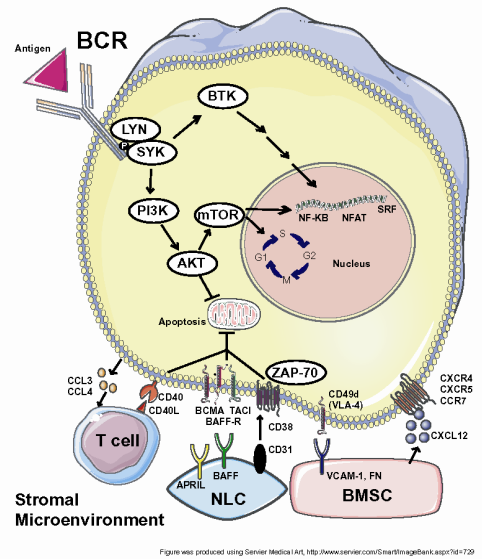
CLL in 2022: The Future is Now



Matthew S. Davids, MD, MMSc
Clinical Research Director | Division of Lymphoma | Dana-Farber Cancer Institute
Associate Professor of Medicine | Harvard Medical School

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Disclosures:

SAB/Consultant: AbbVie, Adaptive Biosciences, Ascentage Pharma, Astra-Zeneca, BeiGene, BMS, Celgene, Eli Lilly, Genentech, Janssen, Merck, Ono Pharma, Secura Bio, Takeda, TG Therapeutics

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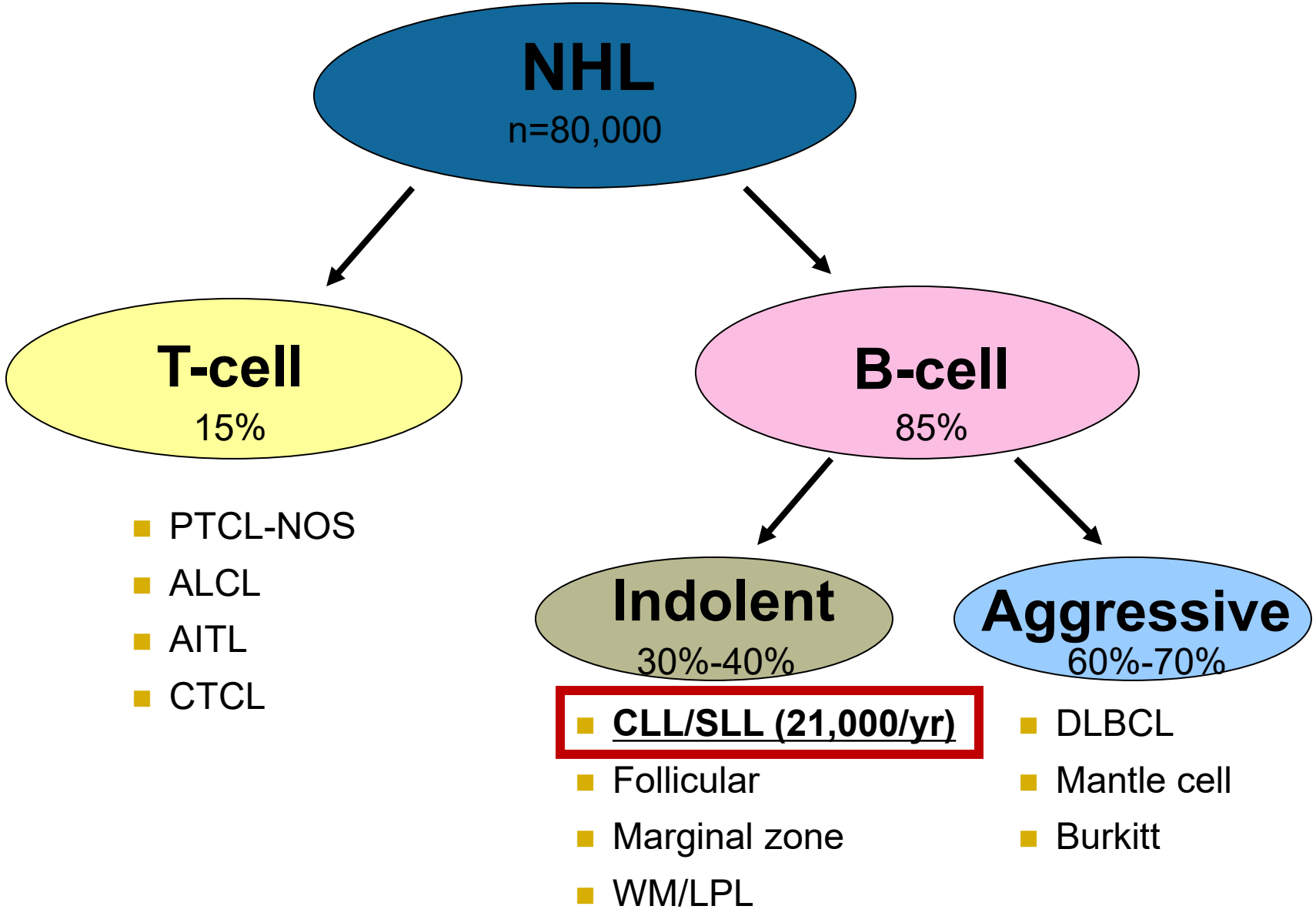
Honoraria: Aptitude Health, BioAscend, Curio Science, Research to Practice

The Big Picture



SEER Database, 2022

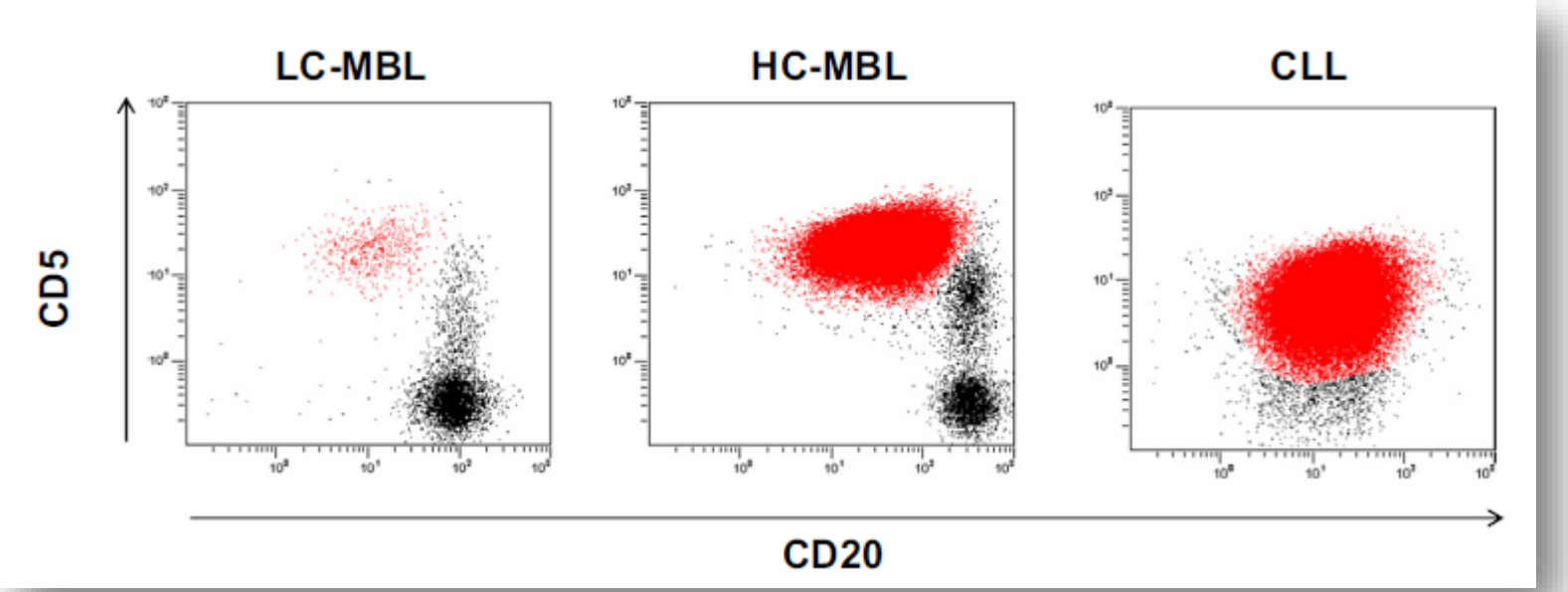
CLL Fast Facts

- Chronic lymphoproliferative disorder of monoclonal B cells
- ~21K new cases / yr in the US, much higher prevalence
- Median age at diagnosis is 68
- Most common presentation: asymptomatic lymphocytosis

- ABC count > 5,000 (CD5+CD23+CD19+dimCD20+dimIg+)
- Monoclonal B cell lymphocytosis (MBL): a precursor condition with <5,000 B cells and no other disease manifestations
- Small lymphocytic lymphoma (SLL): <5,000 B cells with other disease manifestations

- CLL patients have tremendous variation in disease course
- Generally thought to be an incurable cancer

Monoclonal B cell Lymphocytosis (MBL)



Low count (LC) MBL

- **<0.5 x 10^9 clonal B cells/L**
- **Generally detected in population screening studies**
- **Can be detected in nearly everyone older than 70 with sensitive enough techniques**

High count (HC) MBL

- **>=0.5 x 10^9 clonal B cells/L**
- **Nearly all pts with CLL had prior MBL**
- **Most pts with MBL will not develop CLL**
- **Estimated risk is 1-2% per year**

Scarfo and Ghia, Seminars in Oncology, 2016

Monoclonal B cell Lymphocytosis (MBL)

Table 2. Risk factors for MBL onset and progression to CLL requiring therapy

Risk factors for MBL onset	Risk factors for MBL progression to CLL
Family history of CLL	CD38 positivity
Genetic polymorphisms*	Unmutated *IGHV*
Age	Deletion 17p
Infections†	Elevated B-cell count

*More than 20 single-nucleotide polymorphisms associated with the development of CLL have been reported.[110] At least 6 of these have also been confirmed as risk factors for MBL (rs17483466, rs13397985, rs757978, rs872071, rs2456449, and rs735665),[25] whereas the association of the others with MBL remains under investigation.

†Hepatitis C, pneumonia, influenza, cellulitis, upper respiratory infections, and herpes zoster.[26-28]

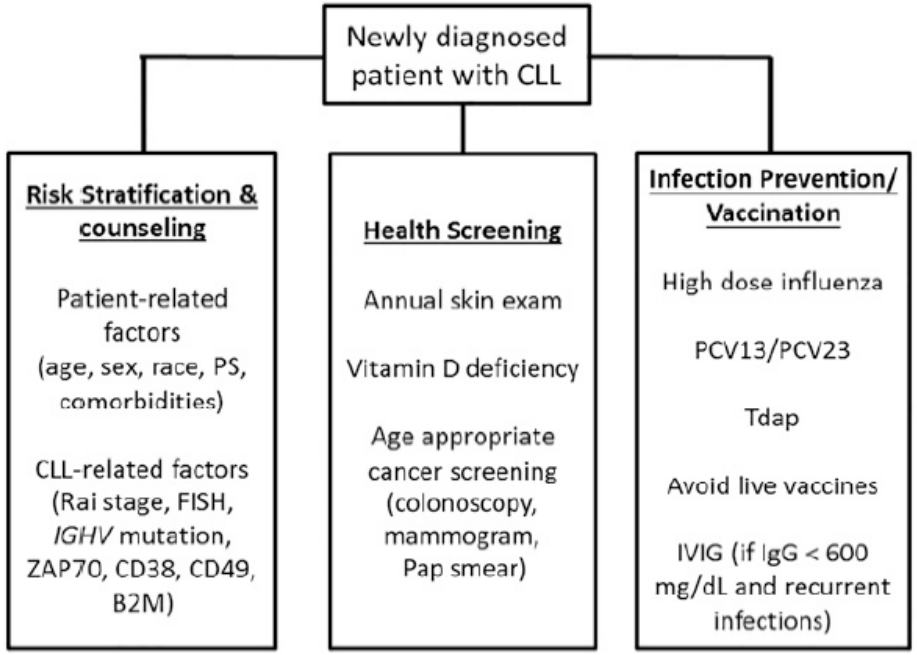
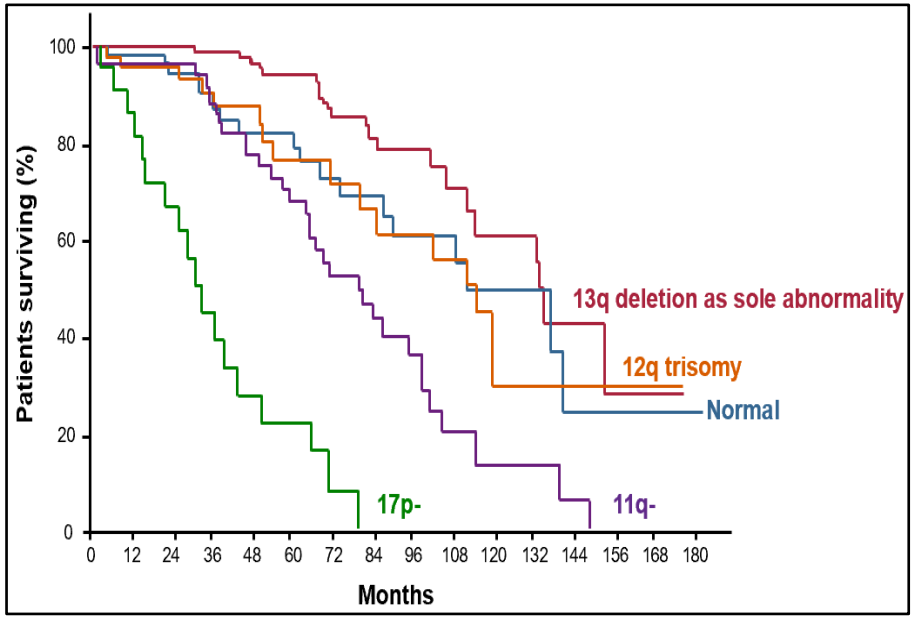


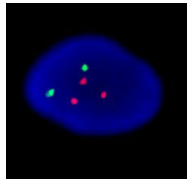
Figure 3. Management of early-stage CLL and SLL. B2M, β-2-microglobulin; IgG, immunoglobulin G; IVIG, intravenous immunoglobulins; MX, mammogram; PCV, pneumococcus vaccine; PS, performance status; Tdap, tetanus diphtheria, acellular pertussis.

Strati and Shanafelt, Blood, 2015

Key Prognostic Markers in CLL

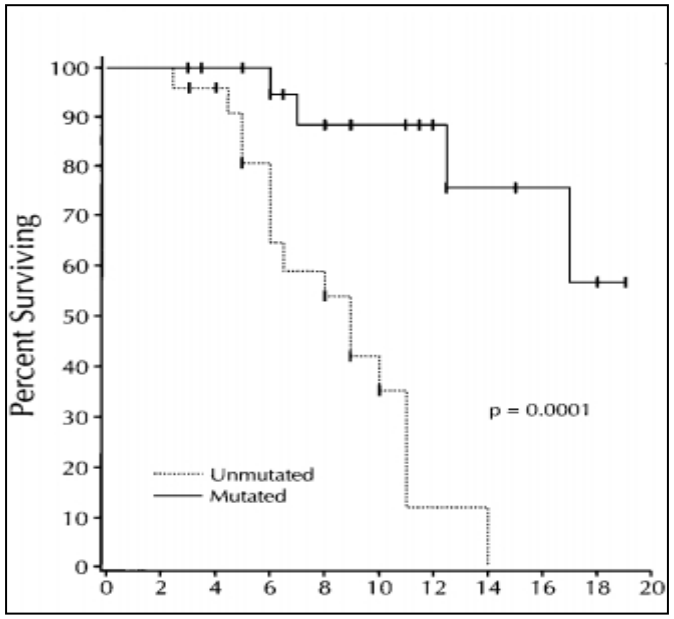
FISH Cytogenetics

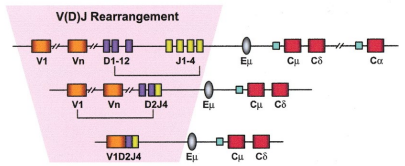




Döhner H, et al. *N Engl J Med*. 2000;343(26):1910-1916.

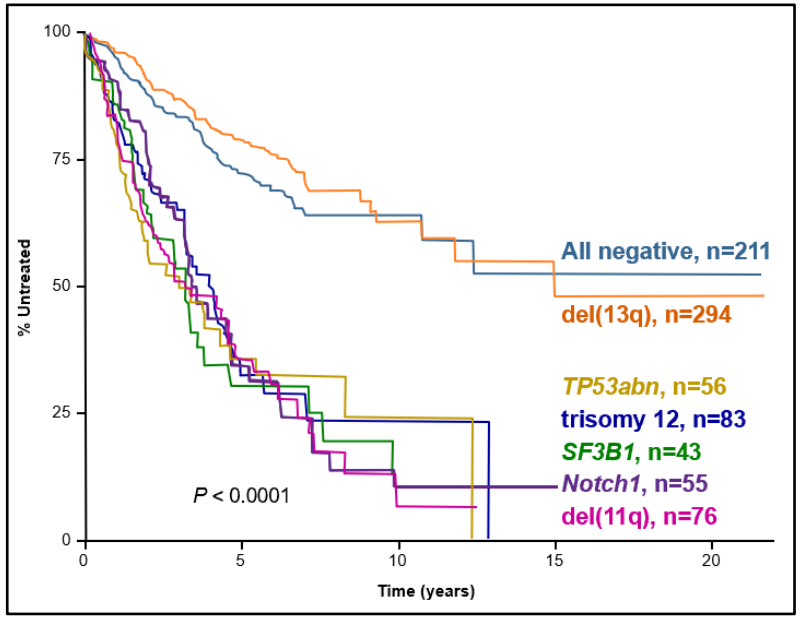
IGHV

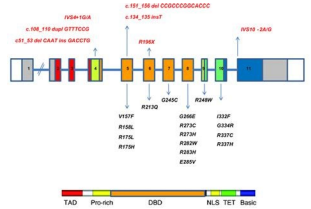




Damle RN, et al. *Blood*. 1999;94(6):1840-1847.

TP53





Baliakas P, et al. *Leukemia*. 2015;29(2):329-336.

Approach to the Newly-Diagnosed Patient with CLL

Indications for Treatment:

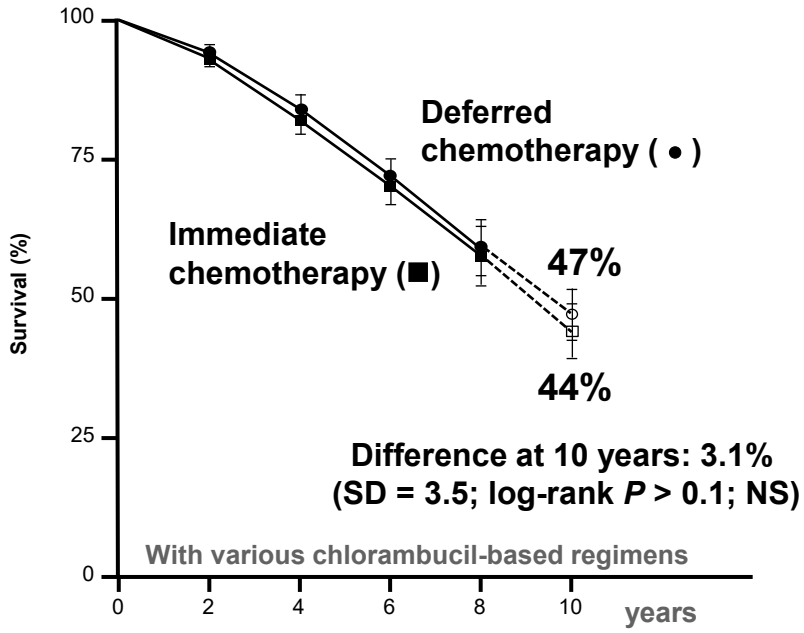
- Cytopenias
- Bulky or rapidly enlarging LAD or splenomegaly
- Symptoms (“B”, fatigue, pain)
- Refractory autoimmune conditions
- +/- LDT < 6 months

Hallek et al., Blood, 2018

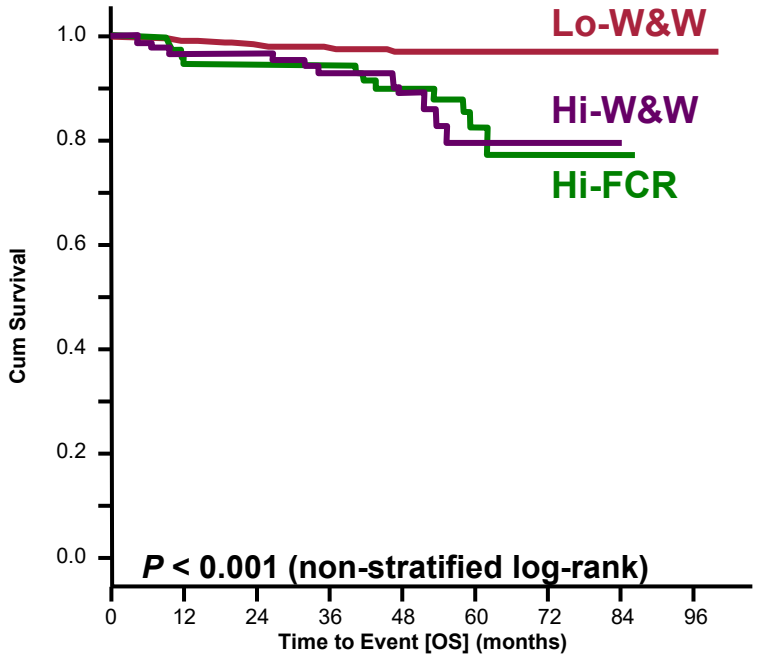
Several Studies Have Evaluated Early Intervention Strategies in Asymptomatic CLL

Meta-Analysis – OS[1]

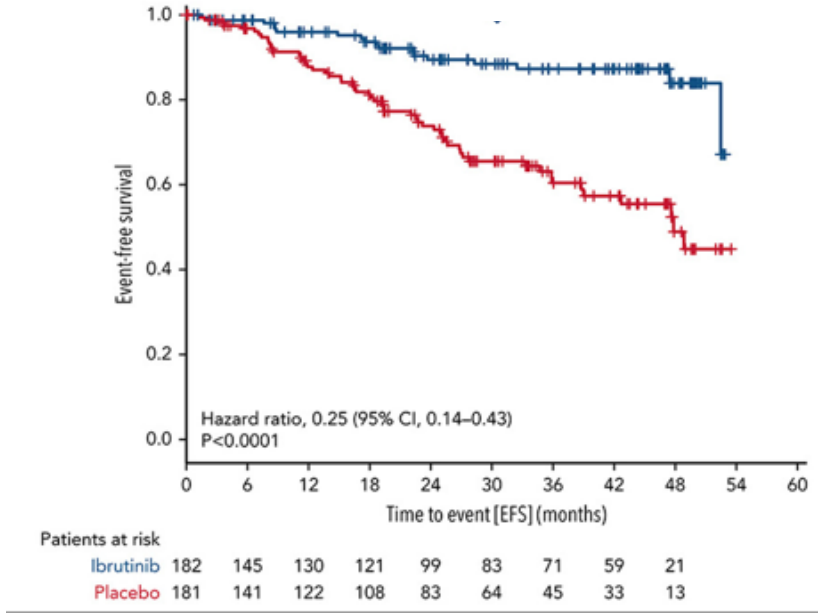
2001 Early-Stage CLL Patients in 5 Trials



CLL7 – OS[2]



