September 10, 2022

19th Annual Indy Hematology Review™

ANNUAL STEVEN COUTRE CHRONIC LYMPHOCYTIC LEUKEMIA MEMORIAL LECTURE:

What Would Steve Do? Treatment of CLL in 2022

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Steven Coutre, who died Nov. 9, established a widely recognized research program at Stanford Medicine to understand and develop treatments for hematological disorders and malignancies.

Courtesy of the Coutre family

Disclosures:

- *Editor in Chief Seminars in Hematology, compensated by Elsevier*
- *Employee of the National Heart, Lung, and Blood Institute, NIH with research support from Pharmacyclics LLC, an Abbvie company; Acerta LLC, a member of the AstraZeneca Group; Merck; Nurix; Genmab; Verastem*

Drugs discussed that have non-FDA indications

Drugs discussed with non-FDA indications

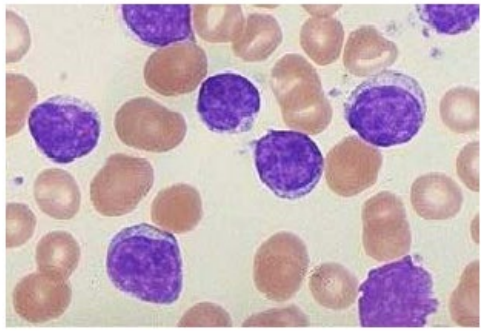
*Zanubrutinib
*Ofatumumab
*Pirtobrutinib

Drugs with FDA indications

- Acalabrutinib
- Ibrutinib
- Venetoclax
- Obinutuzumab
- Rituximab
- Chlorambucil
- Bendamustine
- Fludarabine
- Cyclophosphamide

Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma

Diagnosis



Flow cytometry: CD19+, CD5+, CD23+, weak surface Ig, dim CD20+
Morphology: typical >90% small mature looking lymphocytes

- **CLL:** Lymphocytosis, >5,000 clonal B-cells/μl
- **MBL:** <5,000 clonal B-cells/uL, no cytopenias
- **SLL:** nodal disease, <5,000 B-cells/uL in circulation

- **Not** necessary/recommended: bone marrow biopsy, **CT, PET**

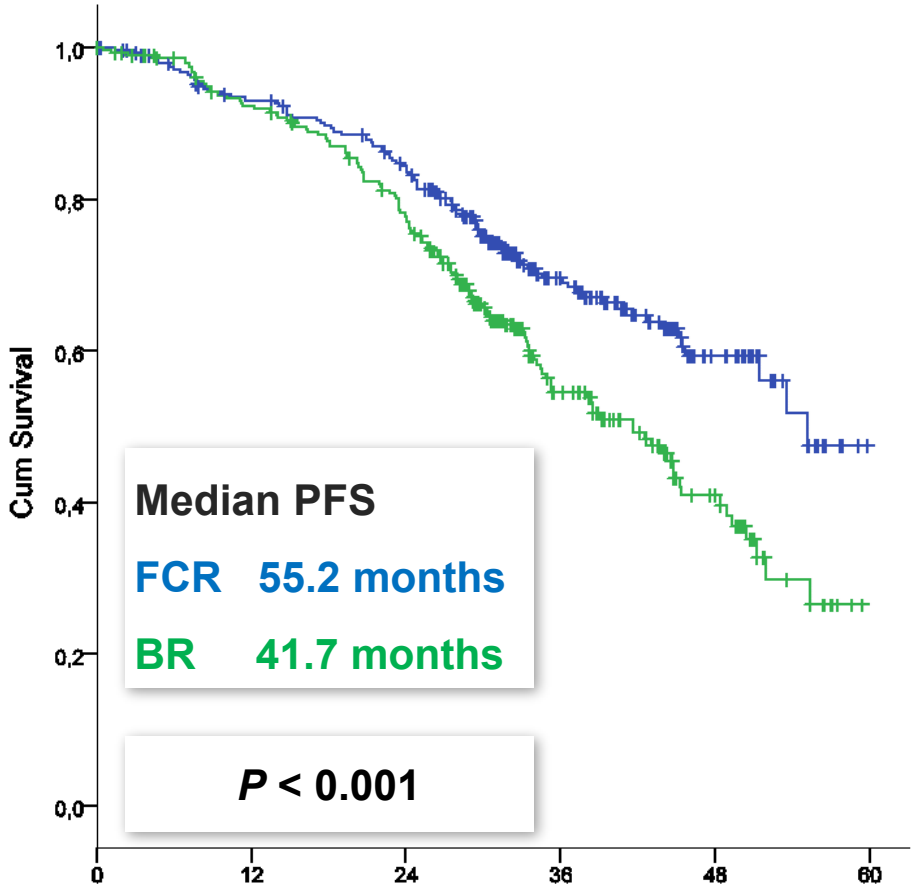
iwCLL guidelines
Hallek et al, Blood 2018

Prognostic markers

Clinical	Stage Lymphocyte doubling time
Genetic	**IGHV** mutational status **mutated = favorable** **FISH** Low risk: del 13q Intermediate risk: trisomy 12 High risk: **del 17p**, del 11q **Mutations** Favorable: MYD88 Unfavorable: **TP53,** NOTCH1, SF3B1, BIRC3, ATM
Flow cytometry	CD49d, CD38 positive = unfavorable
Serum	LDH, β2-microglobulin

Chemoimmunotherapy

FCR vs BR for fit patients (33-81 years)



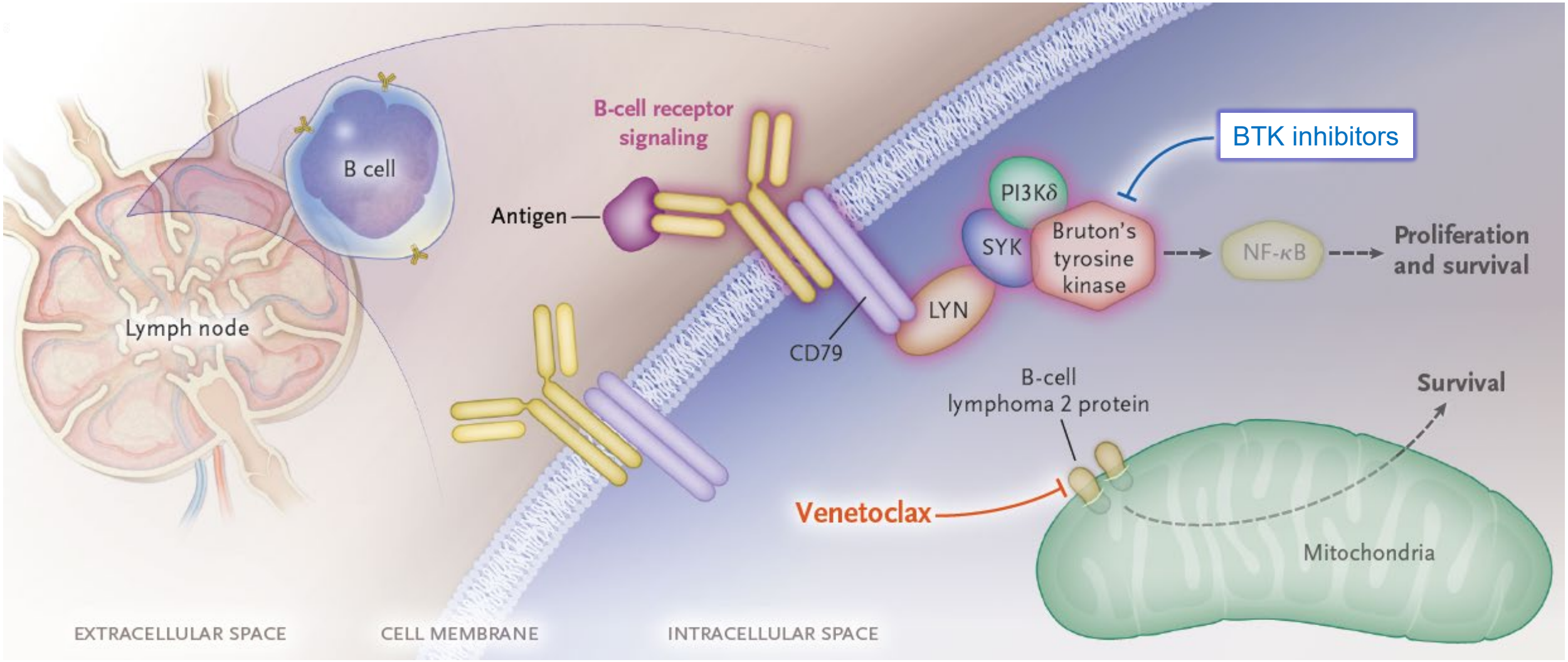
BR has inferior PFS (HR = 1.6) than FCR, less toxicity, no difference in OS

Eichhorst, et al, Lancet Oncology 2016

Lessons from chemoimmunotherapy

- Del(17p) poor response with inferior survival
- Duration of response can exceed 10 years after FCR – but only for young patients, IGHV mutated, without adverse cytogenetic markers
- Relevant risk of MDS/AML (2-5%) after chemoimmunotherapy
- Addition of anti-CD20 antibody to chemotherapy improves PFS and in some studies OS
- Randomized study shows improved PFS for chlorambucil with obinutuzumab over chlorambucil with rituximab

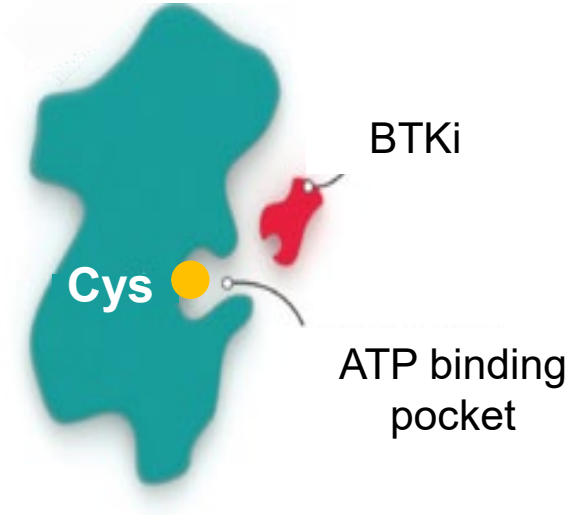
Targeting the critical pathogenic pathways in CLL



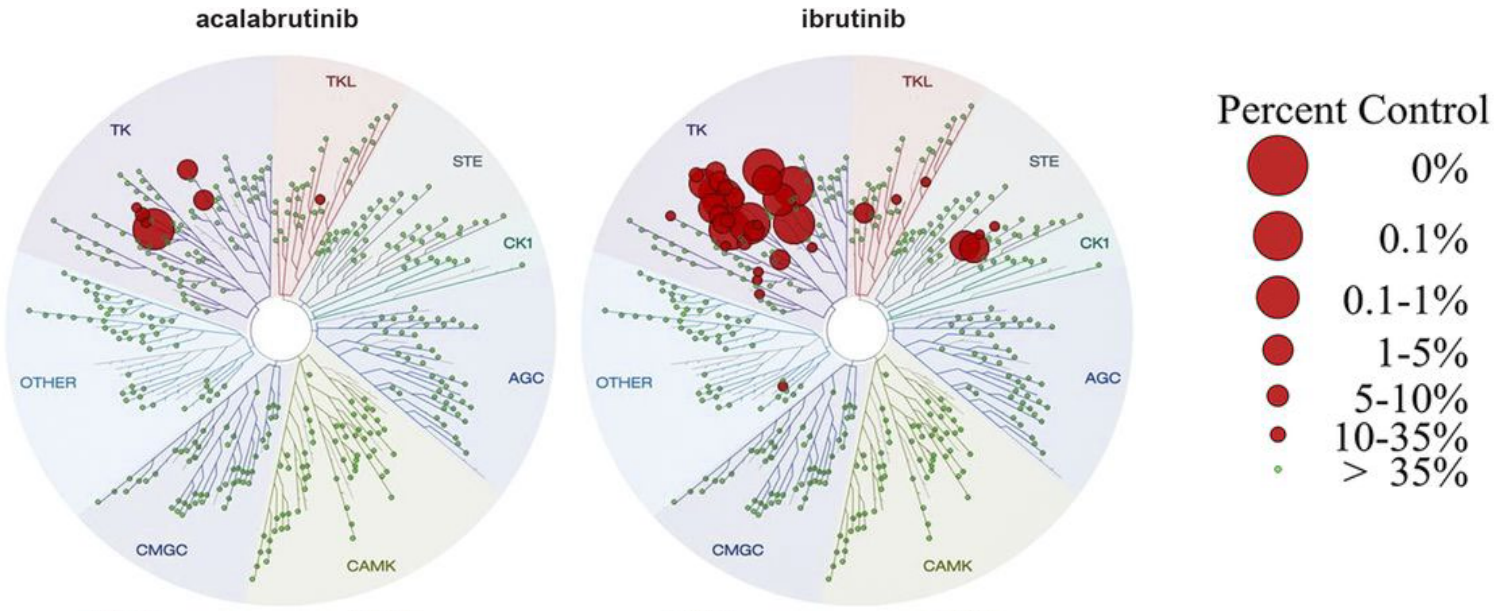
NEJM 2019. 380;22 p2170

Covalent Bruton Tyrosine Kinase (BTK) inhibitors

Covalent (irreversible) BTK inhibitors



Ibrutinib
Acalabrutinib
Zanubrutinib

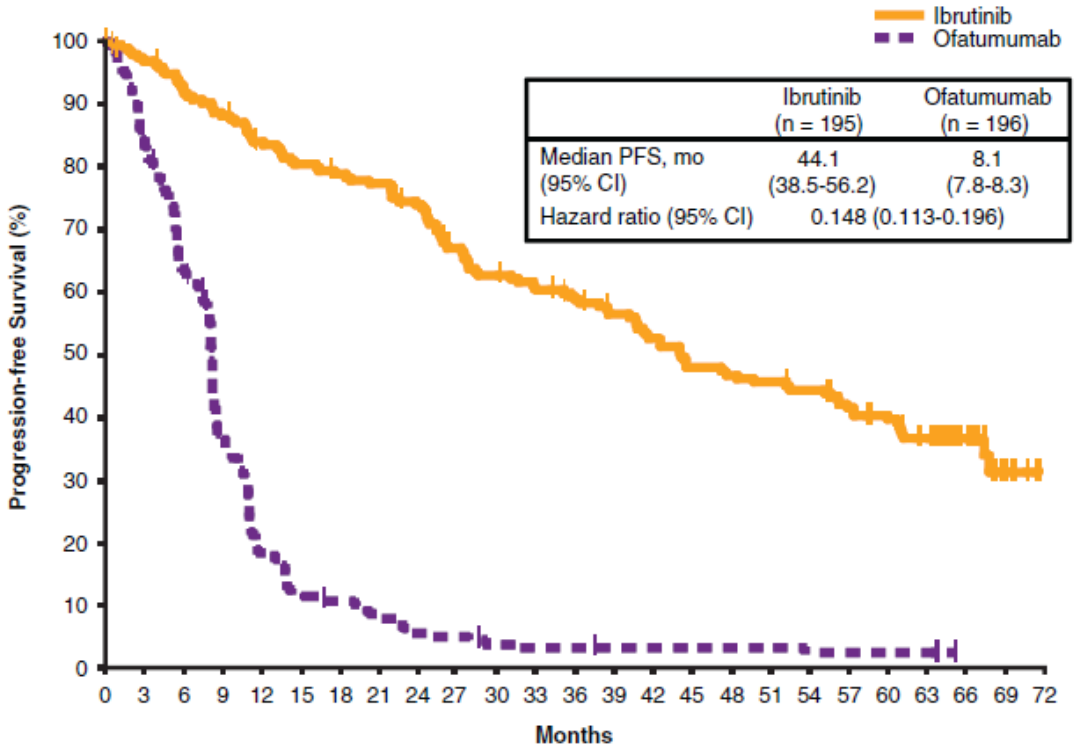


- Initial studies used continuous dosing until disease progression or intolerance

