Venetoclax

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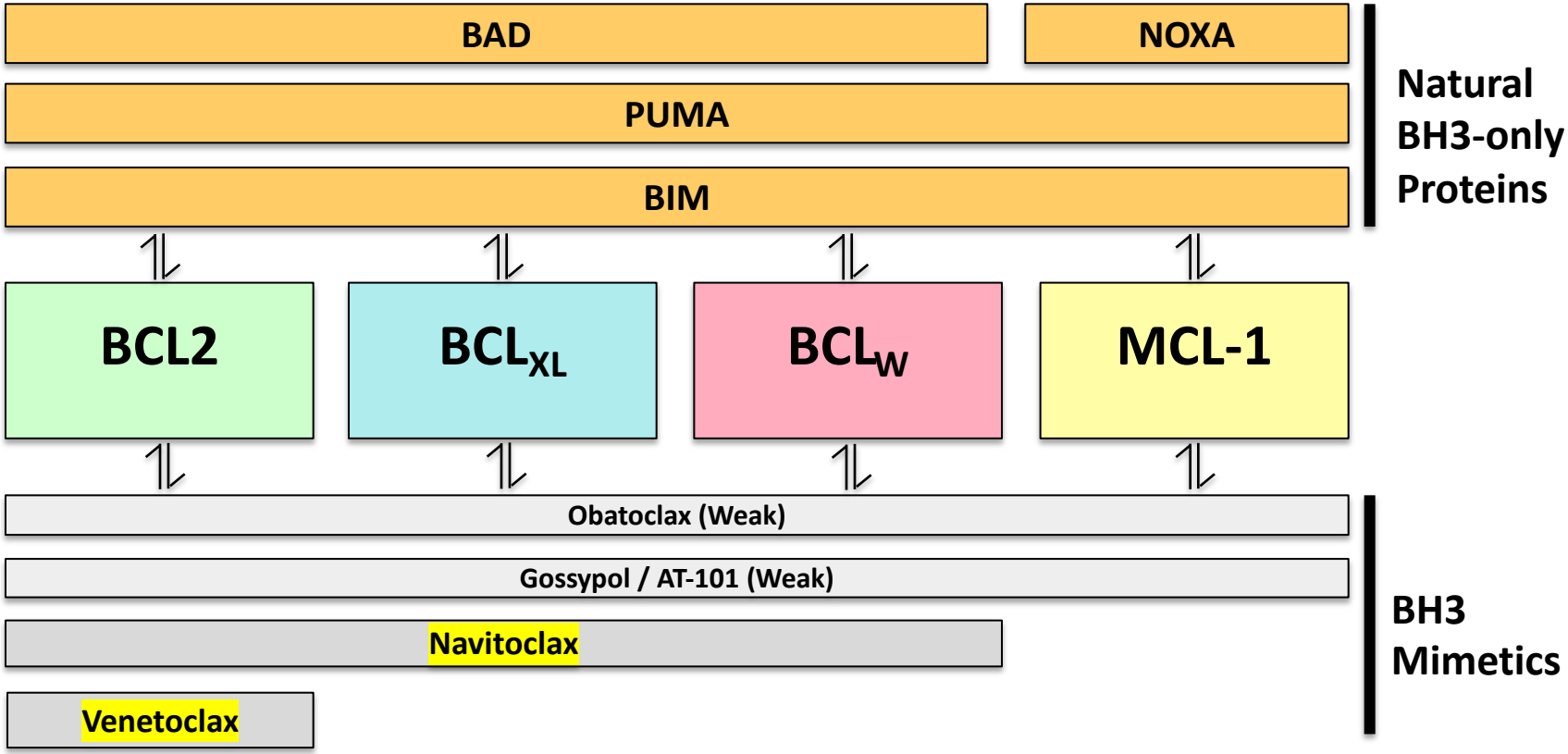
Disclosure of Constantine TAM

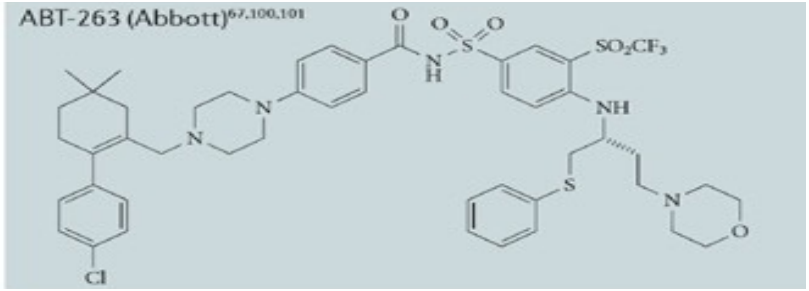
Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
Janssen	x					x	
AbbVie	x					x	
BeiGene	x					x	
LOXO						x	
AstraZeneca						x	

BH3-Mimetics in the Clinic

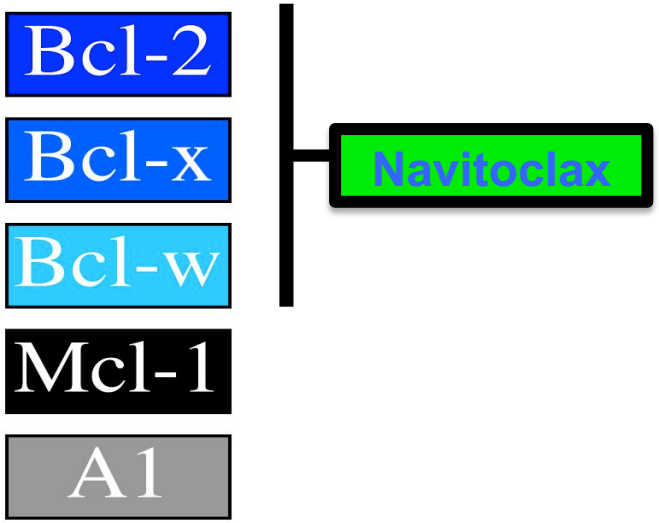


Tam Semin Oncol 2015

Navitoclax



Park, J Med Chem, 2008

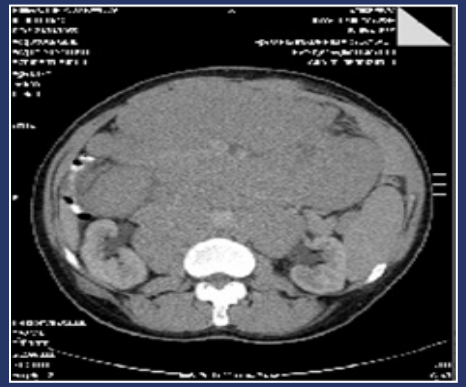


- ABT-263 (navitoclax) entered clinical trials, having better oral bioavailability than ABT-737
- Phase I studies show 35% response rate as a single agent in relapsed refractory CLL (Roberts, JCO, 2012)

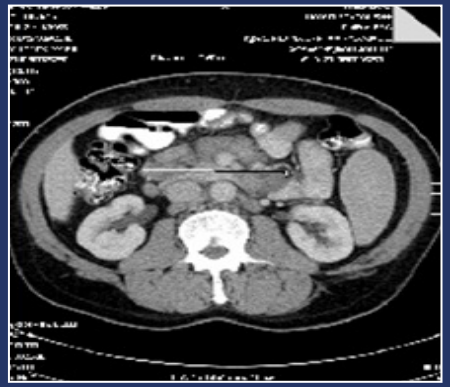
Navitoclax (ABT-263) Phase II study in CLL: Rapid cytoreduction in refractory CLL

- 44 year-old man, Rai stage 3, del(11q)
  - Prior treatments: R-FC x 6 (PR 15 months) then R-CHOP x 6 (PR 6 months)
  - Tumor lysis after first 100 mg dose

