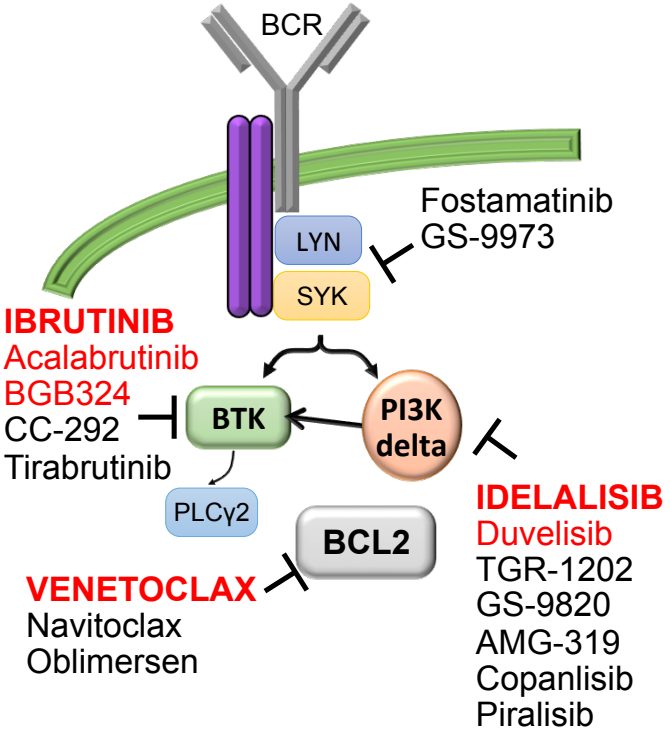
Quesiti aperti nella Leucemia linfatica cronica (LLC)

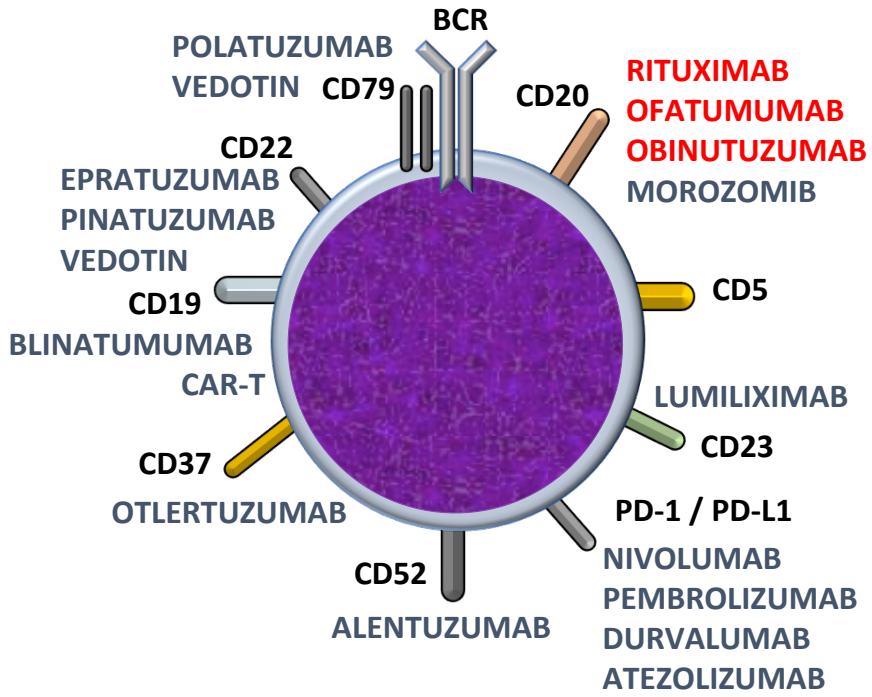
Quale sequenza e quale combinazione per i nuovi farmaci?

Livio Trentin

UOC Ematologia, Dip. Medicina
Università degli Studi di Padova

New targets – New drugs for CLL Treatment





NEW APPROVED DRUGS LAST 3-4 YEARS

- **OBINUTUZUMAB**

  first line unfit patients in combination with chlorambucil

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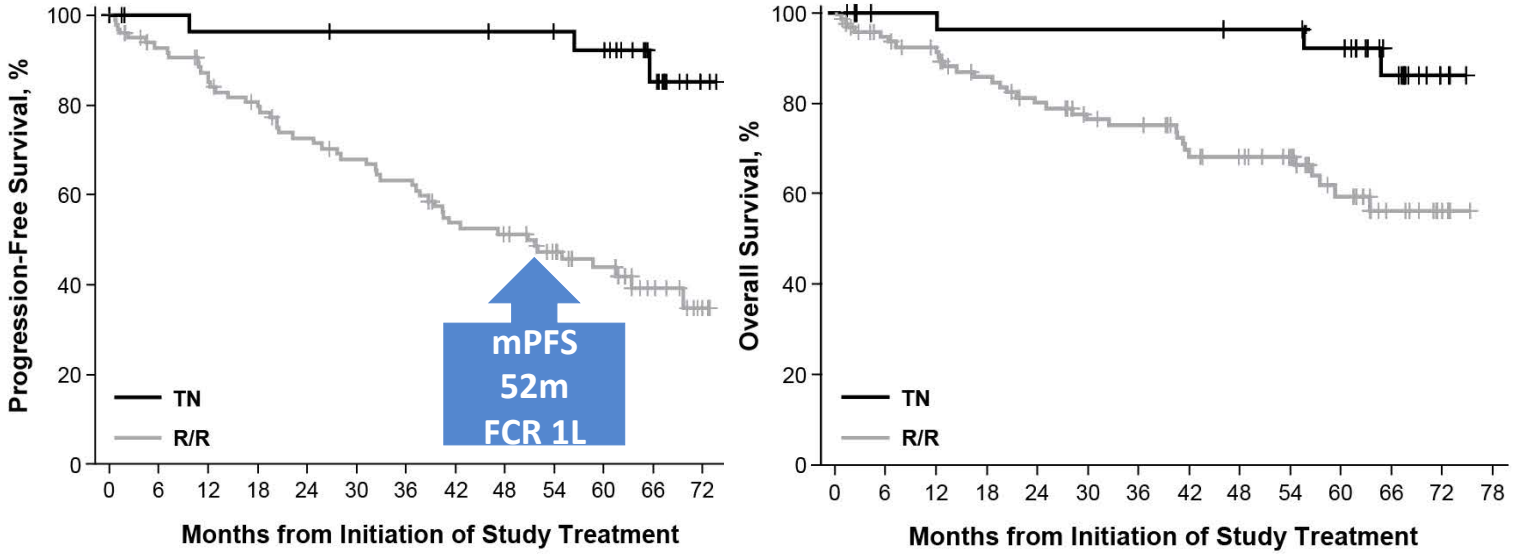
IBRUTINIB, 5-YEAR FOLLOW-UP

- 5 years follow-up of phase II study PCYC-1102/1103: **31 TN, 101 R/R**

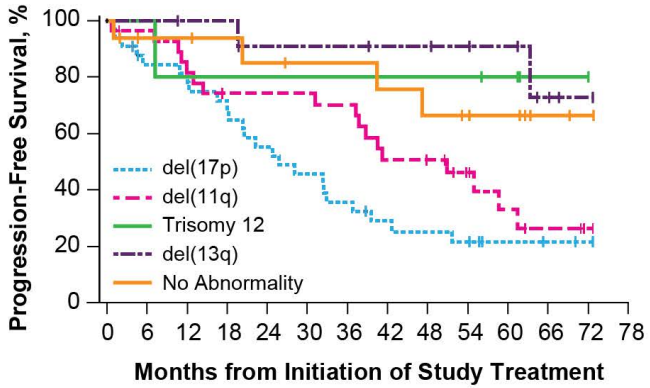
- median PFS 52 months for R/R. **5-year PFS 44% for R/R but 92% for TN**
- median OS not reached for R/R. 5-year OS 57% but 93% for TN

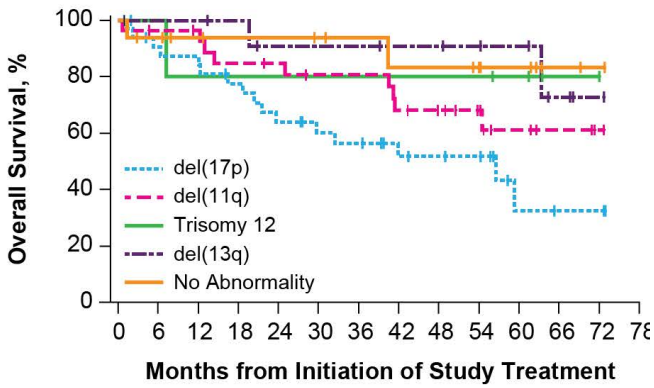


O'Brien S. et al, Blood 2018

IBRUTINIB, 5-YEAR FOLLOW-UP

FISH and Complex karyotype impact on the survival of patients





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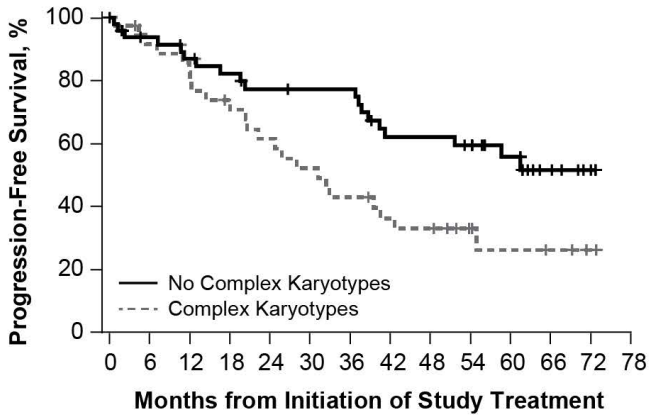

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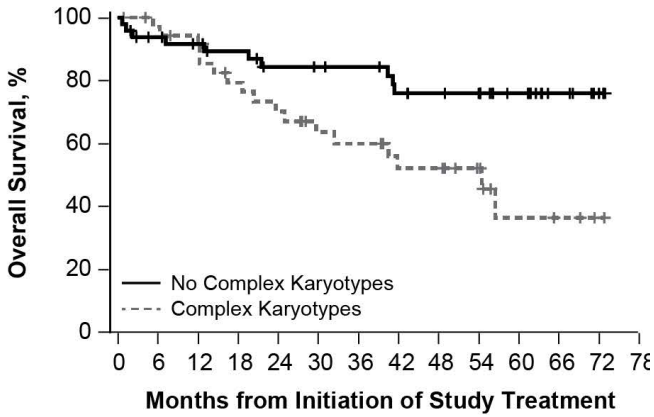
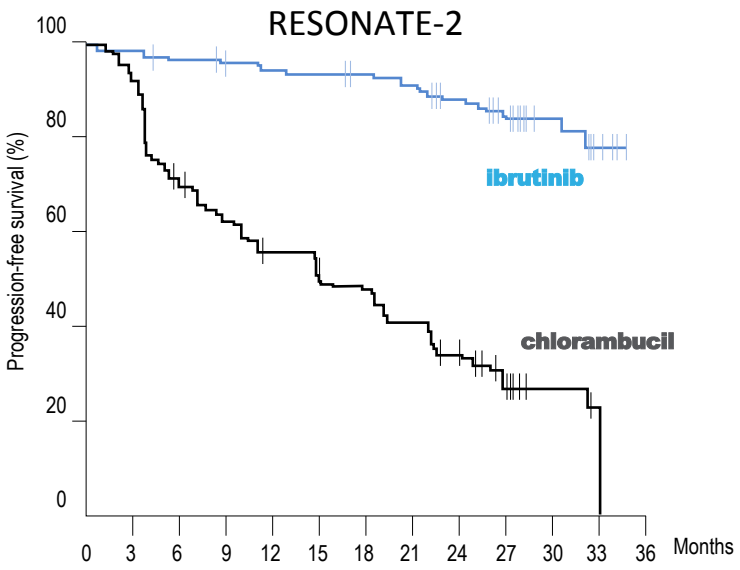


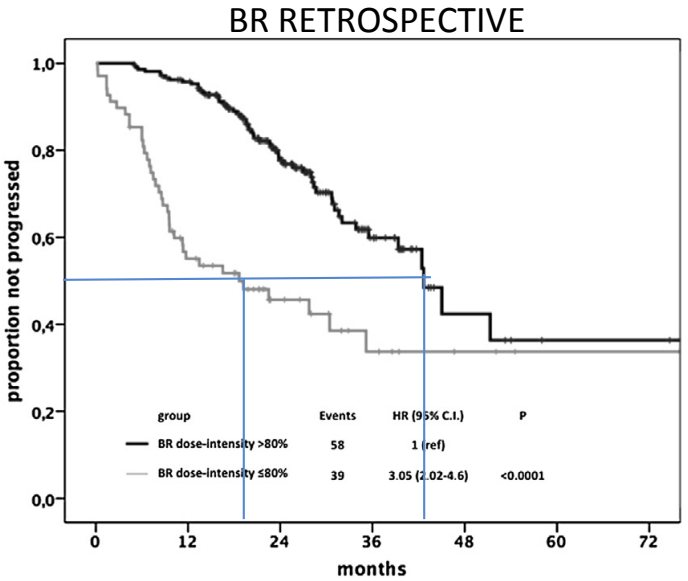
O'Brien S. et al, Blood 2018

IBRUTINIB 1L, Resonate 2

- RESONATE-2 included 269 TN patients (1:1) with >65 years, median age 73 years
- 92% had ECOG 0-1; 31% CIRS >6; 21% 11q; 43% U-IGVH **NO 17p-**

