Update on Therapy Options for Untreated and Relapsed CLL

Scott Huntington

February 8, 2024

YaleNewHavenHealth
Smilow Cancer Hospital

Yale CANCER CENTER
A Comprehensive Cancer Center Designated by the National Cancer Institute

Agenda

- Case presentation/goals of CLL treatment
- Review of first-line treatment options
- Discuss R/R CLL in 2024

First-line CLL patients in your clinic

80 yo F with mutated IgHV and del13q CLL

- CLL diagnosed 20 years ago, slow progression
- ALC 250k, platelets downtrading to 90k
- Comorbidities of interest – afib on AC

70 yo M with unmutated IgHV and del11q CLL

- CLL diagnosed 5 years ago, now with bothersome adenopathy and new anemia
- Mild HTN managed on 2 medications

60 yo M with unmutated IgHV and del17p CLL

- CLL diagnosed 1 year ago, ALC doubling <6 months, worsening anemia and thrombocytopenia
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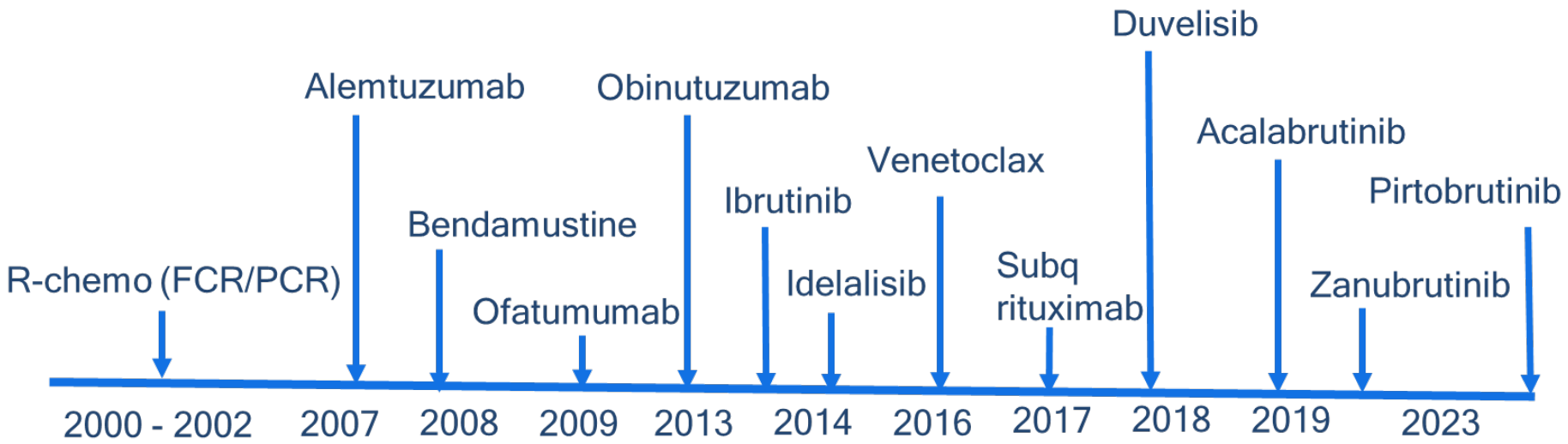
Goal of CLL Treatment: Prolong life while maintaining an excellent QOL

One size does not fit all

Front-line CLL treatment timeline

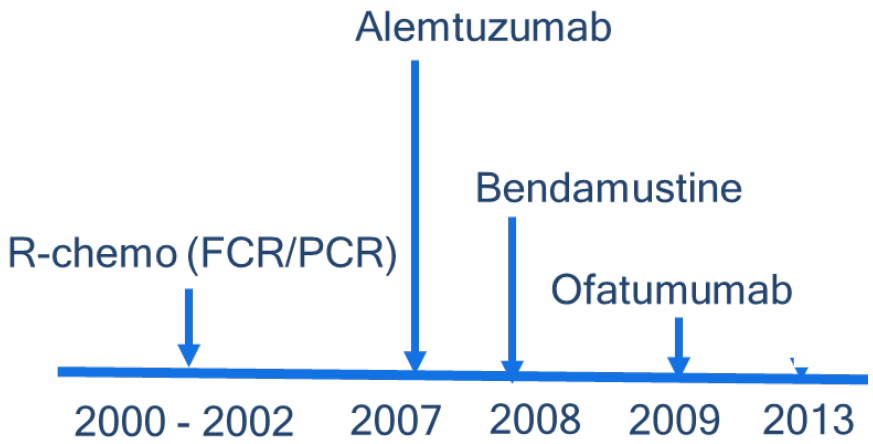


Pre-2000:

1947: Chlormethine
1955: Prednisone
1957: Chlorambucil
1959: Cyclophosphamide
1991: Fludarabine
1997: Rituximab

Adapted from Parikh SA et al. *Nature*. 2020.

Front-line CLL treatment timeline



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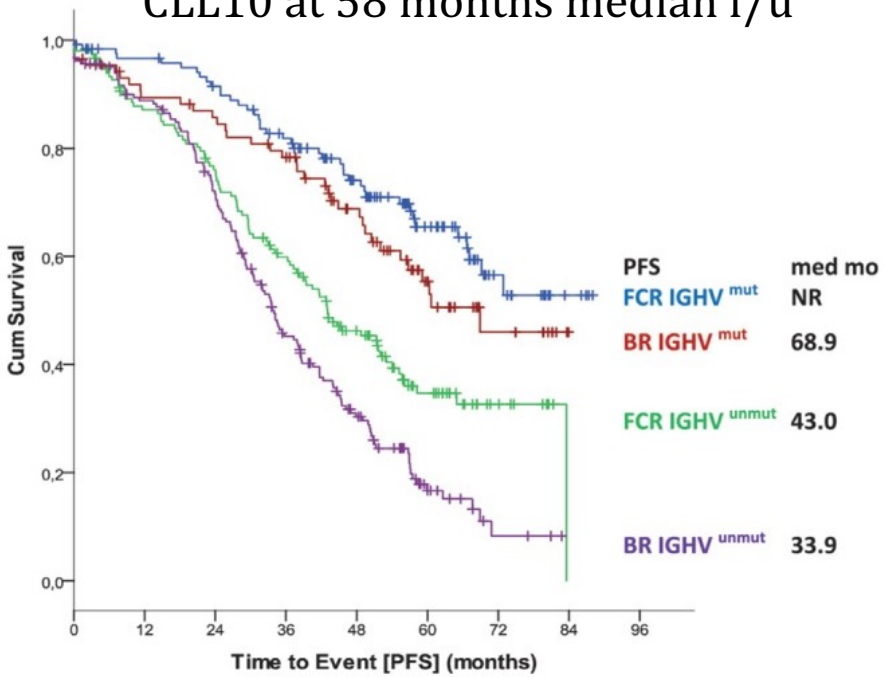
CLL10 at 58 months median f/u

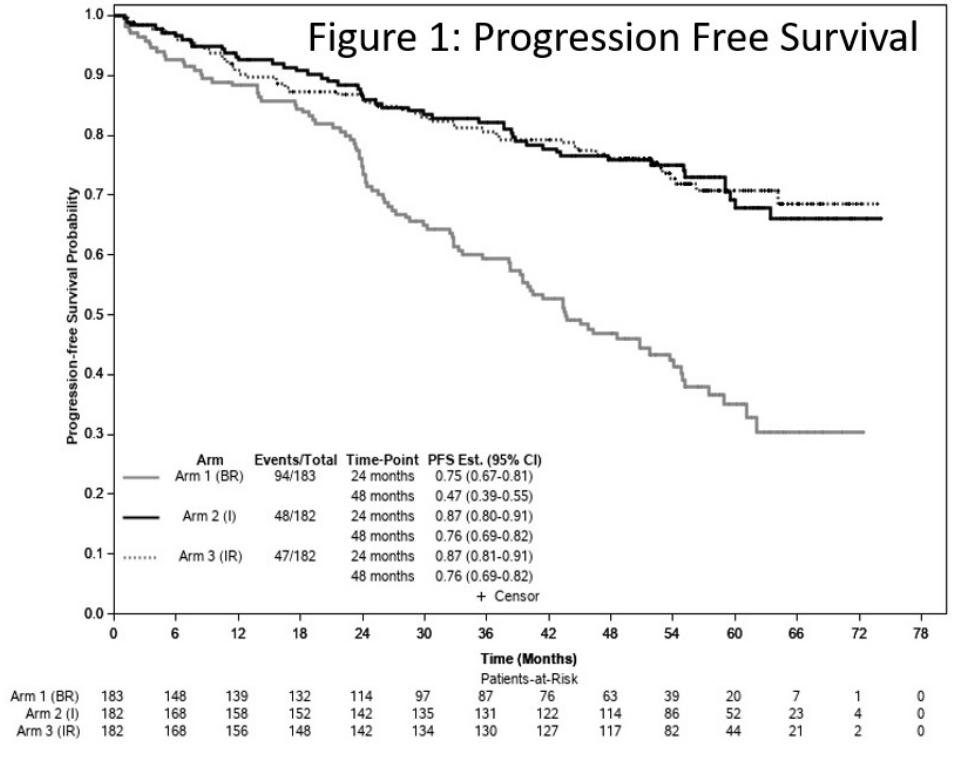


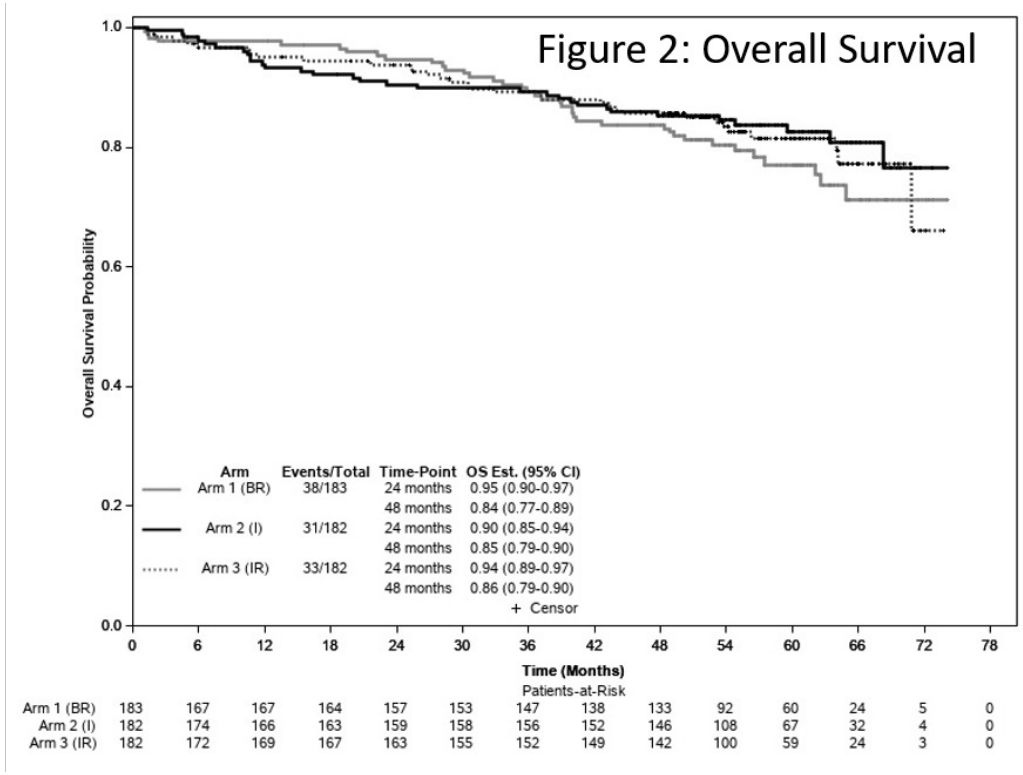
Number at risk	0	12	24	36	48	60	72	84	96
FCR IGHV mut	123	113	105	91	71	41	15	4	0
BR IGHV mut	87	74	70	63	45	24	10	0	-
FCR IGHV unmut	152	126	109	82	53	26	9	0	-
BR IGHV unmut	183	156	124	74	44	13	3	0	-

Kutsch et al. *Hemasphere* 4.1 (2020).

BTKi: R-chemo vs. 1st generation (ibrutinib)

Alliance A041202: >65 yo treatment naive: BR vs. Ibr vs. R-Ibr (median f/u 55 months)

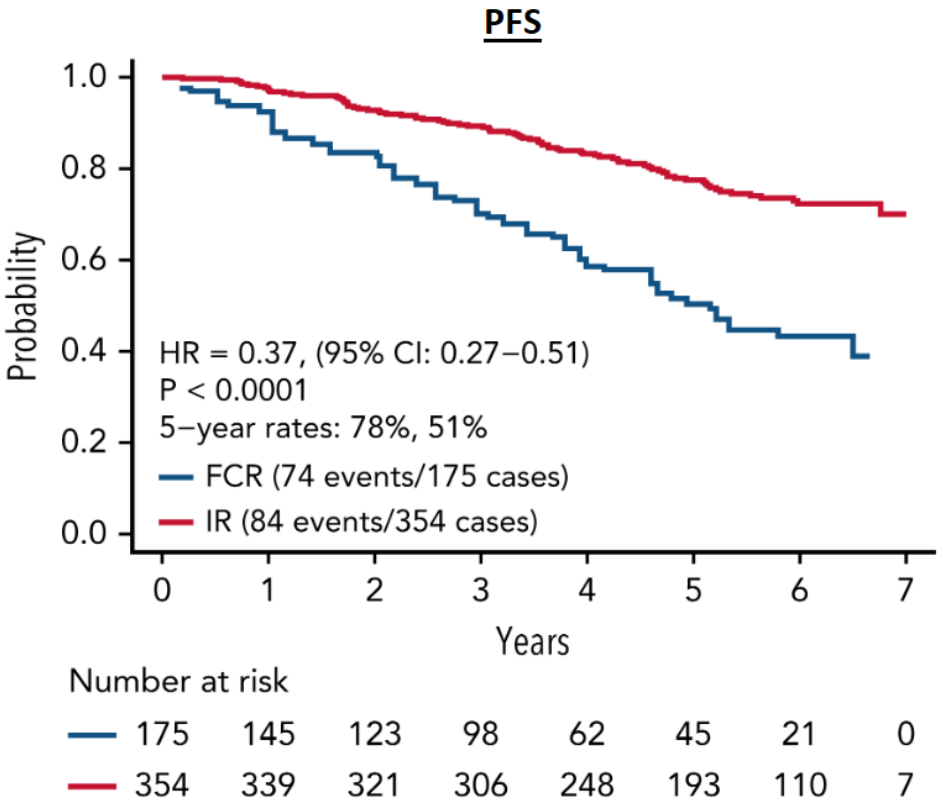


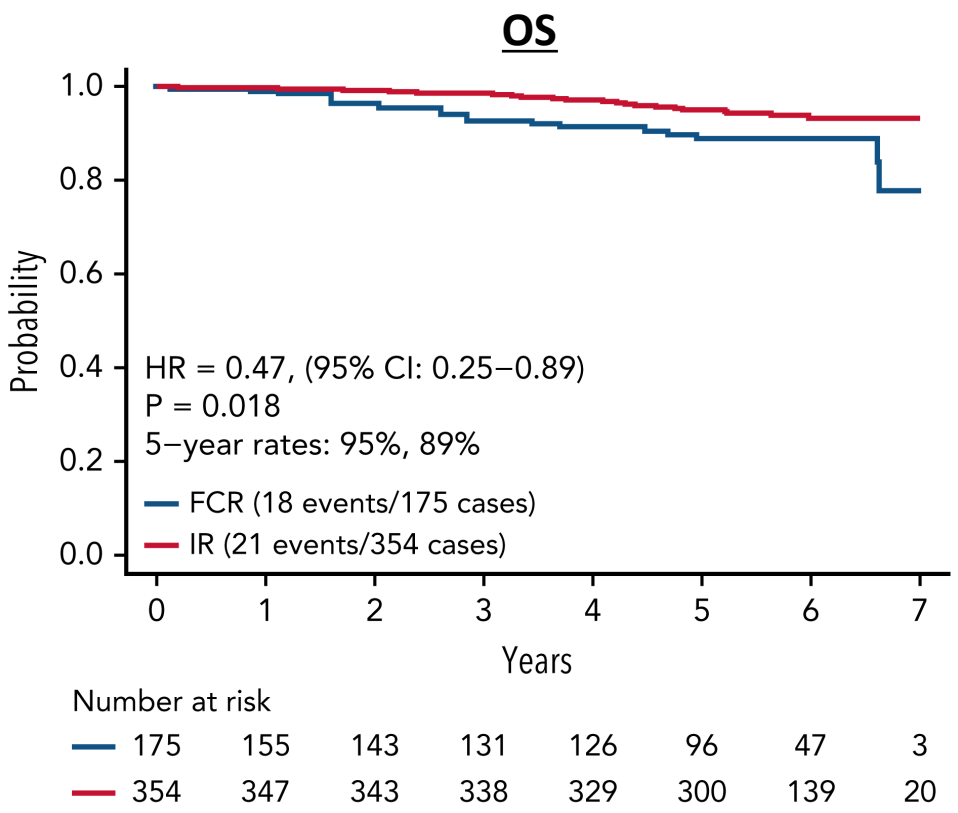


Alliance A041202 update at ASH 2021 (Woyach et al, abst 639)

BTKi: R-chemo vs. 1st generation (ibrutinib)

E1912: <70 yo, treatment naïve: FCR vs. R-Ibr (median f/u of 70 months)





Shanafelt et al. Blood, 140.2 (2022): 112-120.