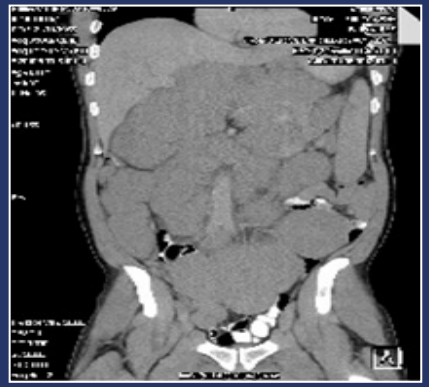
Baseline



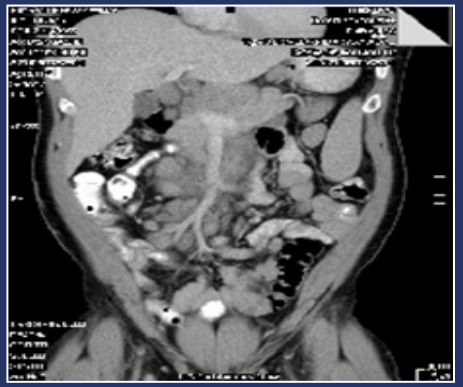
Week 10



Baseline



Week 10



19 month PR on study

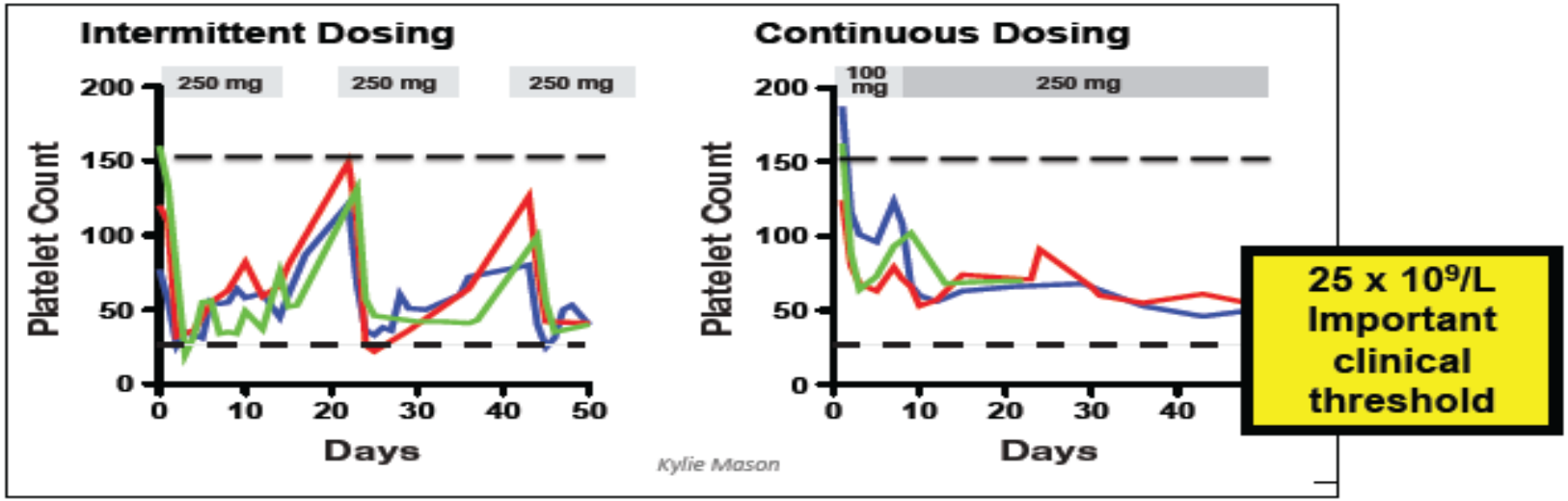
PR, partial response.

Seymour J, *et al.* EHA 2011. Abstract 0534 (oral presentation).

BH3 mimetics: navitoclax

Dose limiting toxicity thrombocytopenia➔ in mice anti- $BCLx_L$ effect

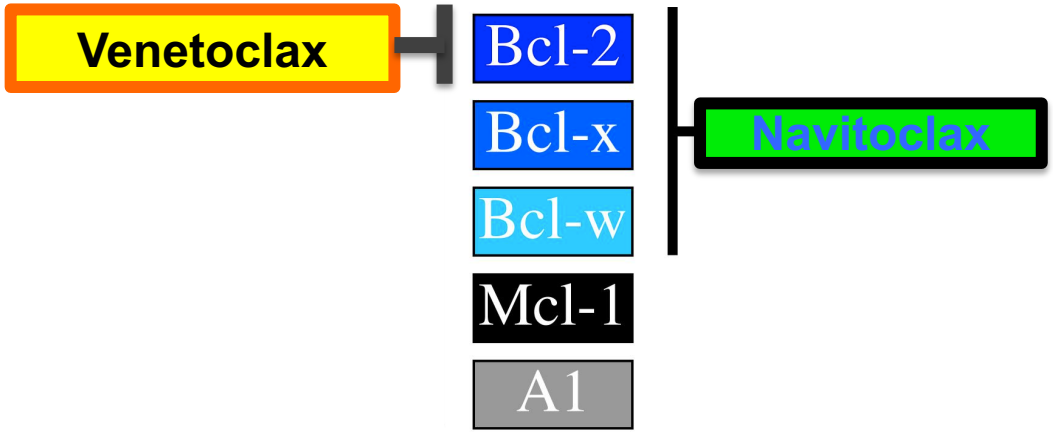
(Mason, Cell, 2007)



Thrombocytopenia limits the dose of navitoclax that can be safely given to patients

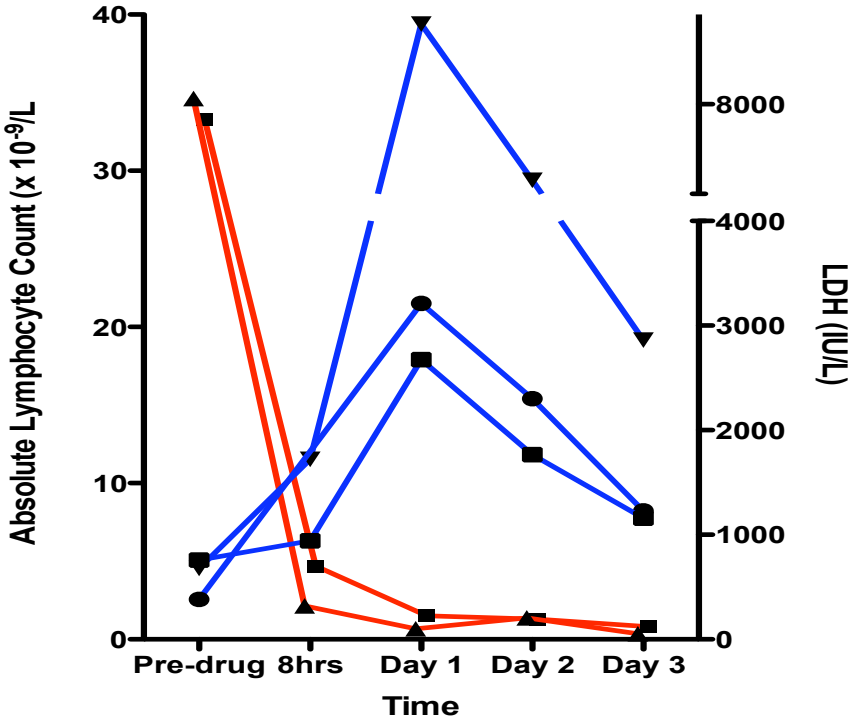
ABT-199: Venetoclax

- Selectively targets BCL2
- Compared with navitoclax, venetoclax has significantly less binding to $BCLx_L$ and BCLw
- Potential for giving higher doses without thrombocytopenia resulting in better clinical response rates



ABT-199 induces rapid reduction in CLL

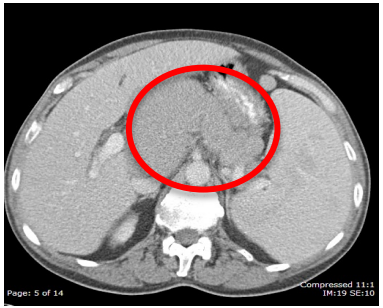
- Single dose of 200mg (n=2) or 100mg (n=1)
- Rapid reduction in CLL within 24hrs
- Evidence of tumor lysis in all 3 patients, one with transient disseminated intravascular coagulation



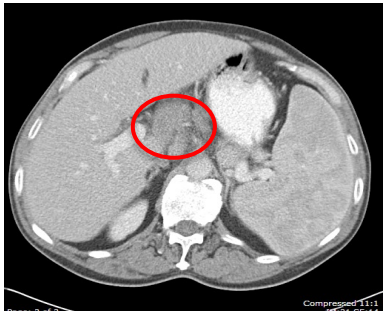
Souers et al, 2013 Nat Med
Roberts et al, 2012 EHA Congress