Barf, J Pharmacol Exp Ther. 2017

Randomizes trials of BTKi in relapsed/refractory CLL

Resonate: ibrutinib vs ofatumumab

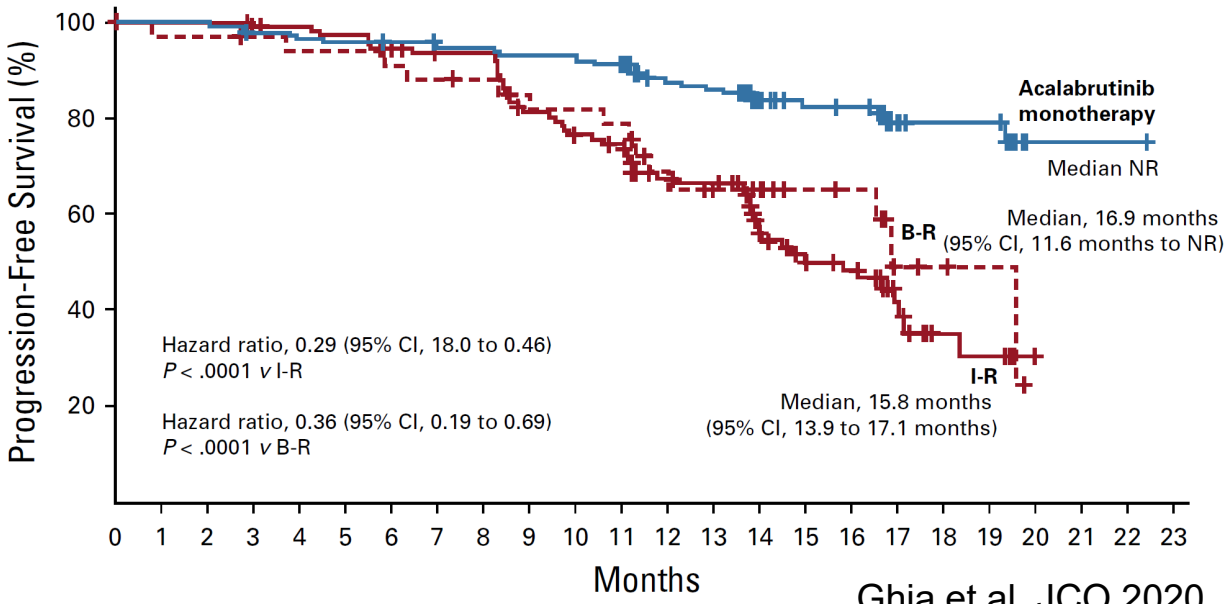


Median follow up 65.3 months

- ✓ Median OS 67.7 vs 65.1 months (68% cross-over to ibrutinib)
- ✓ Only 16% discontinued because of adverse event

Munir et al, AJH 2019

Ascend: acalabrutinib vs Idela-R or BR



Ghia et al, JCO 2020

With ~4 years of follow-up:

- ✓ PFS at 42 months: 62% vs 19%
- ✓ For acalabrutinib no diff in PFS for yes/no del(17p)
- ✓ OS at 42 months: 78% vs 65% (52% cross-over to acalabrutinib

Jurczak et al, poster at ASCO 2022

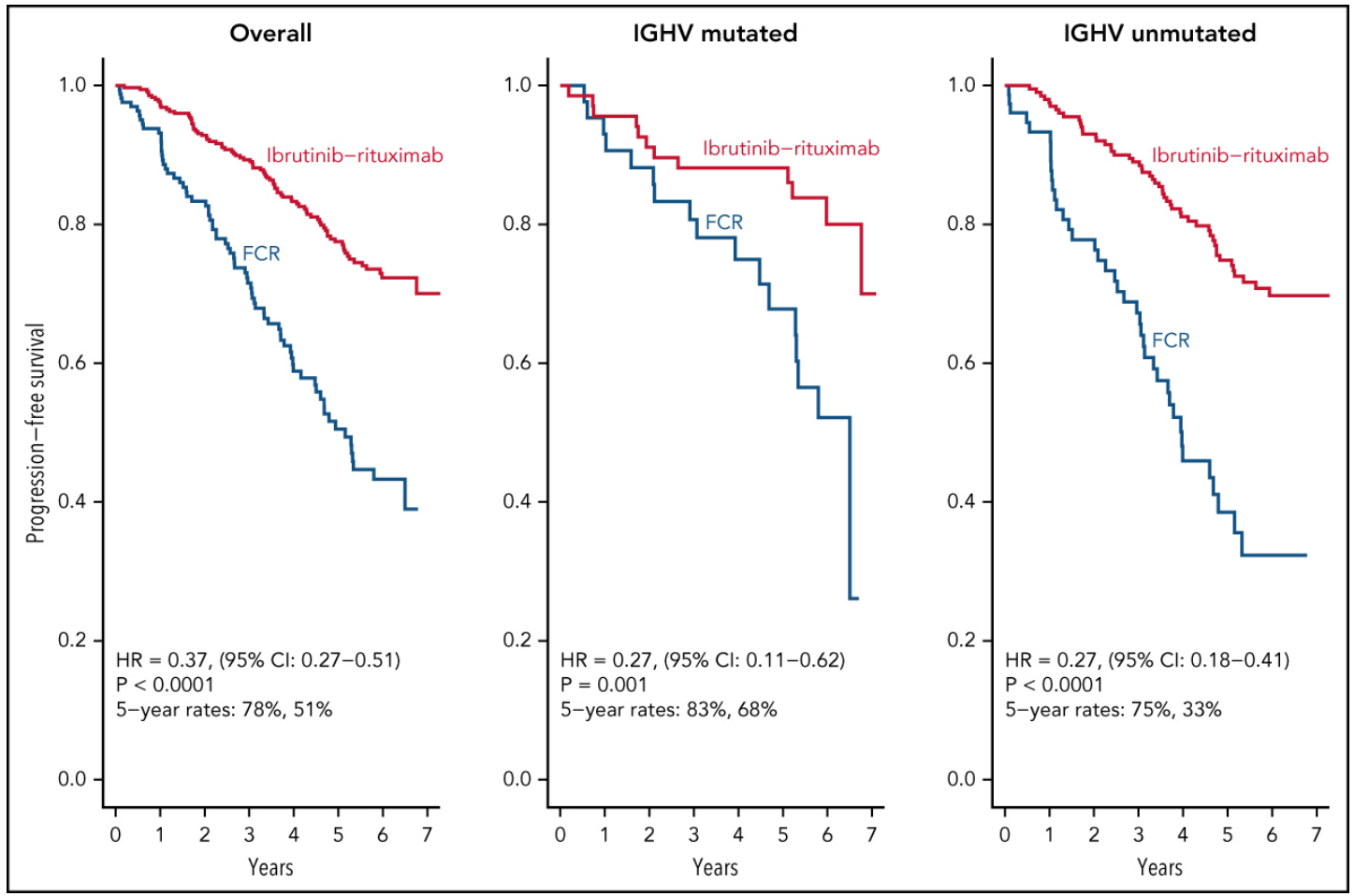
Long-term outcomes for first-line ibrutinib-rituximab vs chemoimmunotherapy

E1912 trial
- 529 treatment-naïve patients
- ≤ 70 years old
- no del17p13 by FISH

Randomized 2:1 to
- IR: continuous ibrutinib and rituximab x6 (n=354)
- 6 cycles FCR (n=175)

At median follow-up 5.8 years:
IR vs FCR
- ✓ PFS 78% vs 51% (P<0.0001)
- ✓ OS 95% vs 89% (p=0.018)

Progression-free survival



Shanafelt et al. Blood 2022

Adverse events and treatment discontinuations on ibrutinib-rituximab

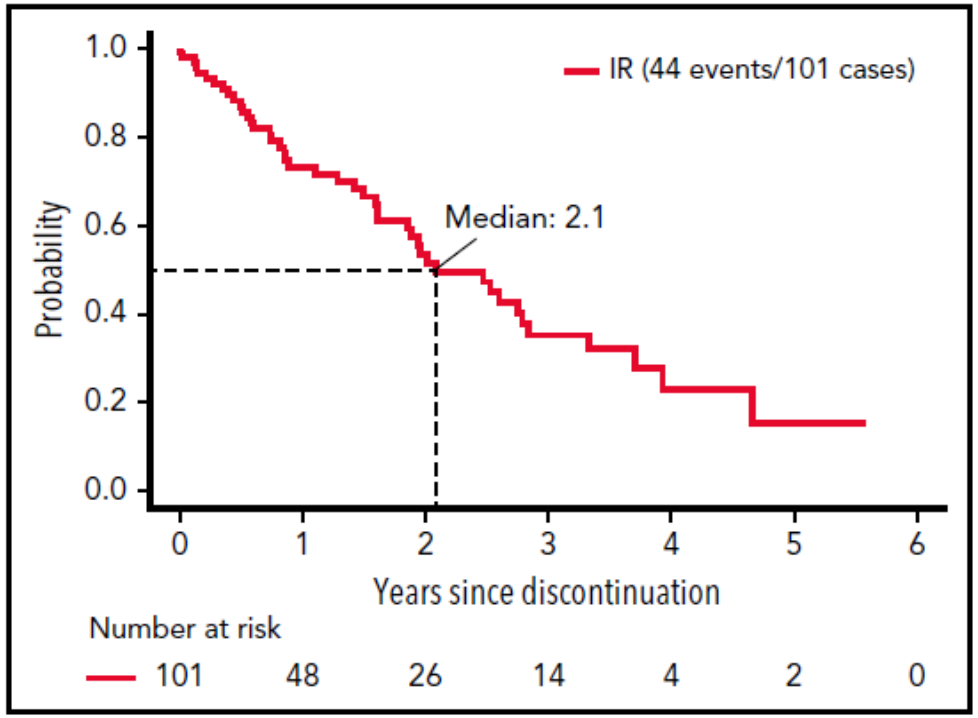
Reasons for IR discontinuations 138 (40%) of 354 patients	
Progression or death	26.8%
Adverse event	55.8%
Withdrawal or other reason	17.4%

Grade ≥3 adverse events more common with IR:
Arthralgia (5.4%), Hypertension (11.4%), cardiac (7.7%)

7-year PFS was ~80% for patients who were able to remain on ibrutinib.

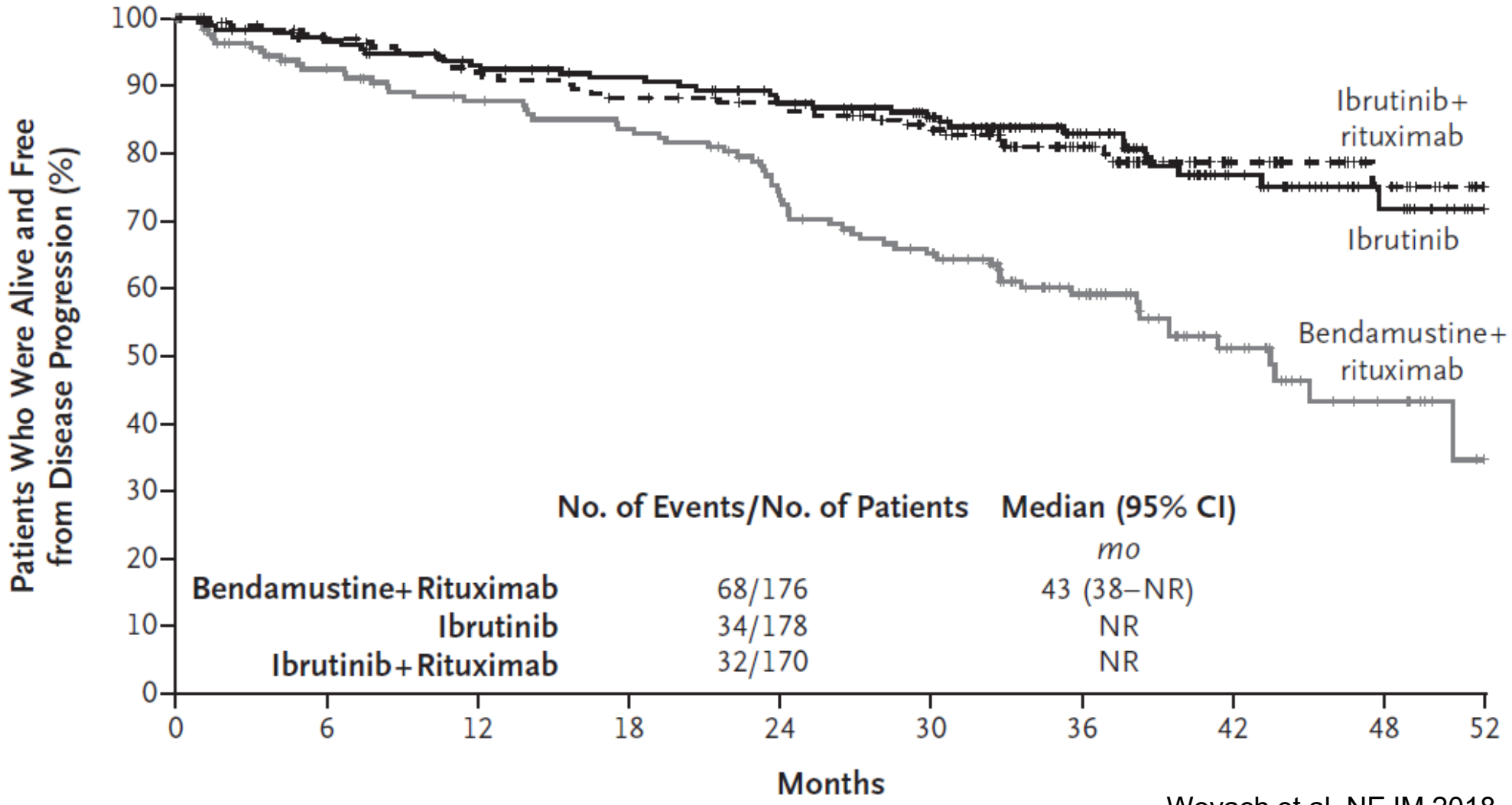
PFS from discontinuation of ibrutinib

Discontinuation for reasons other than progression. Median time patients had been on ibrutinib was 25.9 months (0.2-82 months)



