Chronic Lymphocytic Leukemia 2021

A Decade of Remarkable Progress

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What is CLL?

- The most common adult leukemia
- Cancer of the lymphocytes, involves the bone marrow
- Often an indolent course
- Others have large lymph nodes, anemia or other low blood counts

Who is CLL?

- Typical patient is 70 years old and without symptoms
- Easy to diagnose
- Staging systems help predict the clinical course, but they "lump" rather than "split"
- Better predictors of disease course and outcome available (prognostic factors)

Risk Assessment

- Stage (Rai, Binet)
- CLL-IPI
- Age
- "Fitness"
  - Performance status
  - CIRS
- Cytogenetic (FISH) abnormalities
- *TP53* mutation
- *IGHV* mutation status

Rai Staging System

Stage	Findings	Survival (mo)
0	Lymphocytosis only	> 120
I	+ Adenopathy	95
II	+ Enlarged spleen and/or liver	72
III	Lymphocytosis + Hgb < 11	30
IV	Lymphocytosis + Plt < 100,000	30

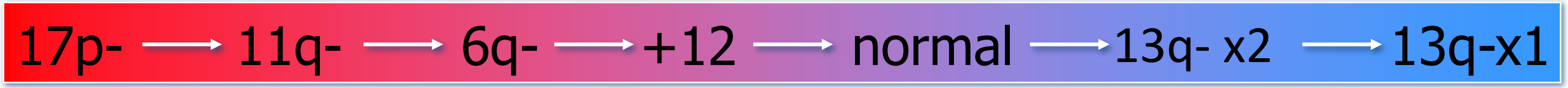
Rai KR, et al. *Blood.* 1975;46:219-234

82% of CLL Patients Abnormal

Abnormality	No. Patients (%)
13q deletion	178(55)
11q deletion	58(18)
trisomy 12	53(16)
17p deletion	23 (7)

Dohner et al. *N Engl J Med.* 2000;343:1910-1916.

Hierarchy for FISH Anomalies: Risk Categories



Most aggressive

Less aggressive

NCI-WG Indications to Treat

- Constitutional symptoms referable to CLL
- Progressive marrow failure (Rai III/IV)
- Autoimmune anemia +/- thrombocytopenia poorly responsive to corticosteroids
- Massive (>6cm) or progressive splenomegaly
- Massive (>10cm) or progressive lymphadenopathy
- Progressive lymphocytosis (>50% over 2mo or doubling < 6mo)

Cheson BD, et al. *Blood*. 1996;87:4990-4997.

Hallek M, et al. *Blood.* 2008;111:5446-5456.

Previously untreated, younger / fit patient

55-year-old male was treated for upper respiratory tract infection; peripheral blood lymphocytosis noted

Follow-up several months later demonstrated persistence of peripheral blood lymphocytosis with otherwise normal counts

Patient has COPD (current smoker), sleep apnea

ECOG PS is 0, and he works full time

Peripheral blood immunophenotyping showed monoclonal population of B-cells, co-expressing CD19, CD5, $CD20^{dim}$, and CD23

Physical exam showed small nodes (< 2 cm) in the cervical chain, with no other physical findings

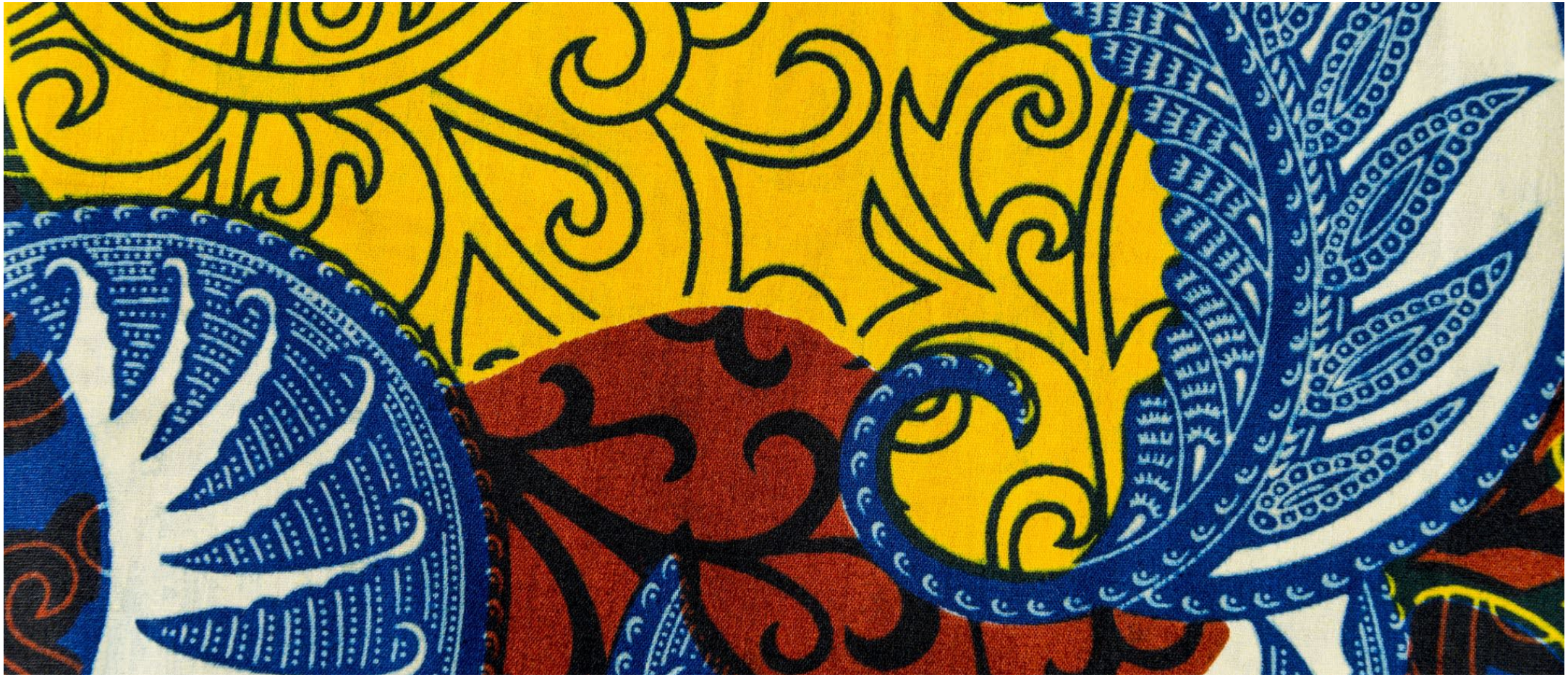
- Patient is diagnosed with asymptomatic CLL, and is observed for 2 years
- Now, he is complaining of progressive fatigue, night sweats most nights, and modest progression of lymphadenopathy is observed
- Genetic risk features:

  FISH showing isolated del(13q),
  IGHV mutated
- Physical exam reveals 2-cm cervical and axillary nodes bilaterally; no palpable organomegaly
- WBC of 88.4 x 10^9/L, ALC of 79.3 x 10^9/L, Hb of 8.7 g/dL, platelet count of 122 x 10^9/L

Define Your Goal of Treatment

- What is your goal of treatment?
  - Longest efficacy?
  - Safety?
- What are your treatment options?
  - FCR
  - Ibrutinib
  - Acalabrutinib
  - Venetoclax and obinutuzumab

