Novel Strategies Combining Bruton Tyrosine Kinase (BTK) and Bcl-2 Inhibitors for CLL

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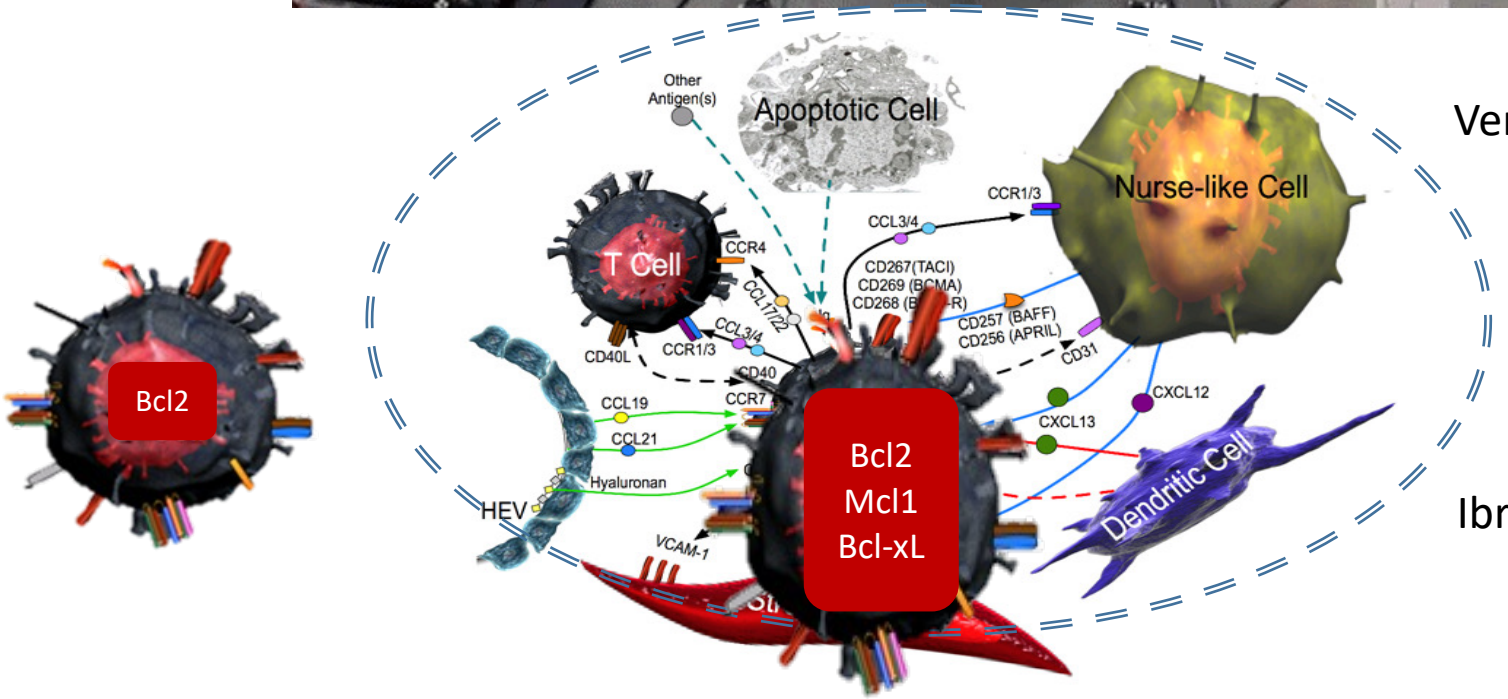
Chairman Hovon CLL study group