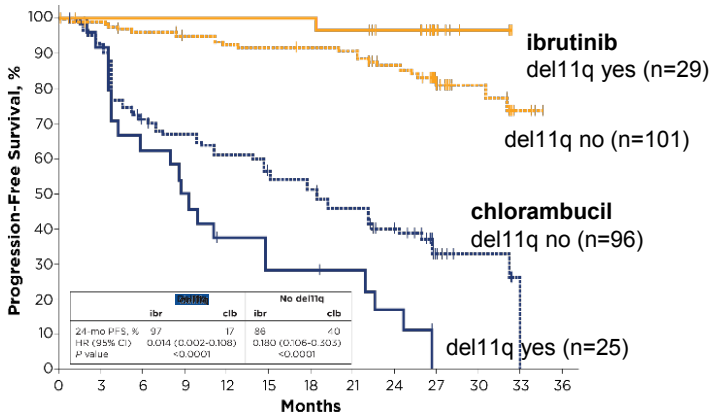
- **Provide much better disease control than other treatment such as BR**



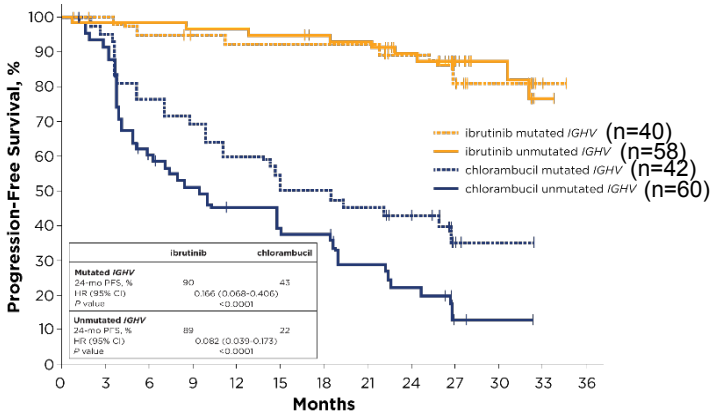


Barr P. et al ASH 2016 oral 234; Gentile M, Eu J Cancer 2016

IBRUTINIB 1L, higher response in 11q and U-IGHV pts



Ibrutinib led to 99% reduction in risk of progression or death in high-risk del11q subgroup and 82% reduction in those without del11q, compared to chemotherapy



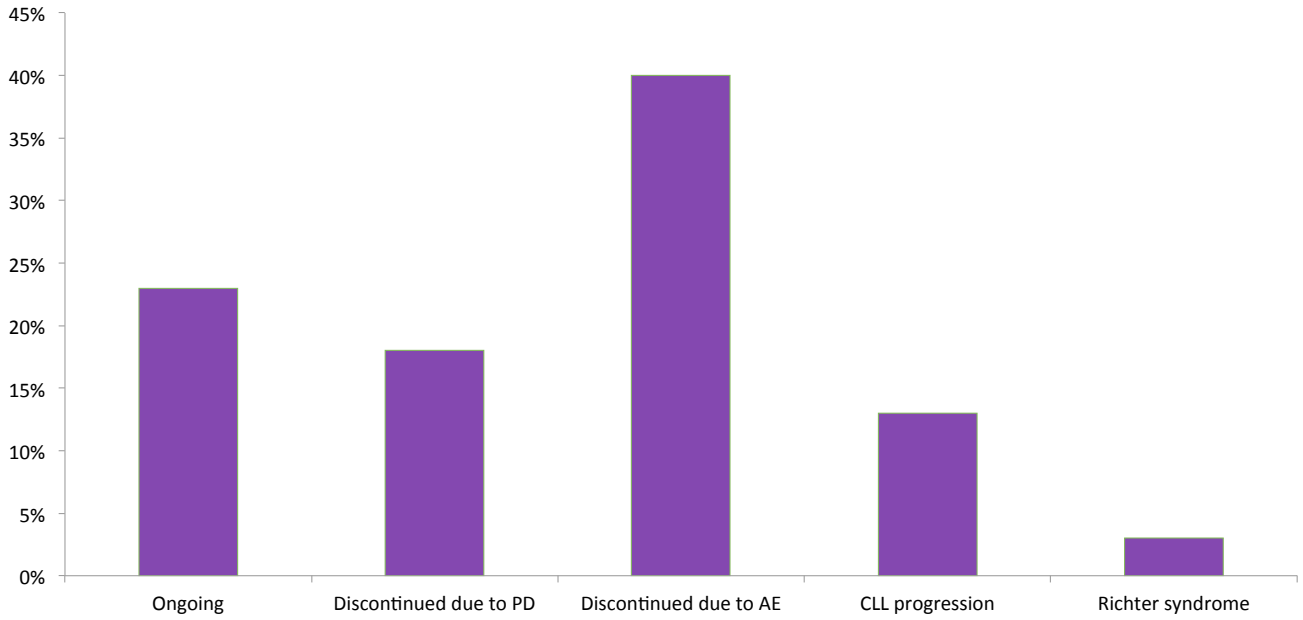
Ibrutinib led to 83% and 92% reduction in the risk of progression or death in patients with mutated and unmutated *IGHV*, respectively, compared to chemotherapy

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.

ASH 2016 abstract #234, Updated Efficacy/Safety RESONATE-2; Barr et al.

IDELALISIB, DISCONTINUATION

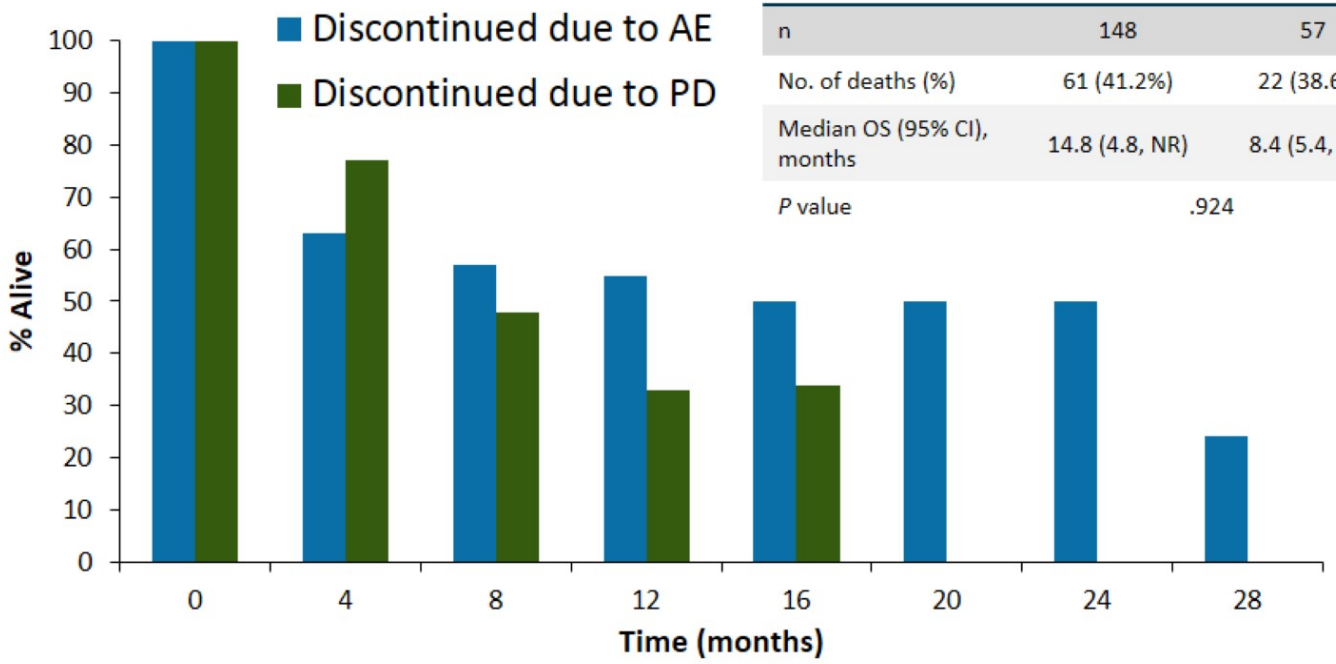
- Pooled data from 2 phase, 3 clinical trials.
- N=369 patients
- (196 Idelalisib+Rituximab, 173 Idelalisib+Ofatumumab)



Furman RR, NEJM 2015; Jones JA, JCO 2015

IDELALISIB, DISCONTINUATION

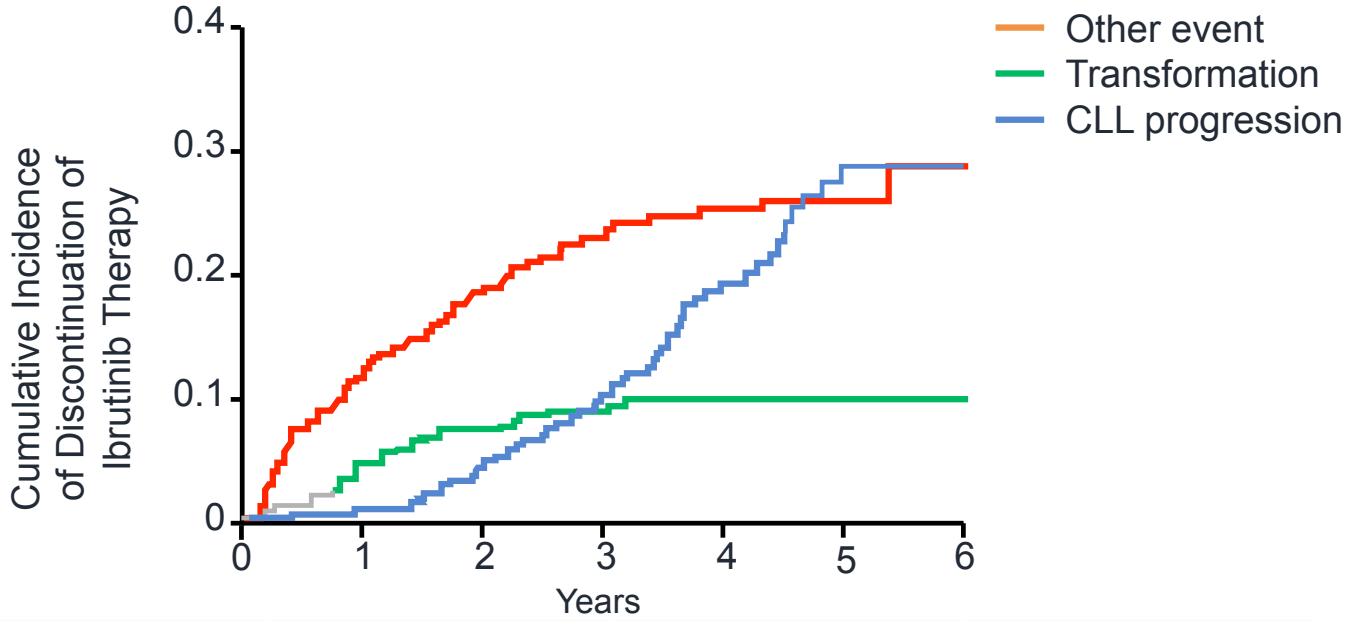
- Outcome of patients who discontinue idelalisib
- 205 patients, pooled data from phase 3 trials



	Discontinued due to AE	Discontinued due to PD
n	148	57
No. of deaths (%)	61 (41.2%)	22 (38.6%)
Median OS (95% CI), months	14.8 (4.8, NR)	8.4 (5.4, NR)
P value	.924	

Brown J, ASCO 2016

IBRUTINIB DISCONTINUATION

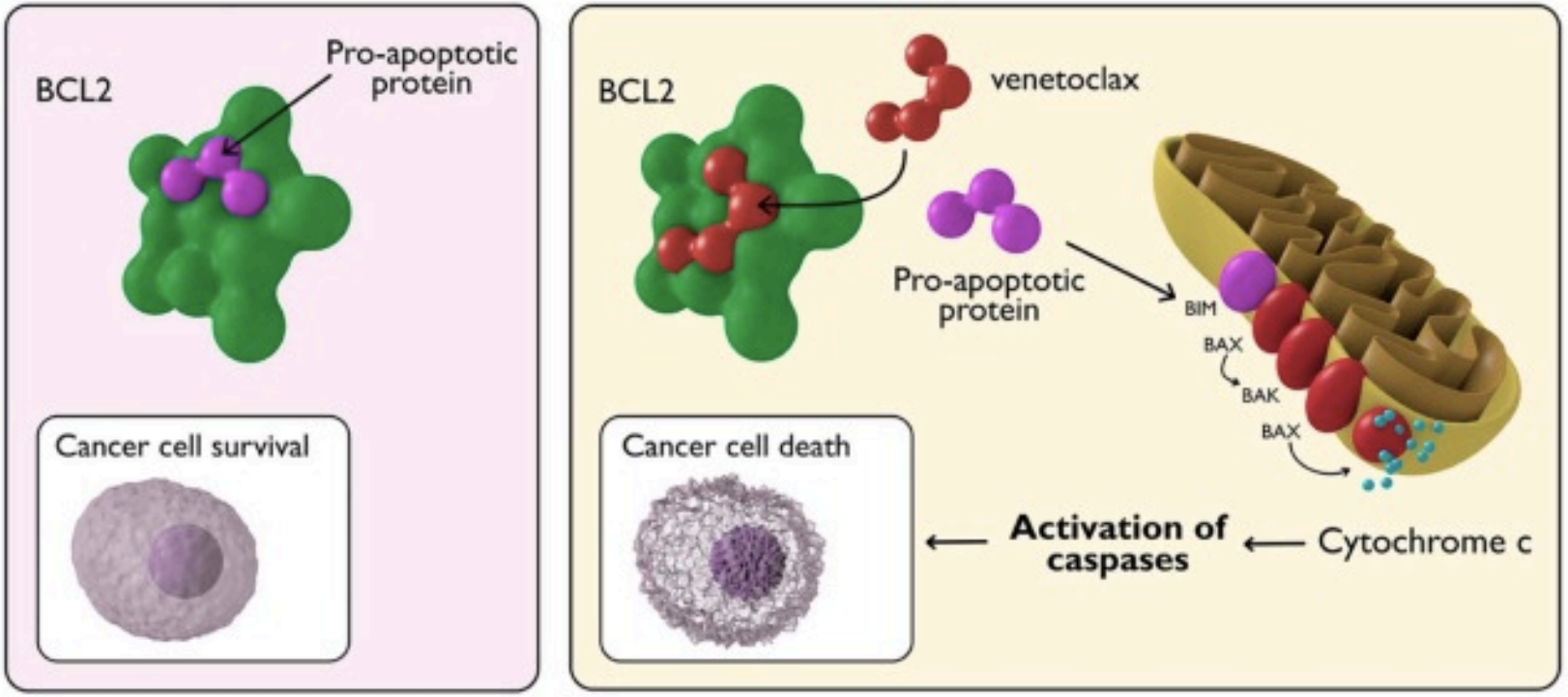


DISCONTINUATION	2 years (%)	3 years (%)	4 years (4%)
CLL progression	5	10.8	19.1
Transformation	7.3	9.1	9.6
Other events (AE)	18.7	23.9	25

Woyach J, et al. J Clin Oncol. 2017;35:1437-1443.