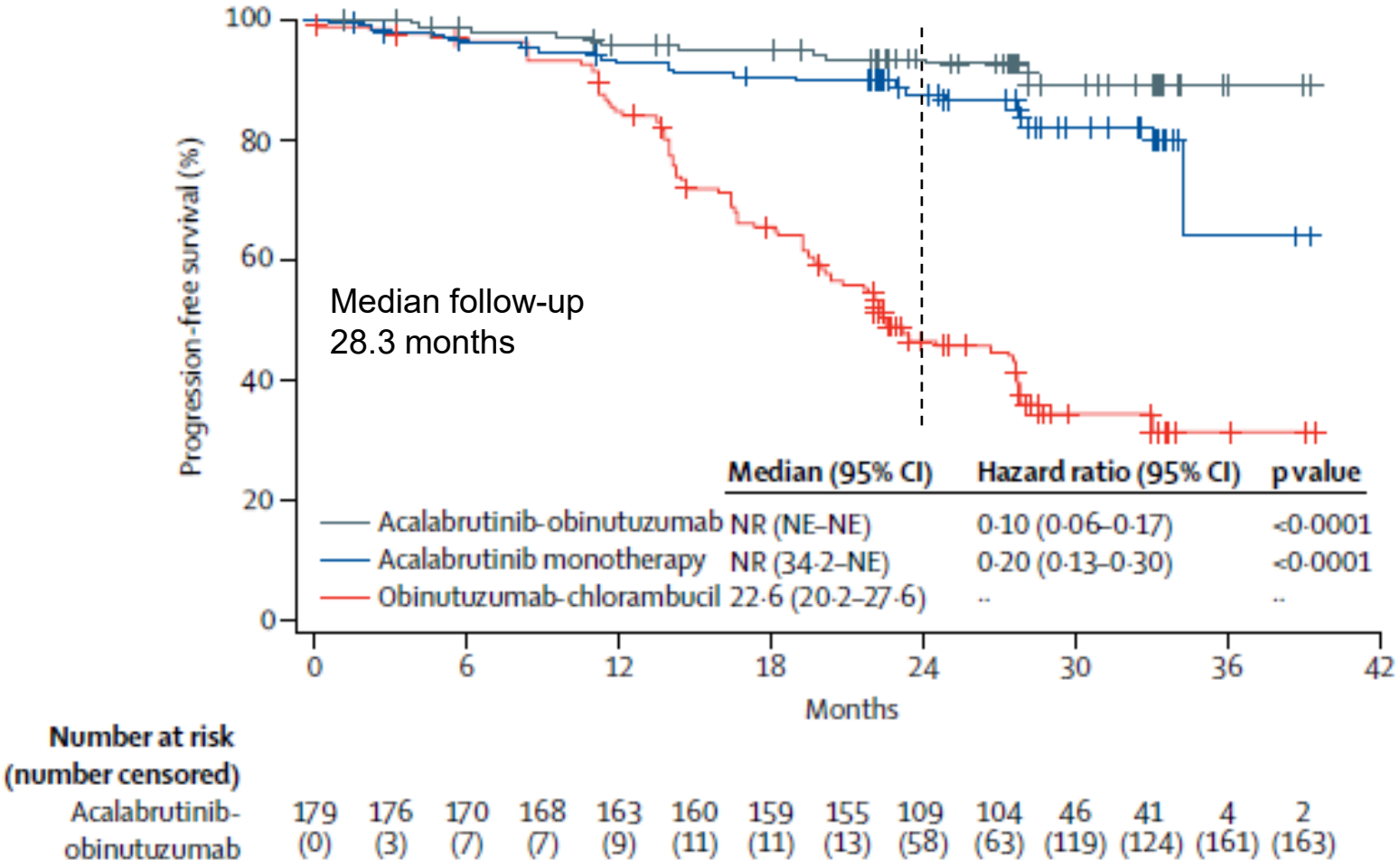
Shanafelt et al. Blood 2022

The Alliance study: ibrutinib for front-line therapy of CLL



Woyach et al, NEJM 2018

Elevate TN: superior outcome with first-line acalabrutinib +/- obinutuzumab compared with chemoimmunotherapy



Estimated PFS at 2 years:

93% (87 – 96%)

87% (81 – 92%)

47% (39 – 55%)

Sharman et al. Lancet Oncol 2020

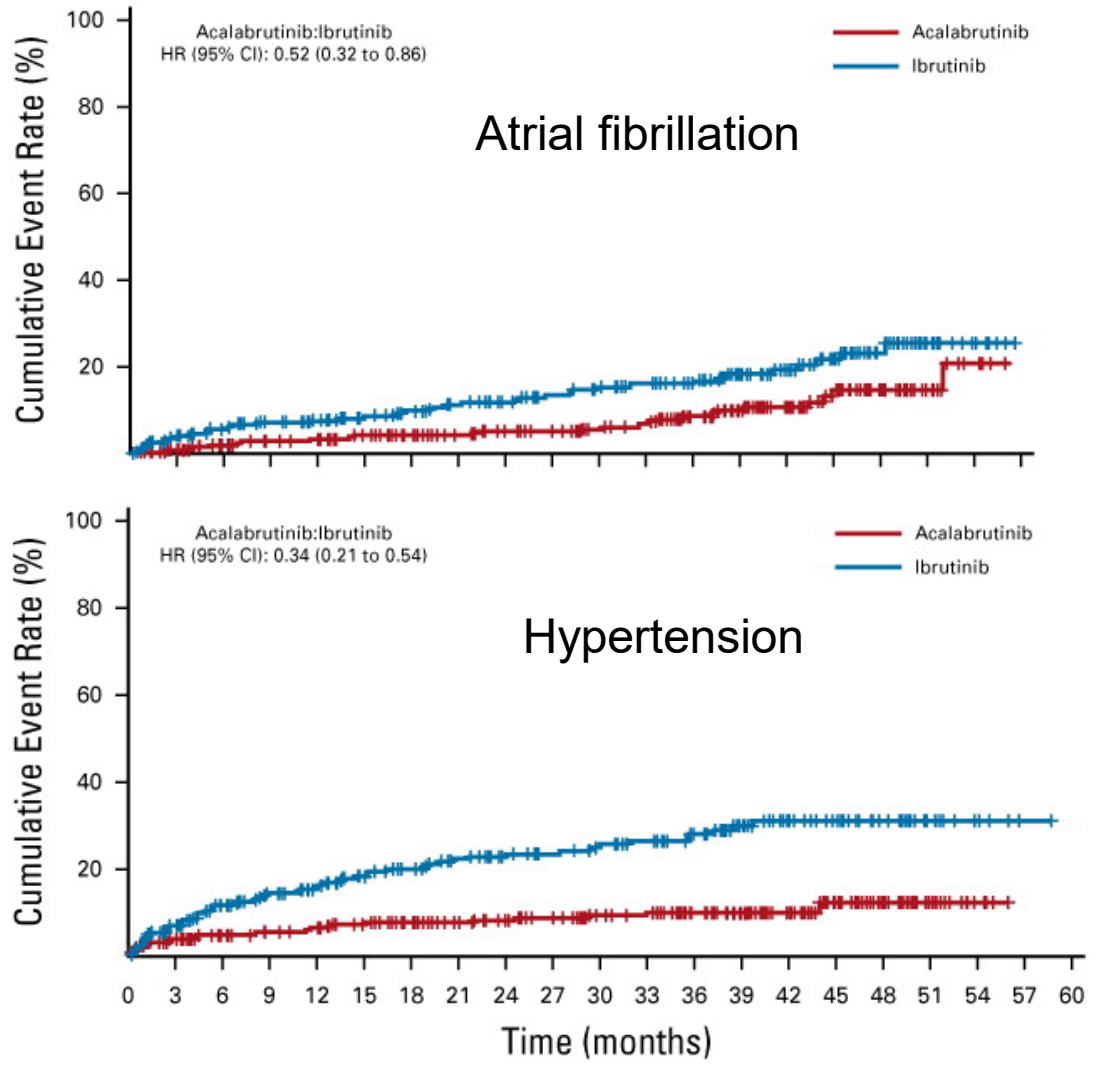
Randomized phase III trial of acalabrutinib versus ibrutinib in r/r CLL

Median follow-up of 40.9 months, median PFS 38.4 months in both arms (non-inferiority)

Most common adverse events (bold = significant difference)

	Acalabrutinib N=266		Ibrutinib N=263	
Event	**Any**	**G≥3**	**Any**	**G≥3**
Diarrhea[a,b]	34.6	1.1	**46.0**	**4.9**
Headache[a,b]	**34.6**	**1.5**	20.2	0
URT infection	26.7	1.9	24.7	0.4
Fatigue[b]	20.3	**3.4**	16.7	0
Arthralgia[a]	15.8	0	**22.8**	0.8
Hypertension[a,b]	8.6	4.1	**22.8**	**8.7**
Pneumonia	17.7	10.5	16.3	8.7
Contusion[a]	11.7	0	**18.3**	0.4
Rash	9.8	0.8	12.5	0
Atrial fibrillation[a]	9.0	4.5	**15.6**	3.4
UT infection[a]	8.3	1.1	**13.7**	2.3
Back pain[a]	7.5	0	**12.9**	0.8
Epistaxis	7.1	0.4	10.6	0.4
Muscle spasms[a]	6.0	0	**13.3**	0.8
Dyspesia[a]	3.8	0	**12.2**	0

Adverse events are reported as individual MedDRA preferred terms. Higher incidences are shown in bold text for terms with statistical differences. [a]Descriptive two-sided *P*≤.05 Barnard's exact test for all-grade AE; [b]Descriptive two-sided *P*≤.05 for grade 3 or higher adverse events.



Byrd et al, JCO 2021

Additional adverse events and considerations

Ventricular arrhythmia

AE	Acalabrutinib		Ibrutinib	
	Any grade	Grade ≥3	Any grade	Grade ≥3
Cardiorespiratory arrest	1	1	0	0
Cardiac arrest	0	0	2	2
Any ventricular arrhythmia	0	0	3	1

Byrd et al, JCO 2021

- Patients treated with acalabrutinib had a >8 fold increase in ventricular arrhythmia and sudden death.
- Ventricular arrhythmias may be a class-effect of BTKi-therapies, and vigilance is needed.

Bhat et al, Blood 2022

Dose modifications for ibrutinib

Hold drug and reduce dose with grade 2 cardiac failure, grade 3 arrhythmias

USPI May 2022

Hemorrhage with ibrutinib and acalabrutinib

Low grade common, serious ~3-4%
Consider withholding ibrutinib and acalabrutinib 3-7 days pre- and post-surgery
Clinical trials generally excluded warfarin use

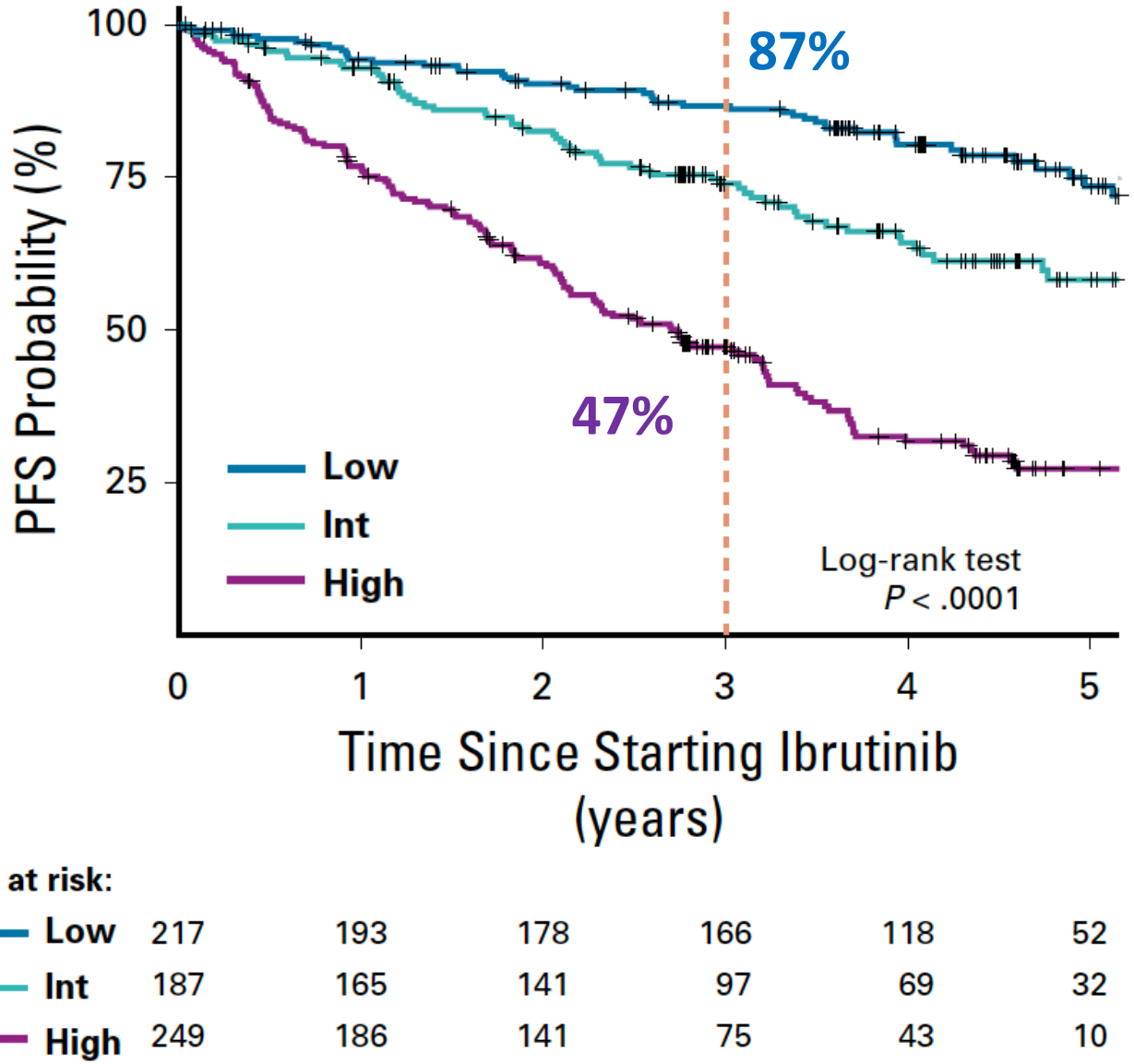
Drug interactions for ibrutinib and acalabrutinib