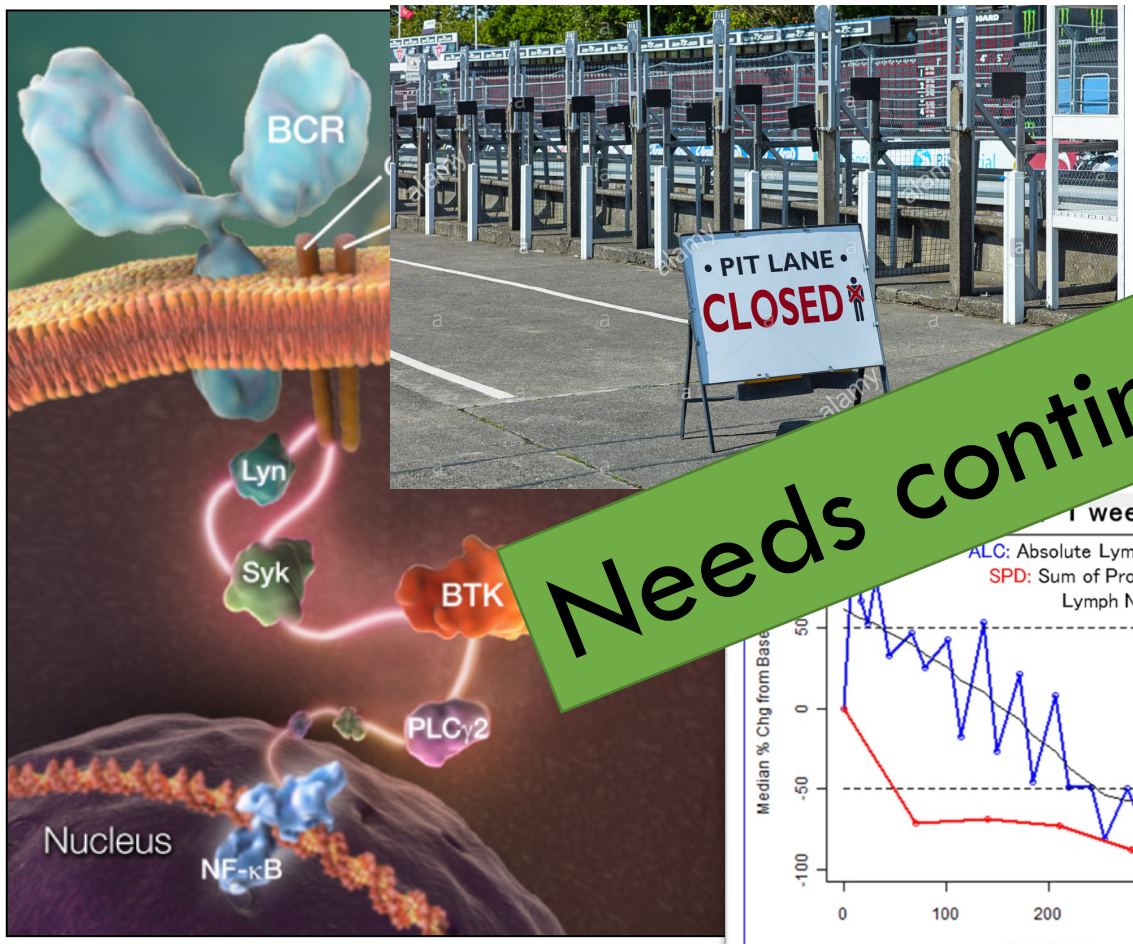
The key role of the TME



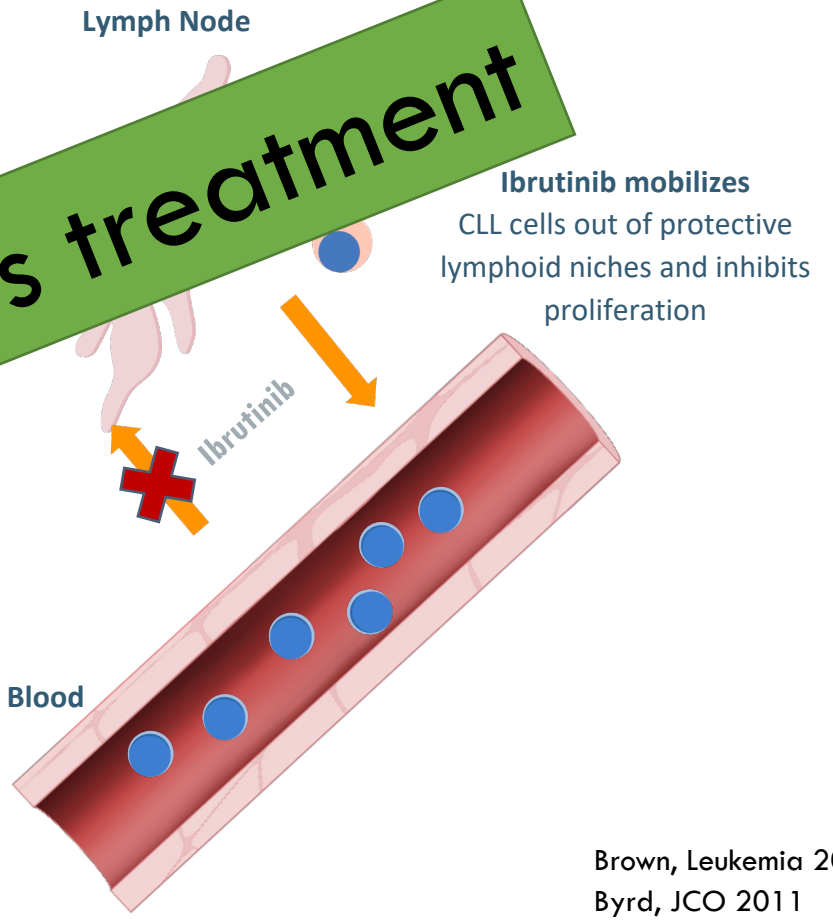
Venetoclax active in blood, less in LNN

Ibrutinib active in LNN, less in marrow

BTK-inhibition targets adhesion and homing to lymph node

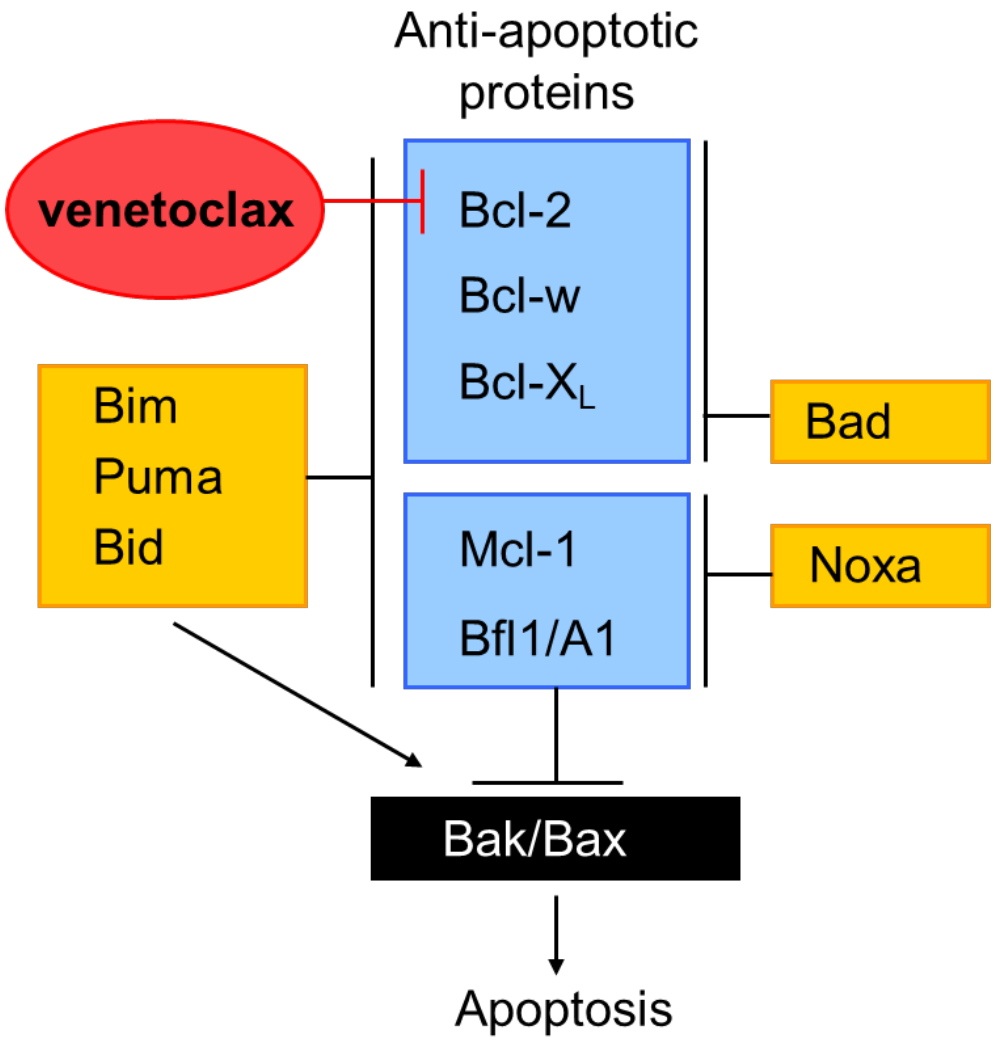


Needs continuous treatment



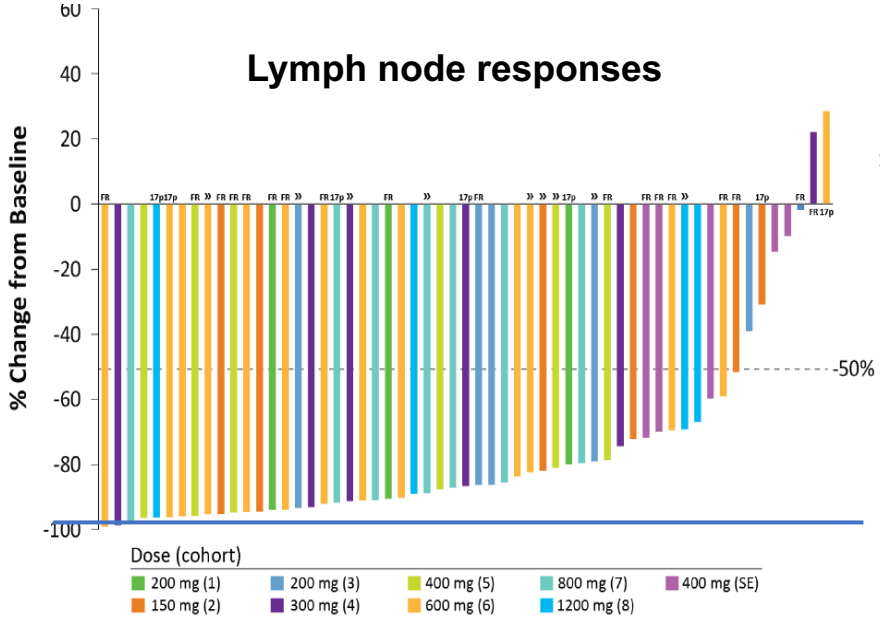
Brown, Leukemia 2018
Byrd, JCO 2011

Venetoclax sensitivity differs between compartments

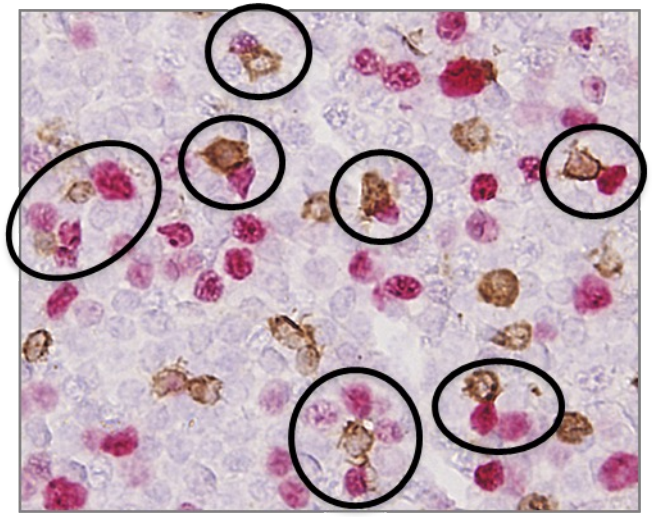


Blood responses

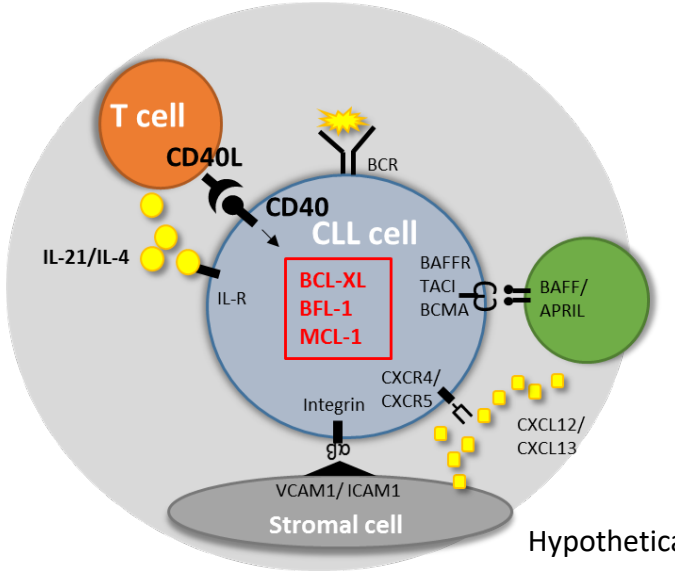
Lymph node responses



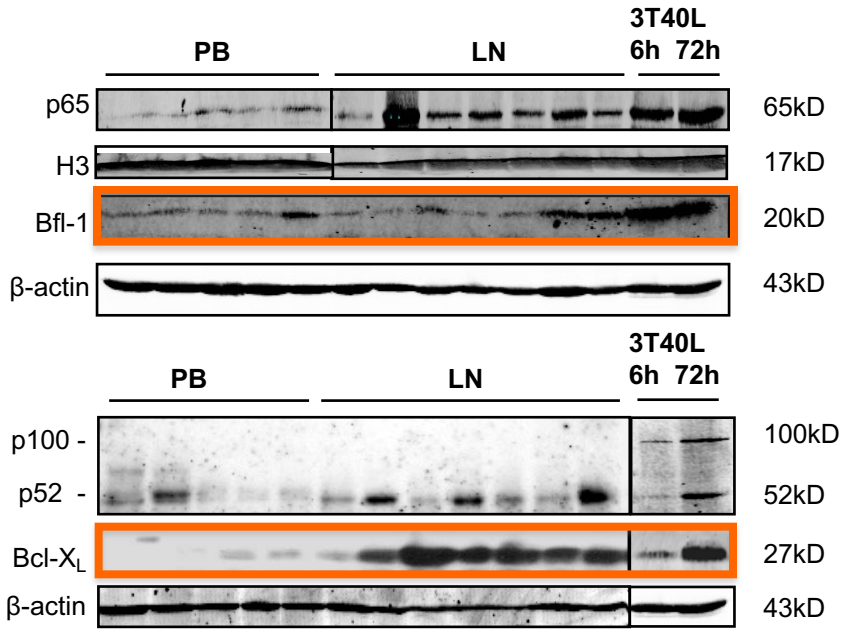
Bfl-1, Bcl-XL and Mcl-1 expression increased in CLL LN

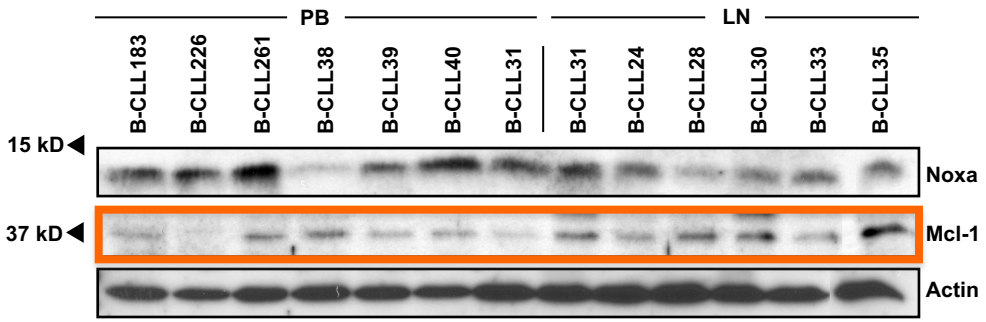


Many Ki67+ CLL cells are in close contact with CD3+ T cells.