Lymphocyte Counts (Red; n = 2) and LDH (Blue; n = 3) post first dose

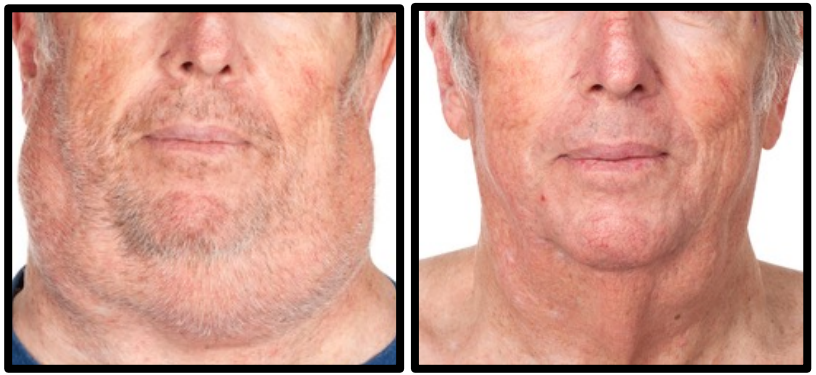
Phase I Venetoclax Response



Baseline



6 weeks of venetoclax

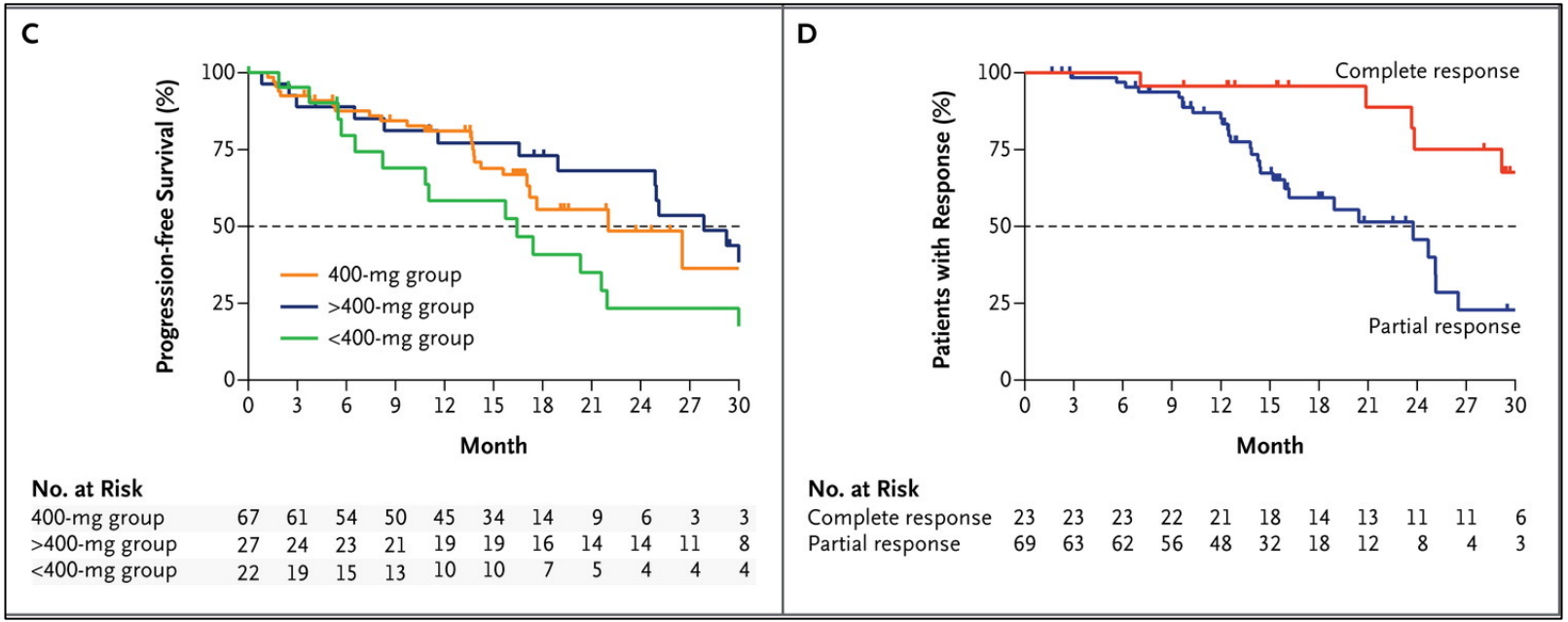


Images courtesy of MA Anderson

Durability of benefit depends on dose and response

Progression-free survival: impact of dose

Duration of response: impact of depth of response

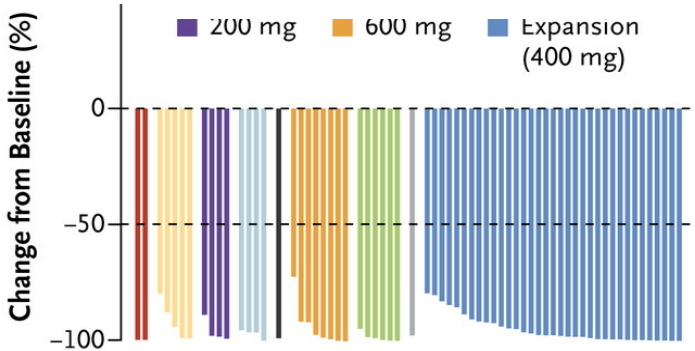


Roberts et al NEJM 2016

The dose studied ranges from <400, 400 and >400mg. The dose registered in Singapore is 400mg

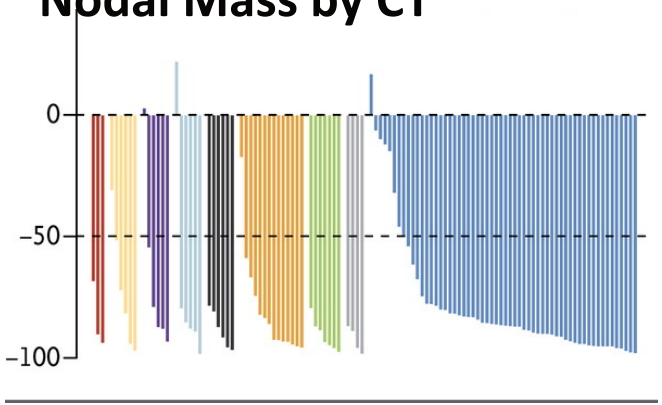
Venetoclax – responses in all compartments

