ALMA MATER STUDIORUM
UNIVERSITÀ DI BOLOGNA
DIPARTIMENTO DI
SCIENZE MEDICHE E CHIRURGICHE

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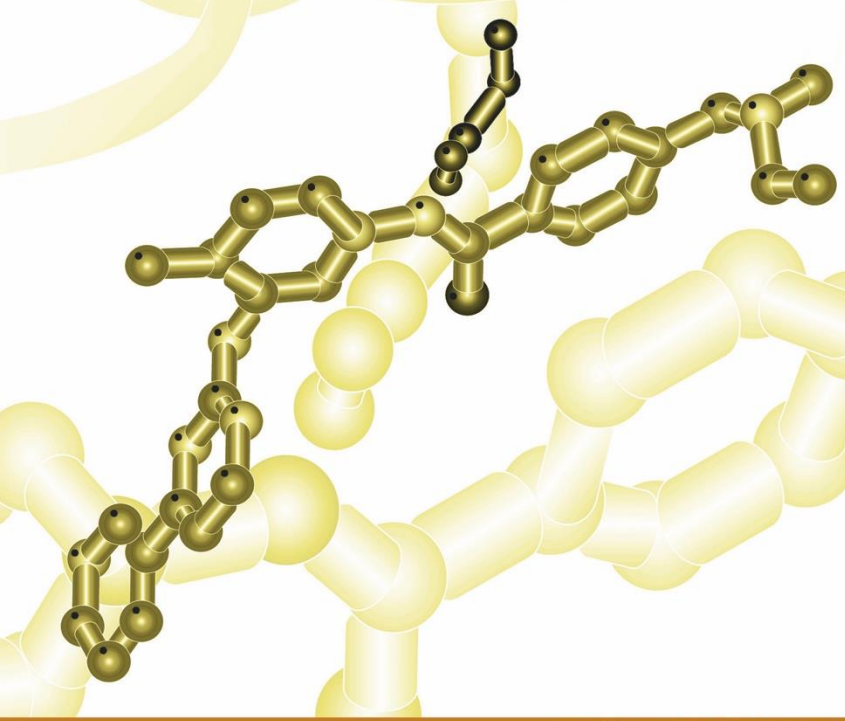

New Drugs in Hematology

President: Pier Luigi Zinzani
Co-President: Michele Cavo

Bologna,
Royal Hotel Carlton
January 15-17, 2024

BOLOGNA BOLOGNA, ROYAL HOTEL CARLTON

Chronic Lymphocytic Leukemia

VENETOCLAX

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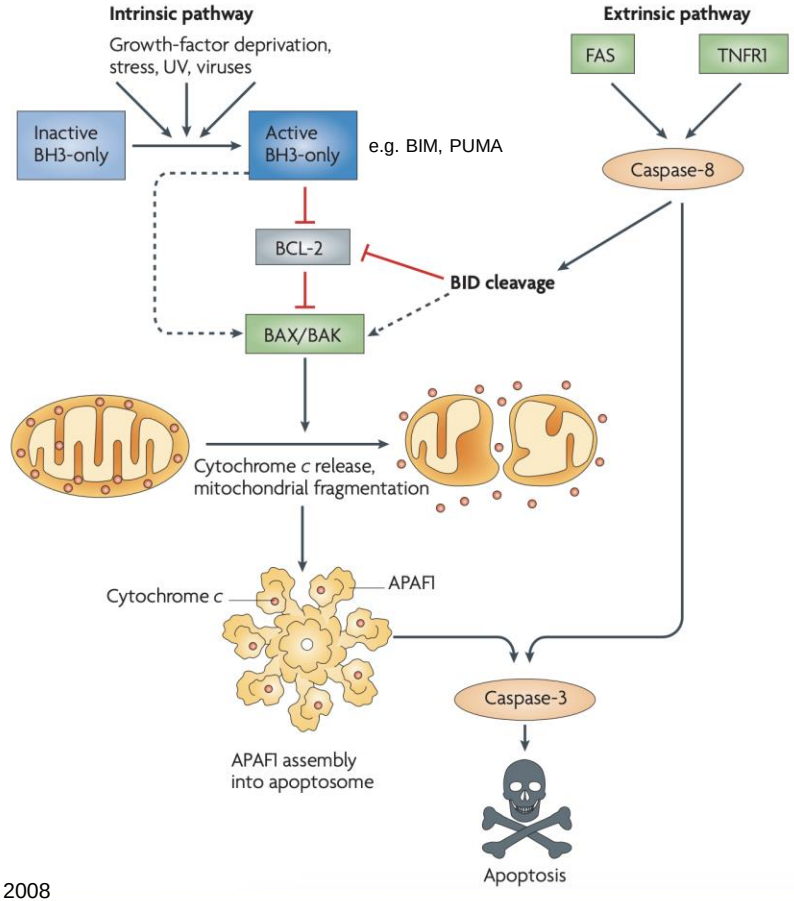
University Hospital of Cologne
Dep. I of Internal Medicine