VENETOCLAX

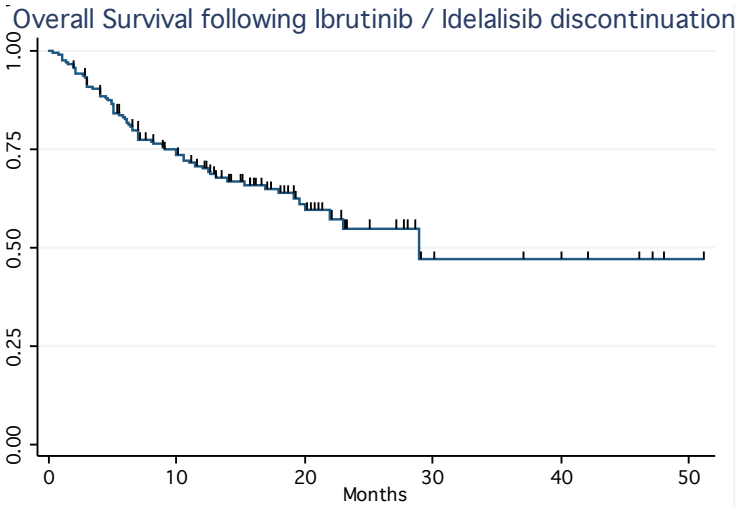
- Venetoclax is highly selective for targeting the BH3 domain of BCL2

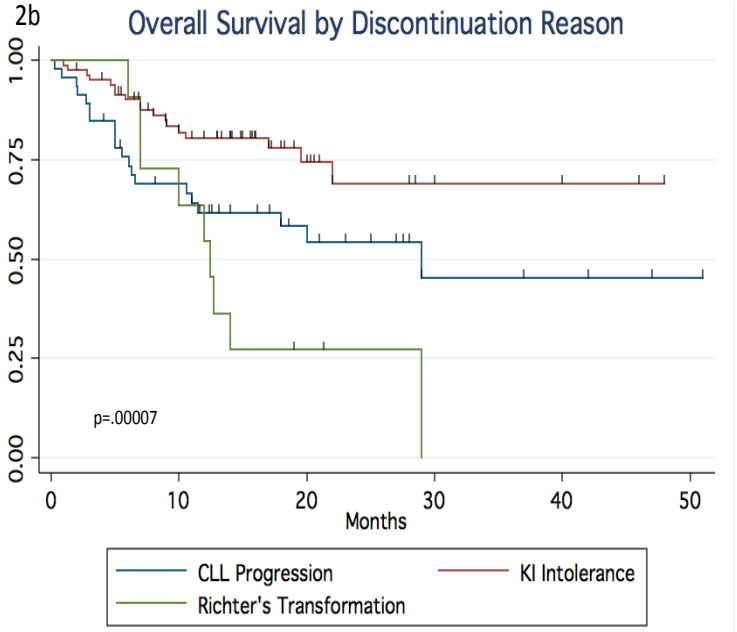


Mihalyova J, Experimental hematology 2018

After BCRi stop, real life

- Multicenter retrospective analysis on 178 patients (143 ibrutinib and 35 idelalisib)
- PFS and OS were longer if BCRi were stopped for intolerance rather than progression or Richter's transformation



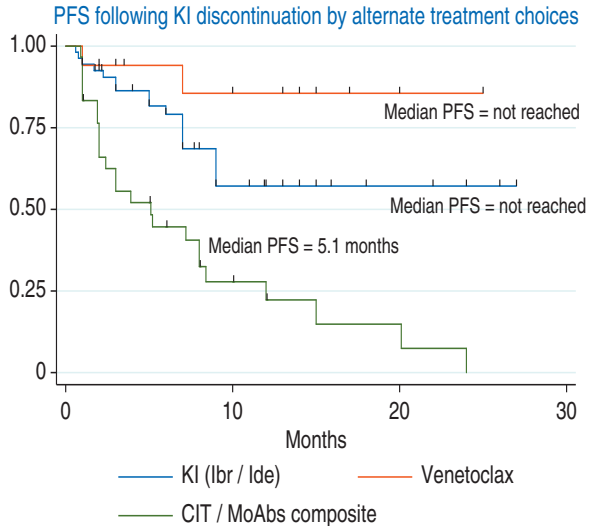


Mato A, Blood 2016

After BCRi stop, VENETOCLAX

- At BCRi failure, the use of an alternative BCRi or Venetoclax provide higher ORR and longer PFS as compare to chemoimmunotherapy
- Venetoclax, single agent, was able to induce 32% of CR

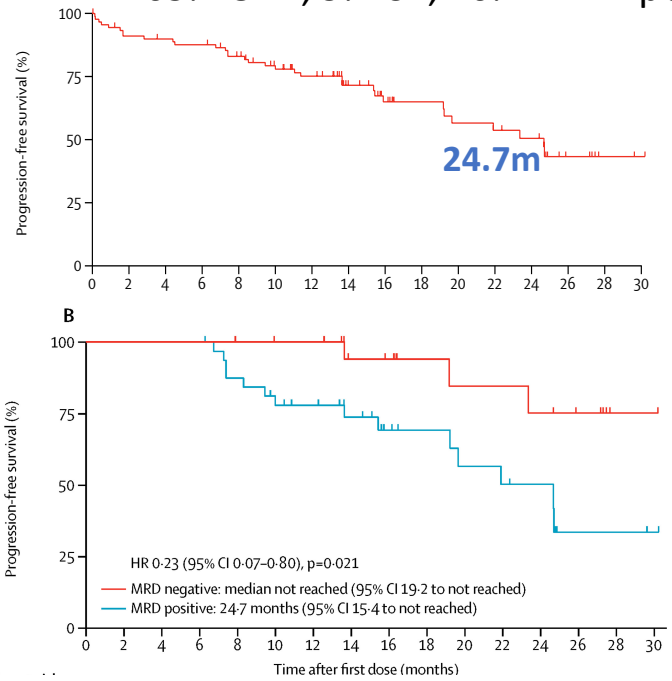
	Idelalisib after Ibrutinib	Ibrutinib after Idelalisib	BCL2-I
ORR	46%	75%	**74%**
CR	0%	5	**32%**
PR/PR-L	46%	70%	42%
SD	39%	15%	16%
PD	15%	10%	10%



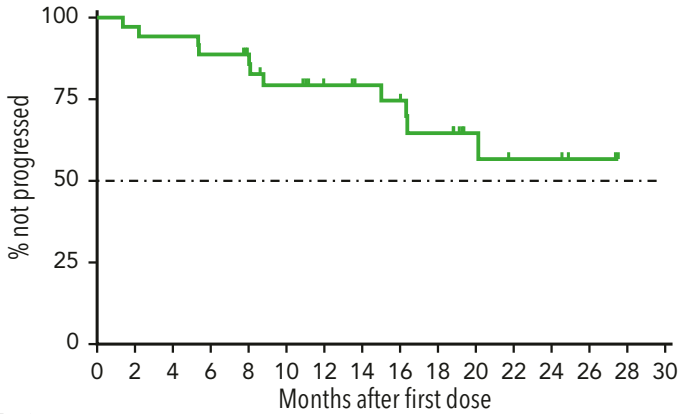
Mato A, Blood 2016; Mato A, Annals of Oncology 2017

VENETOCLAX, after BCRi

- 91pts patients R/R after **IBRUTINIB**
- 47% 17p-, 29% high-risk TLS
- median of 4 previous therapies
- 65% ORR, 9% CR, 26% MRD- pb



- 36 pts patients R/R after **IDELALISIB**
- 31% 17p-, 25% high-risk TLS
- median of 3 previous therapies
- 67% ORR, 8 % CR, 22% MRD- pb



Jones, Lancet Oncology 2017; Coutre S, Blood 2018

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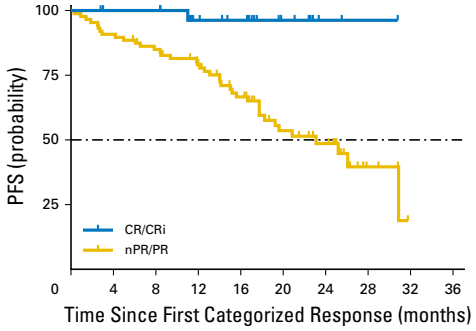
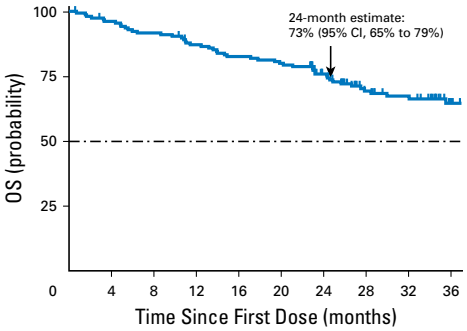
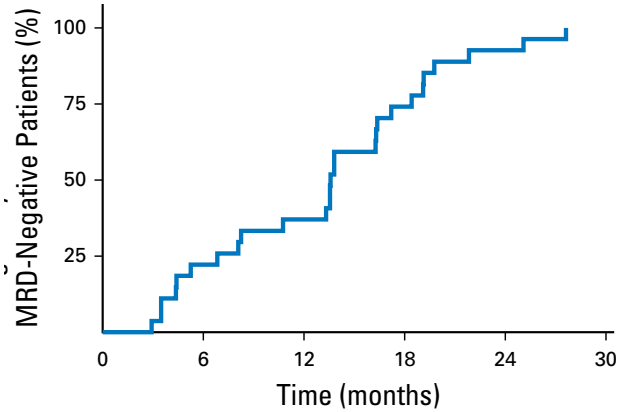
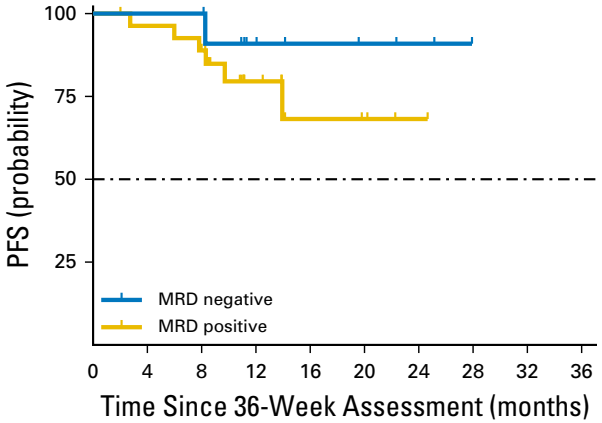
VENETOCLAX, phase II in 17p-

- **A new highly effective drug able to achieve complete response and MRD negativity in heavily treated patients**
- 158 patients all 17p-, **5 TN**, median age 67, 10% received BCRi
- TLS risk: 23% low, 38% intermediate, **39% high**
- ORR 77% with CR 20%. Median follow-up of 26.6m, median PFS 27.2m but not reached for CR







