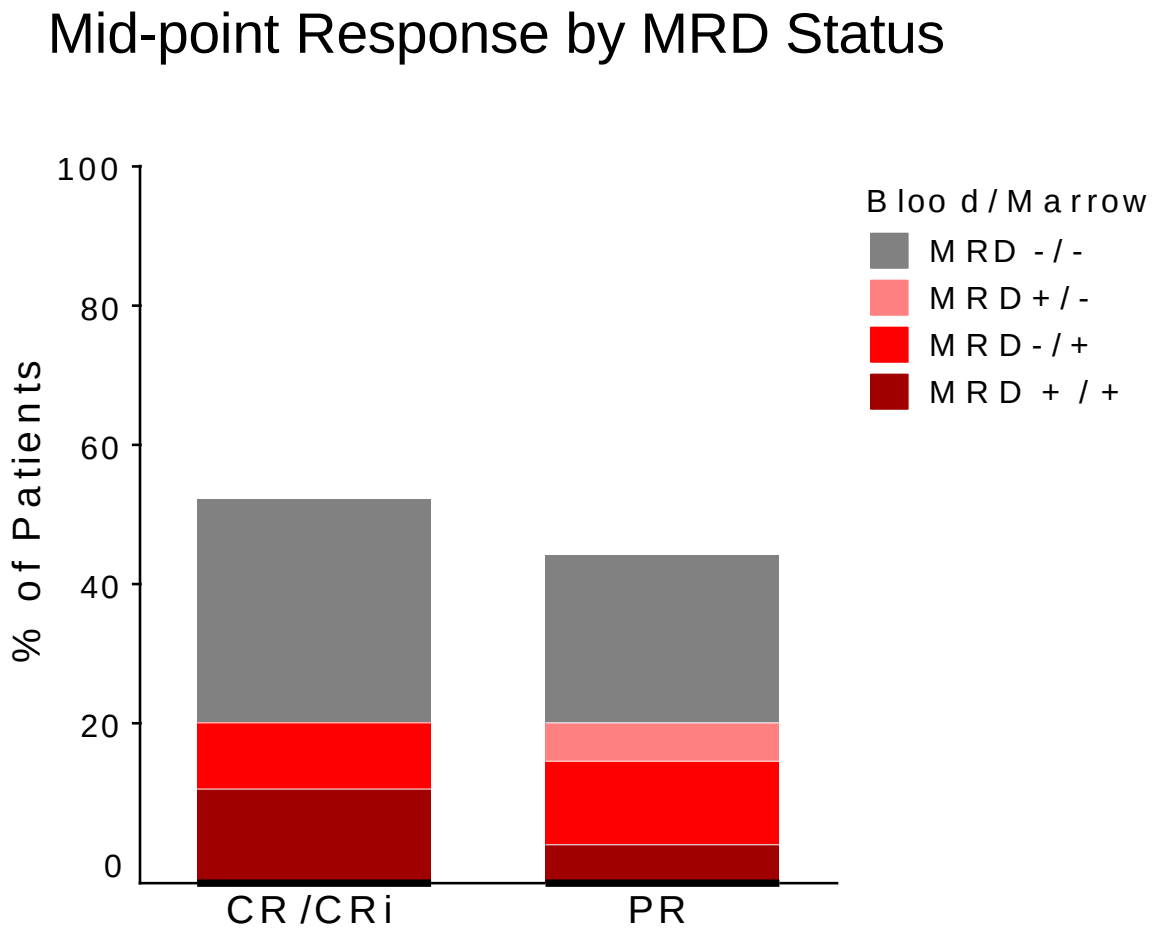
- CRi was due to cytopenias (4/8, 50%) or cytopenias + hypocellular marrow (4/8, 50%)
- 6/11 (55%) PR patients met count and marrow requirements for CR but had LN >1.5cm
- All but 1 patient had no morphologic evidence of CLL in the bone marrow

CR = complete remission, CRi = CR with incomplete marrow recovery, PR = partial remission, NR = not reached

Rogers, K et al. ASH 2017, Abstract #431

IBR + VEN + Obin (post-Cycle 8): Analysis of Minimal Residual Disease (MRD) (n=25)