Disclosures of Othman Al-Sawaf

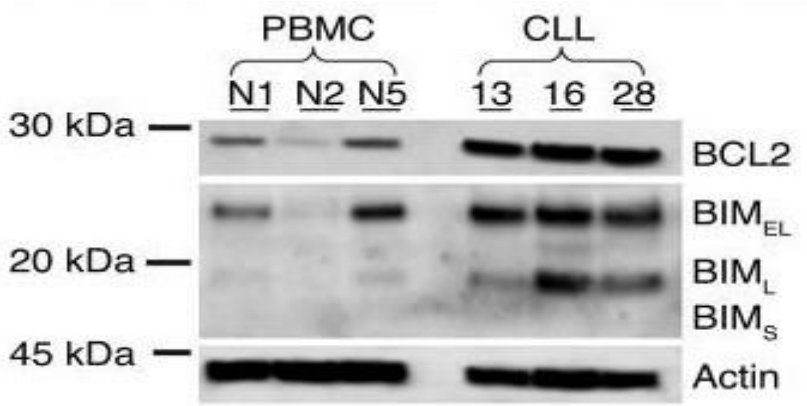
Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
AbbVie	x				x	x	
AstraZeneca					x	x	
AbbVie					x	x	
Adaptive					x	x	
Ascentage						x	
BeiGene	x				x	x	
Gilead					x	x	
Janssen	x				x	x	
Roche	x				x	x	

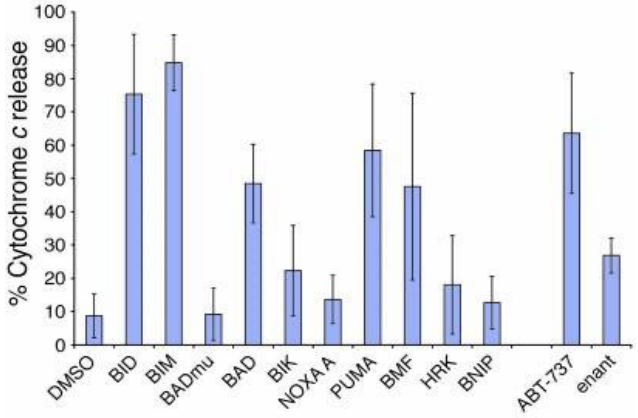
Bcl-2 in intrinsic and extrinsic pathways of apoptosis



Youle & Strasser, *Nature Reviews Molecular Cell Biology*, 2008

CLL survival depends on Bcl-2 signalling

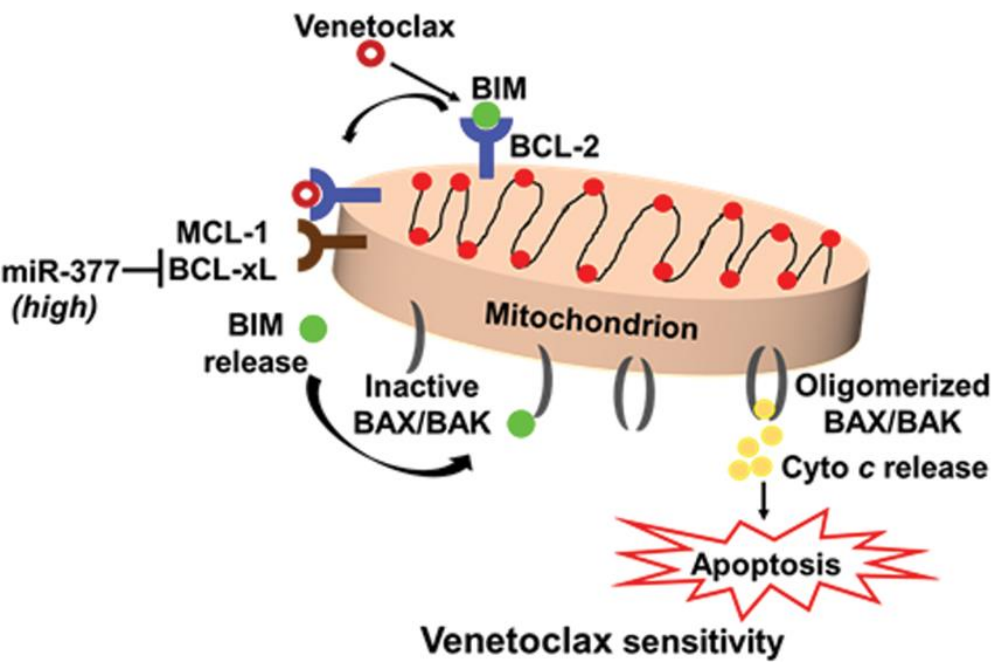




Particular sensitivity of CLL cells to BCL2 antagonism arises BCL2 tonically sequestering proapoptotic BIM in CLL.

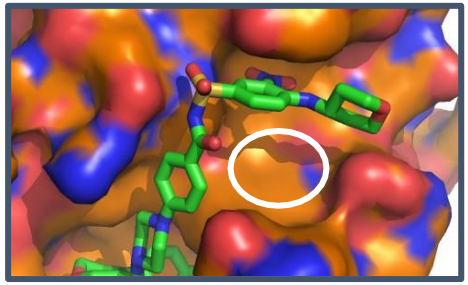
Del Gaizo Moore V, et al. *J Clin Invest*. 2007

Inhibiting Bcl-2 to induce apoptosis

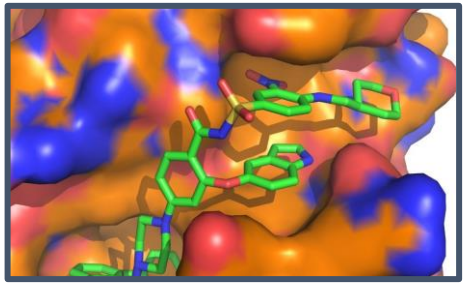


Kapour et al, *Cell Death & Disease*, 2020

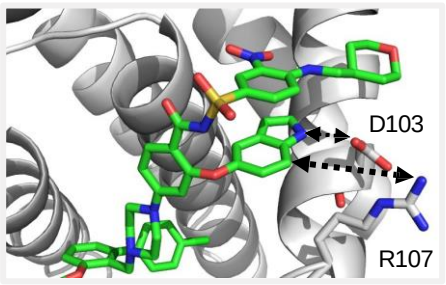
The Bcl-2 inhibitor ABT-199



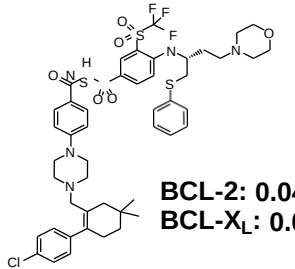
Vacated P4 pocket is an opportunity to build in potency and selectivity