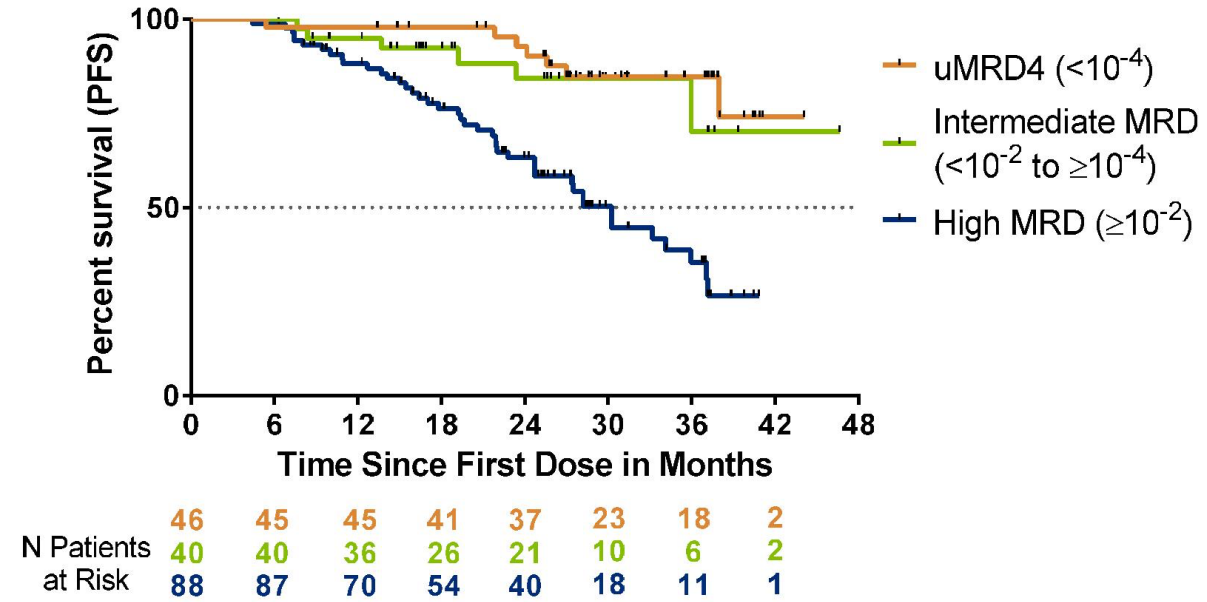


Stilgenbauer S, JCO 2018

Minimal Residual Disease Status with Venetoclax Monotherapy Is Associated with Progression-Free Survival in Chronic Lymphocytic Leukemia

MRD and PFS data from two phase 2 studies of venetoclax monotherapy in patients with R/R CLL were pooled

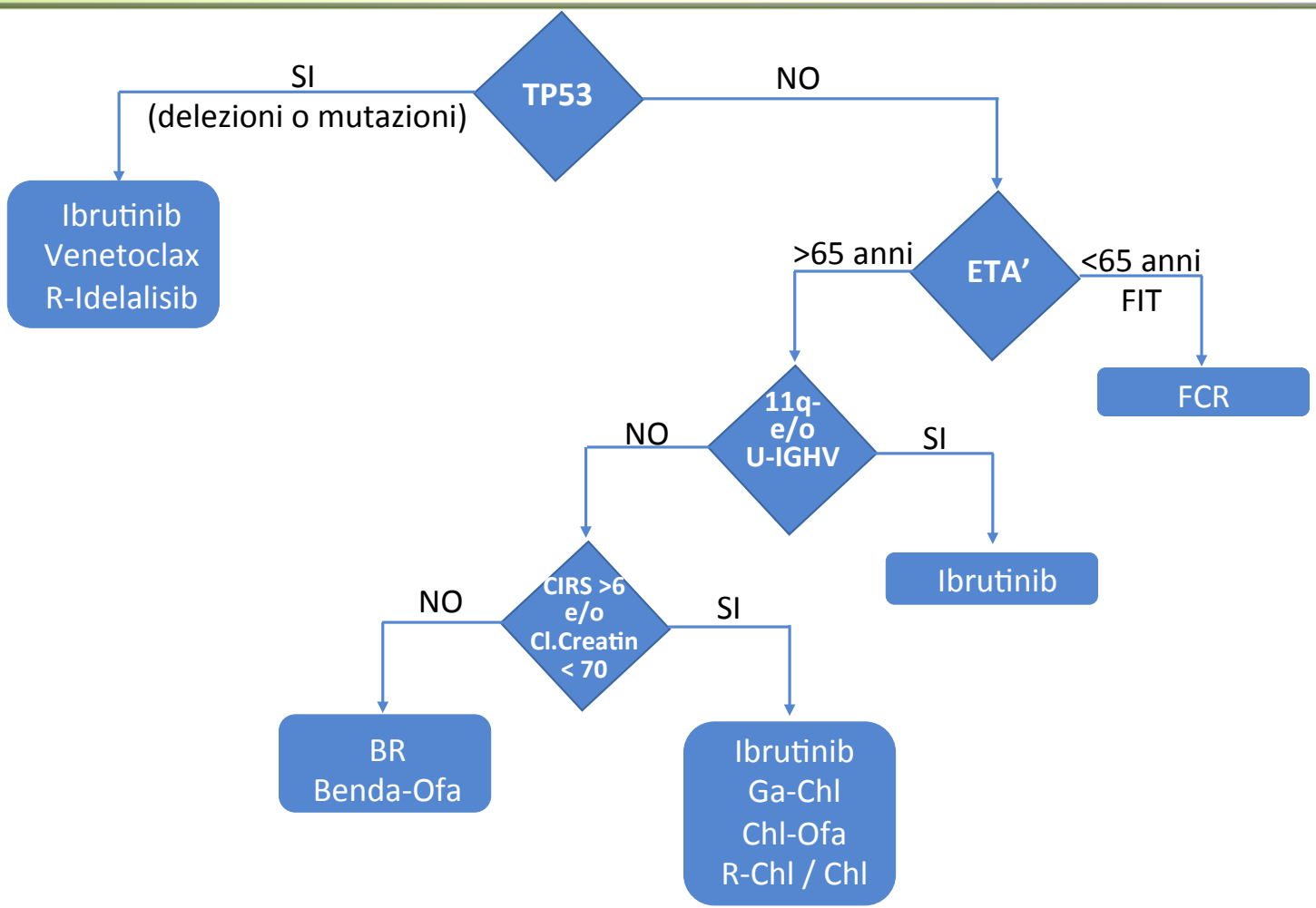
Figure 2. Progression-free Survival for Patients with uMRD, Intermediate, and High PB MRD



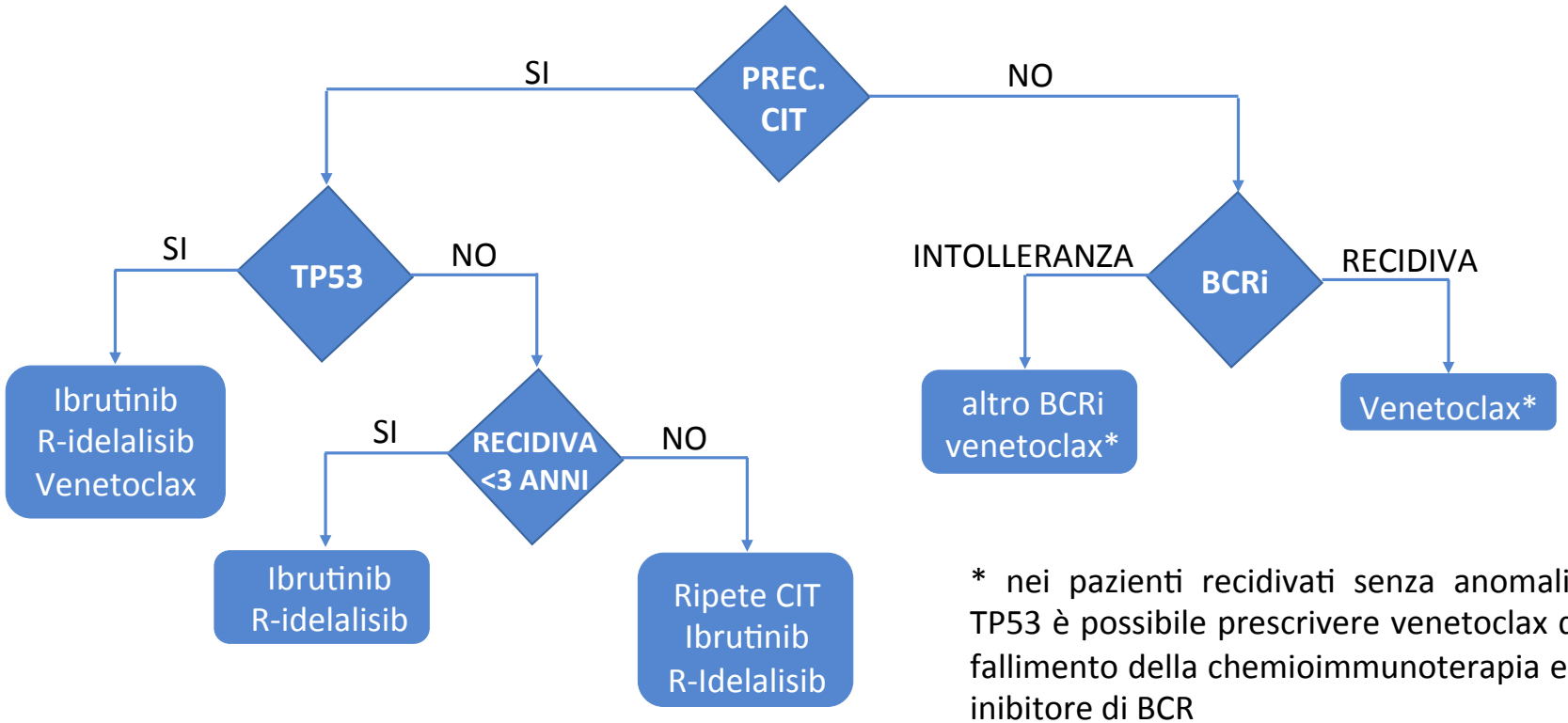
Black dash indicates censored subject. MRD, minimal residual disease; PB, peripheral blood; uMRD, undetectable minim residual disease.

Wierda et al, ASH 2018

PAZIENTI CON LLC ATTIVA 1°Linea



PAZIENTI LLC (R/R)



* nei pazienti recidivati senza anomalie di TP53 è possibile prescrivere venetoclax dopo fallimento della chemioimmunoterapia ed un inibitore di BCR

Rationale for Novel Agents/Combination in Development: Potential benefits

- Improve efficacy and achieve deeper responses by combining agents with different mechanisms of action
- Avoid development of emerging resistant clones
- Provide time-limited therapy with MRD negativity
- Reduce toxicity by shortening duration of use and exposure to drug

MURANO Study

Relapsed/refractory CLL (N=389)

- ≥18 years of age
- Prior 1–3 lines of therapy, including ≥1 chemo-containing regimen
- Prior bendamustine only if DoR ≥24 months

Stratified by:

- Del(17p) by local labs
- Responsiveness to prior therapy*
- Geographic region

R 1:1

C1D1

VEN 5-week ramp-up

Venetoclax 400 mg orally once daily to PD, cessation for toxicity, or **max. 2 years** from Cycle1 Day1

Rituximab
375 mg/m^2 Day 1, Cycle 1;
500 mg/m^2 Day 1 Cycles 2–6

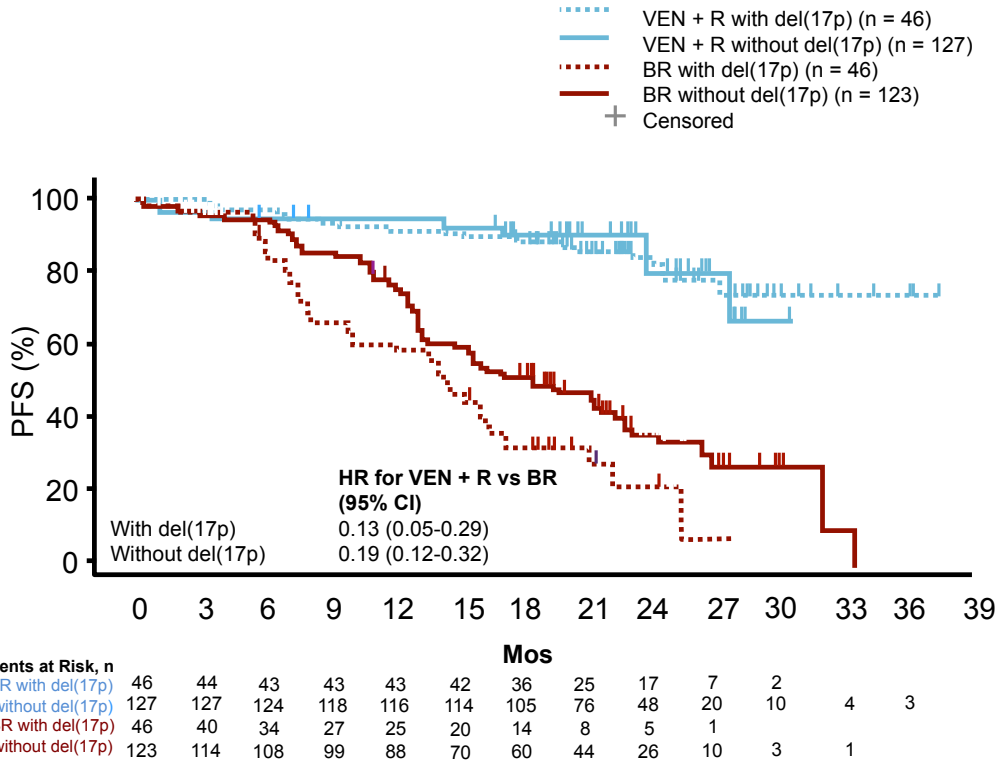
Bendamustine
70 mg/m^2 Days 1 and 2 Cycles 1–6
+
Rituximab

Primary Endpoint	INV-assessed PFS
Major Secondary Endpoints	• IRC-CR ⇒ IRC-ORR ⇒ OS (hierarchical testing) • IRC-assessed PFS and MRD-negativity
Key Safety Endpoints	Overall safety profile, focusing on serious adverse events and Grade ≥3 adverse events
Interim Analysis	Approximately 140 INV-assessed PFS events (75% of total information)

NCT02005471
*High-risk CLL – any of following features: del(17p) or no response to front-line chemotherapy-containing regimen or relapsed ≤12 months after chemotherapy or within ≤24 months after chemoimmunotherapy.

