Management of Relapsed/Refractory (R/R) CLL and Novel Investigational Approaches

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Conflicts of Interest – J Gribben

I have the following financial relationships to disclose.

Honoraria:	AbbVie, Acerta, AZ, Celgene/BMS, Gilead/Kite, Janssen, Morphosys, Novartis, Pharmacyclics, Roche/Genentech, TG Therapeutics
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Case Presentation: Dr Kale

78-year-old woman (CAD s/p CABG, HTN, DM2, Stage III chronic kidney disease)

- Presents with bilateral axillary lymphadenopathy on routine mammogram; no constitutional symptoms
- Diagnosis: Small lymphocytic lymphoma
- Patient initially observed off treatment
  - 1 year later develops night sweats with 20-lb weight loss
- Venetoclax/obinutuzumab

Case Presentation: Dr Lamar

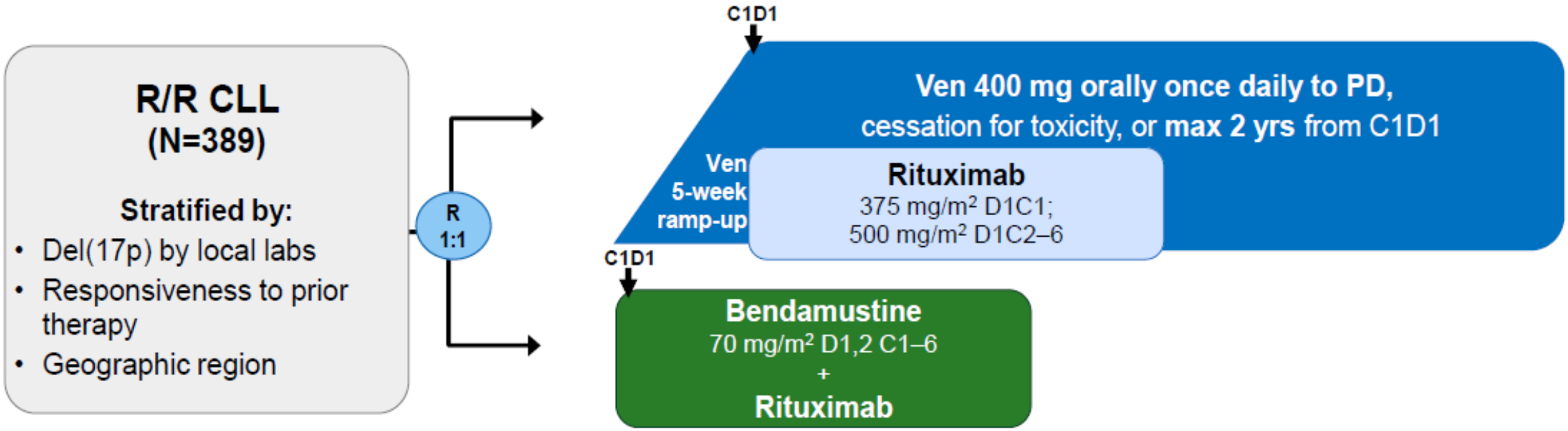
72-year-old man

- Presents with bulky, bilateral cervical adenopathy
- Diagnosis: Chronic lymphocytic leukemia (normal cytogenetics)
- Ibrutinib x 6 months
  - Atrial fibrillation requiring anticoagulation, with subsequent hematuria
  - Ibrutinib dose reduction to 140 mg

R/R CLL

- Novel agents are replacing chemoimmunotherapy in the treatment of CLL
- Agents approved include BTK inhibitors, BCL2 inhibitors and PI3K inhibitors
- Most agents explored initially in R/R setting and initially in comparison with ineffective salvage therapy
- Increased efficacy in all subgroups (except *IGHV* mutated), but especially in *TP53* deleted/mutated cases
- *TP53* abnormalities much more common in R/R setting
- Increasing data emerging on the use of these agents in combination

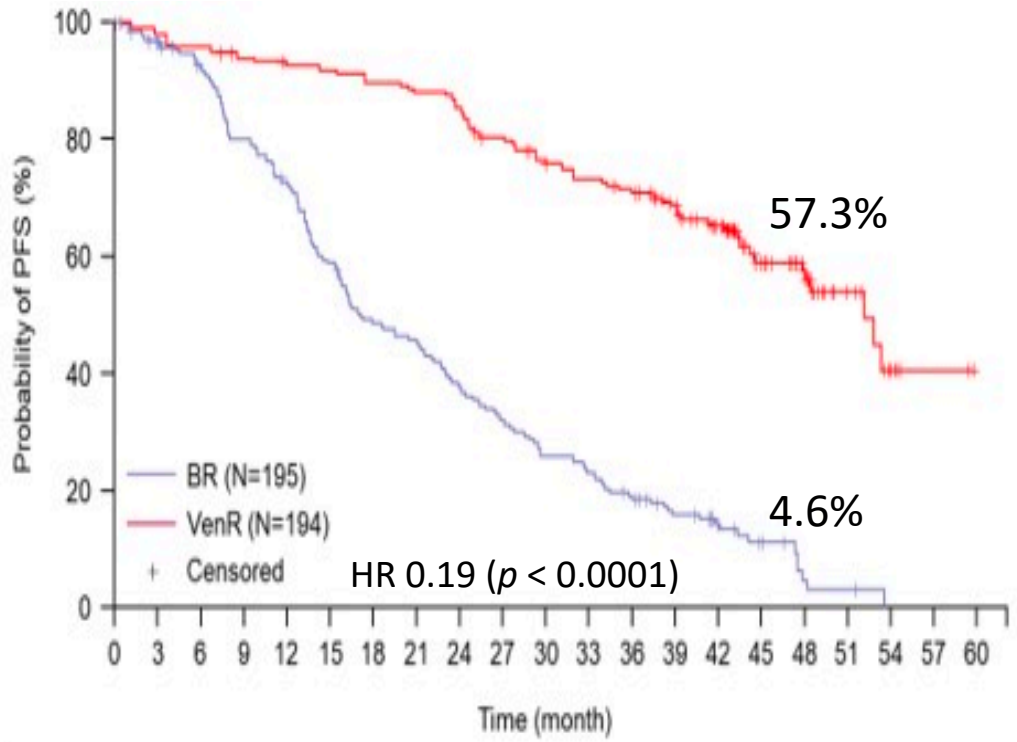
MURANO study design



- **Primary endpoint:** investigator assessed PFS; secondary endpoints include rate of undetectable MRD (uMRD)
- Clinical response and MRD in PB/BM during venetoclax single-agent and at follow-up visits were assessed every 3 months for 3 years, then every 6 months thereafter, or until PD
- Primary analysis was pre-planned at 140 PFS events; follow-up analysis was presented yearly since then

