Treatment options for younger, fit patients with CLL

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Pre-treatment workup

Treatment Indications

- Anemia and/or thrombocytopenia (hemoglobin <10 g/dL or platelets <100 x10^9/L)
- Symptomatic splenomegaly (≥6 cm below the left costal margin)
- Symptomatic lymphadenopathy (≥10 cm in longest diameter)
- Lymphocytosis increase of more than 50% over a 2-month period or lymphocyte doubling time (LDT) of less than 6 months
- Autoimmune anemia and/or thrombocytopenia that is poorly responsive to corticosteroids or other standard therapy
- Symptomatic or functional extranodal involvement (e.g. skin, kidney, lung, spine)
- Constitutional symptoms:
  - Unintentional weight loss of ≥10% within the previous 6 months;
  - Significant fatigue (i.e. inability to work or perform usual activities);
  - Fevers higher than 100.5°F or 38.0°C for 2 or more weeks; or
  - Night sweats for ≥1 month without evidence of infection

Hallek M et al. *Blood.* 2018;131:2745-2760.

Courtesy of Paul M Barr, MD

iwCLL Recommended Testing Before Treatment

Diagnostic Test	Practice Recommendation
History, physical, infection status	Always
CBC, chemistry, Igs, DAT	Always
Serum β2 microglobulin	Desirable
Marrow aspirate and biopsy	When needed (unclear cytopenia)
CT scan of chest, abdomen, pelvis	If possible
IGHV mutational status	Always*
FISH for add(12), del(13q), del(11q), del(17p) in peripheral blood	Always
TP53 mutation	Always
Conventional karyotyping	Not generally indicated**

*Does not need to be repeated before subsequent therapy

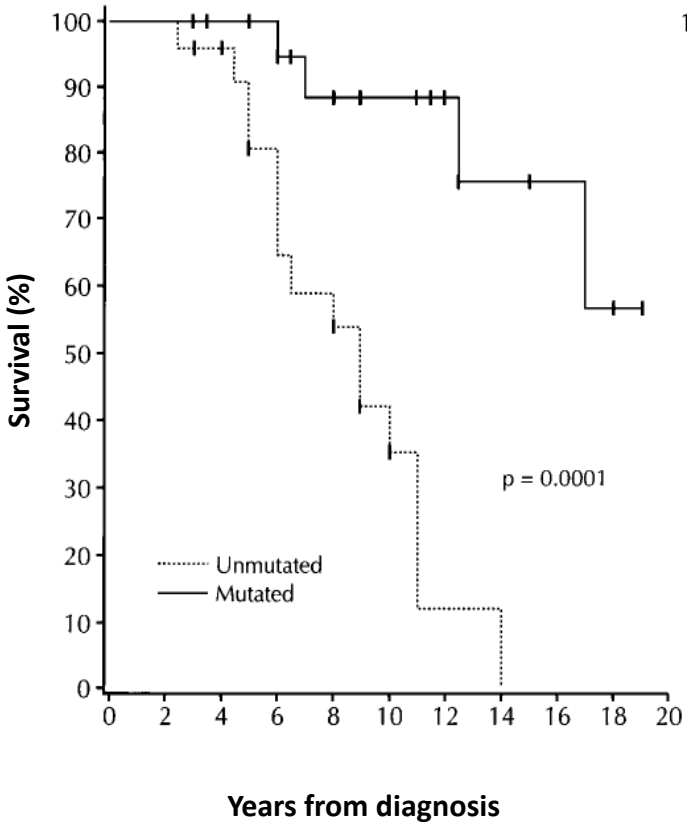
**Conventional karyotyping (with specific stimulation) may be useful before therapy, if established methodology is available

CBC = complete blood count; IGHV = immunoglobin heavy chain variable region; iwCLL = International Workshop on Chronic Lymphocytic Leukemia.

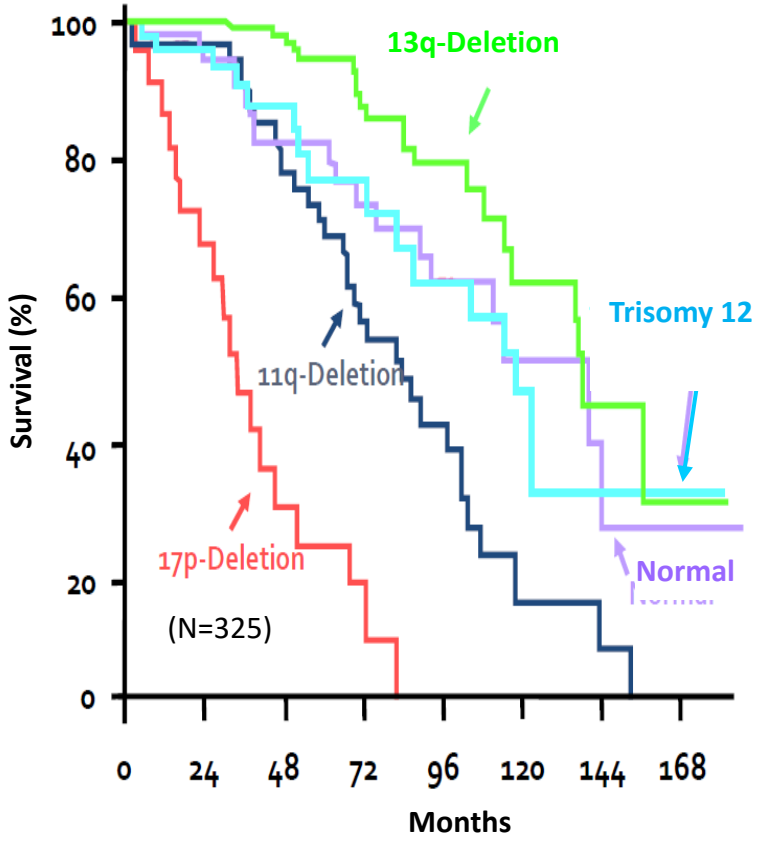
Hallek M et al. *Blood*. 2018;131:2745-2760.