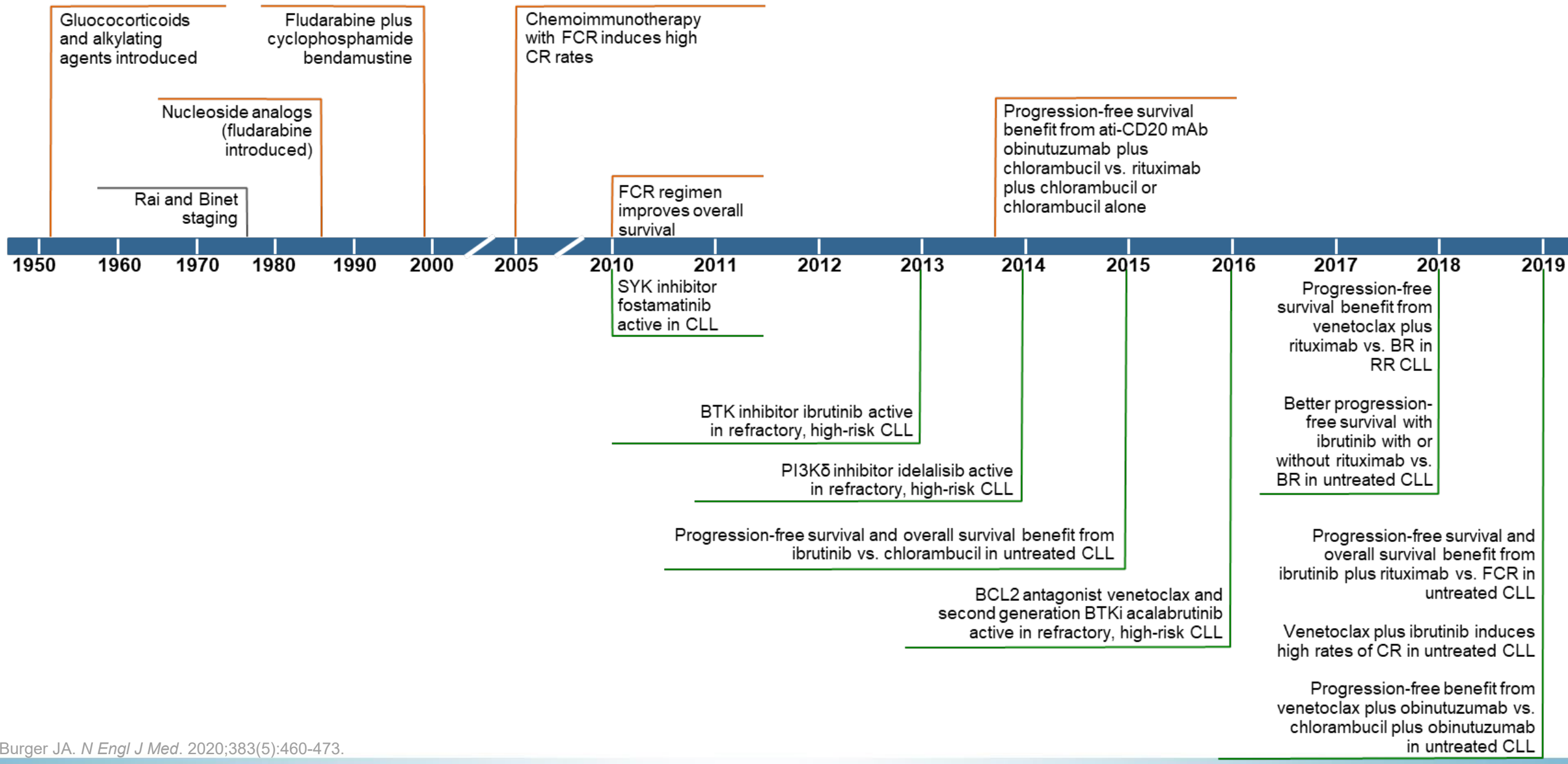
CLL12 – EFS[3]



NO DIFFERENCE IN OS

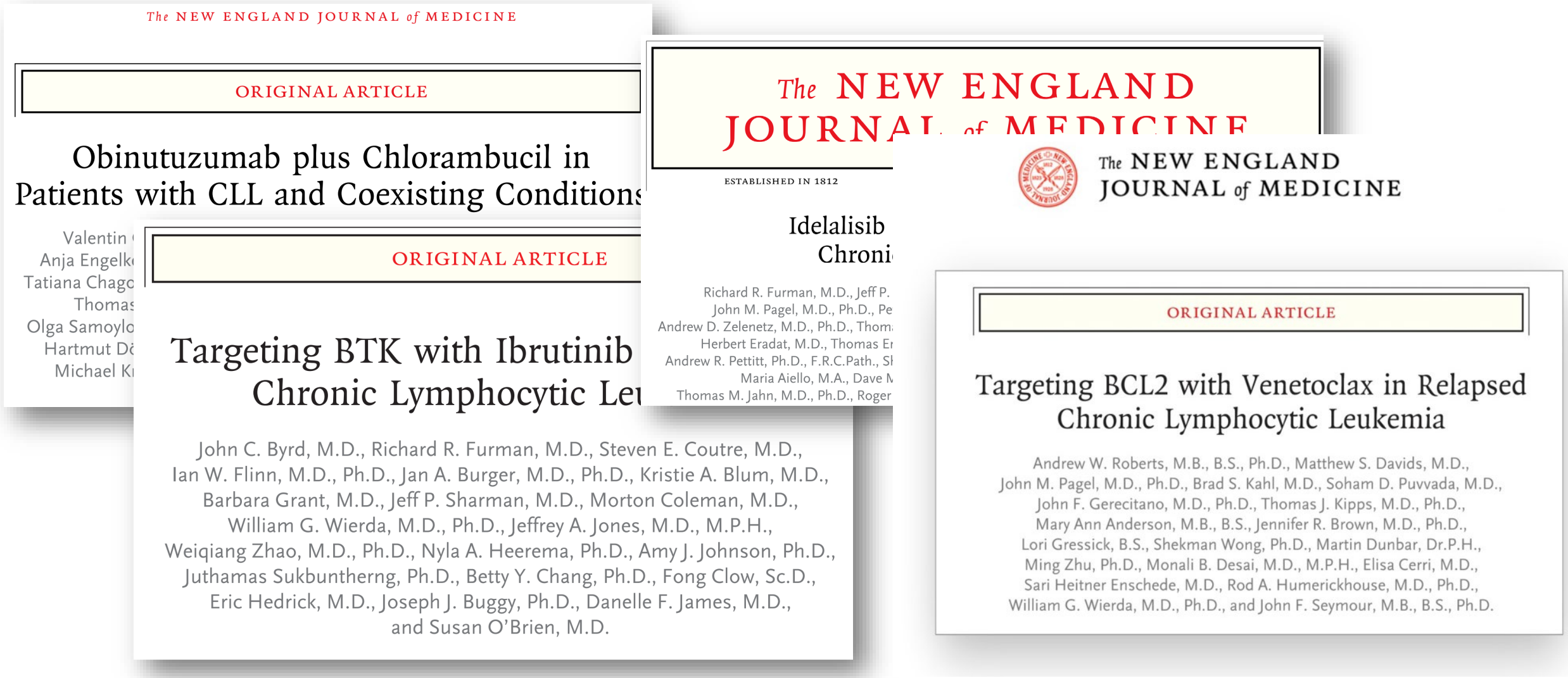
[1] CLL Trialists' Collaborative Group. *J Natl Cancer Inst*. 1999;91(10):861-868. [2] Herling CD, et al. *Leukemia*. 2020;34(8):2038-2050. [3] Langerbeins, et al. *Blood*. 2022

Milestones in Clinical CLL Research



Burger JA. *N Engl J Med*. 2020;383(5):460-473.

NAs have transformed the CLL therapeutic landscape



A Diverse Array of Novel Agents Are Highly Active in CLL

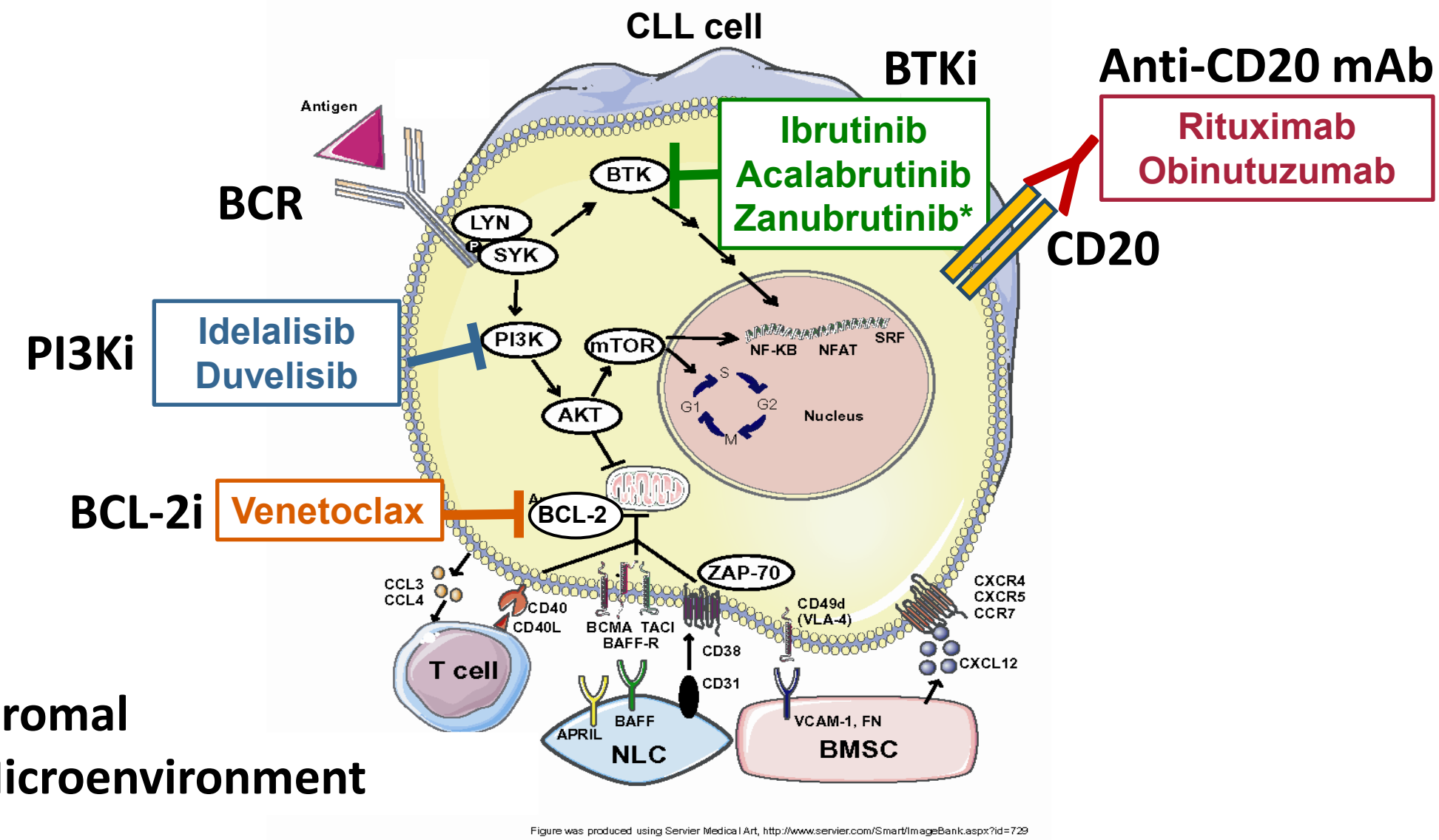


Figure was produced using Servier Medical Art, http://www.servier.com/Smart/ImageBank.aspx?id=729

*Not approved in CLL

Adapted from Davids MS, et al. *Blood*. 2012;120(17):3501-3509.

Revolution in CLL therapy

Chemotherapy

Novel agent monotherapy

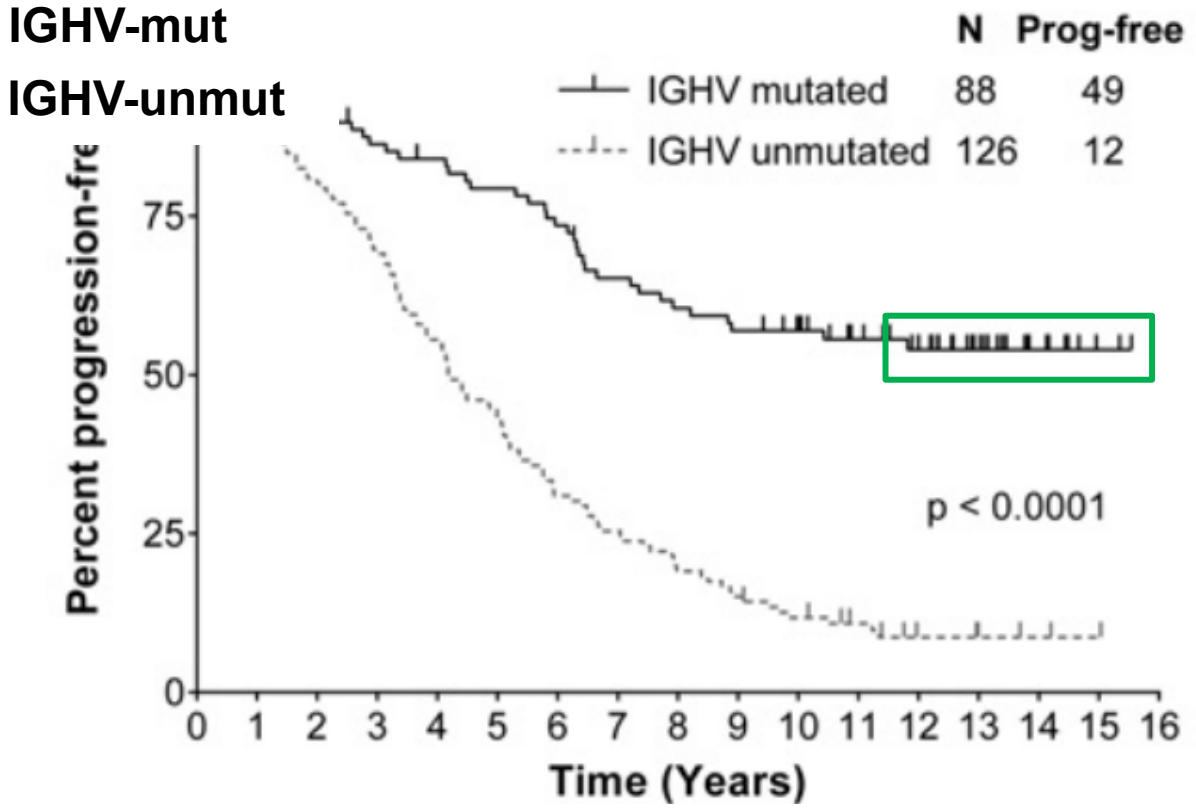
Novel agent combos, CAR-T

Chemoimmunotherapy

Treatment-Naïve CLL

FCR can provide functional cure in mutated IGHV CLL

MDACC – FCR 300

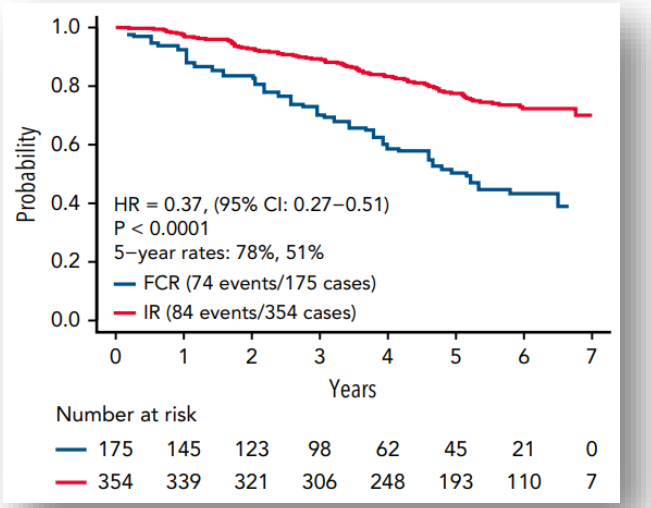


Thompson et al., *Blood*, 2016

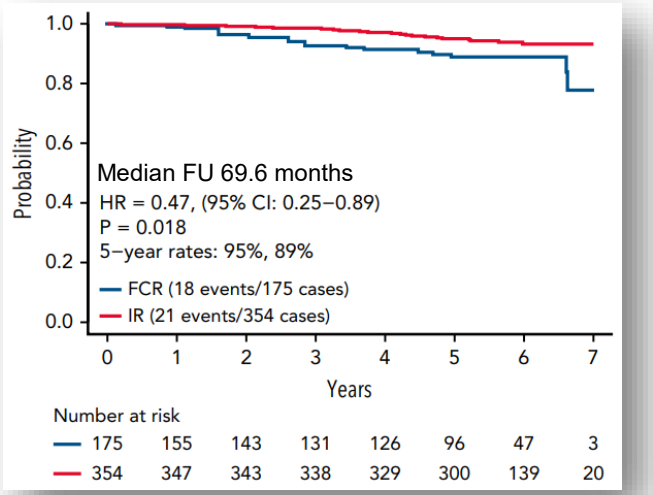
Phase 3 data of IR vs. FCR: PFS and possibly also OS benefit of continuous ibrutinib-based therapy

ECOG 1912 Trial (US)

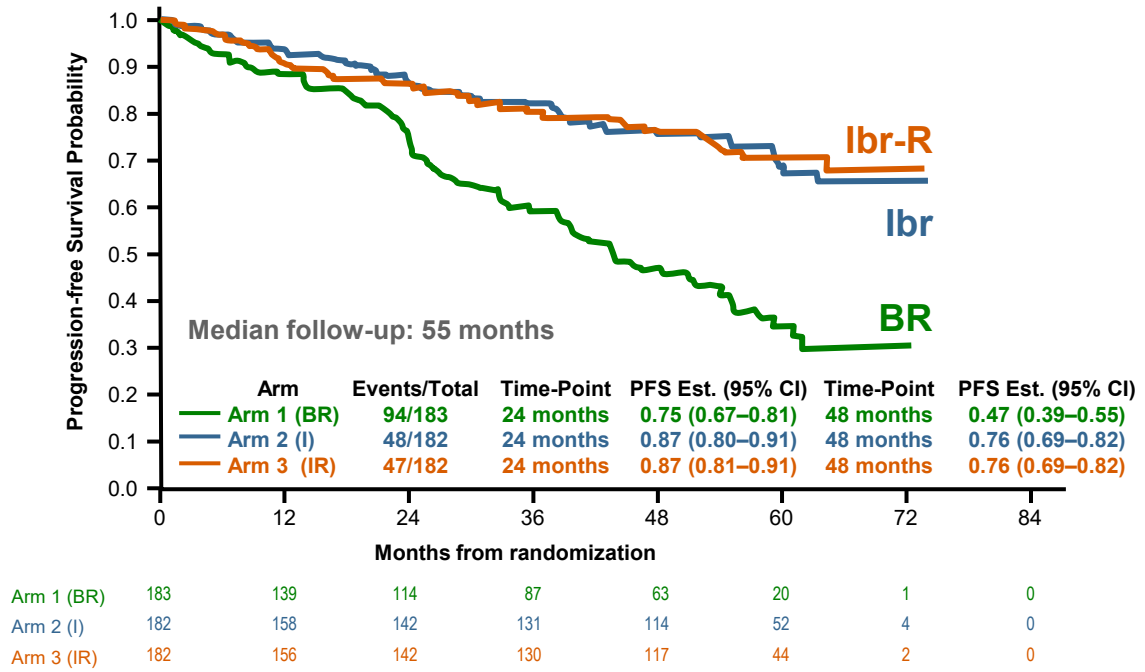
PFS



OS



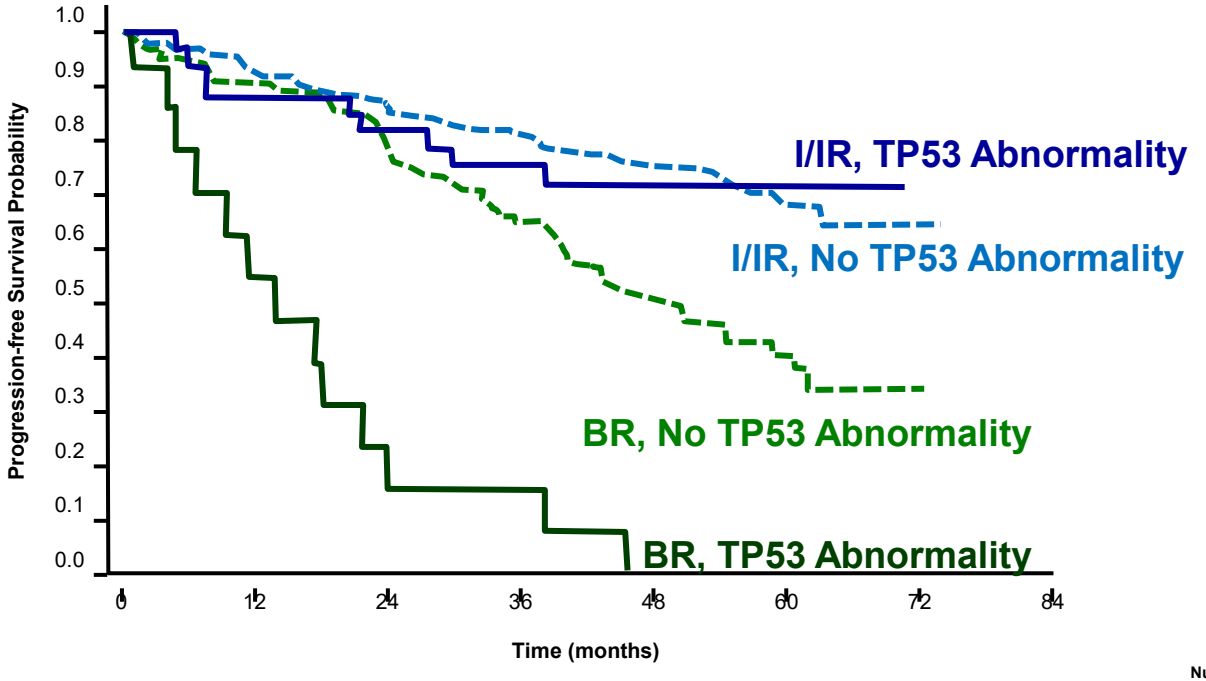
Older patients with TN CLL also benefit from ibrutinib: Phase 3 ALLIANCE A041202



Woyach JA, et al. *N Engl J Med*. 2018;379(26):2517-2528, Woyach et al ASH 2021.