Seymour et al., NEJM 2018;

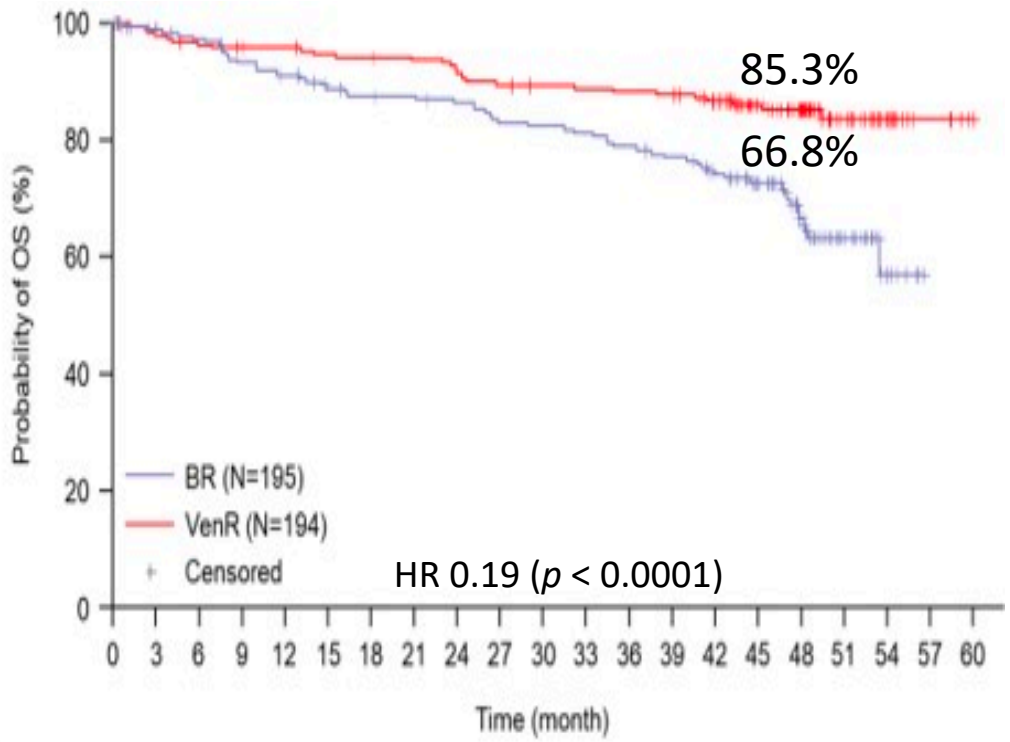
MURANO – Updated 4-year outcomes



No. of patients at risk:

BR	195	178	165	143	129	104	85	80	66	56	45	40	32	23	14	9	3	2	
VenR	194	190	185	179	176	174	170	167	161	150	141	134	130	118	101	55	40	14	7	2

BR, bendamustine plus rituximab; ITT, intention to treat; PFS, progression-free survival; VenR, venetoclax plus rituximab



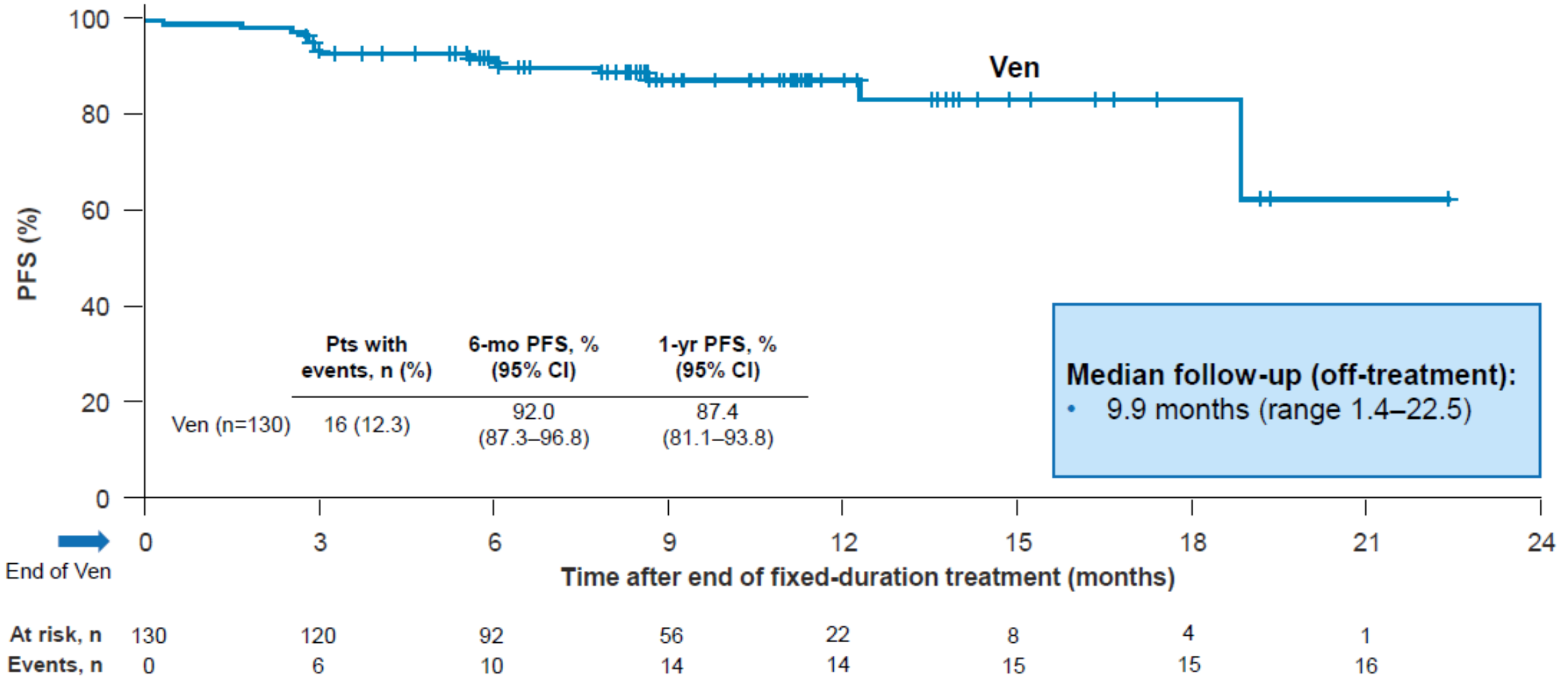
No. of patients at risk:

BR	195	181	175	167	162	155	152	150	147	141	140	138	134	130	116	94	58	29	7	
VenR	194	190	185	183	182	179	178	176	173	168	166	165	164	163	154	110	84	34	15	6	1

BR, bendamustine plus rituximab; ITT, intention to treat; OS, overall survival; VenR, venetoclax plus rituximab

Seymour et al ASH 2019 355
Sunday 7.30 -9 .00 Hall E1

MURANO: modest progression in the first 12 months after completion of venetoclax



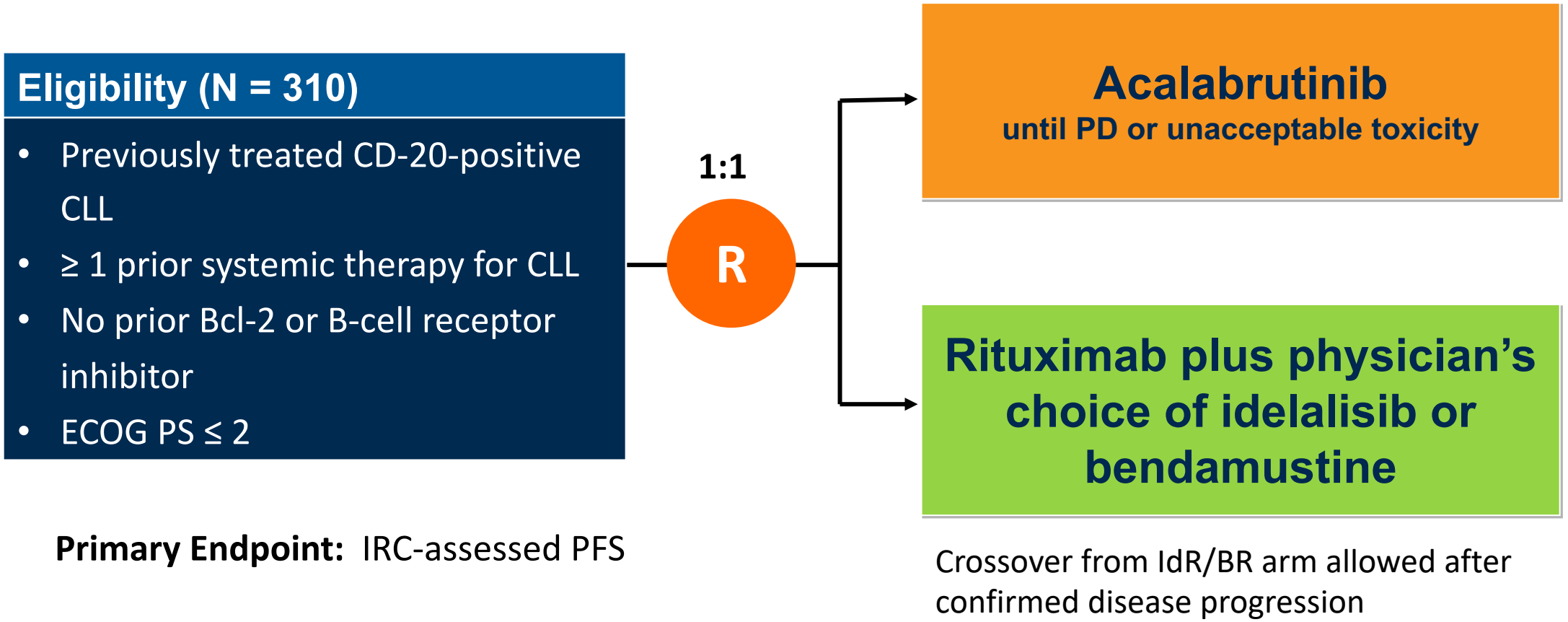
Seymour et al., ASH 2018; abstract 184

Key questions

- MURANO demonstrated clear benefit of novel agent over best salvage chemoimmunotherapy
- What order should we offer novel agents?
- What is the efficacy of one agent versus another?
- Will “new” novel agents displace first generation drugs?
  - Study of trial comparing Acalabrutinib against Ibrutinib is fully accrued and we await outcome of ELEVATE RR