- MRD was measured by 4-color flow cytometry on blood and bone marrow
- 14/24 (58%) of patients had U-MRD4 in both compartments
  - 8/13 (46%) CR/CRi
  - 6/11 (55%) PR



The limit of MRD detection is >1 x 10-4

Rogers, K et al. ASH 2017, Abstract #431

IBR + VEN + Obin (post-Cycle 8): Hematologic Treatment-Related Adverse Events*

Adverse Event	Grade 1/2 n (%)	Grade 3/4 n (%)	Any Grade n (%)
Thrombocytopenia	12 (48)	9 (36)	21 (84)
Lymphopenia*	11 (44)	8 (32)	19 (76)
Neutropenia	7 (28)	12 (48)	19 (76)
Leukopenia*	10 (40)	9 (36)	19 (76)
Lymphocytosis*	5 (20)	1 (4)	6 (24)
Anemia	4 (16)	0 (0)	4 (16)

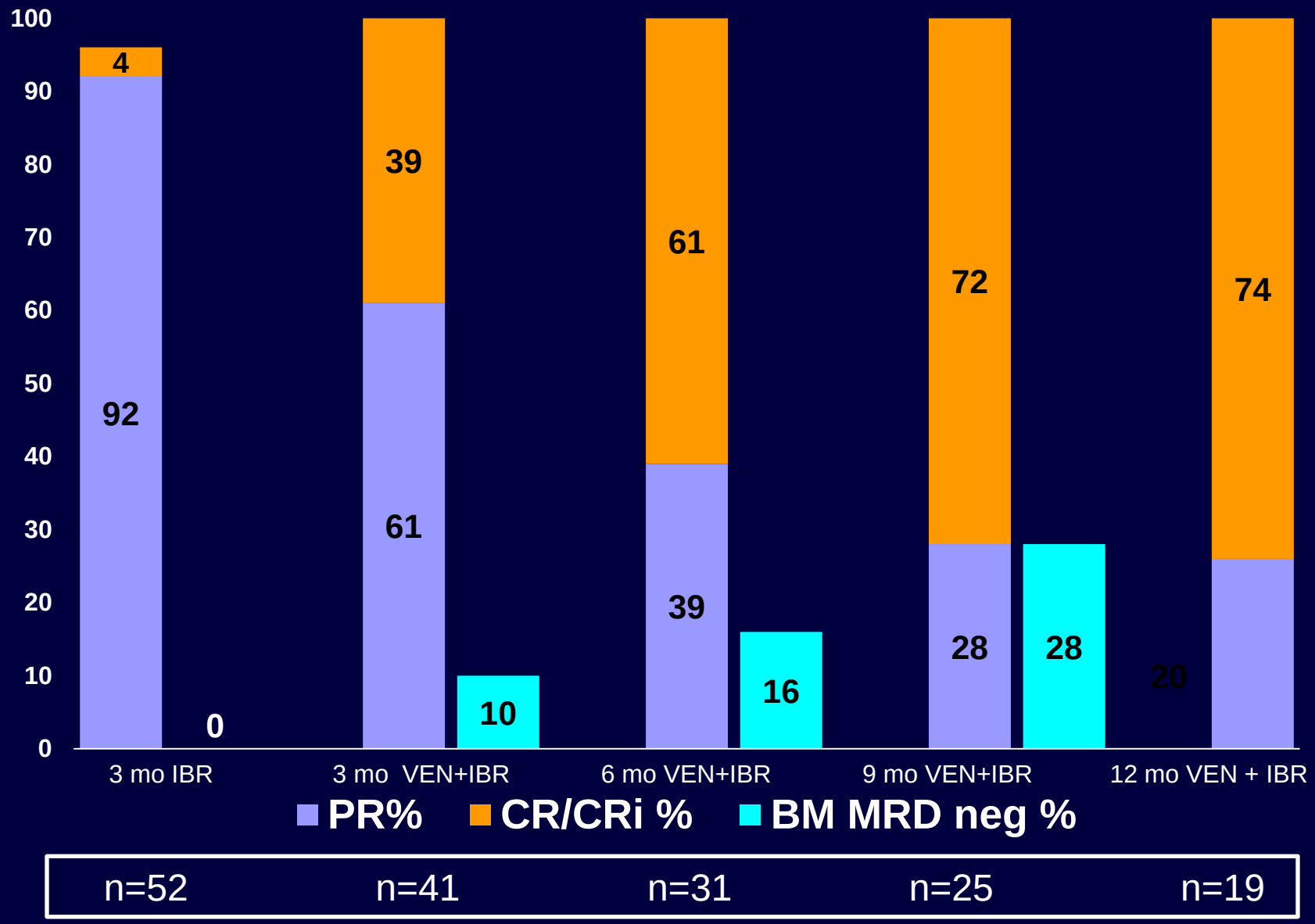
*Anticipated therapeutic drug effect

- Hematologic adverse events were the most frequently reported toxicity
- There were no cases of neutropenic fever