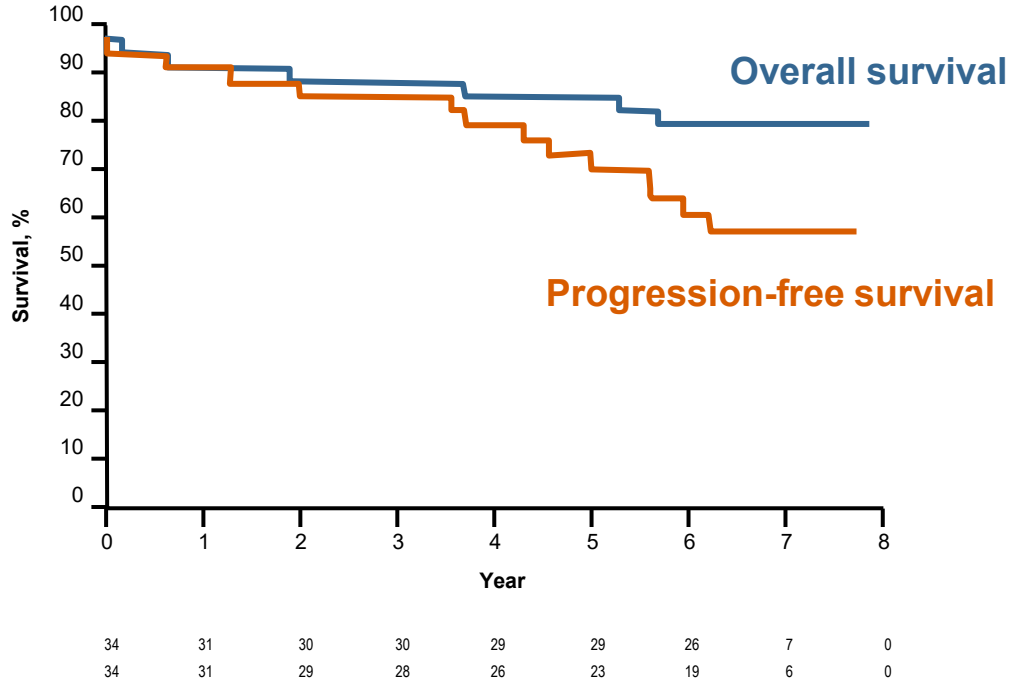
Ibrutinib Can Provide Durable Response Even for *TP53* Aberrant CLL

ALLIANCE
PFS with or without *TP53*



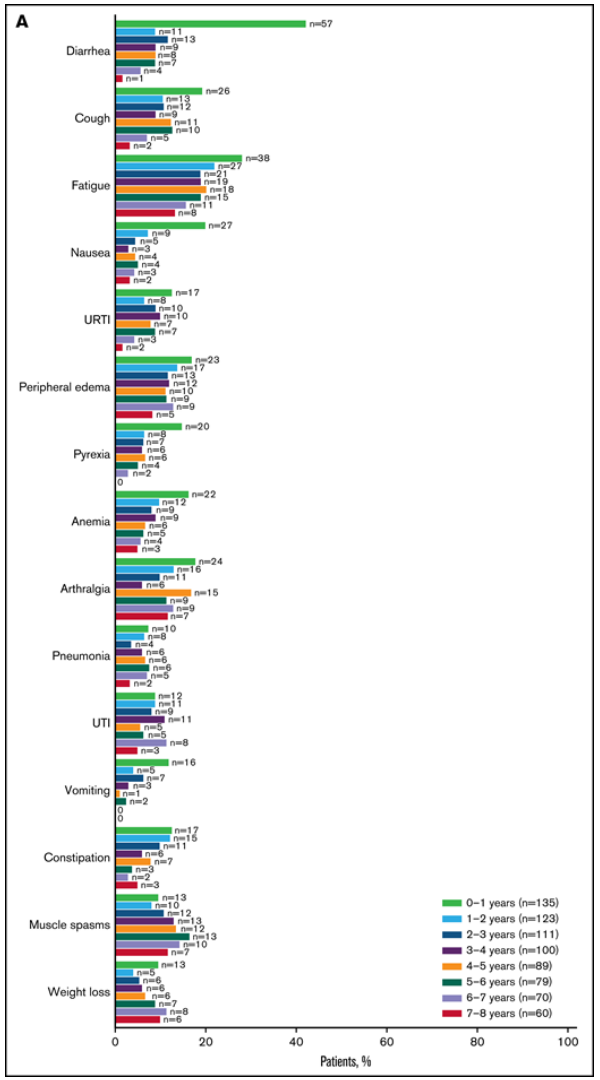
Woyach JA, et al. *Blood.* 2021; 138 (Supplement 1): 639.

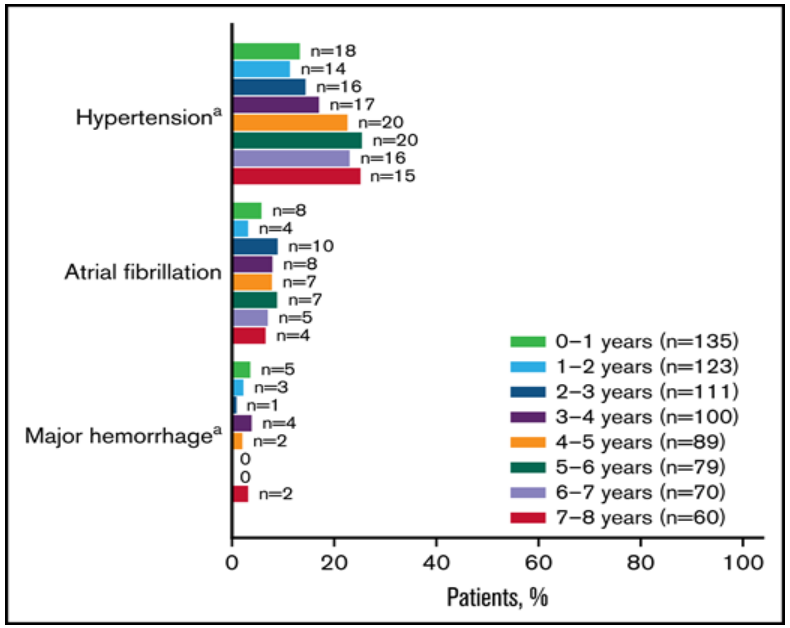
NHLBI
Overall and Progression-free Survival



Ahn IE, et al. *N Engl J Med*. 2020;383(5):498-500.

Discontinuation rates with ibrutinib are high, and are due mostly to AEs





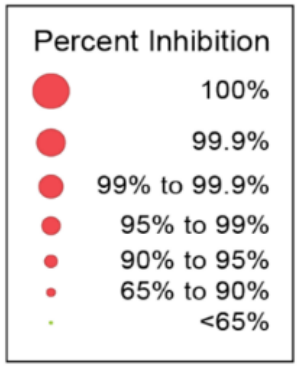
- 42% of patients still on ibrutinib at 8 years
- Most common reason for discontinuation was AEs (24%)

Barr et al., *Blood Advances*, 2022

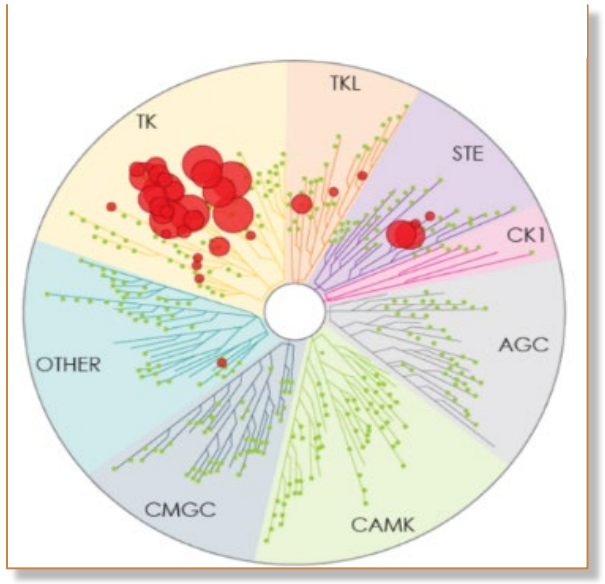
- Discontinuation due to AEs may be even more common in the real-world setting (41% discontinuation at median of 17 mo.)

Mato et al., *Haematologica*, 2018

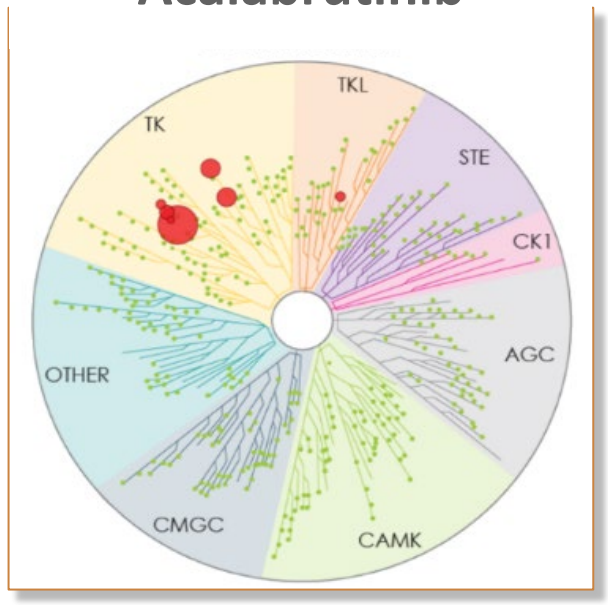
Different BTKi have different levels of specificity for BTK



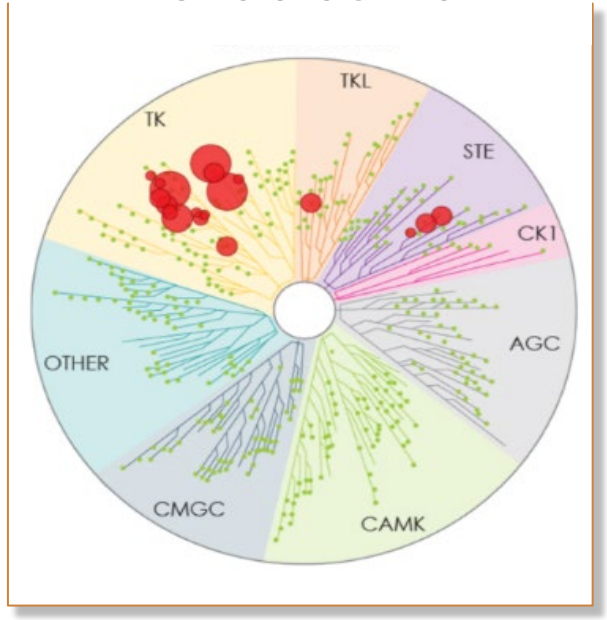
Ibrutinib



Acalabrutinib



Zanubrutinib



Kaptein A, de Bruin G, Emmelot-van Hoek M, et al. *Blood*. 2018;132(Suppl 1):1871.

4-Year Follow-Up of ELEVATE-TN:
Acalabrutinib ± Obinutuzumab vs Obinutuzumab + Chlorambucil in TN CLL

RANDOMIZED 1:1:1

Acalabrutinib + Obinutuzumab (A+O)
Acala 100 mg PO BID until PD or unacceptable toxicity
6 cycles

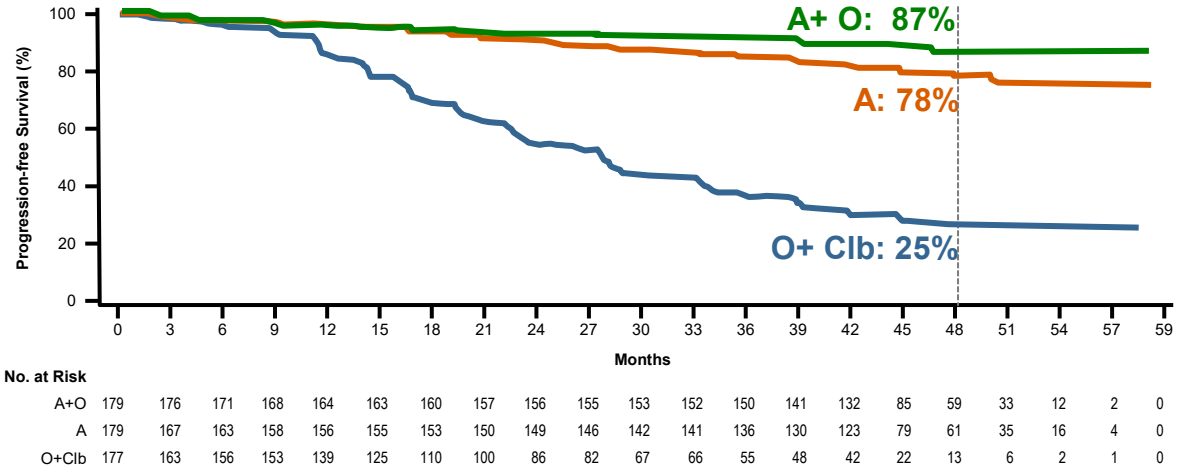
Acalabrutinib Monotherapy (A)
Acala 100 mg PO BID until PD or unacceptable toxicity
Crossover from O+Clb to A allowed after IRC-confirmed PD

Obinutuzumab + Chlorambucil (O+Clb)
6 cycles

Primary endpoint: IRC-assessed PFS (A+O vs O+Clb)
Secondary endpoints: IRC-assessed PFS (A vs O+Clb), INV-assessed PFS, ORR, TTNT, OS, uMRD, safety

Key Eligibility Criteria
- Age ≥65 years or >18 to <65 years with comorbidities (defined as CrCl 30-69 mL/min and CIRS-G >6)
- Untreated CLL requiring treatment per iwCLL 2008 criteria
- ECOG PS ≤2
- No significant cardiovascular disease

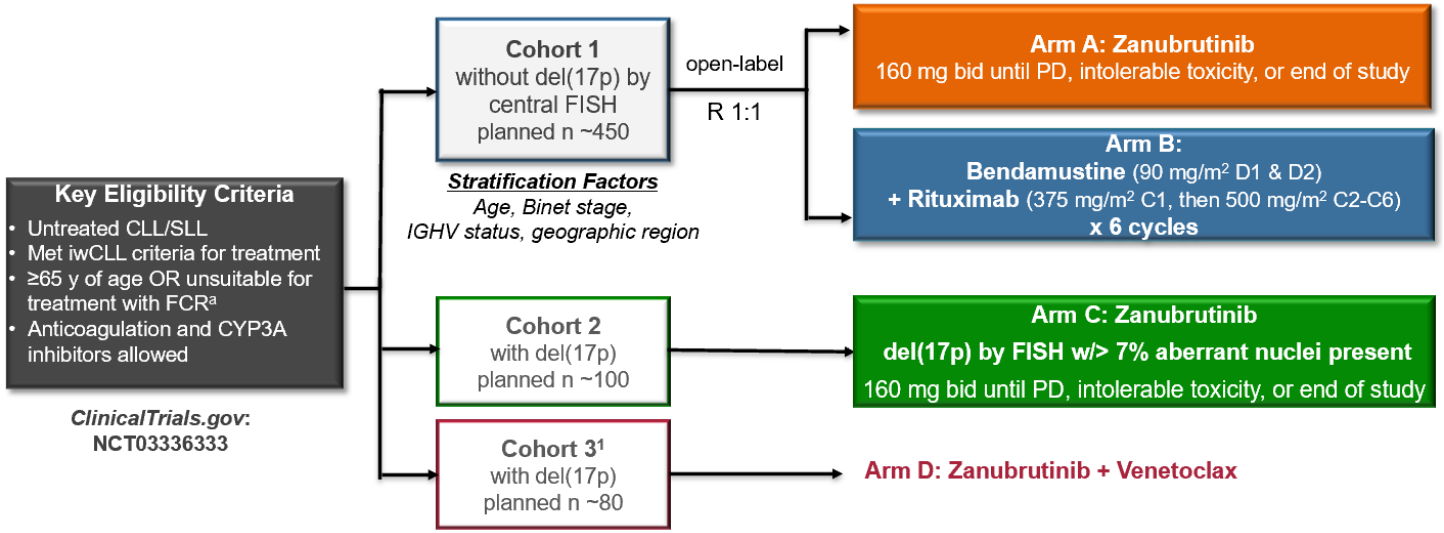
INV-Assessed PFS Overall



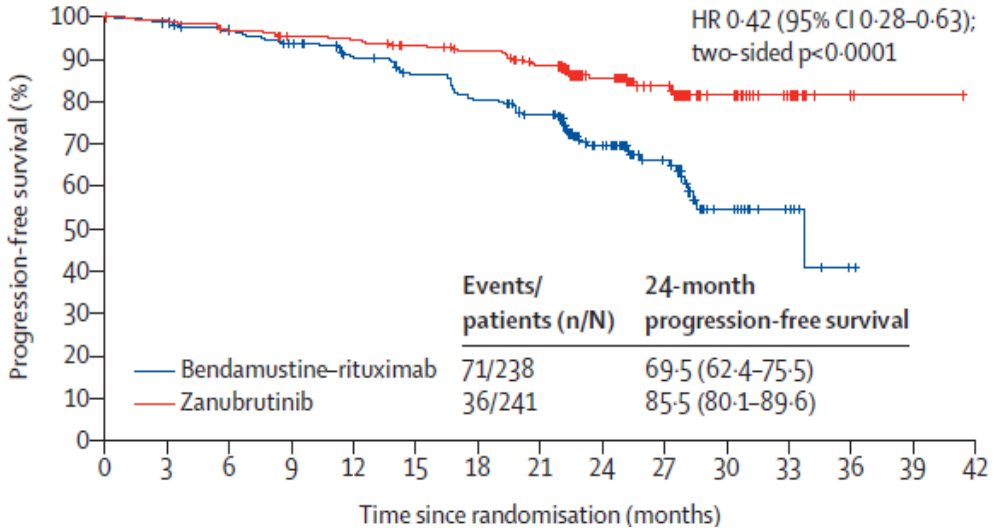
	HR (95% CI)	*P*
A+O vs O+Clb	0.10 (0.07, 0.17)	< 0.0001
A vs O+Clb	0.19 (0.13, 0.28)	< 0.0001
A+O vs A	0.56 (0.32, 0.95)	< 0.0001

Sharman JP, et al. [published online ahead of print, 2022 Jan 1]. *Leukemia*. 2022;10.1038/s41375-021-01485-x.

Phase 3 SEQUOIA study of zanubrutinib

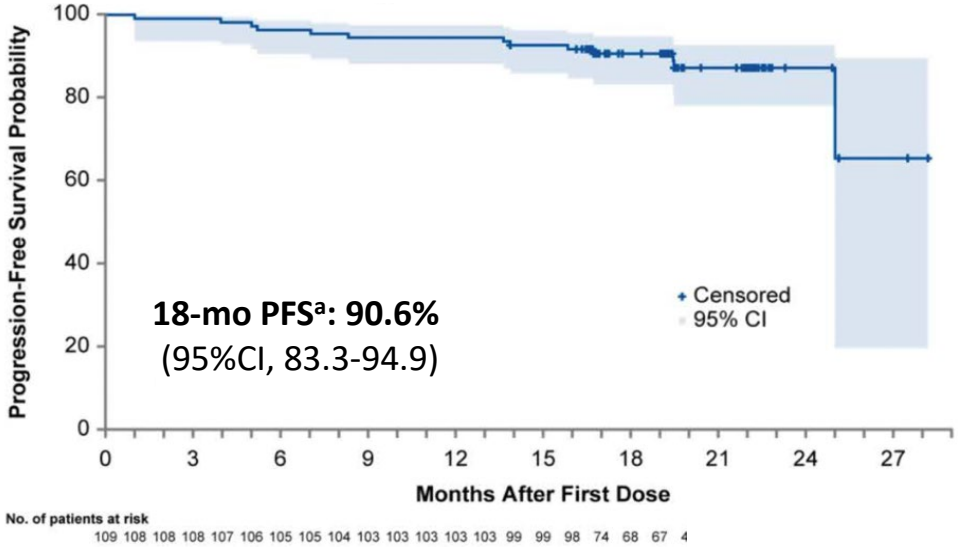


Zanu vs. BR PFS in non-del(17p)



Tam et al. *The Lancet Oncology*. 2022;23(8):1031-1043

Zanu PFS in del(17p)



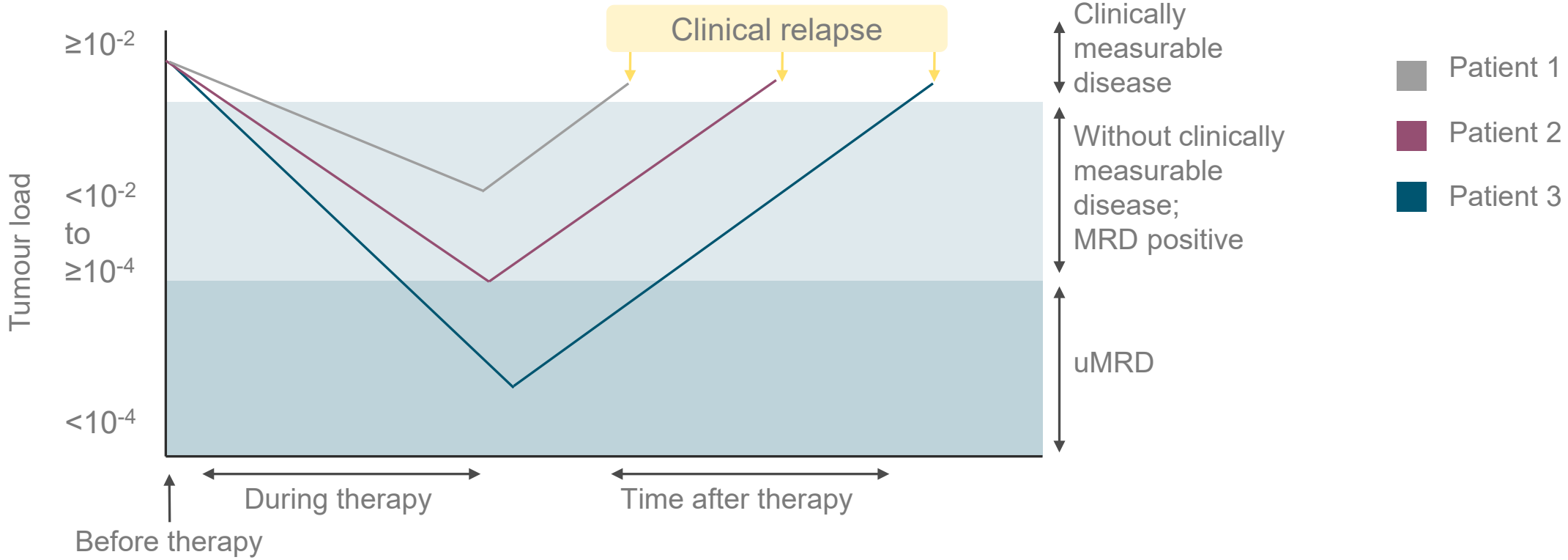
Brown JR, et al. *Blood.* 2020; 136 (Supplement 1): 11–12

What are some limitations of novel agent monotherapy?