Courtesy of Paul M Barr, MD

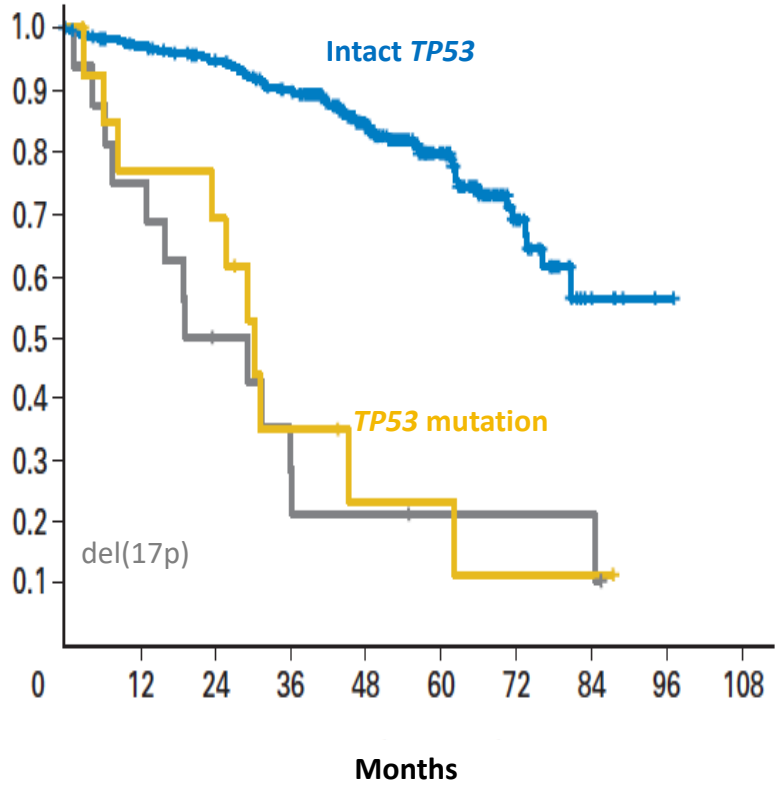
iwCLL: Risk Factor Testing



Damle RN et al. *Blood*. 1999;94:1840-1847.



Döhner H, et al. *N Engl J Med*. 2000;343:1910-1016.



Zenz T et al. *J Clin Oncol.* 2010;28:4473-4479.