Addition of indole enhances BCL-2 affinity 100-fold
Cell killing activity restored

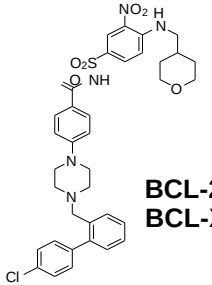


Azaindole makes additional H-bond w/ BCL-2
BCL-2 affinity enhanced

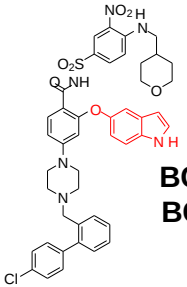


BCL-2: 0.04 nM
BCL-X_L: 0.05 nM

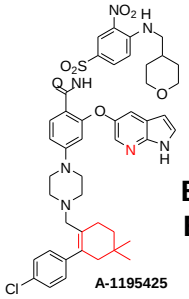
ABT-263



BCL-2: 25 nM
BCL-X_L: >660 nM



BCL-2: 0.23 nM
BCL-X_L:>660 nM

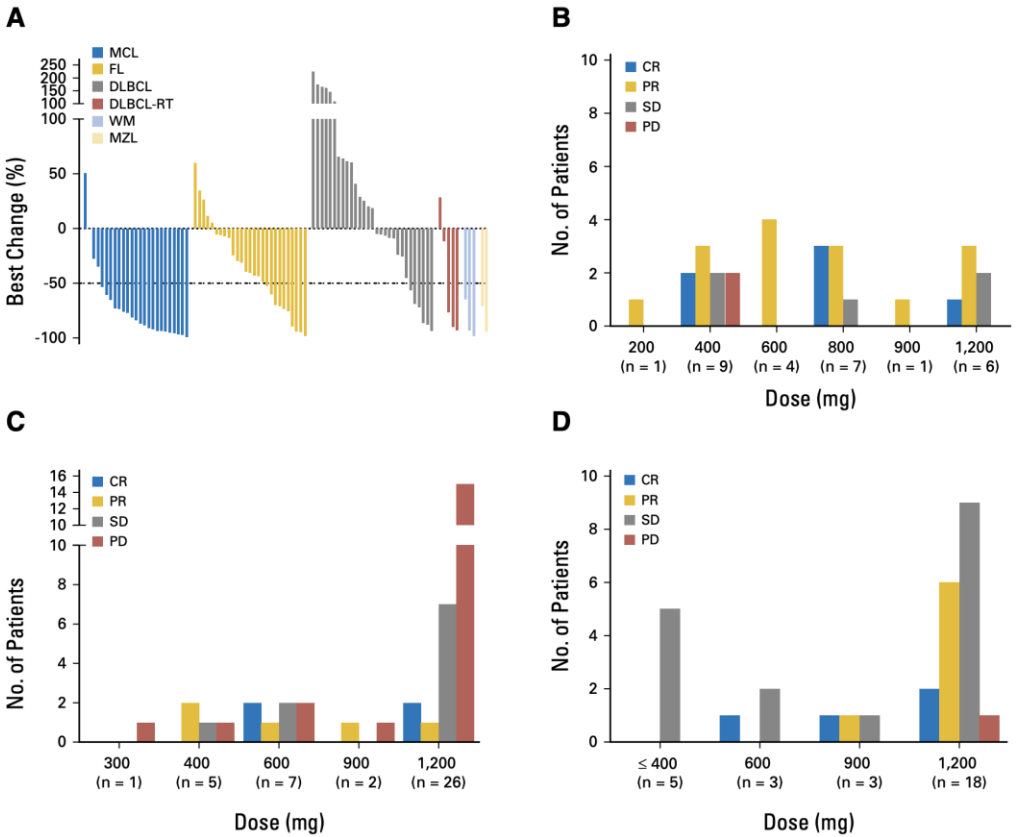


ABT-199

BCL-2: <0.01 nM
BCL-X_L: >40 nM

Souers AJ, et al. *Nat Med*. 2013

Venetoclax in B-NHL



Davids et al, *J Clin Oncol*, 2017

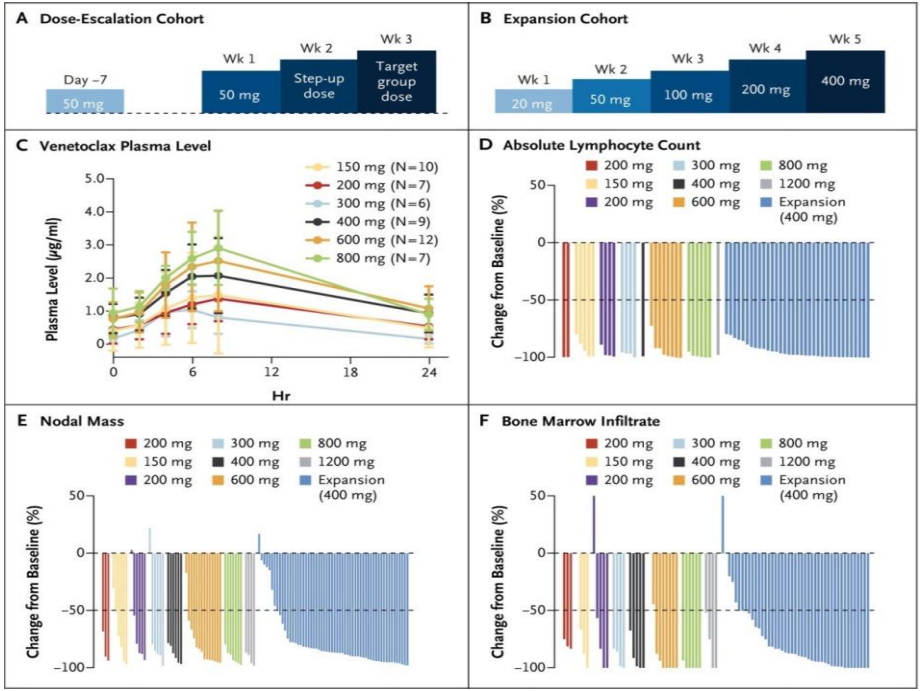
Venetoclax in CLL

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Targeting BCL2 with Venetoclax in Relapsed Chronic Lymphocytic Leukemia