- Achievement of CR and uMRD is rare
- Resistance mutations already described
- Ongoing drug-drug interaction risk
- Ongoing toxicities
- Long term adherence issues
- Co$t

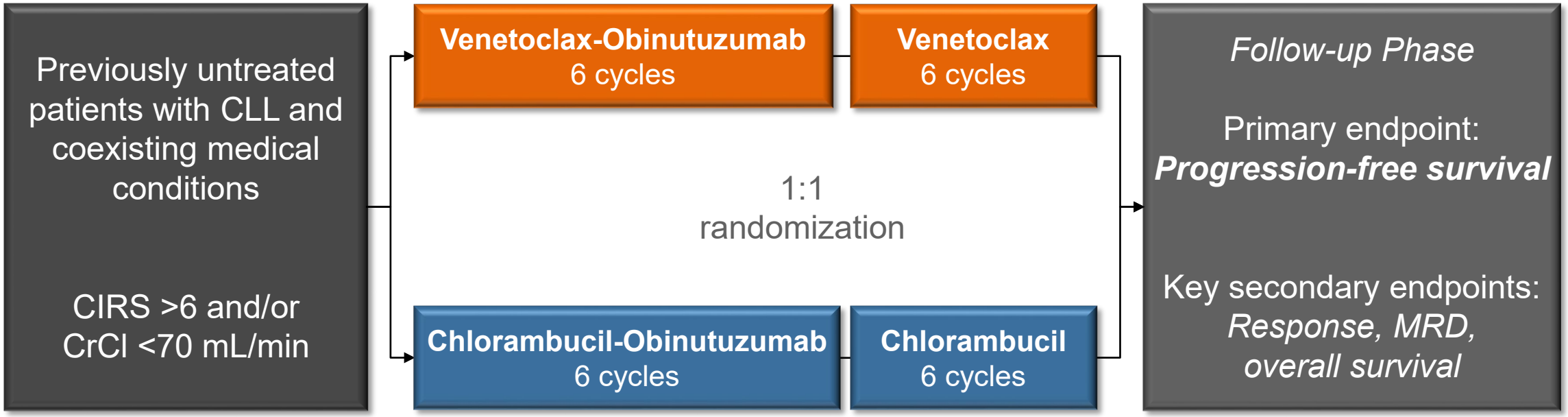
Achieving undetectable minimal residual disease (uMRD) is associated with longer PFS

uMRD IS A KEY GOAL OF FIXED-DURATION TREATMENT REGIMENS



Adapted from Böttcher et al. 2013

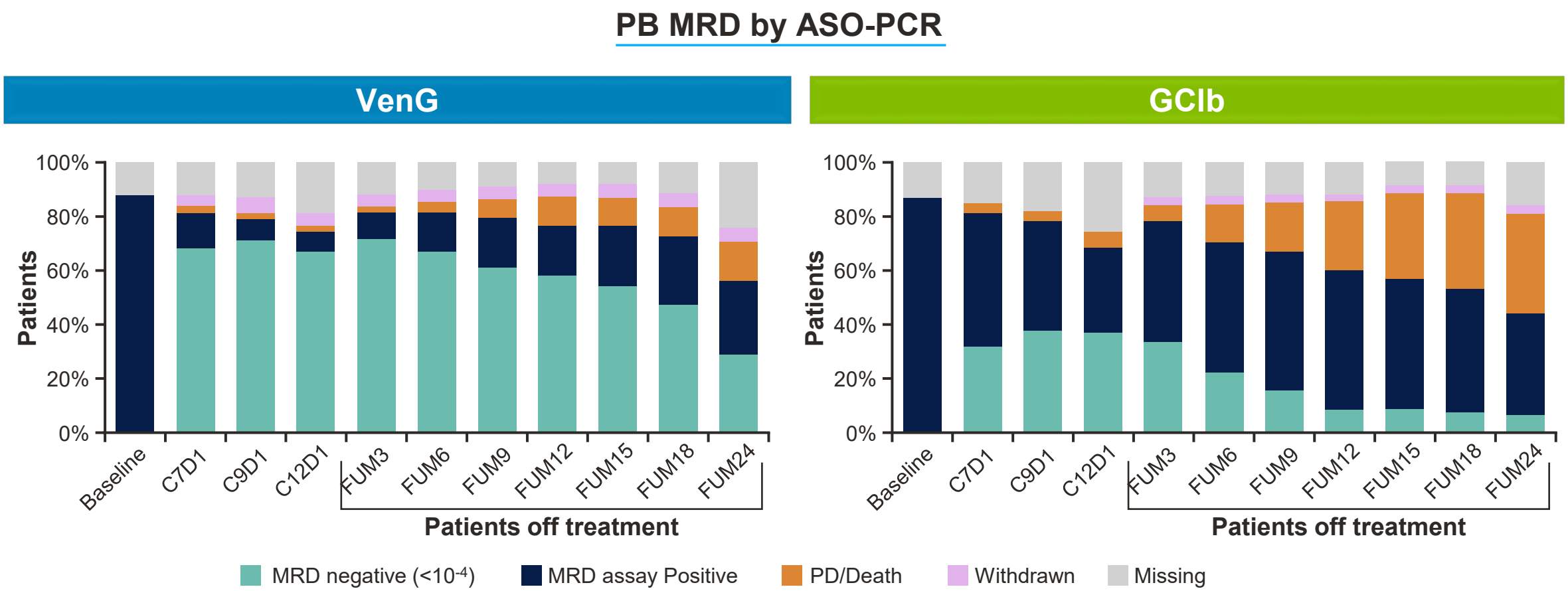
Phase 3 CLL14 Study of Ven-G vs Chl-G in Patients With TN CLL With Coexisting Medical Conditions



CIRS, Cumulative Illness Rating Scale; Clb-G, chlorambucil, obinutuzumab; CLL, chronic lymphocytic leukemia; CrCl, creatinine clearance; MRD, minimal residual disease; PB, peripheral blood; TN, treatment-naive, Ven-G, venetoclax, obinutuzumab.

Al-Sawaf, et al. *Blood.* 2020;136(supplement 1): 22-23.

VenG achieves uMRD for most patients

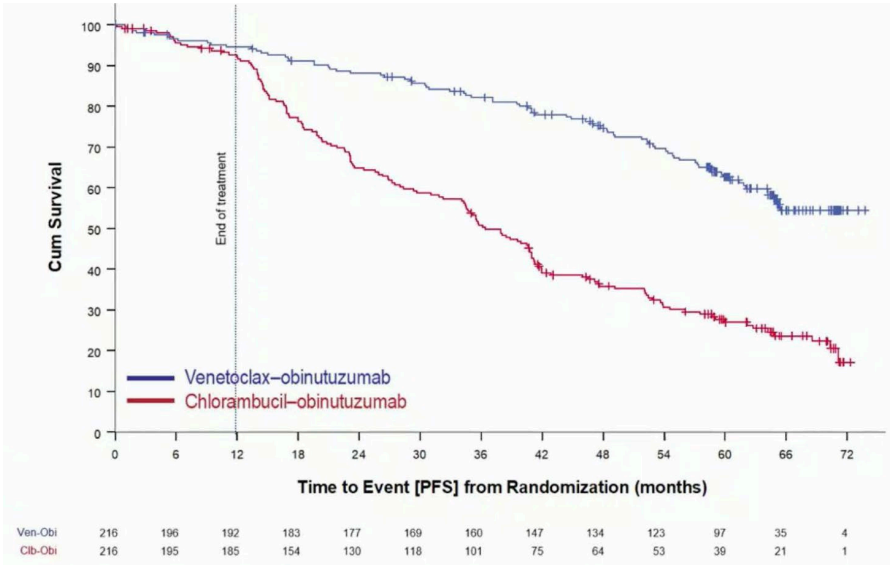


MRD-negativity rates were more sustainable after completion of therapy with VenG than with GClb as assessed by ASO-PCR

Al-Sawaf O, et al. Lancet Oncology, 2020

5-year follow-up of Ven-Obin in CLL14 in frontline CLL

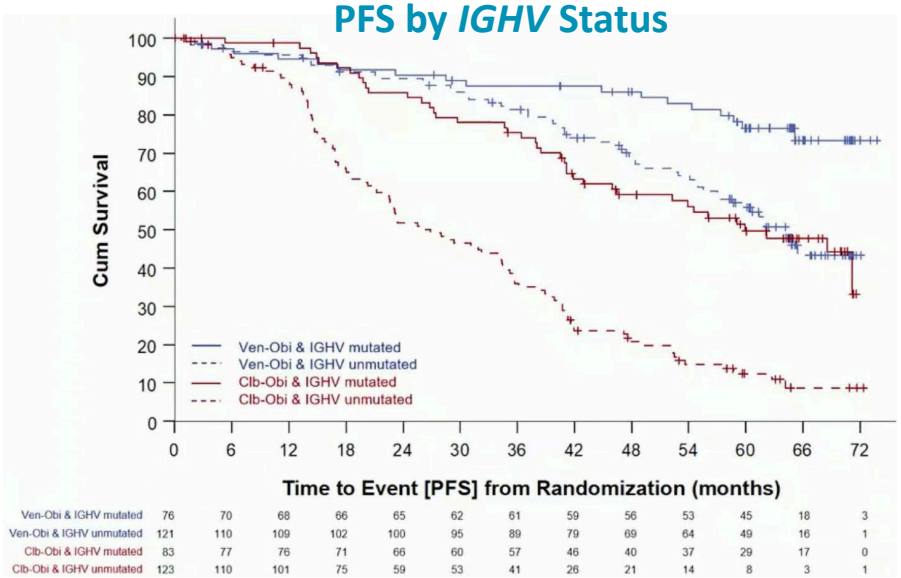
PFS: All Patients



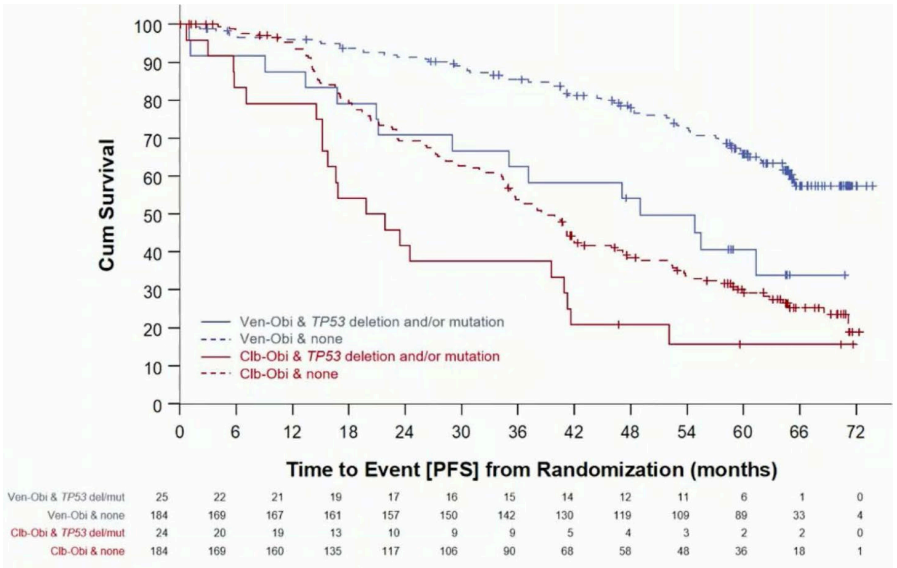
PFS by Subgroup		Ven-Obi (n=216)	Clb-Obi (n=216)
All patients	Median, months	NR	36.4
	5-year rate, %	62.6	27.0
	HR (95% CI); *P* value	0.35 (0.26-0.46); <0.0001	
Median, months			
TP53 del/mut	No	NR (n=184)	38.9 (n=184)
	Yes	49.0 (n=25)	19.8 (n=24)
IGHV status	Mut	NR (n=76)	59.9 (n=83)
	Unmut	64.2 (n=121)	26.9 (n=123)

Median observation time: 65.4 months

PFS by *IGHV* Status



PFS by *TP53* Status



Al-Sawaf O, et al. EHA 2022. Abstract S148.

Less drug exposure = less toxicity

Most frequent ≥ grade 3 adverse events	Venetoclax-obinutuzumab (N=212)		Chlorambucil-obinutuzumab (N=214)	
	During Treatment	After Treatment	During Treatment	After Treatment
Neutropenia	51.9%	4.0%	47.2%	1.9%
Thrombocytopenia	13.7%	0.5%	15.0%	0.0%
Anemia	7.5%	1.5%	6.1%	0.5%
Febrile neutropenia	4.2%	1.0%	3.3%	0.5%
Infusion-related reaction	9.0%	0.0%	9.8%	0.5%
Tumour lysis syndrome	1.4%	0.0%	3.3%	0.0%
Neoplasms	1.4%	6.4%	1.4%	1.9%

Al-Sawaf et al, EHA 2020

Cost Effectiveness of Frontline CLL Therapies

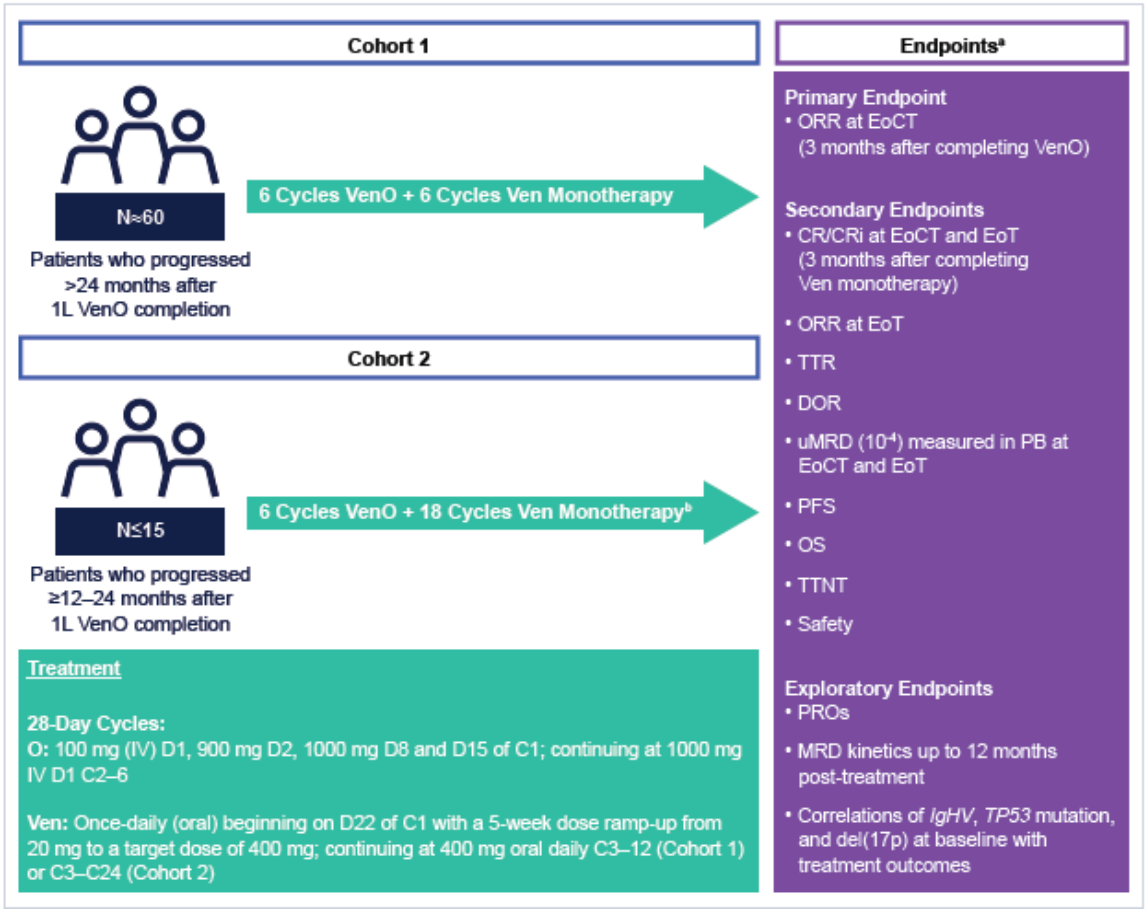
Treatment	Total costs ($)	Life-years gained	QALYs gained	Incremental costs ($)	Incremental life-years gained	Incremental QALYs gained	ICER ($/QALY)
VenG	$291,012	13.01	6.521	–	–	–	–
GClb	$491,040	13.01	6.188	$200,028	0	−0.333	VenG is dominant
BR	$595,771	12.31	5.815	$304,759	−0.70	−0.706	VenG is dominant
Ibr	$1,045,472	12.31	6.004	$754,460	−0.70	−0.517	VenG is dominant
Ibr + G	$1,779,412	13.02	6.543	$1,488,400	0.01	0.022	$67,856,575
Ibr + R	$1,040,860	12.22	5.946	$749,848	−0.79	−0.576	VenG is dominant
Acala	$1,870,749	13.55	7.194	$1,579,737	0.54	0.672	$2,349,304
Acala + G	$1,947,166	13.56	7.482	$1,656,154	0.55	0.961	$1,724,052

TABLE 2 Cost-Effectiveness of VenG Compared With Other Treatments
Acala = acalabrutinib; B = bendamustine; Clb = chlorambucil; G = obinutuzumab; Ibr = ibrutinib; ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life-year; R = rituximab; Ven = venetoclax.

Chatterjee et al, JMPC, 2021

A phase 2 study of venetoclax plus obinutuzumab retreatment in patients with relapsed CLL

Study Design



OBJECTIVES

The ReVenG study will assess whether patients with chronic lymphocytic leukemia who completed first-line venetoclax + obinutuzumab (VenO) can derive clinical benefit with VenO retreatment following disease progression

1. The primary objective is to evaluate the overall response rate of VenO retreatment in patients who progressed >24 months after first-line VenO
2. The secondary objective is to quantify time-to-event efficacy endpoints and to assess the safety of VenO retreatment in patients who progressed >24 months after first-line VenO

STUDY OVERVIEW

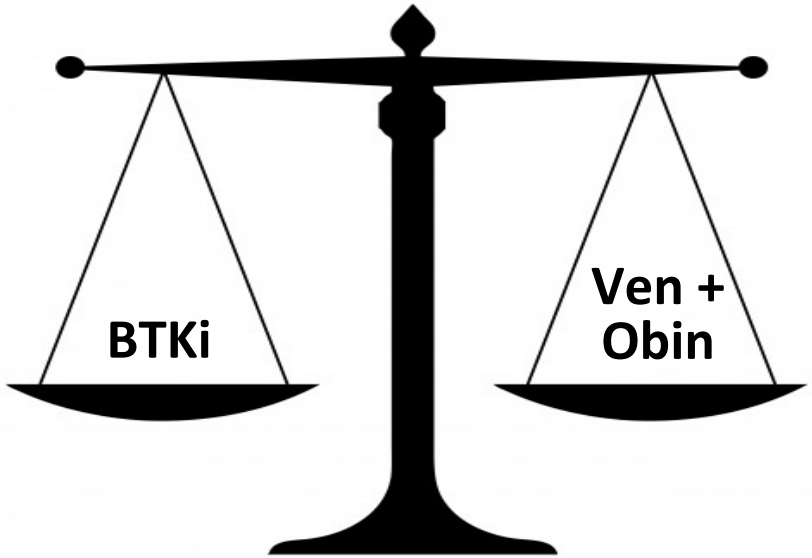
Multicenter	International	Open-Label	Phase 2	Up to 75 Patients Are Planned for Enrollment	NCT04895436 Planned Initiation in December 2021

DEUTSCHE STUDIENGRUPPE CLL

Dana-Farber Cancer Institute

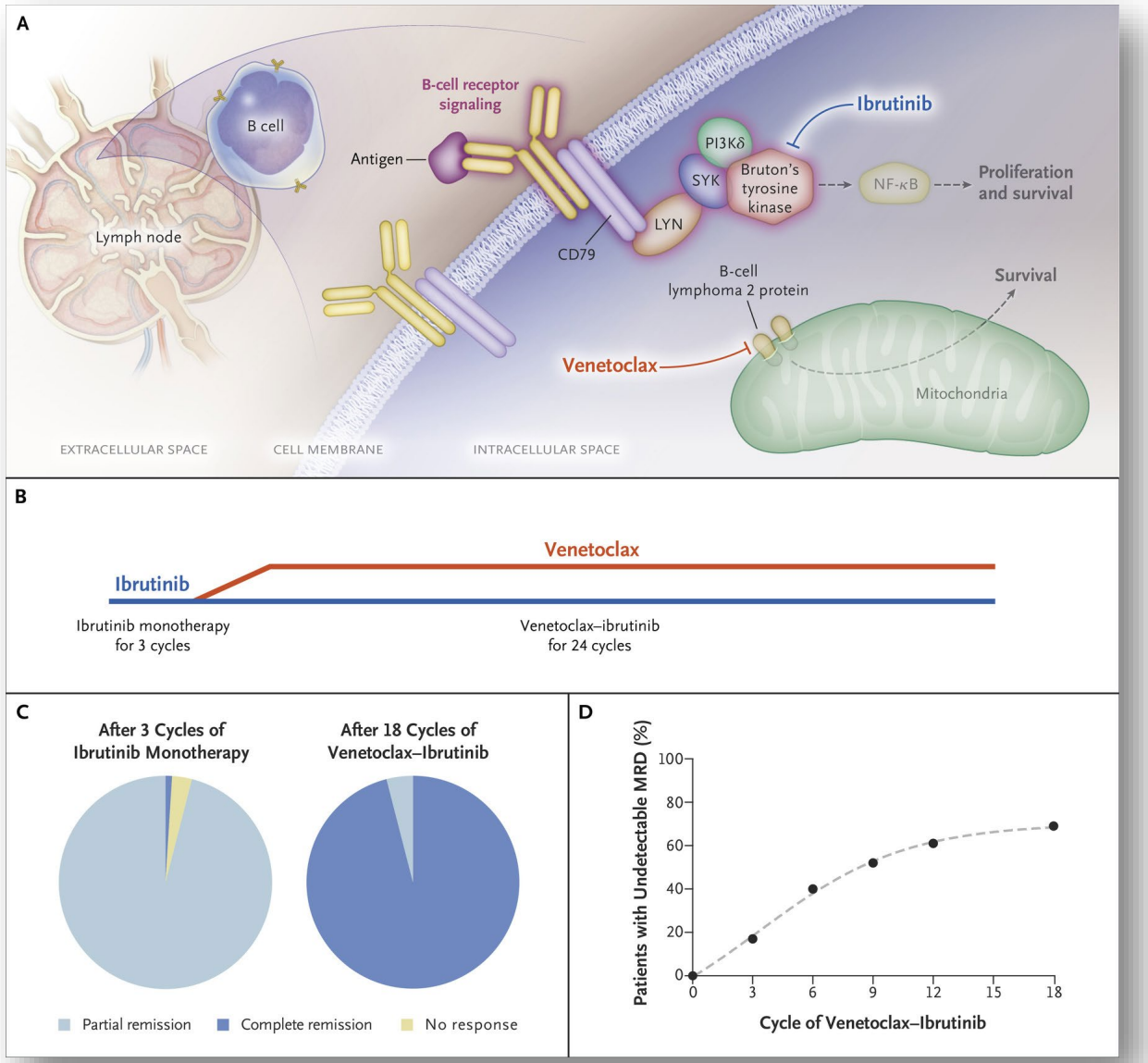
Davids MS et al., ASH 2021, Abstract 2634

Frontline BTKi vs Ven + Obin: Factors to Consider

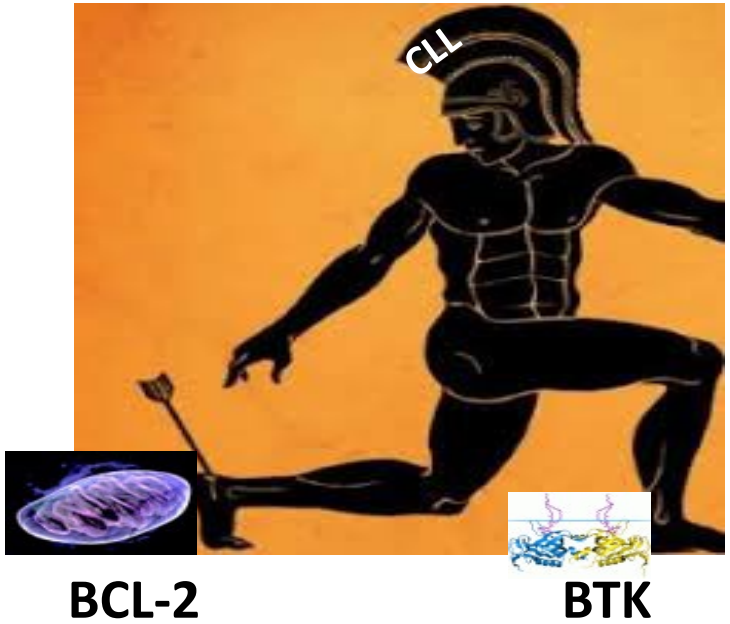


- Convenience (no infusions, TLS monitoring)
- Longer-term efficacy data
- Phase 3 data compared to FCR and BR (ibrutinib)
- Propsective data for efficacy of ven at time of ibrutinib progression
- 1-year time-limited therapy
- No known cardiac or bleeding risks
- Less concern for long-term adherence
- Cost-saving