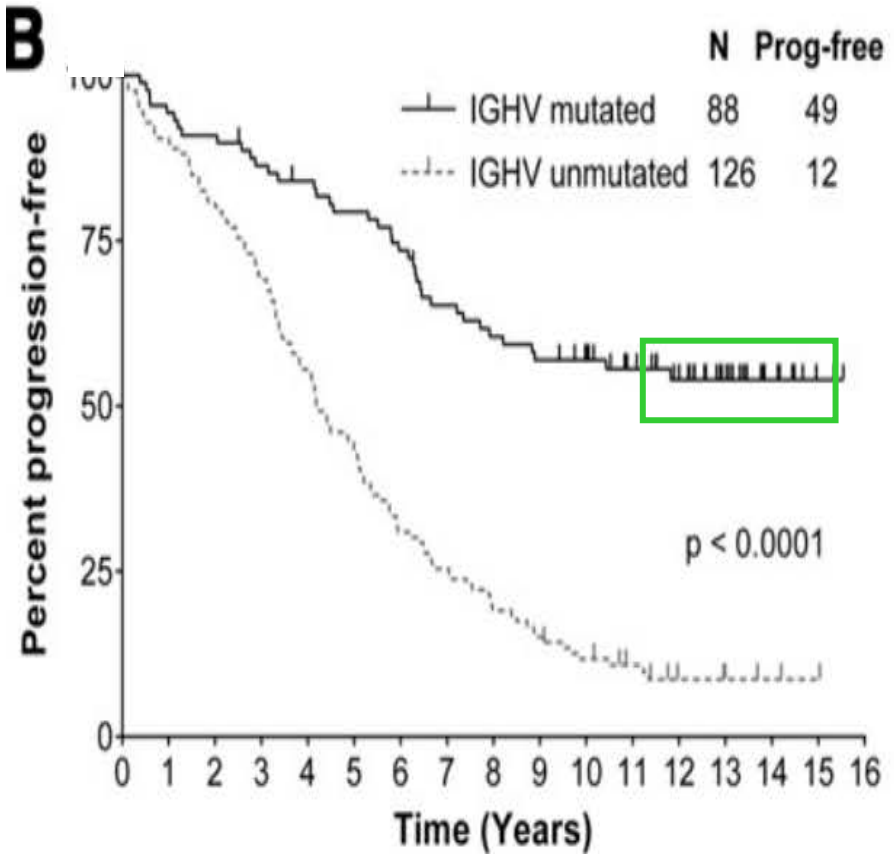
Courtesy of Paul M Barr, MD

Clinical Trials

Focus on BTK inhibitors

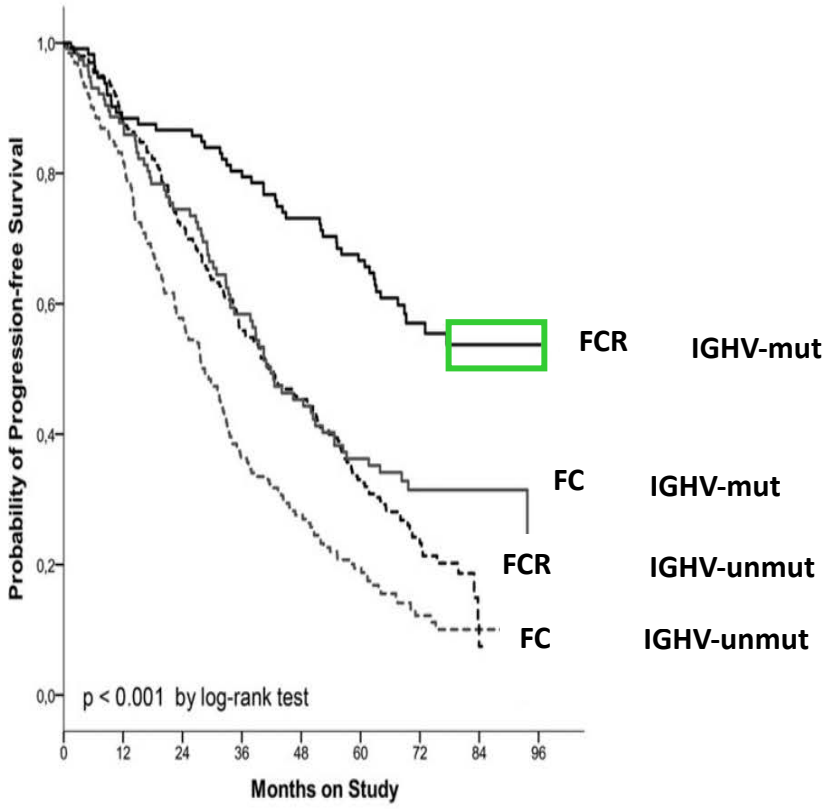
Curative Potential of FCR in Mutated IGHV CLL?

MDACC – FCR 300



Thompson PA et al. *Blood.* 2016;127(3):303-309.

GCLLSG – CLL8



Fischer K et al. *Blood.* 2016;127(2):208-215.

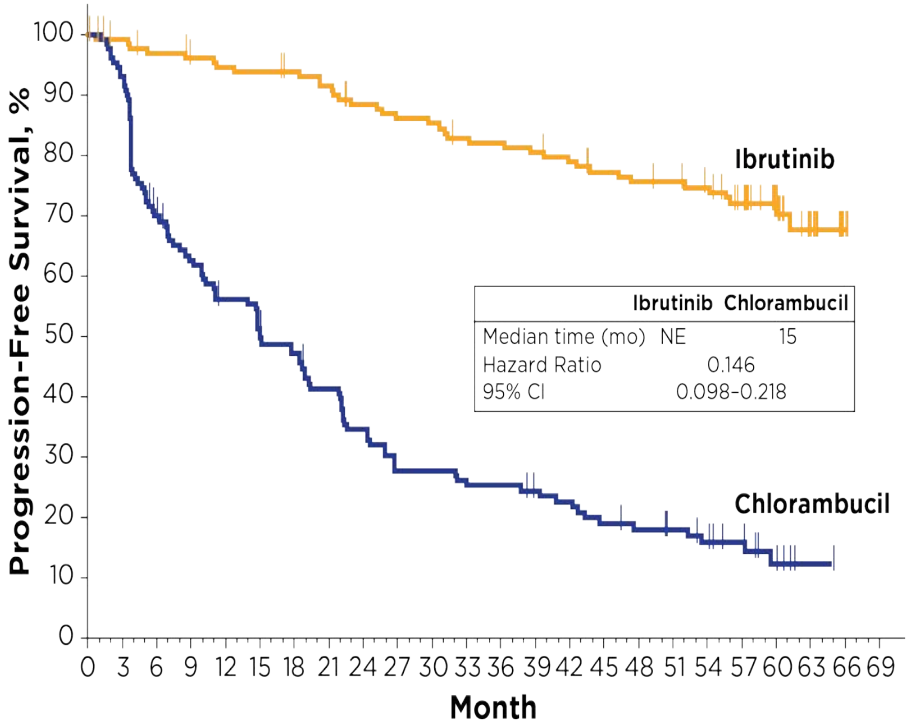
FCR = fludarabine, cyclophosphamide, rituximab; IGHV = immunoglobin heavy chain variable region gene; GCLLSG = German CLL Study Group; MDACC = MD Anderson Cancer Center