Avoid co-administration with strong **CYP3A** inhibitors / inducers, consider dosing modifications with moderate CYP3A inhibitors

Risk stratification of CLL patients treated with ibrutinib using a 4-factor model

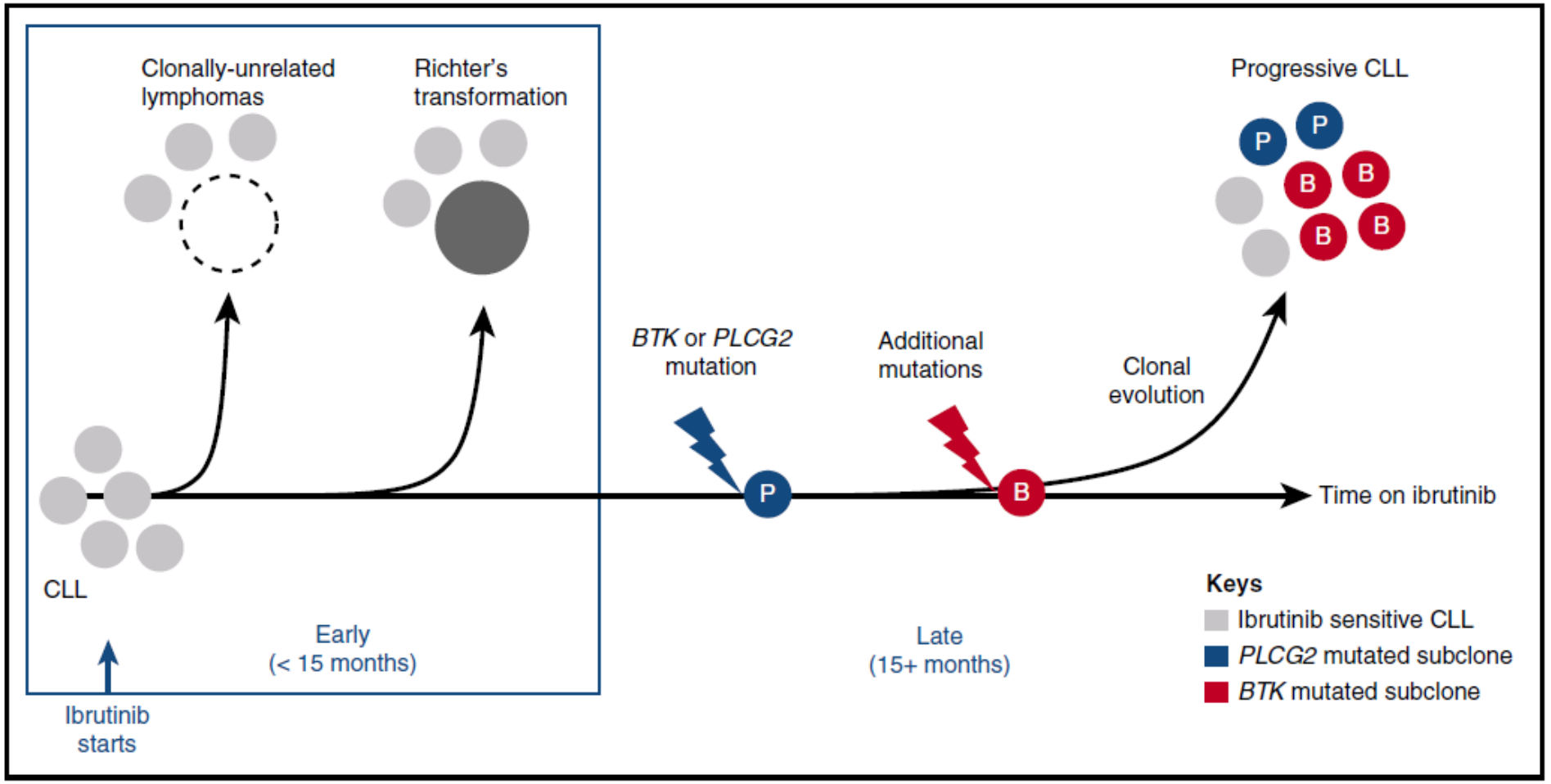
Adverse Factors
TP53 aberration
Relapsed/refractory CLL
B2M > 4.0 mg/L
LDH > 250 U/L

# of Adverse Factors	Risk Group
0-1	Low
2	Int
3-4	High



Ahn et al, JCO 2020

Biology of progressive disease on ibrutinib (covalent BTK inhibitors)



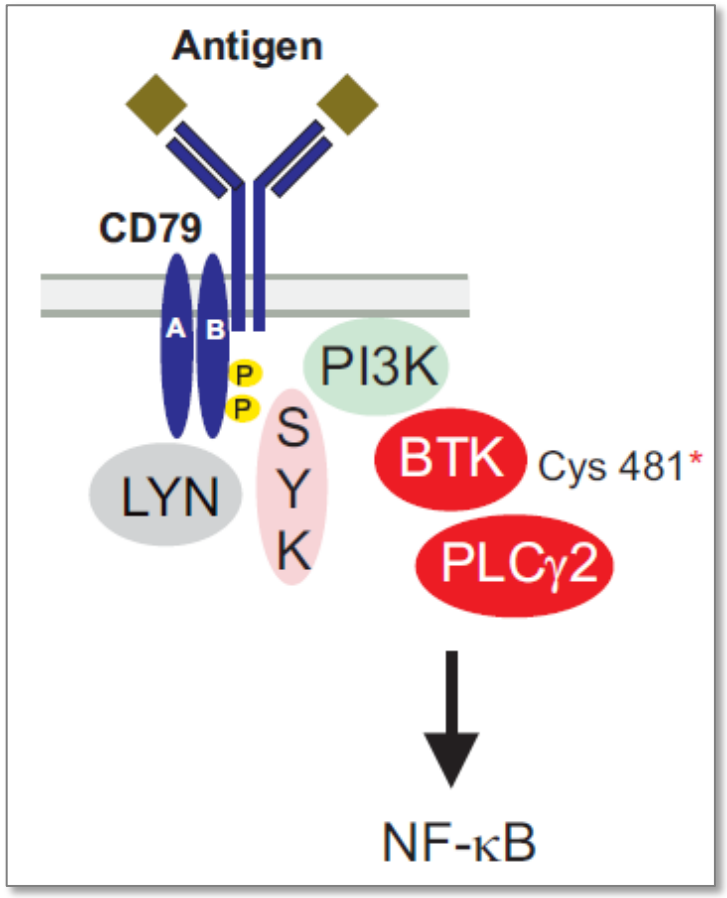
Specific mutations are found in up to 85% of patients progressing with CLL.

Ahn, Blood 2017
Woyach, JCO 2017
Burger, Nat Com 2016
Kadri, Blood Adv 2017
Byrd, Blood 2020

Ahn et al, Blood 2017

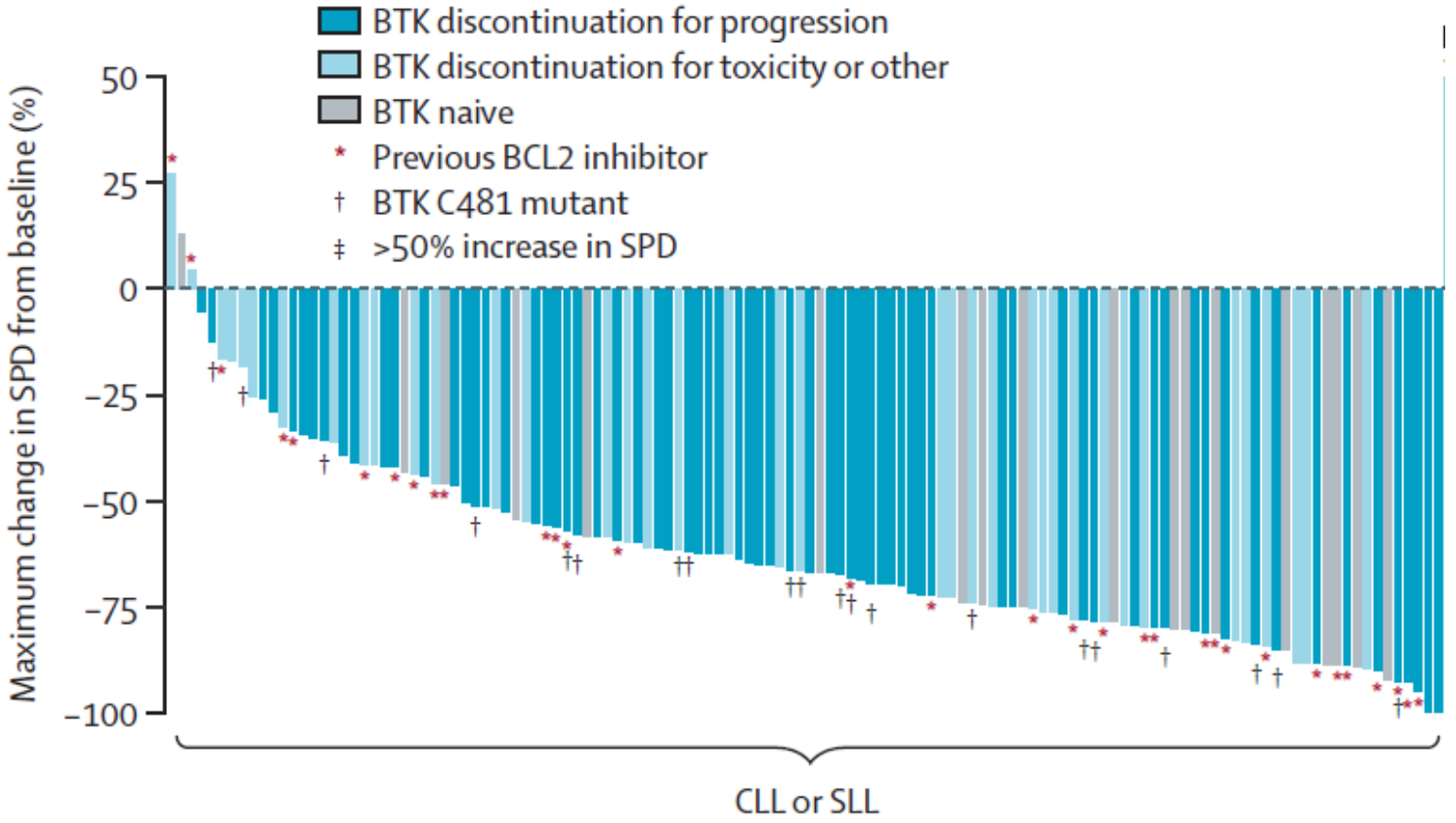
Targeting resistance to covalent BTKi

BTK and PLCG2 mutations



Pirtobrutinib (LOXO-305): a selective, non-covalent BTK inhibitor

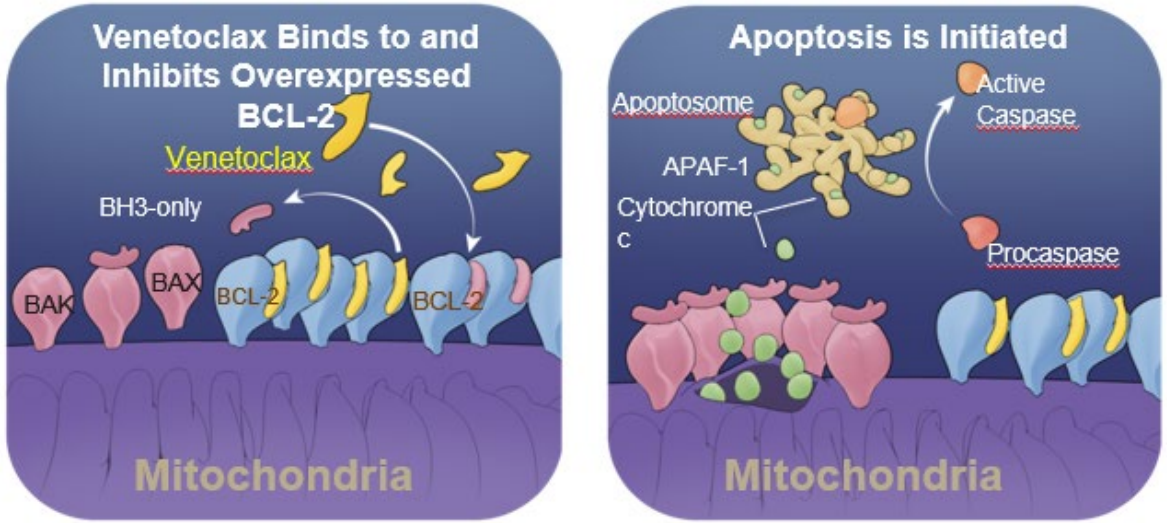
ORR 62% in CLL patients previously treated with covalent BTKi