IBRUTINIB

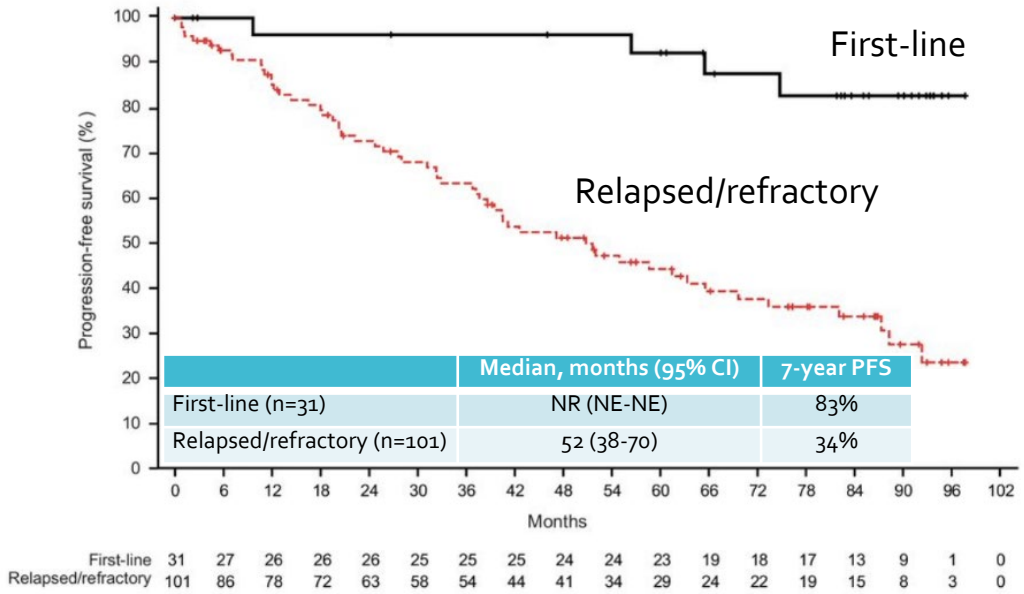


PCYC1102 Phase Ib/II Trial

First CLL/SLL Trial

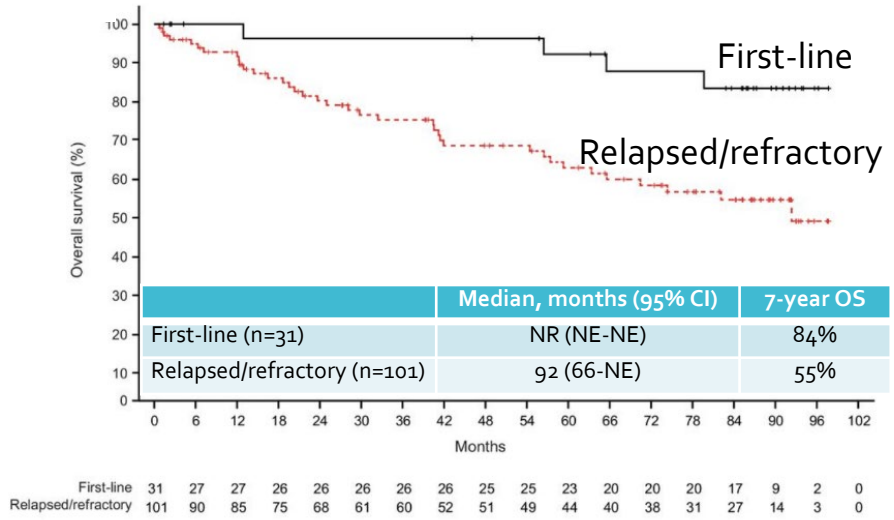
Long-term Survival Outcomes

Progression-Free Survival



	Median, months (95% CI)	7-year PFS
First-line (n=31)	NR (NE-NE)	83%
Relapsed/refractory (n=101)	52 (38-70)	34%

Overall Survival



	Median, months (95% CI)	7-year OS
First-line (n=31)	NR (NE-NE)	84%
Relapsed/refractory (n=101)	92 (66-NE)	55%

Median follow up 87 months

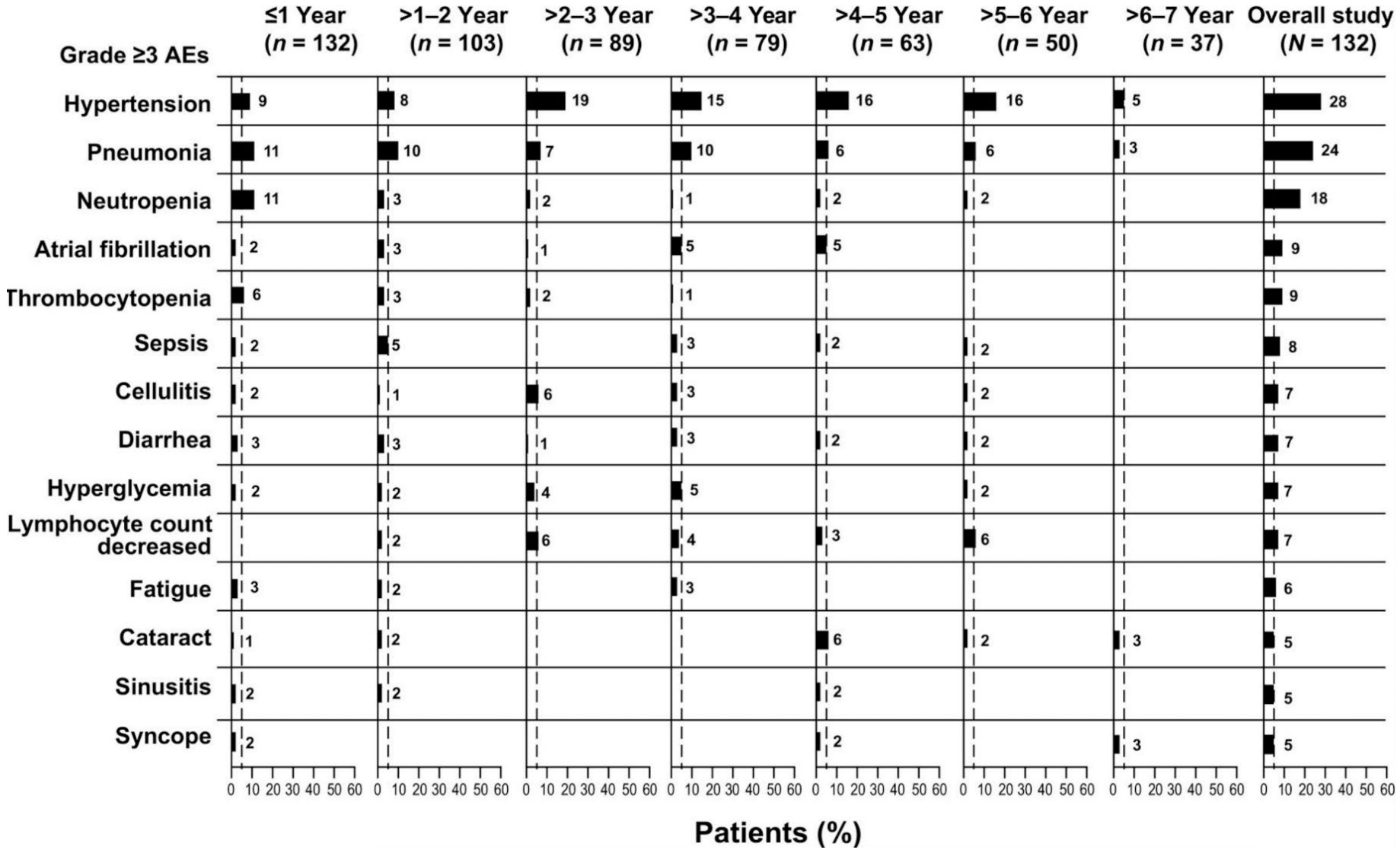
	Median PFS (mo)	7-Year PFS
TN (n = 31)	NR	83%
R/R (n = 101)	52	34%