Peripheral Blood Lymphocytes

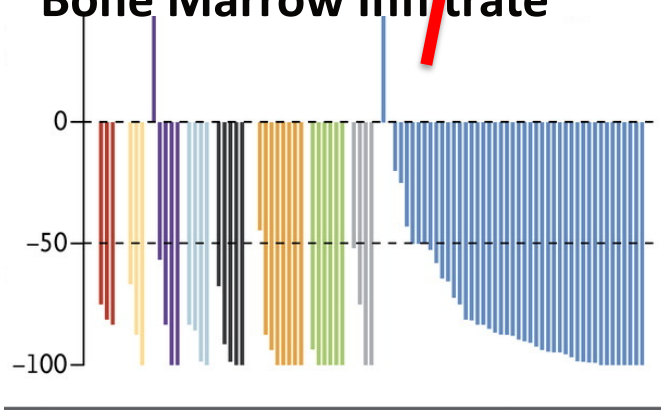


17 patients in CR were tested for MRD – 6 (35%) were MRD-negative

Nodal Mass by CT



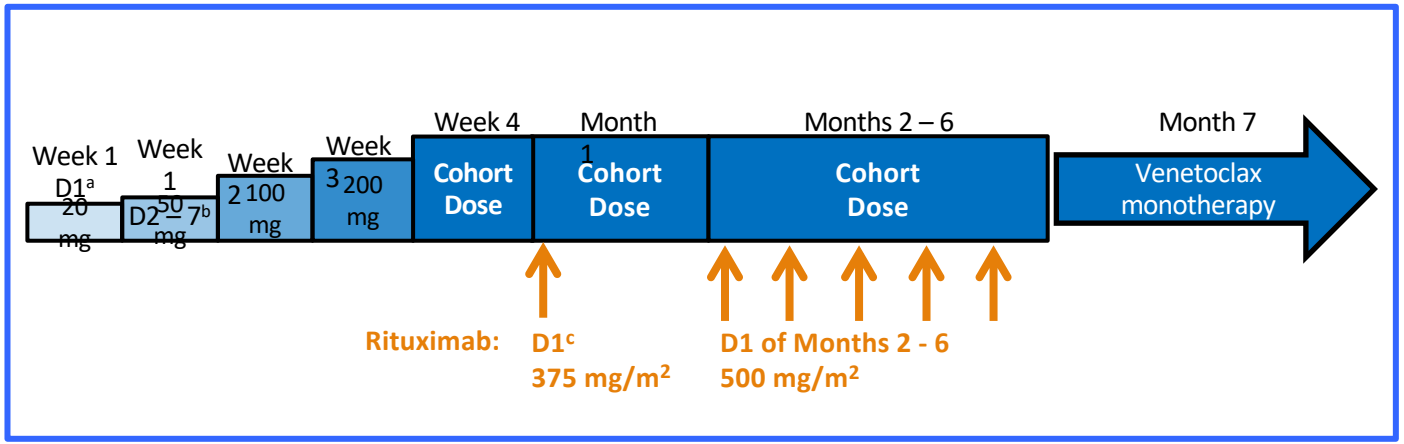
Bone Marrow Infiltrate



Roberts, et. al.; NEJM, 2016

Adding Rituximab To Venetoclax

Final Escalation Strategy:



D, day
[a] Test dose
[b] Protocol amendment permits 20 mg for first week, as needed, if one or more electrolytes meet Cairo-Bishop criteria and/or if there is ≥ 30% decrease in ALC with first dose
[c] May be split and administered over 2 consecutive days (Month 1 D1 and D2)

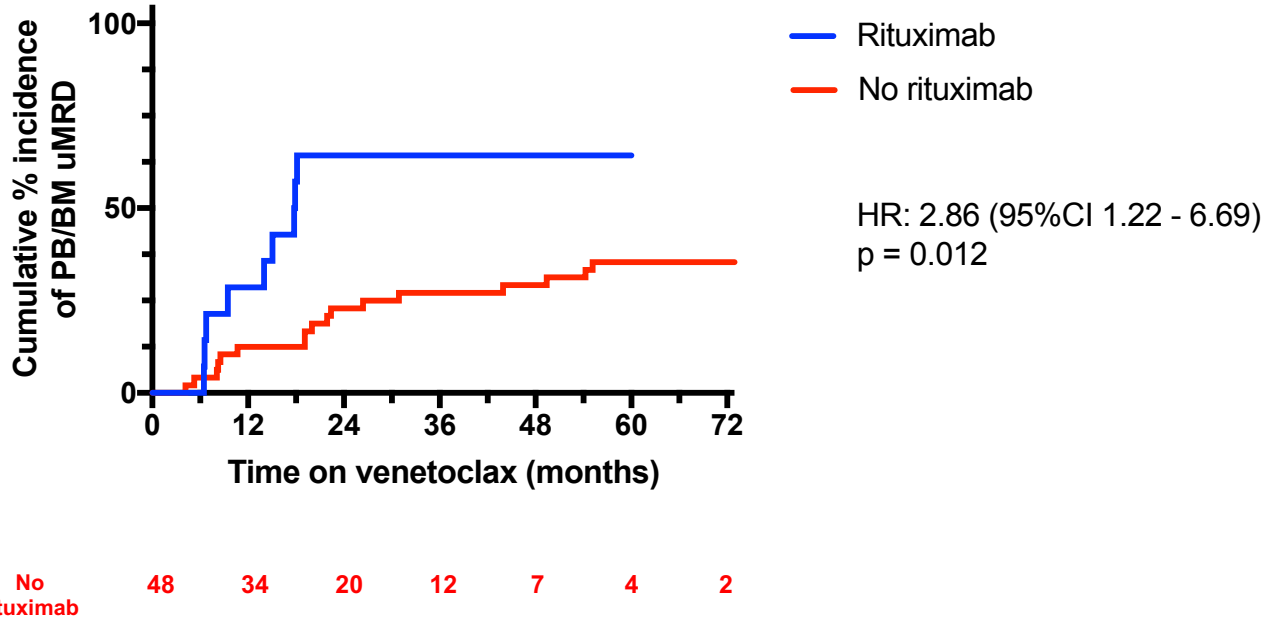
Dose escalation phase: 200, 300, 400, 500, 600mg/day cohorts (n = 41)

Safety expansion phase: 400mg/day cohort (n = 8)

Data pooled for these safety and efficacy analyses

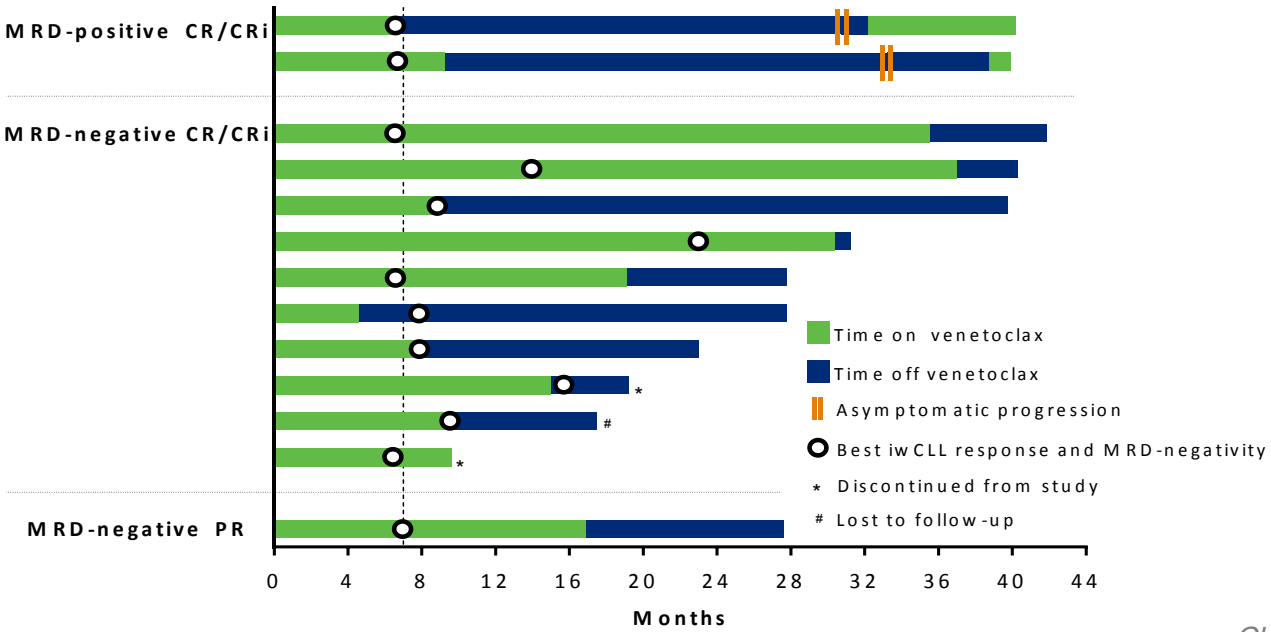
Roberts EHA 2015

Rituximab combination therapy is the dominant factor associated with uMRD attainment