BCL-2 and BCR pathway are the Achilles' Heels of CLL Pathophysiology



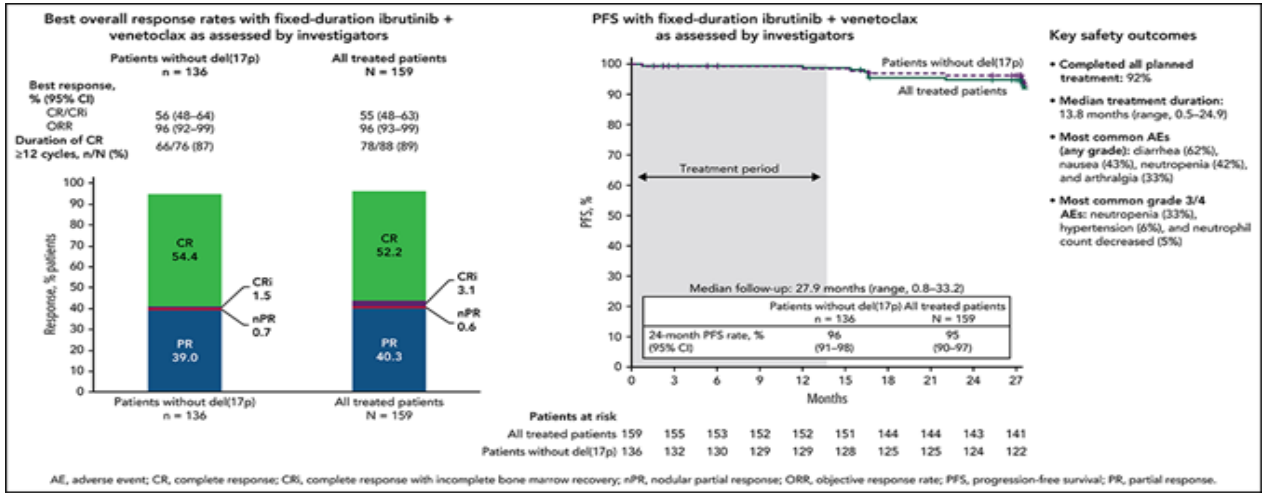
Wiestner, NEJM, 2019



BCL-2 **BTK**

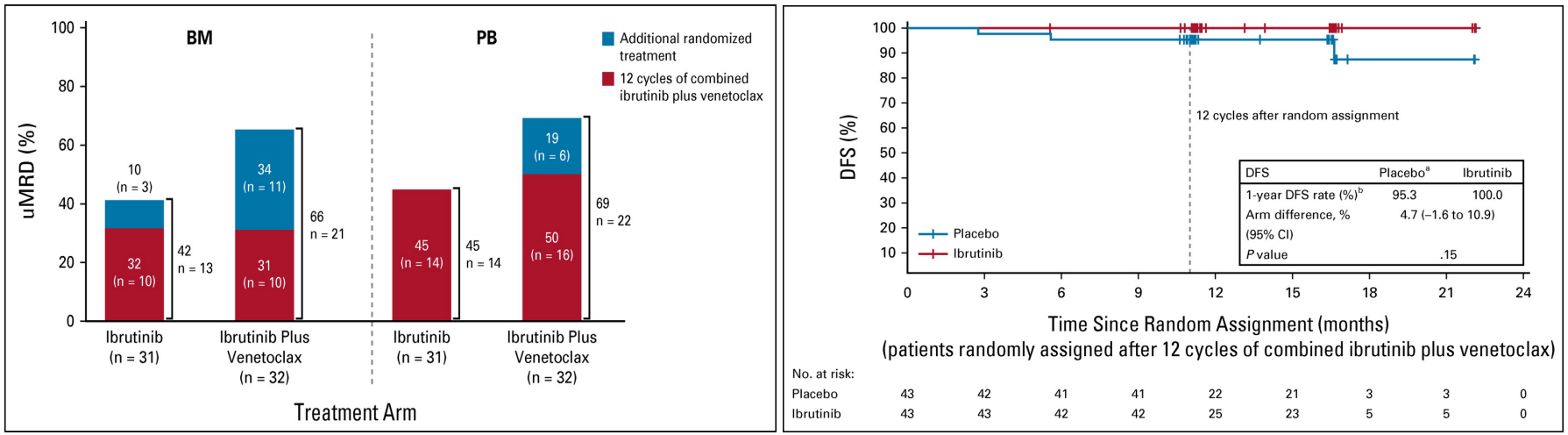
Doublets: BTKi/BCL-2i combos are active, though follow-up is short

CAPTIVATE FD Cohort



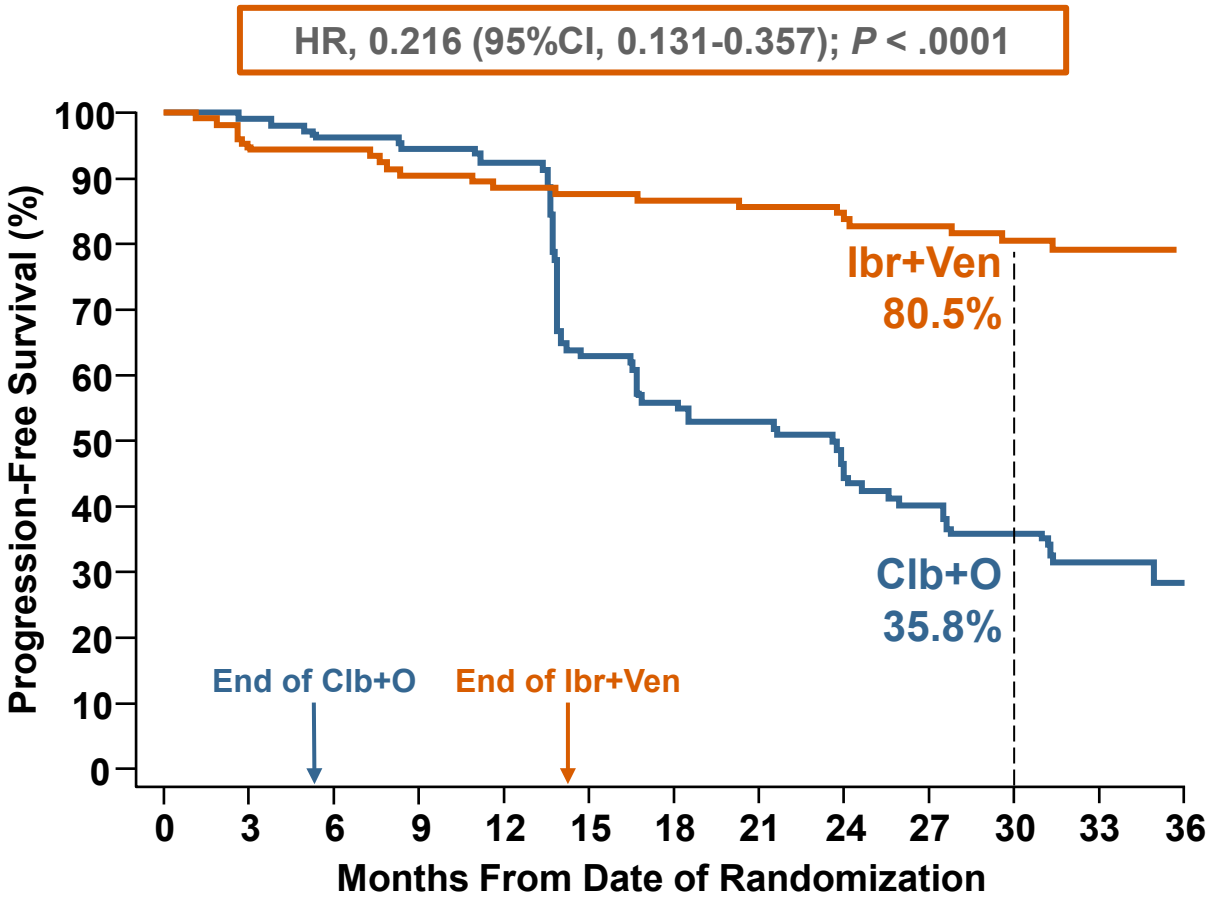
Tam et al., *Blood*, 2022

CAPTIVATE MRD Cohort



Wierda et al., J Clin Oncol, 2021

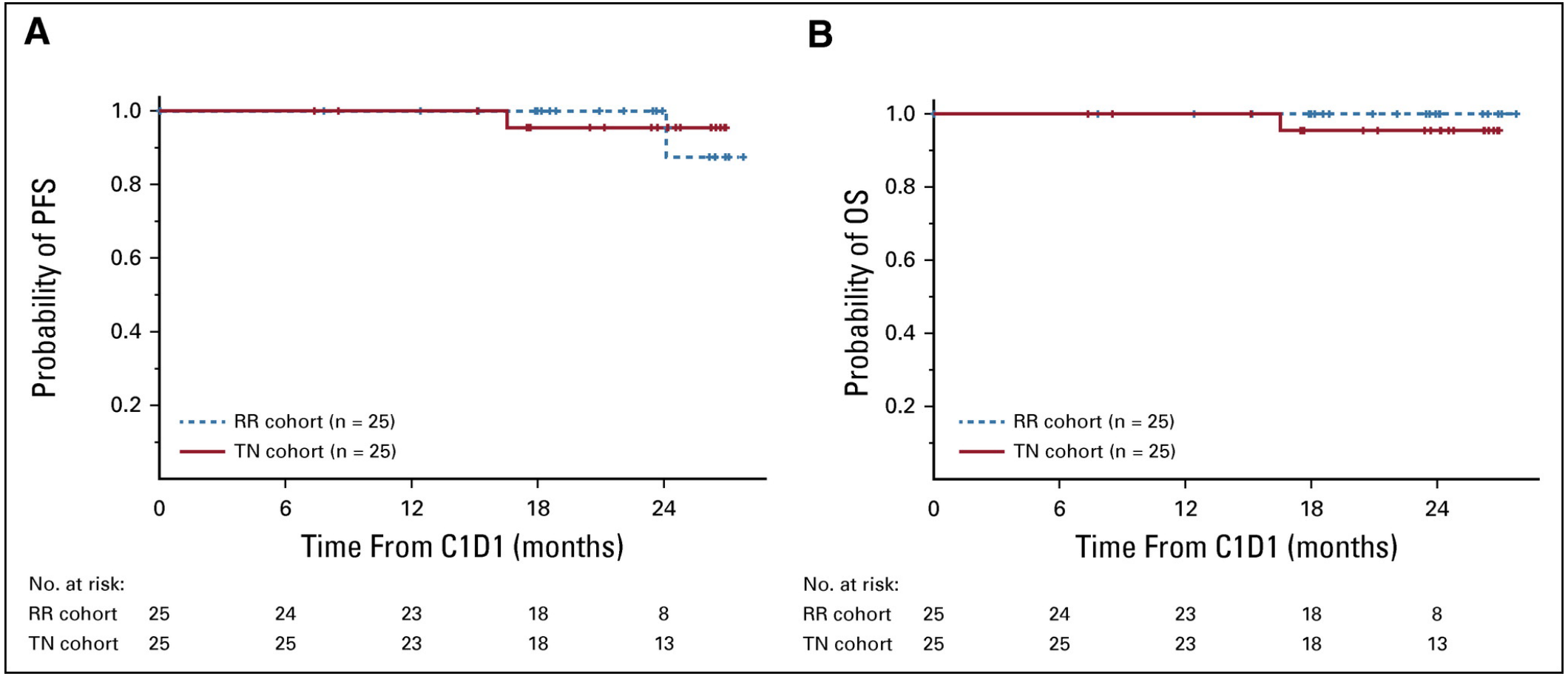
Phase 3 GLOW Study: superior PFS with Ibr+Ven vs Clb+O in older patients



- **With median follow-up of 34.1 months:**
  - Overall survival HR 0.76 (95% CI, 0.35-1.64)
    - 11 deaths for Ibr+Ven vs 16 for Clb+O
    - 4 on treatment deaths due to CV complications in IV arm

Munir T. et al. Presented at: 2021 ASH Annual Meeting and Exposition; December 11-14, 2021; Atlanta, GA. Abstract 70.

Triplet therapy with IVO is active but ibrutinib-related toxicities are observed

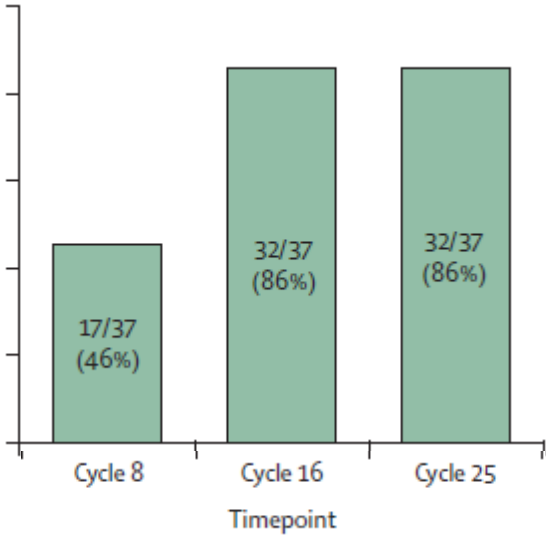


Rogers et al., J Clin Oncol, 2020

Triplets with more specific BTKi are also active and have excellent tolerability

Phase 2 AVO Trial

BM MRD Response



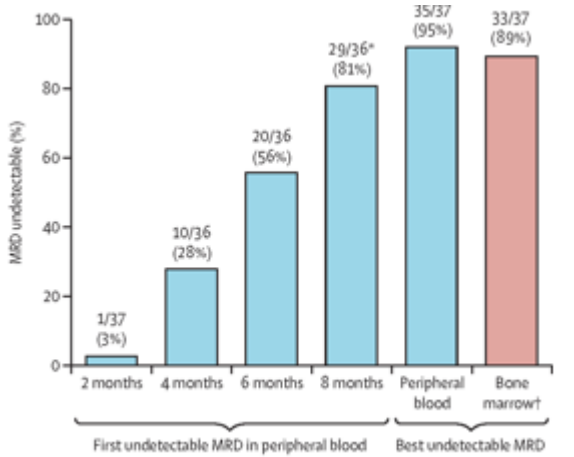
Safety profile

AEs (N=37), %		All Grades	Grade ≥3
Most frequent hematologic	Neutropenia	84	43
	Thrombocytopenia	81	27
	Anemia	59	5
Non-hematologic (≥50%)	Fatigue	89	3
	Headache	76	3
	Bruising	59	0
AEs of special interest	IRR	25	3
	Hypertension	11	0
	Atrial fibrillation	3	3
	Laboratory TLS	5	5

Davids MS, et al. *Lancet Oncol*. 2021.

Phase 2 BOVen Trial

MRD Response



Safety profile

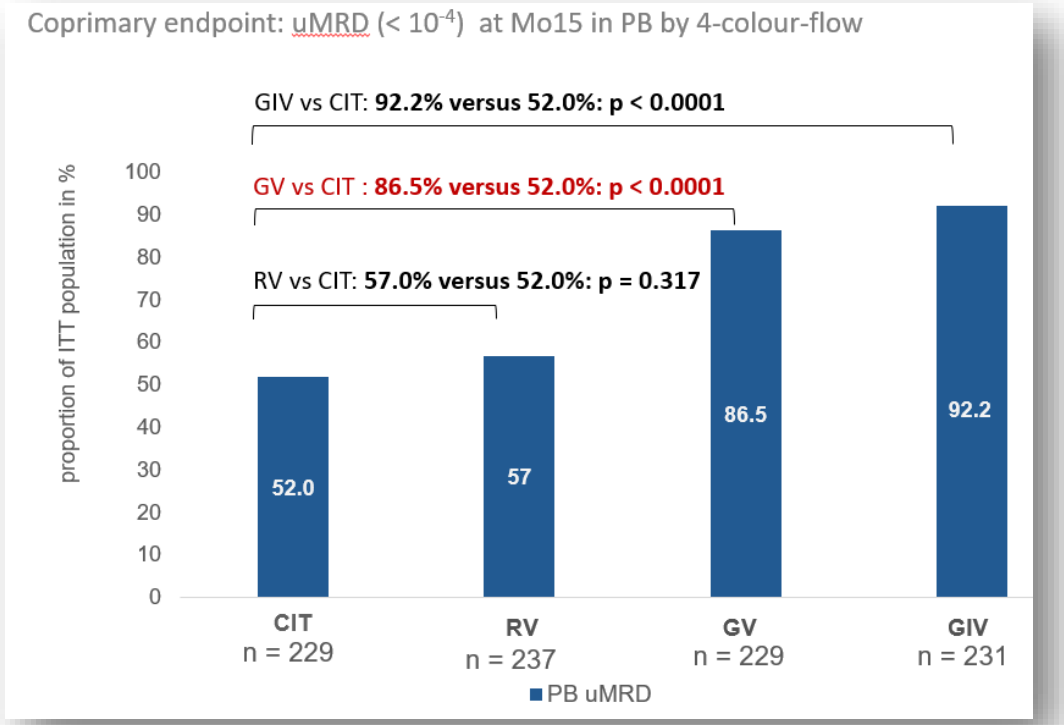
	Grade 1–2	Grade 3	Grade 4
Thrombocytopenia	20 (51%)	3 (8%)	0
Fatigue	20 (51%)	1 (3%)	0
Neutropenia	13 (33%)	2 (5%)	5 (13%)
Bruising	20 (51%)	0	0
Diarrhoea	18 (46%)	0	0
Infusion-related reaction	15 (39%)	1 (3%)	1 (3%)
Anaemia	16 (41%)	0	0
Cough	14 (36%)	0	0
Rash	10 (26%)	3 (8%)	0
Nausea	12 (31%)	0	0
Constipation	11 (28%)	0	0
Nasal congestion	10 (26%)	0	0
Gastroesophageal reflux disease	10 (26%)	0	0
Insomnia	9 (23%)	0	0
Myalgia	9 (23%)	0	0
Arthralgia	8 (21%)	0	0

Soumerai, JD, et al. *Lancet Haem*, 2021

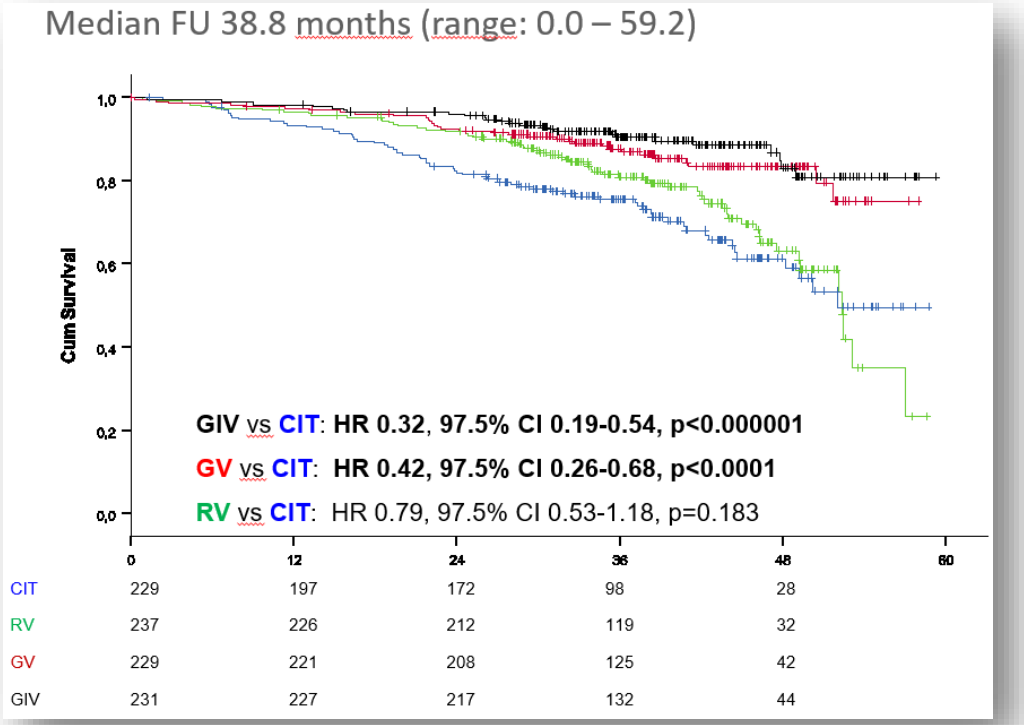
How do triplet combos compare to doublets?

CLL13

MRD



PFS



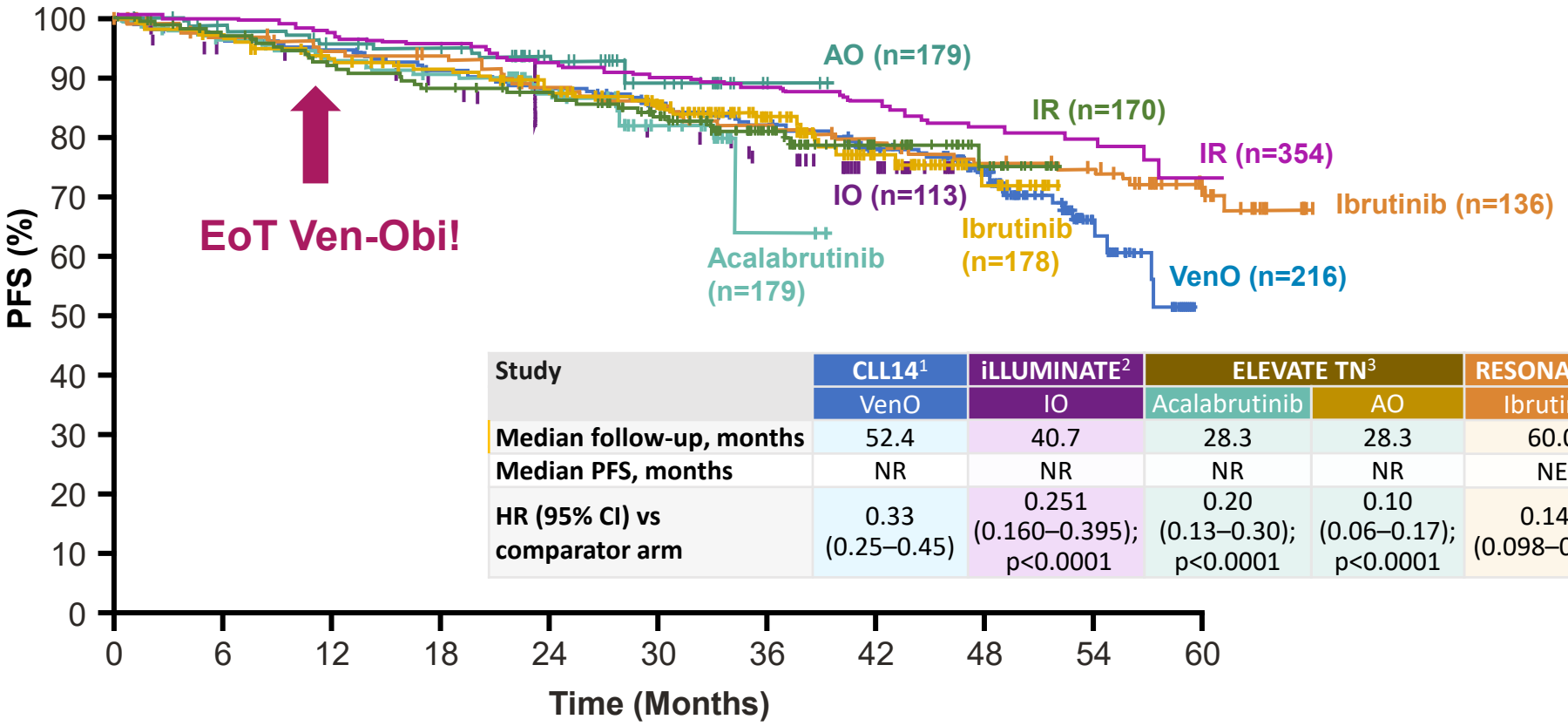
Ongoing ECOG and ALLIANCE studies are comparing IVO to IO

PFS	Median months	3y PFS (%)
CIT	52.0	75.5
RV	52.3	80.8
GV	Not reached	87.7
GIV	Not reached	90.5

Eichhorst B, et al. ASH 2021

Eichhorst B, et al. EHA 2022

Where do we go from here for frontline CLL treatment?