Seymour JF, et al. ASH 2017. Abstract LBA-2.

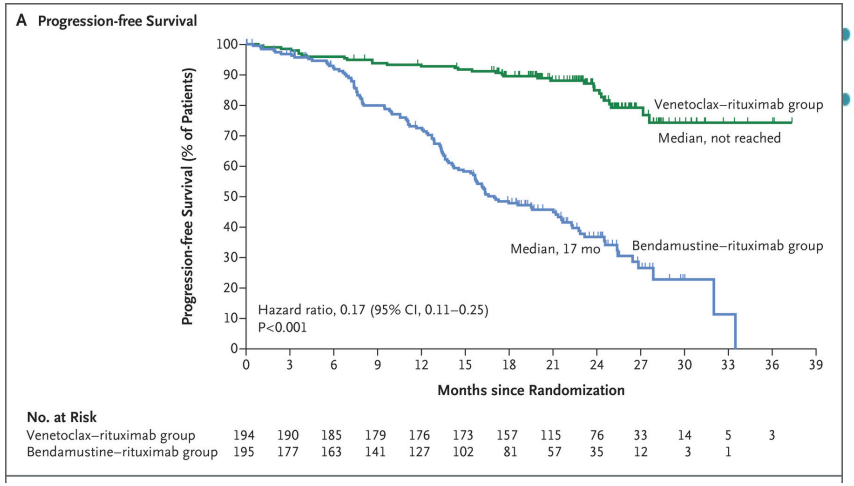
MURANO Interim Analysis: Investigator-Assessed PFS by del(17p) Status



VEN + R consistently favored across subgroups stratified by del(17p) status, *TP53* status, baseline *IGHV* status number of prior treatments, refractory vs relapse to last treatment

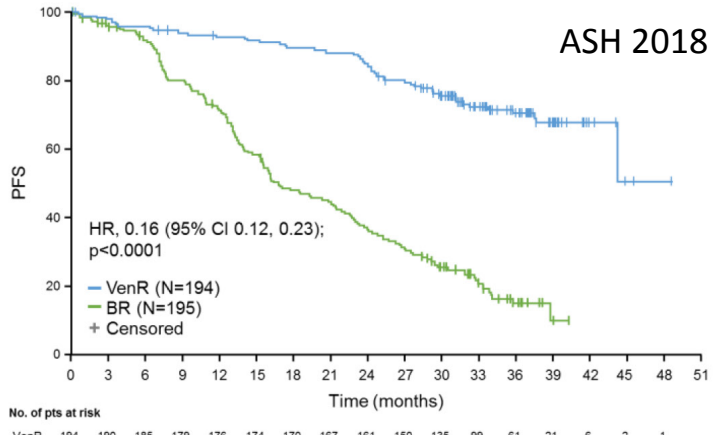
Seymour JF, et al. ASH 2017. Abstract LBA-2.

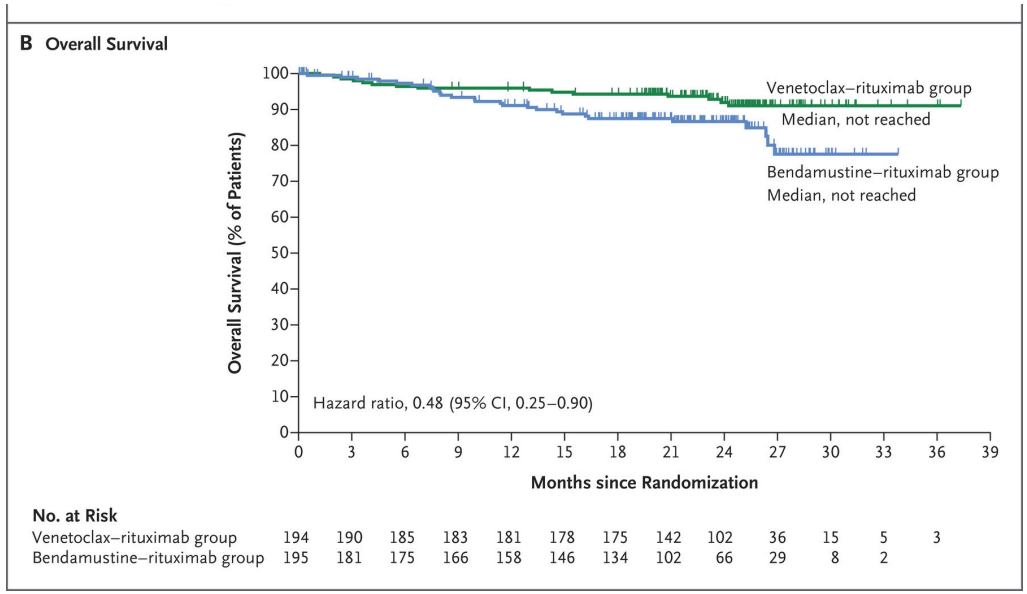
MURANO: Venetoclax + Ri vs BR in R/R CLL



- Phase 3 study of VenR (n = 194) vs BR (n = 195)
- Significant improvement in ORR, PFS, and OS with VenR vs BR

Seymour JF, et al. NEJM 2018.

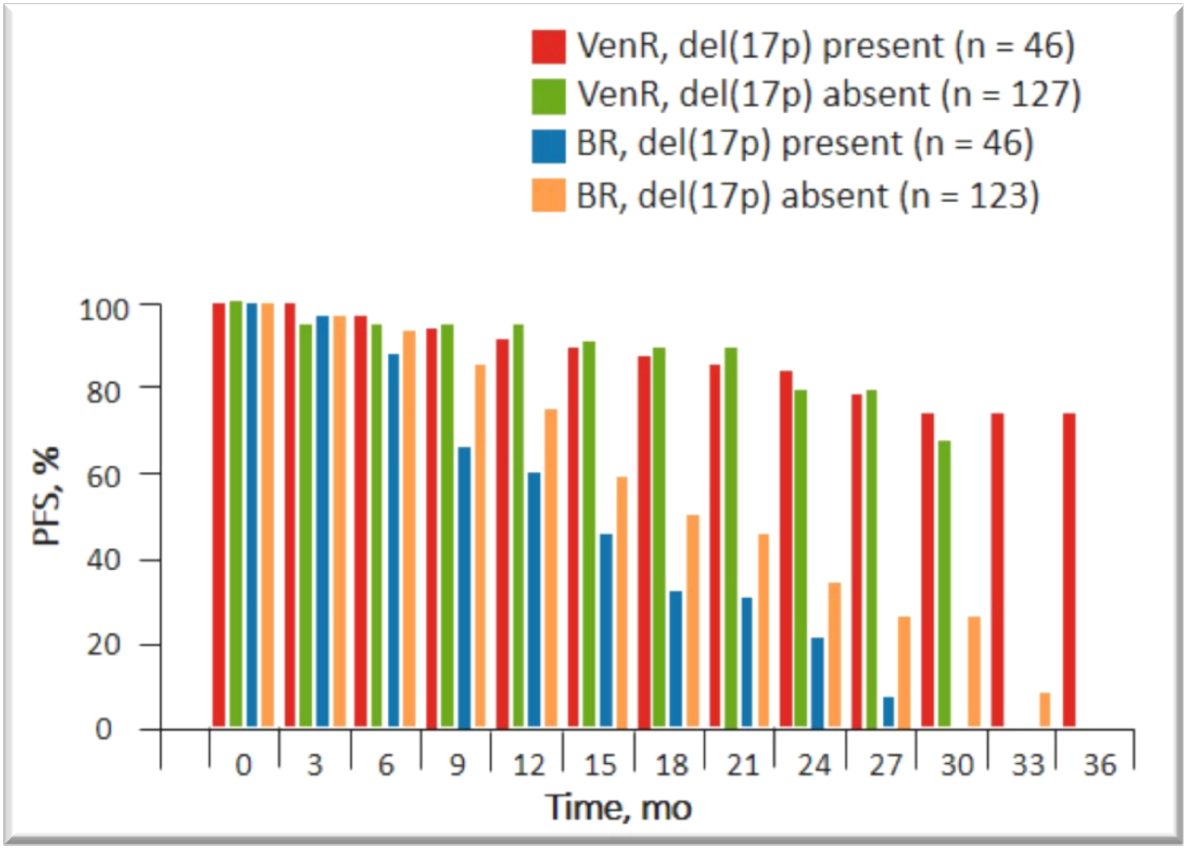




MURANO: VenR vs BR in Patients with Del(17p) and TP53 and IGHV Mutation Status

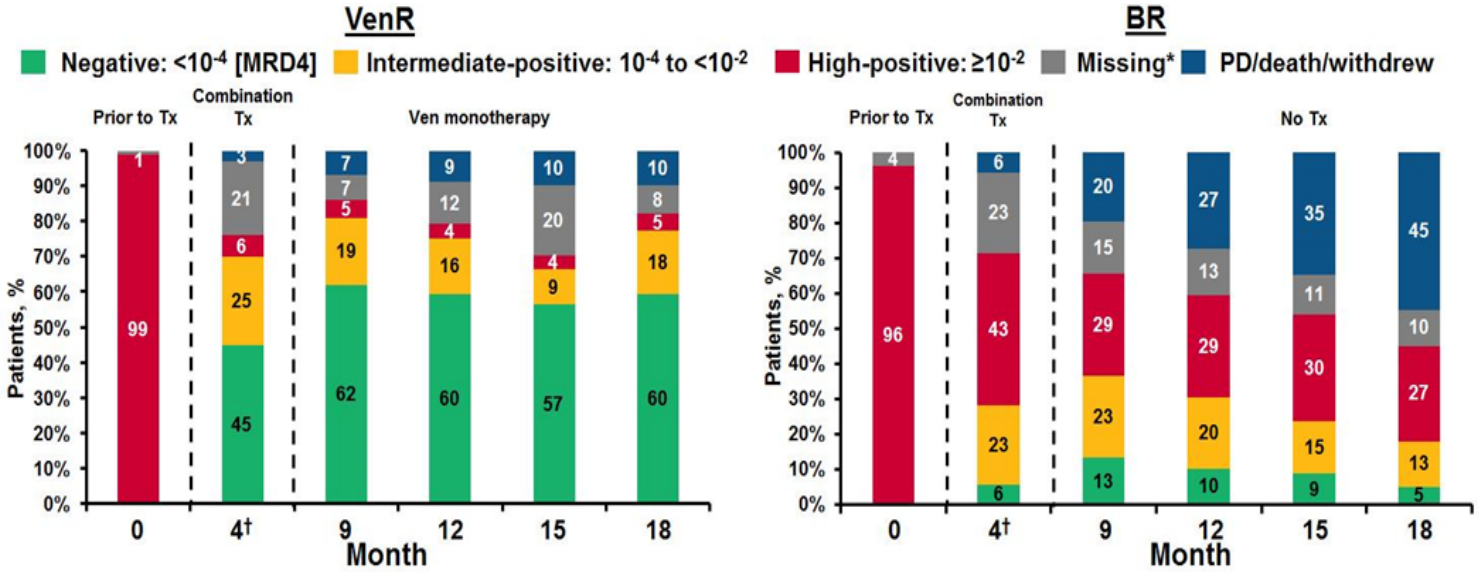
Median PFS (months) in high-risk subgroups

Subgroup	VenR	BR	HR (95% CI)
Del(17p)			
Absent	NR	21.4	0.19 (0.12, 0.32)
Present	NR	15.4	0.13 (0.05, 0.29)
TP53 mutation			
Unmutated	NR	21.2	0.15 (0.09, 0.25)
Mutated	NR	12.9	0.19 (0.10, 0.36)
***IGHV* mutation**			
Unmutated	NR	15.7	0.16 (0.10, 0.26)
Mutated	NR	22.9	0.11 (0.04, 0.31)