Hypothetical Lymph node environment

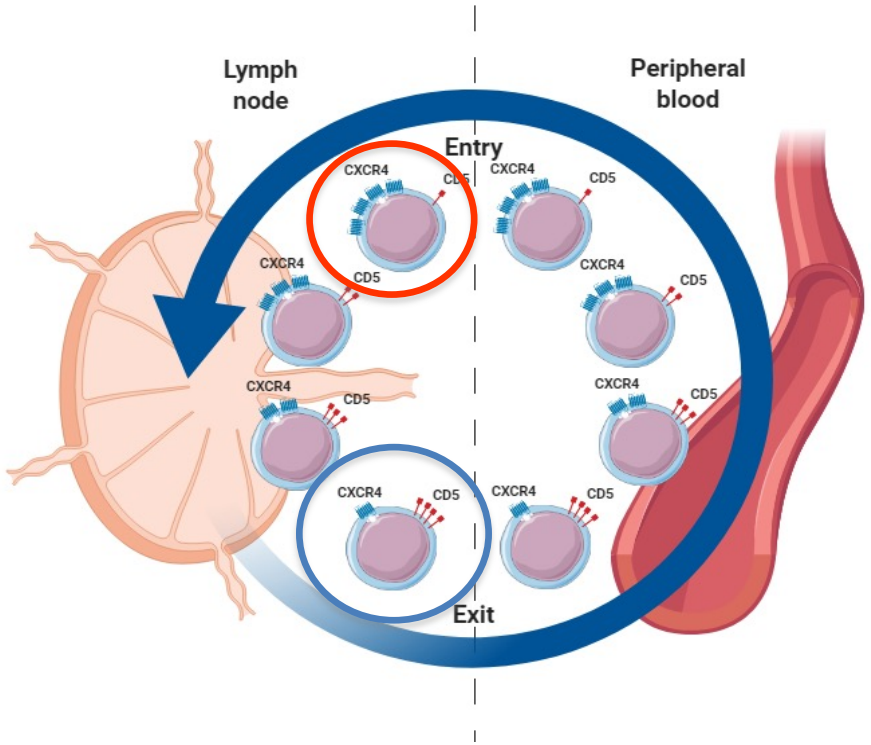




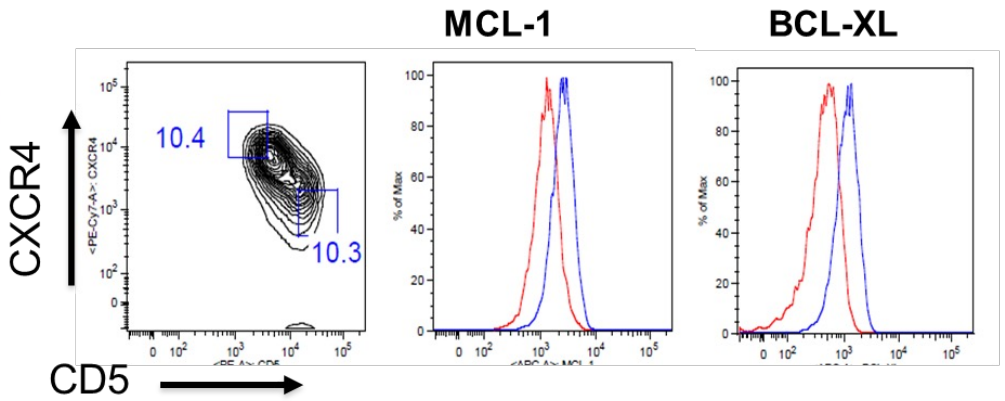
Noxa/Mcl1 balance altered in CLL LN
Smit LA et al, Blood 109: 1660, 2007.

Tromp J et al Oncogene 29: 5071, 2010

Using a FACS trick to explore expression levels of anti-apoptotic proteins in the lymph node



(Calissano etal. Mol Med. 2011)



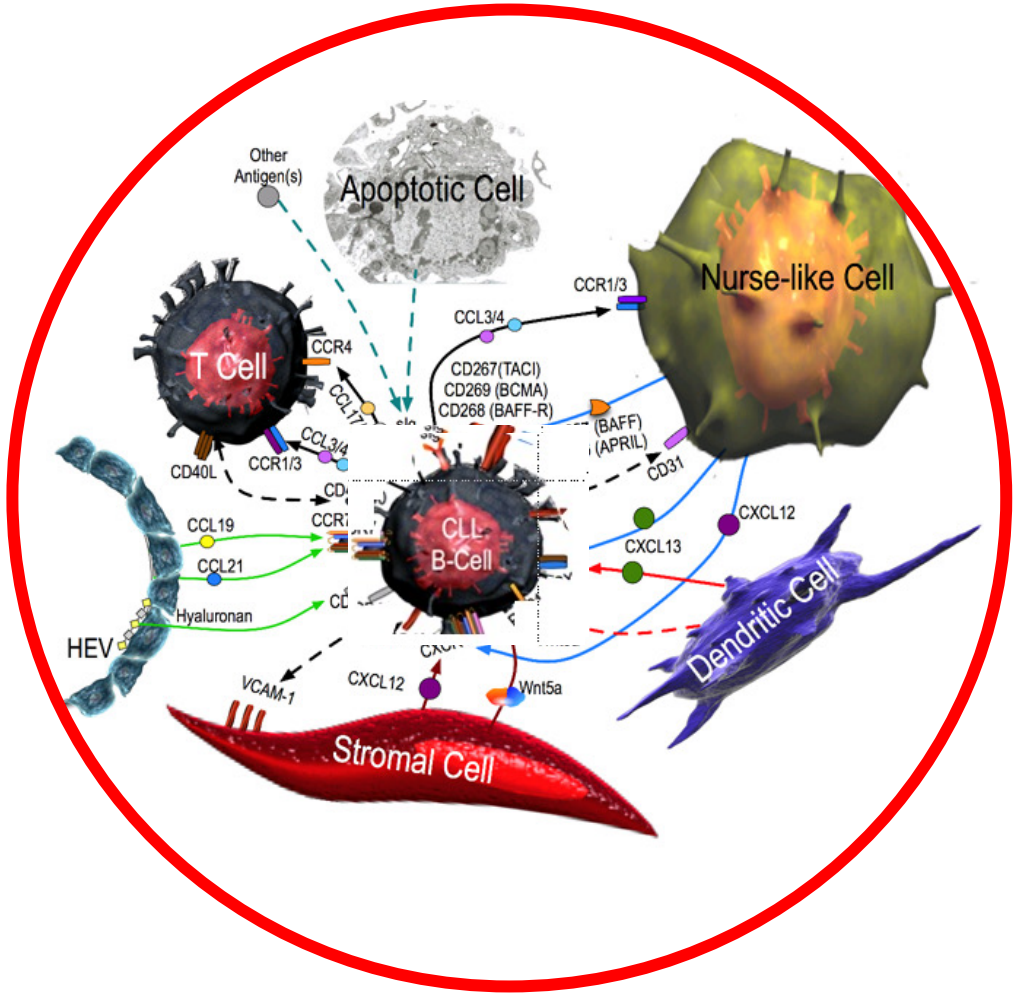
CXCR4^{high}CD5^{dim} 'old' CLL cells

CXCR4^{dim}CD5^{high} LN emigrant CLL cells

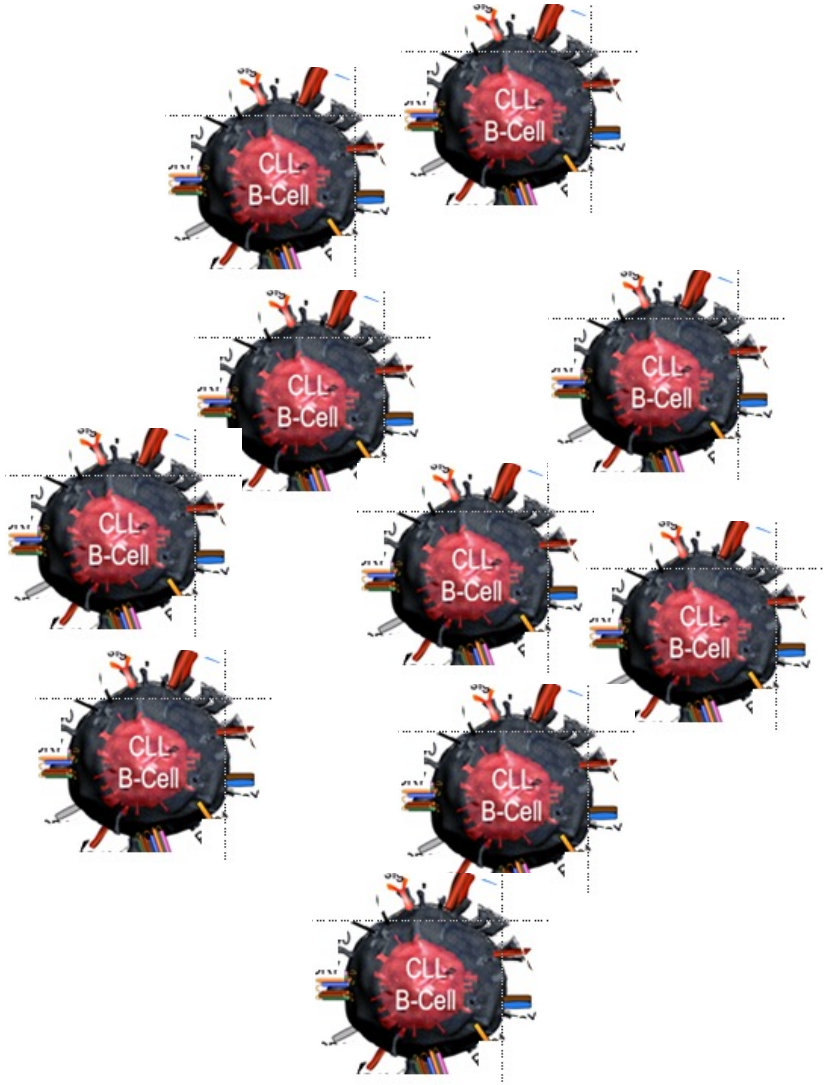
Differences in Mcl-1 & Bcl-XL in recent LN emigrants and 'old' returning cells