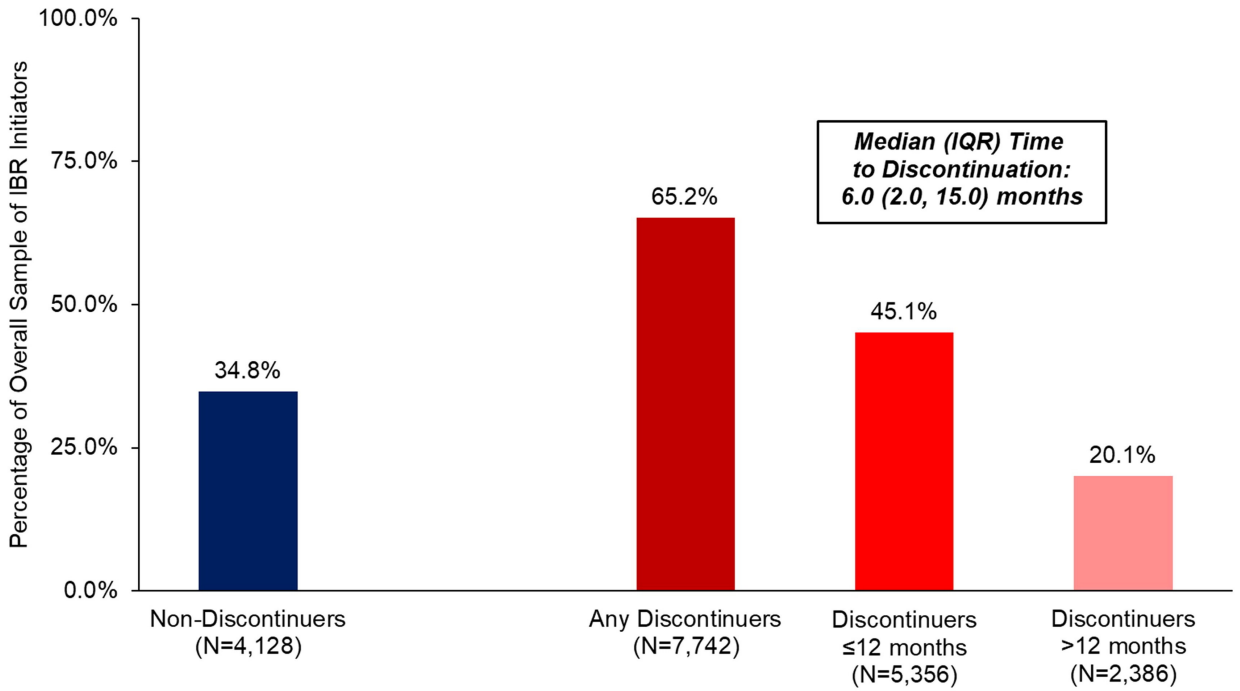
BTKi: 1st generation real-world experience

Early discontinuation is very common

All Medicare beneficiaries with CLL newly initiating ibrutinib treatment between 2014-2018
(n = 11,870)

- 65.2% discontinued ibrutinib over a median follow up 2.1 years
- 45.1% discontinued within 12 months

EHR/chart review studies show adverse events are the most common (60-80%) reason for discontinuation in patients treated with ibrutinib in the front-line setting

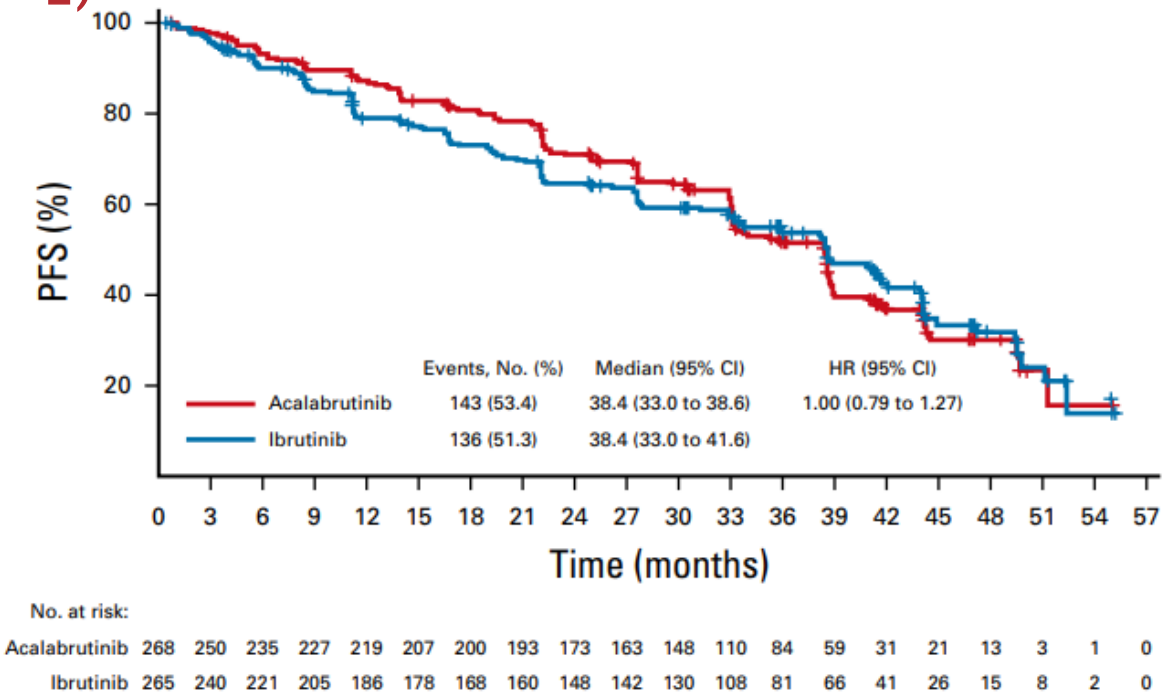


Huntington et al. *Leukemia & Lymphoma* (2023): 1-10.

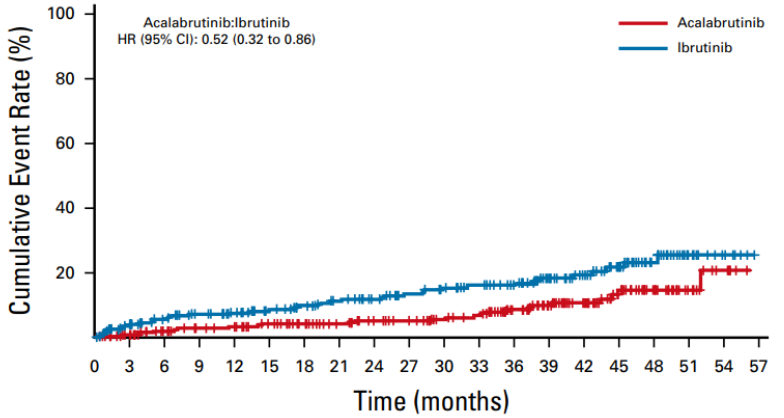
Mato et al; *Haematologica* 103.5 (2018): 874.

BTKi – 1st gen vs 2nd gen (greater BTK specificity)

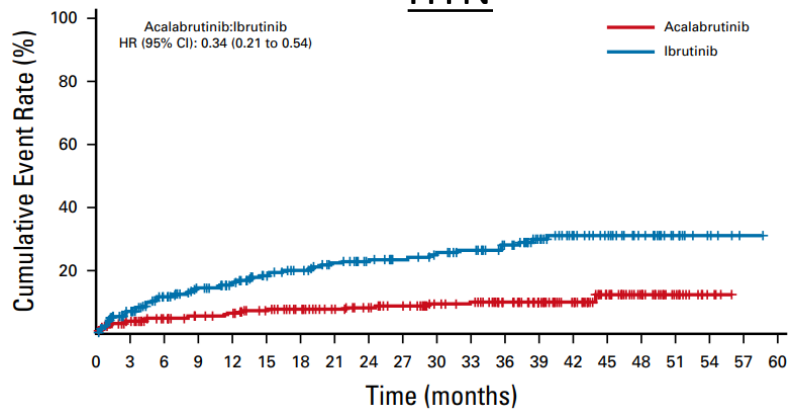
Ibrutinib vs. Acalabrutinib for del17p and/or del11q R/R setting (median prior lines: 2)



A-Fib



HTN



Discontinuations because of adverse events occurred in **14.7% of acalabrutinib** vs**. 21.3% of ibrutinib-treated patients**

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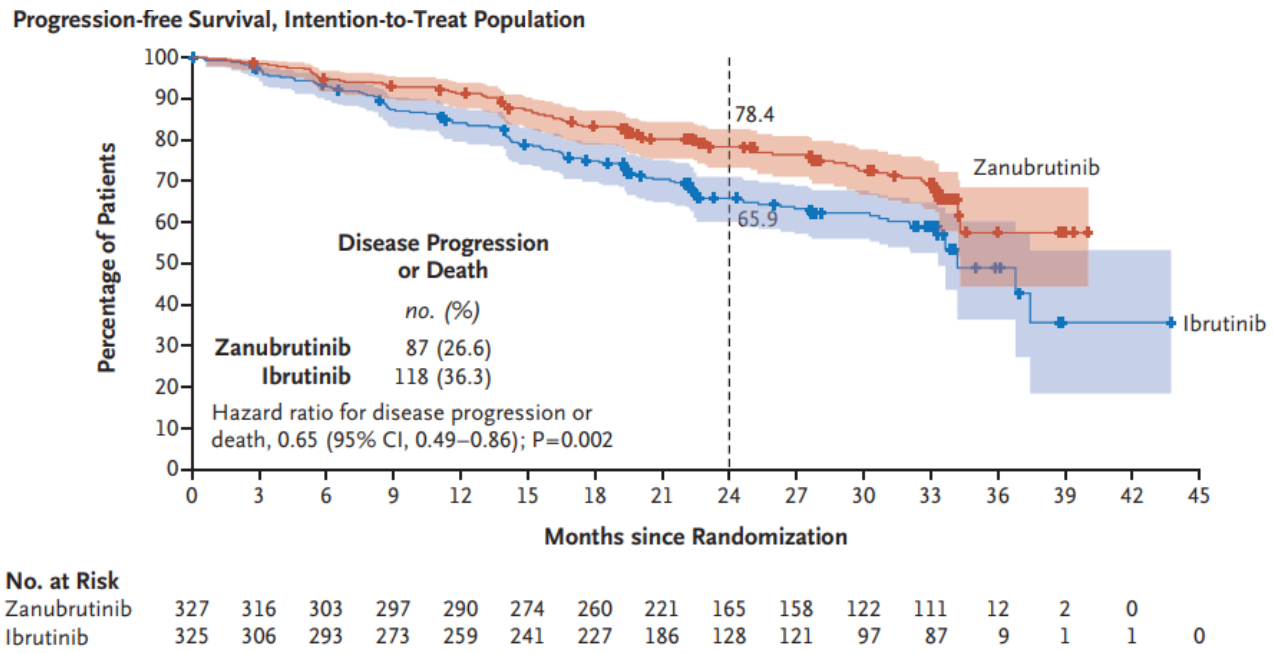
Byrd JC et al. J Clin Oncol. 2021 Nov 1;39(31):3441-3452

BTKi – 1st gen vs 2nd gen (greater BTK specificity)

Ibrutinib vs. Zanubrutinb in R/R setting (median prior lines: 1)



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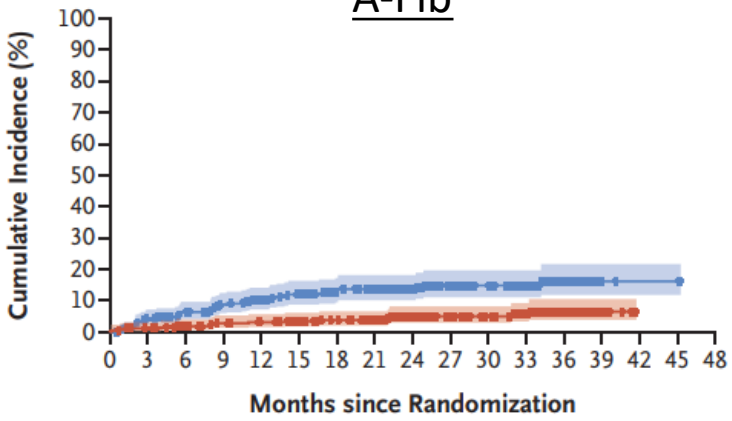

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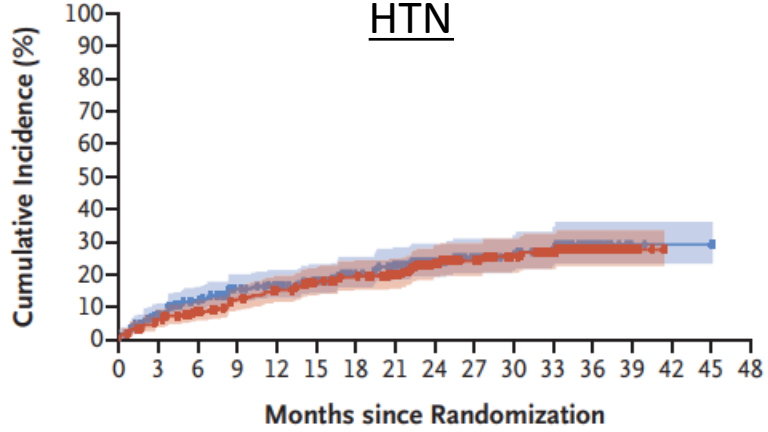

Discontinuations because of adverse events occurred in **16.2% of zanubrutinib** vs**. 22.8% of ibrutinib-treated patients**

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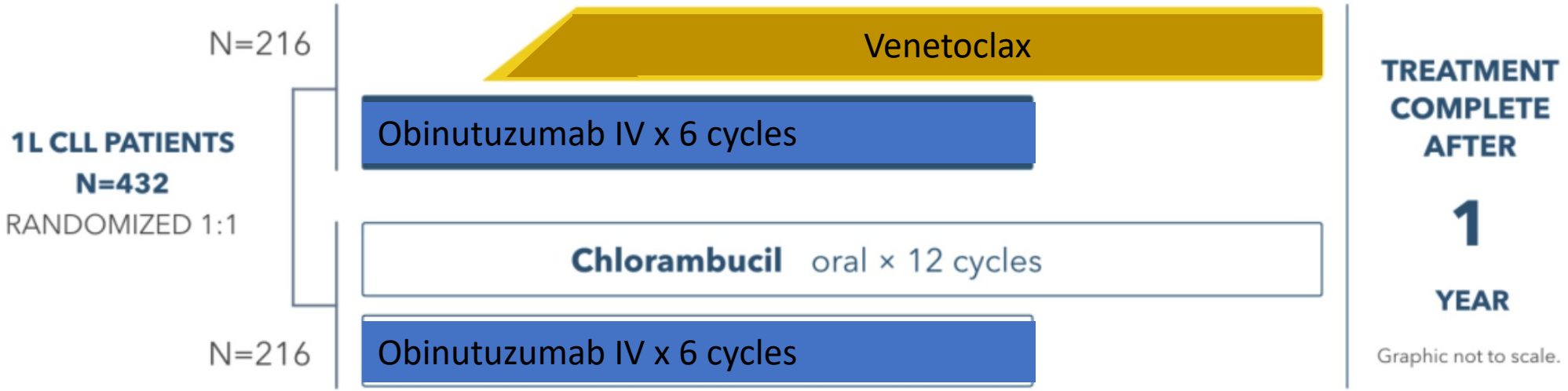
Brown et al. NEJM 388.4 (2023): 319-332.