Seymour JF, et al. *N Engl J Med*. 2018;378:1107-1

MURANO, deep MRD response

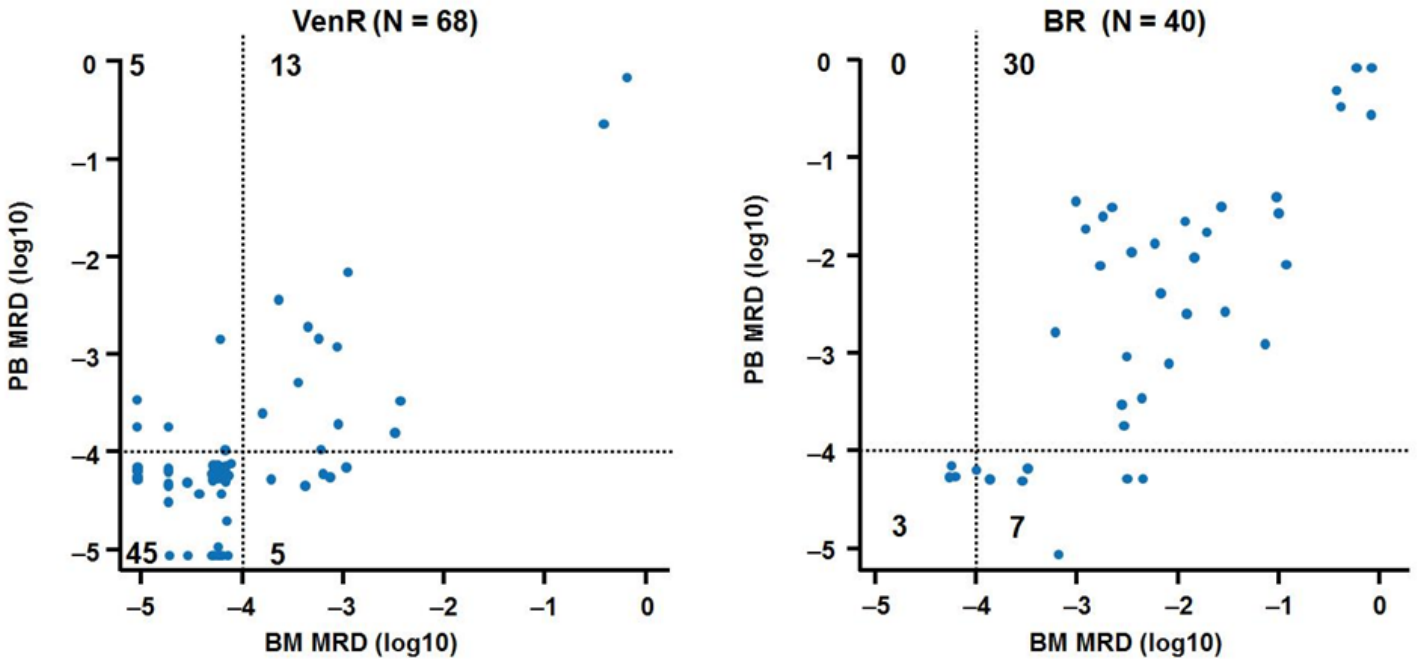


Most MRD positive assay patients in the VenR arm were **intermediate-positive (10^{-4} to $<10^{-2}$).**

Most MRD positive assay patients in the BR arm were **high-positive ($>10^{-2}$).**

Hillmen P, et al. Abstract S805.EHA 2018.

MURANO, high concordance between PB and BM MRD



Hillmen P, et al. Abstract S805.EHA 2018.

MURANO, PB MRD Negativity with VenR vs BR by del(17p) and TP53 and IGHV Mutation Status

	MRD Negative, n/N (%)	
	VenR	BR
ITT population	121/194 (62)	26/195 (13)
Del(17p) and/or TP53 mutated		
Yes	41/72 (57)	4/75 (5)
No	70/106 (66)	19/95 (20)
IGHV		
Unmutated	75/123 (61)	18/123 (15)
Mutated	34/53 (64)	8/51 (16)

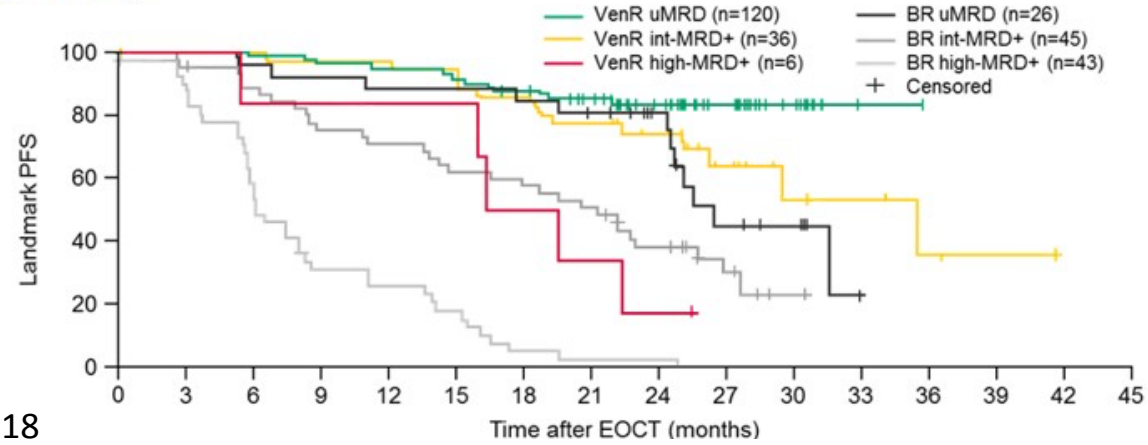
Hillmen P, et al. *J Clin Oncol*. 2018;36(suppl; Abstract 7508).

First Prospective Data on Impact of Minimal Residual Disease on Long-Term Clinical Outcomes after Venetoclax Plus Rituximab Versus Bendamustine Plus Rituximab: Phase III MURANO Study

Table 1. MRD status in pts at EOCT and end of therapy (24 mo from C1D1)

% of pts	VenR (N=194)		BR (N=195)	
	Mo 9 (EOCT)	Mo 24	Mo 9 (EOCT)	Mo 24
uMRD	62	48	13	2
Int-MRD+	19	16	23	7
High-MRD+	5	11	29	18
Missing	7	7	15	7
PD/death/withdrew	7	18	20	66

Figure 1. Landmark PFS analysis according to PB MRD status at EOCT response visit (ITT population)



Including pts who have not progressed, died or withdrawn from study before EOCT response visit. MRD PB status derived from combining ASO-PCR and flow cytometry results

AP Kater, SH 2018

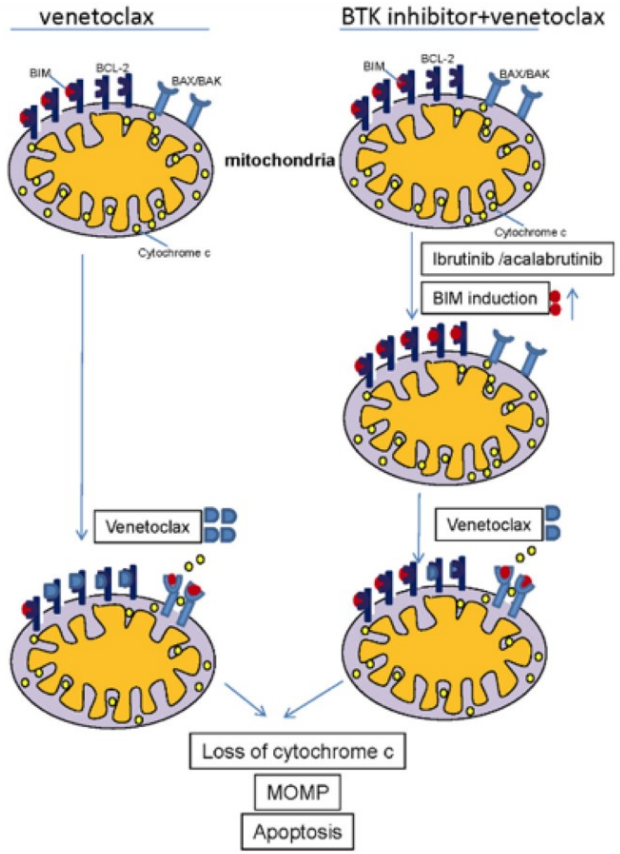
WHAT'S IN THE NEXT FUTURE?

1. Ibrutinib is the best 1st L therapy for high-risk patients (U-IGHV, TP53, 11q, CK)
2. Only few of them achieve MRD- and treatment is still progression/intollerance
3. Low-risk patients can still received chemotherapy (FCR and BR)…but secondary cancer and MDS/LAM are still critical questions

CAN WE IMPROVE THE DEEP AND DURANTION OF RESPONSE?

Combining BTK inhibitor and BCL2 Inhibitor

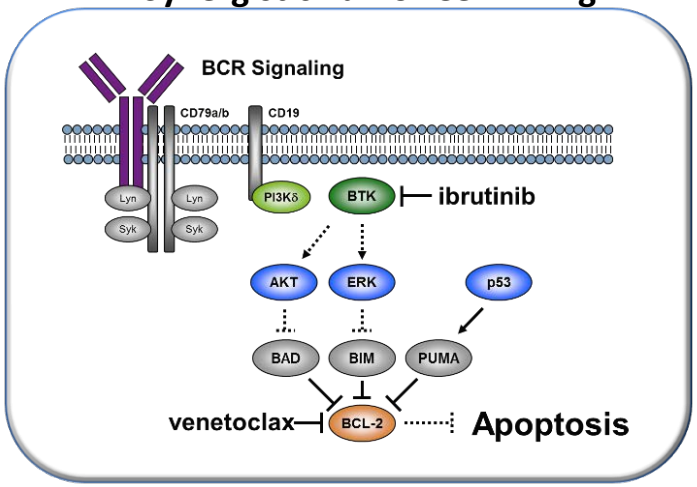
- BTK inhibitor monotherapy rarely induces CR and duration of response is limited in patients with high-risk CLL
- Patients treated with a BTK inhibitor may acquire somatic resistance mutations (eg, BTK C481S)
- Preclinical data suggest potential benefit in combination of BTK inhibitor and BCL2 inhibitor



Reprinted by permission from Springer Nature. Deng J, et al. *Leukemia*. 2017;31:2075-2084. Bruton's tyrosine kinase inhibition

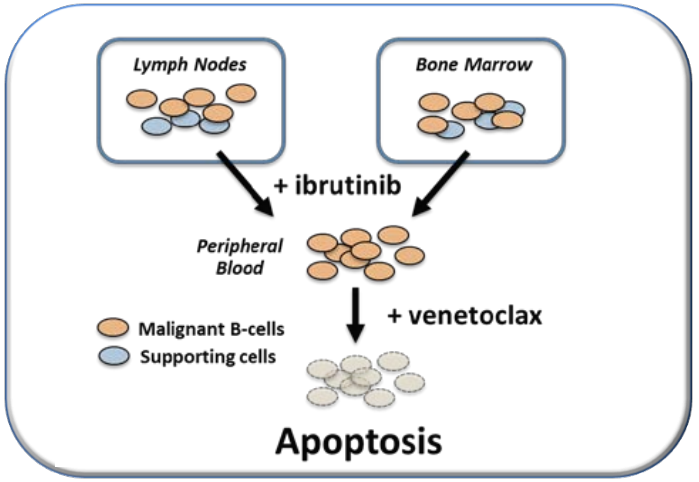
Rationale to Combine BTK inhibitor and BCL2 Inhibitor

Synergistic Tumor Cell Killing



- BTK inhibition liberates BAD, which antagonizes BCL-2
- BTK inhibition upregulates BIM, which is bound by BCL-2, priming it for the action of venetoclax

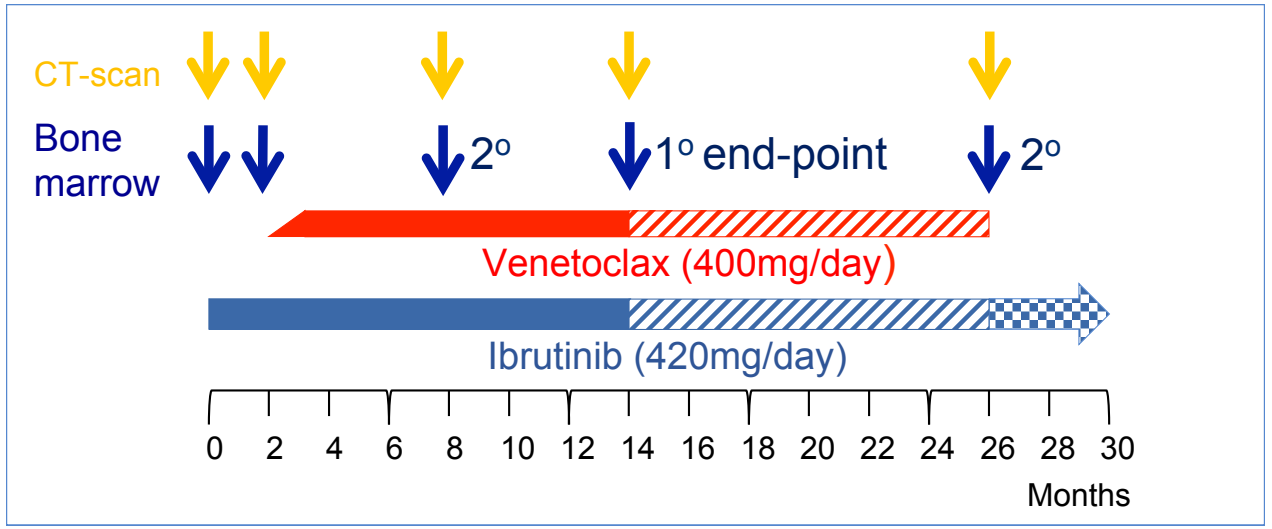
Tumor Cell Mobilization/Sensitization



- BTK inhibition mobilizes malignant B-cells from lymph nodes/bone marrow into peripheral circulation
- Malignant B-cells are more sensitive to venetoclax in peripheral blood