	Median OS (mo)	7-Year OS
TN (n = 31)	NR	84%
R/R (n = 101)	92	55%

Byrd et al. Clin Cancer Research 2020; 26:3918-3927

PCYC1102 Phase Ib/II Trial

Safety

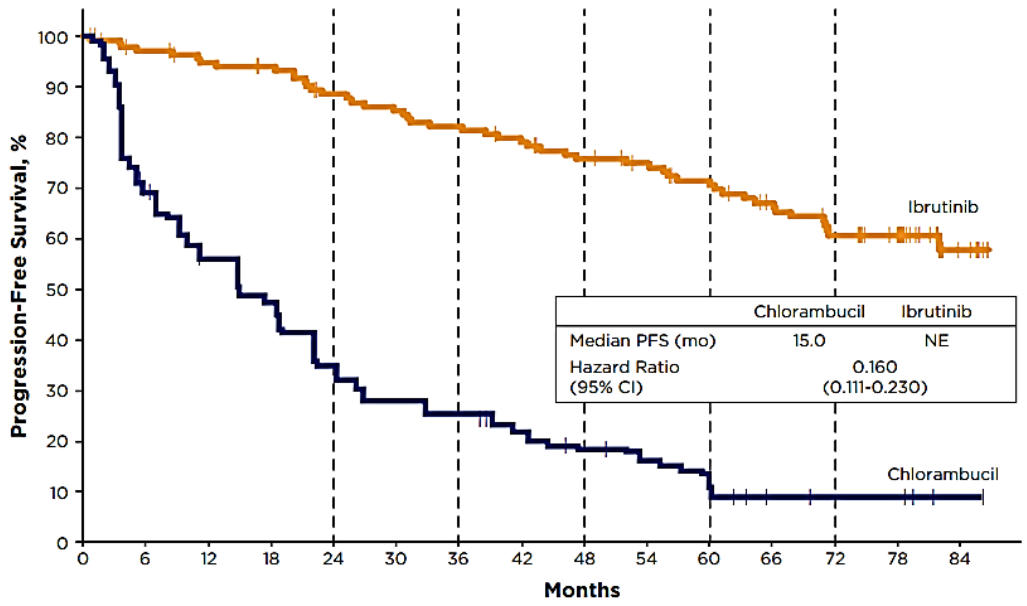


Byrd et al. Clin Cancer Research 2020; 26:3918-3927

RESONATE-2

Progression-free Survival

Seven-year follow-up of patients receiving ibrutinib for first-line treatment of CLL



- At 6.5 years, 61% of ibrutinib-treated patients and 9% (HR [95% CI]: 0.160 [0.111–0.230]) of chlorambucil-treated patients were estimated to be progression-free and alive
- 78% of ibrutinib-treated patients were estimated to be alive at 6.5 years
- Ibrutinib also resulted in improved OS vs chlorambucil: 83% vs 68% at 60 months; HR (95% CI): 0.450 (0.266–0.761)

Ghia et al. EHA 2021 ; Burger et al. Leukemia 2020; 34:787-798

RESONATE-2

Around half of the patients remain on ibrutinib with up to 7 years follow-up

	Ibrutinib n=136
Median duration of ibrutinib treatment, months (range)[a]	74.0 (0.7–86.8)
Continuing ibrutinib on study, n (%)	64 (47)
Discontinued ibrutinib, n (%)	
AE	31 (23)
PD[b]	16 (12)
Death	11 (8)
Withdrawal by patient	9 (7)
Investigator decision	4 (3)

[a]One patient received no doses of ibrutinib;
[b]Two patients discontinued due to Richter's transformation.

Ibrutinib was well tolerated with onset of most new grade ≥3 AEs decreasing over time

Ghia et al. EHA 2021

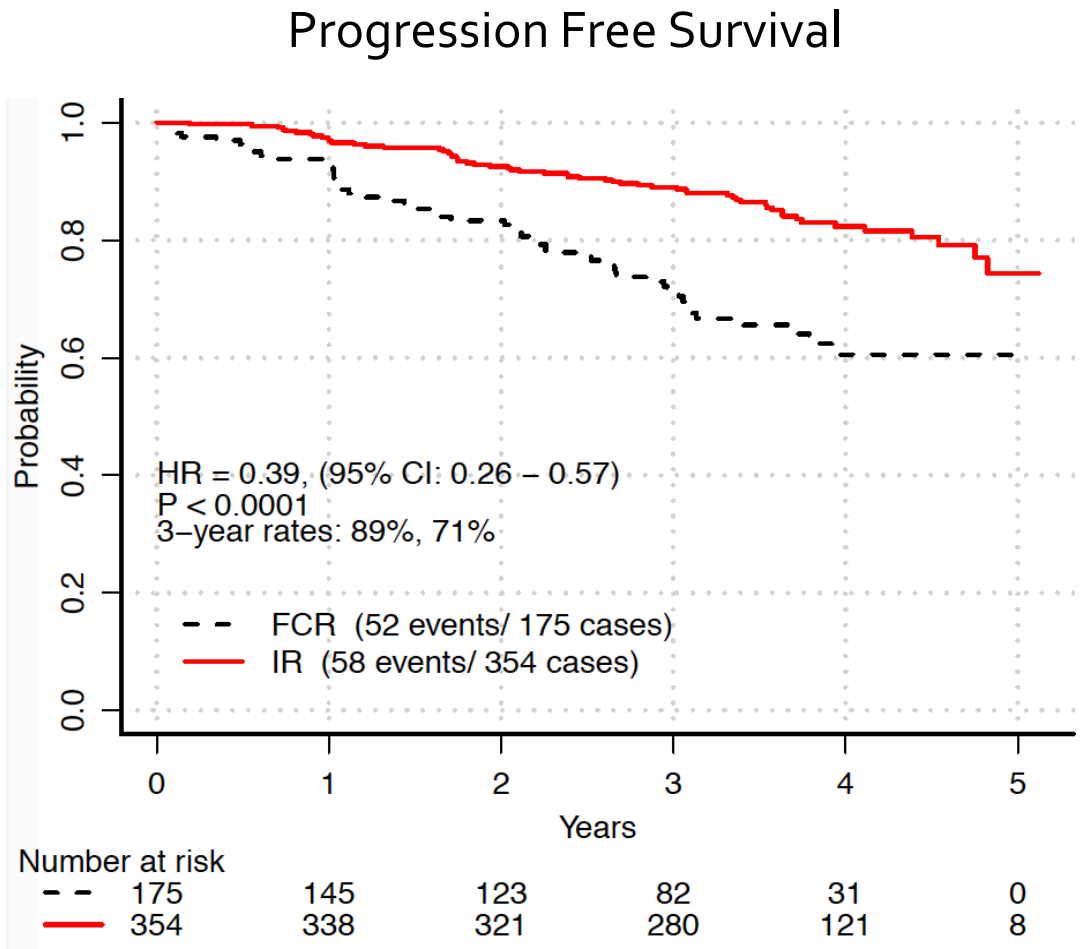
Update From the E1912 Trial Comparing Ibrutinib & Rituximab to FCR in Younger Patients with Previously Untreated Chronic Lymphocytic Leukemia (CLL)

Tait Shanafelt, Xin Victoria Wang, Neil E. Kay, Susan O'Brien, Jacqueline Barrientos , Curt Hanson, Harry Erba, Rich Stone, Mark Litzow, Marty Tallman

Shanafelt et al. ASH 2019. Abstract 33. NCT02048813
Shanafelt et al., N Engl J Med 2019;381(5):432-443

Updated Results E1912

PFS (median follow-up 45 months)