Courtesy of Paul M Barr, MD

RESONATE-2

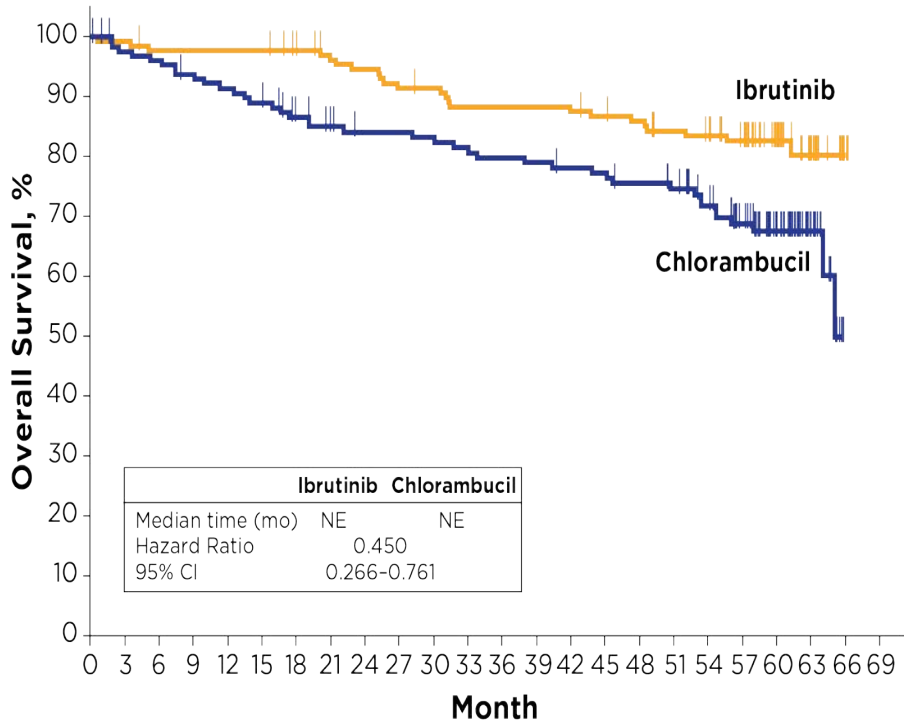
Five-year Follow-up of First-line Ibrutinib

Progression-Free Survival



At 5 years, 70% of ibrutinib-treated patients and 12% of chlorambucil-treated pts were estimated to be progression-free and alive (HR [95% CI]: 0.146 [0.098–0.218])

Overall Survival



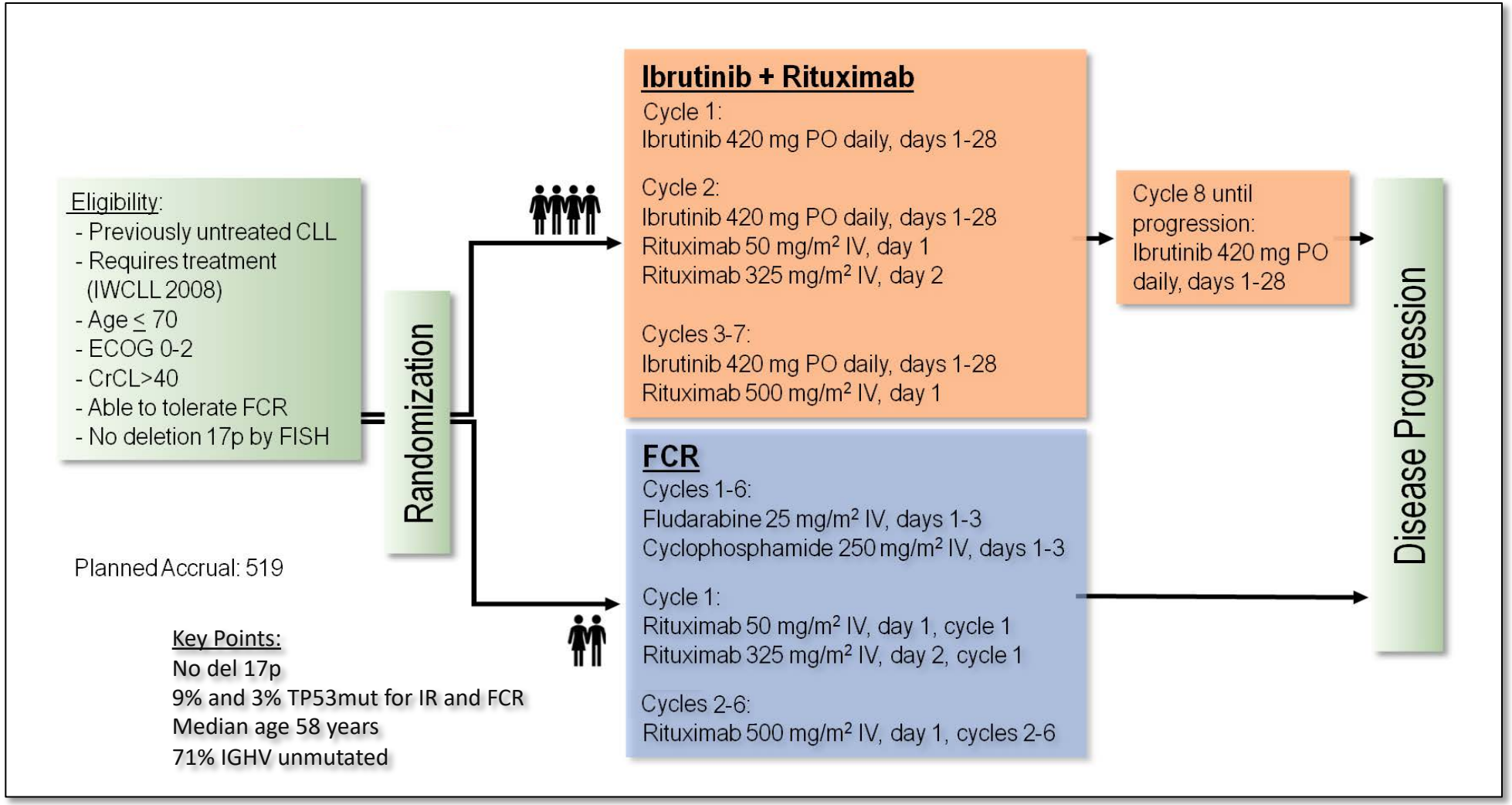
Improved OS for ibrutinib vs chlorambucil: 5-yr estimates, 83% vs 68%; HR (95% CI): 0.450 (0.266–0.761)

HR = hazard ratio; OS = overall survival

Tedeschi A et al. 2019 Congress of the European Hemagology Association (EHA). Abstract S107.