Haselager Blood 2021

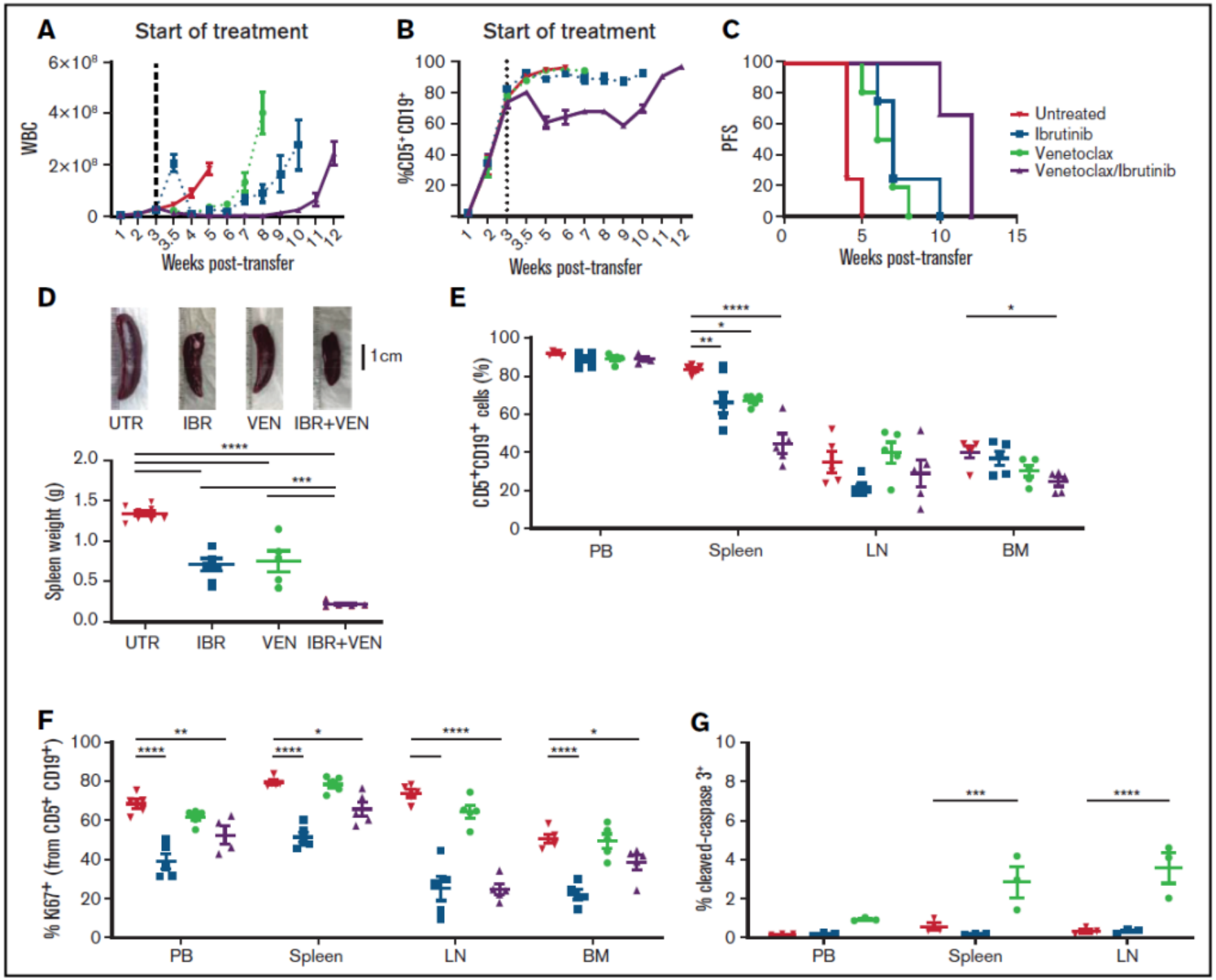
Combining Venetoclax with……



BTK-i



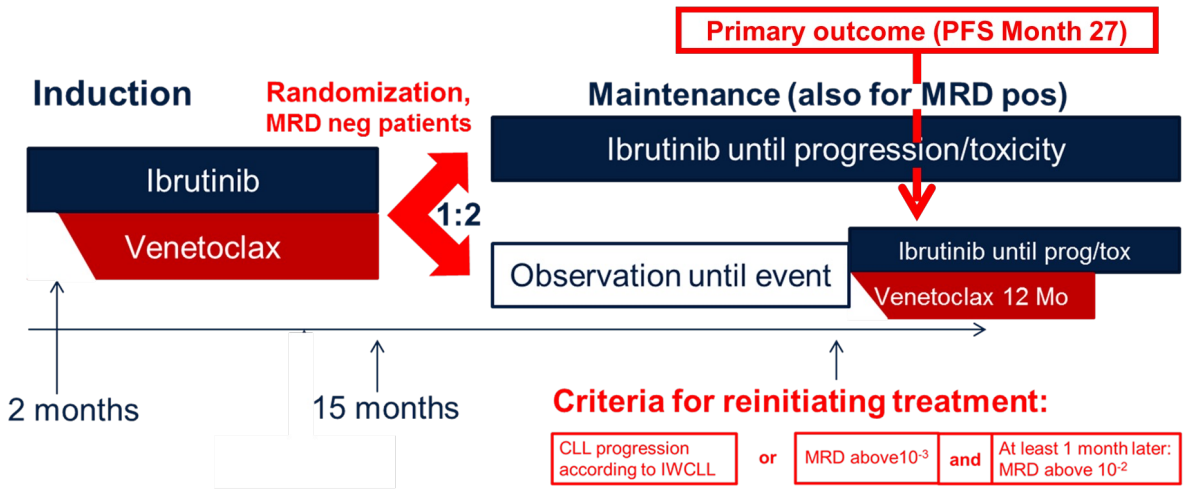
Venetoclax

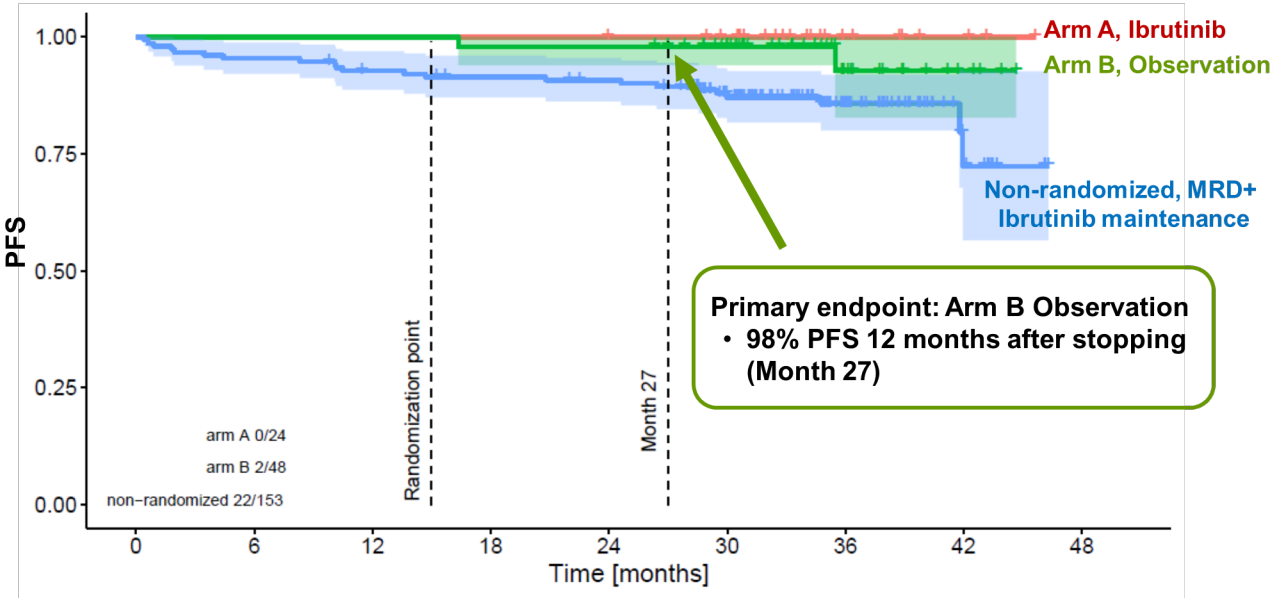


Kater, Blood Adv. 2022

Efficacy data

Minimal residual disease-guided stop and start of venetoclax plus ibrutinib for patients with relapsed or refractory chronic lymphocytic leukaemia (HOVON141/VISION): primary analysis of an open-label, randomised, phase 2 trial





	N
Non-randomized Ibrutinib	153
Arm A Ibrutinib	24
Arm B Observation	48

- 7 patients reinitiated ibrutinib-venetoclax during observation due to MRD+
- 6 of 7 achieved de novo CR within 3 cycles
- 7th patient awaits evaluation

Kater AP *Lancet Oncol* 2022; 23: 818–28

Clinical evidence of Ven+Ibr fixed duration 1st-line

Phase 2 CAPTIVATE

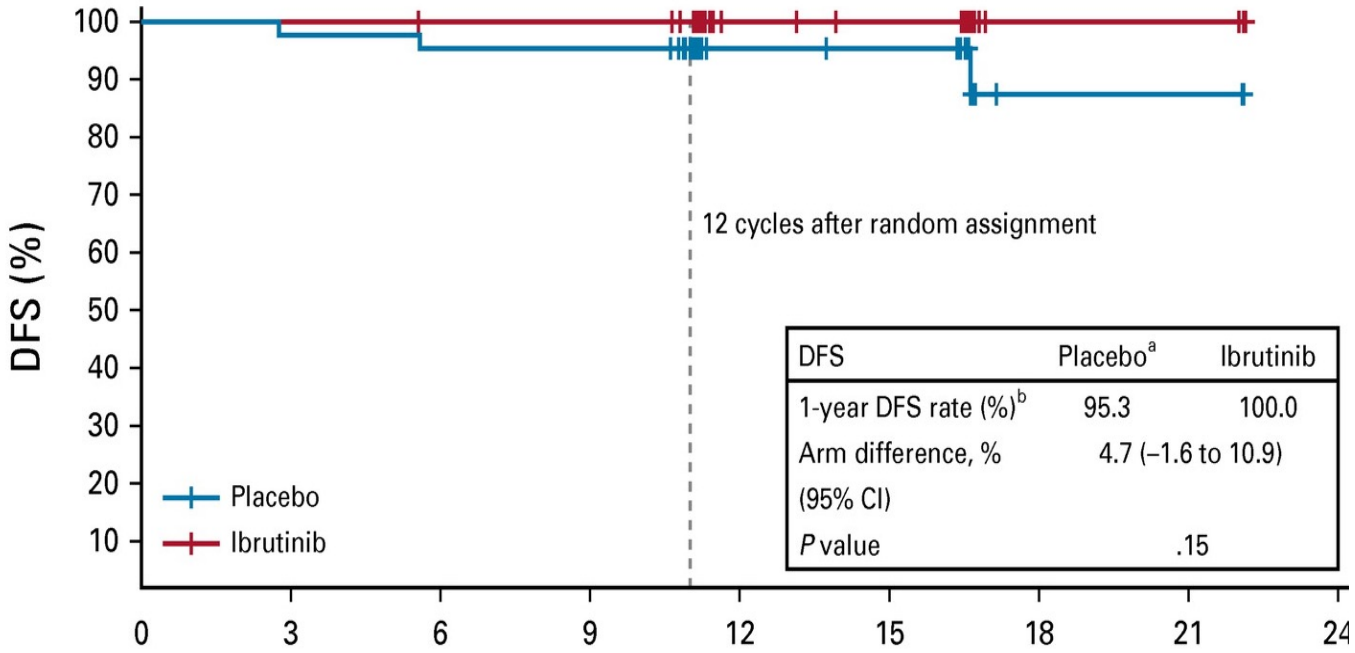
Patients (N=159)
- Previously untreated CLL/SLL
- Active disease requiring treatment per iwCLL criteria[1]
- Aged ≤70 years
- ECOG PS 0–2

Ibrutinib lead-in
Ibrutinib 420 mg once daily (3 cycles[a])

Ibrutinib + Venetoclax
Ibrutinib 420 mg once daily + venetoclax 400 mg once daily (12 cycles[a])