Novel Fixed-duration Options

BCL2 inhibitor - venetoclax

CLL14: 12 months of O-chloramubcil vs. O-venetoclax for 1st line older/comorbid CLL (~60% unmutated IgHV, 10% del17p/TP53mut)



Fischer et al. NEJM. 2019 Jun 6;380(23):2225-36.

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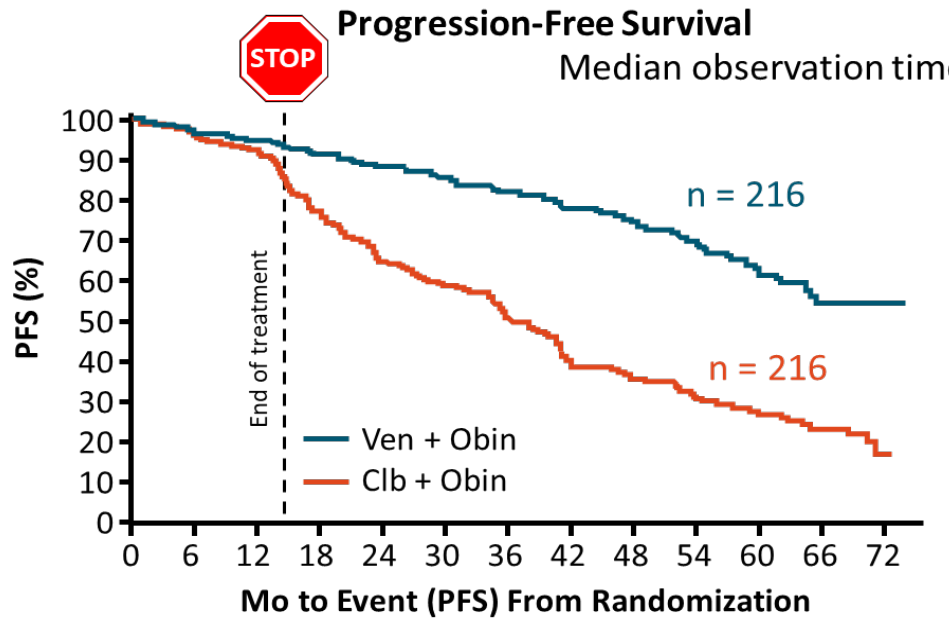

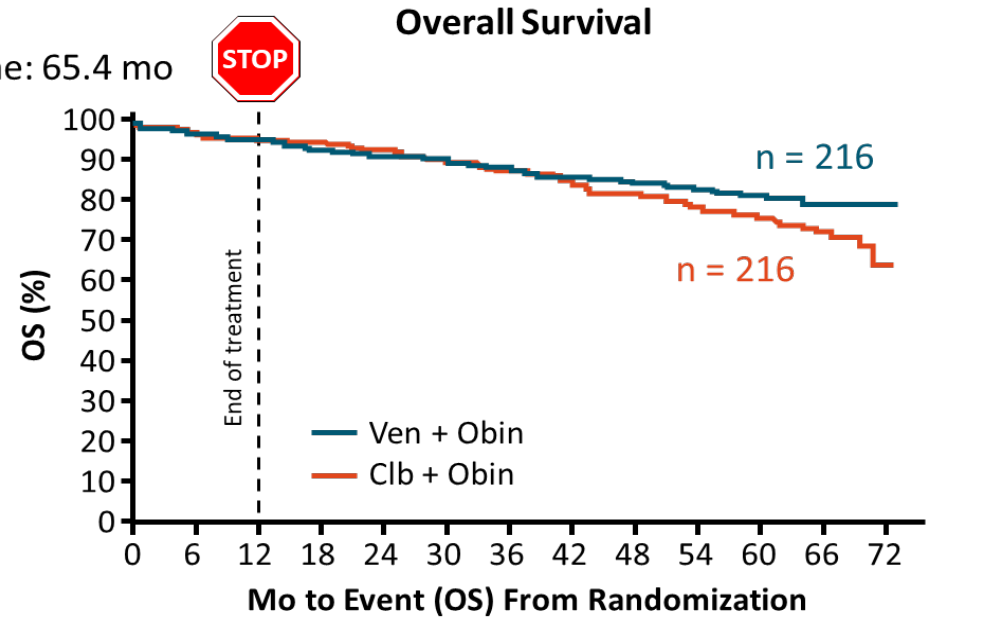

PFS	Ven + Obin	Clb + Obin	HR (95% CI)	*P*
Median PFS, mo	NR	36.4	0.35 (0.26-0.46)	<.0001
5-yr PFS rate, %	62.6	27.0		

OS	Ven + Obin	Clb + Obin	HR (95% CI)	*P*
Median OS, mo	NR	NR	0.72 (0.48-1.09)	.12
5-yr OS rate, %	81.9	77.0		

5 years-TTNT 72.1% vs. 42.8%

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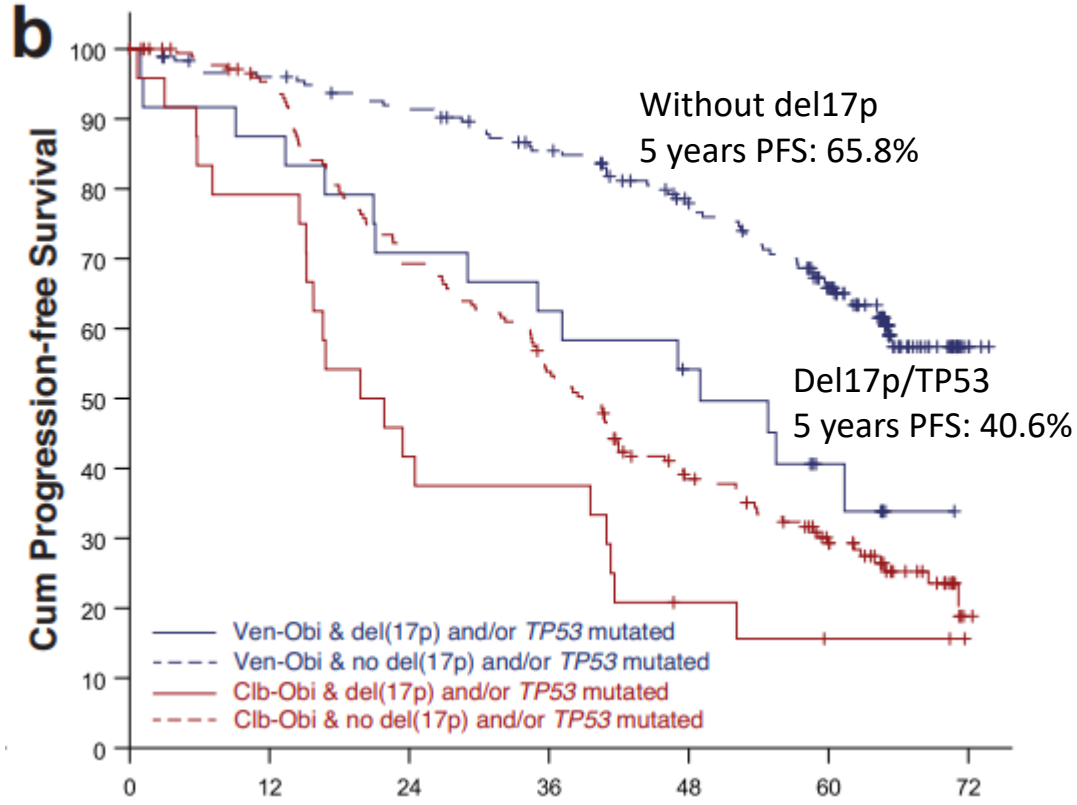
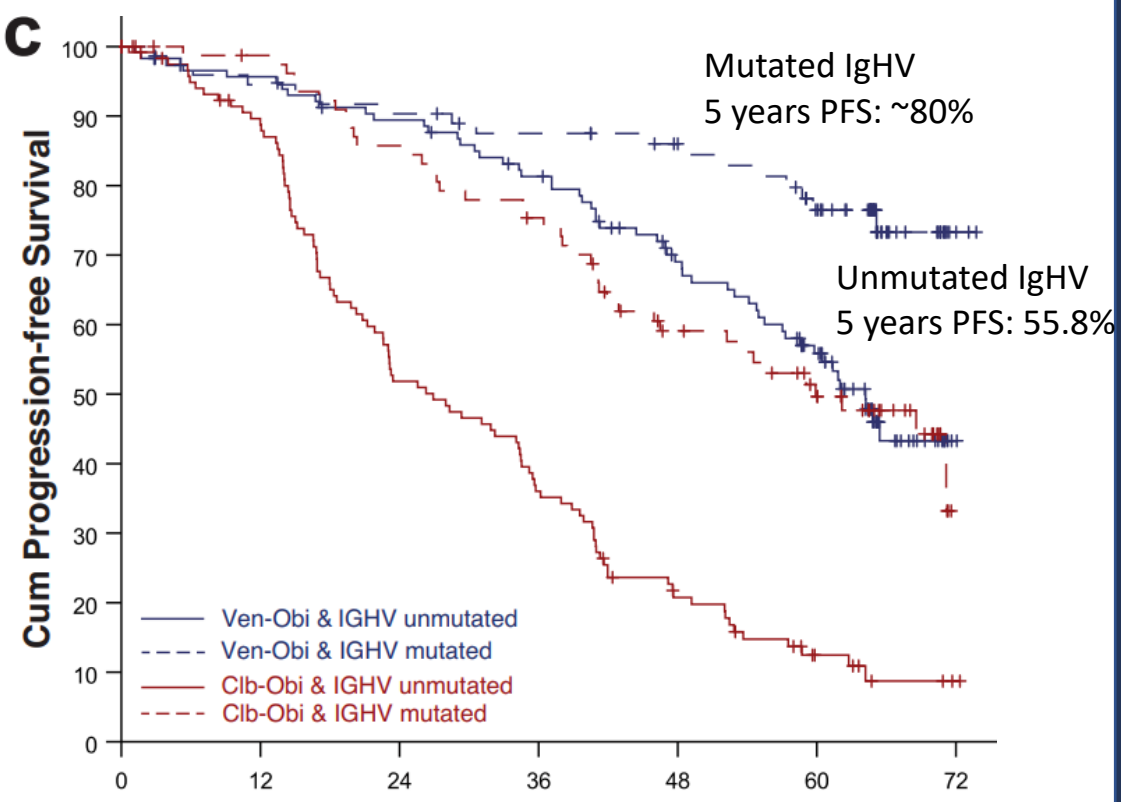
Al-Sawaf O et al. *Nature Commun*. 2023;14:2147.

BCL2 inhibitor - venetoclax

CLL14: nonDel17p and IgHV mutated have particularly durable responses to Ven-O





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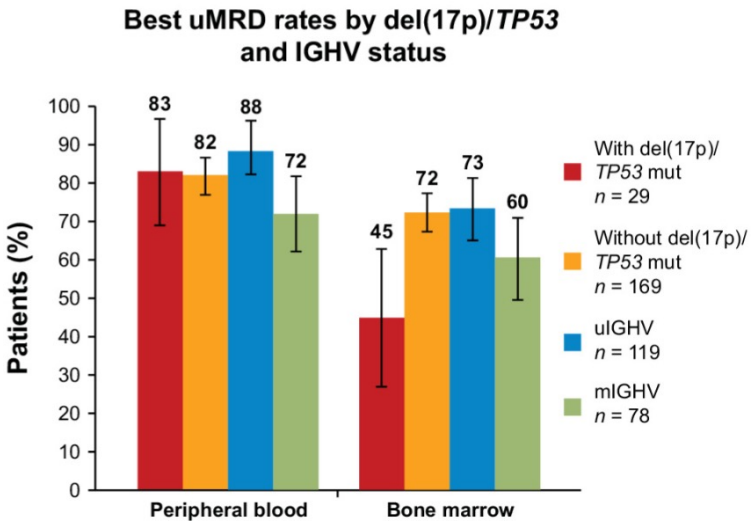
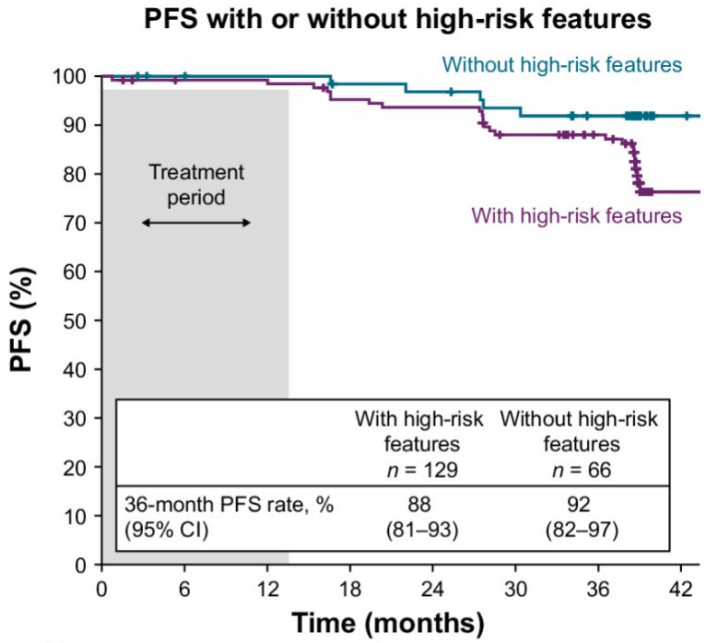
What about BTKi + BCL combinations?