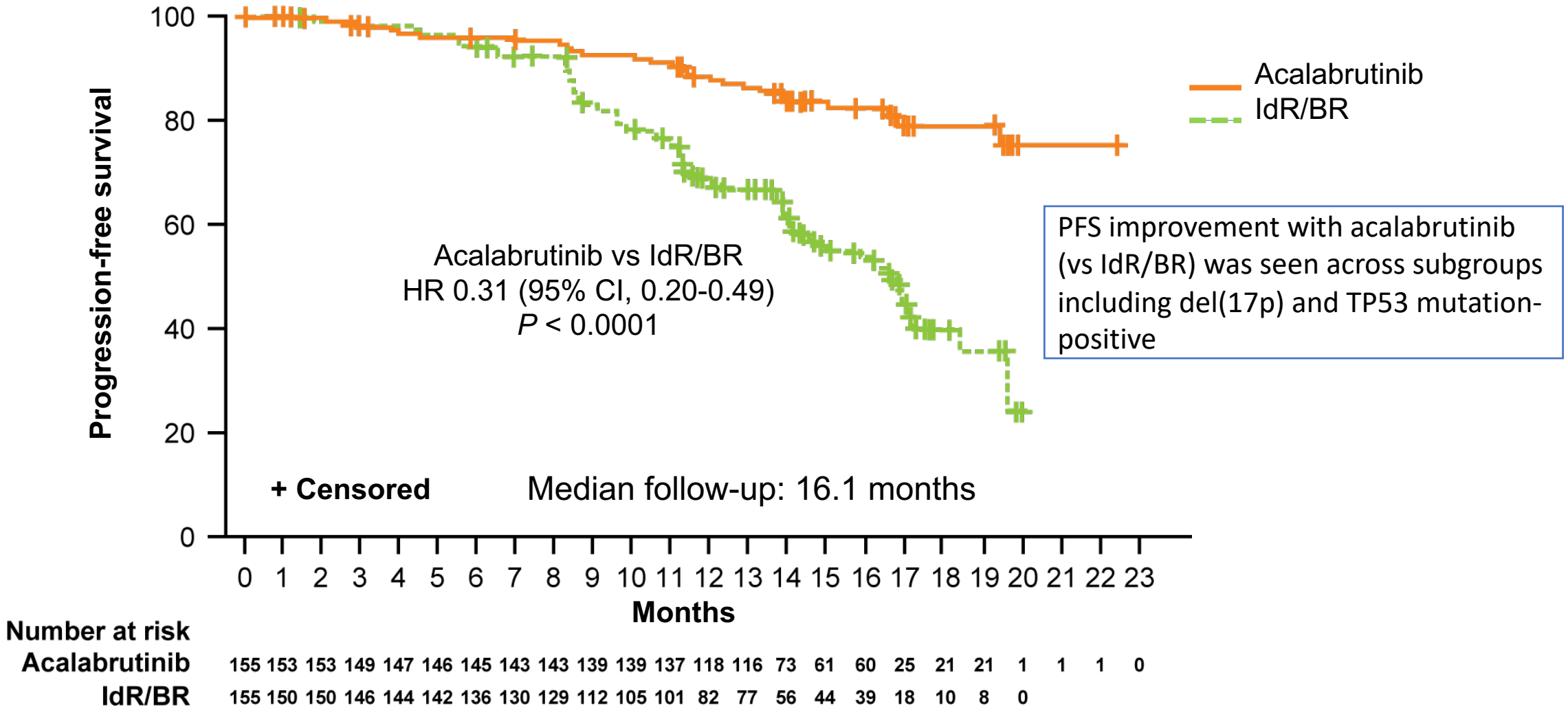
Phase III ASCEND (ACE-CL-309) Schema

Acalabrutinib in Relapsed/Refractory CLL



Clinicaltrials.gov, Accessed December 4, 2019; Ghia et al. Proc EHA 2019; LB2606.

ASCEND Primary Endpoint: IRC Progression-Free Survival



PFS improvement with acalabrutinib (vs IdR/BR) was seen across subgroups including del(17p) and TP53 mutation-positive

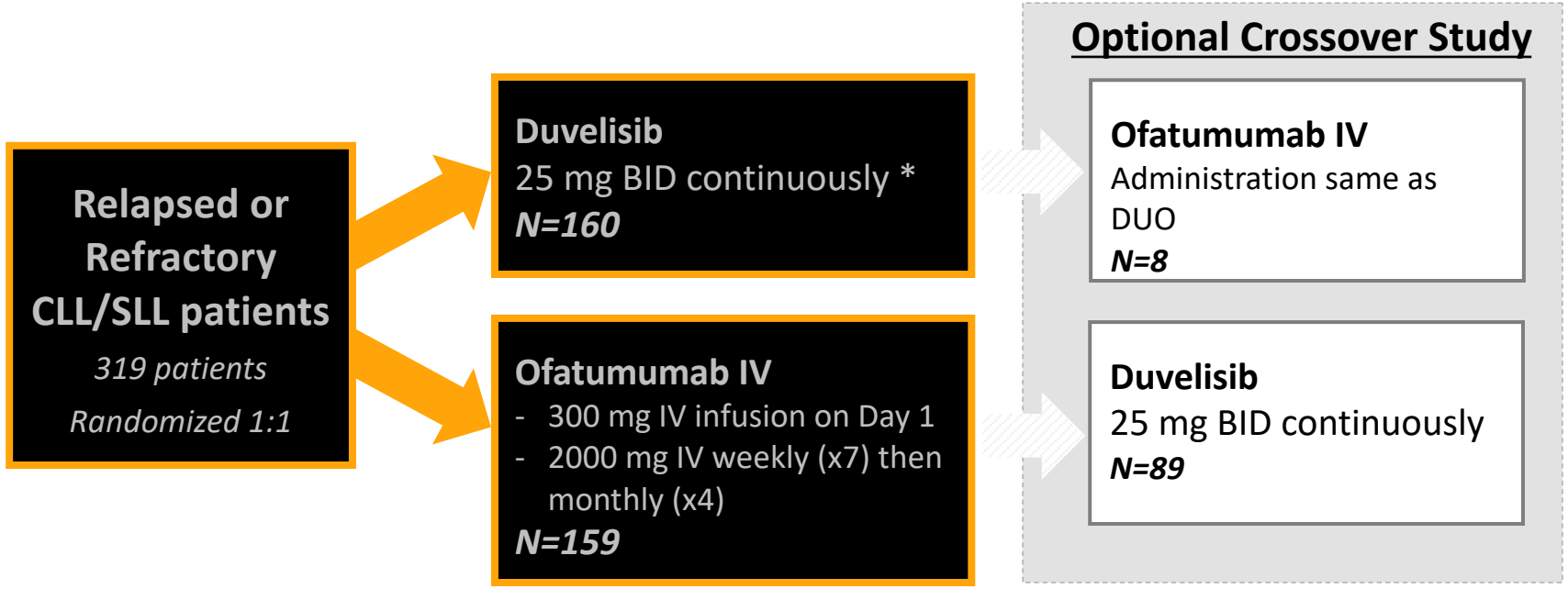
Ghia P et al. *Proc EHA* 2019;Abstract LB2606.