Courtesy by D. James, PCYC

CLARITY: Venetoclax + Ibrutinib in R/R CLL



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

Hillmen *et al.* ASH 2017; Abst 428

CLARITY: Venetoclax + Ibrutinib in R/R CLL

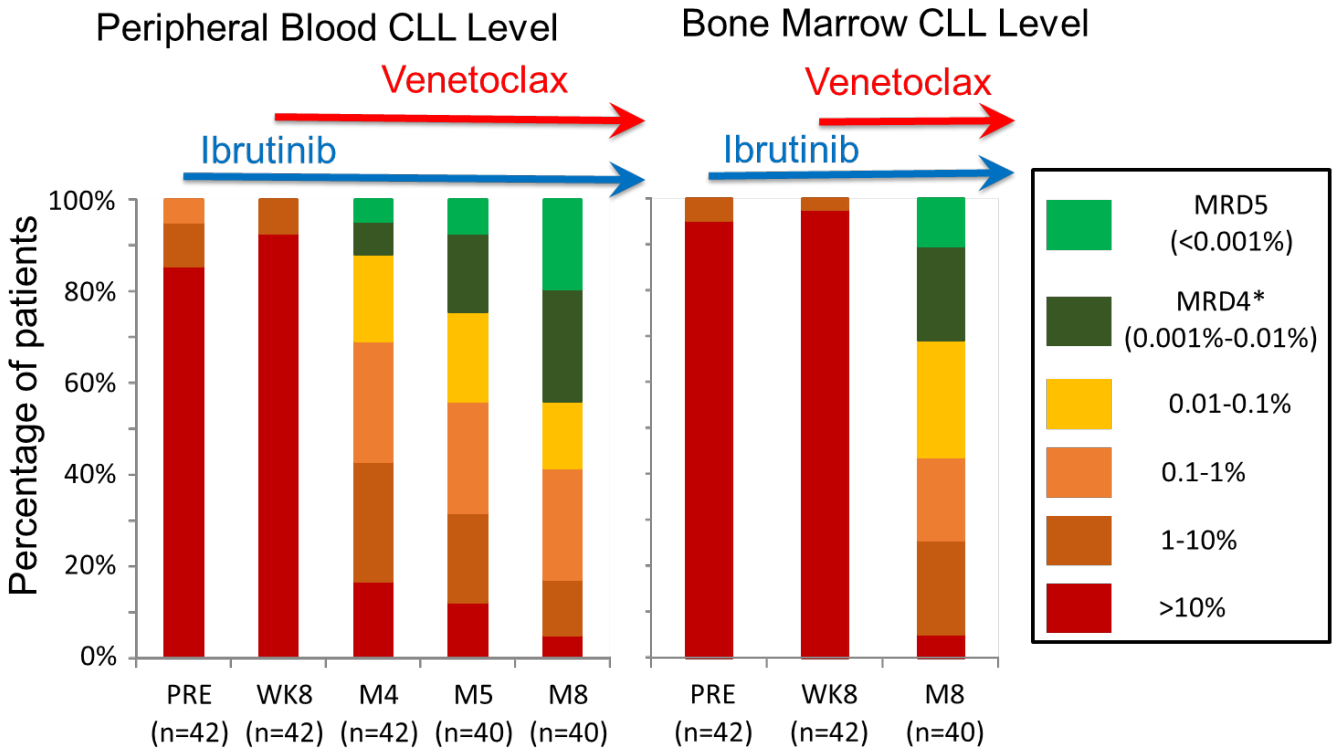
- Feasibility study (N = 50) to determine whether ibrutinib + venetoclax achieves MRD in the PB and/or BM (< 0.01% CLL cells)

Outcomes in Evaluable Patients After 6 Months of Venetoclax Treatment

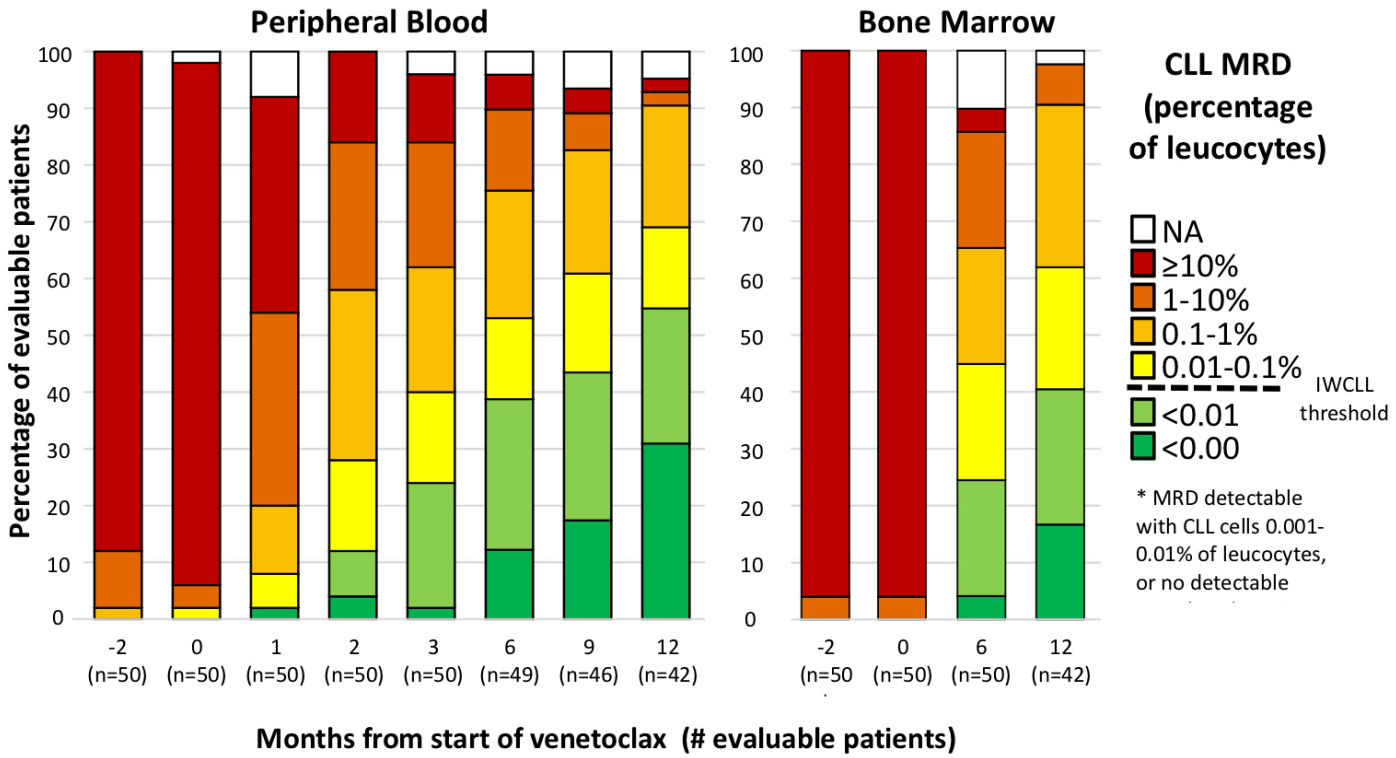
Response rate (n = 38)	
ORR, %	100
CR, %	39
CRi, %	8
PR, %	53

MRD negativity rate	
In PB, %	37
In BM, %	32

Hillmen P, et al. *Blood*. 2017;

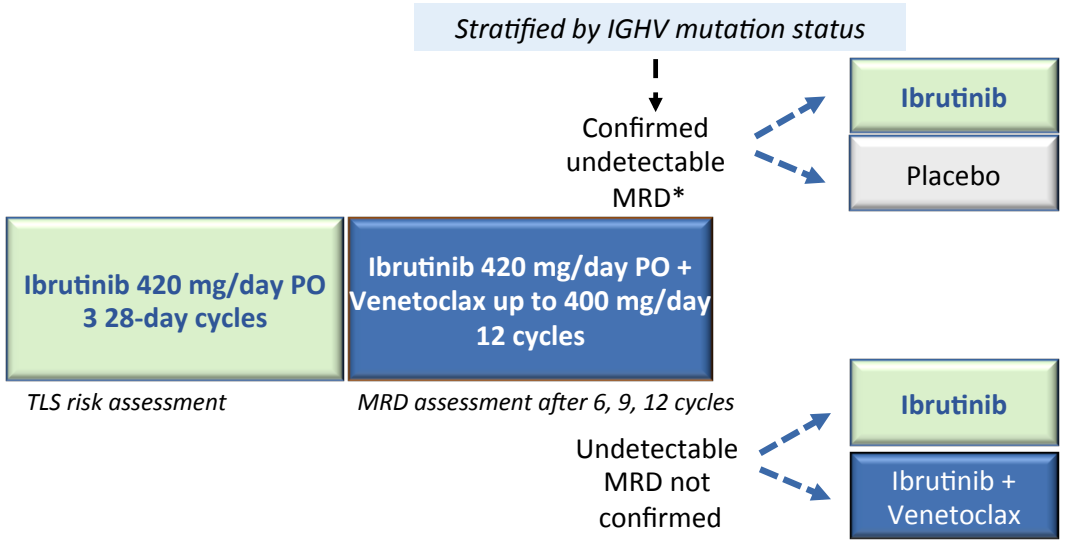


CLARITY: Ibrutinib Plus Venetoclax in Relapsed/Refractory CLL: Results of the Bloodwise TAP Clarity Study



CAPTIVATE: Phase II Ibrutinib + Venetoclax in TN CLL

Patients with untreated CLL/ SLL requiring treatment, ECOG PS 0/1, < 70 yrs of age (N = 164)



CAPTIVATE

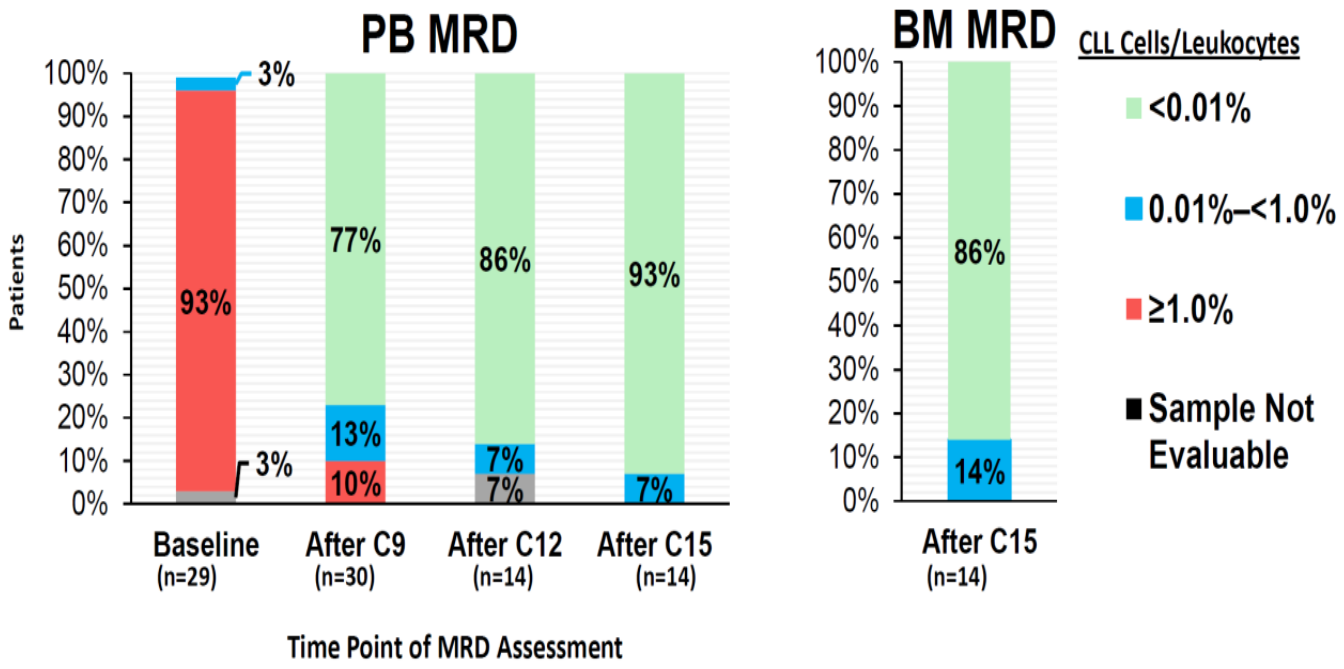
Clinical Trial to **A**ssess **P**otential of **T**runcated **I**brutinib and **V**enetocl**A**x **T**reatm**E**nt

- Ibrutinib lead-in to debulk disease, reduce risk of venetoclax-associated tumor lysis
- MRD status after 12 cycles of combination used to separate patients for randomization
- Prespecified interim analysis of first 30 patients to complete 6 cycles of combination

*Serial undetectable blood MRD at least 3 cycles apart + undetectable marrow MRD.

Wierda WG, et al. ASCO 2018. Abstract 7502.

CAPTIVATE: Ibrutinib + Venetoclax in TN CLL



Wierda WG, et al. ASCO 2018. Abstract 7502.