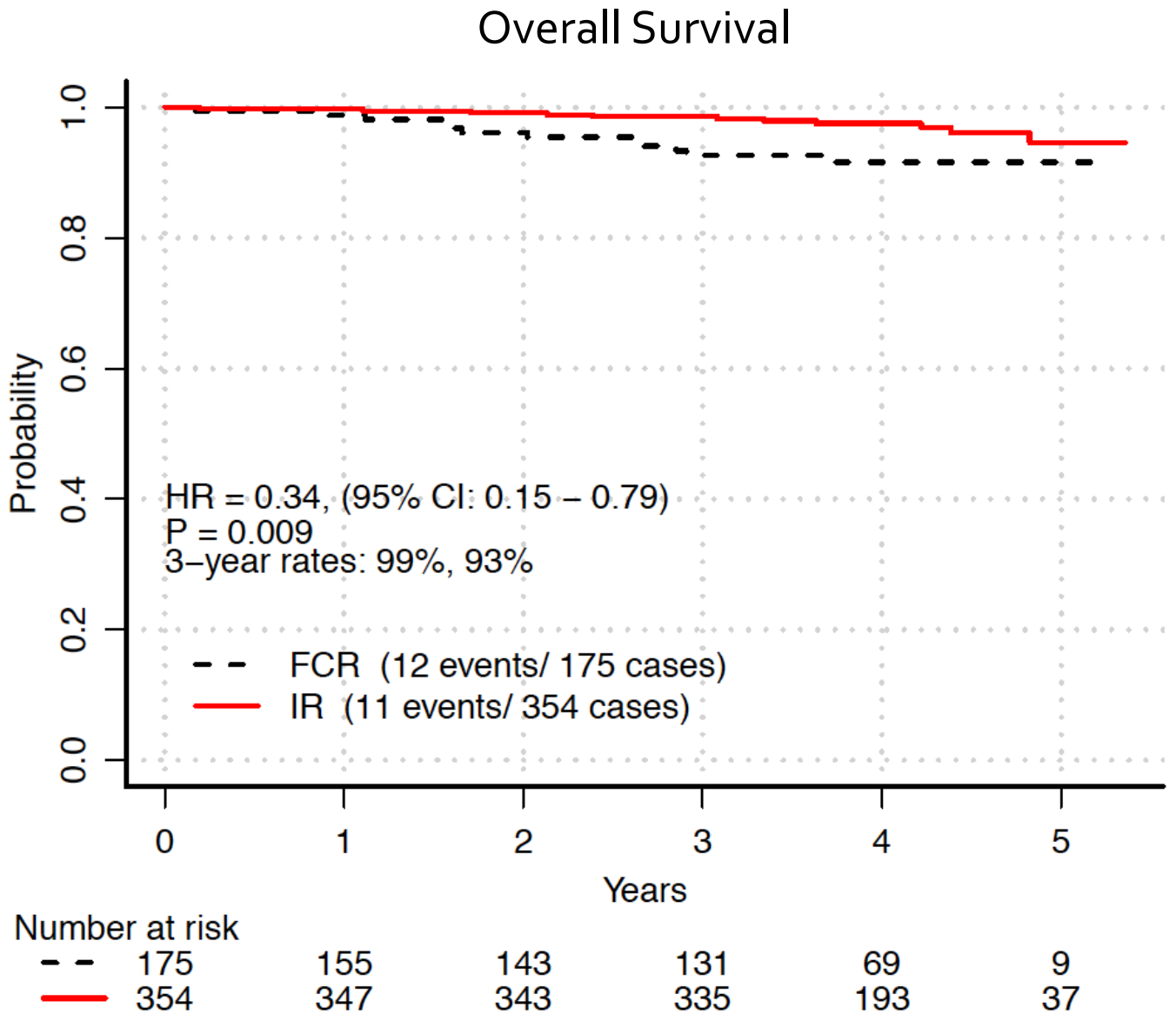
- 110 PFS events were observed
  - –includes 15 deaths without documented progression
- Overall there have been 23 deaths
- Hazard ratio (HR) for PFS is stable and continues to favour IR over FCR
  - –(HR=0.39; 95% CI 0.26-0.57; p < 0.0001)

IR was superior to FCR in unmutated CLL [HR 0.28 (0.17-0.48)] but not in mutated CLL [0.42 (0.16-1.16)]

Shanafelt et al. ASH 2019. Abstract 33. NCT02048813
Shanafelt et al., N Engl J Med 2019;381(5):432-443

Updated Results E1912

Overall Survival



Shanafelt et al. ASH 2019. Abstract 33. NCT02048813
Shanafelt et al., N Engl J Med 2019;381(5):432-443

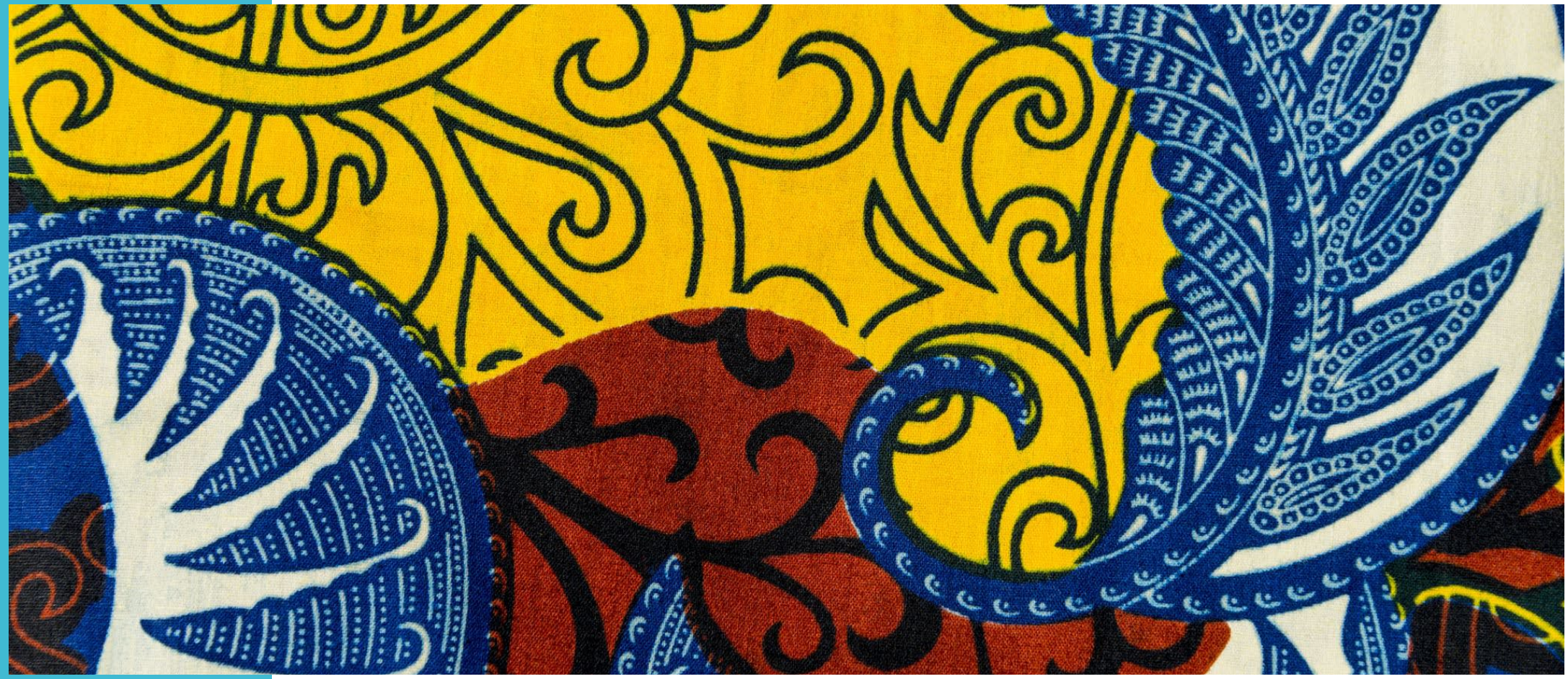
Reasons for Ibrutinib Discontinuation

Reason for Discontinuation	All Patients Who Started IR N=352	Patients Discontinuing Treatment N= 95
Progression or death	23 (7%)	23 (24%)
Adverse event	48 (14%)	48 (51%)
Other reason*	24 (7%)	24 (25%)

*Other health conditions, patient preference, lost to follow-up

Shanafelt et al. ASH 2019. Abstract 33. NCT02048813
Shanafelt et al., N Engl J Med 2019;381(5):432-443

ACALABRUTINIB



ELEVATE-TN Study Design

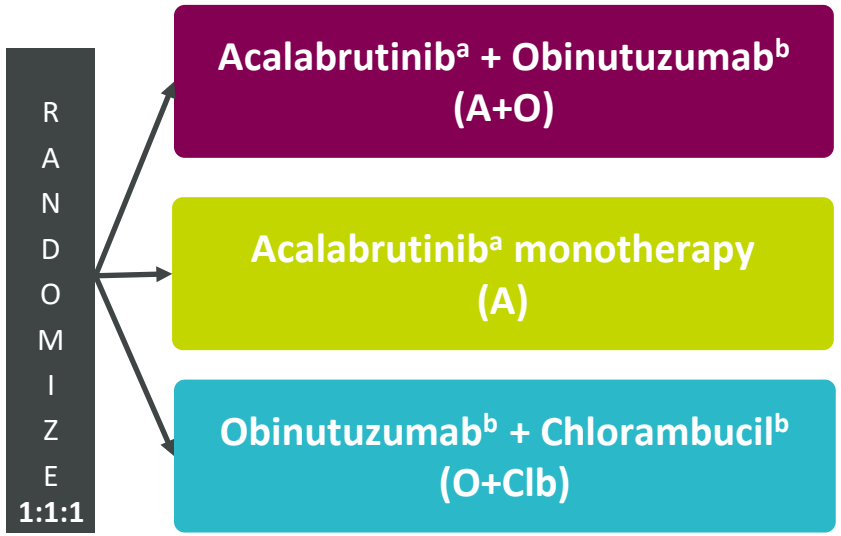
TN CLL (N=535)