ASCEND: Select ≥Grade 3 Adverse Events

Adverse Event	Acalabrutinib (n = 154)	Id/R (n = 118)	BR (n = 35)
Any	49%	90%	49%
Neutropenia	16%	40%	31%
Anemia	12%	7%	9%
Pneumonia	5%	8%	3%
Diarrhea	1%	24%	0
Thrombocytopenia	4%	8%	3%
ALT increased	1%	8%	3%
Neutrophil count decreased	1%	8%	3%
AST increased	1%	5%	3%
Transaminases increased	0	5%	0

Ghia P et al. *Proc EHA* 2019;Abstract LB2606.

DUO: A Phase 3 Randomized Study in Relapsed/Refractory CLL/SLL



Response per modified iwCLL/IWG Criteria **

- **Assessed by independent review committee (IRC)**
- **Cycle 3 (C3), C5, C7, C11, C15, C19, every 6 months thereafter**
- **CT scan, CBC , disease related symptoms, BM biopsy *****
- **Survival assessment every 6 months**

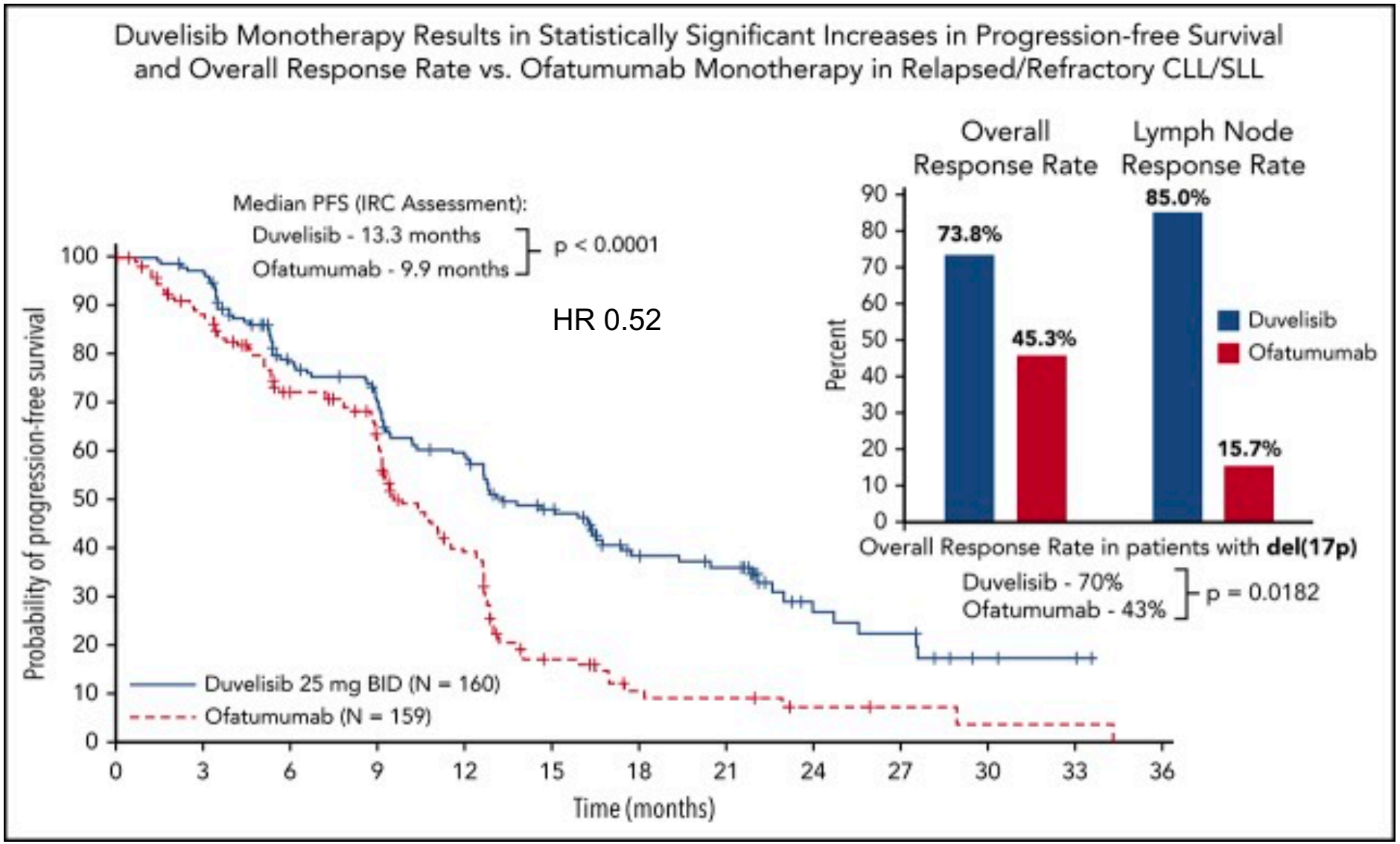
Endpoints

- **PFS (primary)**
- **ORR, DOR, OS (secondary)**
- **Safety (AEs and lab abnormalities)**

* Patients may have stopped treatment at C18 for CR/PR >3 months at discretion of Investigator
** Lymphocytosis not considered disease progression; PR = 2 Group A and 1 Group B Criteria
*** Required for confirmation of CR/CRi