Study	CLL14[1]	iLLUMINATE[2]	ELEVATE TN[3]		RESONATE-2[4]	Alliance 202[5]		ECOG 1912[6]
	VenO	IO	Acalabrutinib	AO	Ibrutinib	Ibrutinib	IR	IR
Median follow-up, months	52.4	40.7	28.3	28.3	60.0	38.0	38.0	48.0
Median PFS, months	NR	NR	NR	NR	NE	NR	NR	-
HR (95% CI) vs comparator arm	0.33 (0.25–0.45)	0.251 (0.160–0.395); p<0.0001	0.20 (0.13–0.30); p<0.0001	0.10 (0.06–0.17); p<0.0001	0.146 (0.098–0.218)	0.39 (0.26–0.58); p<0.001	0.38 (0.25–0.59); p<0.001	0.39 (0.26–0.57); p<0.0001

1. Al-Sawaf O, *et al.* ASH 2020; oral presentation 127; 2. Moreno C, *et al.* iwCLL 2019; poster presentation 2069;
3. Sharman JP, *et al. Lancet* 2020; **396:**1278–1291; 4. Burger JA, *et al. Leukemia* 2020; **34:**787–798;
5. Woyach JA, *et al. N Engl J Med* 2018; **379:**2517–2528; 6. Shanafelt TD, *et al.* ASH 2019; oral presentation 33.

(Slide adapted from O. Al-Sawaf)

The CLL17 trial is comparing continuous BTKi to time-limited venetoclax-based doublets

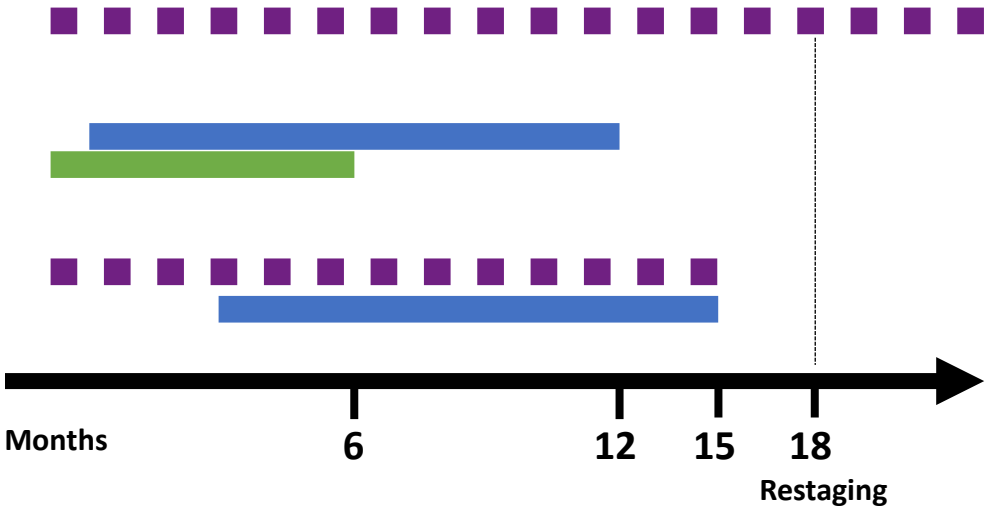
CLL17[1,2]

Phase 3 trial in 1L CLL, including those with adverse prognostic factors

- Ibr mono
- Ven + Obin
- Ven + I

Stratification by fitness, del(17p)/*TP53*^{mut}, IGHV

RANDOMIZATION[2]



Ibrutinib D1 420 mg PO daily until PD or intolerance

Venetoclax 400 mg PO daily (C1 D22 – C12 D28)
Obinutuzumab 1000 mg IV (C1 D1(2)/8/15, C2–6 D1)

Ibrutinib 420 mg PO daily (C1 D1 – C15 D28)
Venetoclax 400 mg PO daily (C4 D1 – C15 D28)

1. ClinicalTrials.gov. NCT04608318. Available at: https://www.clinicaltrials.gov/ct2/show/NCT04608318 (accessed August 2021);
2. DCLLSG. CLL17 Trial. Available at: https://www.dcllsg.de/en/trial/cll17/CLL17_Synopsis_v1.2_20200923.pdf (accessed August 2021)

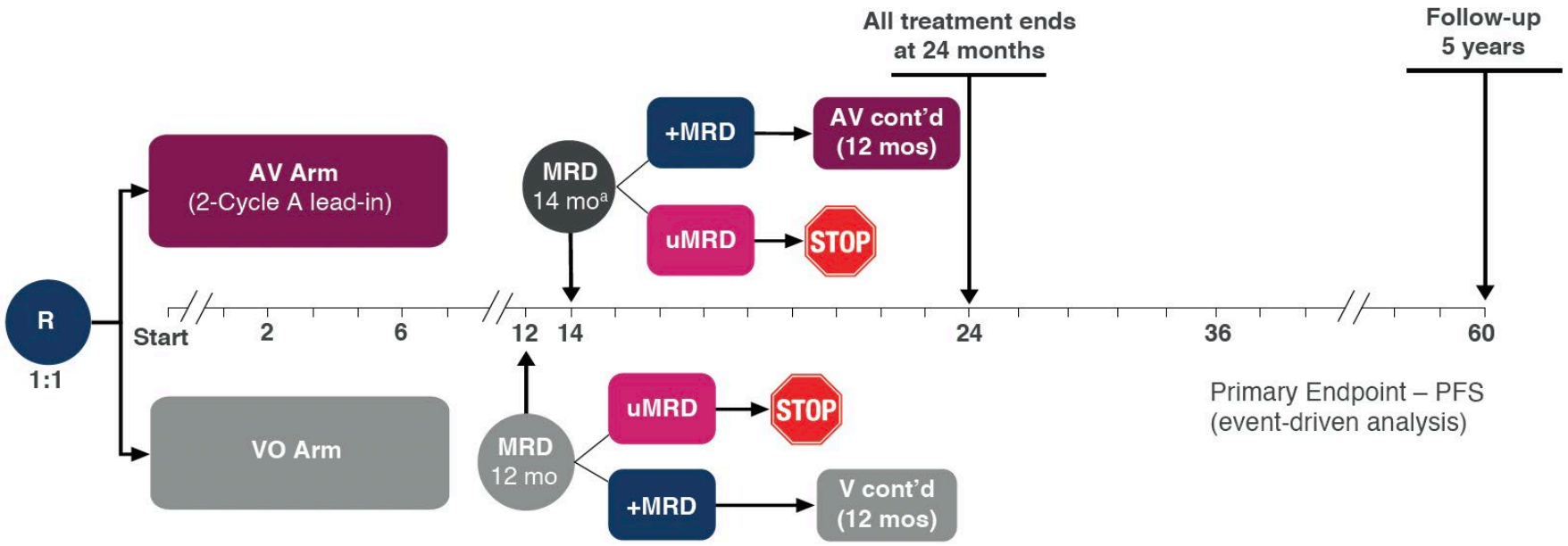
The global MAJIC phase 3 study seeks to define the optimal MRD-guided venetoclax doublet for frontline CLL treatment

- N=~750 patients to be recruited
- Global study with ~40 sites
- FPI: Sept 2022

Key Eligibility Criteria

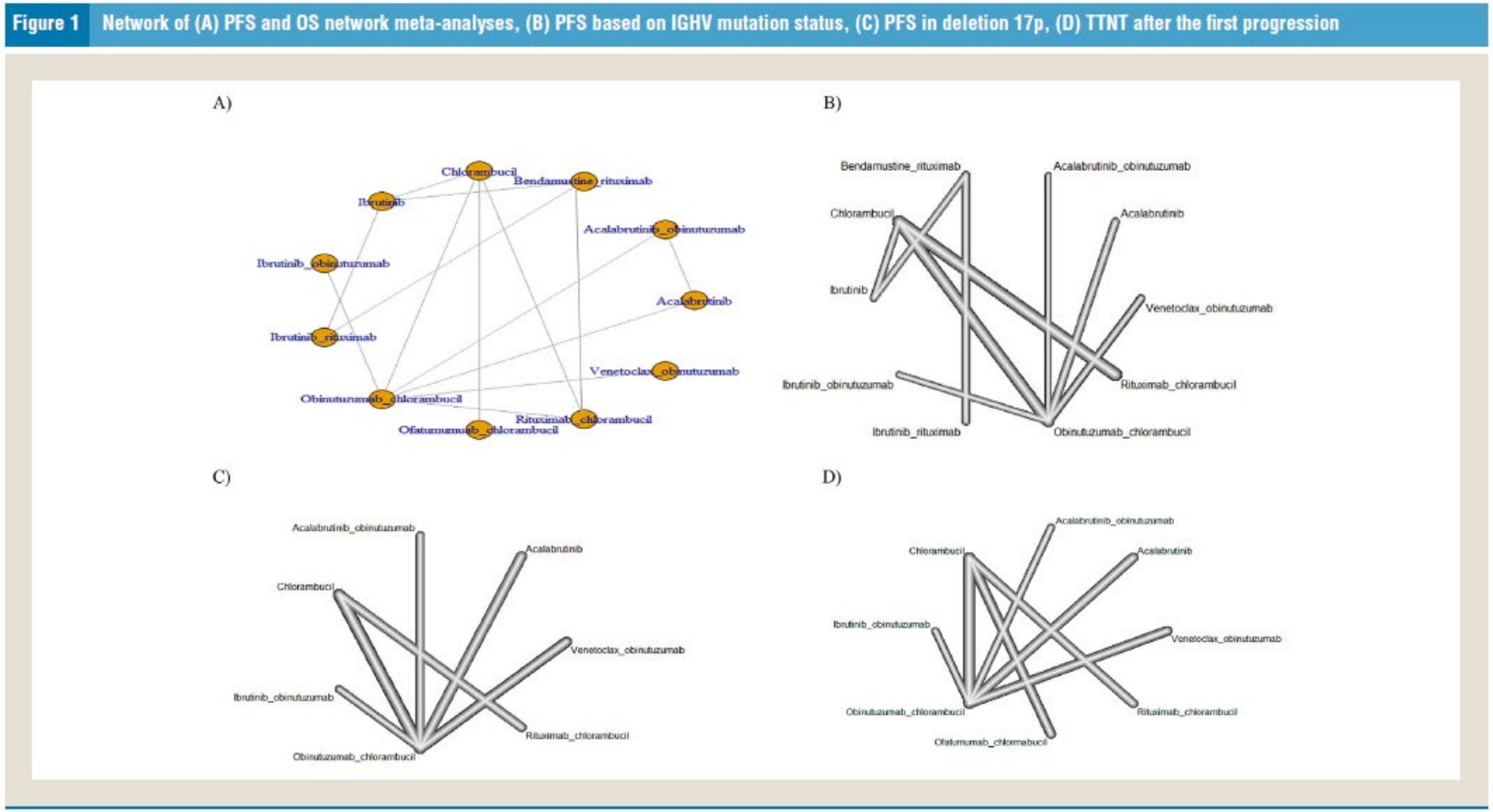
- TN CLL/SLL requiring treatment per 2018 iwCLL guidelines
- ECOG PS 0-2
- Anti-thrombotic agents permitted except for warfarin or equivalent vitamin K antagonists

Primary endpoint: INV-assessed PFS



Davids et al., ASH, 2021. Abstract 1553

Comparative Efficacy of First-Line Treatments of CLL: Network Meta-Analyses of Survival Curves



- **NMA on the Kaplan-Meier curves of 8 trials (11 treatments) to look at PFS, TTNT, OS with 5-year follow-up**

Alrawashdh et al., Clin Lymph, Myel, Leuk, 2021

Comparative Efficacy of First-Line Treatments of CLL: Network Meta-Analyses of Survival Curves

Figure 2 (A) Progression-free survival proportions over 5-years of follow-up as obtained from the fixed lognormal network meta-analysis, (B) HRs of progression or death for each treatment compared with Ibrutinib over time as obtained from as obtained from the fixed lognormal network meta-analysis
Note: Ibrutinib and ibrutinib-plus-rituximab curves are overlapped.

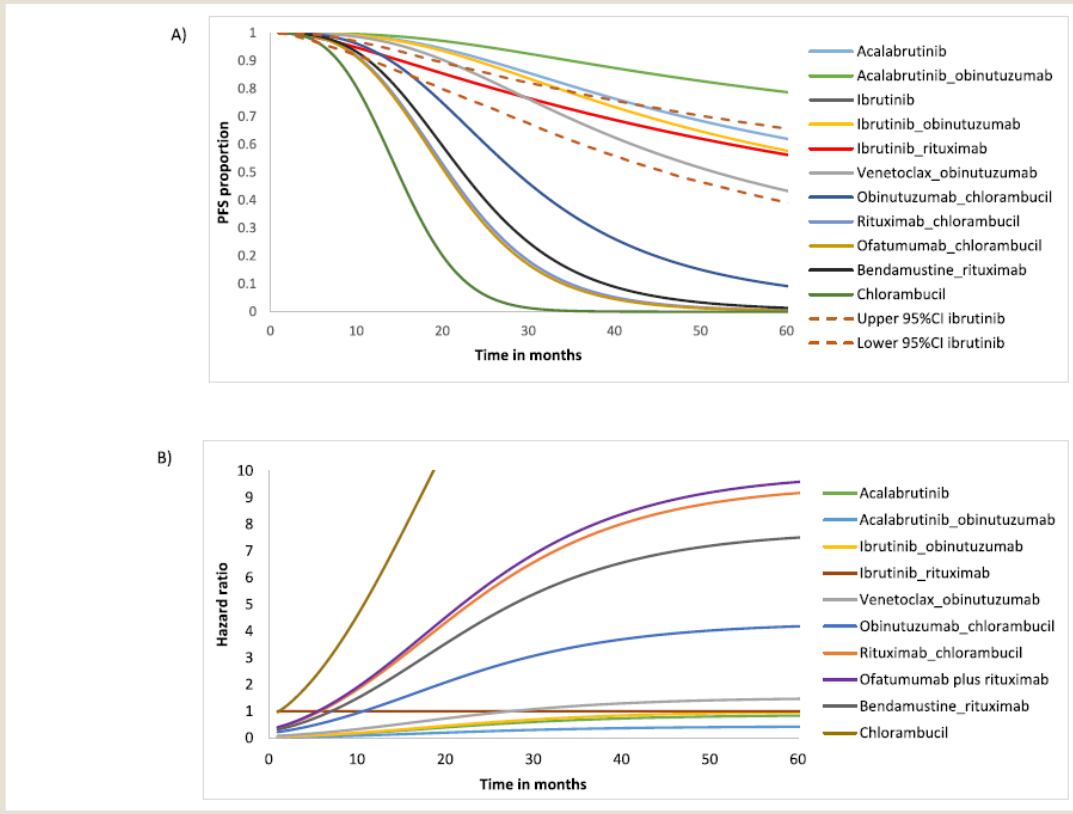


Table 2 Estimated Median Progression-Free Survival as Obtained From the Fitted Fixed Lognormal Model in the Net-Work Meta-Analysis

Treatment	Median PFS in months (95% CrI)
Acalabrutinib	87 (46.0-NR)
Acalabrutinib-plus-obinutuzumab	NR (70.0-NR)
Bendamustine-plus-rituximab	24.4 (13.1–37.0)
Chlorambucil	14.6 (9.1–20.0)
Ibrutinib	73 (46-NR)
Ibrutinib-plus-obinutuzumab	75 (41.0-NR)
Ibrutinib-plus-rituximab	75 (25-NR)
Obinutuzumab-plus-chlorambucil	28.5 (26.3–35.7)
Ofatumumab-plus-chlorambucil	20.5 (14.1–26.0)
Rituximab-plus-chlorambucil	20.6 (15.2–27.4)
Venetoclax-plus-obinutuzumab	51.8 (35.0- NR)

Abbreviations: NR = not reached; PFS = progression free survival.

- **Acala-obin associated with superior 5-yr PFS over ibrutinib, which was superior to other regimens**
- **Marked 5-yr OS for many regimens but no difference ascertained**

Alrawashdh et al., Clin Lymph, Myel, Leuk, 2021

Relapsed/Refractory CLL

Phase 3 RESONATE: Ibrutinib is Superior to Ofatumumab in R/R CLL

CLL/SLL diagnosis

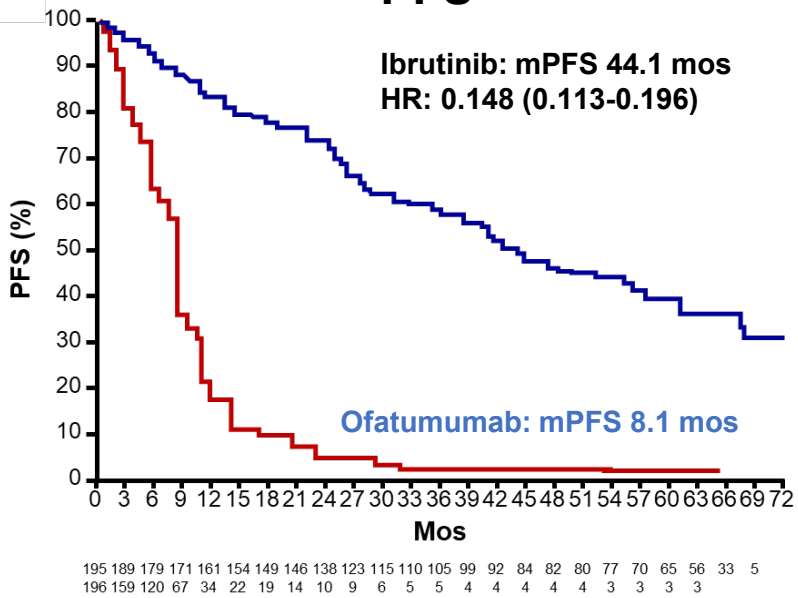
N=391

- ≥ 1 prior therapy
- ECOG PS 0-1
- Measurable nodal disease by CT

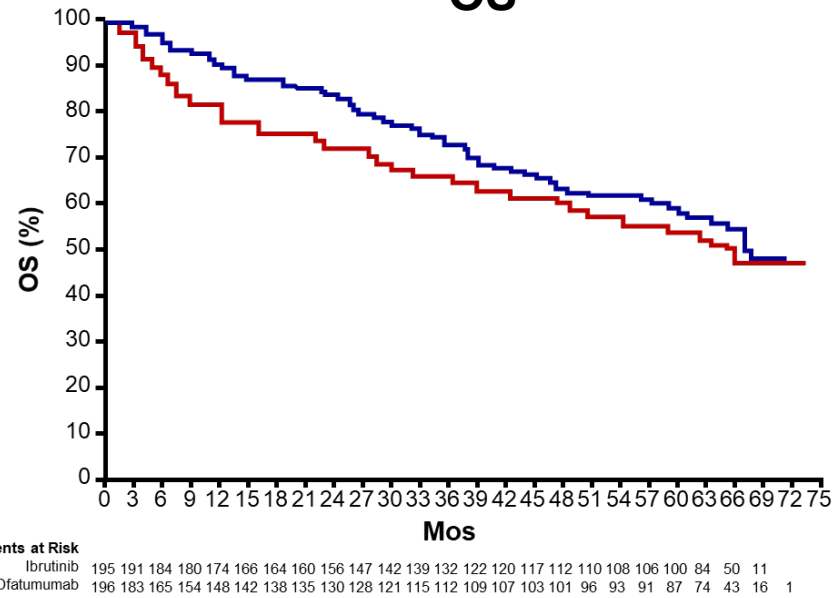
→ **Ibrutinib** QD

→ **Ofatumumab** (300 mg followed by 2000 mg x 11 doses for 24 wks)

PFS



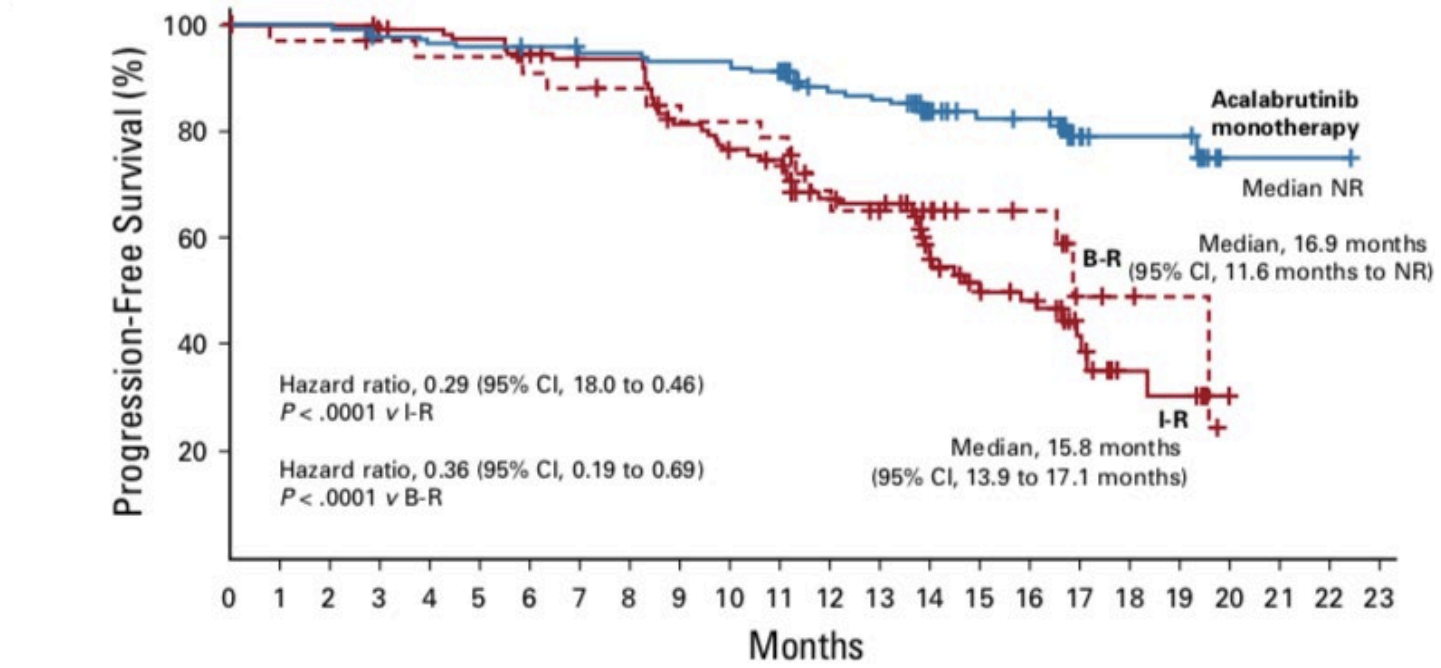
OS



- Median follow-up 65.3 months
- Long-term treatment with ibrutinib is tolerable and continues to show sustained PFS and OS regardless of high-risk cytogenetics

Munir, et al. *Am J Hematol*. 2019;94(12):1353-1363.