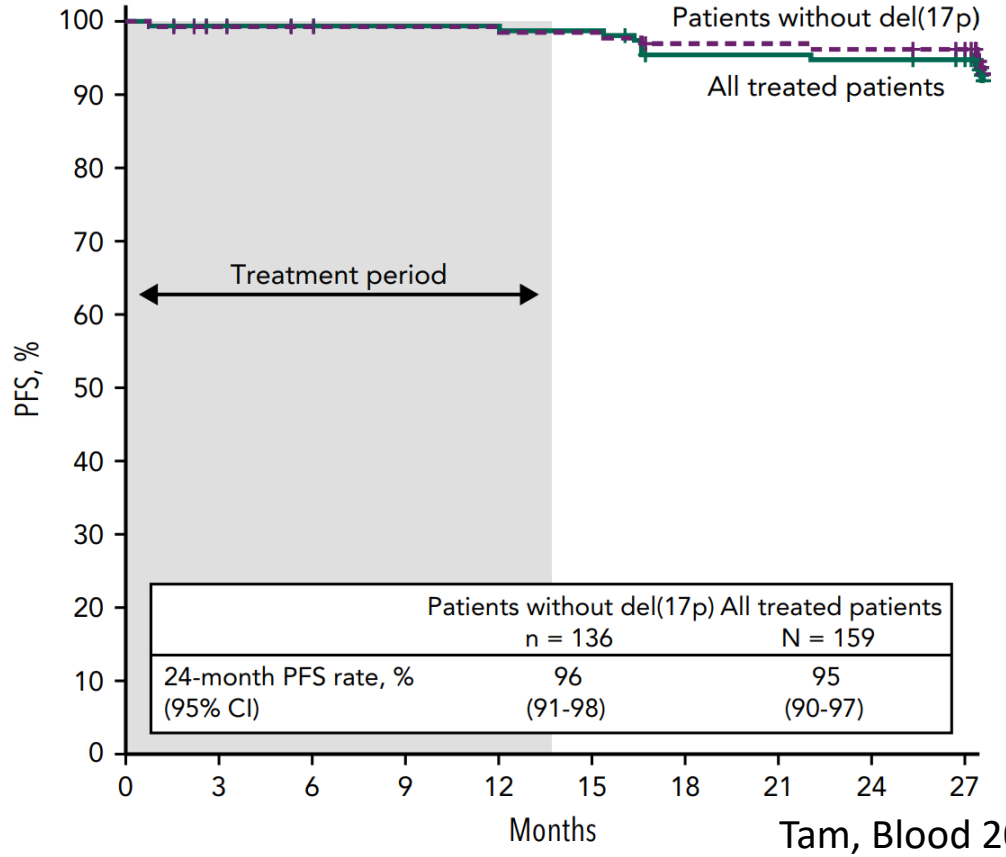
MRD-guided discontinuation

Follow-up



DFS	Placebo[a]	Ibrutinib
1-year DFS rate (%)[b]	95.3	100.0
Arm difference, % (95% CI)	4.7 (–1.6 to 10.9)	
P value	.15	

Wierda, JCO 2021



	Patients without del(17p) n = 136	All treated patients N = 159
24-month PFS rate, % (95% CI)	96 (91-98)	95 (90-97)

Tam, Blood 2022

Clinical evidence of Ven+Ibr fixed duration 1st-line

Phase 3 GLOW

Patients (N=106)
- Previously untreated CLL/SLL
- ≥ 65 years of age or < 65 years with CIRS > 6 or CrCL < 70 mL/min

Ibrutinib lead-in
Ibrutinib 420 mg once daily (3 cycles[a])

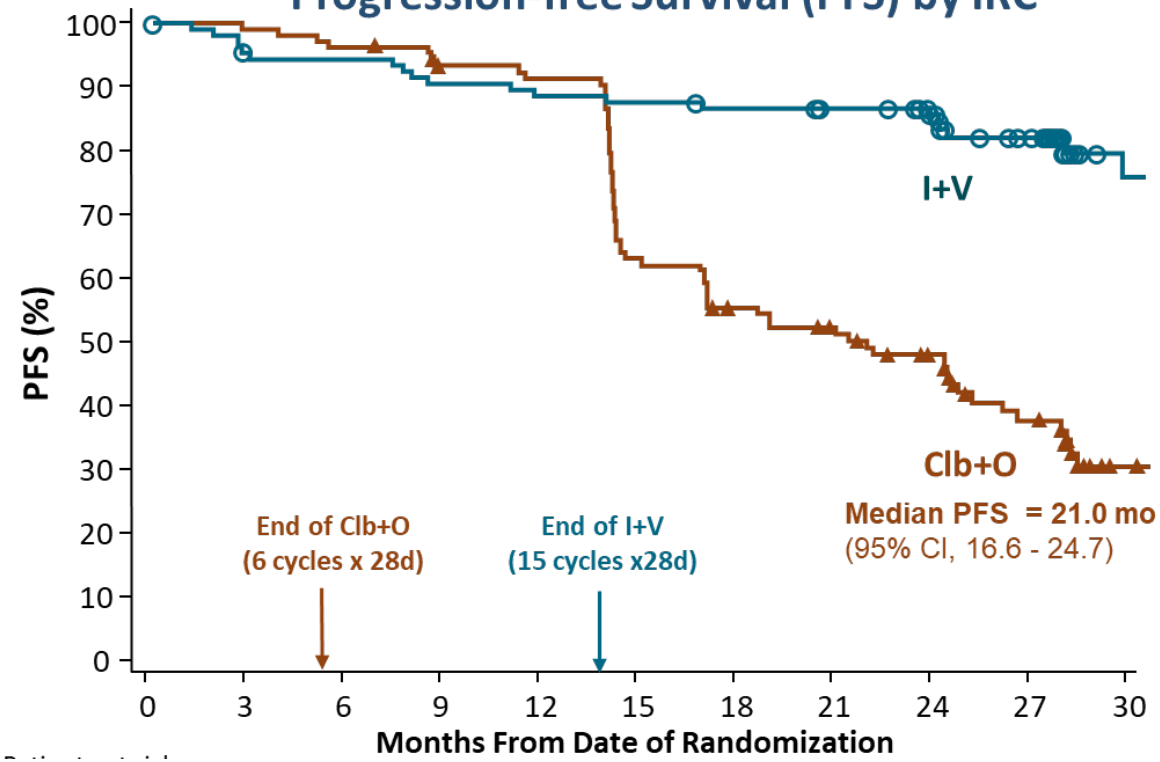
→

Ibrutinib + Venetoclax
Ibrutinib 420 mg once daily + venetoclax 400 mg once daily (12 cycles[a])

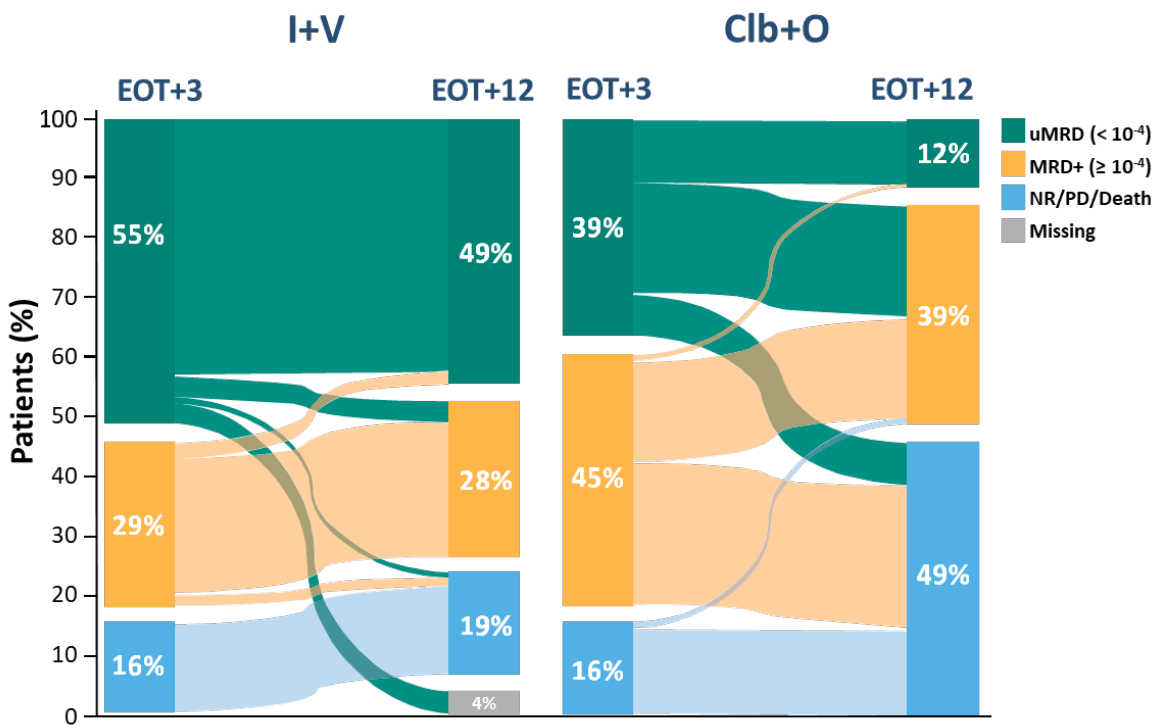
→ **Follow-up**

Responses (ITT):
- CR: 39%
- uMRD: PB 55% / BM 52%

Progression-free Survival (PFS) by IRC



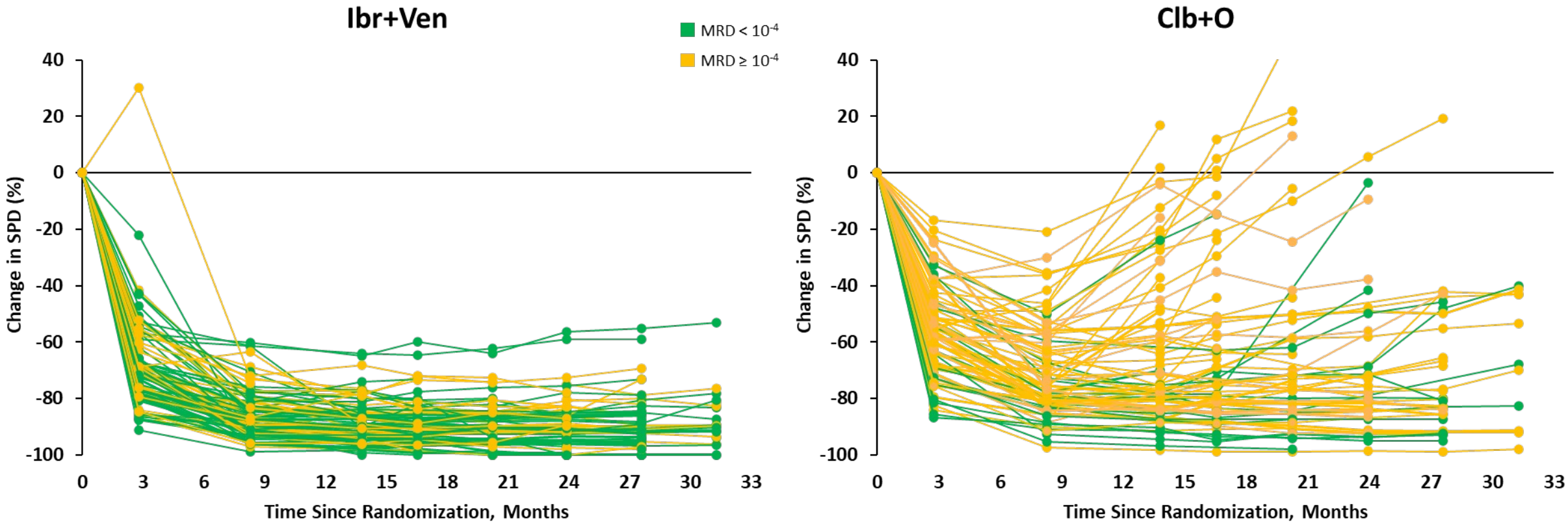
Peripheral Blood MRD (NGS)