Flinn et al Blood. 2018;132(23):2446-2455

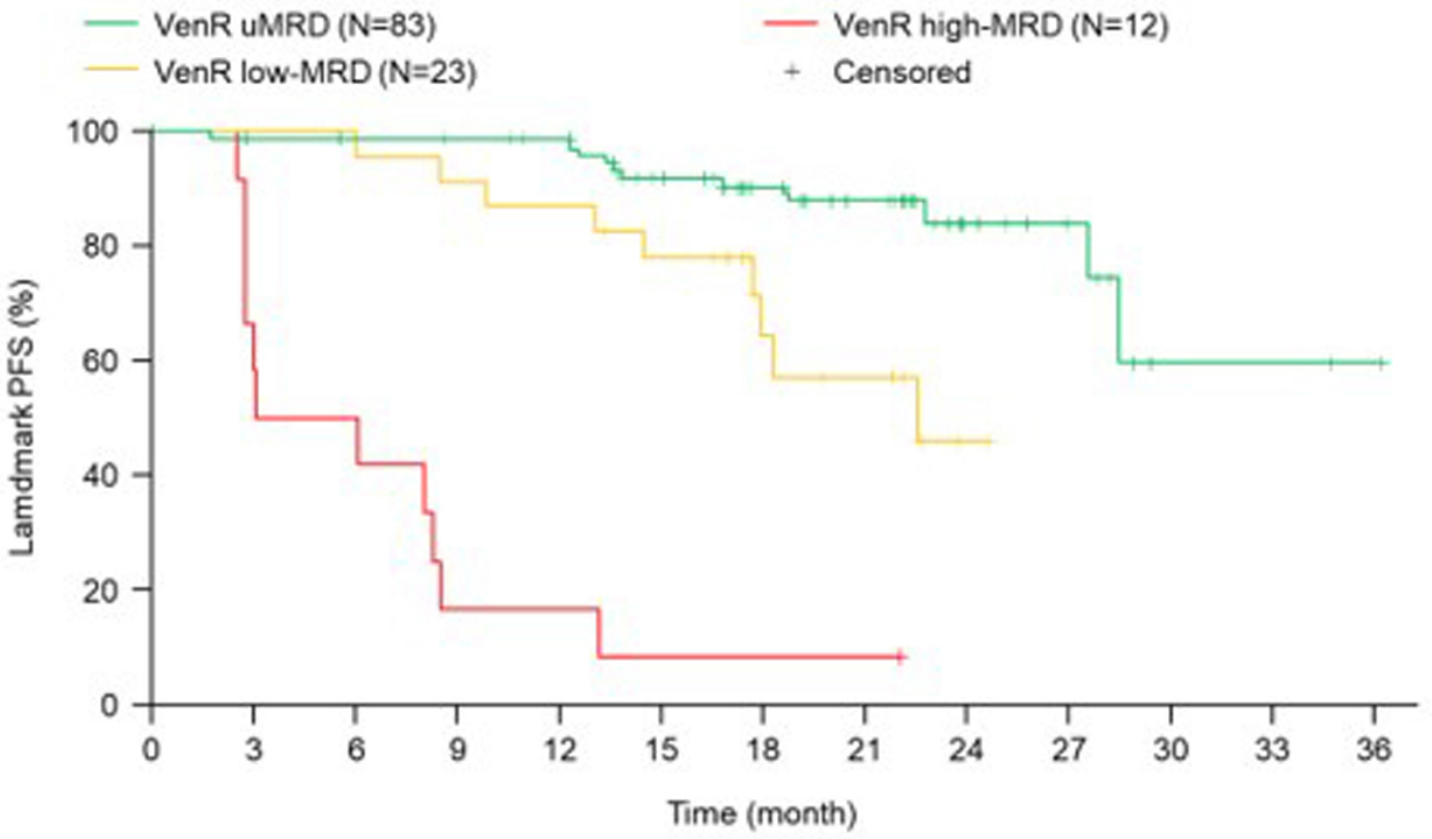
DUO – Primary Endpoint – PFS by IRC



Flinn et al Blood. 2018;132(23):2446-2455

MURANO: Goal of therapy is eradication of MRD

Landmark PFS Analysis based on MRD at EOT



No. of patients at risk:

VenR uMRD	83	78	77	76	74	63	42	33	13	9	2	2	1
VenR low-MRD	23	23	23	21	20	17	9	7	1				
VenR high-MRD	12	8	6	2	2	1	1	1					

BR, bendamustine plus rituximab; EOT, end of treatment; ITT, intention to treat; PFS, progression-free survival; uMRD, undetectable minimal residual disease; VenR, venetoclax plus rituximab

Ability to drive deep MRD neg responses allows drug discontinuation

Question is how durable will be the response

What will be the impact of retreatment at progression?

What other approaches enable MRD eradication in R/R CLL?

Seymour et al ASH 2019 355
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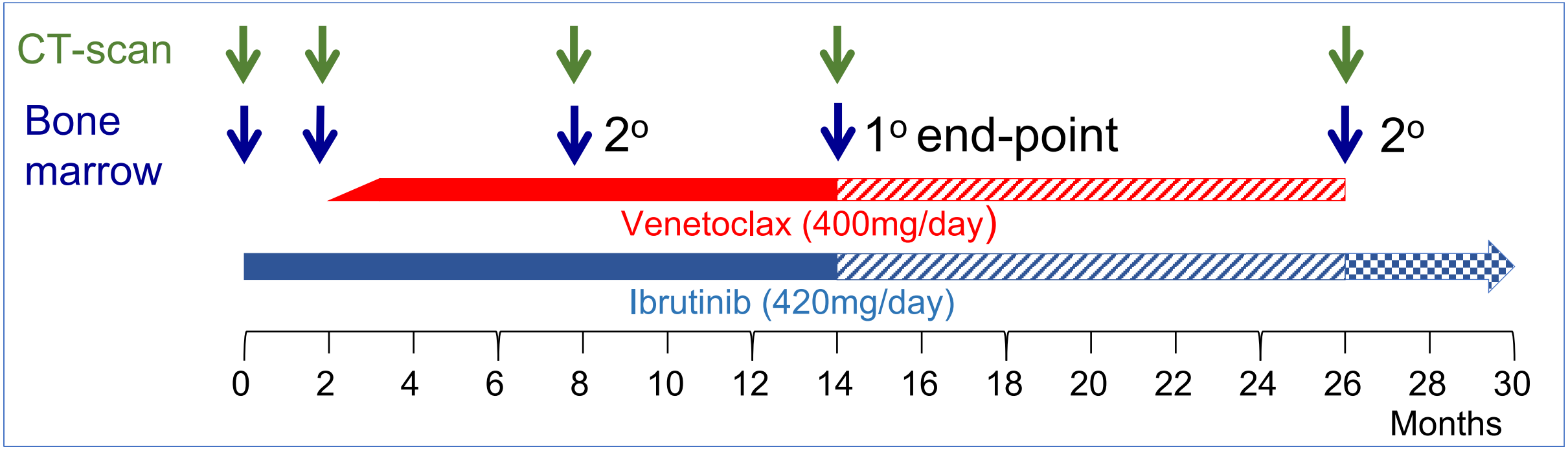
CLARITY – Ibrutinib plus venetoclax Treatment Schedule and Stopping Rules