Andrew W. Roberts, M.B., B.S., Ph.D., Matthew S. Davids, M.D., John M. Pagel, M.D., Ph.D., Brad S. Kahl, M.D., Soham D. Puvvada, M.D., John F. Gerecitano, M.D., Ph.D., Thomas J. Kipps, M.D., Ph.D., Mary Ann Anderson, M.B., B.S., Jennifer R. Brown, M.D., Ph.D., Lori Gressick, B.S., Shekman Wong, Ph.D., Martin Dunbar, Dr.P.H., Ming Zhu, Ph.D., Monali B. Desai, M.D., M.P.H., Elisa Cerri, M.D., Sari Heitner Enschede, M.D., Rod A. Humerickhouse, M.D., Ph.D., William G. Wierda, M.D., Ph.D., and John F. Seymour, M.B., B.S., Ph.D.



Roberts et al, *N Engl J Med*, 2016

Venetoclax in CLL

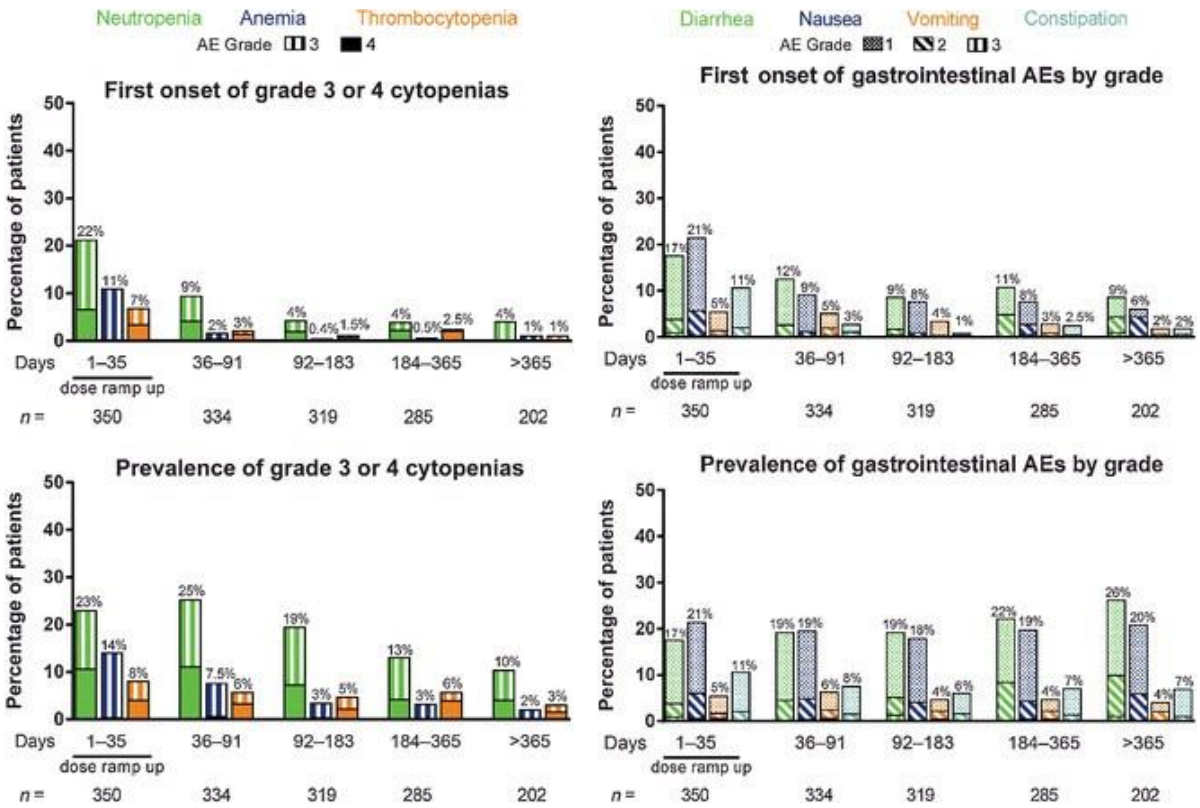
ABT-199 clinical trials suspended after patient death $ABBV

Following a death due to tumor lysis syndrome, AbbVie ($ABBV) have suspended the ABT-199 clinical trial program. ABT-199 is a promising new drug in development for chronic lymphocytic leukemia (CLL) that was about to enter phase 3 drug development by the company.