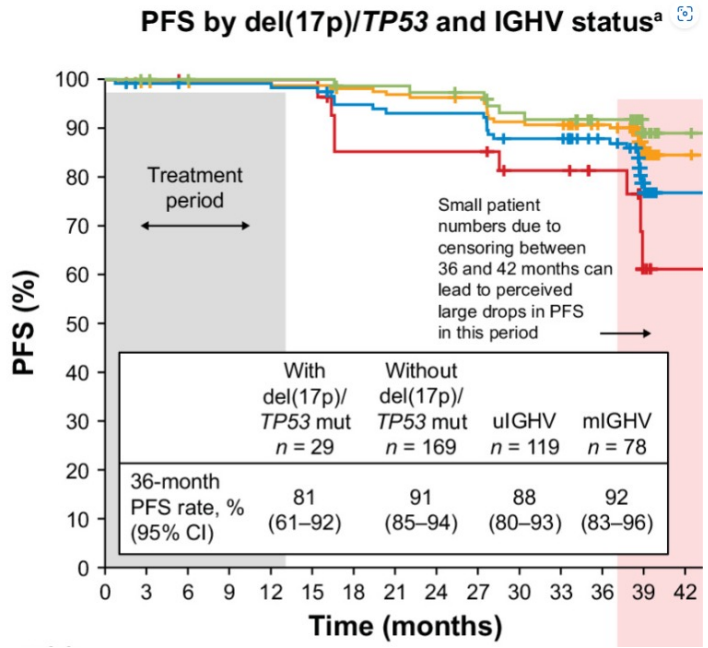
BTKi + venetoclax

CAPTIVATE: International phase II using 3 cycles of ibrutinib followed by ibrutinib/venetoclax x 12

Findings from the fixed-duration cohort (n = 159) and placebo group in uMRD cohort (n = 43)



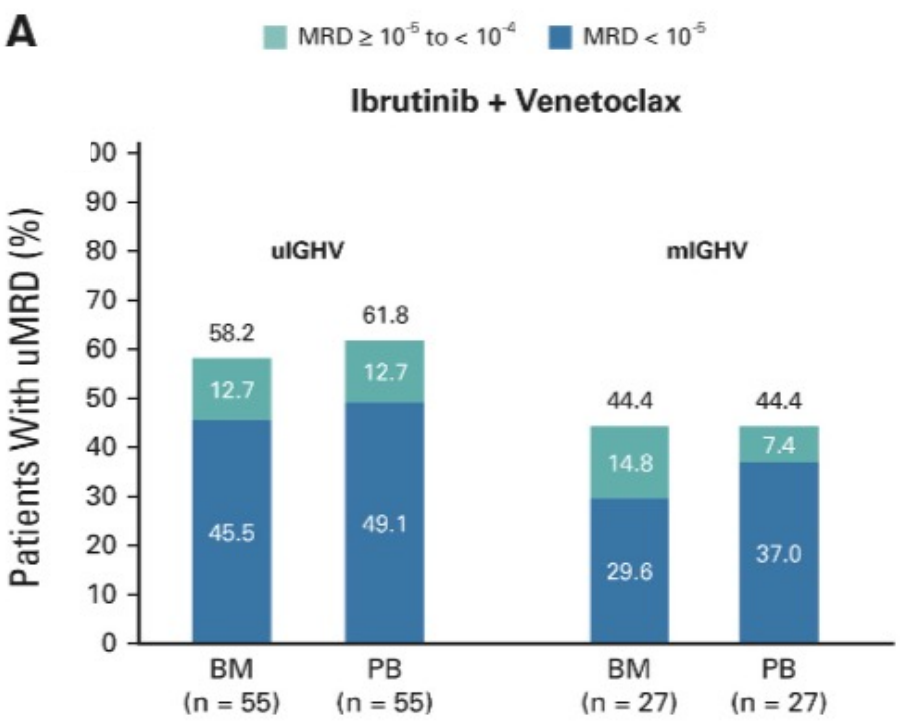


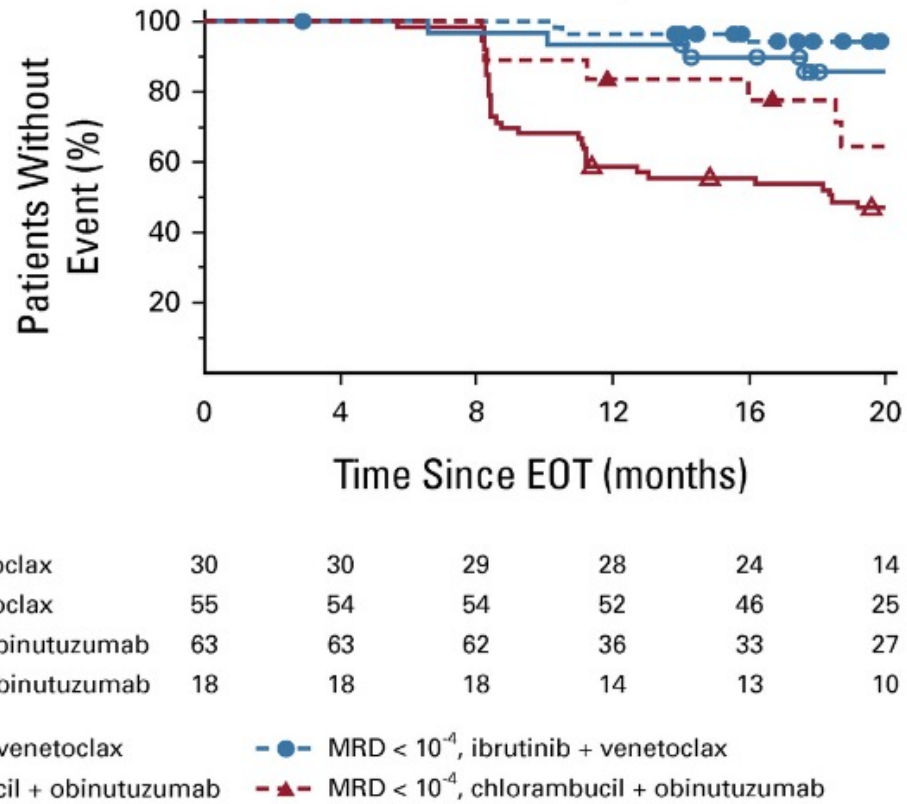


Allan, et al. "*Clinical Cancer Research* (2023): OF1-OF9.

BTKi + venetoclax

GLOW: O-chlorambucil vs. Ibr-Ven Fixed Duration (age 65+ or CIRS >6), n = 211



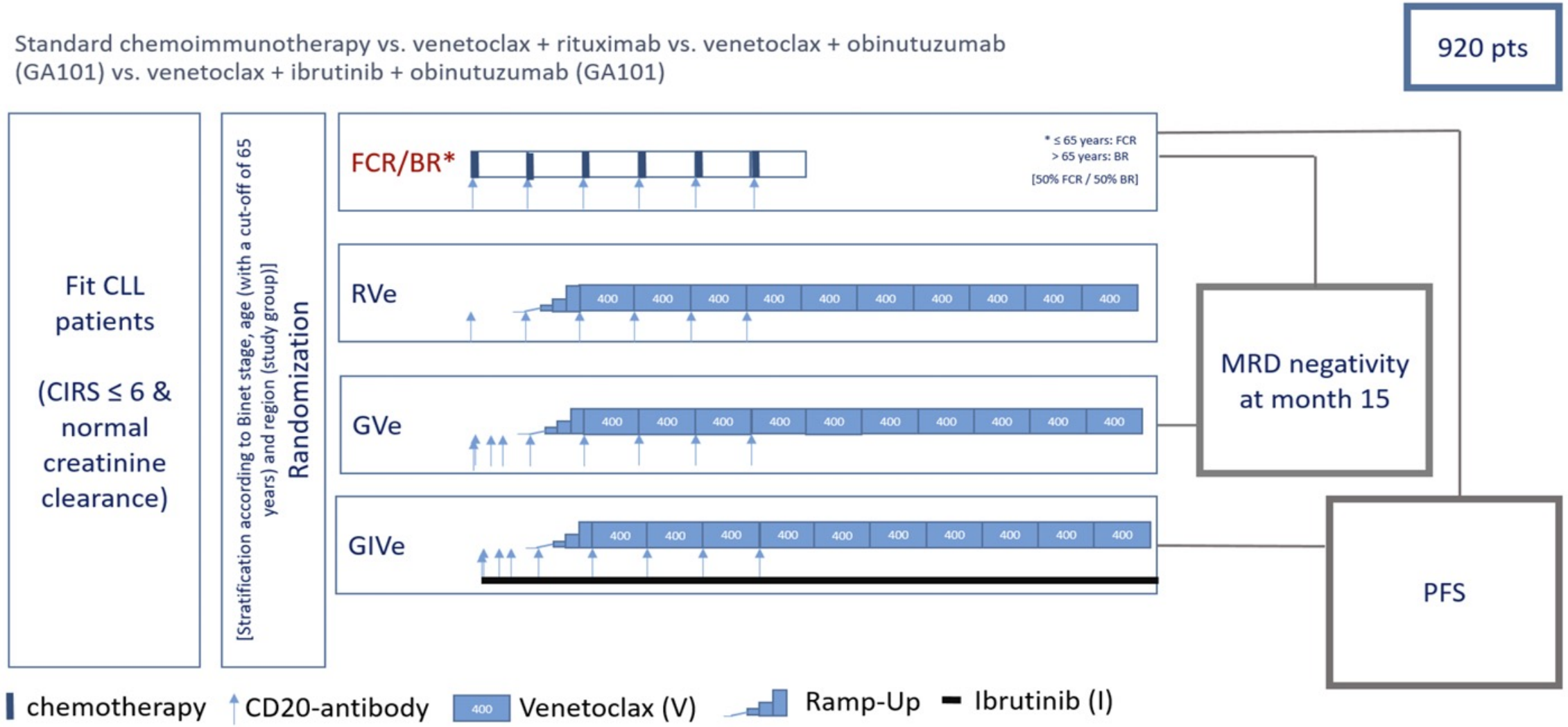


At median f/u 34.1 months, OS identical

GLOW led to EMA approval, ibr/ven not approved by FDA

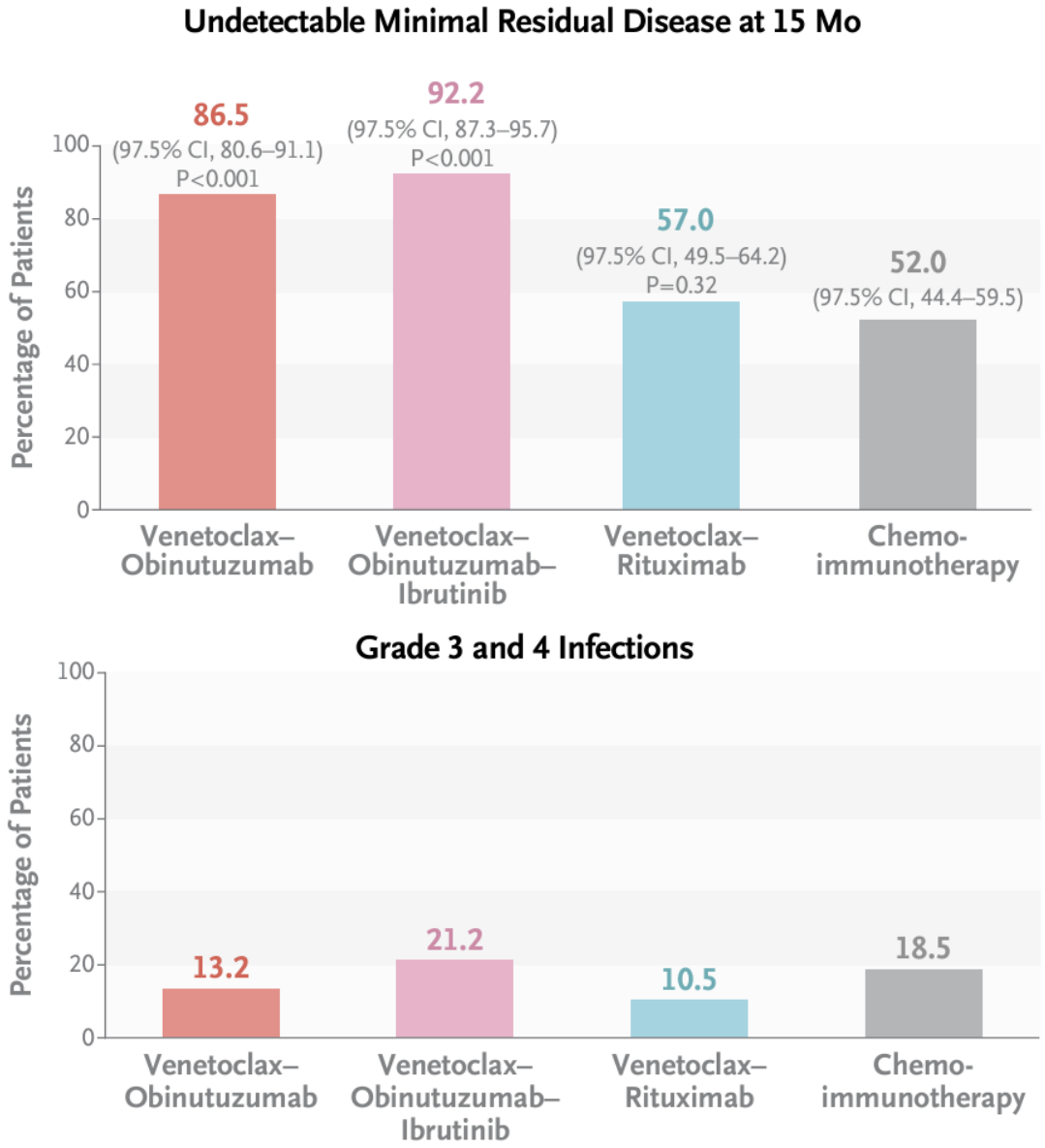
Munir, et al. *Journal of Clinical Oncology* 41.21 (2023): 3689.

BTKi + venetoclax + Obinutuzumab (CLL13)

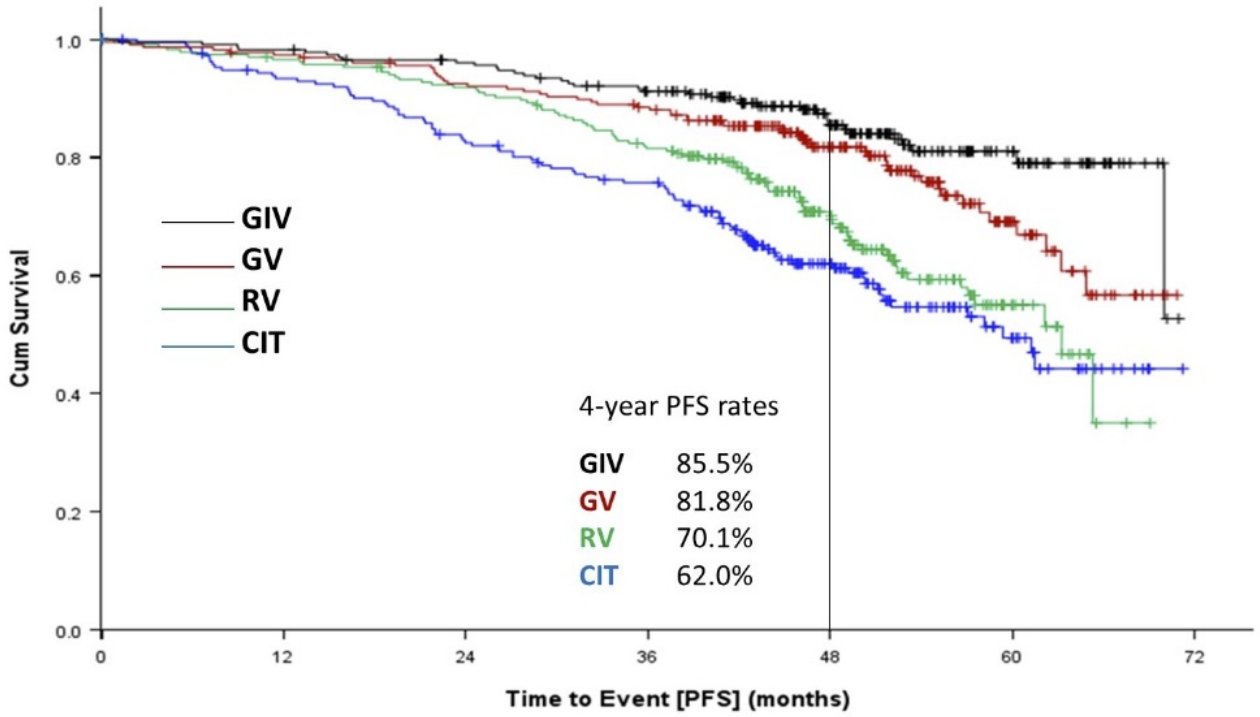


von Tresckow et al *Integr Cancer Sci Therap* 4 (2017).

Venetoclax + Obinutuzumab +- ibrutinib > R-chemo



PFS at median f/u 50.7 months



Eichhorst B et al. *N Engl J Med.* 2023;388(19):1739-1754.
Fürstenau et al. Blood. 2023 Nov 28;142:635.