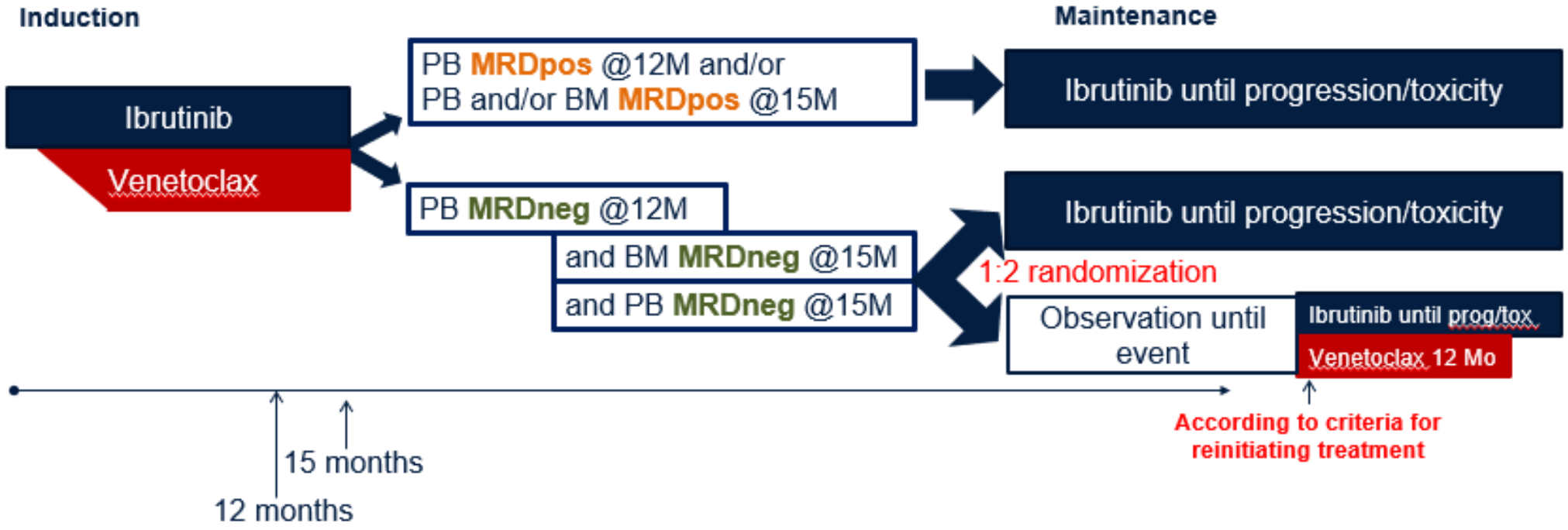
Stopping rules: Duration of therapy is double time to MRD4 negative

1) MRD negative (<0.01%) at M8 stop I+V at M14
2) MRD negative (<0.01%) at M14 or M26 stop I+V at M26
3) MRD positive (≥0.01%) at M26 continue ibrutinib monotherapy