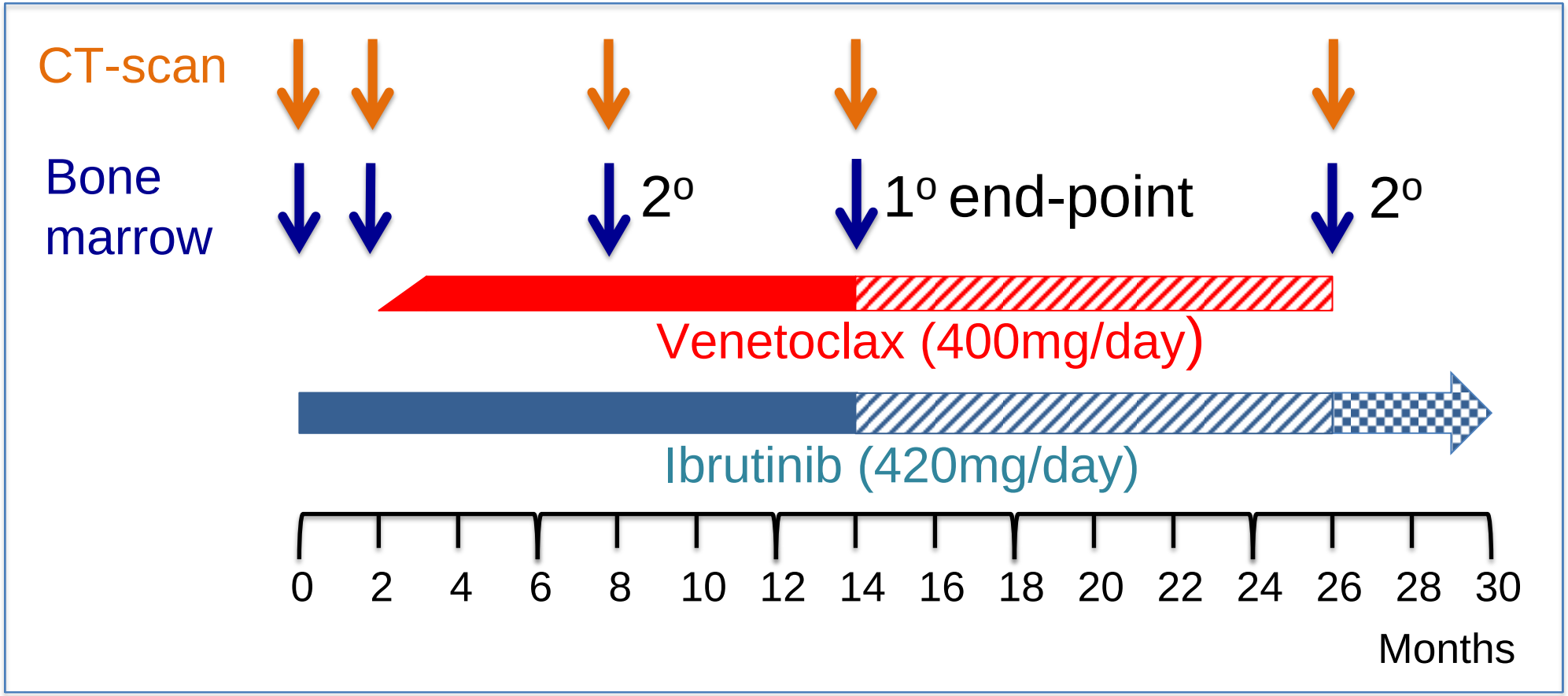
*All hematologic AEs of any grade

Rogers, K et al. ASH 2017, Abstract #431

IBR + VEN: Responses in R/R Cohort



Ibrutinib + Venetoclax for R/R CLL: Treatment Schedule



- VEN and IBR stop at 14 months if 8 month BM is U-MRD4
- VEN and IBR stop at 26 months if 14 month BM is U-MRD4
- IBR alone continues if 26 month BM is MRD positive

Hillmen, P et al. ASH 2017, Abstract #428

IWCLL Responses at Month 8 (6 months I+V)

38 patients reached at least Month 8, having received 6+ months IBR+VEN and have had a clinical response assessment, bone marrow and CT-scan

	No.	CR	CRi	PR	ORR
All patients*	**38**	**15 (39%)**	**3 (8%)**	**20 (53%)**	**38 (100%)**