Key Inclusion Criteria

- Age ≥65 years, or >18 to <65 years with comorbidities
  - Creatinine clearance 30–69 mL/min (by Cockcroft-Gault equation)
  - CIRS-G score >6
- Untreated CLL
  - Requiring treatment per iwCLL 2008 criteria[1]
- ECOG PS score ≤2
- Adequate hematologic, hepatic, and renal function

Stratification

- del(17p), y vs n
- ECOG PS 0–1 vs 2
- Geographic region (N America, W Europe, or other)



Primary endpoint

- PFS (IRC-assessed): A+O vs O+Clb

Secondary/other endpoints

- PFS (IRC-assessed): A vs O+Clb
- PFS (INV-assessed)
- ORR (IRC- and INV-assessed)
- Time to next treatment
- OS
- uMRD
- Safety

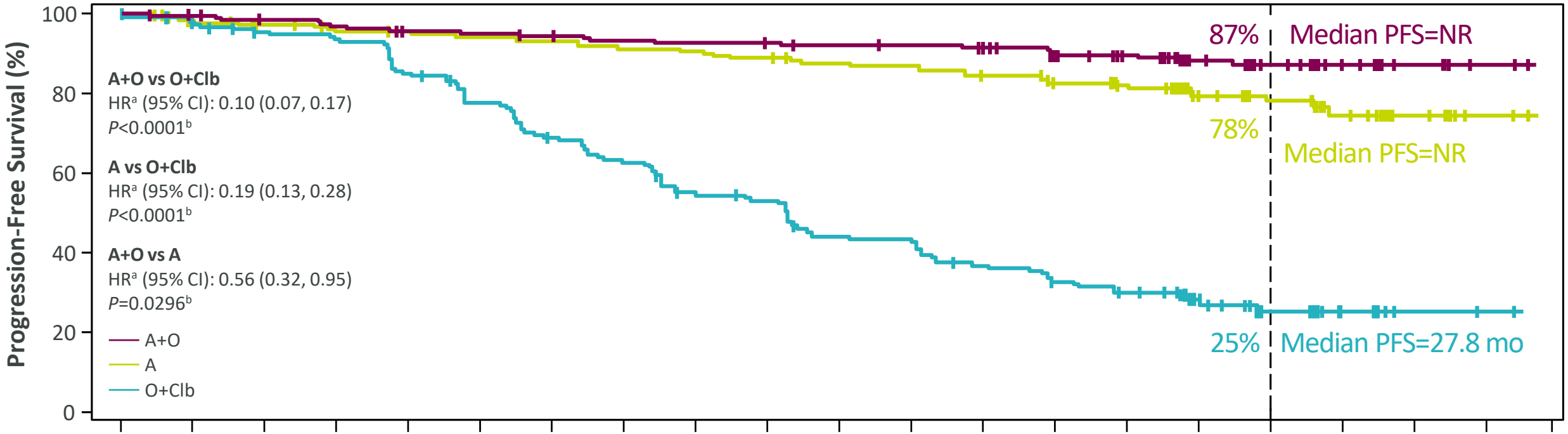
***Crossover** from O+Clb to A was allowed after IRC-confirmed progression*

Note: After interim analysis,[2] PFS assessments were by investigator only

Key exclusion criteria: Significant cardiovascular disease (uncontrolled or symptomatic arrhythmias, congestive heart failure, or myocardial infarction within 6 months of screening, or any Class 3 or 4 cardiac disease as defined by the New York Heart Association Functional Classification, or QTc >480 msec at screening)

NCT02475681.
Data cutoff: September 11, 2020.
[a]Continued until disease progression or unacceptable toxicity at 100 mg PO BID; [b]Treatments were fixed duration and administered for 6 cycles.
A, acalabrutinib; CIRS-G, Cumulative Illness Rating Scale-Geriatric; Clb, chlorambucil; CLL, chronic lymphocytic leukemia; ECOG PS, Eastern Cooperative Oncology Group performance status; INV, investigator; IRC, independent review committee; O, obinutuzumab; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; TN, treatment-naïve; uMRD, undetectable minimal residual disease.
1. Hallek M, et al. *Blood*. 2008;111:5446-56. 2. Sharman J, et al. *Lancet*. 2020;395:1278-91.

Investigator-assessed PFS Overall



Number at risk																				
A+O	179	176	171	168	164	163	160	157	156	155	153	152	150	141	132	85	59	33	12	2	0
A	179	167	163	158	156	155	153	150	149	146	142	141	136	130	123	79	61	35	16	4	0
O+Clb	177	163	156	153	139	125	110	100	86	82	67	66	55	48	42	22	13	6	2	1	0

[a]Hazard ratio was based on stratified Cox-Proportional-Hazards model; [b]*P*-value was based on stratified log-rank test.
A, acalabrutinib; CI, confidence interval; Clb, chlorambucil; HR, hazard ratio; NR, not reached; O, obinutuzumab; PFS, progression-free survival.

Events of Clinical Interest

Table 1. Events of Clinical Interest

	A+O (n=178)		A (n=179)		O+Clb (n=169)	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3	Any Grade	Grade ≥3
Cardiac events[a]	37 (20.8)	14 (7.9)[b]	34 (19.0)	15 (8.4)[c]	13 (7.7)	3 (1.8)
Atrial fibrillation	7 (3.9)	1 (0.6)	11 (6.1)	2 (1.1)	1 (0.6)	0
Bleeding	84 (47.2)	5 (2.8)	75 (41.9)	5 (2.8)	20 (11.8)	0
Major bleeding[d]	7 (3.9)	5 (2.8)	7 (3.9)	5 (2.8)	2 (1.2)	0
Hypertension	14 (7.9)	6 (3.4)	13 (7.3)	5 (2.8)	7 (4.1)	6 (3.6)
Infections	134 (75.3)	42 (23.6)	132 (73.7)	29 (16.2)	75 (44.4)	14 (8.3)
SPMs	28 (15.7)	13 (7.3)	24 (13.4)	5 (2.8)	7 (4.1)	3 (1.8)
SPMs excluding non-melanoma skin	15 (8.4)	10 (5.6)	11 (6.1)	4 (2.2)	3 (1.8)	2 (1.2)

Data are n (%) unless otherwise specified. Median duration of exposure was 46.6 months for A+O, 45.7 months for A, and 5.6 months for O+Clb.
[a]Cardiac events that occurred in >1 patient (any grade; other than atrial fibrillation) in any group include angina pectoris, palpitations, atrioventricular block complete, myocardial ischemia, tachycardia, bradycardia, cardiac failure, left ventricular failure, myocardial infarction, pericardial effusion, acute myocardial infarction, and supraventricular tachycardia. [b]Cardiac events (grade ≥3) that occurred in >1 patient (other than atrial fibrillation) include atrioventricular block complete (n=3), angina pectoris (n=2), myocardial ischemia (n=2), and myocardial infarction (n=2). [c]Cardiac events (grade ≥3) that occurred in >1 patient (other than atrial fibrillation) include acute myocardial infarction (n=3), cardiac failure (n=2), and myocardial infarction (n=2). [d]Defined as any serious or grade ≥3 hemorrhagic event, or any grade hemorrhagic event in the central nervous system.