Mato et al, Lancet 2021

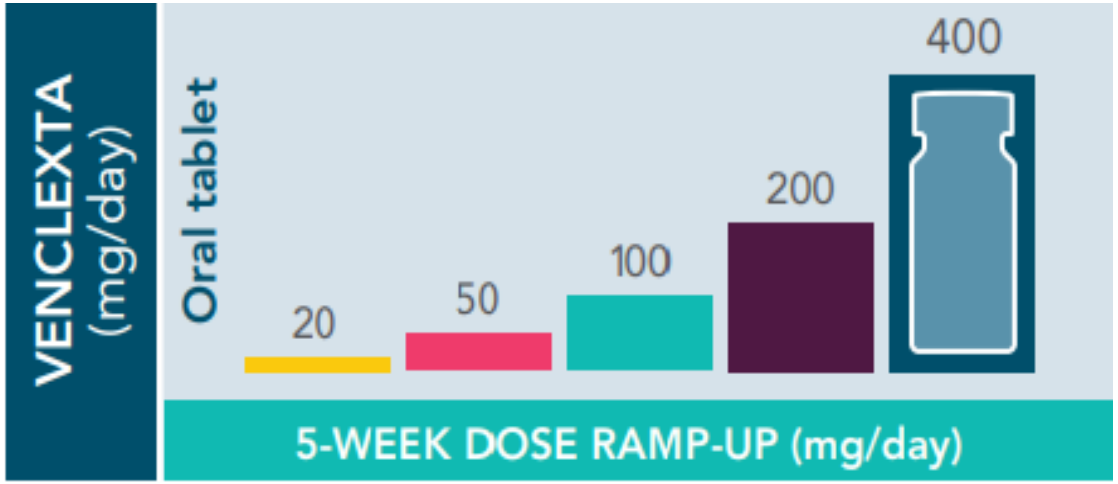
Targeting the BCL2 survival pathway with venetoclax

- Venetoclax is an orally bioavailable, selective BCL2 inhibitor, directly inducing apoptosis in CLL cells independent of p53



- First-in-human study of venetoclax showed a 79% ORR in relapsed/refractory CLL (Roberts et al., *NEJM* 2015)

- Main toxicity in early trials: tumor lysis syndrome
- Stepped up dosing with close monitoring of TLS labs, supportive care (allopurinol, hydration)



- Intensity of monitoring depends on TLS risk:

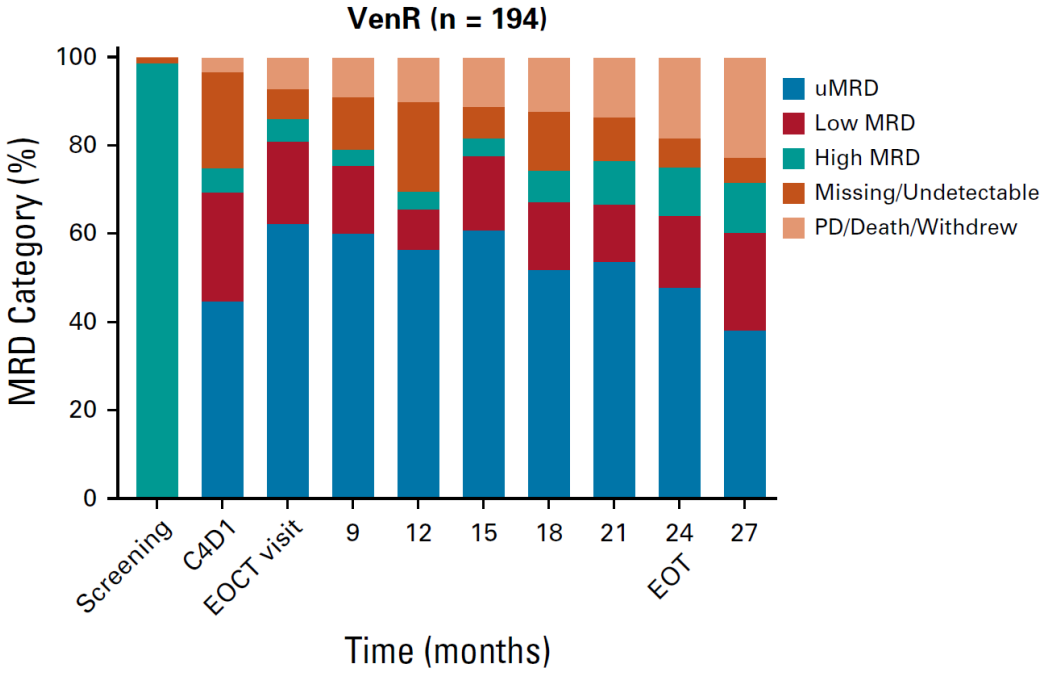
✓ High risk: any node ≥10cm or any ≥5cm and ALC ≥25,000/uL → in hospital for 20mg and 50mg

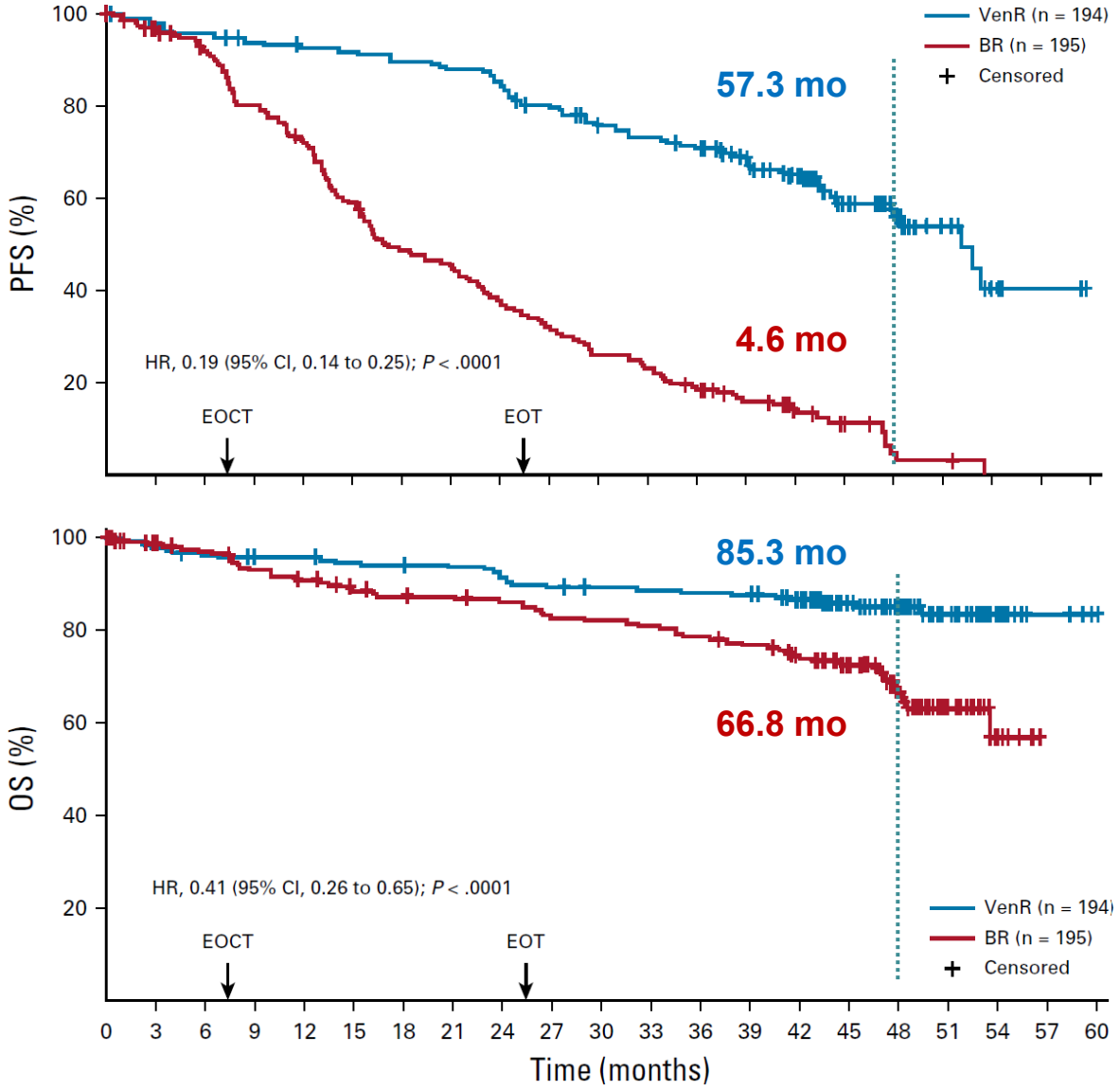
✓ Medium risk: any node ≥5cm or ALC ≥25,000/uL → outpatient monitoring

Venetoclax plus rituximab for relapsed/refractory CLL

Murano study: 389 patients with r/r CLL randomized to 2 years of venetoclax (+rituximab for the first 6 cycles) vs BR
4-year follow-up

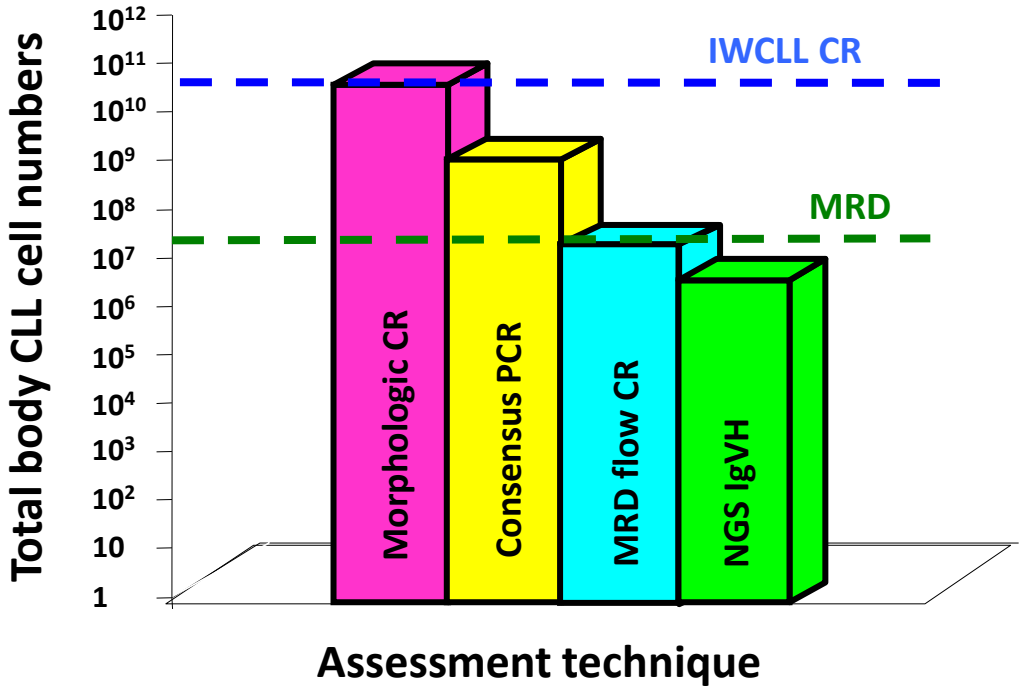
Minimal residual disease undetectable (uMRD): <1 CLL cell in 10,000 leukocytes (10^{-4})