Phase 3 ASCEND: IRC-Assessed PFS superior for acalabrutinib vs Idela-R or B-R



No. at risk (censored)

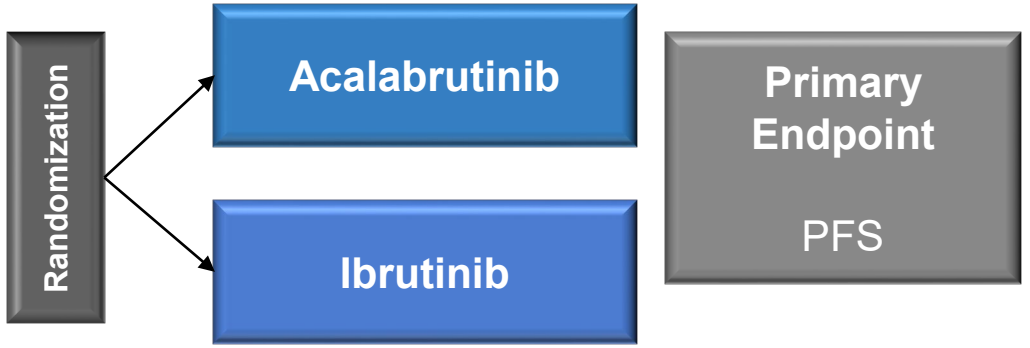
Acalabrutinib monotherapy	155	153	153	149	147	146	145	143	143	139	139	137	118	116	73	61	60	25	21	21	1	1	1	0
	(0)	(2)	(2)	(3)	(3)	(3)	(4)	(5)	(5)	(5)	(5)	(5)	(19)	(19)	(59)	(70)	(71)	(104)	(108)	(108)	(127)	(127)	(127)	(128)
I-R	119	116	116	113	112	110	105	100	100	85	79	76	62	59	41	33	29	14	7	6	0			
	(0)	(3)	(3)	(5)	(6)	(6)	(8)	(12)	(12)	(14)	(15)	(16)	(23)	(25)	(36)	(40)	(42)	(54)	(59)	(59)	(65)			
B-R	36	34	34	33	32	32	31	30	29	27	26	25	20	18	15	11	10	4	3	2	0			
	(0)	(1)	(1)	(2)	(2)	(2)	(2)	(2)	(3)	(4)	(4)	(4)	(6)	(7)	(10)	(14)	(15)	(19)	(20)	(21)	(22)			

Ghia P, et al. *J Clin Oncol.* 2020 May 27. [Epub ahead of print]

Phase 3 ELEVATE-R/R: Acalabrutinib vs Ibrutinib in R/R High-risk CLL

R/R High-risk CLL
N=533

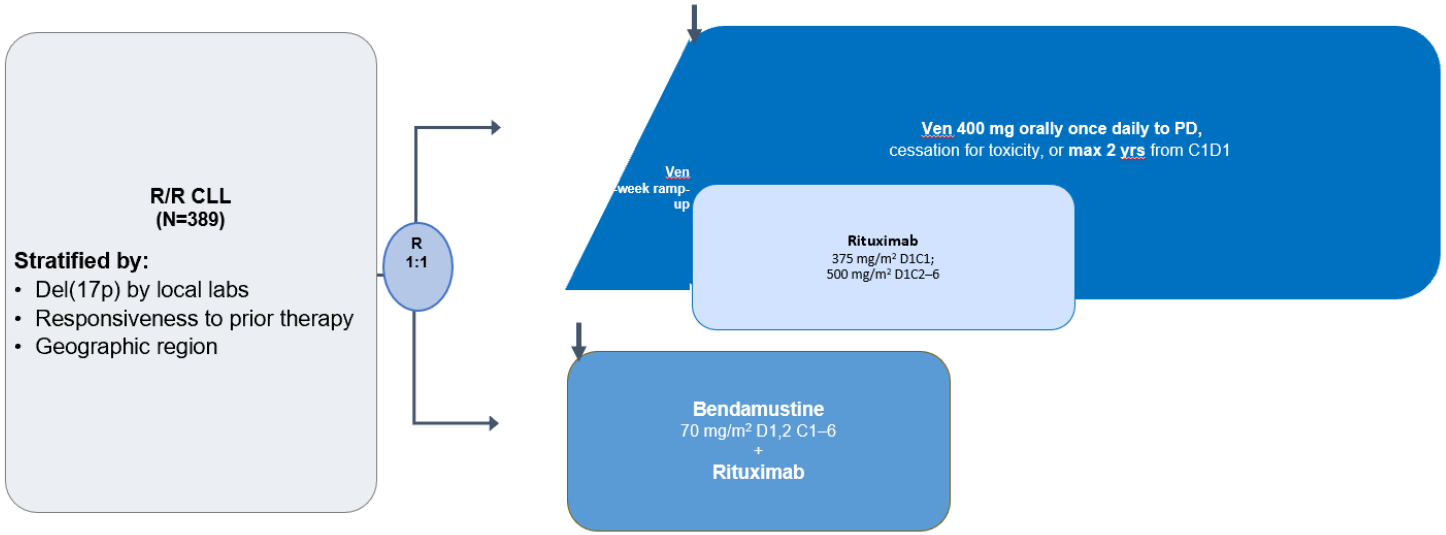
- ≥ 1 prior therapies for CLL
- ECOG of 0-2; Active disease meeting ≥1 of the IWCLL 2008 criteria for requiring treatment; Must have ≥ 1 high-risk prognostic factors (17p del and/or 11q del by central laboratory)
- No prior exposure to ibrutinib or to a BCR inhibitor or a BCL-2 inhibitor

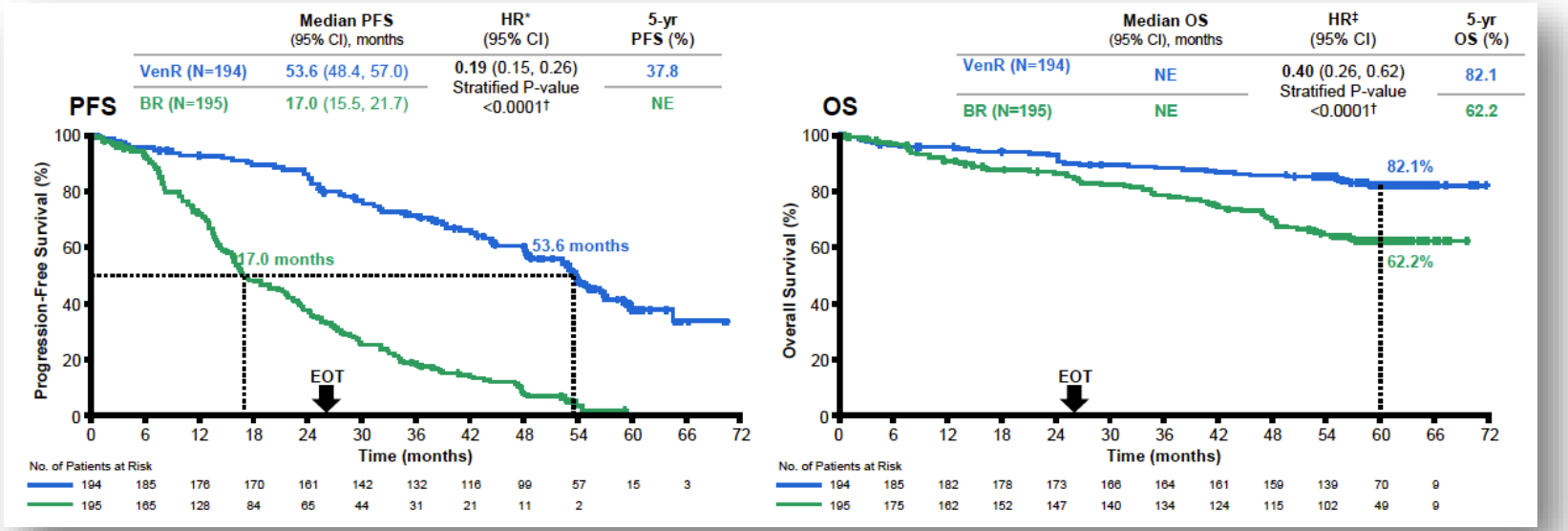


- **Key Points:**
  - **Acalabrutinib demonstrated noninferiority to ibrutinib** (PFS)
    - At a median follow-up of 40.9 months (range, 0.0-59.1), the mPFS was 38.4 months for both acalabrutinib and ibrutinib (HR, 1.00; 95% CI, 0.79-1.27).
  - Incidence of any-grade atrial fibrillation was significantly lower with acalabrutinib vs ibrutinib, at rates of 9.4% vs 16%, respectively.
  - Overall, AEs led to treatment discontinuation in 14.7% of acalabrutinib-treated pts vs 21.3% of ibrutinib-treated pts

Byrd, et al. *J Clin Oncol.* 2021; 39 (suppl 15; abstr 7500)

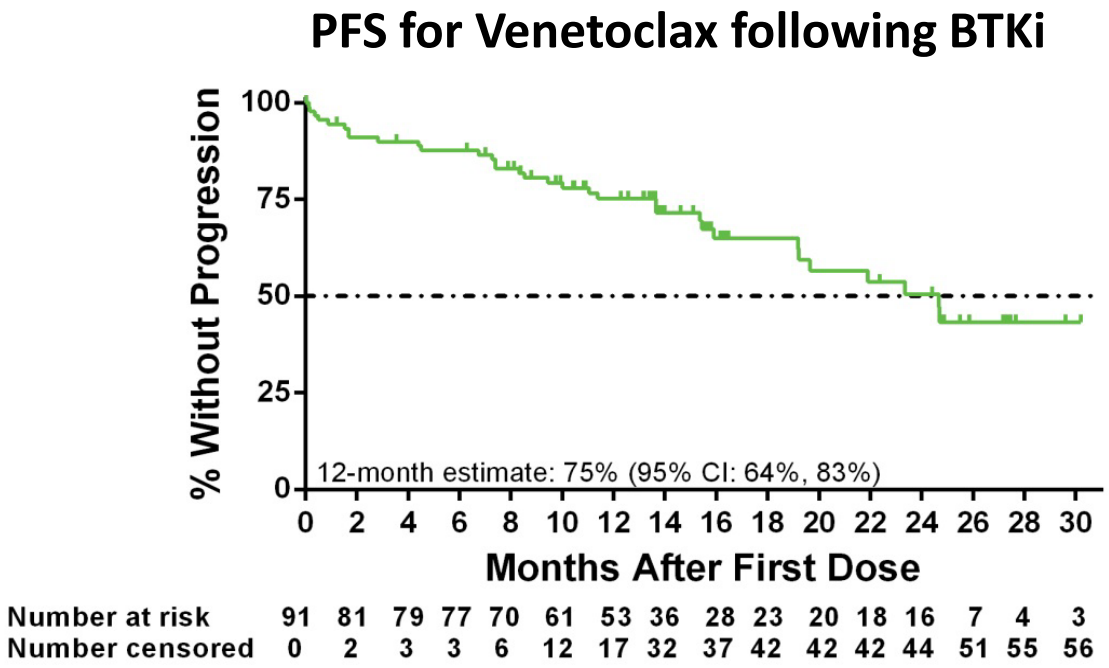
5-Year Analysis from the Phase 3 MURANO study of VenR vs. BR in R/R CLL





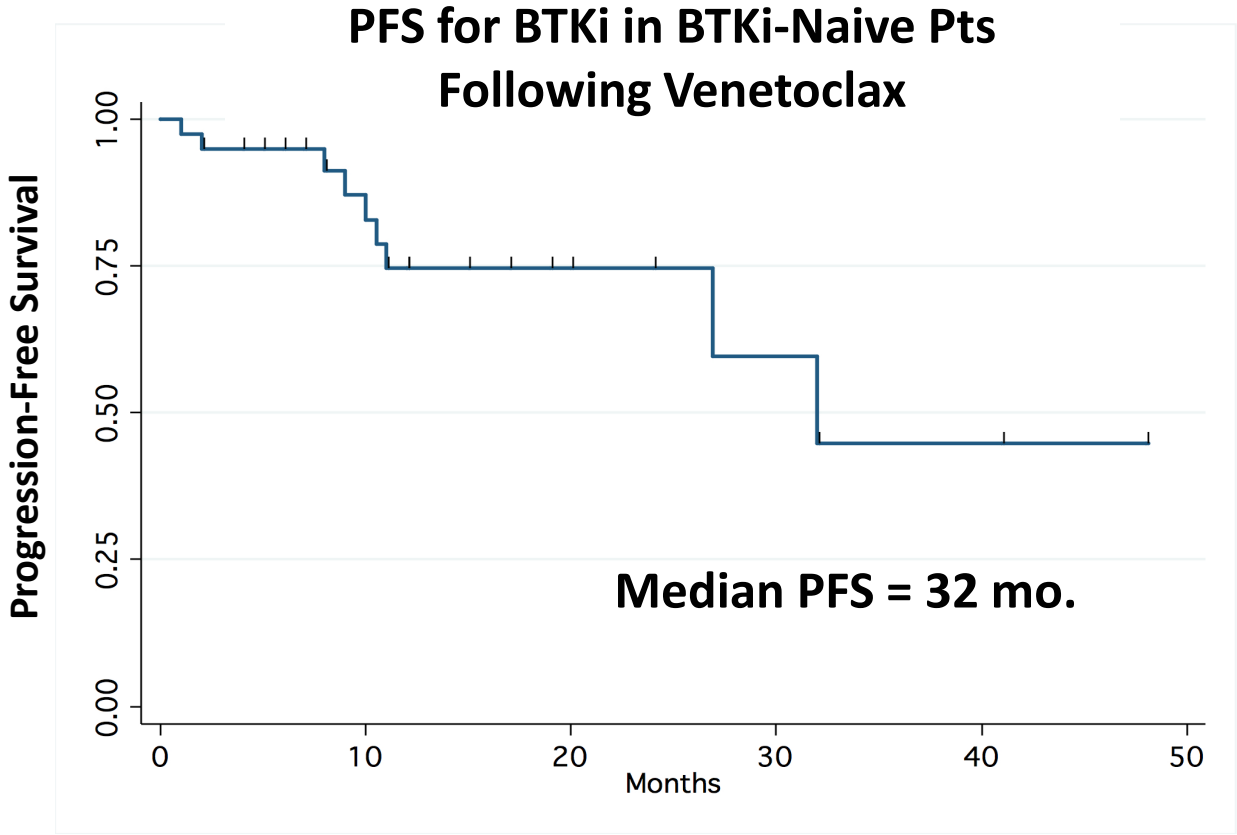
Kater AP, et al. ASH 2020. Abstract 125.

Either sequence of BTKi -> Ven or Ven -> BTKi can be effective



- Ven ORR: 65%, CR/CRi rate: 9%

Jones et al., *Lancet Oncol*, 2018

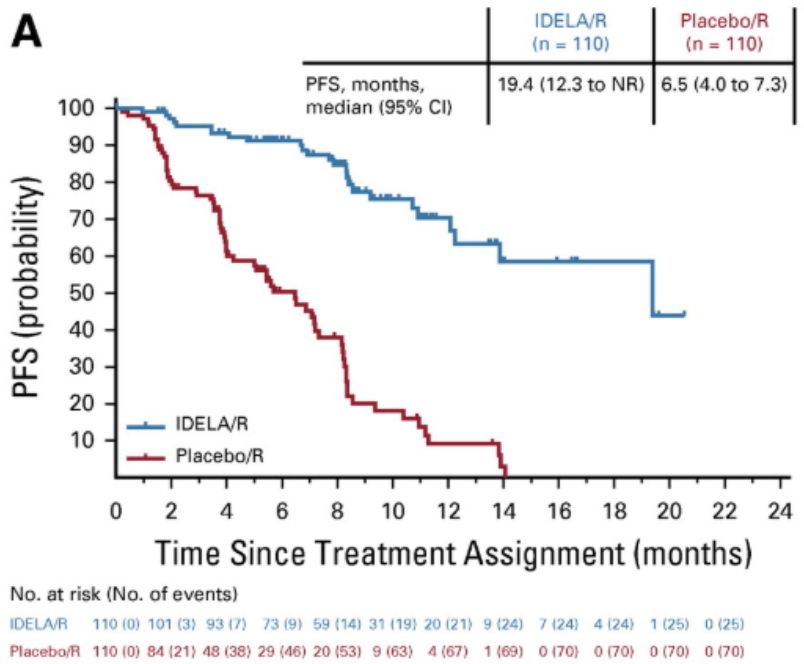


- BTKi ORR: 84% (n = 44) in BTKi-naïve pts vs 54% (n = 30) in BTKi-exposed pts

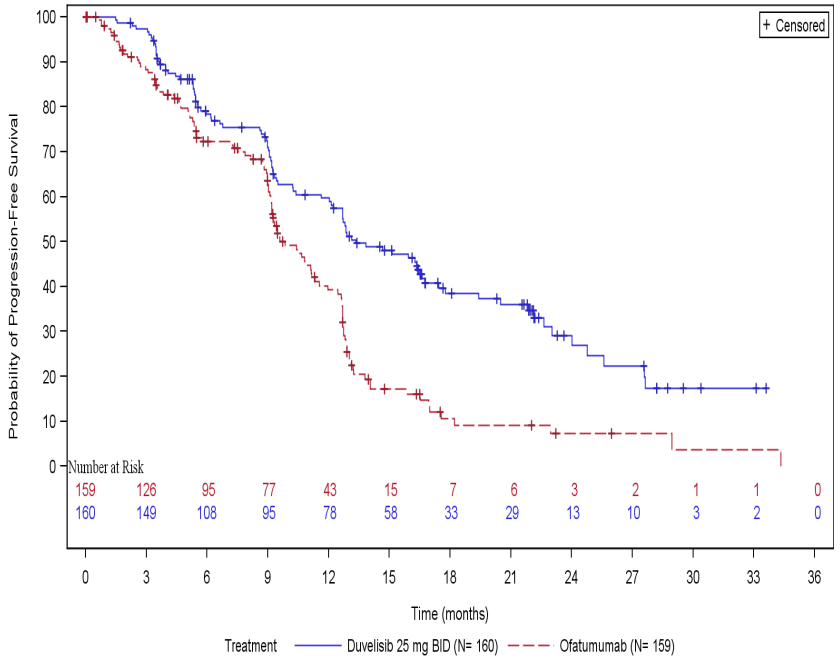
Mato AR, et al. *Clin Cancer Res*. 2020 Mar 20. [Epub ahead of print]

PI3Ki are also efficacious, with manageable toxicity profiles

Idelalisib + Rituximab



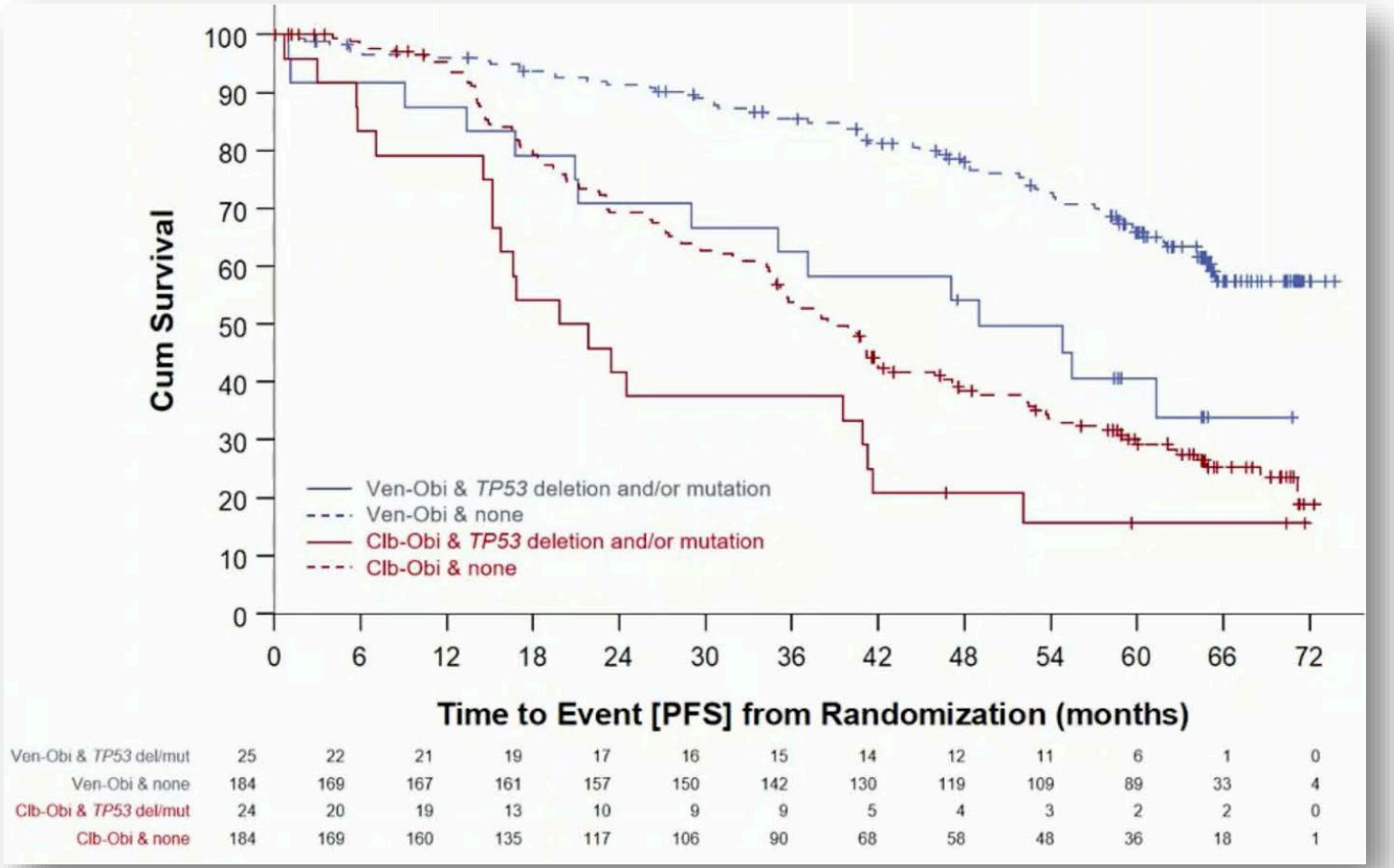
Duvelisib



- **Immune-mediated toxicities: transaminitis, diarrhea/colitis, pneumonitis plus infection**

What are the unmet needs now in CLL?

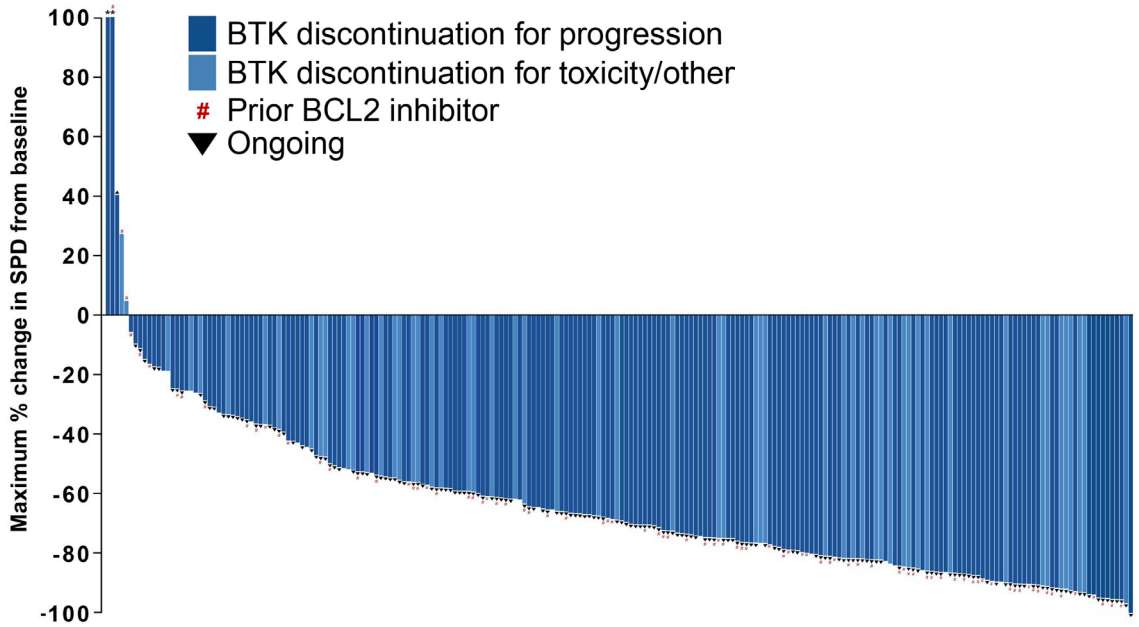
Time-limited therapy for patients with *TP53* aberrant CLL



Al-Sawaf O, et al. EHA 2022. Abstract S148.