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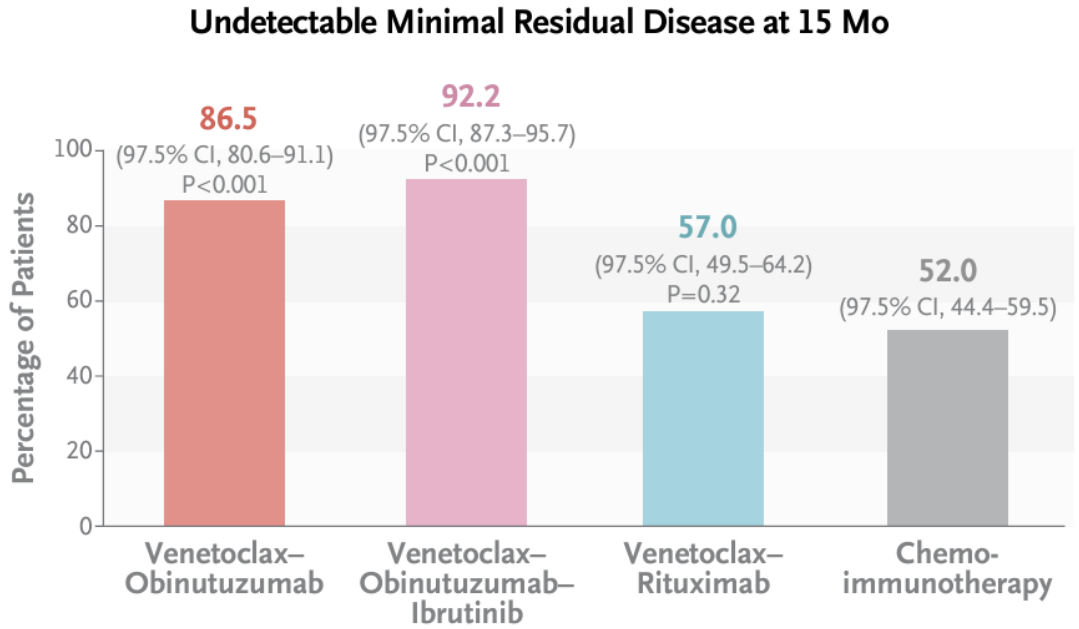

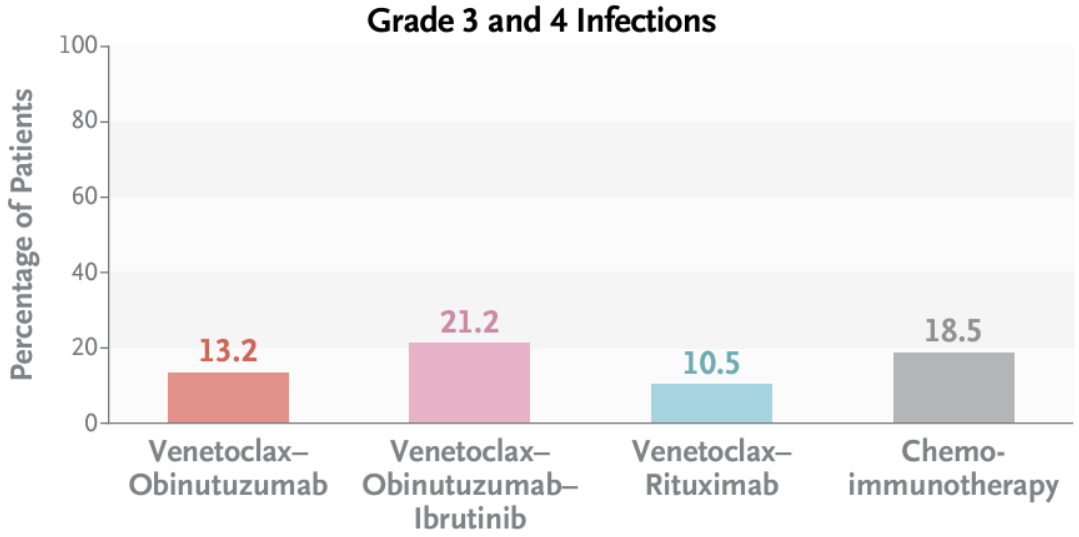

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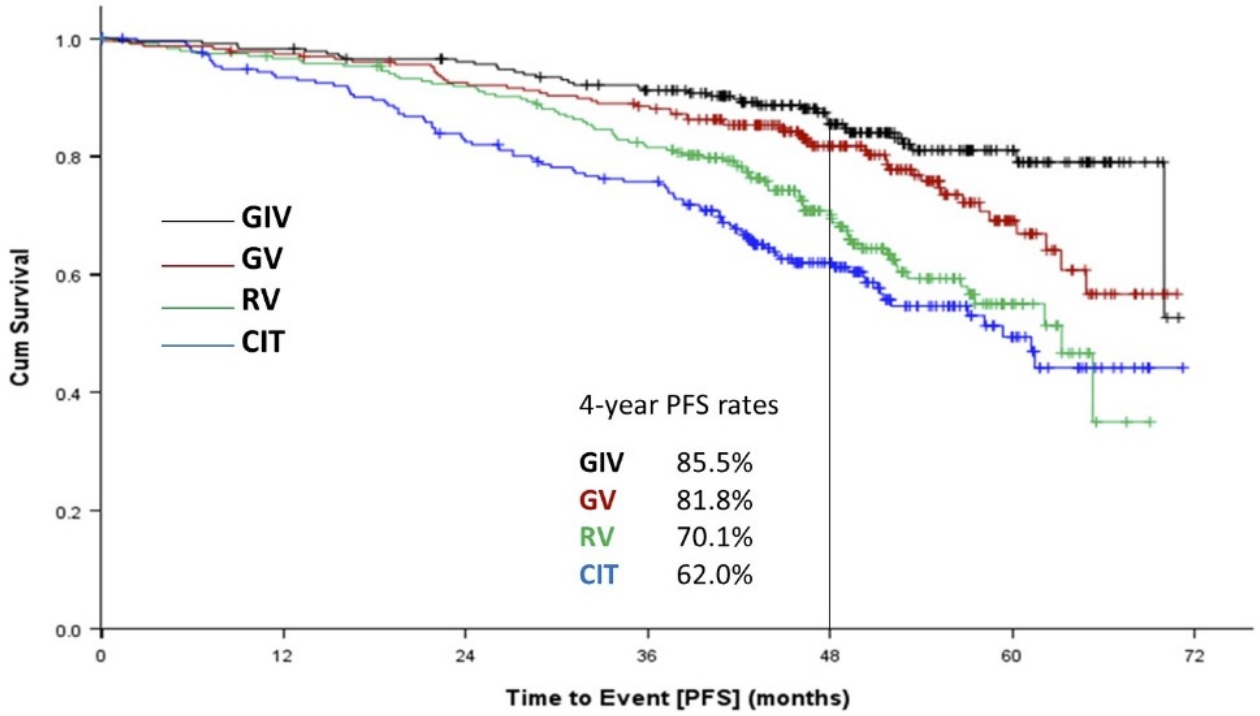

	4-years TTNT		4-years OS
GIV	96%	GIV	95%
GV	90.4%	GV	95.1%
RV	86.2%	RV	96.2%
CIT	77.2%	CIT	93.5%

Eichhorst B et al. *N Engl J Med.* 2023;388(19):1739-1754.
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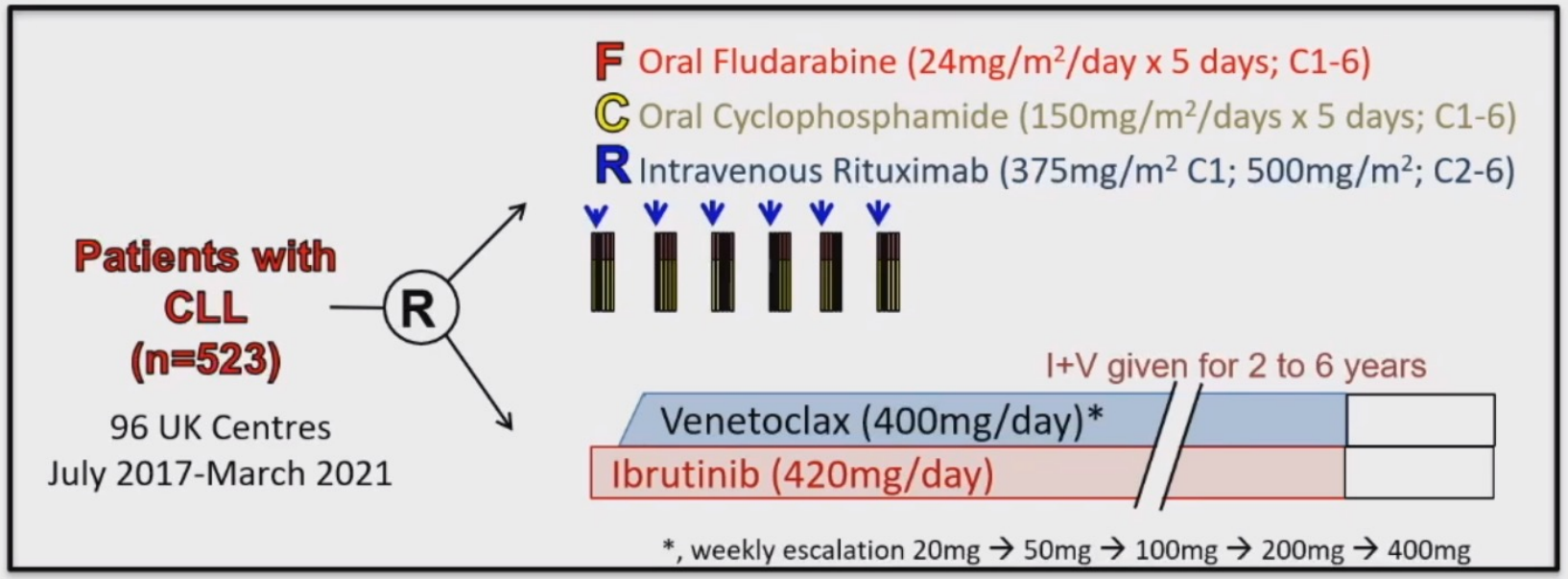
BTKi + venetoclax (FLAIR)

Flair

FCR vs I+V: Trial design



Primary end-point:
To assess whether I+V is superior to FCR in terms of PFS

Key secondary end-points:
Overall survival
Response incl. MRD
Safety and toxicity

Key Inclusion Criteria:

- Previously untreated CLL requiring therapy by IWCLL criteria
- Considered fit for FCR
- ≤75 years old

Key Exclusion Criteria:
Prior therapy for CLL; History of Richter's transformation; >20% TP53 deletion by FISH; Concomitant warfarin (or equivalent) Symptomatic cardiac failure or angina

NCRI National Cancer Research Institute

Hillmen *et al.*, Abstract 631, ASH 2023

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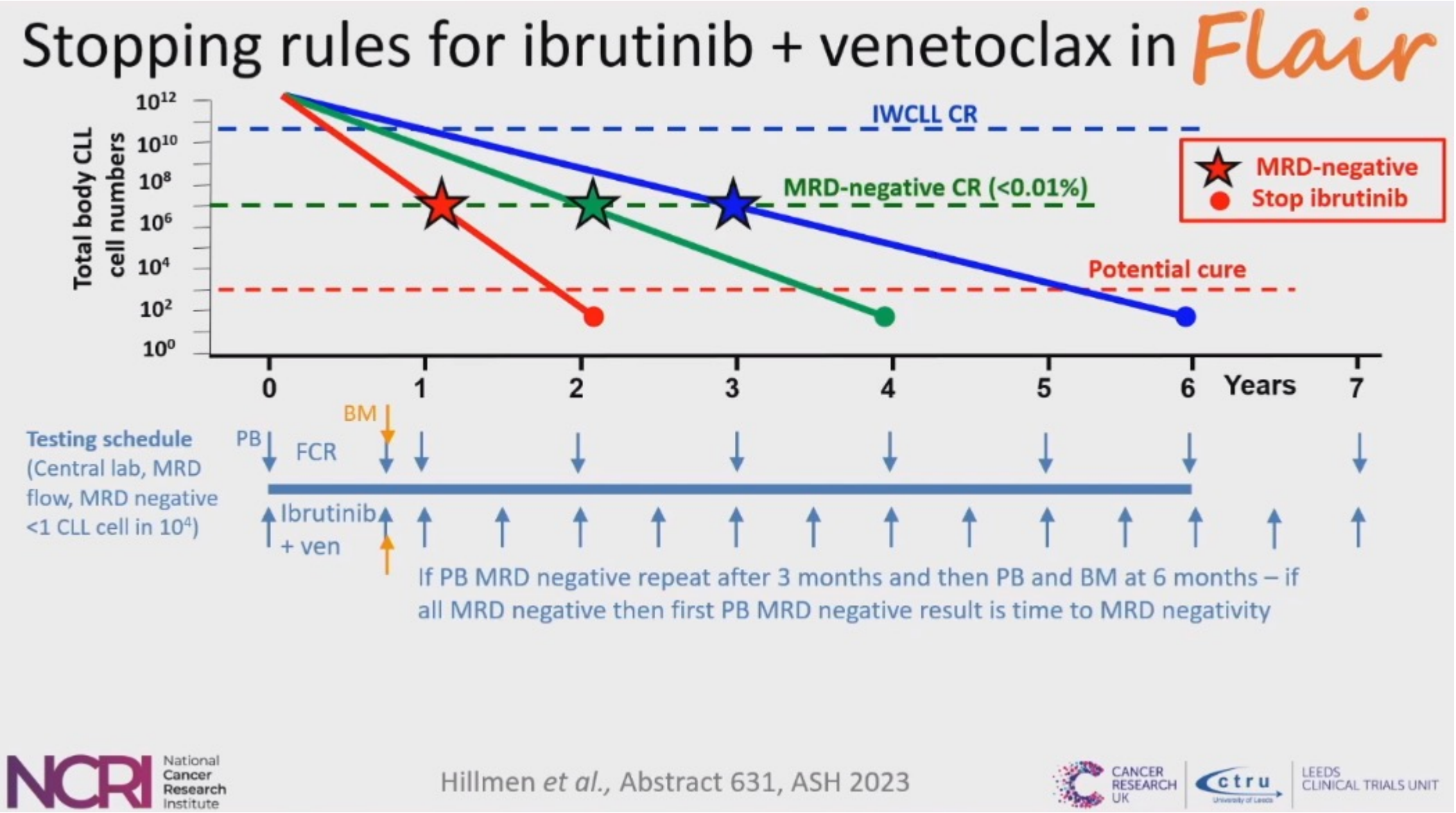
BTKi + venetoclax (FLAIR)



Hillmen *et al.*, Abstract 631, ASH 2023

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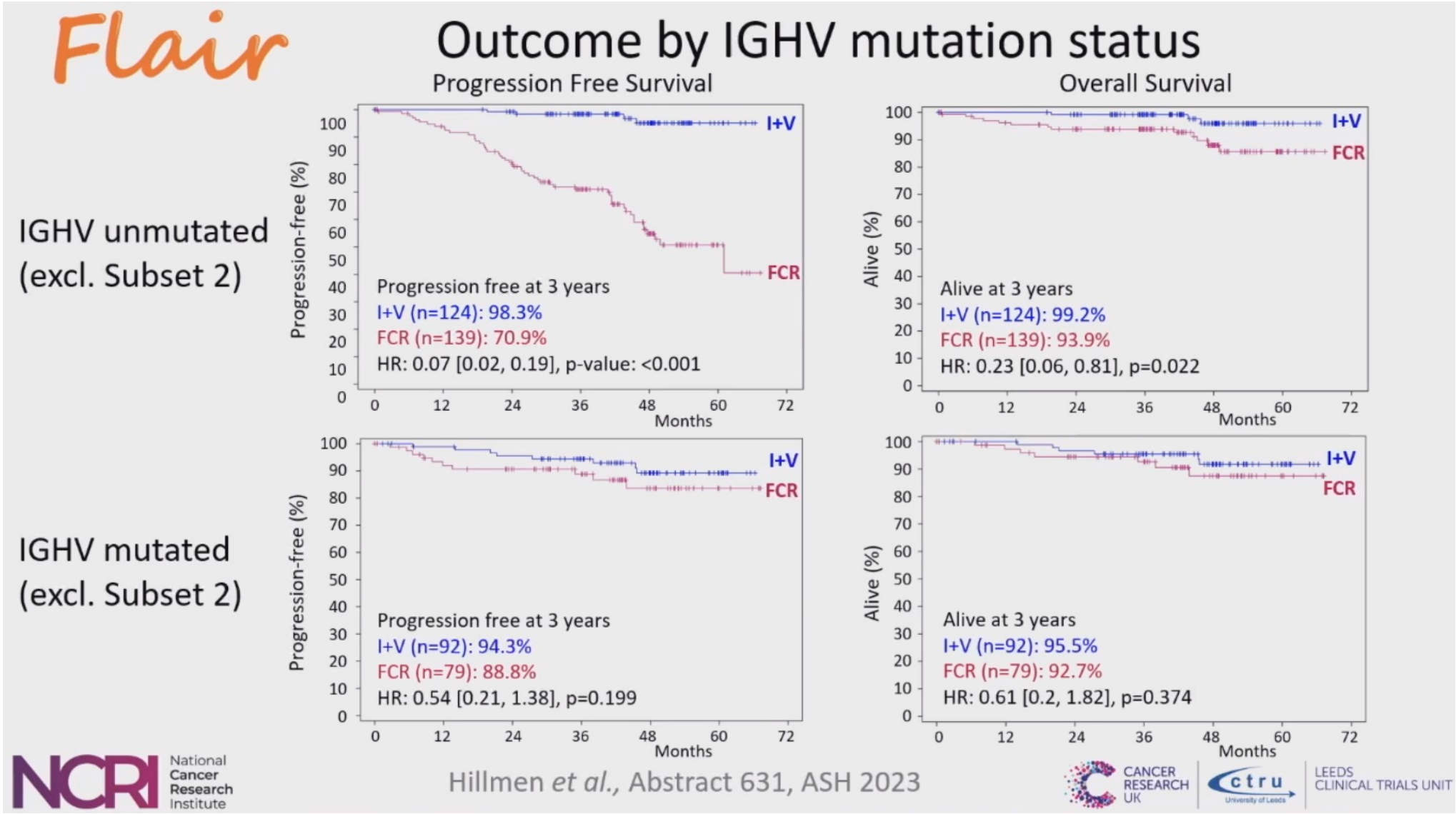