Durability of complete responses following cessation of venetoclax

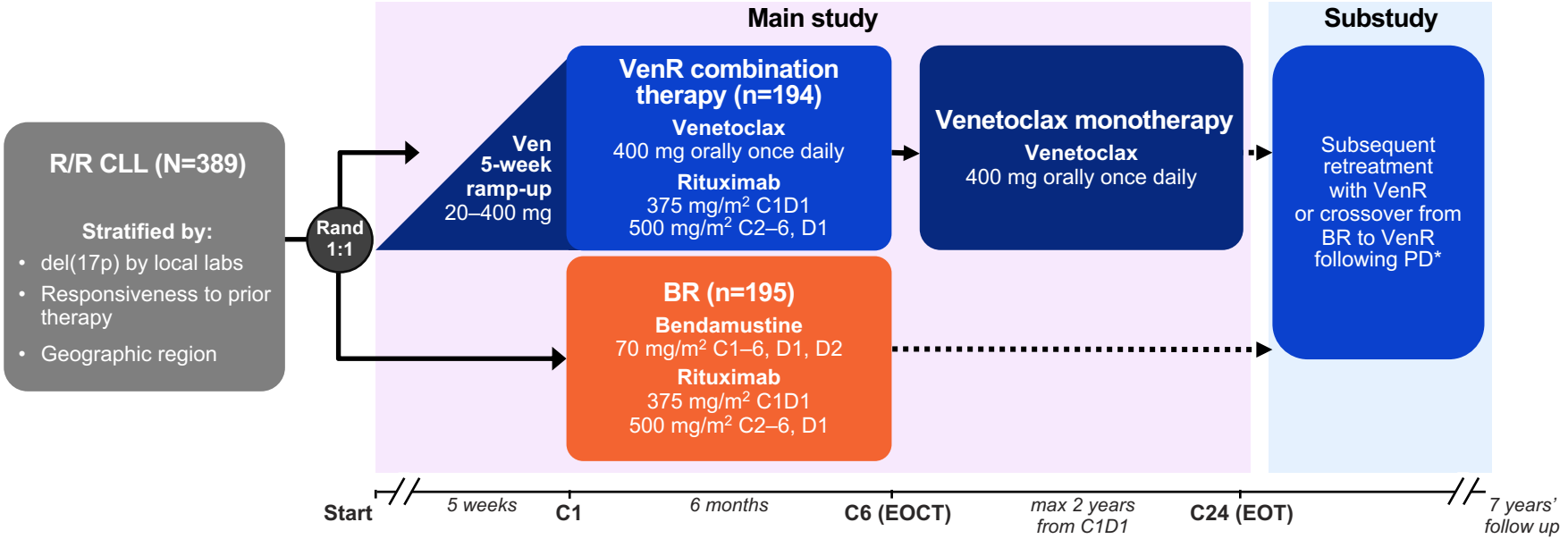
- 13 patients deep objective response (CR/CRi or MRD-negative PR)
- Stopped venetoclax after a median of 10 months of treatment (range: 4.5 – 35.5)



Choi, et. al., SOHO, 2016

MURANO (NCT02005471): 7 Year Update (EHA 2023)

- Global, Phase III, open-label, randomized study[1]



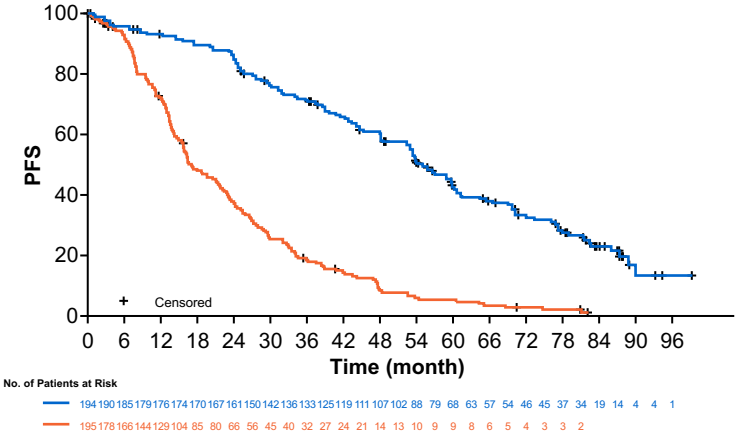
- Superior PFS and OS was observed with fixed-duration VenR vs BR in patients with R/R CLL[1]
- At 48 months of follow up, deep responses with uMRD† were associated with favorable PFS[2]

*Investigator-assessed PD according to International Workshop on Chronic Lymphocytic Leukemia (iwCLL) criteria. †uMRD is defined as <1 CLL cell/10,000 leukocytes.
BR, bendamustine-rituximab; C, cycle; D, day; del(17p), deletion 17p; EOCT, end of combination treatment; EOT, end of treatment; max, maximum; OS, overall survival; PD, progressive disease; PFS, progression-free survival; Rand, randomization; (u)MRD, (undetectable) minimal residual disease.

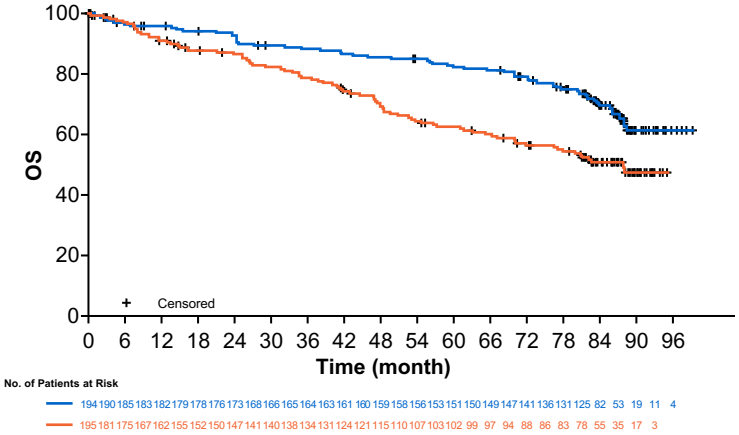
1. Seymour JF, et al. N Engl J Med 2018;378(12):1107–20.
2. Kater AP, et al. J Clin Oncol 2020;38(34)4042–54.

PFS and OS benefits with VenR over BR were sustained at 7 years

	Median PFS (95% CI), months	HR* (95% CI)	7-year PFS (%)
VenR (n=194)	**54.7** (52.3–59.9)	**0.23** (0.18–0.29) Stratified P-value <0.0001†	**23.0**
BR (n=195)	**17.0** (15.5–21.7)		**NE**



	Median OS (95% CI), months	HR‡ (95% CI)	7-year OS (%)
VenR (n=194)	**NE**	**0.53** (0.37–0.74) Stratified P-value <0.0002†	**69.6**
BR (n=195)	**87.8** (70.1–NE)		**51.0**



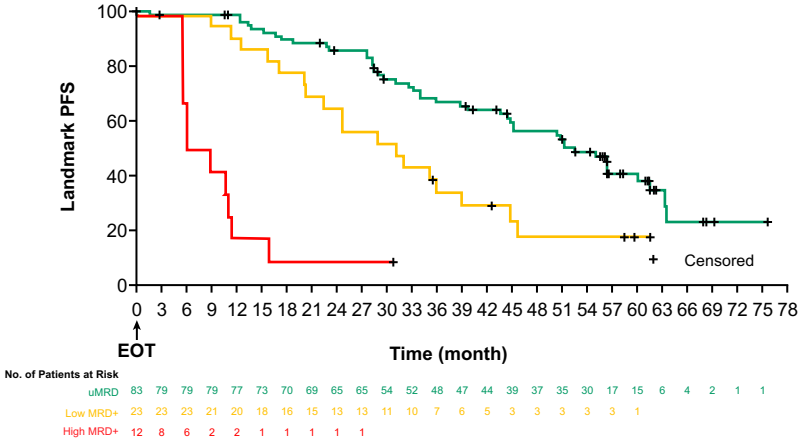
- Median follow up for efficacy (range) was 86.8 months (0.3–99.2) for VenR and 84.4 months (0.0−95.0) for BR
- No new safety signals were identified since the 5-year data cut,[1] with all patients outside of the AE reporting window§

*Stratified HR is presented, unstratified HR=0.25. †P-values are descriptive only. ‡Stratified HR is presented, unstratified HR=0.54. §All AEs were reported until 28 days after the last dose of Ven or 90 days after last dose of R, whichever was longer. After this, only deaths, serious AEs, or AEs of concern that were believed to be Ven-related were reported. AE, adverse event; CI, confidence interval; HR, hazard ratio; NE, not estimable.