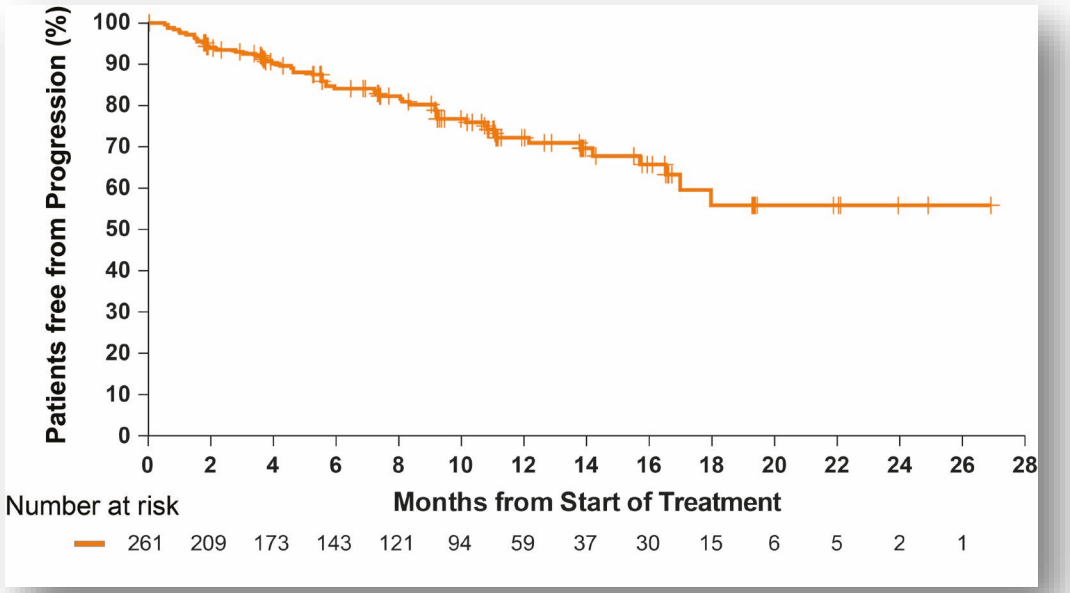
BTKi/BCL-2i Double-Refractory Patients

BRUIN Phase 1/2 Trial of Pirtobrutinib in R/R CLL/SLL



Efficacy evaluable BTK pre-treated CLL/SLL Patients	n = 252
Overall Response Rate, % (95% CI)	**68 (62 – 74)**
Best response	
CR, n (%)	2 (1)
PR, n (%)	137 (54)
PR-L, n (%)	32 (13)
SD, n (%)	62 (25)

PFS in at least BTK pre-treated patients



Median follow-up 9.4 months

Median PFS: Not Estimable (95% CI: 17.0 months – NE)

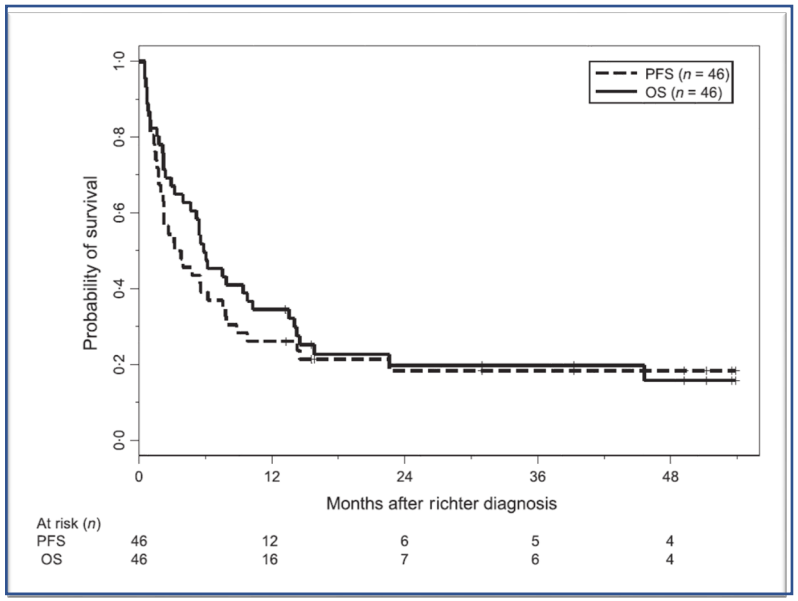
- **No DLTs reported and MTD not reached**
- **1% (n=6) of patients permanently discontinued due to treatment-related AEs**

Mato AR, et al. ASH 2021:Abstract 391.

Richter's syndrome

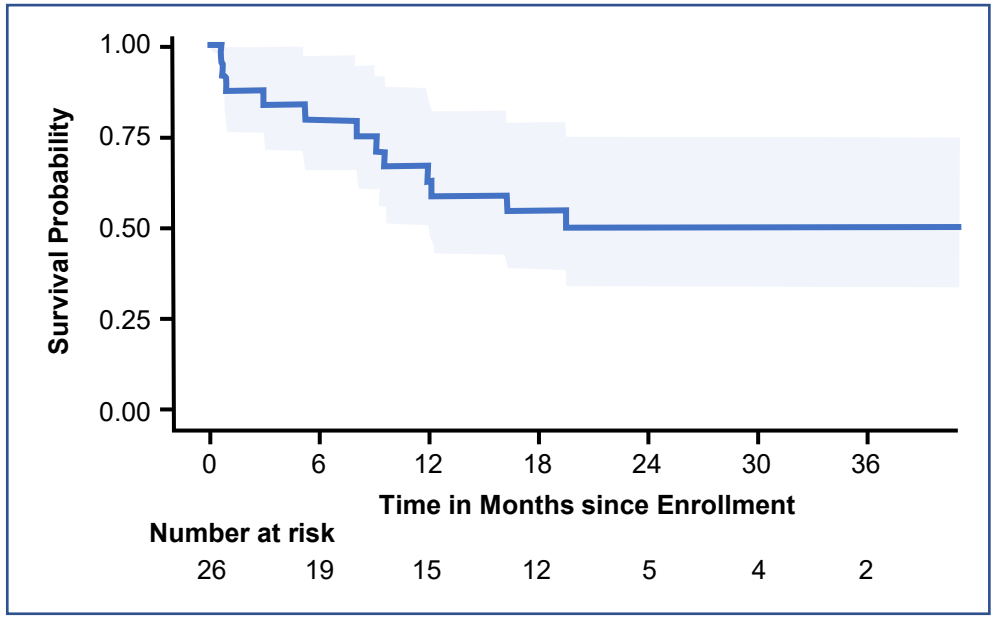
- **Historically median OS is only in the range of 6-12 mo**
- **CR with chemo alone is typically short-lived**
  - CR rates ~5%-20%, median OS ~6 mo.
- **Recent study adding venetoclax to R-EPOCH led to 50% CR rate, 19.6 mo. median OS**

R-EPOCH



Rogers et al. *Br J Haematol*. 2017

Venetoclax + R-EPOCH



Davids and Rogers et al. *Blood*. 2022

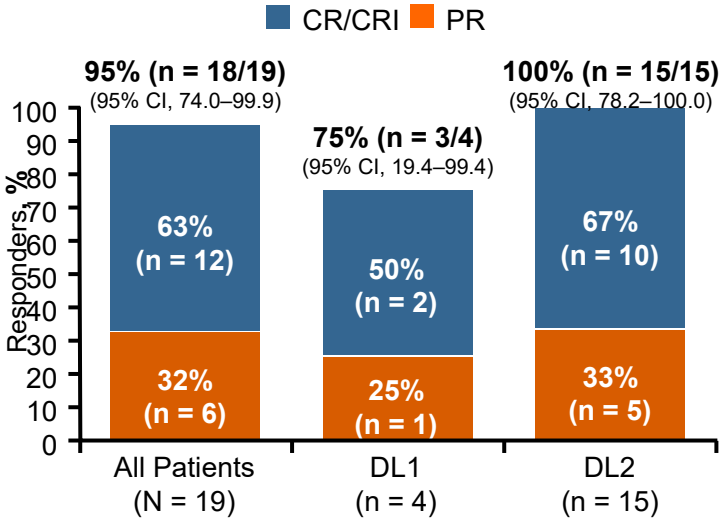
RIC allo-HSCT has curative potential in CLL but also serious risks

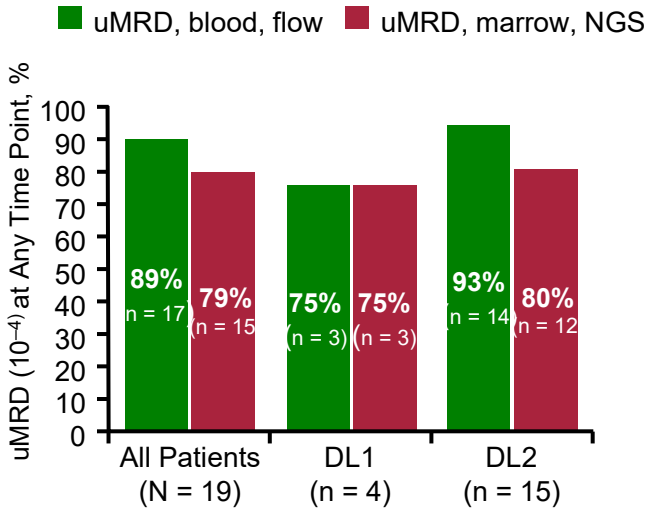
	Fred Hutchinson Cancer Center[38]	German CLL Study Group[41,45]	MD Anderson Cancer Center[40]	Dana Farber Cancer Institute[39]
Number of patients	82	90	86	76
Conditioning regimen	Flu/low-dose TBI	Flu/Cy ± ATG	Flu/Cy ± R	Flu/Bu
Donors, % (sibling/MUD)	63/37	41/59	50/50	37/63
Median follow-up, mo	60	72	37	61
Median PFS, %	39 (5 y)	38 (6 y)	36 (6 y)	43 (6 y)
Median OS, %	50 (5 y)	58 (6 y)	51 (6 y)	63 (6 y)
Early mortality, % (<100d)	<10	<3	<3	<3
NRM, %	23	23	17	16
Acute grade 3-4 GVHD, %	20	14	7	17
Severe chronic GVHD, %	53	55	56	48

ATG, antithymocyte globulin; Bu, busulfan; Cy, cyclophosphamide; Flu, fludarabine; MUD, matched unrelated donor; R, rituximab; TBI, total body irradiation.

Gribben J, *Blood*, 2017

CAR-T in CLL:
TRANSCEND CLL 004: Ph 1 Cohort of Liso-cel with Ibrutinib

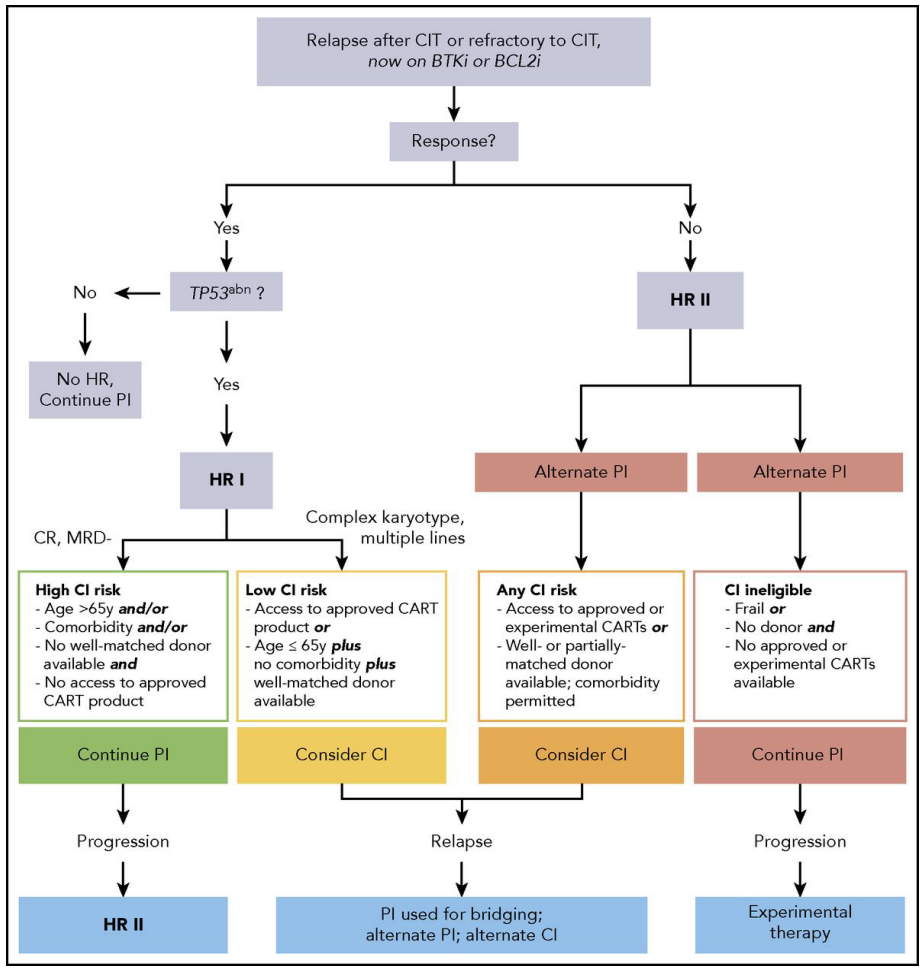




Cytokine release syndrome (CRS)	
All-grade CRS, n (%)	14 (74)
Median time to CRS onset, days (range)	6.5 (1–13)
Median duration of CRS, days (range)	6 (3–3)
Grade 3 CRS, n (%)	1 (5)
Neurological events (NEs)	
All-grade NEs, n (%)	6 (32)
Median time to NE onset, days (range)	8 (5–12)
Median duration of NE, days (range)	6.5 (1–8)
Grade 3 NEs, n (%)	3 (16)
Management of CRS and/or NEs, n (%)	
Tocilizumab only	2 (11)
Corticosteroids only	3 (16)
Tocilizumab and corticosteroids	3 (16)

Wierda, et al. ASH 2020:Abstract #544

Cellular Therapy in CLL: EBMT Guidelines



Refractoriness to	*TP53* abnormality present (del17p/*TP53*^{mut})	High risk Category
CIT only	yes	**I – CIT-resistant** *(BTKi- and BCL2i-sensitive)*
CIT + BTKi **or** CIT + BCL2i **or** BTKi + BCL2i (+/- CIT)	yes or no	**II – CIT- and PI-resistant** *(BTKi- and/or BCL2i-refractory)*

Dreger, et al. *Blood*, 2018

How have all of these new treatment approaches impacted survival?

Annals of Hematology (2021) 100:2501–2512
https://doi.org/10.1007/s00277-021-04600-1

ORIGINAL ARTICLE

Survival trends in chronic lymphocytic leukemia across treatment eras: US SEER database analysis (1985–2017)

Neda Alrawashdh[1,2] · Joann Sweasy[3] · Brian Erstad[4] · Ali McBride[4] · Daniel O. Persky[3,5] · Ivo Abraham[1,4]

Received: 30 March 2021 / Accepted: 4 July 2021 / Published online: 19 July 2021

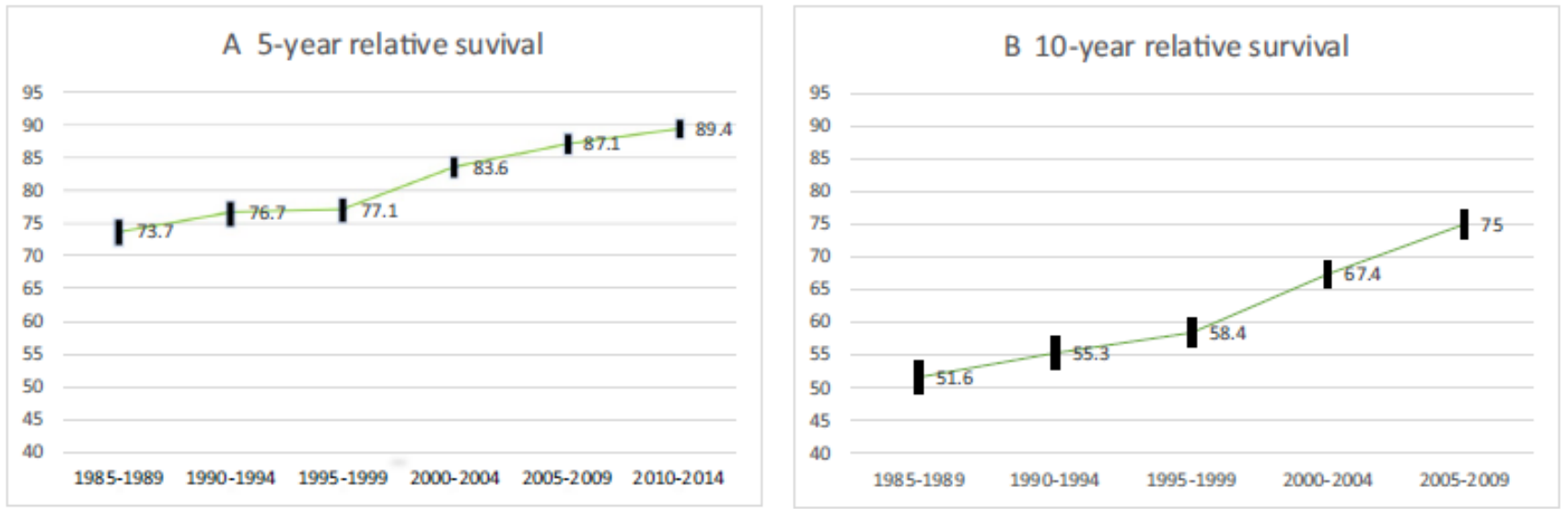


Fig. 1 Point estimates of **A** 5-year relative survival and **B** 10-year relative survival with 95%CI by year of disease diagnosis

Alrawashdh et al., *Annals of Hematology*, 2021

How have all of these new treatment approaches impacted survival?

Fig. 2 Relative survival curves for up to 120 months of follow-up for patients' cohorts diagnosed between 1985 and 1999 and 2000 and 2015

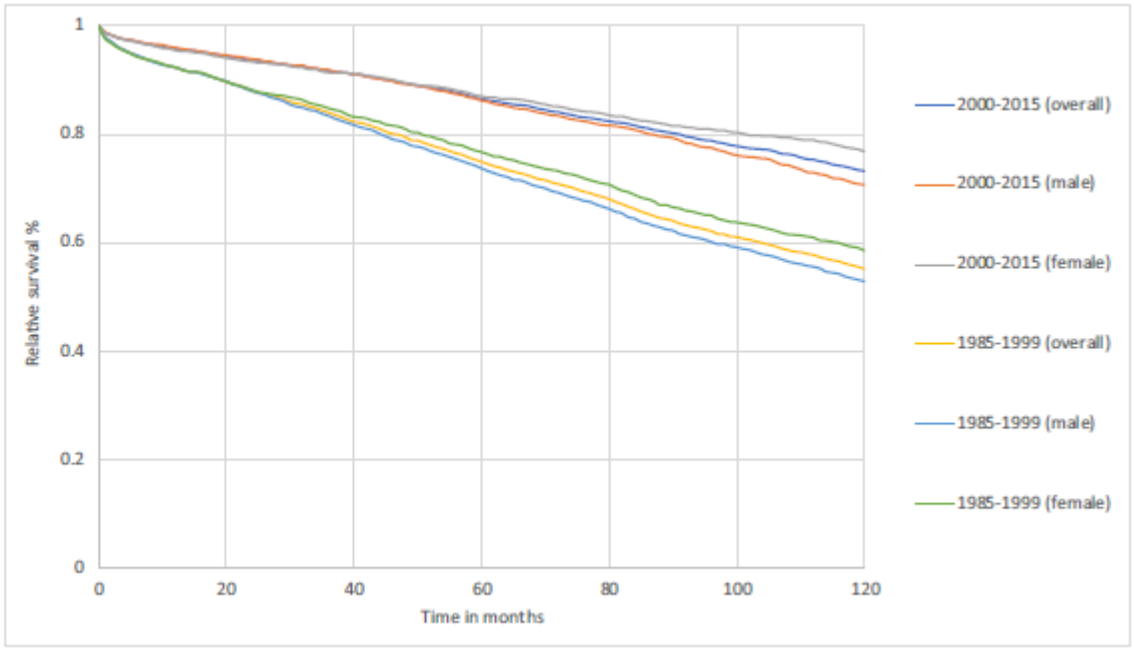


Table 4 Median survival time (months) outputs

Age category at diagnosis	Cohort 1 (diagnosed in 2000–2003)		Cohort 2 (diagnosed in 2004–2007)	
	N	Median (95%CI)	*N*	Median (95%CI)
45–54	492	155 (145–NR)	489	NR
55–64	884	154 (152–NR)	1181	NR
65–74	1156	136 (131–143)	1292	NR
75–84	1142	110 (105–119)	1267	NR
85 +	462	71 (60–85)	513	84 (68–93)

NR, not reached

- **Overall, relative survival improved significantly for CLL patients diagnosed between 1985 and 2015**
- **These improvements were markedly better following the introduction of targeted therapies**

Alrawashdh et al., *Annals of Hematology*, 2021

What will CLL treatment look like in the more distant future?

- *My personal prediction:* intermittent time-limited combo therapy will ultimately win over continuous BTKi mono, as the PFS will likely be similar, but the costs and toxicities will be less with combos

- *Future role for BTKi mono:* there will remain a place for this approach for certain patients (e.g. older patients seeking simplicity), particularly once generic BTKi eventually become available

- *Immune-based approaches:* may be integrated into the treatment paradigm (e.g. bispecific Abs, CAR-T, at least for younger fit patients, especially those with high-risk disease)

- *Much work still to be done*: we need to continue to accrue well to our studies, as there are still many aspects of CLL care that remain to be optimized

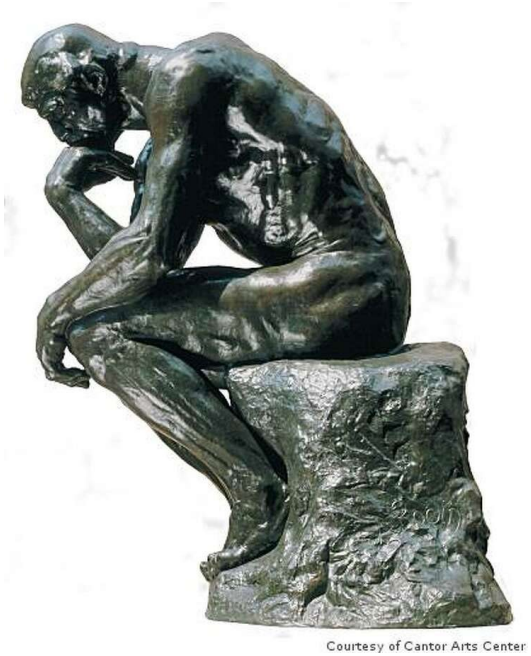
Dana-Farber Cancer Institute

Harvard Medical School

My Take-Home Messages on CLL in 2022

- Role of chemoimmunotherapy in CLL is increasingly limited
- Continuous novel agent monotherapy with BTKi is a highly effective approach
- 2nd-gen BTKi have similar efficacy, better tolerability than ibrutinib
- Ven + CD20 time-limited regimens also provide durable benefit
- Continuous vs time-limited therapy discussions should be individualized
- Ven + BTKi combo data (+/- CD20) are maturing, but not yet standard
- Unmet needs: Double-refractory (post BCL-2 and BTK), Richter's, *TP53* aberrant
- Novel combinations, 3rd-gen, reversible BTKi, and CAR-T are promising
- Overall survival has improved markedly, and will likely continue to improve

Questions?



Courtesy of Cantor Arts Center