FCR/BR relapsed <36 months[1]	17	9 (53%)	2 (12%)	6 (35%)	17 (100%)
Prior idelalisib[2]	7	3 (43%)	0	4 (57%)	7 (100%)

Date of data lock: 01 December 2017

* Percentages were calculated over the total number of patients who have been assessed for response (38 pts)

[1] Percentages calculated over the total number of patients who had FCR/BR and relapsed <36 months and have been assessed for response

[2] Percentages calculated over the total number of patients who had Idelalisib before joining the study and have been assessed for response

Hillmen, P et al. ASH 2017, Abstract #428

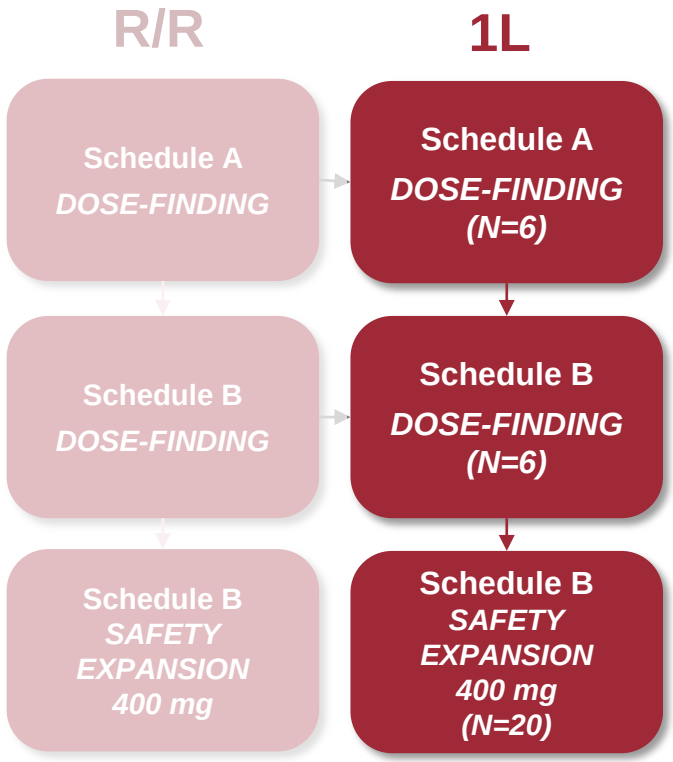
Key secondary end-point: BM MRD at Month 8 (6 months I+V)