IN THE NEXT FUTURE…COMBINATION THERAPY 1L

- **PIVOTAL and FINAL RESULTS WILL BE PRESENT AT ASH 2018**

182 Ibrutinib Plus Venetoclax in Relapsed/Refractory CLL: Results of the Bloodwise TAP Clarity Study

185 Ibrutinib, Fludarabine, Cyclophosphamide, and Obinutuzumab (iFCG) for Firstline Treatment of Patients with CLL with Mutated *IGHV* and without *TP53* Aberrations

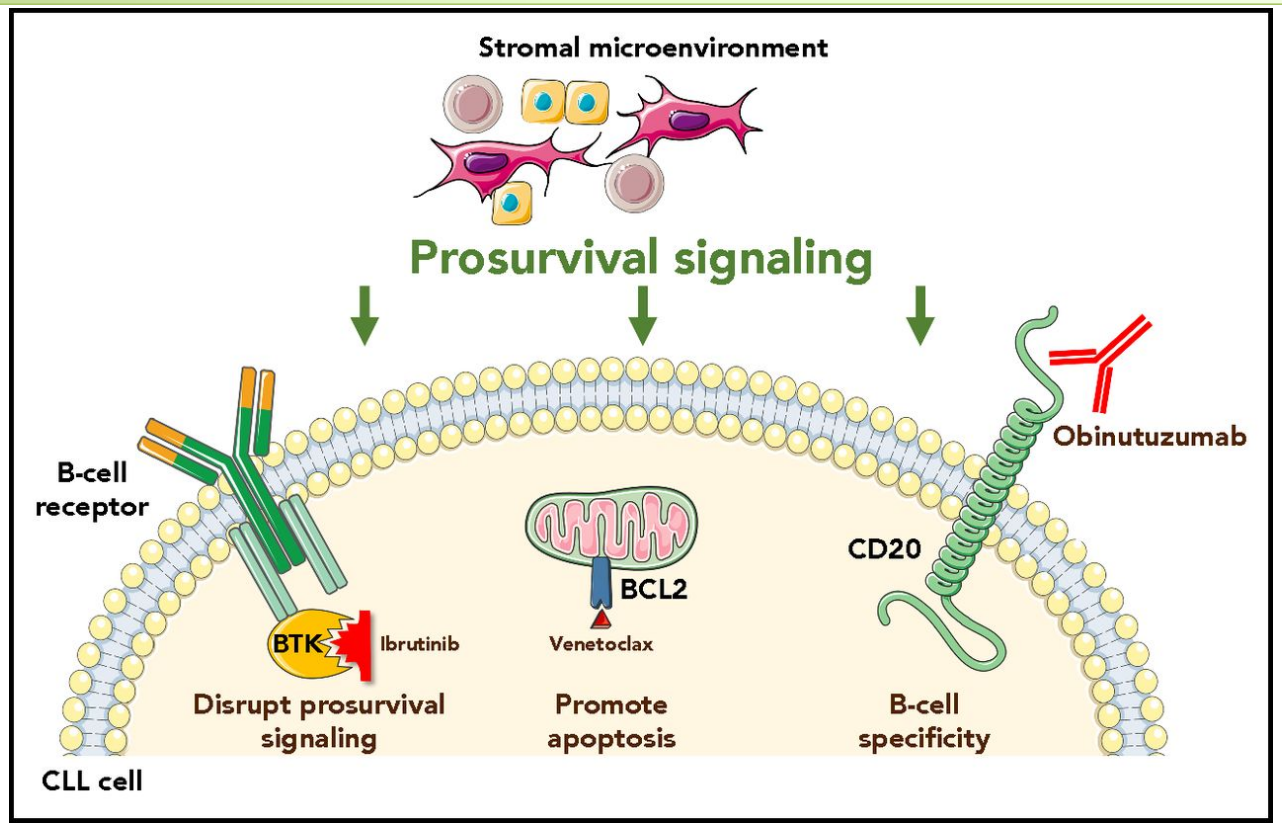
186 Combined Ibrutinib and Venetoclax in Patients with Treatment-Naïve High-Risk Chronic Lymphocytic Leukemia (CLL)

691 Ibrutinib + Obinutuzumab Versus Chlorambucil + Obinutuzumab As First-Line Treatment in Patients with Chronic Lymphocytic Leukemia or Small Lymphocytic Lymphoma (CLL/SLL): Results from Phase 3 iLLUMINATE

CLL14 Venetoclax-Obinutuzumab vs Clorambucil-Obinutuzumab

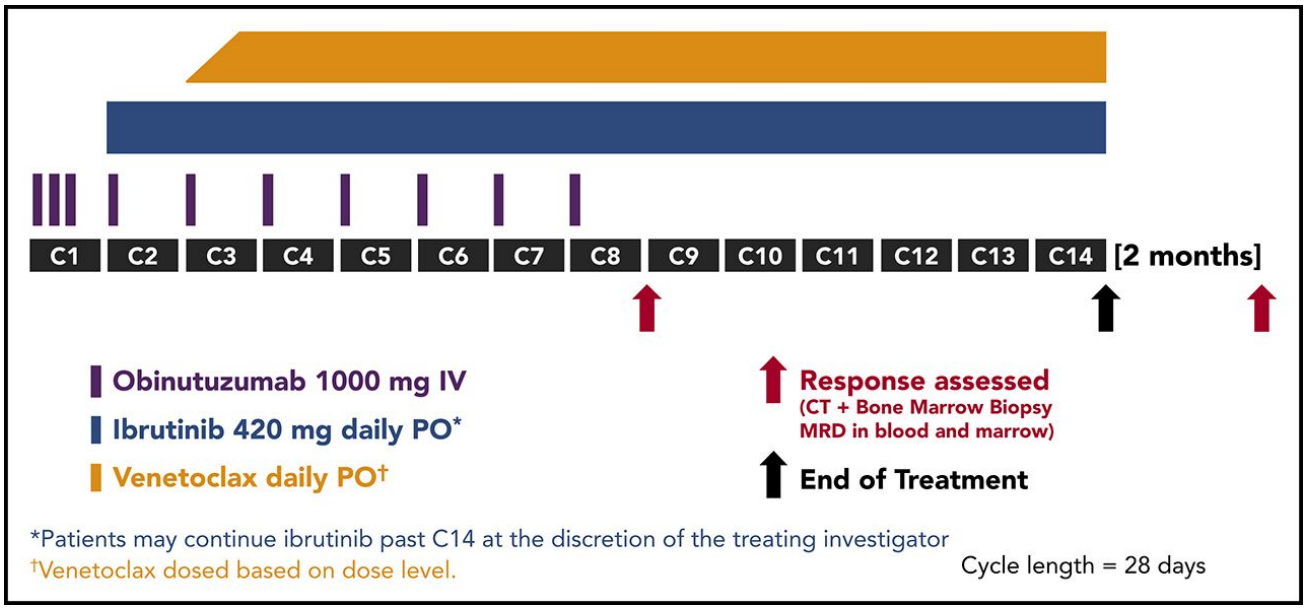
….many other things

Ibrutinib, venetoclax, and obinutuzumab independently target 3 pathways critical for the survival of neoplastic B cells in CLL.



Benjamin L. Lampson, and Matthew S. Davids Blood 2018;132:1547-1548

Phase 1b study of obinutuzumab, ibrutinib, and venetoclax in relapsed and refractory chronic lymphocytic leukemia

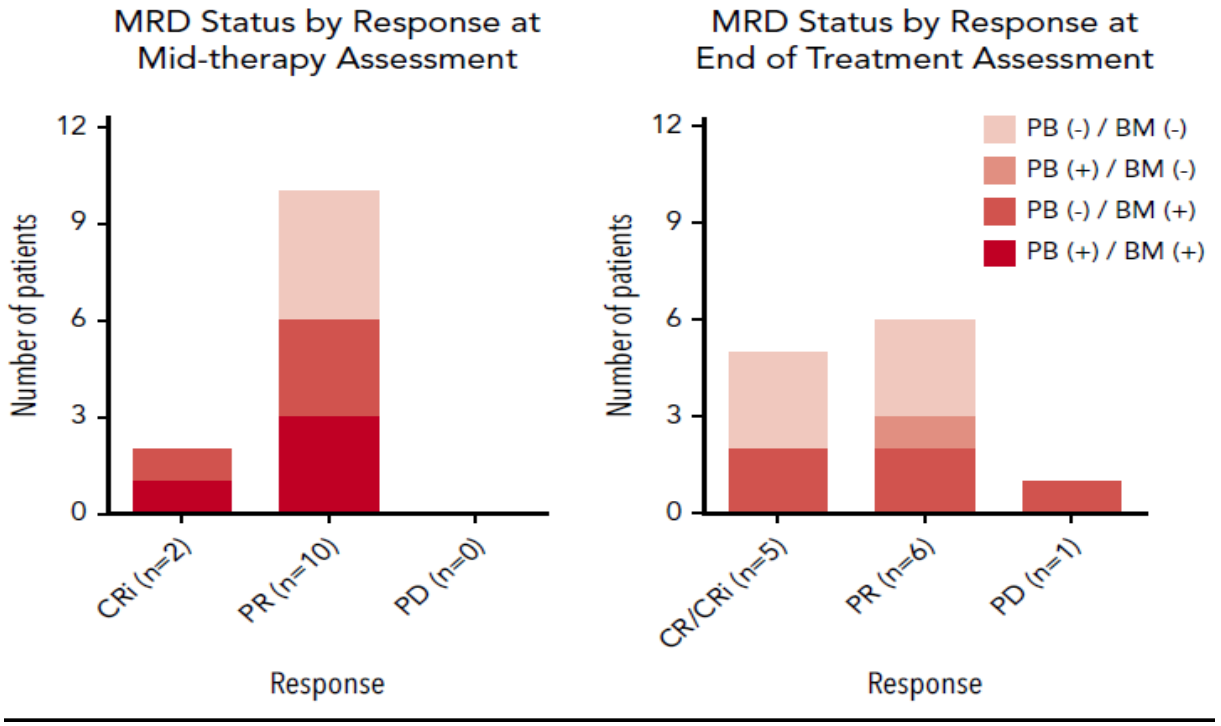


blood

Kerry A. Rogers et al. Blood 2018;132:1568-1572

Phase 1b study of obinutuzumab, ibrutinib, and venetoclax in relapsed and refractory chronic lymphocytic leukemia

ORR 92%; CR/CRi 42%



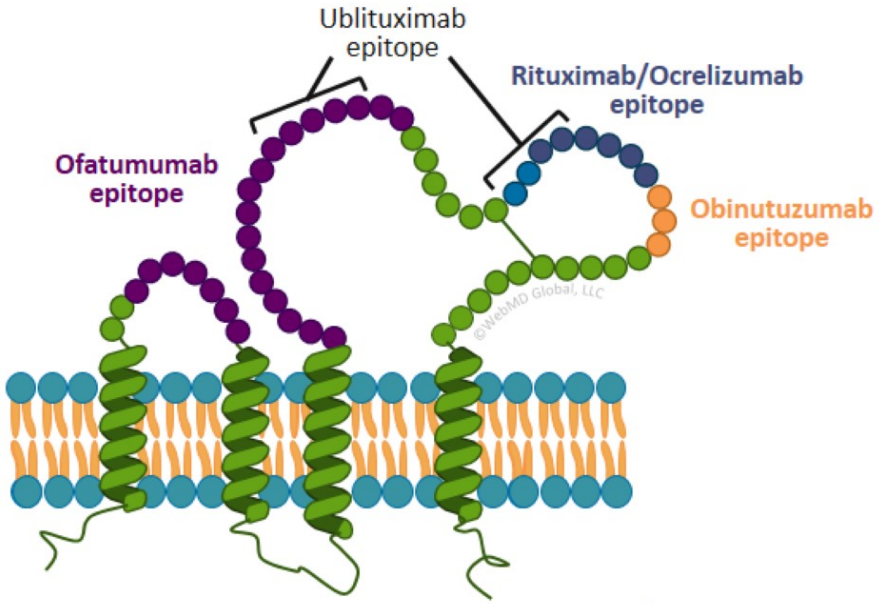
Kerry A. Rogers et al. Blood 2018;132:1568-1572

Novel Agents: Acalabrutinib and Ublituximab

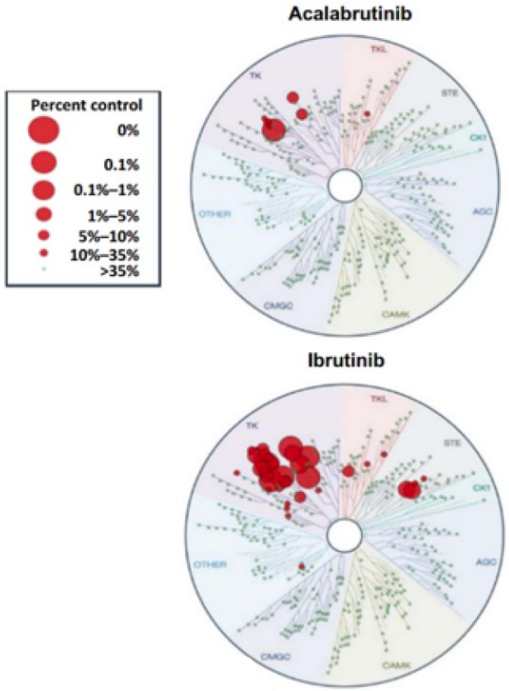
- II generation BTKs (Acalabrutinib, BGB-311, SNS-062)
- PI3K g d inibitors (duvelisib, umbralisib)
- New anti-CD20 mAbs

Novel Agents: Acalabrutinib and Ublituximab

Epitope Binding Sites of Anti-CD20 mAbs[a,b]



Comparative Extent of Kinase Inhibition[c]



Take Home messages

1. La progressione della CLL è eterogenea; le conoscenze della biologia della malattia permetteranno di identificare pazienti ad elevato rischio;
2. Lo studio della citogenetica, oltre che alla ricerca delle mutazioni/ delezioni di p53 e valutazione delle mutazioni somatiche dovrebbero essere prese in considerazione quando si decide di iniziare una terapia;
3. La combinazione di programmi di terapia potrebbe indurre una maggiore profondità. Della risposta e permettere una terapia limitatat nel tempo, forse riducendo resistenze e tossicità!

Quesiti aperti nella Leucemia linfatica cronica (LLC)

Quale sequenza e durata combinazione per i nuovi farmaci

Grazie

Livio Trentin