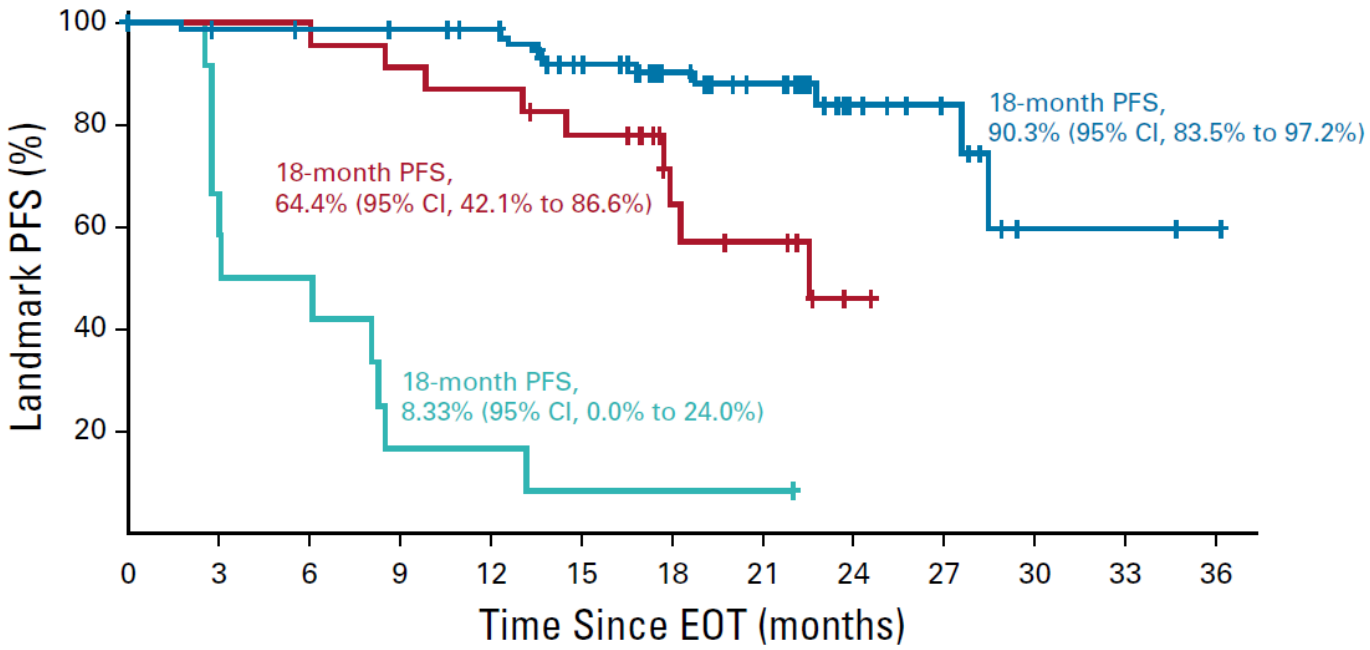


Kater et al, JCO 2020

Minimal residual disease (MRD): depth of response predicts PFS



Courtesy of P. Hillmen



Kater et al, JCO 2020

CLL14: Venetoclax-Obinutuzumab for front-line therapy of CLL

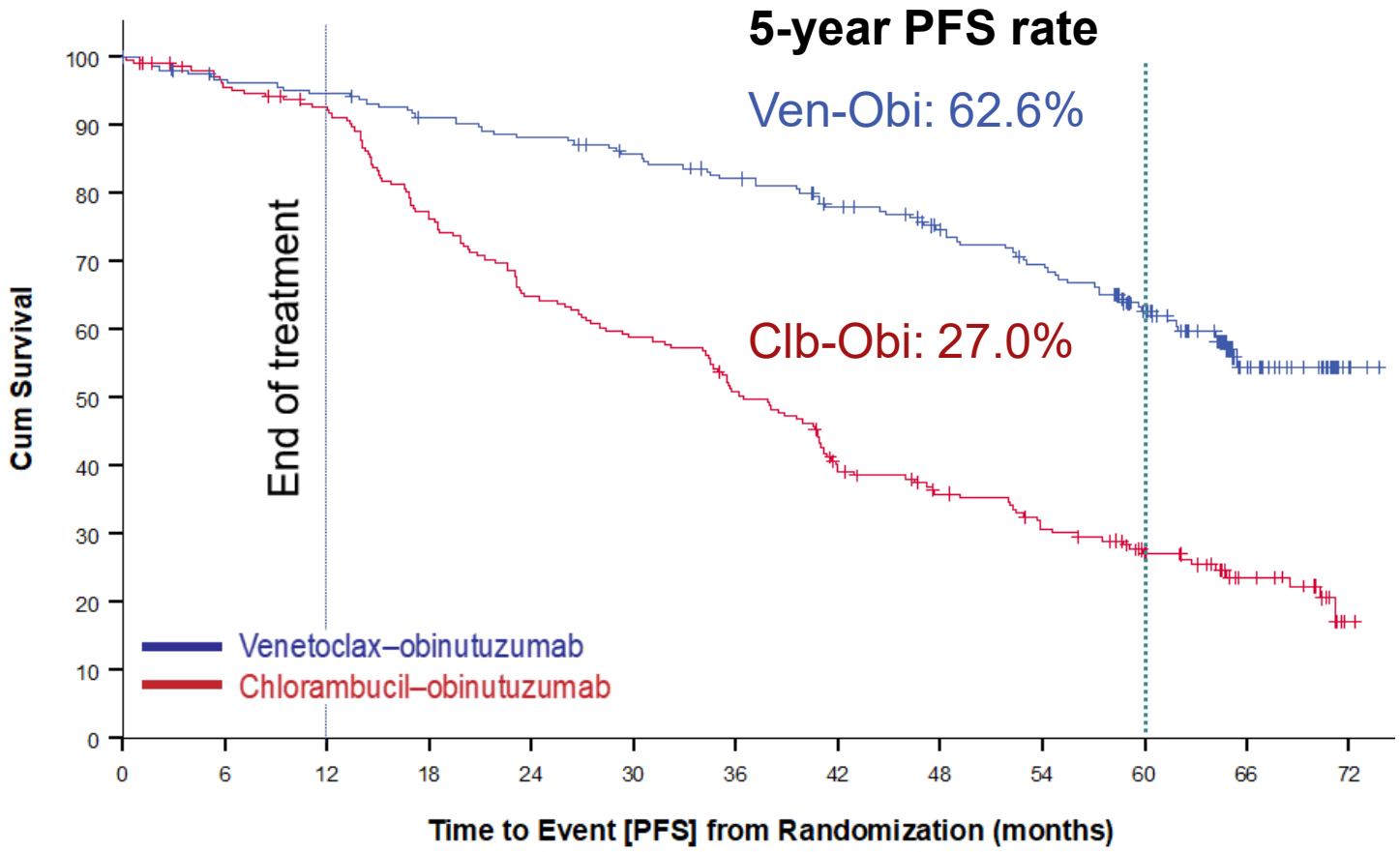
Previously untreated patients with CLL and coexisting medical conditions

CIRS > 6 and/or CrCl < 70mL/min

512 patients

1:1 randomization

Venetoclax–Obinutuzumab 6 cycles	**Venetoclax** 6 cycles
Chlorambucil–Obinutuzumab 6 cycles	**Chlorambucil** 6 cycles



5-year OS rate: Ven-Obi: 81.9% Clb-Obi: 77.0%

HR 0.72, 95% CI [0.48-1.09]

P=0.12

Slide courtesy of O. Al-Sawaf, presented EHA 2022

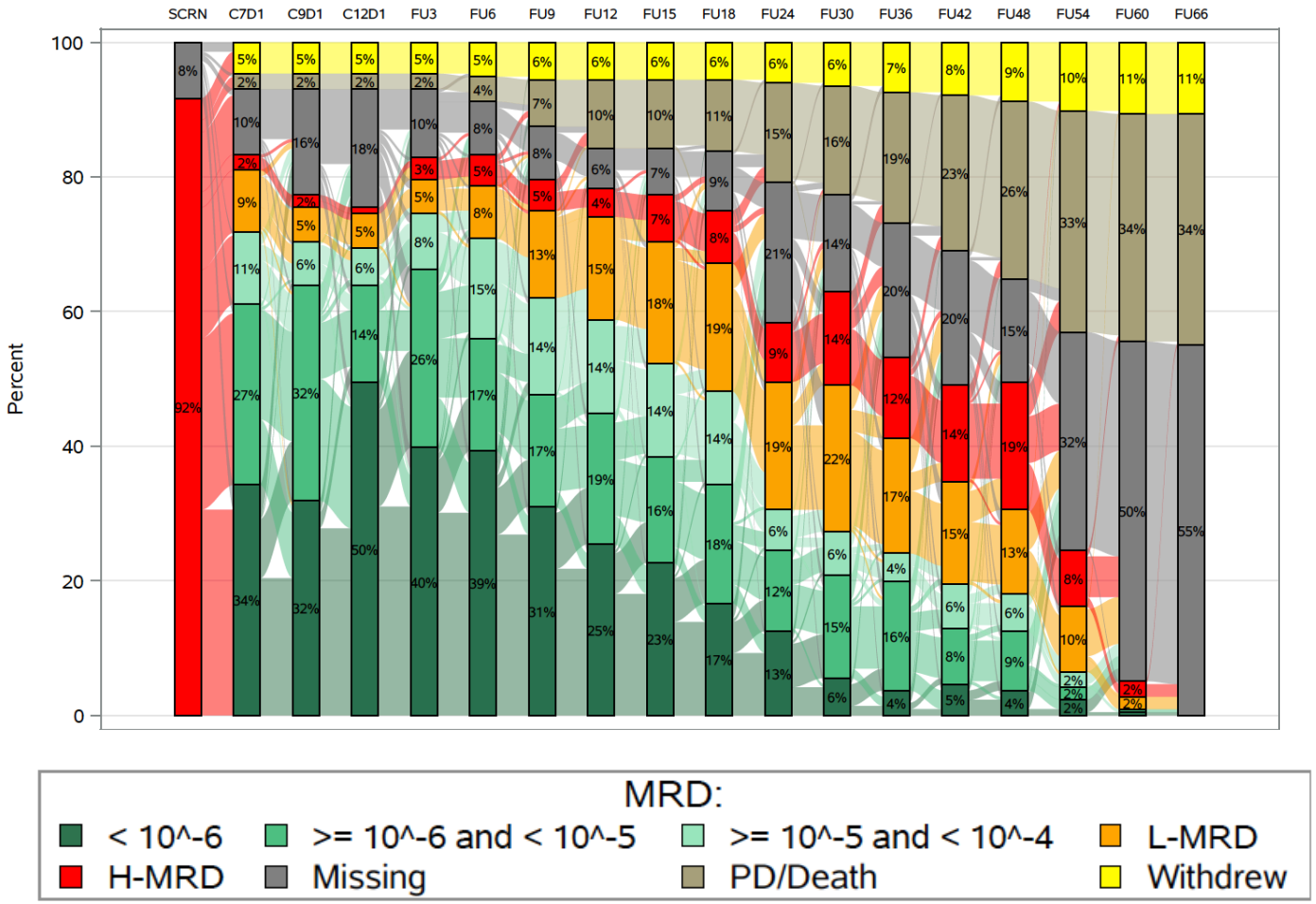
Most frequent grade ≥3 adverse events

	Venetoclax-obinutuzumab (N=212)		**Chlorambucil-obinutuzumab** (N=214)	
	During	**After Treatment**	**During**	**After Treatment**
Neutropenia	51.9%	4.0%	47.2%	1.9%
Thrombocytopenia	14.2%	0.5%	15.0%	0.0%
Anemia	7.5%	2.0%	6.1%	0.5%
Febrile neutropenia	4.2%	1.0%	3.3%	0.5%
Leukopenia	2.4%	0.0%	4.7%	0.0%
Pneumonia	3.8%	3.0%	3.3%	1.4%
Infusion-related reaction	9.0%	0.0%	9.8%	0.5%
Tumor lysis syndrome	1.4%	0.0%	3.3%	0.0%
Second primary malignancy	20.8%		15%	

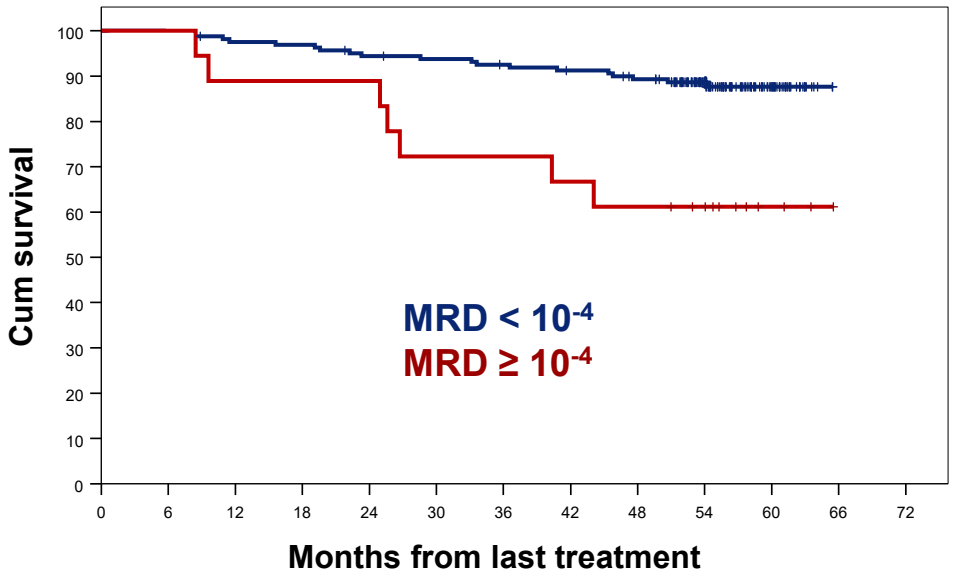
Slide courtesy of O. Al-Sawaf, presented EHA 2022

Longitudinal MRD assessment using NGS in Ven-Obi arm

4 years after Ven-Obi, **39 (18.1%)** of patients had sustained MRD <10^{-4}



Overall survival by MRD status at the end of treatment

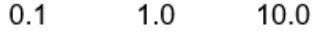


Slide courtesy of O. Al-Sawaf, presented EHA 2022

Factors associated with PFS in multivariable models

Ven-Obi

COX regression PFS	Univariate comparison	Hazard ratio	95% Wald CI
Disease burden category (TLS risk category)			
High	Vs. intermediate/low	2.815	1.773-4.469
Deletion 17p			
del(17p)	vs. no del(17p)	3.150	1.727-5.745



Median PFS

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

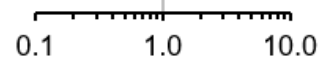
Ven-Obi & *TP53*del/mut: 49.0 m

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

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

Clb-Obi

COX regression PFS	Univariate comparison	Hazard ratio	95% Wald CI
Serum β2 microglobulin			
> 3.5	vs. <= 3.5	1.534	1.037-2.269
IGHV mutational status			
unmutated	Vs. mutated	2.765	1.847-4.141
Deletion 17p			
del(17p)	vs. no del(17p)	2.667	1.413-5.036
Deletion 11q			
del(11q)	vs. no del(11q)	2.056	1.331-3.177
Complex Karyotype			
CKT/HCKT	vs. NCKT	2.761	1.720-4.433



For Ven-Obi, **pre-treatment disease burden** (max. lymph node size >5 cm and absolute lymphocyte count > 25 G/l) and **deletion 17p** are independent prognostic factors for PFS.

Captivate: fixed duration ibrutinib plus venetoclax as first-line therapy of CLL

159 patients aged ≤70 years
- 3 cycles ibrutinib lead in
- 12 cycles ibrutinib plus venetoclax

Primary endpoint: 56% CR rate
uMRD rates 77% (blood), 60% (bone marrow)

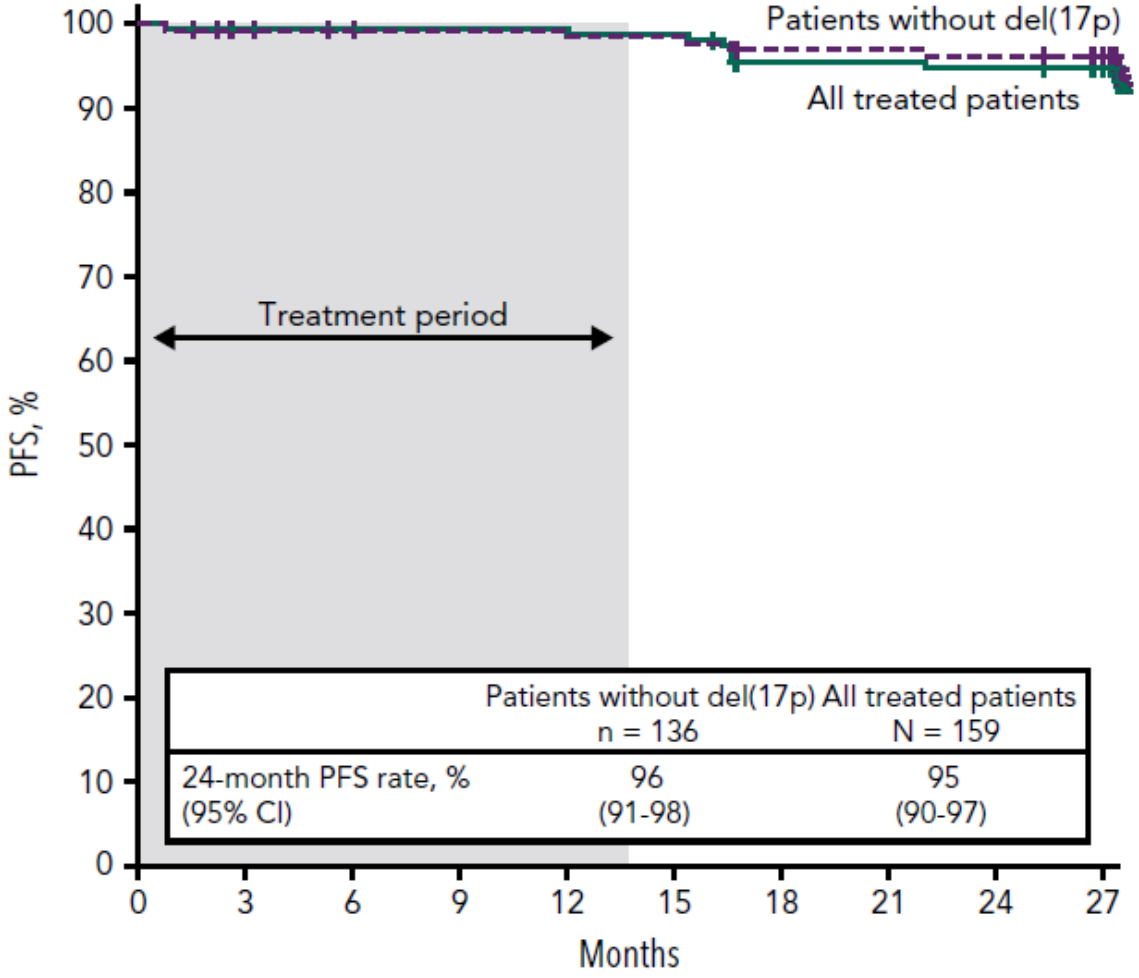
Ibrutinib lead in reduced high-risk TLS group from 21% to 1%.