Courtesy of Paul M Barr, MD

ECOG-E1912



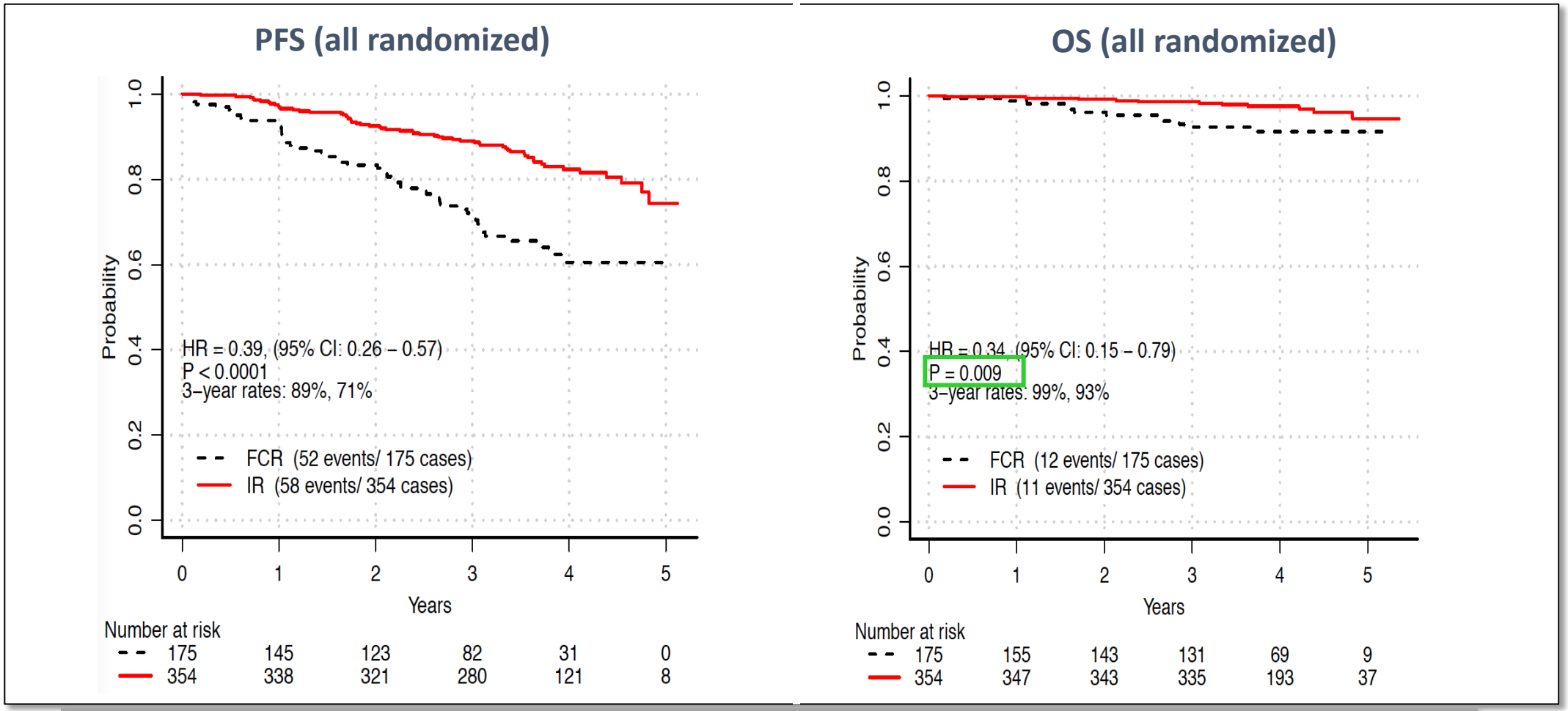
CrCl = creatinine clearance; ECOG = Eastern Cooperative Oncology Group;
FCR = fludarabine, cyclophosphamide, rituximab; FISH = fluorescence in situ hybridization

Shanafelt TD et al. *Blood.* 2019;(suppl 1):Abstract 33.

Courtesy of Paul M Barr, MD

Ibrutinib vs FCR

In Untreated Younger Patients with CLL (E1912)