Sharman et al. ASCO 2021

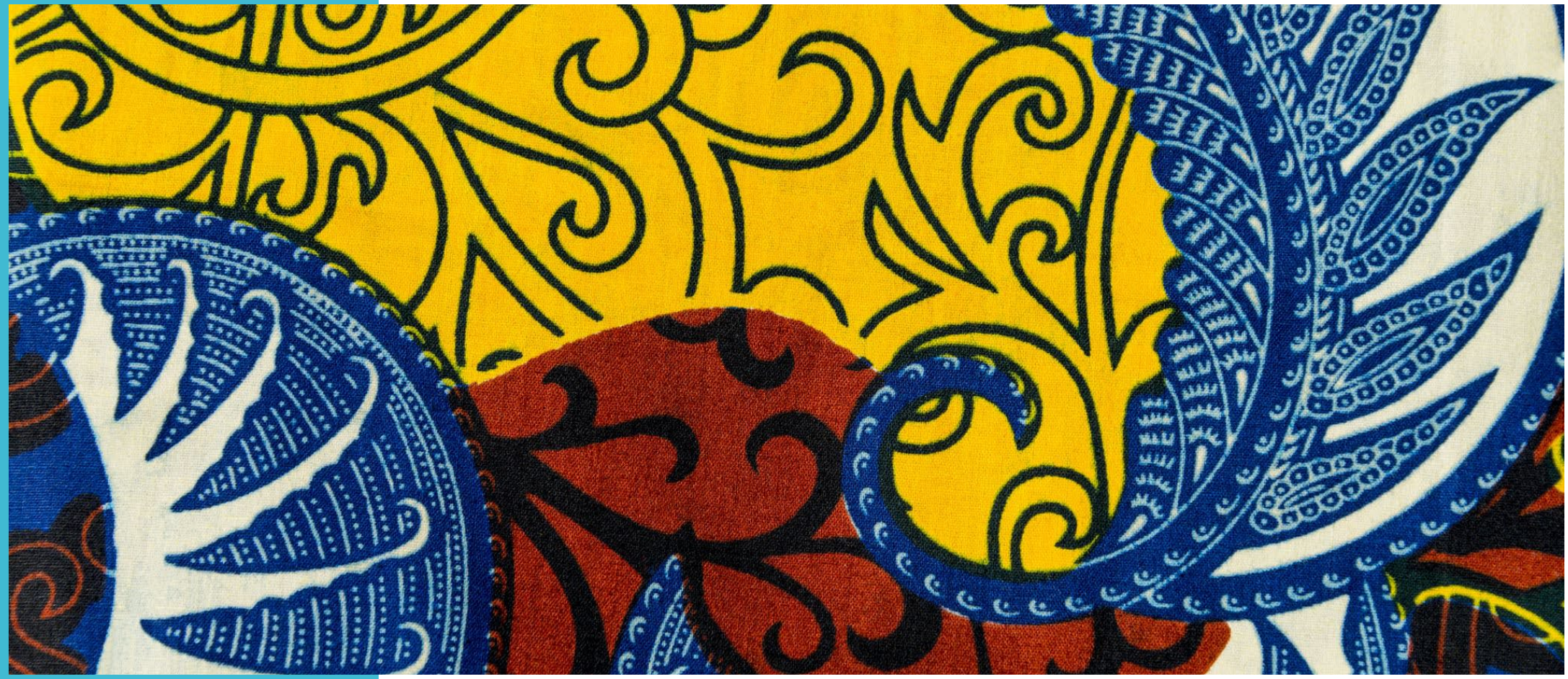
Maximizing the Benefits of Therapy in CLL: Can Time-Limited Therapy Lead to Long-Term Disease Control?

Continuous

OR

Time-limited therapy?