Sustained MRD responses

Kater, NEJMe 2022

Lymph Node Responses Were Better Maintained Over Time With Ibr+Ven vs Clb+O in Patients With Detectable BM MRD

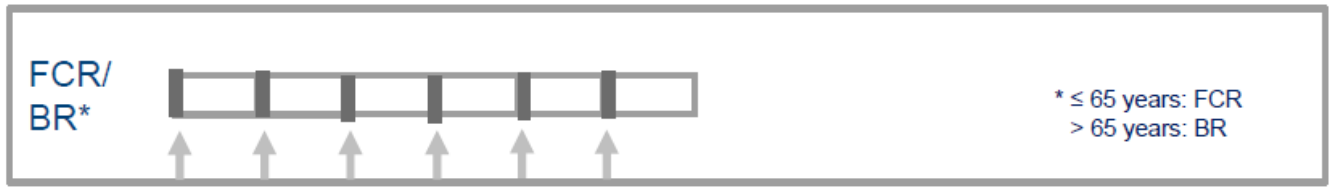
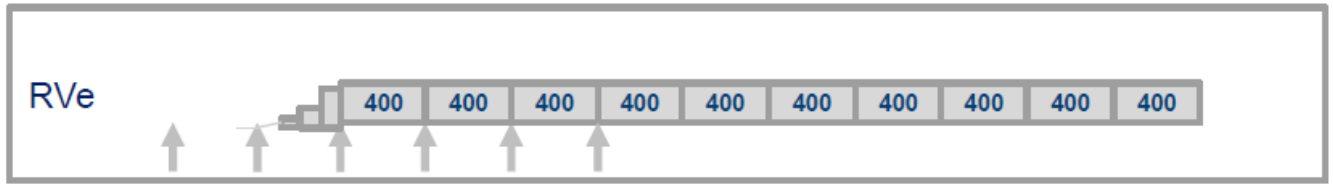
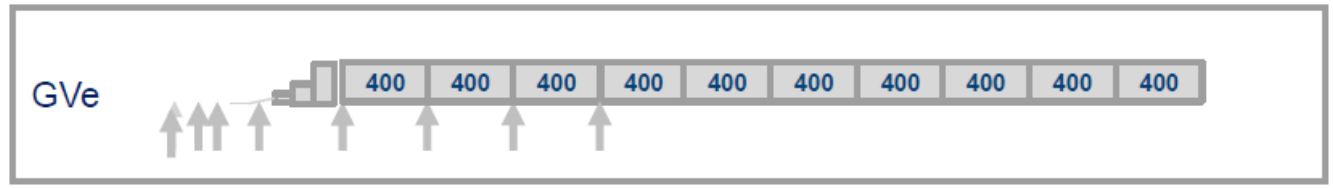
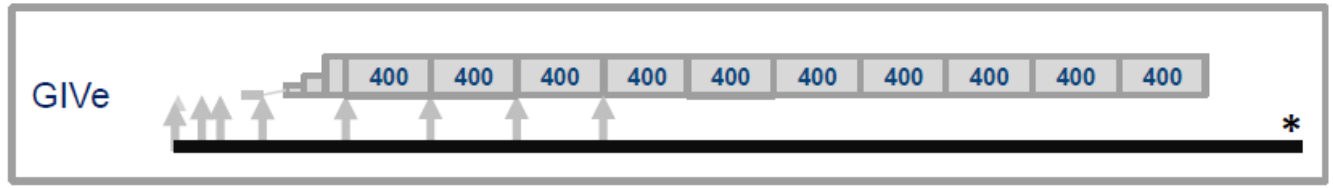


[a] < 10^{-4} at EOT+3.
BM, bone marrow; EOT, end of treatment; SPD, sum of the product of perpendicular dimensions.

Kater, NEJMe 2022

GAIA/CLL13 Study : Treatment regimen

Treatment regimen in 28 days (D) interval cycles (C)

FCR/BR*		Fludarabine 25mg/m² d1-3 iv Cyclophosphamide 250mg/m² d1-3 iv Rituximab 375/500mg/m² d1 iv Bendamustine 90mg/m² d1+2 iv Rituximab 375/500mg/m² d1iv
RVe		Venetoclax ramp up 20 – 400mg po Venetoclax 400mg po C3-C12 Rituximab 375/500mg/m² d1 iv
GVe		Venetoclax ramp up 20 – 400mg po Venetoclax 400mg po C3-C12 Obinutuzumab 1000mg/m² iv d1+8+15 during C1, d1 C2-C6
GIVe		Ibrutinib 420mg po from d1 C1 Venetoclax ramp up 20 – 400mg po Venetoclax 400mg po C3-C12 Obinutuzumab 1000mg/m² iv d1+8+15 during C1, d1 C2-C6

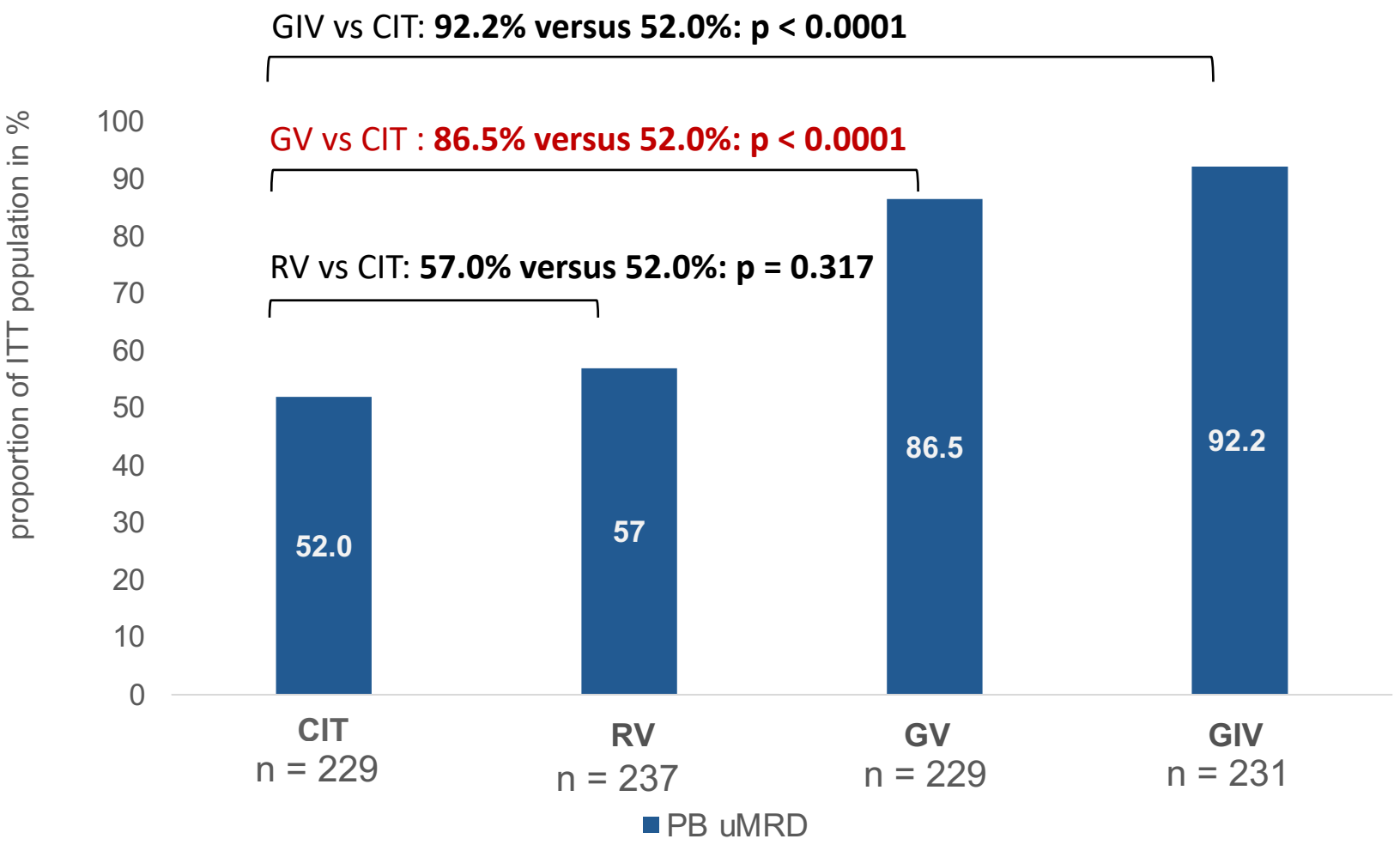
* Continuation of ibrutinib up to cycle 36 allowed, if MRD still detectable

Chemotherapy | CD20-antibody | 400 Venetoclax (V) | Ramp-Up | Ibrutinib (I)