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Goal: Prolong life while maintaining excellent QOL

<u>Low risk disease: death due to CLL is relatively unlikely</u>

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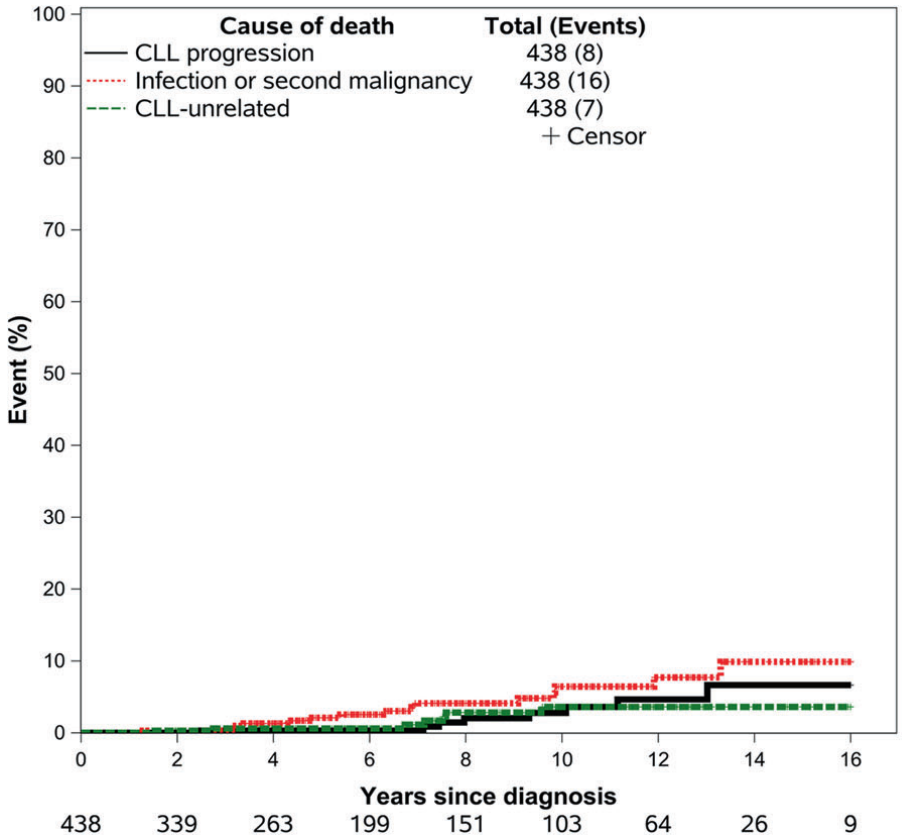

Wang et al. *Blood cancer journal*, *11*(8), 140.

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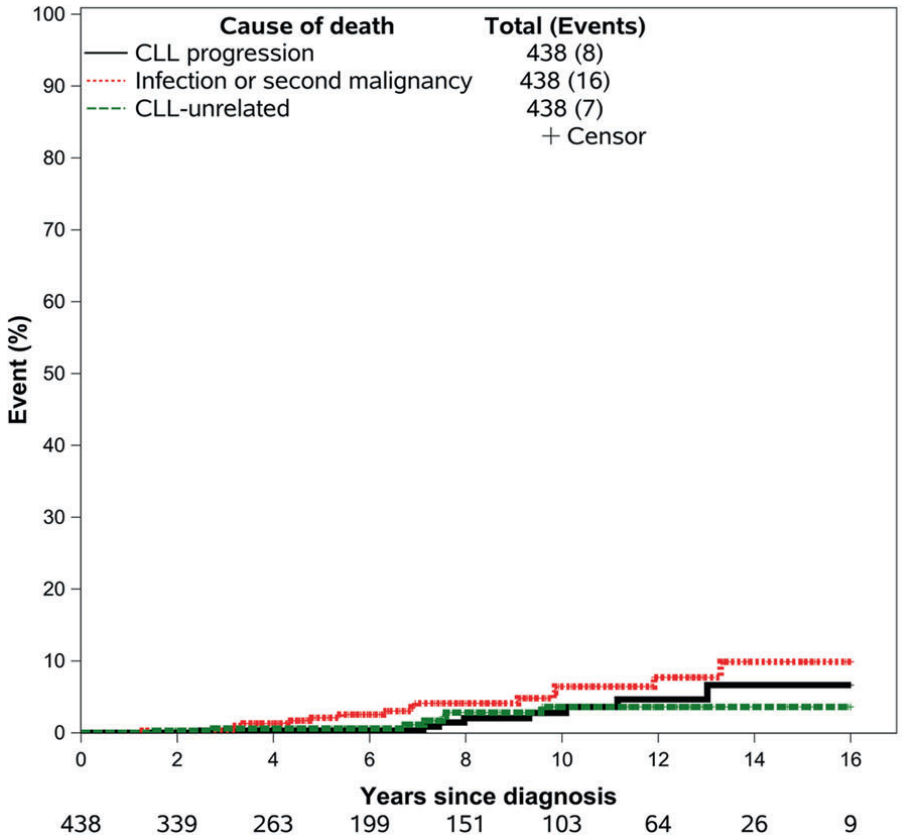
Venetoclax +- (Obinutuzumab)



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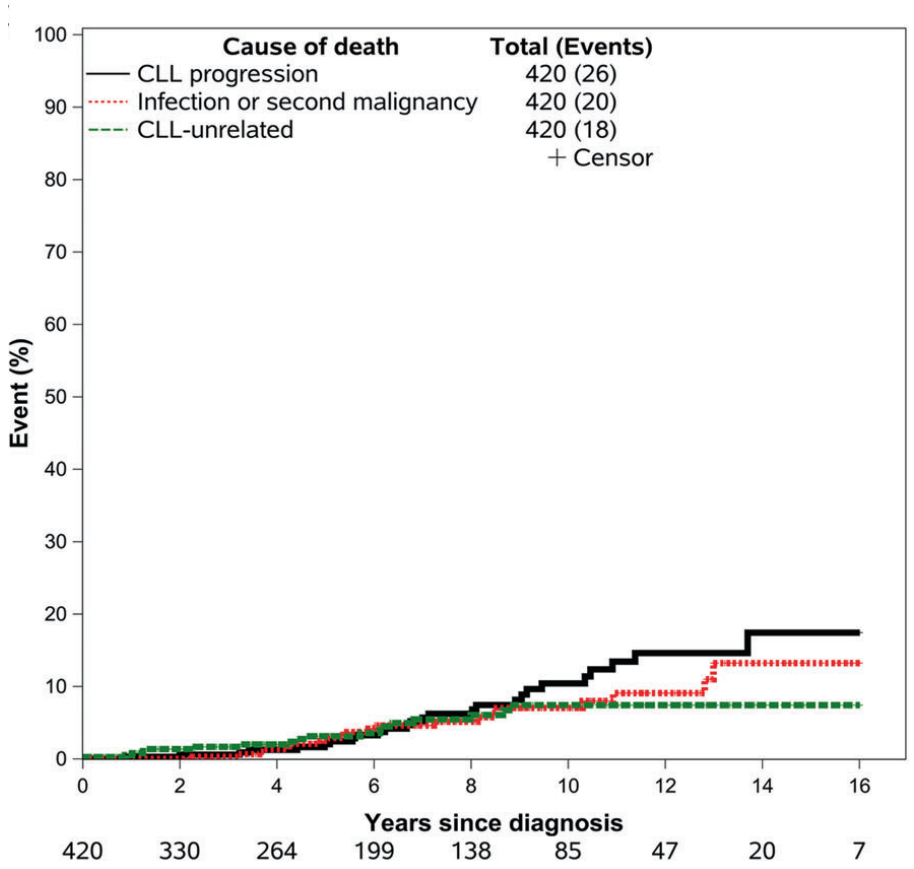

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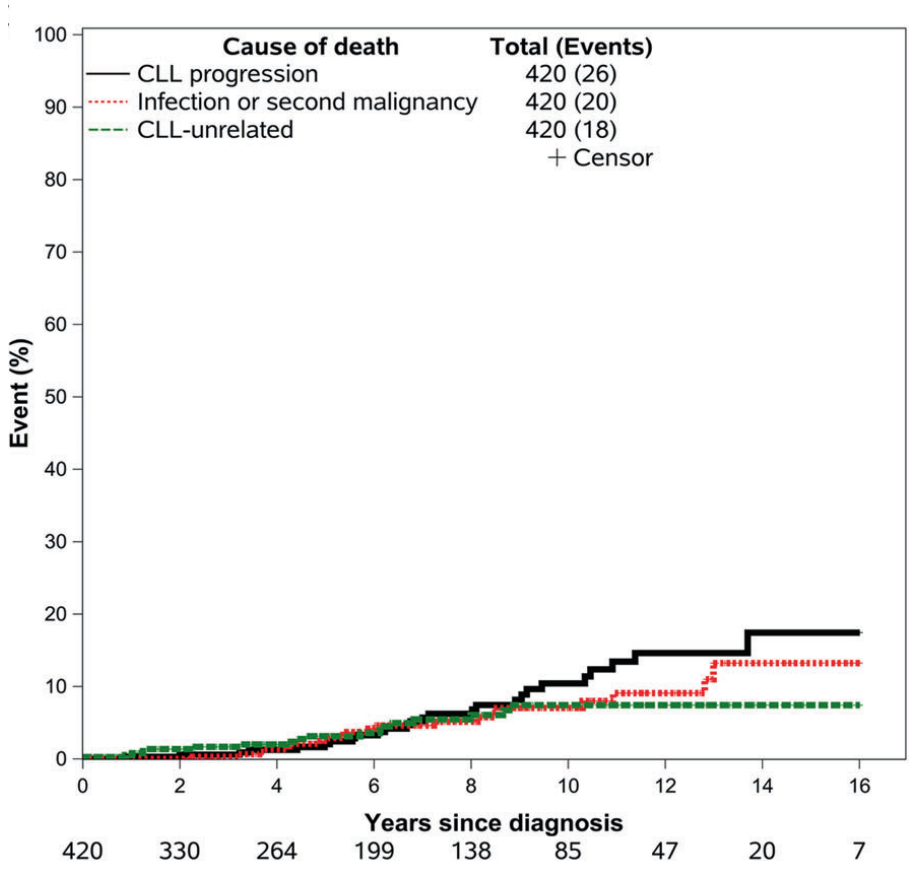
2ng generation BTKi

Ven-Obi

BTKi-BCL2 on study



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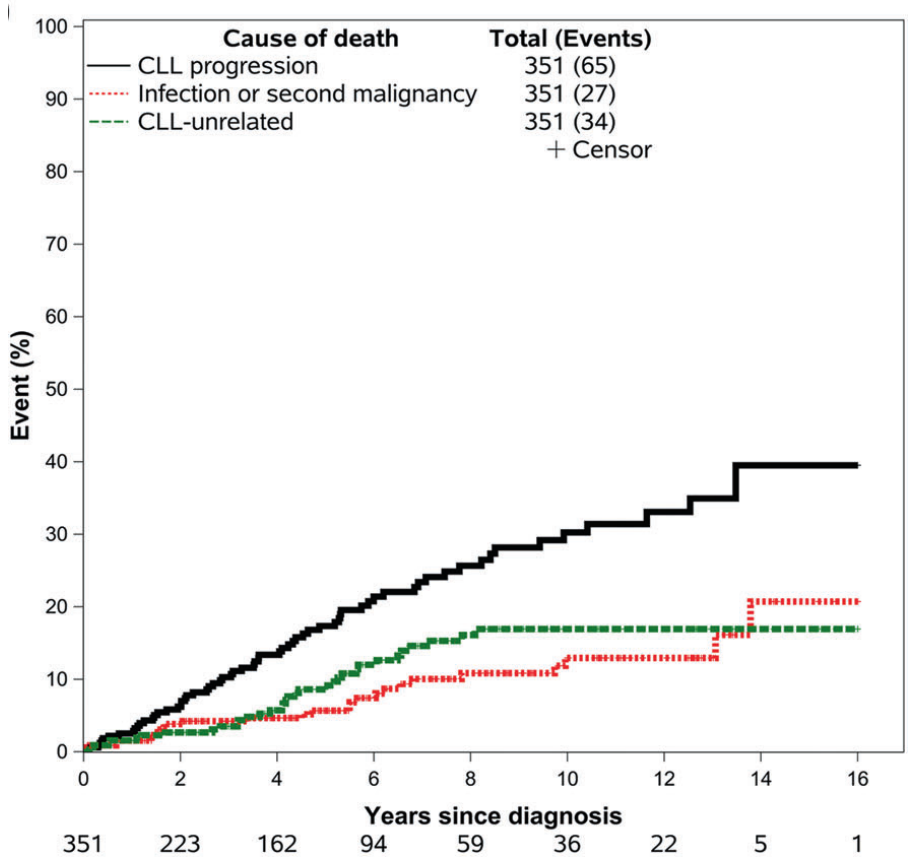
- No comorbidities

High risk disease –CLL is greatest risk for mortality



Wang et al. *Blood cancer journal*, *11*(8), 140.