92% completed all treatment

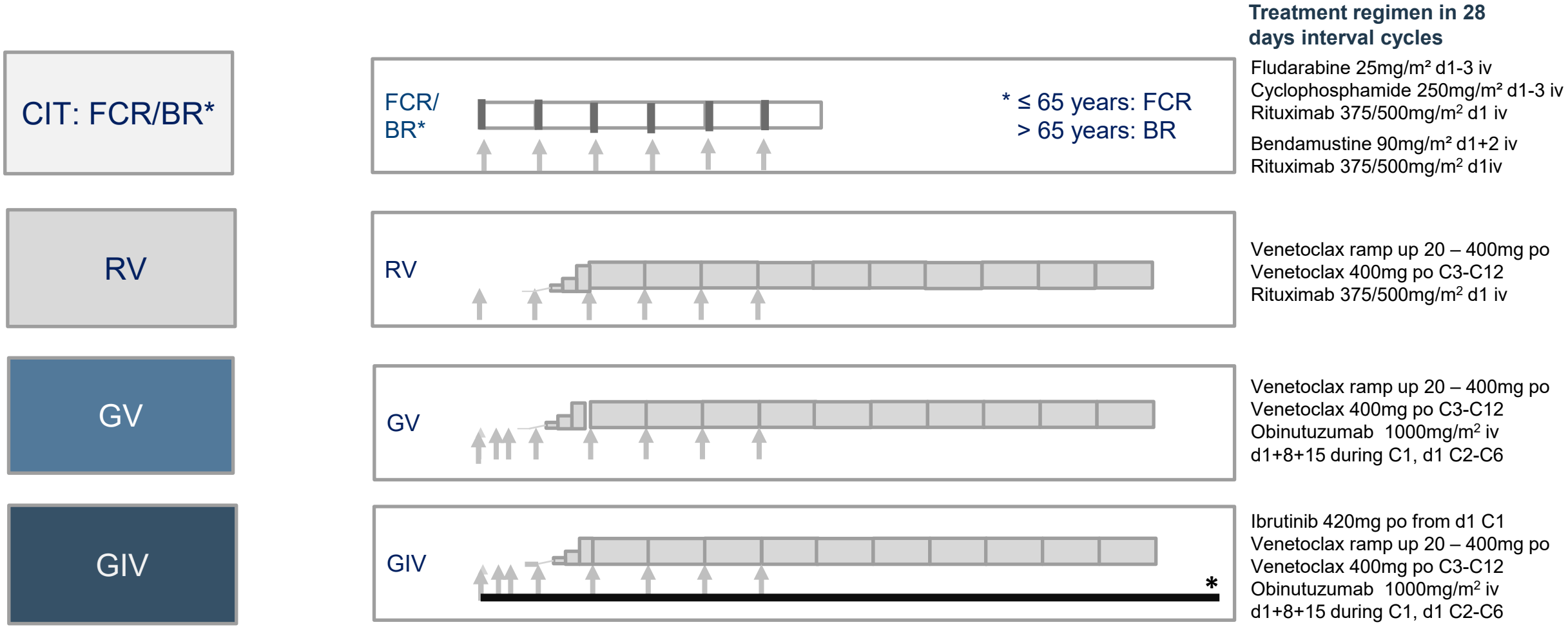
Most common AEs: diarrhea, nausea, neutropenia, arthralgia
Grade 3/4 AEs: neutropenia (33%), hypertension (6%)

Tam et al, Blood 2022

PFS after fixed duration treatment



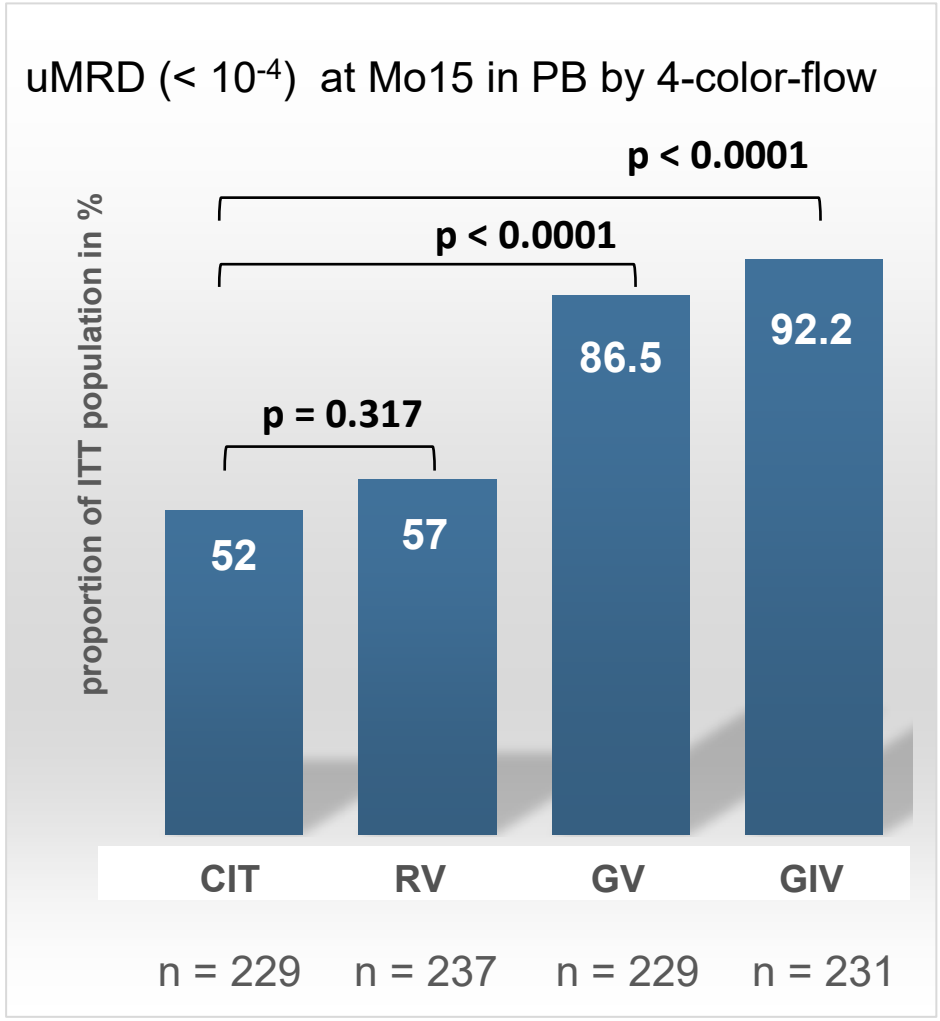
GAIA/CLL13 study: randomized comparison of double and triple therapy



Slide courtesy of B. Eichhorst, presented at EHA 2022

Primary endpoints: rate of uMRD and progression-free survival

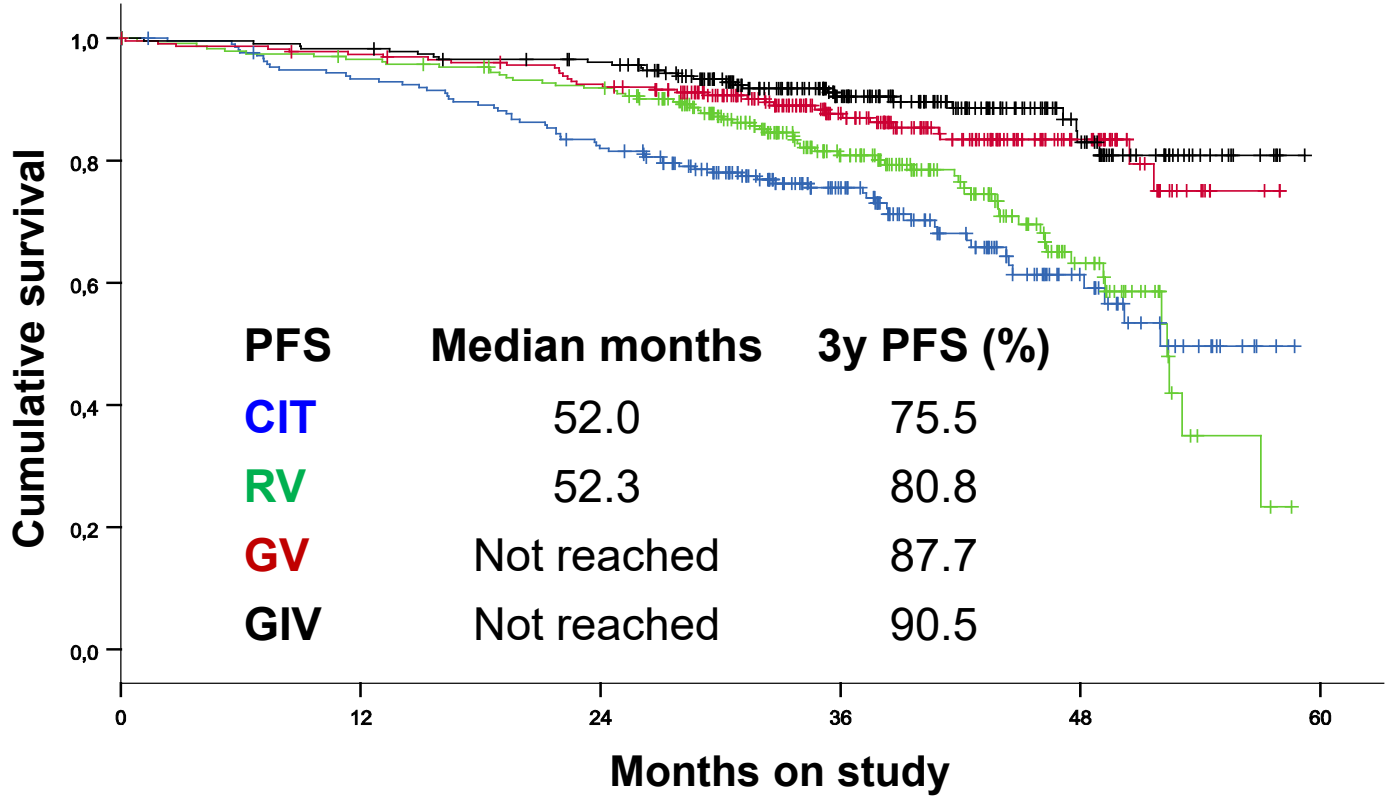
Rate of uMRD (co-primary endpoint)



Slide courtesy of B. Eichhorst, presented at EHA 2022

Progression-free survival (co-primary endpoint)