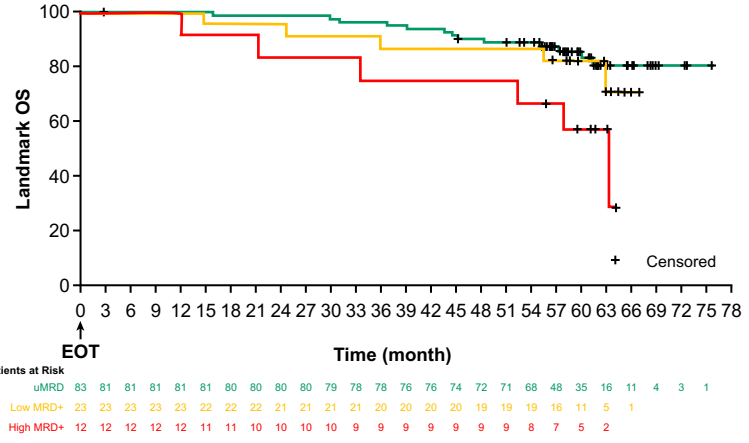
1. Seymour JF, et al. Blood 2022;140(8):839–50.

uMRD at EOT is associated with improved outcomes in the VenR arm

Patients who completed 2 years of Ven without PD*	Median PFS since EOT (95% CI), months	HR (95% CI); P-value†
uMRD (n=83)	**52.5** (44.5–61.5)	
Low MRD+ (n=23)	**29.3** (20.2–37.5)	**vs uMRD:** **3.46** (1.75–6.86); <0.0001
High MRD+ (n=12)	**4.6** (2.8–8.3)	**vs uMRD:** **17.22** (5.70–52.00); <0.0001



Patients who completed 2 years of Ven without PD*	Median OS since EOT (95% CI), months	HR (95% CI); P-value†
uMRD (n=83)	**NE** (NE–NE)	
Low MRD+ (n=23)	**NE** (62.7–NE)	**vs uMRD:** **1.07** (0.34–3.35); NS
High MRD+ (n=12)	**63.1** (51.5–NE)	**vs uMRD:** **2.39** (0.73–7.80); NS



Achievement of uMRD was associated with prolonged PFS in VenR-treated patients

Low MRD+ is defined as ≥1 CLL cell/10,000 leukocytes to <1 CLL cell/100 leukocytes, high MRD+ is defined as ≥1 CLL cell/100 leukocytes. Stratified HR (95% CI) for Low MRD+ vs High MRD+: PFS, 3.22 (1.04–9.97), P=0.0350; OS, 2.27 (0.44–11.69), P=NS.

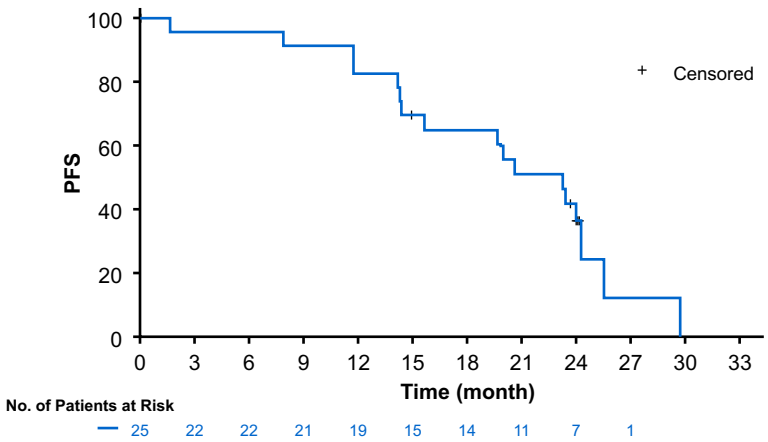
*Investigator-assessed PD according to iwCLL criteria. †Stratified HRs and P-values are presented, P-values are descriptive only. NS, not significant.

VenR retreatment resulted in high response rates, which translated to meaningful PFS amongst retreated patients

- Amongst VenR-retreated patients, median follow up (range) was 33.4 months (2.7–44.0)
  - Median PFS (95% CI) was 23.3 months (15.6–24.3)
  - Best ORR was high at 72.0%; CR rate was 24%
  - Median OS was not reached

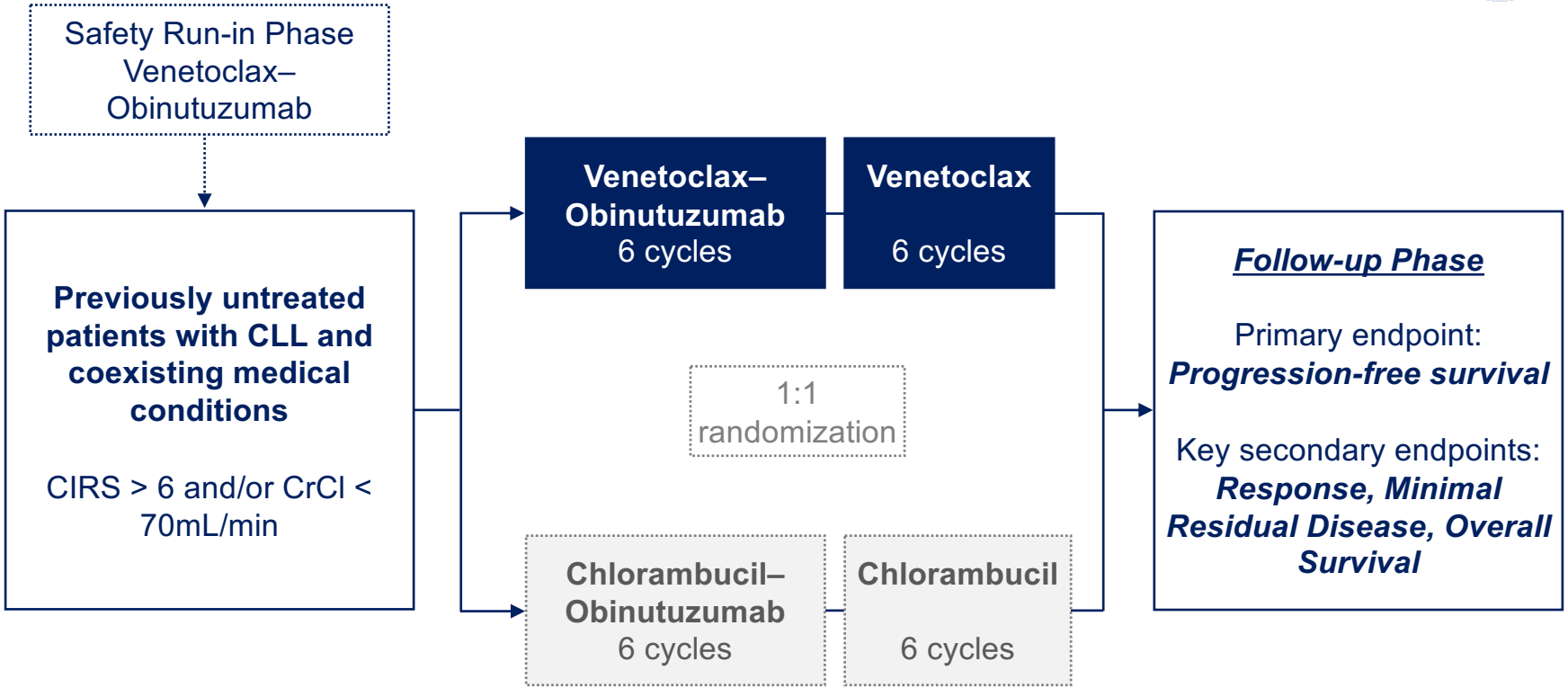
Response rates indicate that VenR retreatment is a viable option for pretreated patients

PFS for VenR-retreated patients in the substudy



CR, complete response.

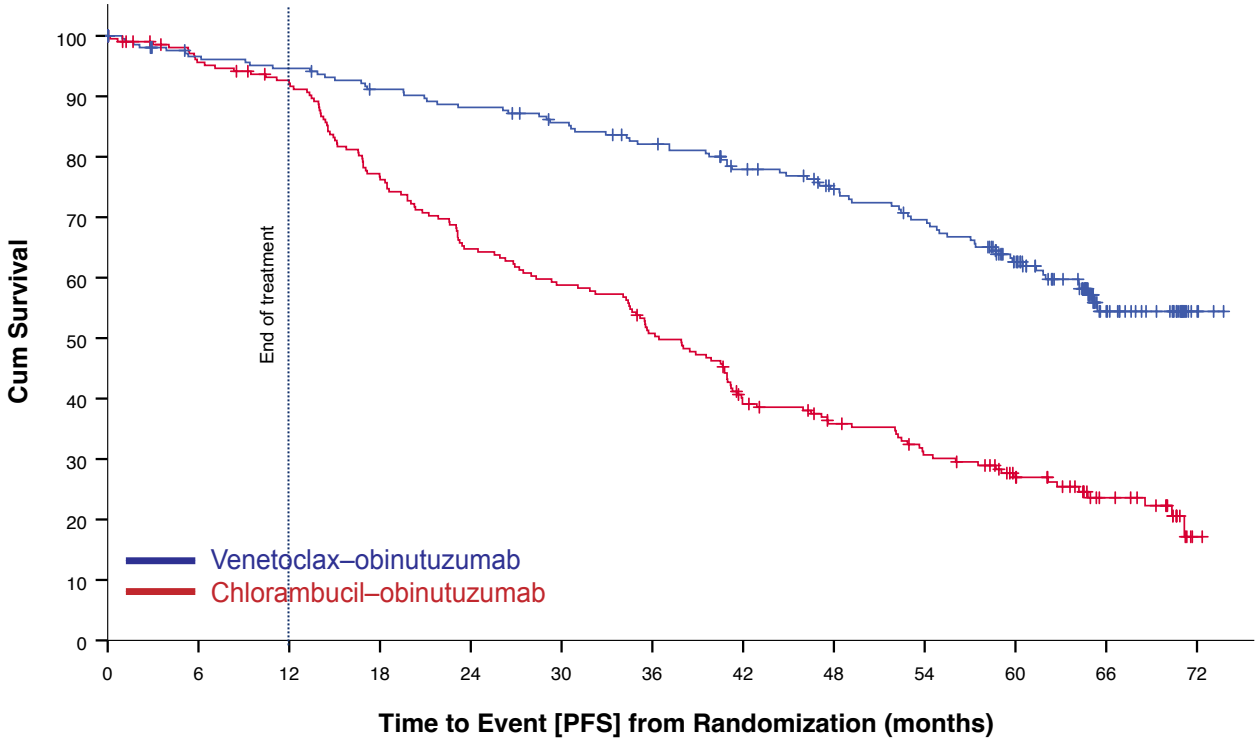
CLL14 FIVE YEAR UPDATE (EHA 2022)