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Goal: Prolong life while maintaining excellent QOL

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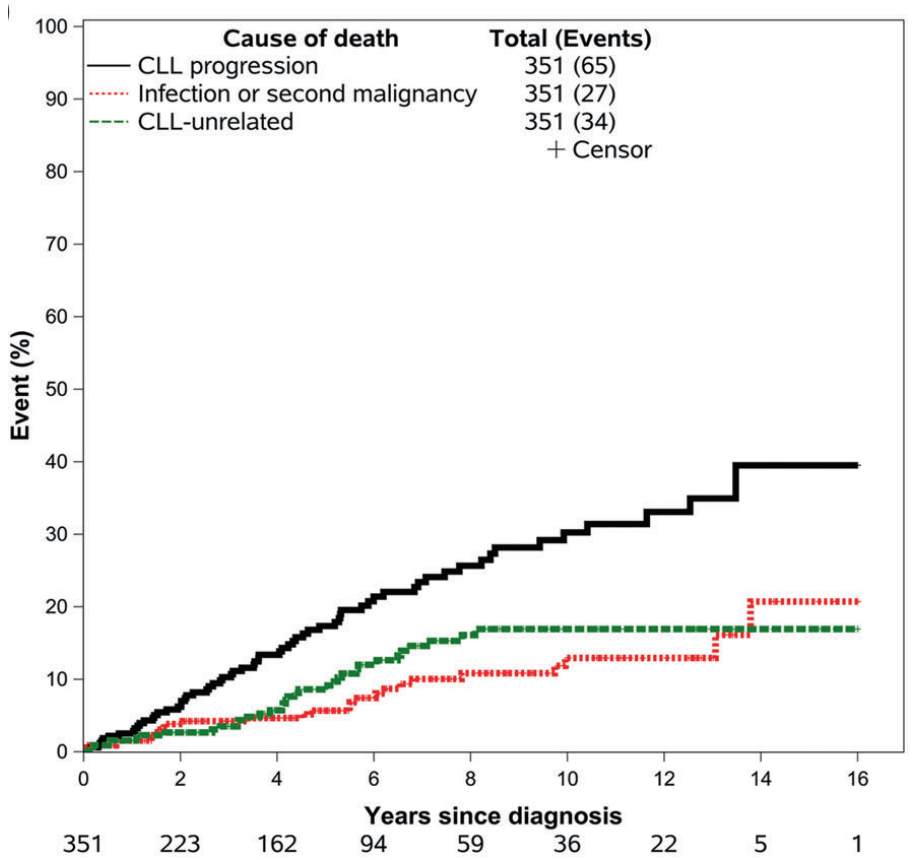
- No comorbidities

BTKi-BCL on study (?MRD driven)
2nd generation BTKi

High risk disease –CLL is greatest risk for mortality



Wang et al. *Blood cancer journal*, *11*(8), 140.

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R/R CLL in the Modern Era

R/R CLL patients in your clinic

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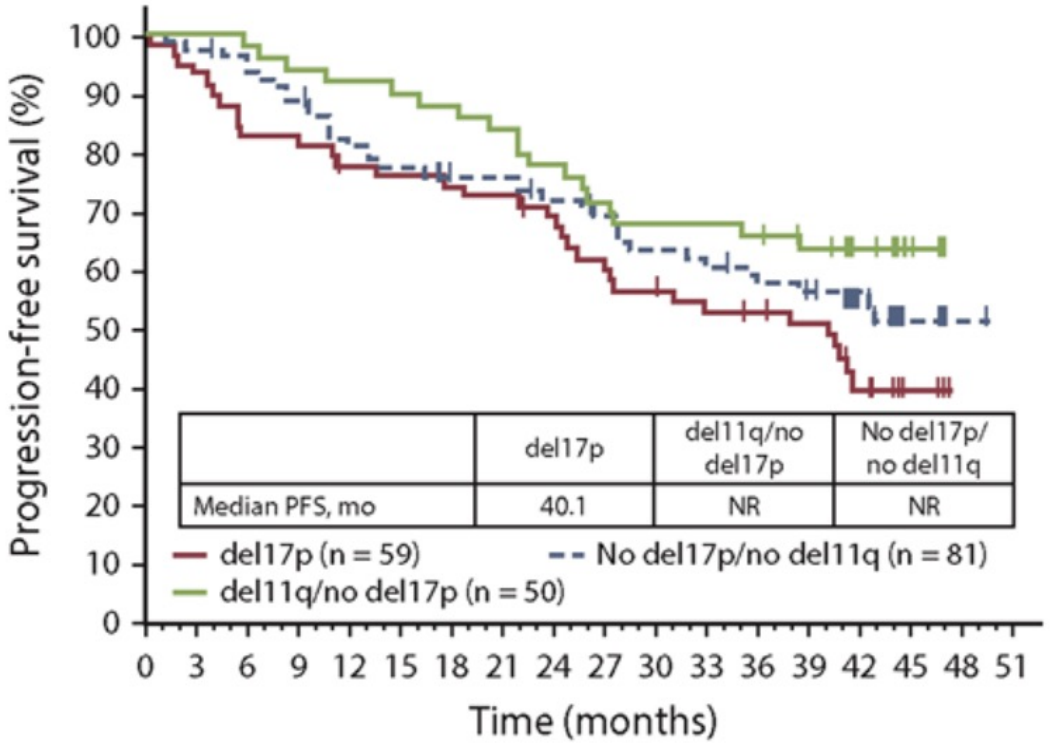
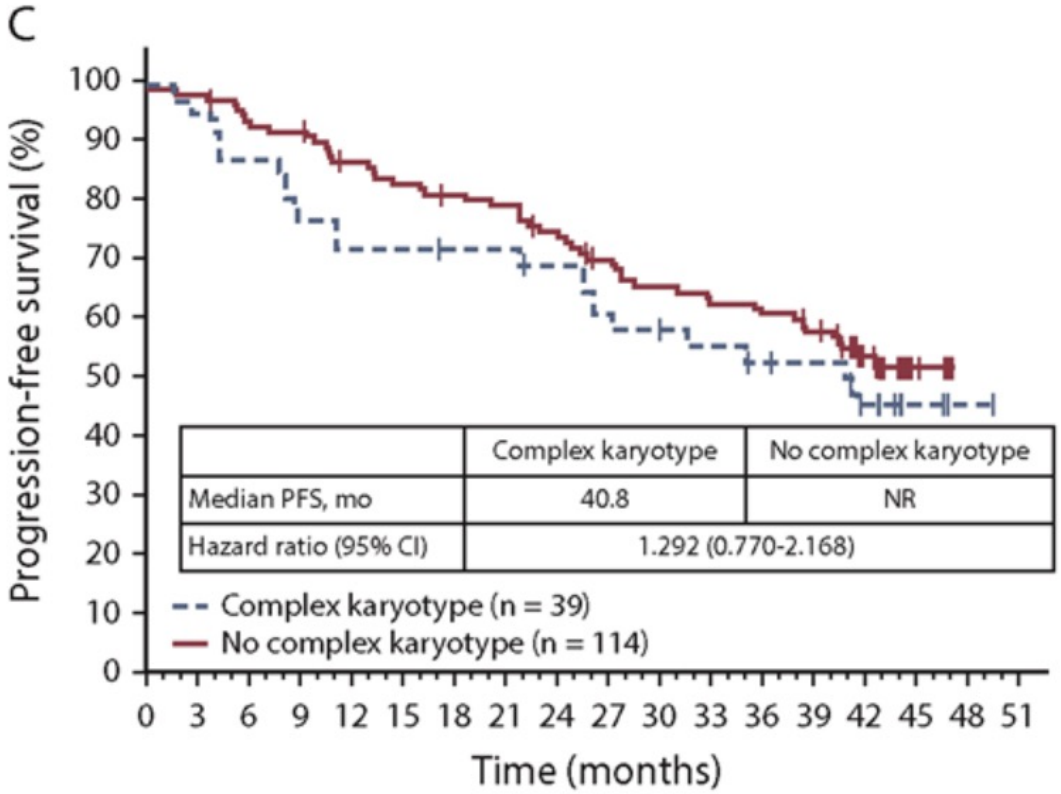
R/R CLL in the Modern Era – BTKi/BCL2 unexposed

RESONATE: 44-month median FU for ibrutinib arm (vs ofa) in R/R CLL (no prior ven)



	del17p	del11q/no del17p	No del17p/ no del11q
Median PFS, mo	40.1	NR	NR



	Complex karyotype	No complex karyotype
Median PFS, mo	40.8	NR
Hazard ratio (95% CI)	1.292 (0.770-2.168)	

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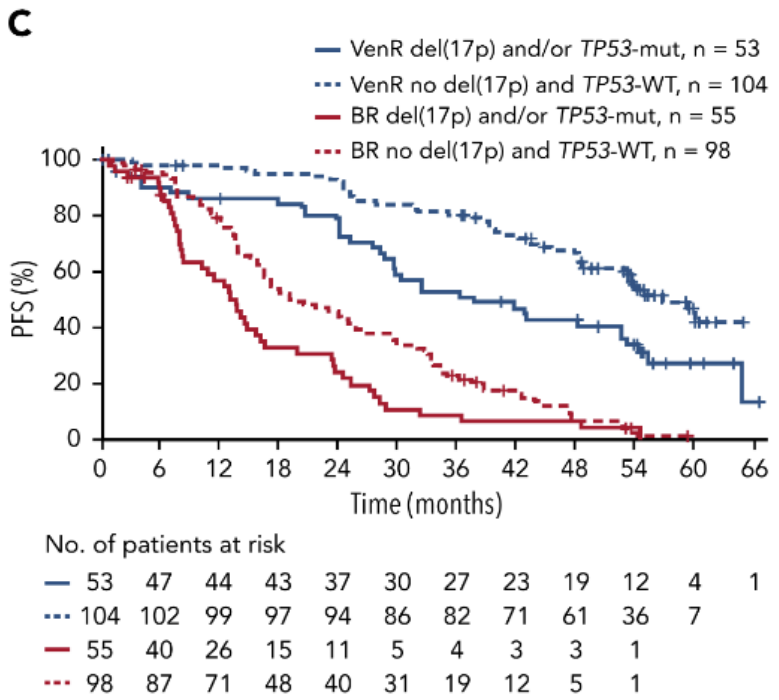
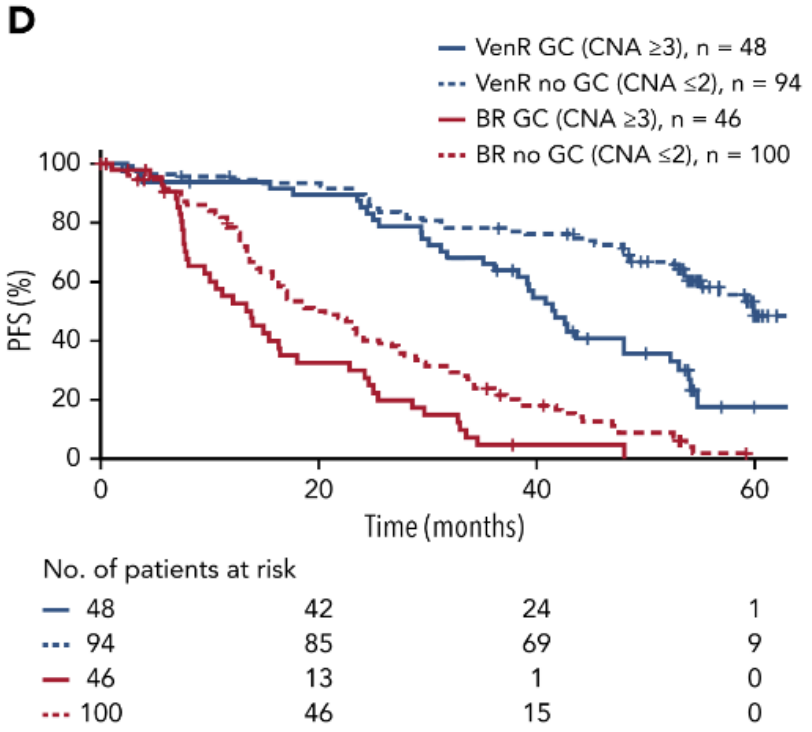
Byrd et al. *Blood, The Journal of the American Society of Hematology* 133, no. 19 (2019): 2031-2042.

R/R CLL in the Modern Era – BTKi/BCL2 unexposed

MURANO: 59-month median FU for R-ven (vs R-benda) in R/R CLL (no prior ven)



Category		Median PFS, months (95% CI)	HR (95% CI); *P* value†	5-year PFS, % (95% CI)
VenR	del(17p) and/or *TP53*-mut	37.4 (29.4, 52.3)	2.04 (1.32, 3.15);	27.3 (13.6, 41.0)
	No del(17p) and *TP53*-WT	56.6 (53.0, NE)	.0010	42.5 (28.9, 56.0)
BR	del(17p) and/or *TP53*-mut	13.4 (8.0, 15.8)	1.67 (1.15, 2.40);	NE
	No del(17p) and *TP53*-WT	19.6 (16.4, 25.4)	.0059	NE



Category		Median PFS, months (95% CI)	HR (95% CI); *P* value†	5-year PFS, % (95% CI)
VenR	GC	41.7 (38.3, 53.0)	2.50 (4.00, 1.56);	17.7 (7.9, 39.7)
	No GC	59.8 (55.1, NE)	<.0001	48.5 (36.3, 64.8)
BR	GC	13.8 (9.5, 22.8)	1.75 (2.56, 1.19);	NE
	No GC	20.5 (16.2, 26.7)	.04	NE

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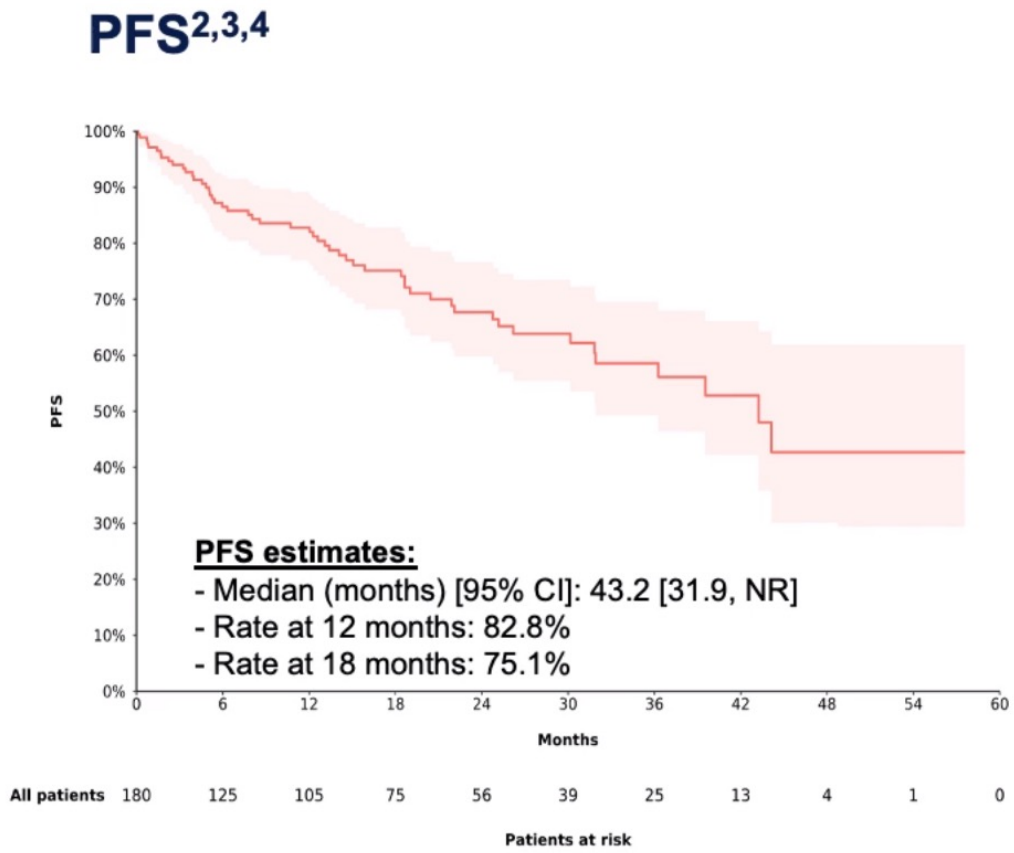
Seymour et al. *Blood, The Journal of the American Society of Hematology* 140, no. 8 (2022): 839-850.