VENETOCLAX + OBINUTUZUMAB

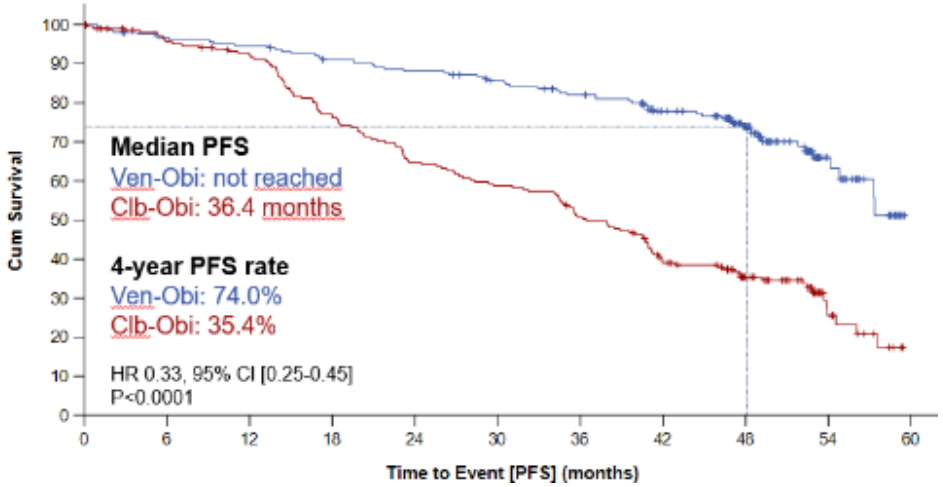


VENETOCLAX PLUS OBINUTUZUMAB

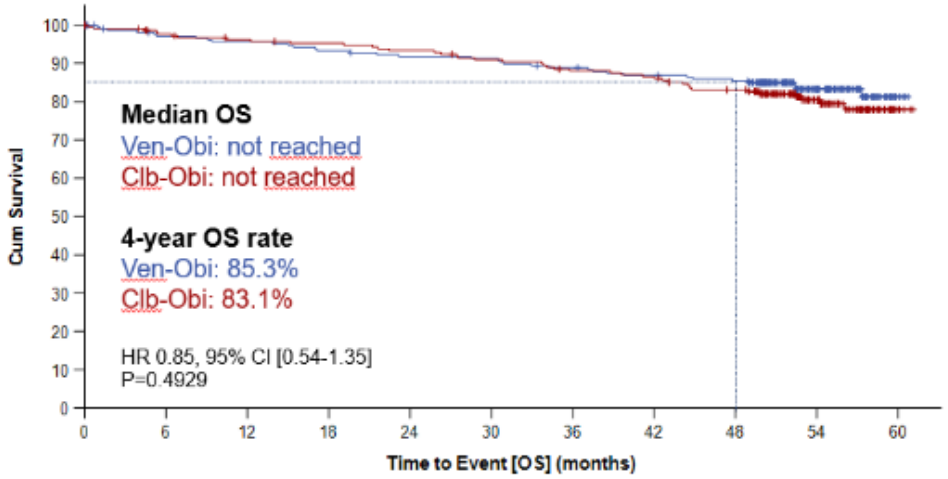
CLL14 Venetoclax + Obinutuzumab

4-year Survival Outcomes:
74% PFS
85.3% OS

Progression-Free Survival



Overall Survival



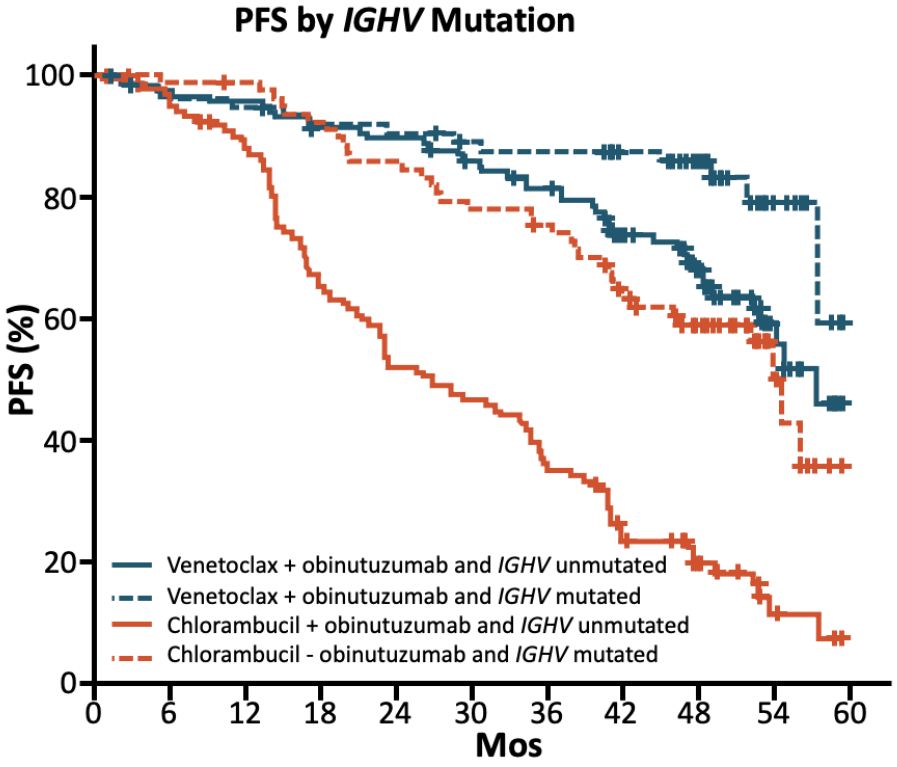
Median observation: 52.4 mos

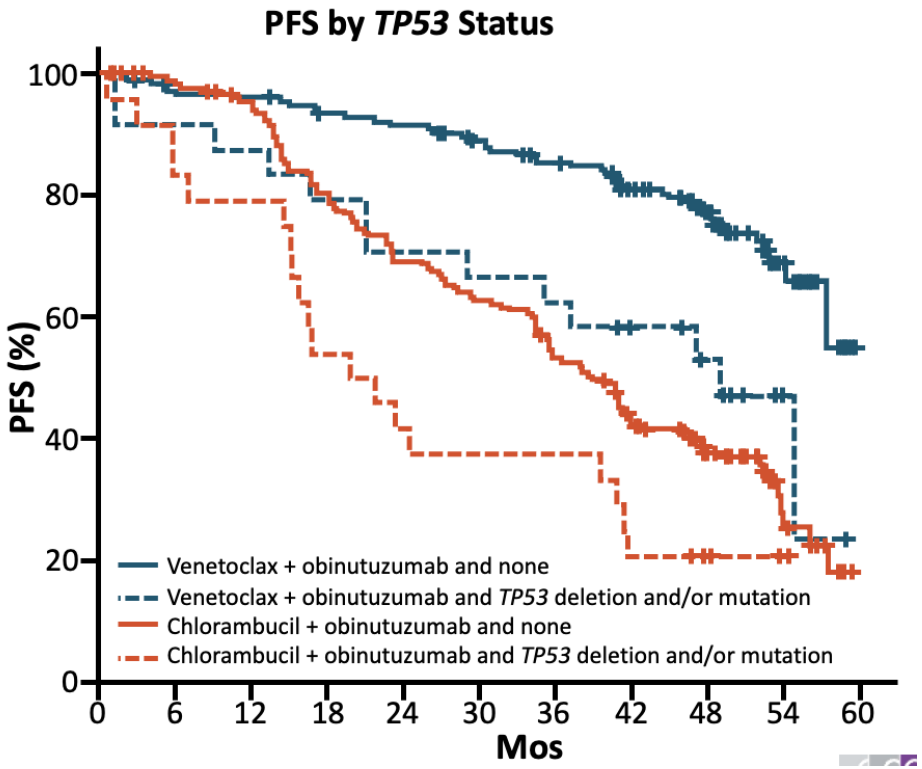
4-year PFS 74.0%; 53% del17p/TP53 mutated

Al-Sawaf O, et al., Presented at ASH 2020 Abstract 127; EHA 2021 Abstract S146

CLL14 Venetoclax + Obinutuzumab

4-year PFS in High-Risk Disease





Median observation: 52.4 mos

4-year PFS 68.0% IGHV unmutated; 53% del17p/TP53 mutated

Al-Sawaf O, et al., Presented at ASH 2020 Abstract 127; EHA 2021 Abstract S146

TOXICITY MANAGEMENT

Ibrutinib and Atrial Fibrillation

79 yo man diagnosed with CLL in JAN2015

- treatment indicated due to significant anemia, adenopathy
- HTN, hyperlipidemia, tobacco use
- started ibrutinib with complete clinical response within 3 months

NOV2016 asymptomatic atrial fibrillation

- Ibrutinib held, cardiac evaluation showed normal EF, no valve abnormality
- treated with amiodarone, apixaban

JAN2017

- restarted ibrutinib at 280mg daily
- no further episodes of afib
- no bleeding

Ibrutinib Adverse Events

Adverse event	Phase 2 follow-up 21 months (n=85)[1]	Phase 3 RESONATE		Phase 3 RESONATE2	
		Follow-up 9 months (n=195)[2]	Follow-up 19 months (n=195)[3]	Follow-up 18 months (n=135)[4]	Follow-up 21 months (n=135)[5]
Atrial fibrillation					
All grades	3 (4)	10 (5)	13 (7)	8 (6)	14 (10)
Grade ≥3	0	6 (3)	7 (4)	2 (1)	6 (4)
Bleeding					
All grades	14 (16)	86 (44)	NR	NR	9 (7)
Grade ≥3	4 (5)	2 (1)	4 (2)	6 (4)	8 (6)
Infection					
All grades	NR	137 (70)	NR	NR	NR
Grade ≥3	NR	47 (24)	59 (30)	NR	31 (23)
Arthralgia					
All grades	23 (27)	34 (17)	44 (23)	22 (16)	27 (20)
Grade ≥3	0	2 (1)	NR	2 (1)	3 (2)
Myalgia					
All grades	16 (19)	19 (10)	NR	NR	NR
Grade ≥3	1 (1)	1 (1)	NR	NR	NR

Stephens D.M & Byrd J.C. Blood 2019;133:1298–1307

Ibrutinib and Arthralgias

63 yo woman requires treatment for her CLL

- Started ibrutinib 420 mg daily with excellent initial clinical response
- At first return visit in 4 weeks complained of arthralgias in hands
- Avid tennis player, unable to play
- Exam shows no joint swelling or erythema

Ibrutinib Adverse Events

Adverse event	Phase 2 follow-up 21 months (n=85)[1]	Phase 3 RESONATE		Phase 3 RESONATE2	
		Follow-up 9 months (n=195)[2]	Follow-up 19 months (n=195)[3]	Follow-up 18 months (n=135)[4]	Follow-up 21 months (n=135)[5]
Atrial fibrillation All grades Grade ≥3	3 (4) 0	10 (5) 6 (3)	13 (7) 7 (4)	8 (6) 2 (1)	14 (10) 6 (4)
Bleeding All grades Grade ≥3	14 (16) 4 (5)	86 (44) 2 (1)	NR 4 (2)	NR 6 (4)	9 (7) 8 (6)
Infection All grades Grade ≥3	NR NR	137 (70) 47 (24)	NR 59 (30)	NR NR	NR 31 (23)
Arthralgia All grades Grade ≥3	23 (27) 0	34 (17) 2 (1)	44 (23) NR	22 (16) 2 (1)	27 (20) 3 (2)
Myalgia All grades Grade ≥3	16 (19) 1 (1)	19 (10) 1 (1)	NR NR	NR NR	NR NR

Stephens D.M & Byrd J.C. Blood 2019;133:1298–1307

Ibrutinib and Arthralgias

- Pooled results from 4 randomized studies in CLL
  - 13% all grade arthralgias
  - Outside of trials, most common reason for discontinuation
  - Early onset, within first 6 months
- Manage symptomatically, as it will usually resolve within 6 months
  - Dose reduction; hold for a week, restart at 280 mg
  - Severe cases: 7 day course of tapering steroids

O'Brien S et al. Clin Lymphoma Myeloma Leuk 2018;18:648–57

EA9161 Study

Key eligibility

- CLL/SLL
- Has indication for treatment
- no del17p
- age 18-70
- ECOG 0-2
- HIV+ acceptable if viral load neg
- GFR > 40 mL/minute
- no Warfarin or VKA
- no prior autoimmune complications requiring treatment

RANDOMIZE

Stratification
- Age
- PS
- Stage
- del11q

VENETOCLAX
Cycles 3-14

IBRUTINIB
Cycles 1-19

OBINUTUZUMAB
Cycles 1-6

Primary endpoint:

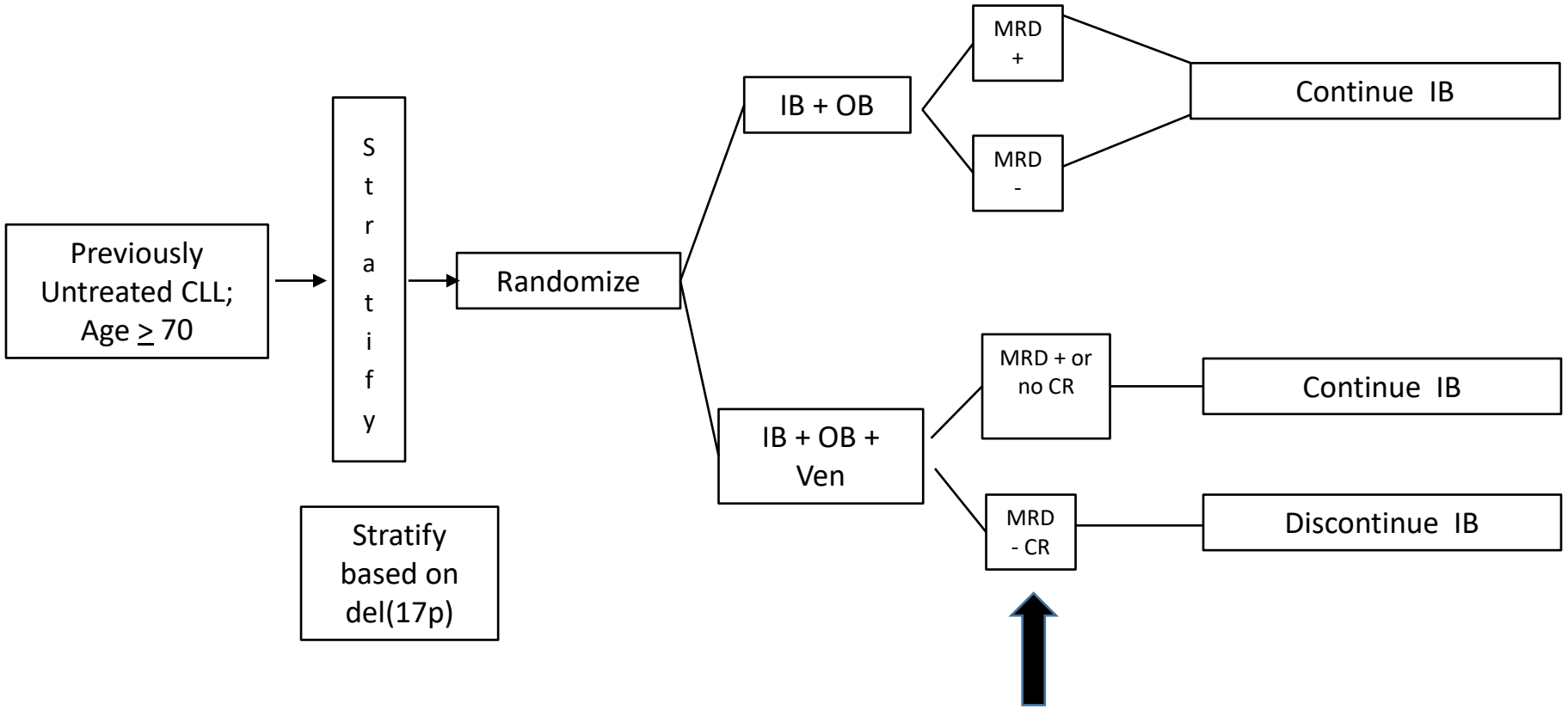
PFS

IBRUTINIB
Cycles 1-19

OBINUTUZUMAB
Cycles 1-6

A041702 Study

Study Schema



Asymptomatic CLL Patients in 2020

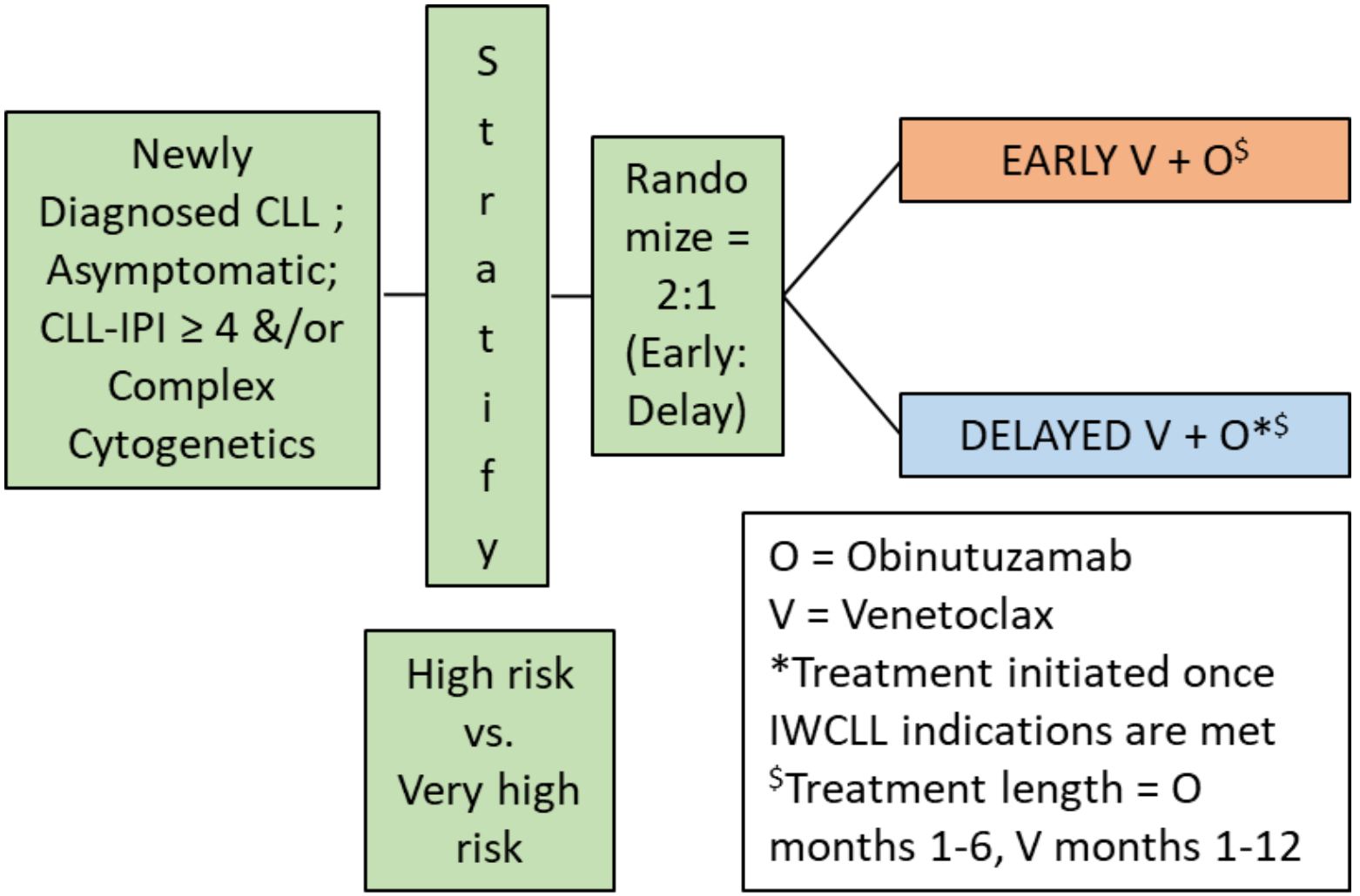
- Current recommendation: “Watch and Wait”
- Prior early intervention studies (chlorambucil, fludarabine) failed to show overall survival benefit
- CLL International Prognostic Index (IPI): Predictor of survival

Characteristic	Points
Del(17p) or TP53 mutation	4
Serum B2M ≥ 3.5mg/L	2
Un-mutated IgVH status	2
Rai Stage I-IV	1
Age > 65 years	1

- 5-year Overall Survival:
  - High (4-6) = 53%
  - Very high (≥7) = 19%
- Treatment-free at 5 year: <50%
- Group of interest for early intervention

CLL-IPI Group, Lancet Oncol 2016; Molica AJH 2016

S1925: EVOLVE Study



1◦ Endpoint: Overall Survival = Accrual goal → 247 patients

2◦ Endpoints:
Safety, ORR, DOR, PFS, PFS2, TTNT, MRD, QOL

Translational Endpoints:
MRD, resistance