The company has issued no press release, but the clinicaltrials.gov web site shows that that clinical trials are suspended, information confirmed at the BIO CEO 2013 meeting in New York earlier this week. Here's a quick snapshot taken on Feb 14, 2013 of what the clinicaltrials.gov site shows:

https://biotechstrategyblog.com/2013/02/abt-199-clinical-trials-suspended-after-patient-death.html/; February 2013

Safety of Bcl-2 inhibition



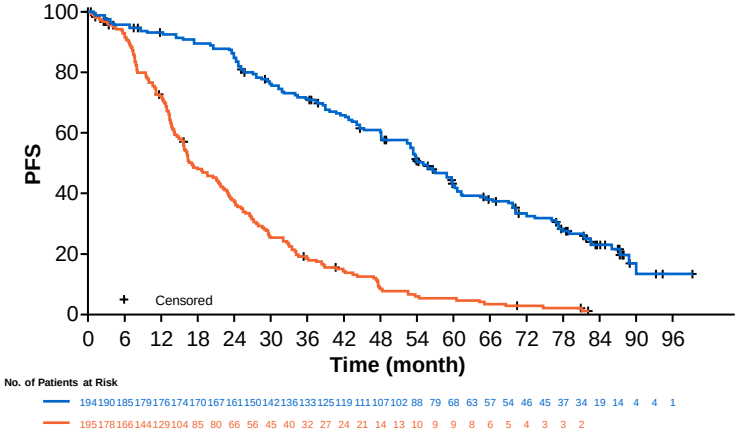
Laboratory TLS risk <2%
No clinical TLS

Davids et al, *Clin Cancer Res*, 2018

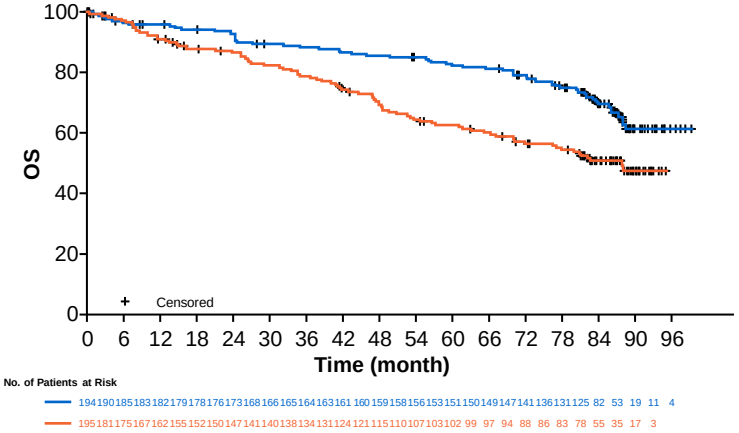
Combinations of venetoclax

MUANO trial in r/r CLL: Ven-R vs BR

	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



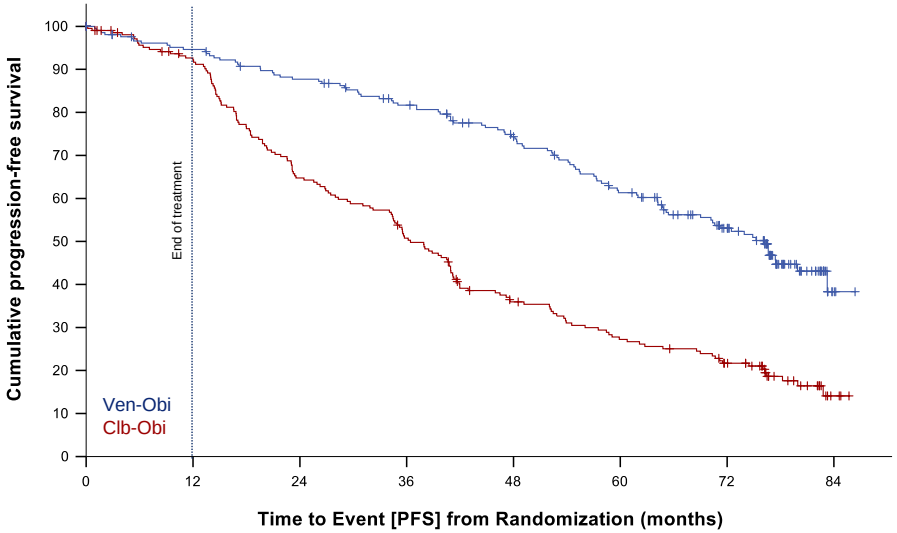
	Median OS (95% CI), months	HR‡ (95% CI)	7-year OS (%)
VenR (n=194)	NE	0.53 (0.37–0.74) Stratified P-value <0.0002†	69.6
BR (n=195)	87.8 (70.1–NE)		51.0