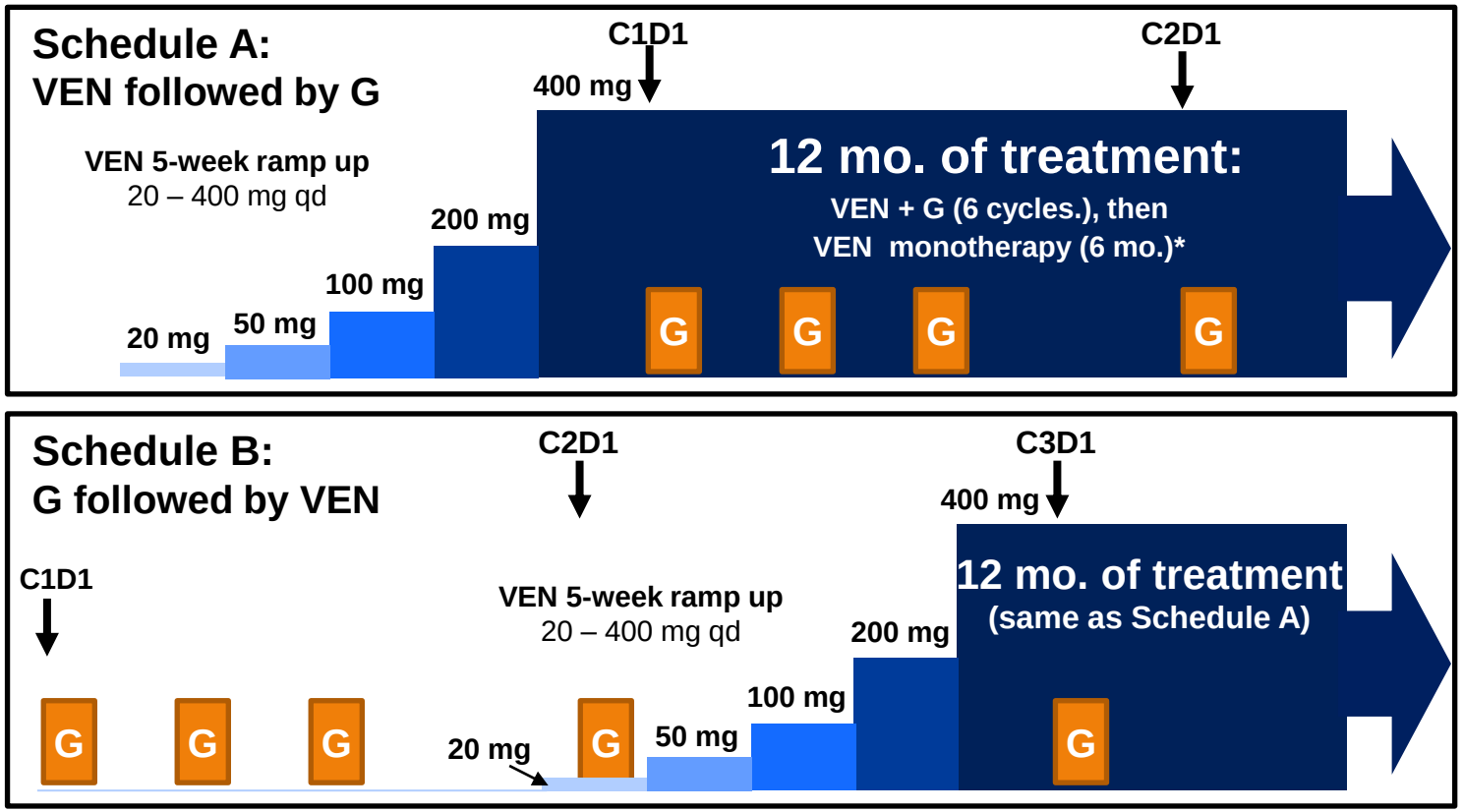
38 patients reached at least Month 8, having received 6+ months IBR+VEN and have had a bone marrow MRD PB or BM <0.01% CLL cells (10^{-4}) by flow cytometry

All at Month 8	PB U-MRD4	BM U-MRD4	Trephine normal
All patients	**15/38 (37%)**	**12/38 (32%)**	**32/38 (84%)**
FCR/BR rel <36 months	9/17 (52%)	7/17 (41%)	16/17 (94%)
Prior idelalisib	4/7 (57%)	3/7 (43%)	7/7 (100%)

Hillmen, P et al. ASH 2017, Abstract #428

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, I et al. ASH 2017, Abstract #430