Median FU 38.8 months



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

GIV vs **CIT**: **HR 0.32, p<0.000001**

GV vs **CIT**: **HR 0.42, p<0.0001**

RV vs **CIT**: HR 0.79, p=0.183

Adverse events ≥ grade 3 in ≥ 5% of patients in at least one arm and of interest

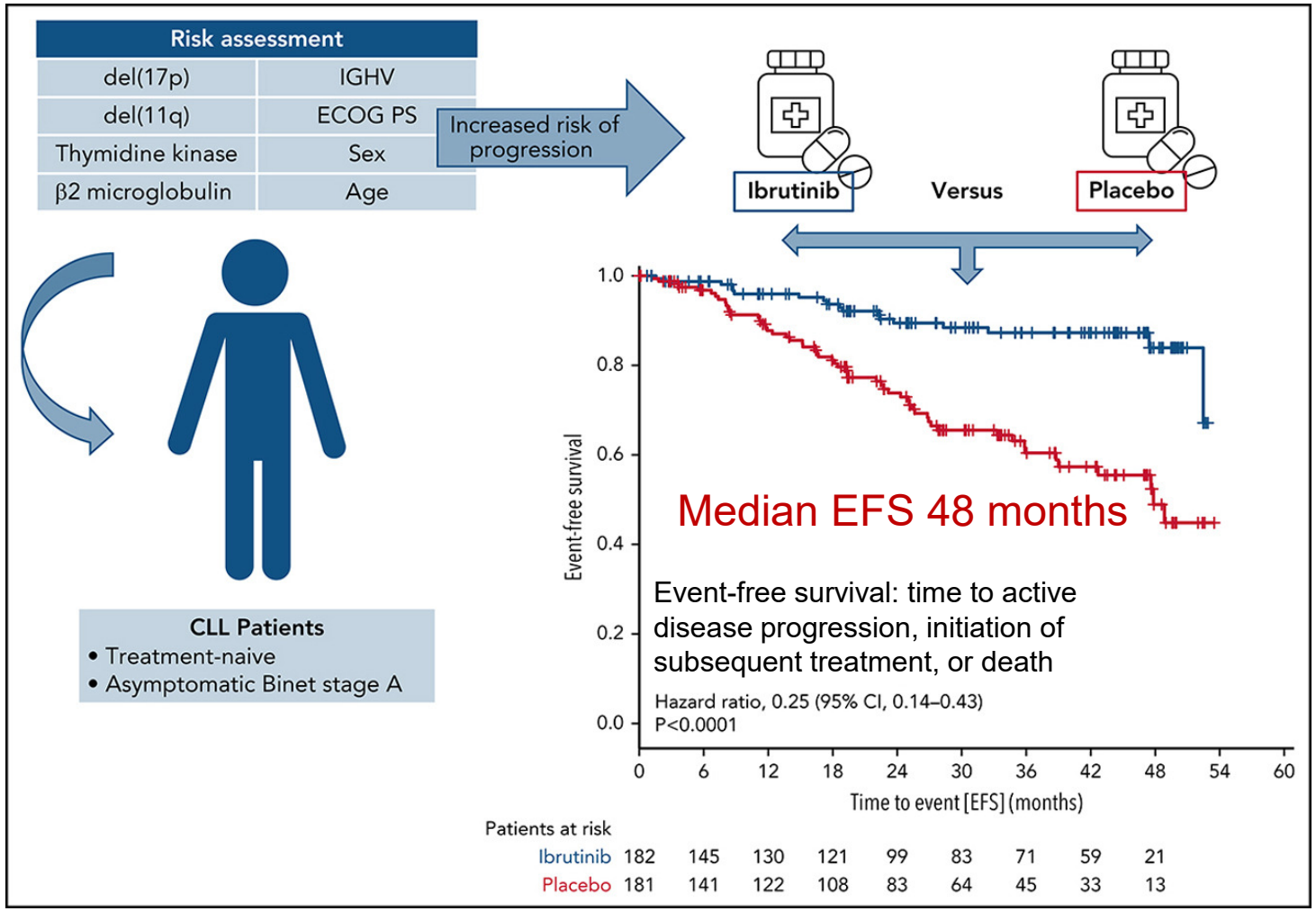
	CIT	RV	GV	GIV
All patients of safety population	**216**	**237**	**228**	**231**
All ≥ CTC grade 3 events (%)	**176 (81.5)**	**173 (73.0)**	**192 (84.2)**	**193 (83.5)**
Blood and lymphatic system (%)	122 (56.5)	103 (43.5)	128 (56.1)	117 (50.6)
Infections and infestations (%)	44 (20.4)	27 (11.4)	34 (14.9)	51 (22.1)
Febrile neutropenia (%)	24 (11.1)	10 (4.2)	7 (3.1)	18 (7.8)
Infusion related reaction (%)	12 (5.6)	19 (8)	26 (11.4)	10 (4.3)
Tumor lysis syndrome (%) *	9 (4.2)	24 (10.1)	19 (8.3)	15 (6.5)
Hypertension (%)	3 (1.4)	5 (2.1)	4 (1.8)	13 (5.6)

* Defined by Cairo-Bishop criteria

Slide courtesy of B. Eichhorst, presented at EHA 2022

Time to leave watch & wait behind?

Double-blind, randomized, placebo-controlled study



Langerbeins, Blood. 2022

No!

Key Points

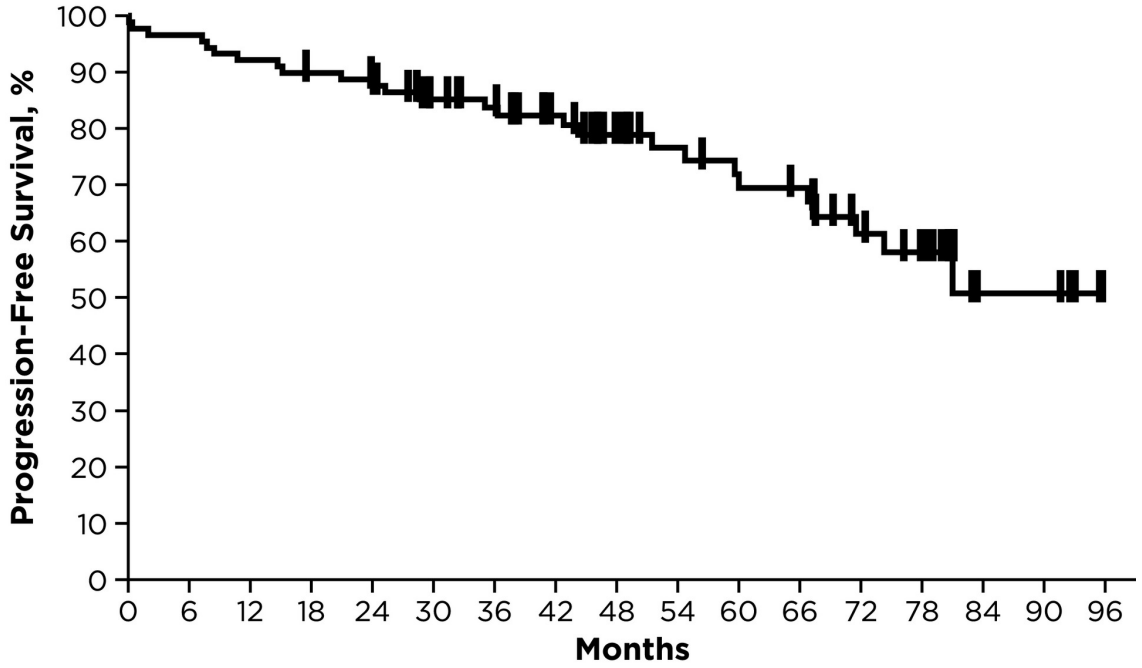
- Ibrutinib is effective in patients with early-stage CLL, but the results do not justify changing the current standard of “watch and wait.”
- Ibrutinib is associated with relevant cardiovascular toxicity.

Any grade AE: ibrutinib / placebo

- Atrial fib: 5.7% / 0.6%
- Hypertension: 11.4% / 4.5%
- Bleeding: 33.5% / 14.8%

First-line treatment for CLL with TP53 disruption (del(17p) or TP53 mutation)

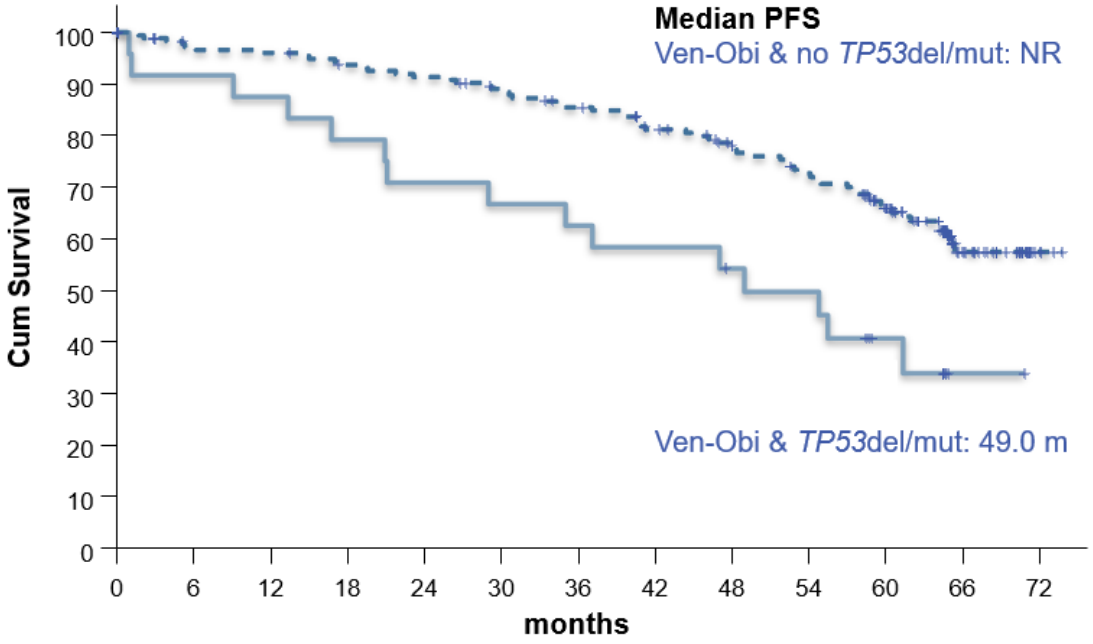
Ibrutinib



- Pooled analysis of 89 patients treated with ibrutinib in first-line
- 4-year PFS 79% (95% CI, 68-87)

Allan at el, Br J Haematol. 2022

Venetoclax-Obinutuzumab

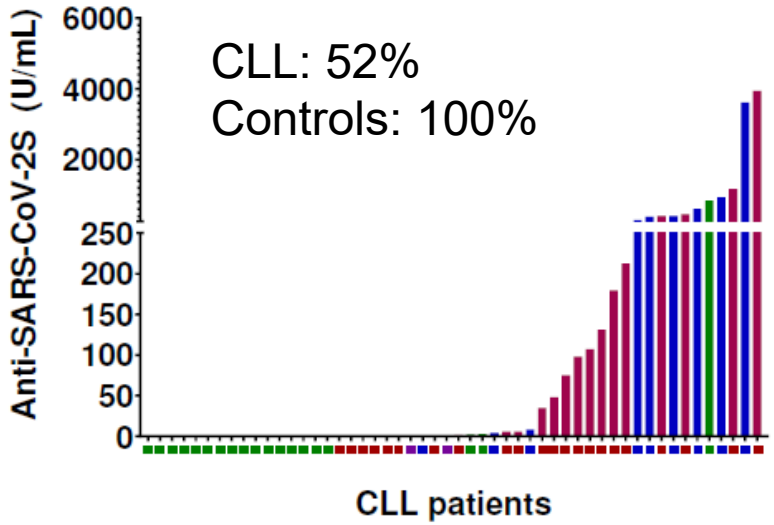


- Ven-Obi time limited 1 year treatment
- Median PFS 49.0 months for patient with TP53 disruption

Al-Sawaf, J Clin Oncol. 2021

Covid-19 and vaccinations in patients with CLL

Response to 2 doses of Pfizer vaccine



Treatment-naïve CLL	55.2%
On BTKi	16.0%
Venetoclax +/- anti-CD20	13.6%

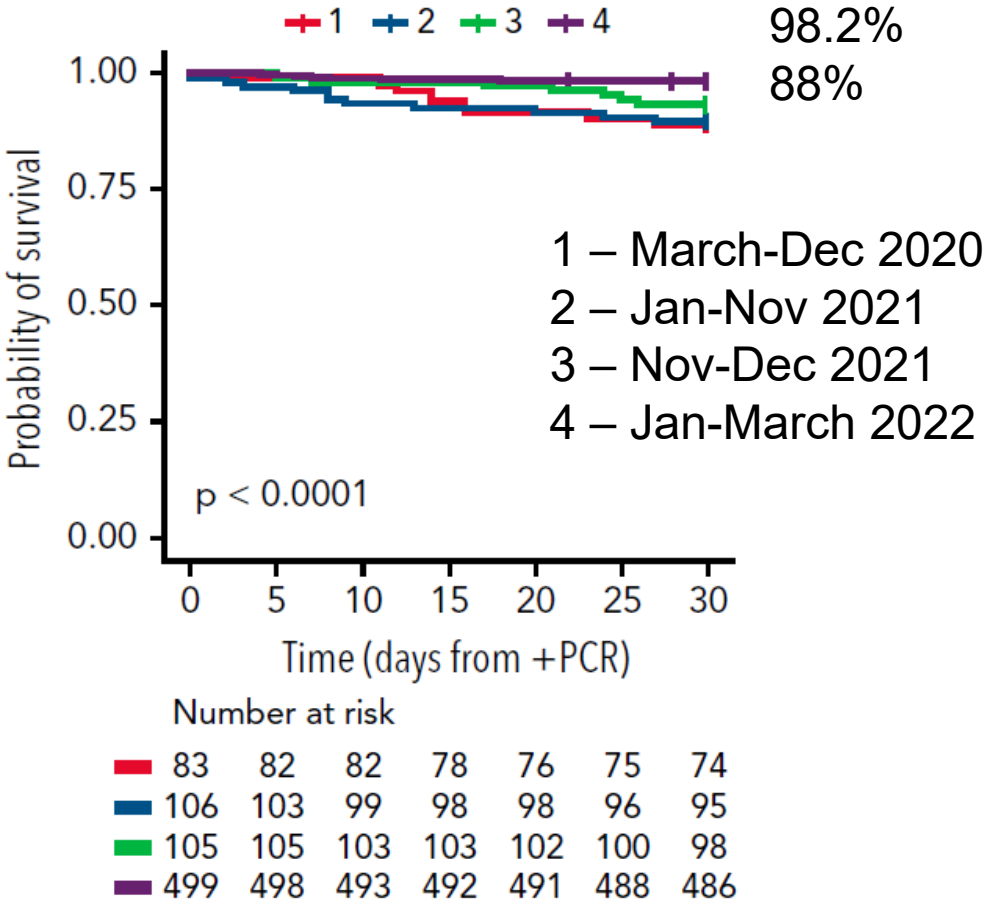
Herishanu et al, Blood 2021

In non-responders to initial series: 24% of all, 40% of treatment-naïve CLL patients responded to the 3rd dose.

Herishanu et al, Blood 2022

30-day OS for CLL patients in Denmark

+ PCR for Covid



Niemann et al, Blood 2022

Sequencing treatment in CLL

Line of Treatment	Therapy	Comments
1st Line	Chemoimmunotherapy (FCR or BR)	Time limited; for young (<65) patients with good prognostic risk; 2-5% risk of MDS/AML
	Acalabrutinib or ibrutinib +/- anti-CD20	Anti-CD20 adds little; high response, low MRD rates; consider risk:benefit with bleeding or cardiac risk factors
	Venetoclax + obinutuzumab, total 1 year duration	High response and MRD rates. Time-limited therapy with long duration of response
2nd Line	Acalabrutinib or ibrutinib (+/- anti-CD20)	See above
	Venetoclax + anti-CD20, total 2 years duration	Venetoclax & rituximab approved regimen, obinutuzumab might be more effective anti-CD20
3rd & subsequent line	***Clinical trials***	Non-covalent BTK inhibitors; BTK degraders; CAR-T cells; T cell engaging bispecific antibodies;
	PI3K inhibitors	Autoimmune side effects and risk of opportunistic infections; responses not very long lasting; negative data on OS
	Allo-SCT	Potential cure. Problematic: advanced age, co-morbidities, toxicity