Fischer et al., New Engl J Med 2019

PROGRESSION-FREE SURVIVAL

Median observation time 65.4 months



Ven-Obi	216	196	192	183	177	169	160	147	134	123	97	35	4
Clb-Obi	216	195	185	154	130	118	101	75	64	53	39	21	1

Median PFS

Ven-Obi: not reached

Clb-Obi: 36.4 months

5-year PFS rate

Ven-Obi: 62.6%

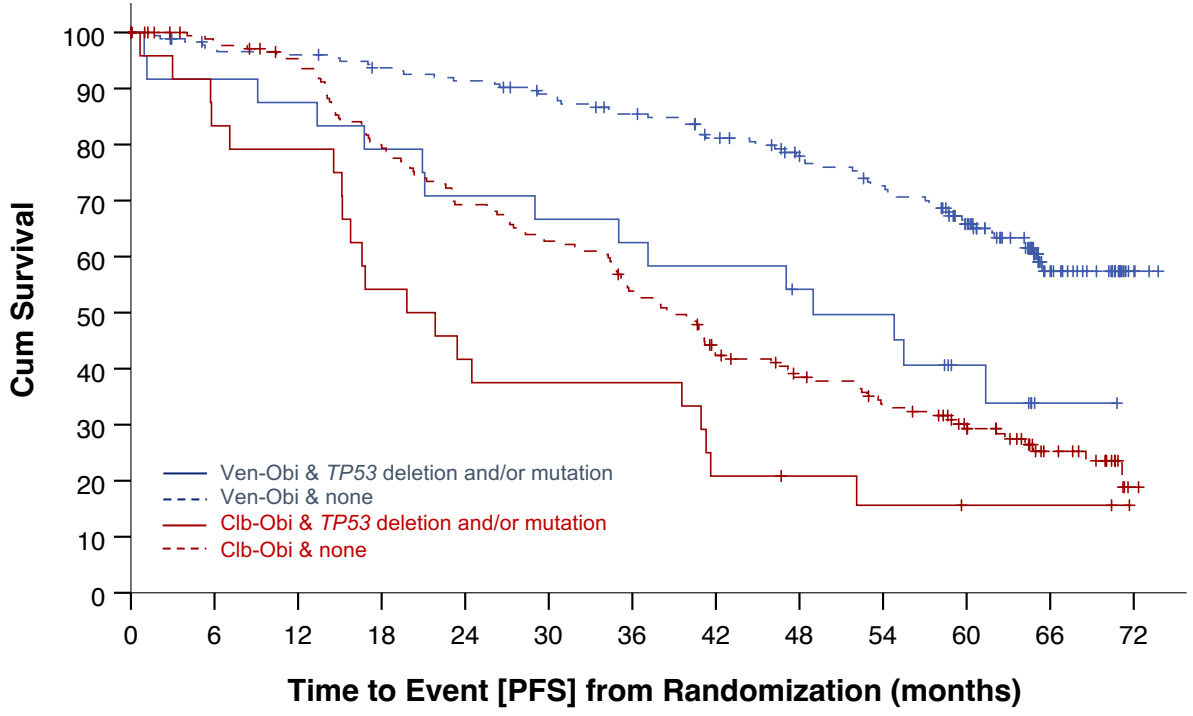
Clb-Obi: 27.0%

HR 0.35, 95% CI [0.26-0.46]

P<0.0001

PROGRESSION-FREE SURVIVAL – *TP53* status

Median observation time 65.4 months



Ven-Obi & *TP53* del/mut	25	22	21	19	17	16	15	14	12	11	6	1	0
Ven-Obi & none	184	169	167	161	157	150	142	130	119	109	89	33	4
Clb-Obi & *TP53* del/mut	24	20	19	13	10	9	9	5	4	3	2	2	0
Clb-Obi & none	184	169	160	135	117	106	90	68	58	48	36	18	1