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

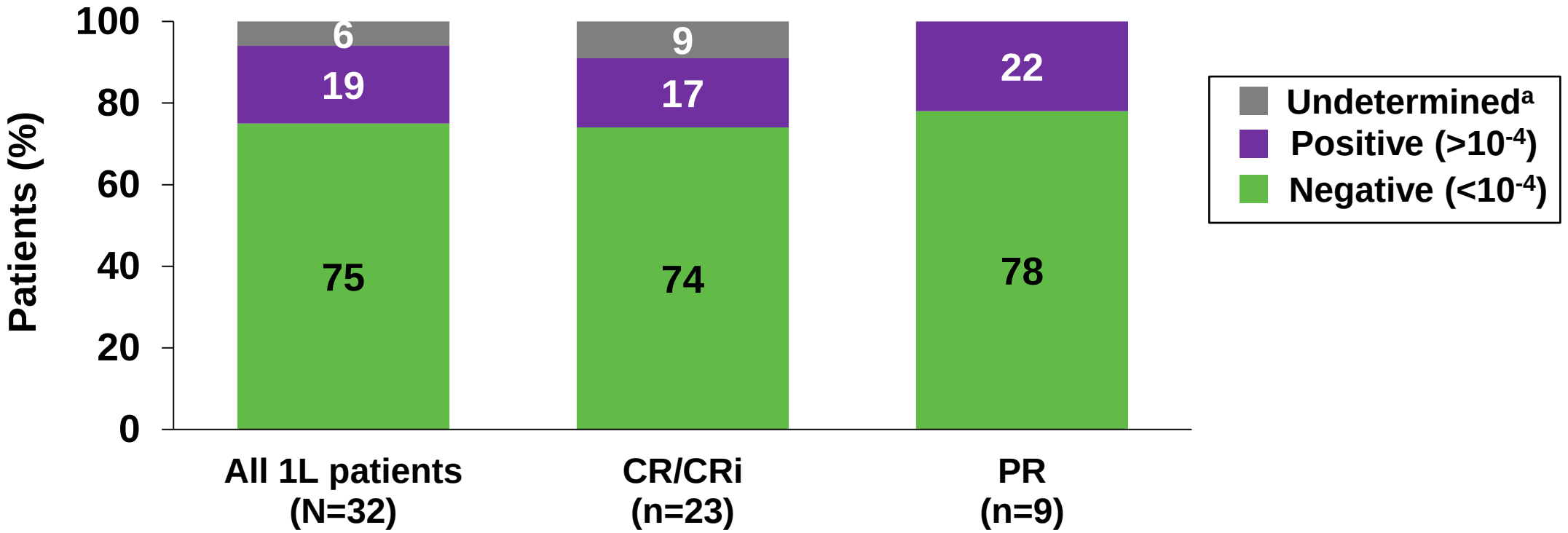
Response n (%)	All 1L patients (N=32)	By cytogenetic abnormalities[b] (n=29)					By *IGHV* mutation status (n=27)	
		del(17p) n=5	del(11q) n=6	Trisomy 12 n=6	No abnormalities n=1	del(13q) n=11	Mut n=11	Unmut n=16
ORR	32 (100)	5 (100)	6 (100)	6 (100)	1 (100)	11 (100)	11 (100)	16 (100)
CR/CRi	23 (72)	3 (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, I et al. ASH 2017, Abstract #430

High Bone Marrow U-MRD4 Rates

Majority of patients achieved BM U-MRD4 at some point on study



- 4 of 7 PR patients with BM U-MRD4 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, I et al. ASH 2017, Abstract #430

Current Questions / Controversies

- Expectation for PFS and U-MRD assoc. similar as with CIT?
- Efficacy of IBR + VEN *vs.* VEN + OBIN (potential first-line standard)? Does drug MOA differentiate? CR or U-MRD rates differentiating?
- Potential benefit with addition of CD20 mAb to VEN + IBR?
- Immune reconstitution, reduced infection, and other cancers?
- Financial tolerability and feasibility?

- How to increase U-MRD rate and shorten fixed duration treatment?
- Responses with retreatment for relapsed?
- Patterns of clonal evolution and mechanisms of resistance?
- Feasibility to studying and compare “time-on-target” & sequencing?

THANK YOU!

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