Eichhorst EHA 2022

Results of coprimary endpoint rate of undetectable minimal residual disease

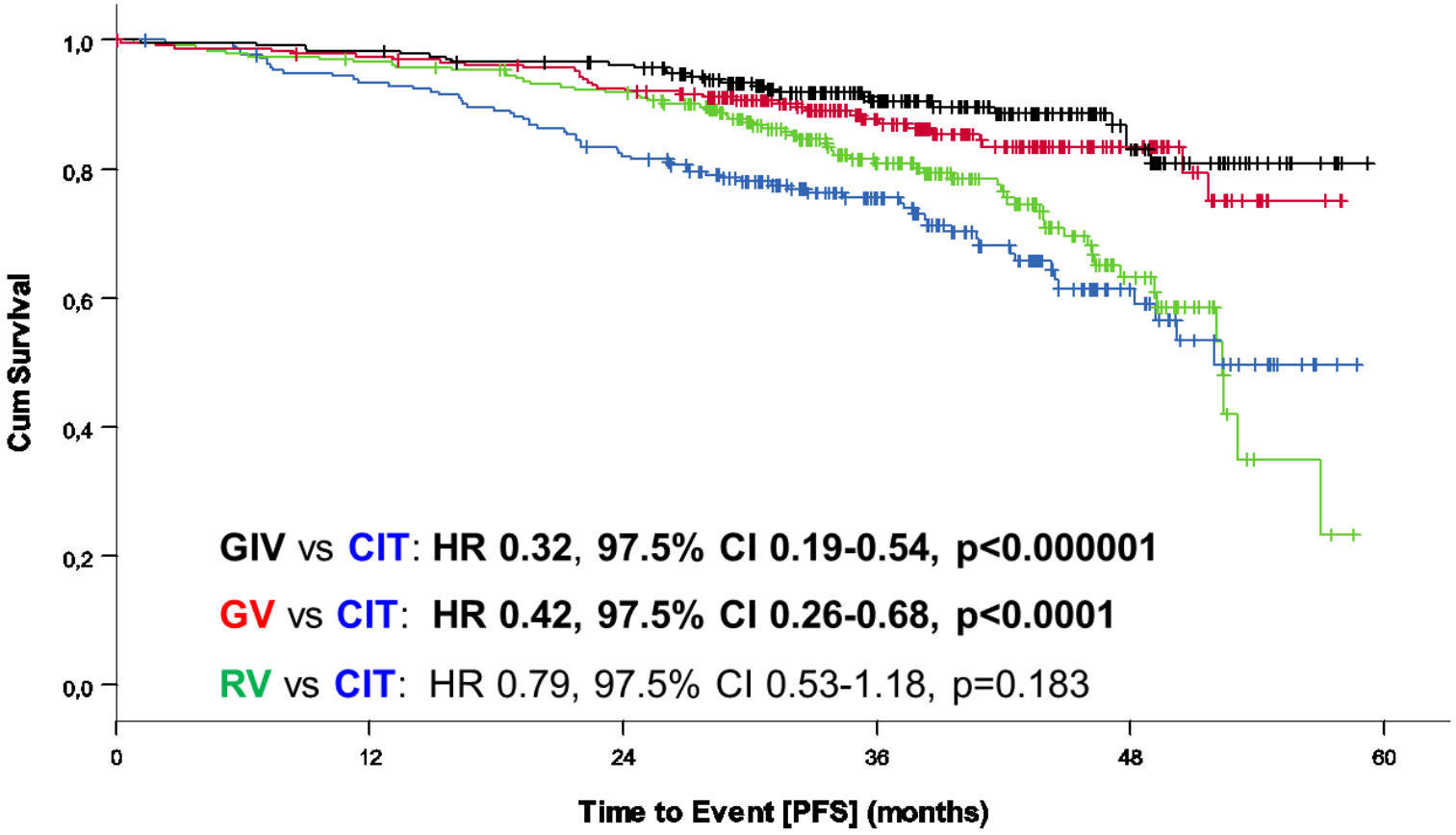
Coprimary endpoint: uMRD (< 10^{-4}) at Mo15 in PB by 4-colour-flow



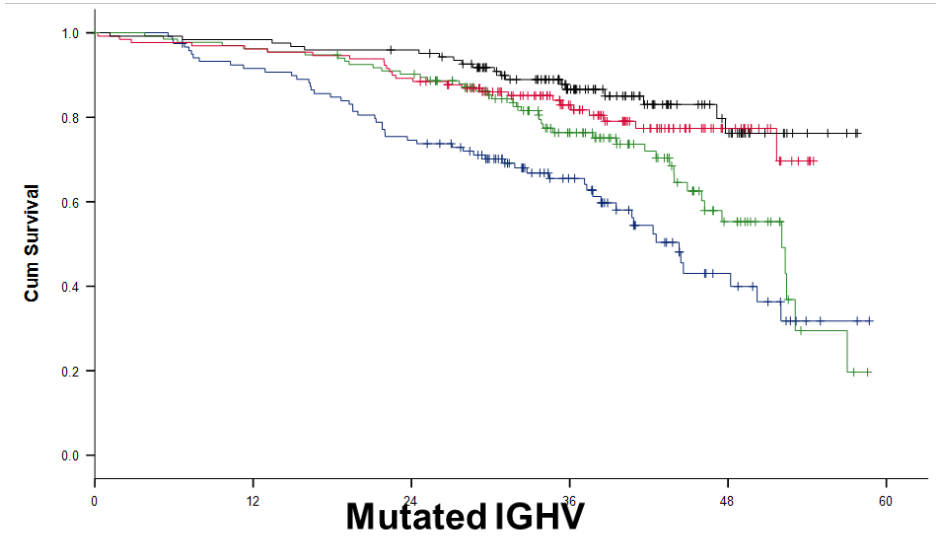
	uMRD%	97.5% CI
GIV	92.2	87.3 – 95.7
GV	86.5	80.6 – 91.1
RV	57.0	49.5 – 64.2
CIT	52.0	44.4 – 59.5

Eichhorst B. et al., ASH 2021: abstract 72

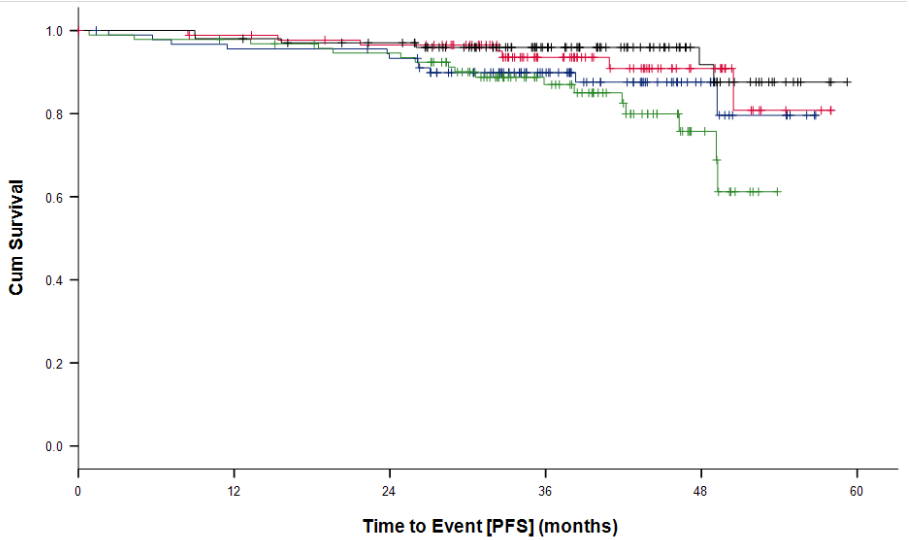
Results of the coprimary endpoint progression-free survival (PFS)



Unmutated IGHV



Mutated IGHV



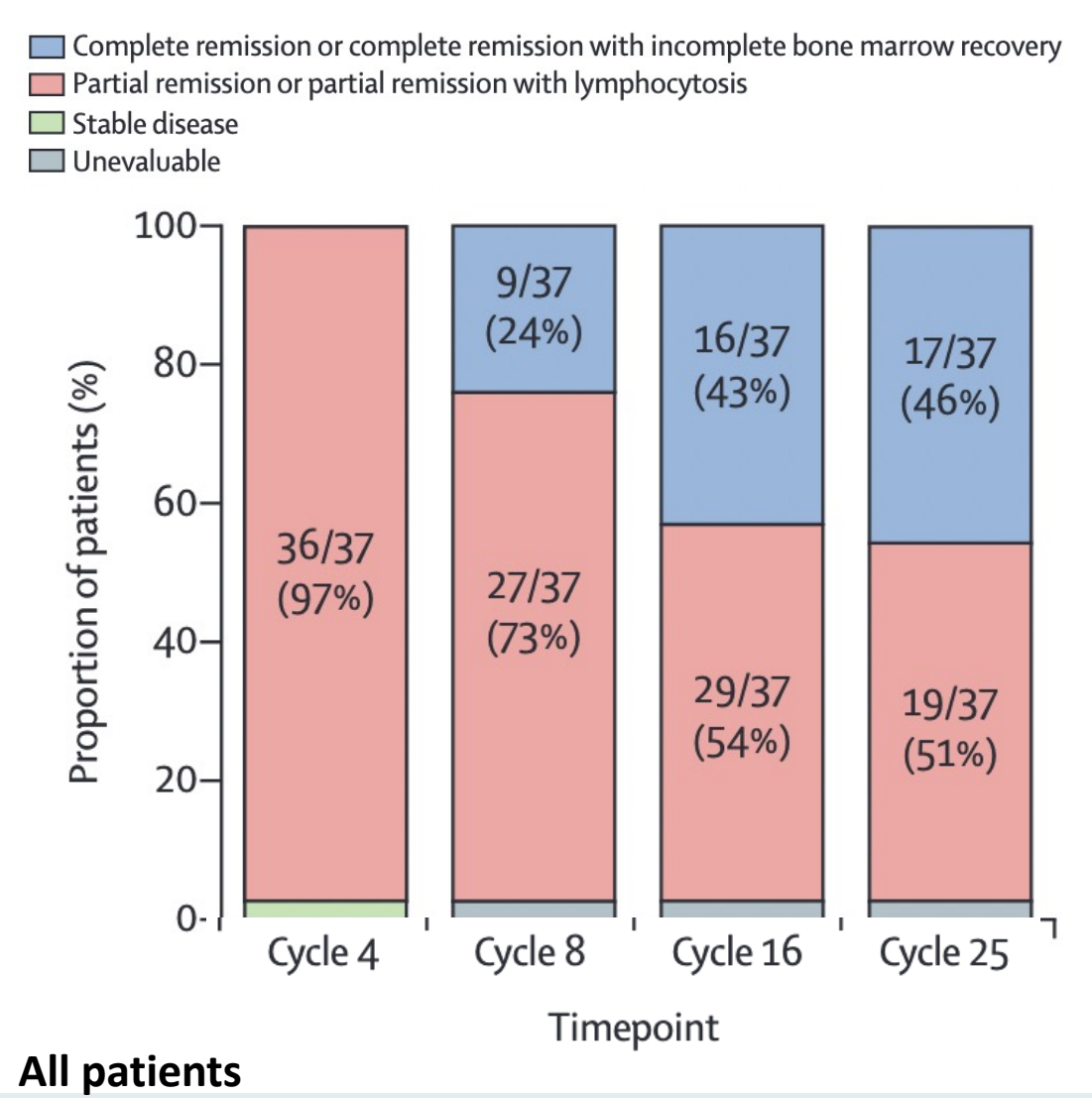
Eichhorst EHA 2022

Acalabrutinib, venetoclax, and obinutuzumab as frontline treatment for chronic lymphocytic leukaemia: a single-arm, open-label, phase 2 study

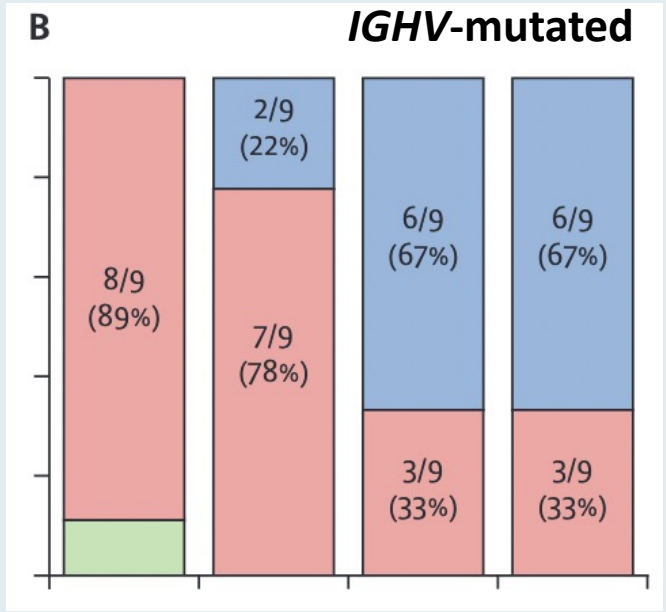
Matthew S Davids, Benjamin L Lampson*, Svitlana Tyekucheva, Zixu Wang, Jessica C Lowney, Samantha Pazienza, Josie Montegaard, Victoria Patterson, Matthew Weinstock, Jennifer L Crombie, Samuel Y Ng, Austin I Kim, Caron A Jacobson, Ann S LaCasce, Philippe Armand, Jon E Arnason, David C Fisher, Jennifer R Brown*