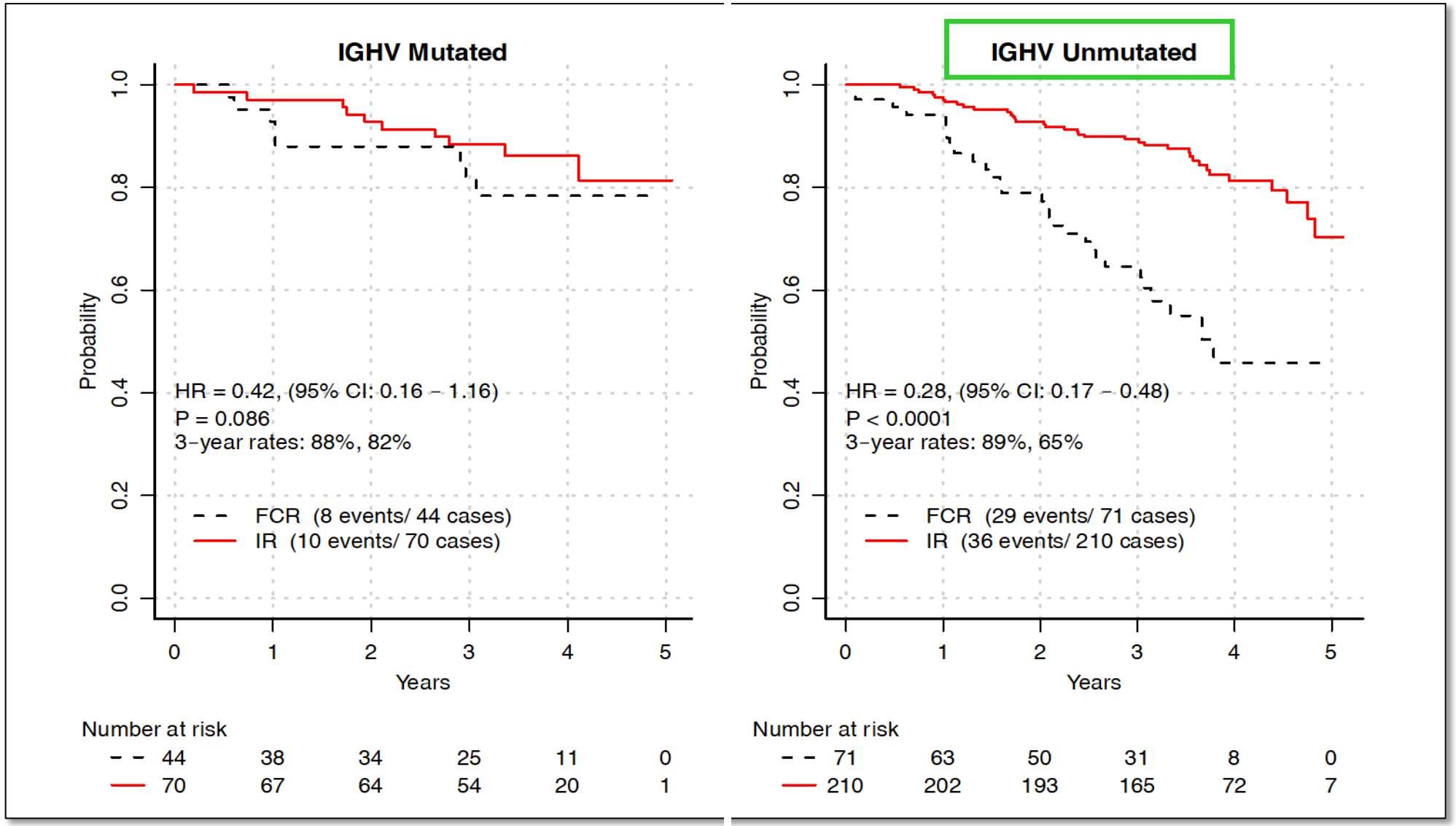


With a median follow-up of 48 months, 73% of IR patients remain on treatment; Only 7% of ibrutinib treated patients progressed while on therapy

Shanafelt TD et al. *Blood.* 2019;(suppl 1):Abstract 33.

Courtesy of Paul M Barr, MD

Progression Free Survival: IGHV Status



Shanafelt TD et al. *Blood.* 2019;(suppl 1):Abstract 33.

Courtesy of Paul M Barr, MD

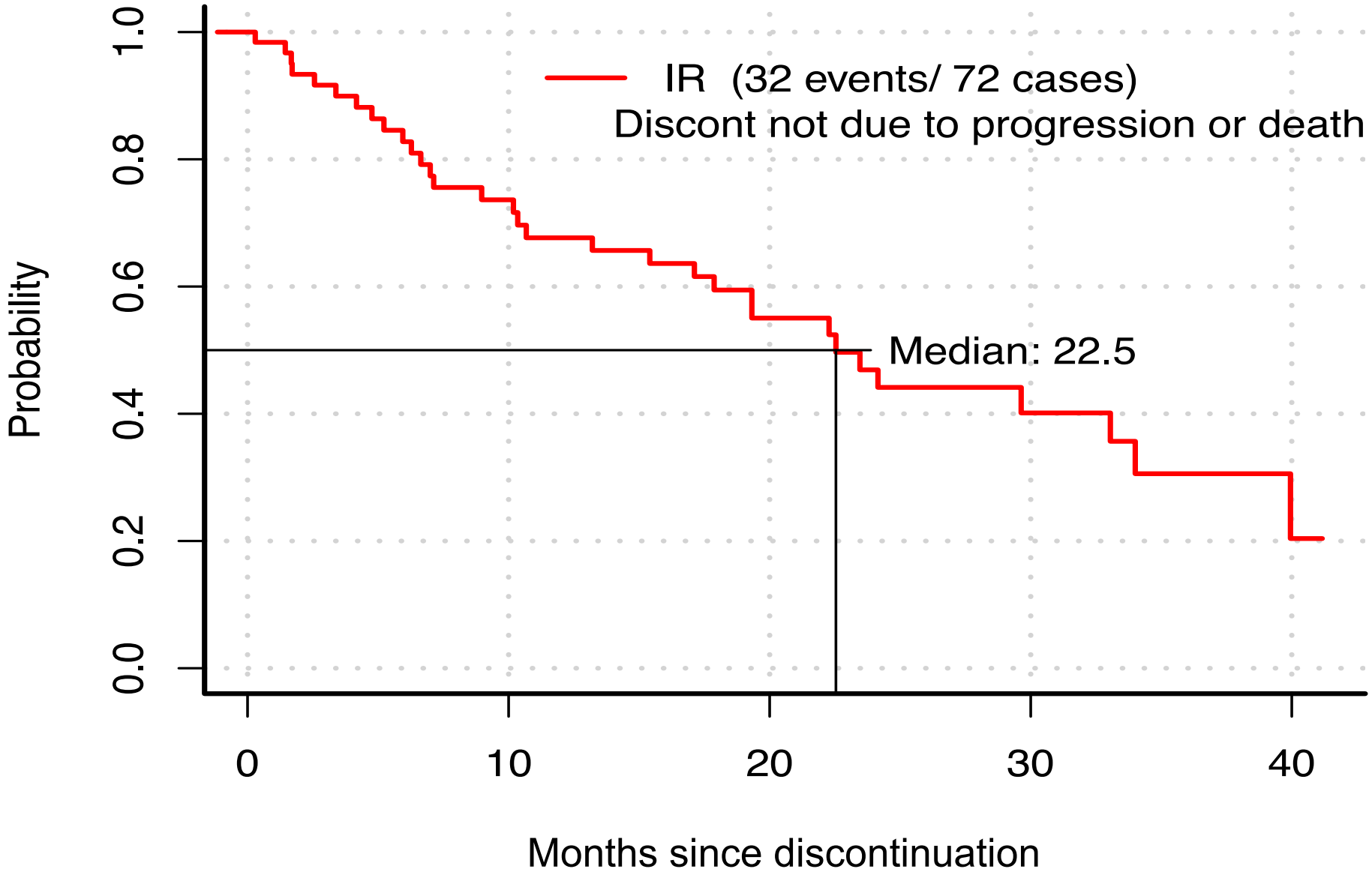
E1912: Grade 3-5 Treatment-related Adverse Events