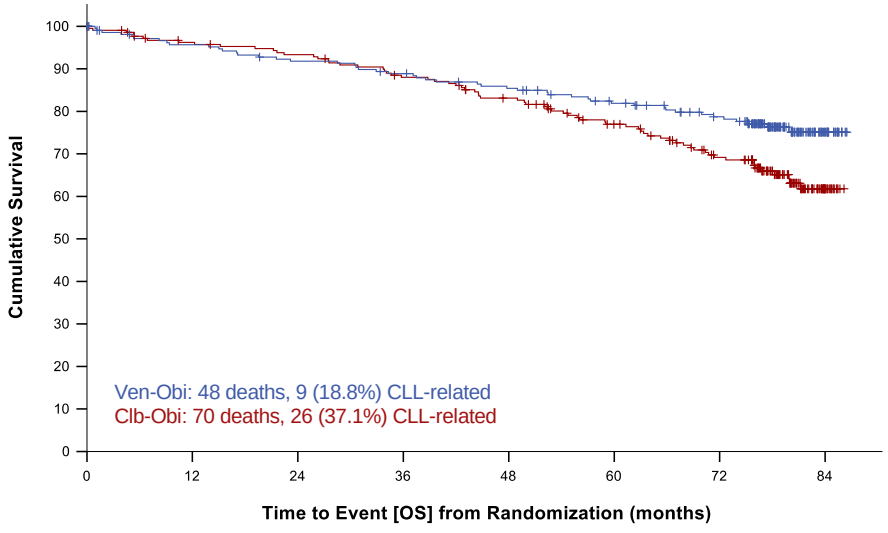
Seymour et al, ICML 2023

Combinations of venetoclax

CLL14 trial in 1L CLL: Ven-Obi vs Clb-Obi



Ven-Obi	216	193	177	160	139	112	79	3
Clb-Obi	216	185	130	101	67	50	36	3



Ven-Obi	216	198	189	182	173	160	144	23
Clb-Obi	216	201	194	181	167	144	118	16

Al-Sawaf et al, ICML 2023

Combinations of venetoclax

CLL14 trial in 1L CLL: Ven-Obi vs Clb-Obi – *most common ≥°3 AEs*

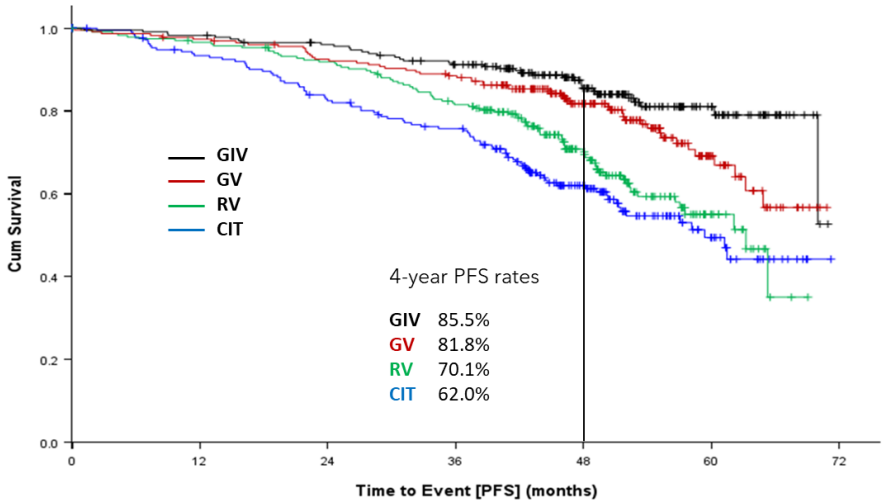
	Venetoclax-obinutuzumab (N=212)		**Chlorambucil-obinutuzumab** (N=214)	
	During Treatment	**After Treatment**	**During Treatment**	**After Treatment**
Neutropenia	51.9%	3.8%	47.2%	1.9%
Thrombocytopenia	14.2%	0.5%	15.0%	0.0%
Anemia	7.5%	1.9%	6.1%	0.5%
Febrile neutropenia	4.2%	0.9%	3.3%	0.5%
Leukopenia	2.4%	0.0%	4.7%	0.0%
Pneunomia	3.8%	3.3%	3.7%	1.4%
Infusion-related reaction	9.0%	0.0%	9.8%	0.5%
Tumour lysis syndrome	1.4%	0.0%	3.3%	0.0%

Al-Sawaf et al, ICML 2023

Combinations of venetoclax

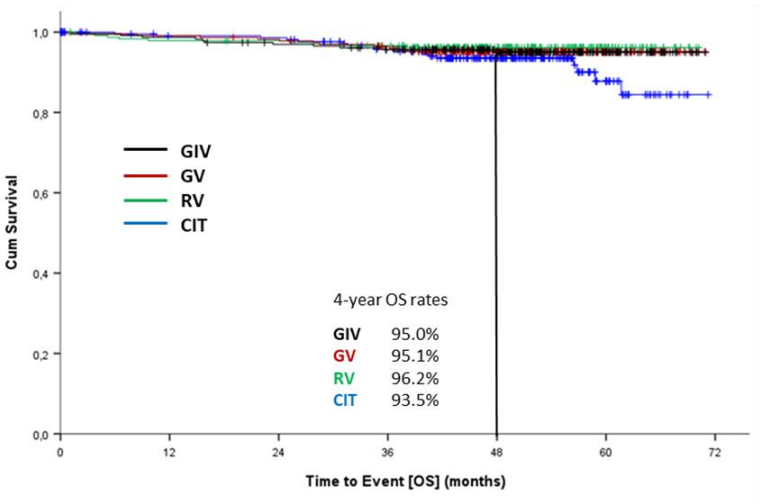
CLL13 trial in 1L CLL: Ven-Obi vs FCR/BR (vs Ven-Obi-I vs Ven-R)

Progression-free survival



Patients at risk						
CIT	229	197	173	156	84	24
RV	237	227	214	188	106	21
GV	229	222	209	198	121	32
GIV	231	227	218	201	130	44