Median PFS

Ven-Obi & no *TP53*del/mut: NR

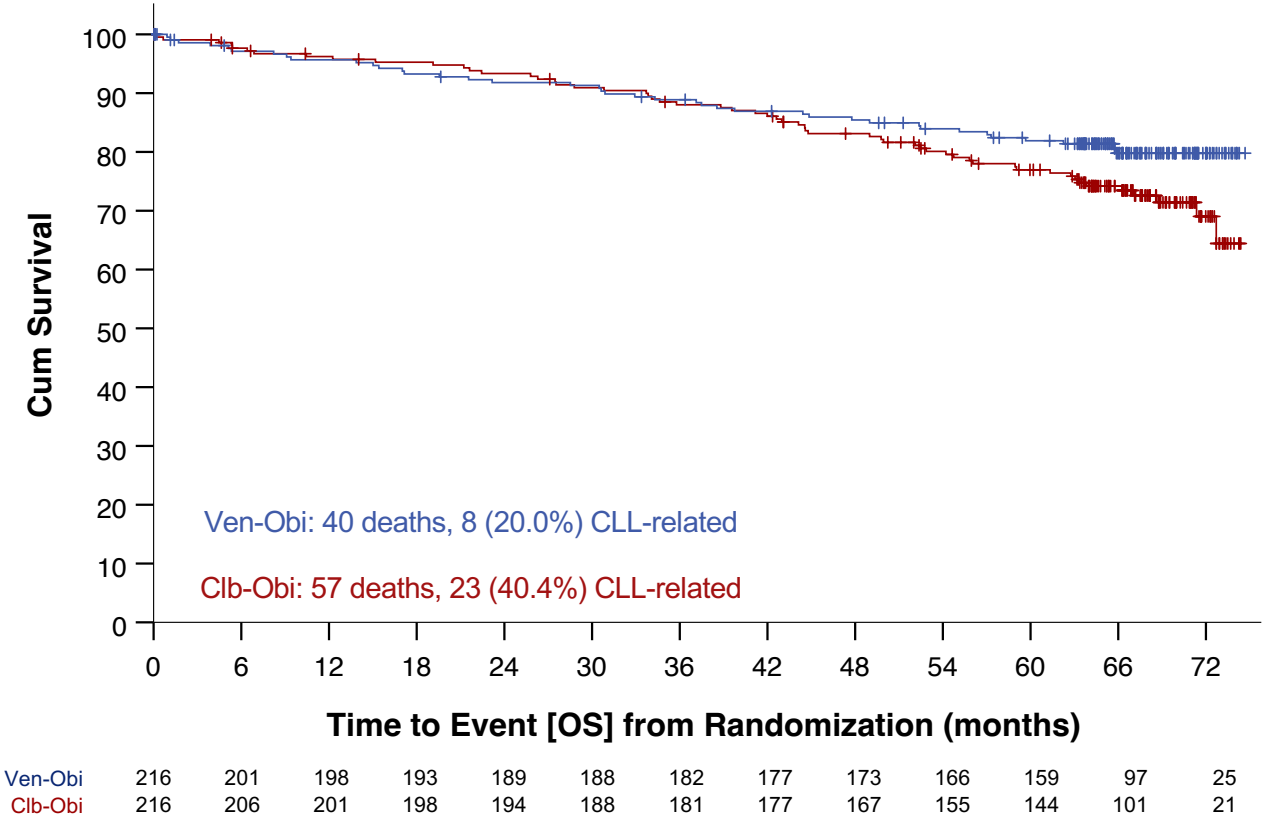
Ven-Obi & *TP53*del/mut: 49.0 m

Clb-Obi & no *TP53*del/mut: 38.9 m

Clb-Obi & *TP53*del/mut: 19.8 m

OVERALL SURVIVAL

Median observation time 65.4 months



Median OS

Ven-Obi: not reached

Clb-Obi: not reached

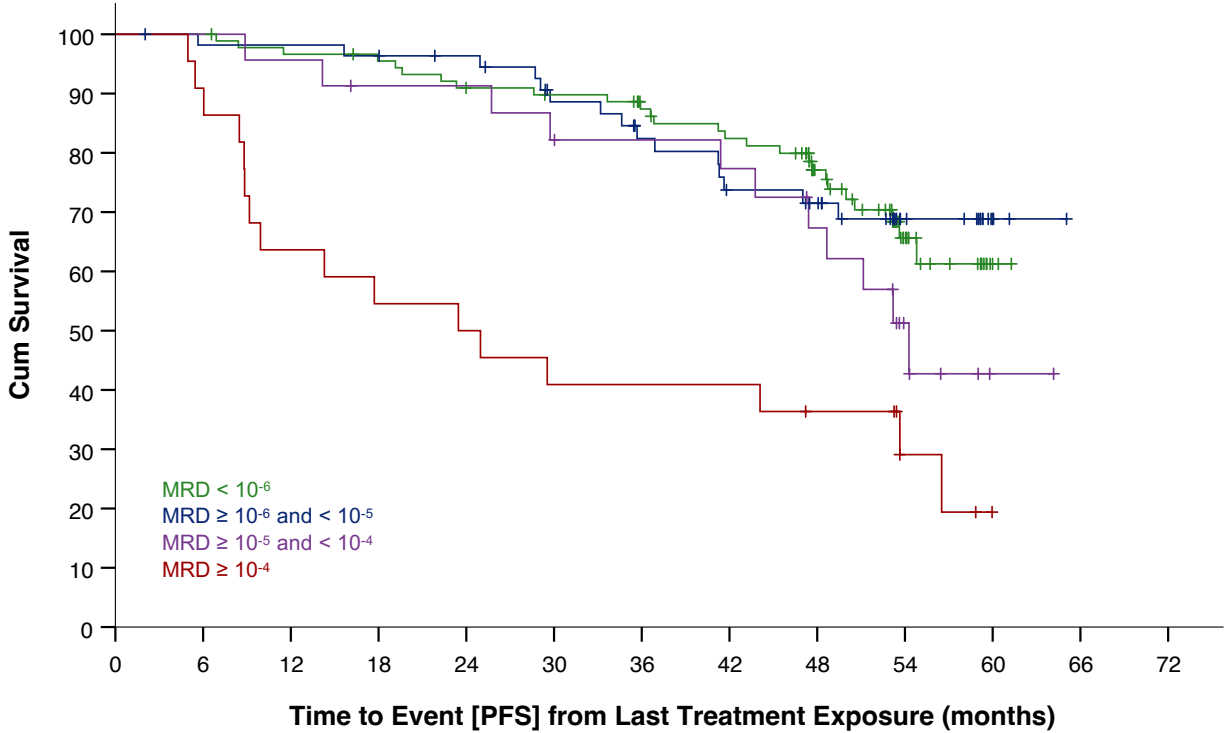
5-year OS rate

Ven-Obi: 81.9%

Clb-Obi: 77.0%

PFS AFTER VEN-OBI ACCORDING TO MRD STATUS

End of treatment MRD status in peripheral blood, by NGS



MRD < 10^{-6}	90	90	86	84	79	77	71	66	48	21	2	0	0
MRD ≥ 10^{-6} and < 10^{-5}	56	54	54	53	51	44	38	33	30	14	3	0	0
MRD ≥ 10^{-5} and < 10^{-4}	23	23	22	20	20	18	17	16	13	6	1	0	0
MRD ≥ 10^{-4}	22	20	14	12	11	9	9	9	7	3	0	0	0

Depth of remission **beyond 10^{-4}** correlates with **long-term PFS**, indicating the value of ultra-sensitive MRD assessments.

CLL13/GAIA: venetoclax-based treatments vs. CIT in younger/fit patients

Fit patients with untreated CLL:
CIRS ≤ 6 & normal CrCl

No *TP53* mutation or del(17p) in central screening

CIT:
FCR/BR*
6 cycles,n=230

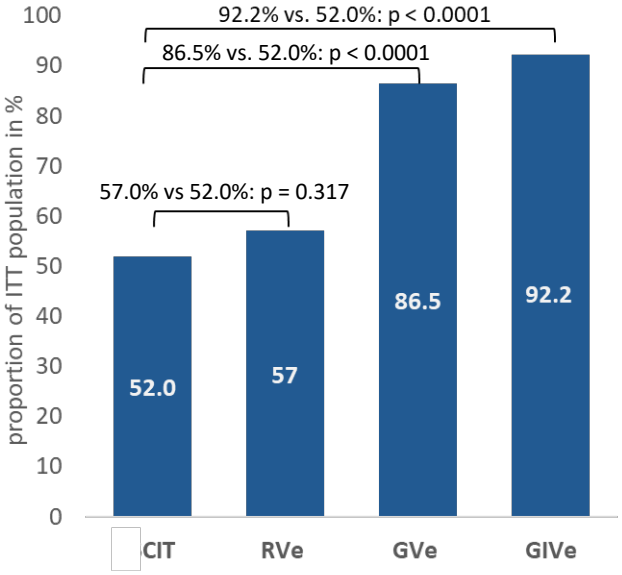
RVe
12 cycles, n=230

GVe
12 cycles, n=230

GIVe
15# cycles, n=230

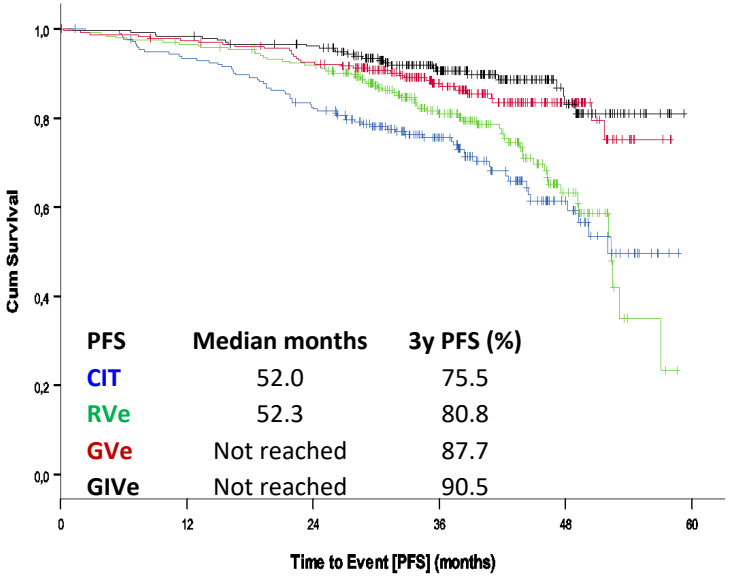
uMRD (< 10^{-4})

at month 15 in PB by 4-colour-flow



PFS

at median FU of 38.8 months



PFS	Median months	3y PFS (%)
CIT	52.0	75.5
RVe	52.3	80.8
GVe	Not reached	87.7
GIVe	Not reached	90.5

* ≤ 65 years: FCR, > 65 years: BR; [50% FCR / 50% BR]
# continuation of ibrutinib up to cycle 36 if MRD detectable

Eichhorst et al, ASH2021 and EHA2022

CONCLUSIONS

- Targeted BCL2 inhibition leads to potent killing in CLL
- Addition of anti-CD20 = faster and deeper response
- Time-limited therapy reduces medical burden and likely decreases rate of resistant BCL2 mutation emergence
- Ven-Obi is a standard-of-care 1L therapy for both older and younger patients