Adverse Event	IR (n=352, %)	FCR (n=158, %)	*P*-value
Anemia	4.3	**15.8**	<0.001
Arthralgia	**5.1**	0.6	0.011
Diarrhea	**2.6**	0.6	0.185
Hemolysis	0	2.5	0.009
Hypertension	**8.5**	1.9	0.003
Neutrophil count decreased	27	**43**	<0.001
Platelet count decreased	3.1	**15.8**	<0.001
Febrile neutropenia	2.3	**15.8**	<0.001
Infection	7.1	8.9	0.477
Sepsis	0.6	**3.2**	0.032
Other infections	7.1	6.3	0.851
Cardiac	**5.4**	0	0.001
Atrial fibrillation	**2.8**	0	0.036
Other cardiac	**3.4**	0	0.022
Any Grade 3 or higher AE	**69.6**	**80.4**	**0.013**

Shanafelt TD et al. *Blood.* 2019;(suppl 1):Abstract 33.

Courtesy of Paul M Barr, MD

E1912: Progression Free Survival Post Discontinuation of Ibrutinib



N=72

Median time of therapy 15.1 months

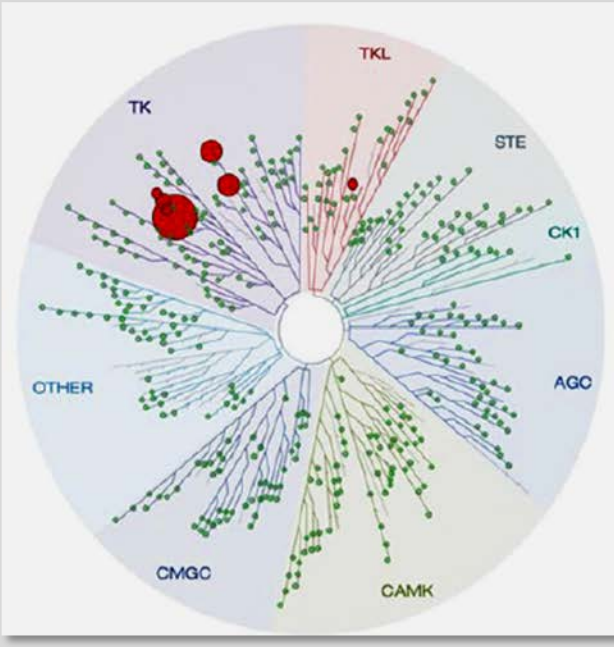
Shanafelt TD et al. ASH 2019; Abstract 33.

Courtesy of Paul M Barr, MD

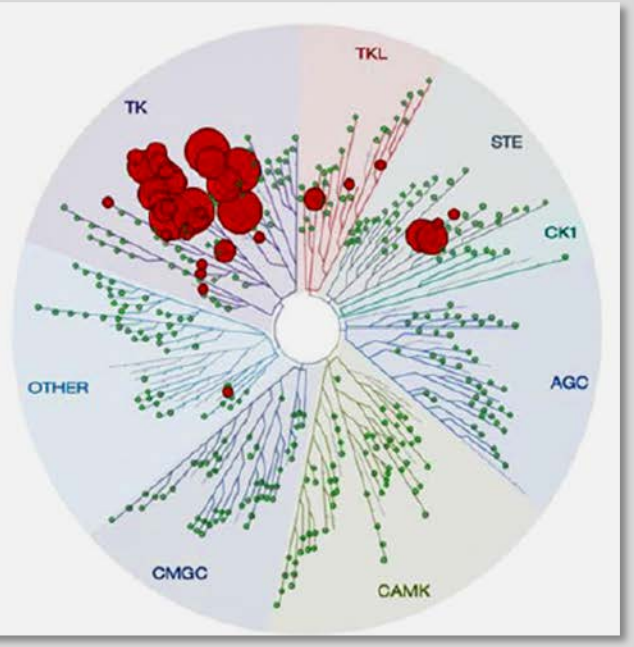
Acalabrutinib vs Ibrutinib

Kinase Selectivity Profiling at 1 μM

Acalabrutinib



Ibrutinib



Larger red circles represent stronger inhibition

Kinase Inhibition Average IC_{50} (nM)		
Kinase	Acalabrutinib	Ibrutinib
BTK	5.1	1.5
TEC	126.0	10
ITK	>1,000	4.9
BMX	46	0.8
TXK	368	2.0
EGFR	>1,000	5.3
ERBB2	~1,000	6.4
ERBB4	16	3.4
BLK	>1,000	0.1
JAK3	>1,000	32
$T_{½}$	1 hour	4-6 hours

BTK = Bruton tyrosine kinase; IC = inhibitory concentration

Byrd JC et al. *N Engl J Med*. 2016;374:323-332.
Herman SEM et al. *Clin Cancer Res*. 2017;23:2831-2841.