Overall survival

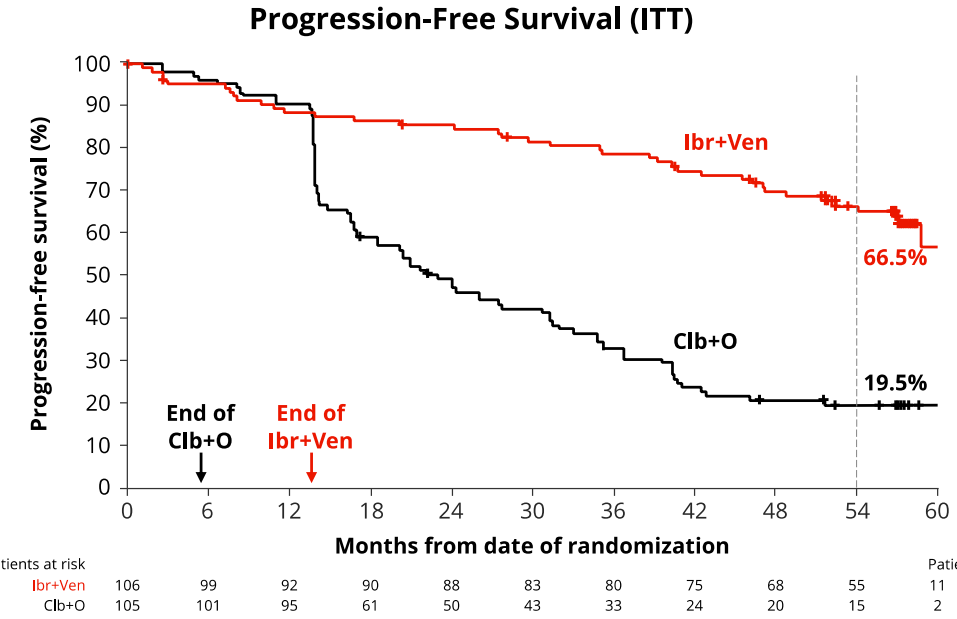


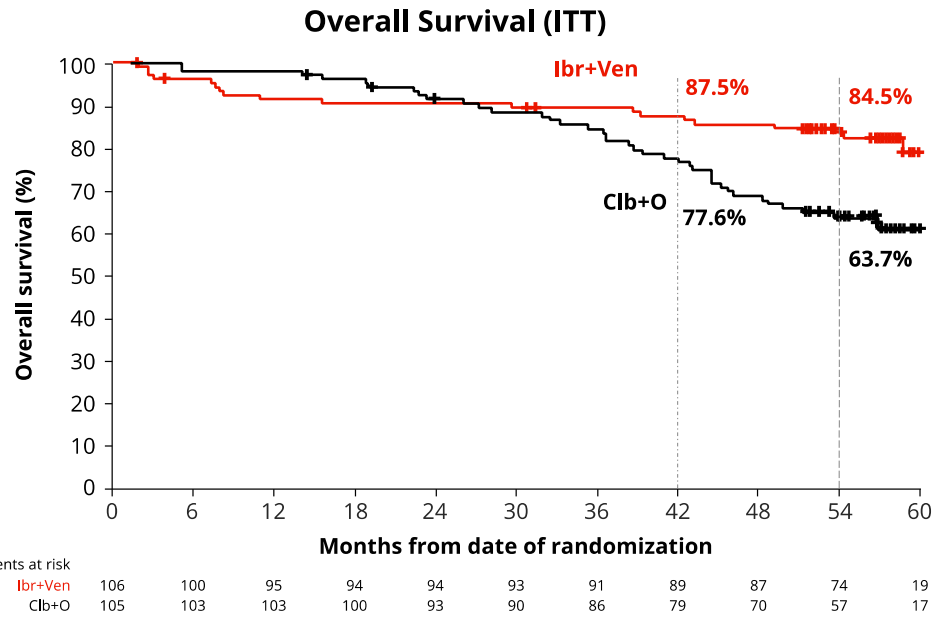
Patients at risk						
CIT	229	209	208	192	120	34
RV	237	231	229	221	142	38
GV	229	227	224	215	136	39
GIV	231	228	220	211	142	48