Hillmen at al J Clin Oncol. 2019 Oct 20;37(30):2722-2729

Venetoclax and ibrutinib for patients with R/R CLL: Phase II VISION HO141 trial

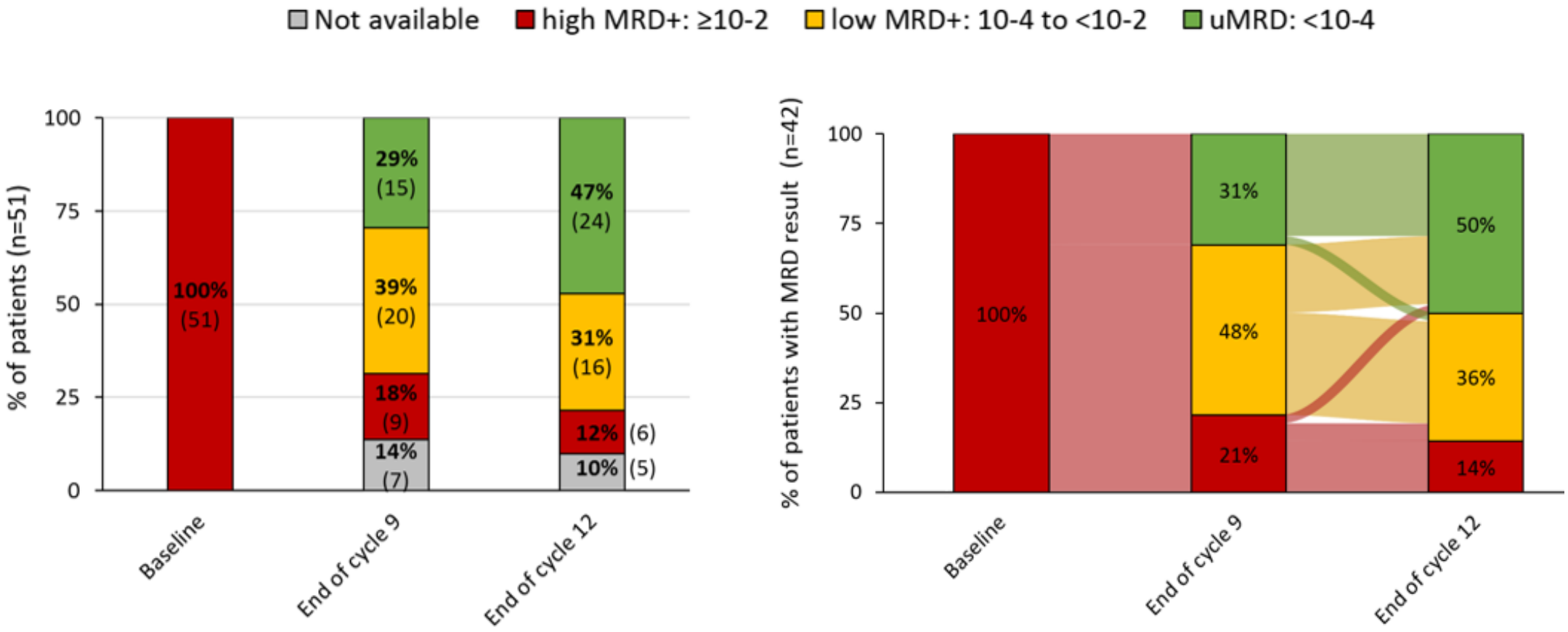
Treatment scheme



- Primary endpoint: PFS at 12 months after stopping therapy (27 months after starting treatment) for patients randomized to stop treatment
- Key secondary endpoints:
  - MRD eradication (<0.01% CLL cells) in blood and marrow at 12 months after stopping ibrutinib + venetoclax
  - Response rate, PFS and OS all arms
  - Toxicity of combination therapy (Grade 2 or higher AEs and SAE)

Kater et al., EHA 2019; S108 (oral presentation)

Safety analysis of venetoclax and ibrutinib for patients with R/R CLL (Phase II VISION HO141 trial)

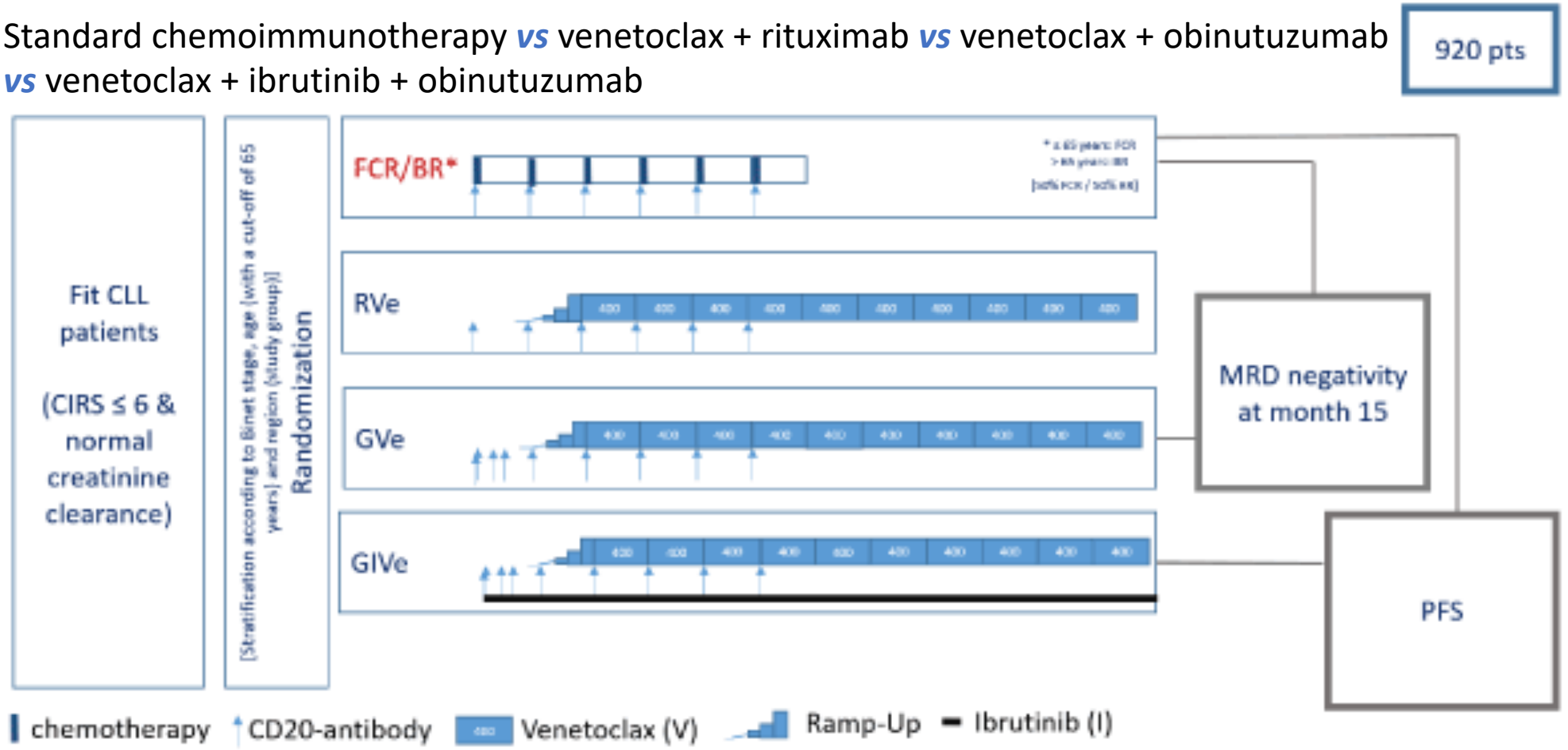


- CR rate: 61% after 9 cycles of treatment
- Undetectable MRD rate increased to 52% after one year of treatment.
- Ibrutinib and venetoclax in R/R CLL showed a favorable benefit-risk profile

Kater et al., EHA 2019; S108 (oral presentation)

CLL13/GAIA Trial

Standard chemoimmunotherapy ***vs*** venetoclax + rituximab ***vs*** venetoclax + obinutuzumab ***vs*** venetoclax + ibrutinib + obinutuzumab



GLOW/CLL3011 trial (NCT03462719)

Randomized Phase III of ibrutinib and venetoclax compared with chlorambucil and obinutuzumab

FLAIR (ISRCTN01844152)

Randomized Phase III of FCR versus ibrutinib monotherapy versus ibrutinib and rituximab versus ibrutinib and venetoclax

Conclusions

- Novel agents have replaced chemoimmunotherapy in R/R CLL
  - BTKi, BCL2i, PI3Ki
- Approaches include continuous therapy with BTKi – Ibrutinib and Acalabrutinib are approved in this setting
- Deep responses with venetoclax allow drug discontinuation either by fixed duration or by eradication of MRD
- Less interest now in combination of novel agents plus chemotherapy
- Novel/novel combinations being explored