R/R CLL in the Modern Era – BCL2 unexposed

Real-world study (n = 184) of patients given venetoclax following BTKi

Prior cBTKi treatment duration (months), Mean ± SD [Median]	24.9 ± 19.7 [20.6]
Type of venetoclax-based therapy received	
Venetoclax monotherapy	115 (62.5)
Venetoclax combination therapy	69 (37.5)
Venetoclax + rituximab	56 (81.2)
Venetoclax + obinutuzumab	13 (18.8)
Line of therapy in which venetoclax-based therapy was initiated, N (%)	
2L	65 (35.3)
3L	67 (36.4)
4L+	52 (28.3)
Reason for discontinuation of prior cBTKi, N (%)[1]	
Intolerance	83 (45.1)
Disease progression	78 (42.4)

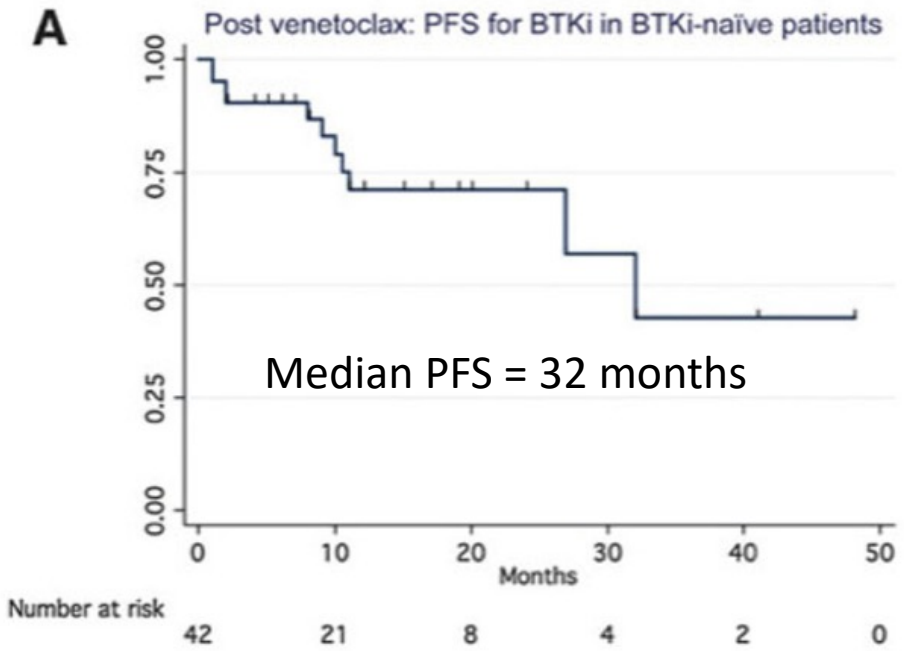


Ghosh et al. Blood. 2023 Nov 28;142:1908.

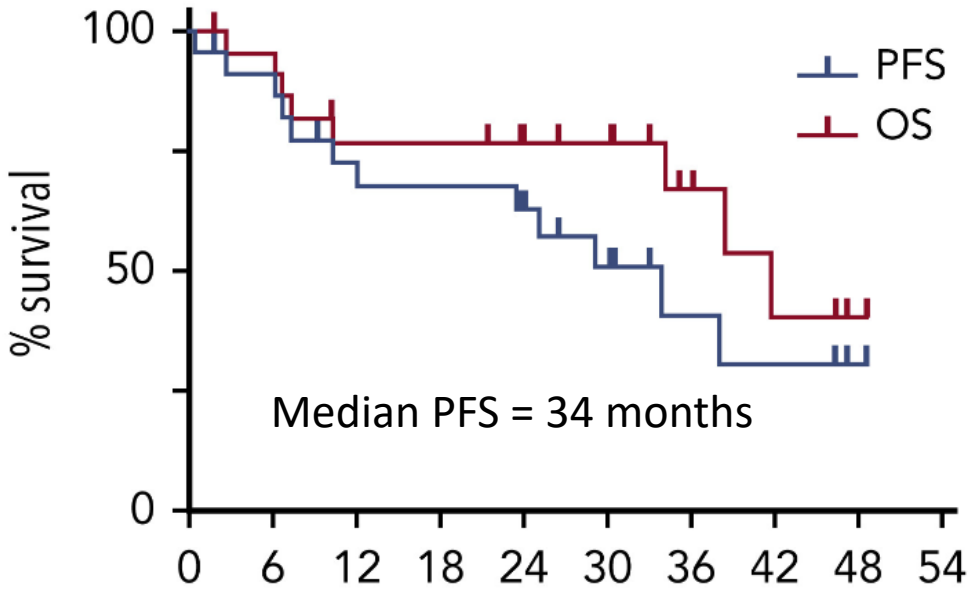
R/R CLL in the Modern Era – BTKi unexposed

Small case series (n = 44 and 23) of patients given BTKi following venetoclax

Multicenter retrospective study
44 pts had prior ven and were BTKi-naive
Median prior lines = 2



23 consecutive pts treated on prior ven-studies
Median prior lines = 4, 70% had del17p
Most progressed while taking continuous ven



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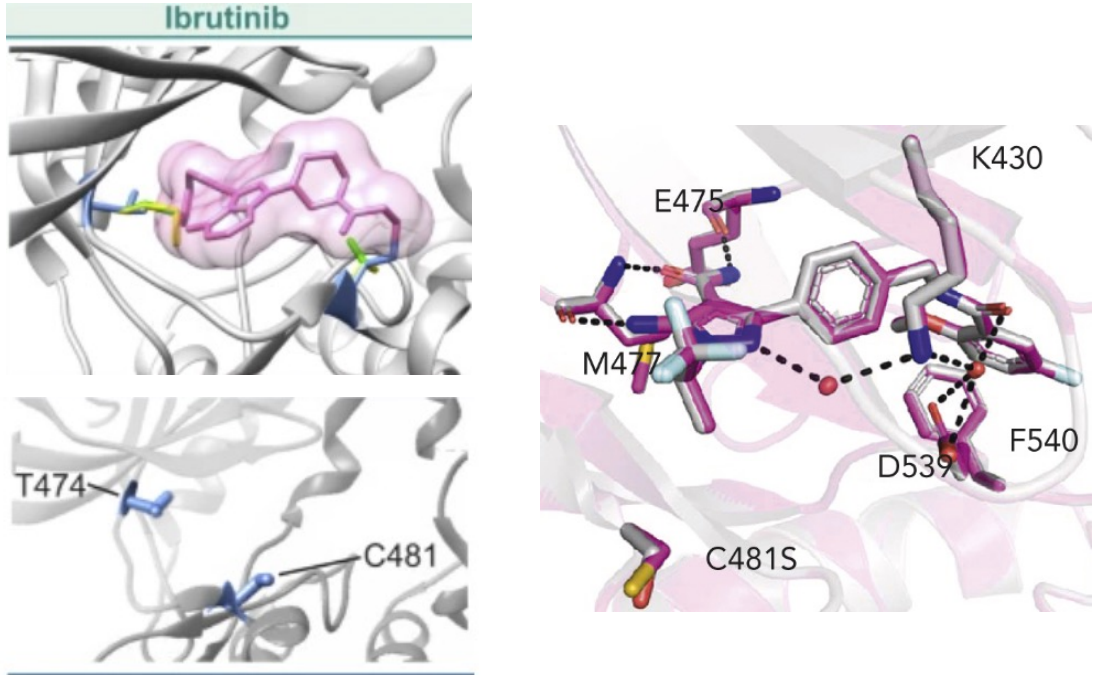
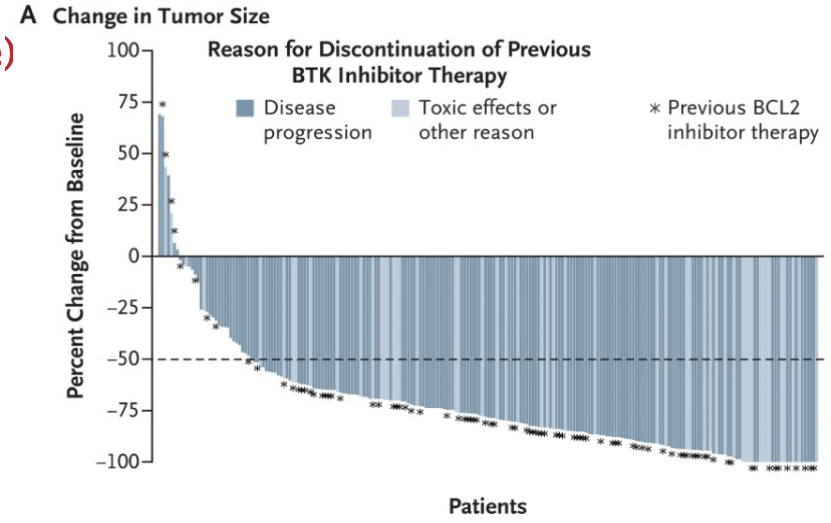
Lin et al. *Blood, The Journal of the American Society of Hematology*, *135*(25), 2266-2270.

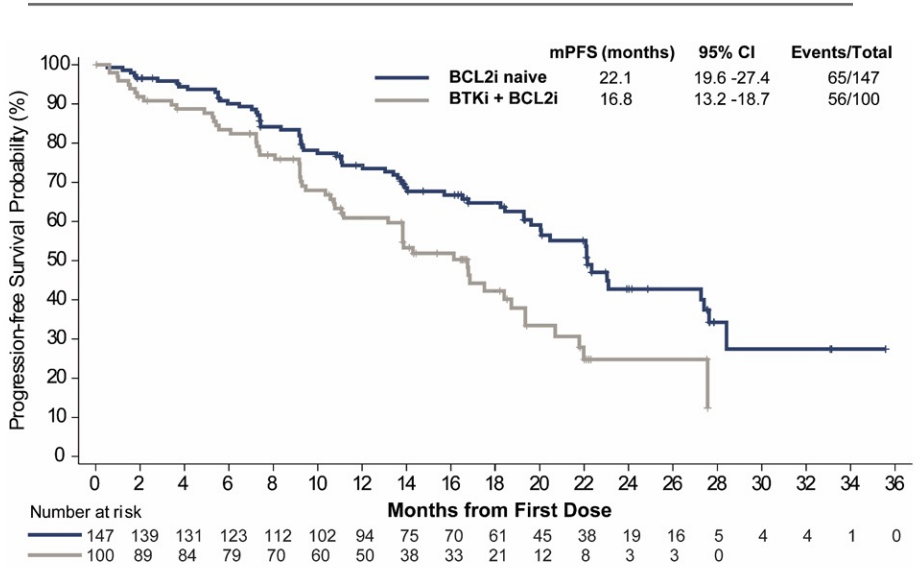
R/R CLL in the Modern Era – cBTKi/BCL2 exposed

BRUIN study – 247 pts with prior BTKi (100 with cBTKi/BCL2 exposure)



Estupiñán HY et al Leukemia. 2021 May;35(5):1317-29.





Mato et al. NEJM 2023 Jul 6;389(1):33-44.

Accelerated FDA approval 12/2023 for R/R CLL post cBTKi and BCL2

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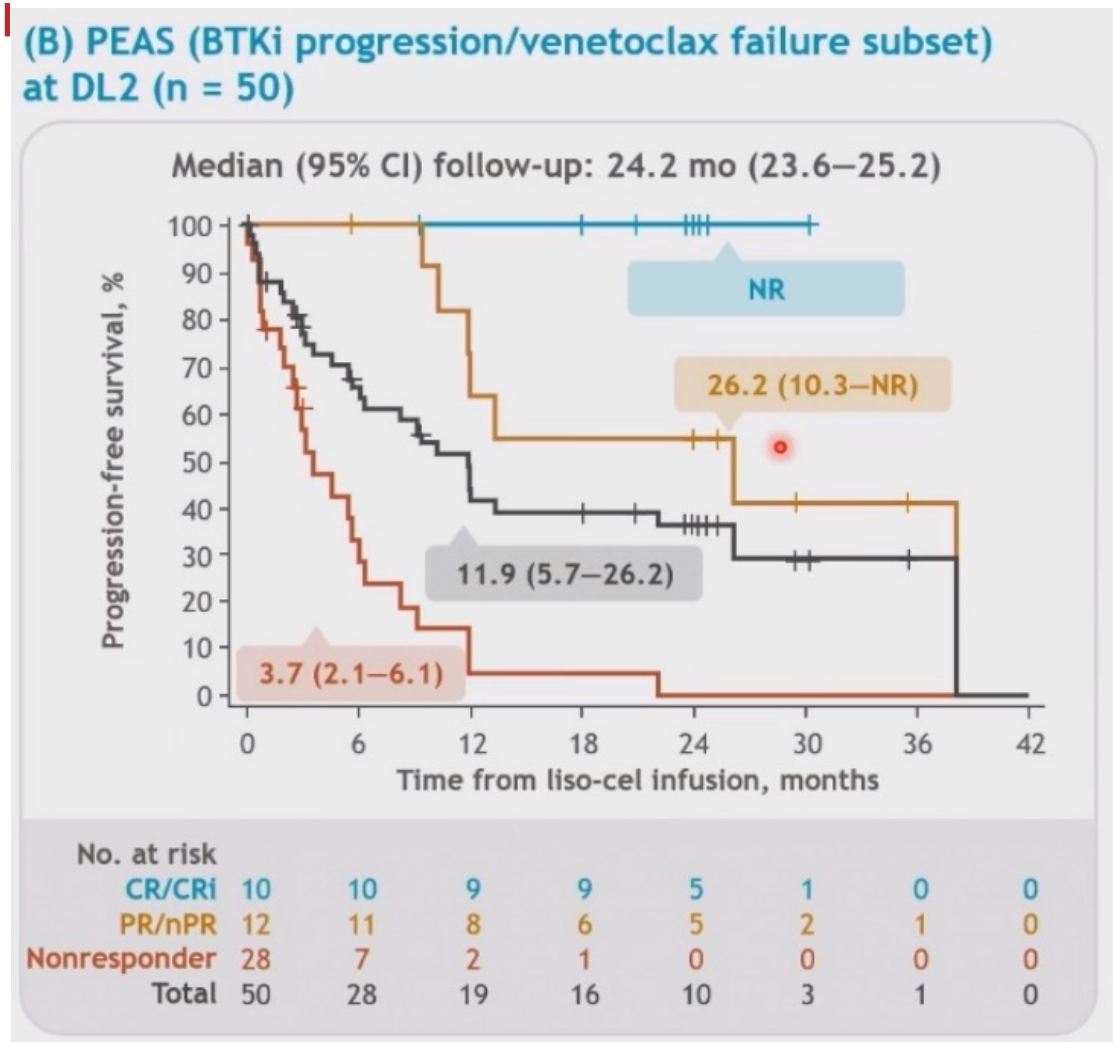
R/R CLL in the Modern Era – cBTKi/BCL2 exposed

CAR-T – 137 pts leukopheresed, 118 received liso-cel (71 had prior BTKi/BCl2)

	BTKi progression/venetoclax failure subset (n = 71)
Median (range) age, y	66.0 (49–78)
Median (range) prior lines of systemic therapy	5 (2–14)
Bulky lymph nodes,[a] n (%)	
Yes	33 (46)
Unknown	8 (11)
High-risk cytogenetics,[b] n (%)	61 (86)
Prior BTKi, n (%)	71 (100)
BTKi refractory[c]	71 (100)
BTKi relapsed[d]	0
BTKi intolerant only	0
Prior venetoclax, n (%)	71 (100)
Venetoclax refractory	68 (96)
Venetoclax relapsed[d]	0
Venetoclax intolerant only	3 (4)



Data under review at FDA (target 3/14/24)

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Siddiqi, Tanya, et al. Blood 142 (2023): 330.

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Venetoclax +- (anti-CD20) [overlap with ibrutinib]

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Pirtobrutinib

Clinical trials

Summary of CLL in 2024

- First-line ibrutinib improves PFS and OS* compared to prior standard chemoimmunotherapy (*FCR)
  - Prolonged/continuous ibrutinib has been shown to be difficult in real-world setting (AE discontinuation > progression)
- Second-generation BTKis with greater BTKi-specificity are better tolerated in RCTs (?real-world AEs/duration)
- Fixed duration venetoclax + obinutuzumab leads to deep and durable remissions – particularly IgHV mutated
  - Adding fixed duration ibrutinib (per CLL13) likely offers little benefit in IgHV mutated
- Fixed duration Ibrutinib + venetoclax leads to deep and durable remissions- particularly in IgHV unmutated subgroup (potential for fixed duration therapy for our highest risk patients)
  - FDA approval is pending, excellent studies using 2nd-generation BTKi with BCL2 are accruing in the US (MAJIC: acala/ven; zanubrutinib/sonrotoclax)
- Non-covalent BTKis (?CAR-T later in 2024) are important options for our cBTKi/BCL2 exposed patients, but duration of response seems relatively limited
  - Refer early for trial consideration (BTK degraders, ROR1 targeting, MALT1 inhibitors all promising)
- RCTs comparing fixed-duration vs. MRD discontinuation with appropriate endpoints (i.e. PFS2, QOL) are needed