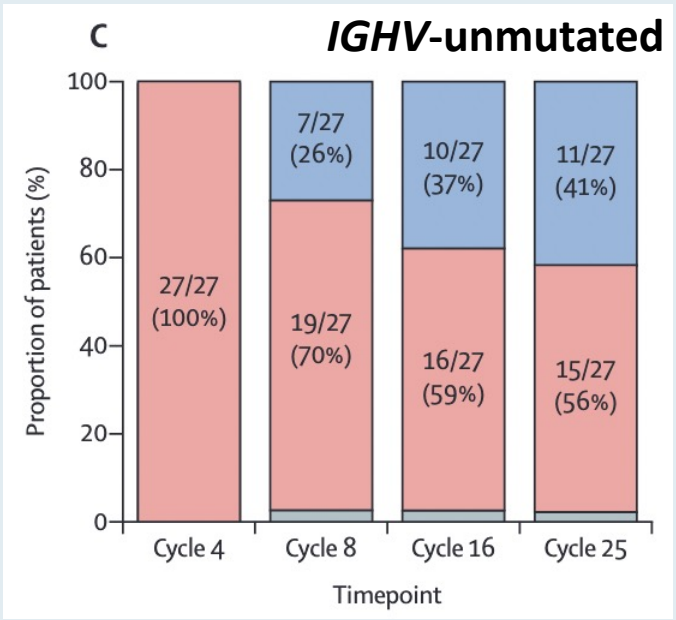
Davids MS et. al, *Lancet Oncol*. 2021;22(10):1391-1402.

Acalabrutinib, venetoclax and obinutuzumab: Response rates at the start of indicated cycles



All patients





Davids MS et. al, *Lancet Oncol*. 2021;22(10):1391-1402.

RTP RESEARCH TO PRACTICE

Updated Results from a Multicenter, Phase 2 Study of Acalabrutinib, Venetoclax, Obinutuzumab (AVO) in a Population of Previously Untreated Patients with CLL Enriched for High-Risk Disease

Ryan C et. al.

ASH 2022; Abstract 344
Saturday, December 10, 2022, 4:15 PM

Toxicity data

Serious toxicity GLOW >> CAPTIVATE

- HR (95% CI) for overall survival: 1.048 (0.454, 2.419), with 11 deaths in I+V arm and 12 in Clb+O arm (Table)
- Causes of death were generally similar in nature for both study arms, with infections (including COVID-19-related pneumonia) and cardiac events most common

Death from Any Cause	During Treatment			During Follow-up	
	I+V (N=106)		Clb+O (N=105)	I+V (N=106)	Clb+O (N=105)
	Ibr lead-in	I+V			
Total, n	**4**	**3**	**2**	**4**	**10**
Infections and Infestations	1	-	1	2	6
Cardiac Disorders	2[a]	-	-	-	2
General Disorders (Sudden Death)	-	2	-	1	-
Neoplasm	1	-	-	-	-
Nervous System Disorders	-	1	-	-	1
Hepatobiliary Disorders	-	-	1	-	-
Respiratory, Thoracic, Mediastinal Dis.	-	-	-	-	1
Progressive Disease/Richter Transform.	-	-	-	1	-

(sudden) cardiac deaths:

- CIRS score ≥ 10
- History of hypertension, cardiovascular disease, and/or diabetes

Treatment cessation mitigates treatment-related toxicities
Ho141/VISION trial in R/R CLL

	Ibrutinib continuation group (n=24)			Treatment cessation group (n=48)			Patients not randomly assigned (n=116)			
	Grade 2	Grade 3	Grade 4	Grade 2	Grade 3	Grade 4	Grade 2	Grade 3	Grade 4	Grade 5
Patients with any adverse event, highest grade only	9 (38%)	7 (29%)	2 (8%)	7 (15%)	7 (15%)	0	37 (32%)	40 (34%)	7 (6%)	1 (1%)
Infections	9 (38%)	5 (21%)	0	5 (10%)	2 (4%)	0	31 (27%)	14 (12%)	2 (2%)	1 (1%)
Neutropenia	0	0	0	0	2 (4%)	0	2 (2%)	2 (2%)	2 (2%)	0
Diarrhoea, abdominal discomfort	2 (8%)	0	0	1 (2%)	0	0	7 (6%)	0	0	0
Bleeding	1 (4%)	1 (4%)	0	0	0	0	10 (9%)	0	0	0
Arthralgia, muscle pain	1 (4%)	0	0	1 (2%)	0	0	3 (3%)	0	0	0
Atrial fibrillation	1 (4%)	0	0	0	0	0	3 (3%)	0	0	0
Malignancies, neoplasm	0	1 (4%)	1 (4%)	3 (6%)	1 (2%)	0	4 (3%)	7 (6%)	0	0
Hypertension	2 (8%)	1 (4%)	0	0	0	0	5 (4%)	2 (2%)	0	0
Headache	0	0	0	2 (4%)	0	0	0	0	0	0
Nail changes	0	0	0	0	0	0	1 (1%)	0	0	0
Other	6 (25%)	2 (8%)	1 (4%)	5 (10%)	3 (6%)	0	30 (26%)	19 (16%)	3 (3%)	0

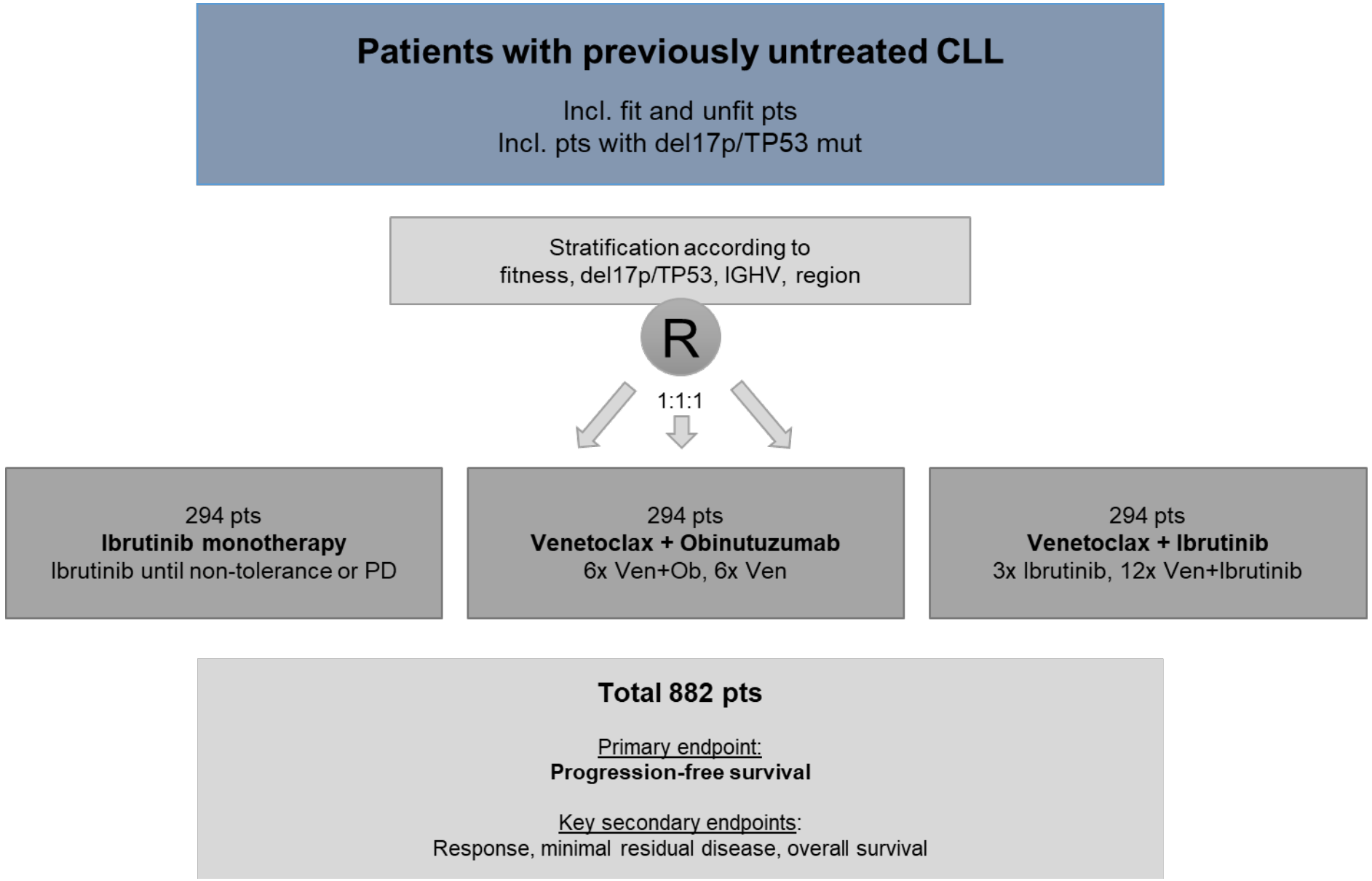
Grade 1 adverse events were not collected.

Table 2: Summary of treatment-related adverse events after cycle 15

Venetoclax + BTKi Based Combinations
Conclusions

- Strong rationale for combination: sensitize to Bcl-2 dependency by inhibition of lymph node migration
- High response rates are sustained after treatment cessation
- MRD is less of a predictive marker for fixed duration venetoclax + BTK-i
- Toxicities similar to single agents
  - Cardiac toxicity of concern in population at-risk

CLL17


Patients with previously untreated CLL
Incl. fit and unfit pts
Incl. pts with del17p/TP53 mut
Stratification according to
fitness, del17p/TP53, IGHV, region
R
1:1:1
294 pts
Ibrutinib monotherapy
Ibrutinib until non-tolerance or PD
294 pts
Venetoclax + Obinutuzumab
6x Ven+Ob, 6x Ven
294 pts
Venetoclax + Ibrutinib
3x Ibrutinib, 12x Ven+Ibrutinib
Total 882 pts
Primary endpoint:
Progression-free survival
Key secondary endpoints:
Response, minimal residual disease, overall survival

Acknowledgements

Clinical collaborations:
- Barbara Eichhorst, Kirsten Fischer, Michael Hallek (GCLLSG
- Carsten Niemann (Nordic CLL studygroup)