Fürstenau et al, ASH 2023

Combinations of venetoclax

GLOW trial in 1L CLL: I+V vs Clb-Obi

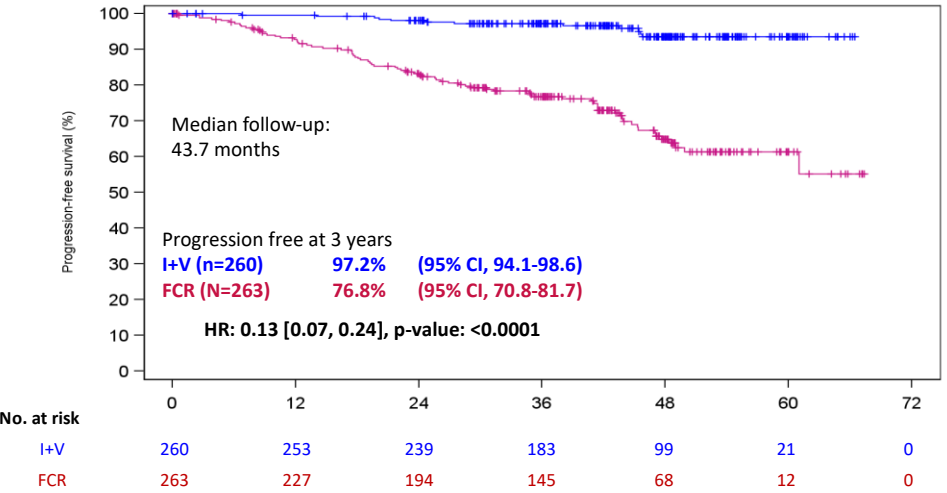


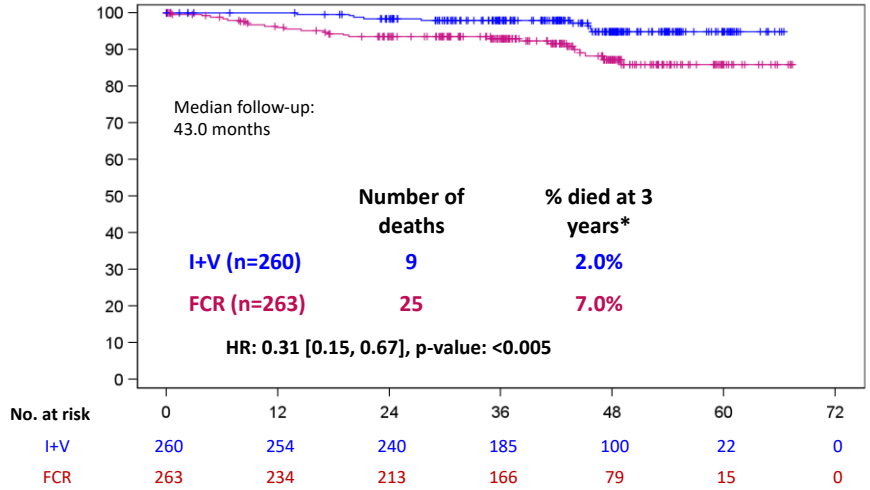


Follows et al, ASH 2023

Combinations of venetoclax

FLAIR trial in 1L CLL: MRD-guided I+V vs FCR

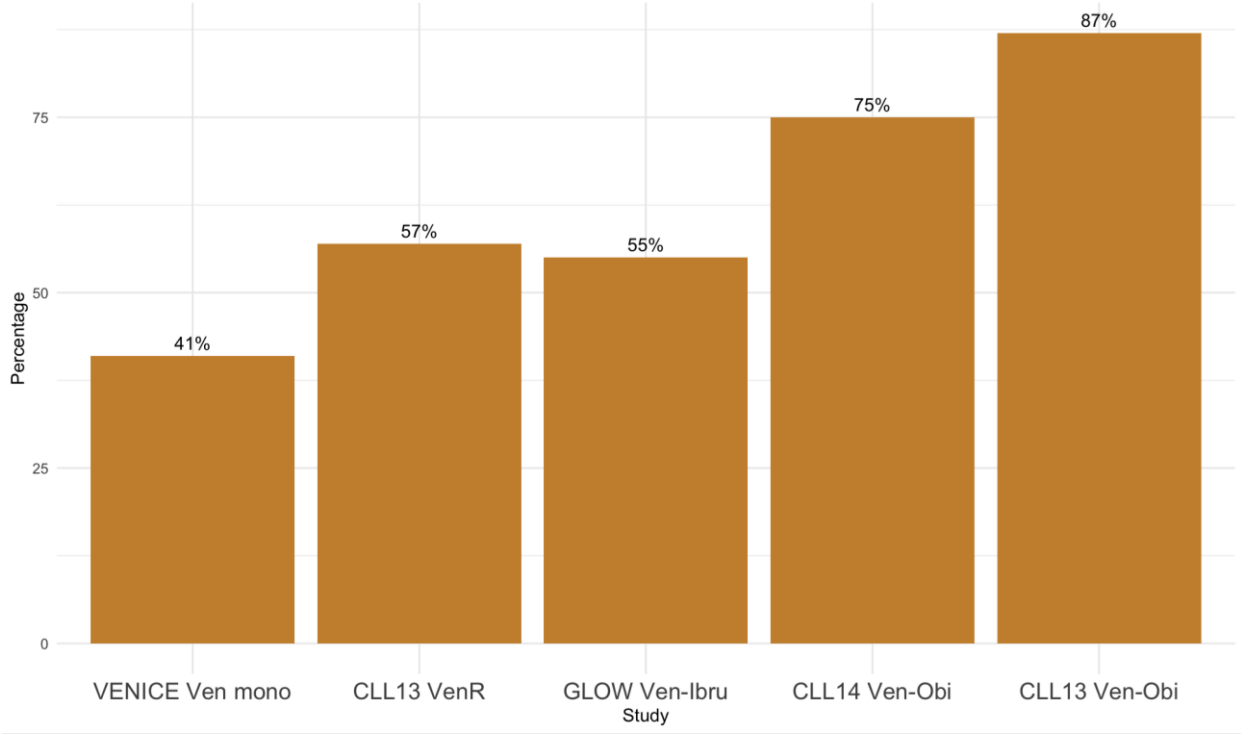




Hillmen et al, ASH 2023

Combinations of venetoclax

MRD outcomes with fixed-duration Ven combinations



Trials with MRD guidance

Combinations of venetoclax

Venetoclax is a backbone for most limited-duration regimens:

- Venetoclax plus
  - CD20 antibody (e.g. rituximab, obinutuzumab)
  - BTK inhibitors (e.g. ibrutinib, acalabrutinib, [zanubrutinib], pirtobrutinib)
  - PI3K inhibitors (e.g. duvelisib)
  - Bispecifics (e.g. epcoritamab)

Quo vadis venetoclax?

Possible caveats of venetoclax:

- TLS risk
- Ramp-up schedule
- Requirement of combination partner for max. uMRD rates

Quo vadis venetoclax?

Possible caveats of venetoclax

- **TLS risk** → *actual risk low, but different pharmacokinetic profile might further mitigate risk*
- **Ramp-up schedule** → *more convenient schedules by next-generation Bcl2-i (e.g. sonrotoclax, lisaftoclax)?*
- Requirement of **combination partner** for max. uMRD → *increased single agent potency by next-generation Bcl2-i?*

Summary

- Compared to other targeted agents, venetoclax induces the highest rates of uMRD
- TLS is a rare adverse event when adequate monitoring and ramp-up schedules are followed
- Venetoclax should always be combined with a CD20 antibody and/or a BTK inhibitor
- Optimal duration of treatment is unknown

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DFG Deutsche Forschungsgemeinschaft

The Al-Sawaf Lab is opening in summer 2024 in Cologne!

Fully funded postdoc & PhD positions available soon!
If you know candidates with interests in **computational biology**, **CLL and cancer**, please feel free to reach out!

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