Courtesy of Paul M Barr, MD

ELEVATE-TN Study Design

Treatment-naive CLL
(n=535)
Age ≥65 or <65 years with coexisting conditions:
- CIRS score >6, or
- creatinine clearance <70 mL/min

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

RANDOMIZE
1:1:1

Acalabrutinib[a] + Obinutuzumab (G)[b]
[a]100 mg PO BID
[b]1000 mg IV on D1, 2, 8, and 15 of Cycle 2, + D1 of subsequent 28-day cycles for a total of 6 cycles

Acalabrutinib
100 mg PO BID

Obinutuzumab (G)[c] + Chlorambucil[d]
[c]1000 mg IV on D1, 2, 8, and 15 of Cycle 1, + D1 of subsequent 28-day cycles for a total of 6 cycles
[d]0.5 mg/kg PO on D1 + 15 of each 28-day cycle for 6 cycles

Primary endpoint
- PFS (assessed by IRC) Acala-G vs G-Clb

Key points
- Median age 70
- Del(17p): 9%
- TP53mut: 11%
- Unmut IGHV: 63%

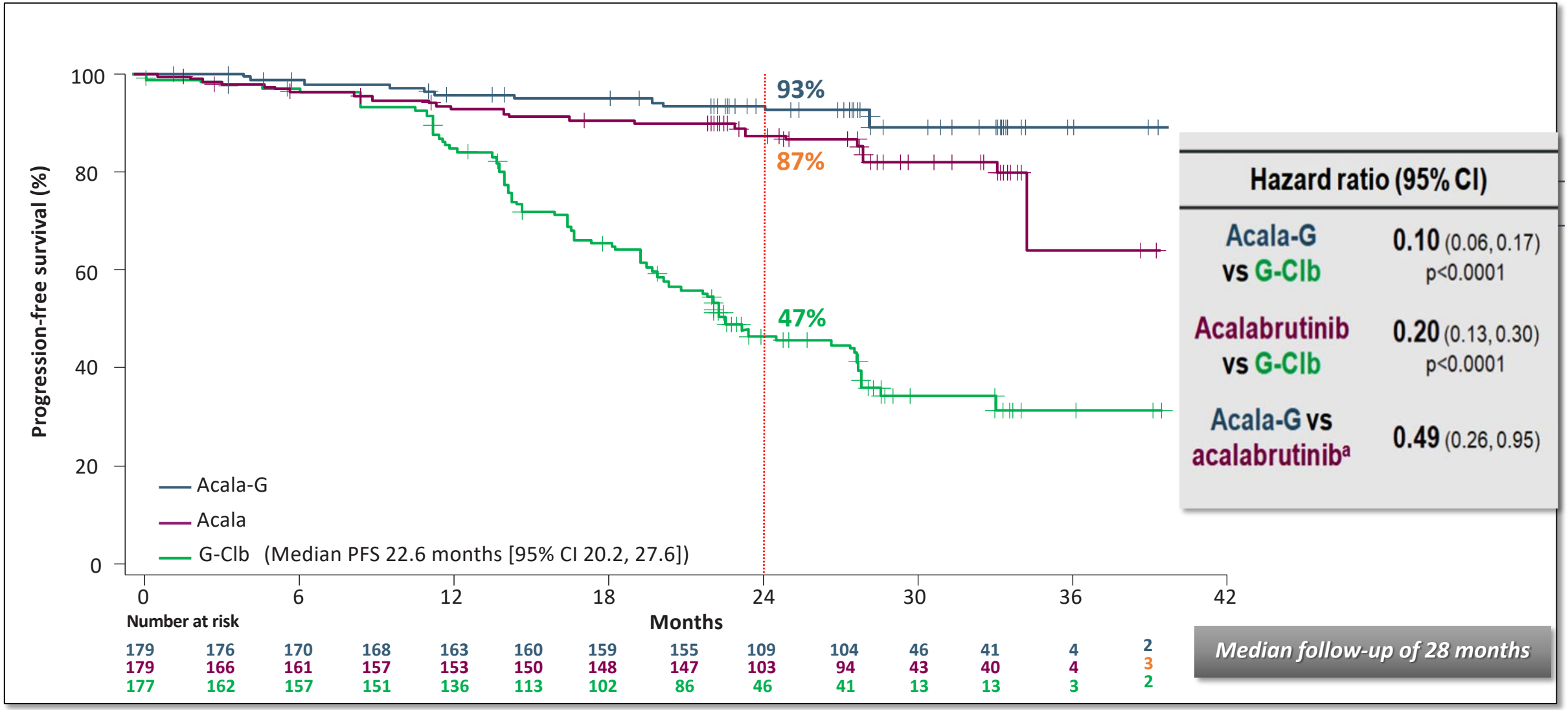
Crossover *from G-Clb to acalabrutinib was allowed after IRC-confirmed progression*

CIRS = Cumulative Illness Rating Scale; ECOG = Eastern Cooperative Oncology Group; IRC = independent review committee

Sharman JP et al. *Blood.* 2019;(suppl 1):Abstract 31.

Courtesy of Paul M Barr, MD

ELEVATE-TN: PFS Benefit of Acalabrutinib



Sharman JP et al. *Blood.* 2019;(suppl 1):Abstract 31.

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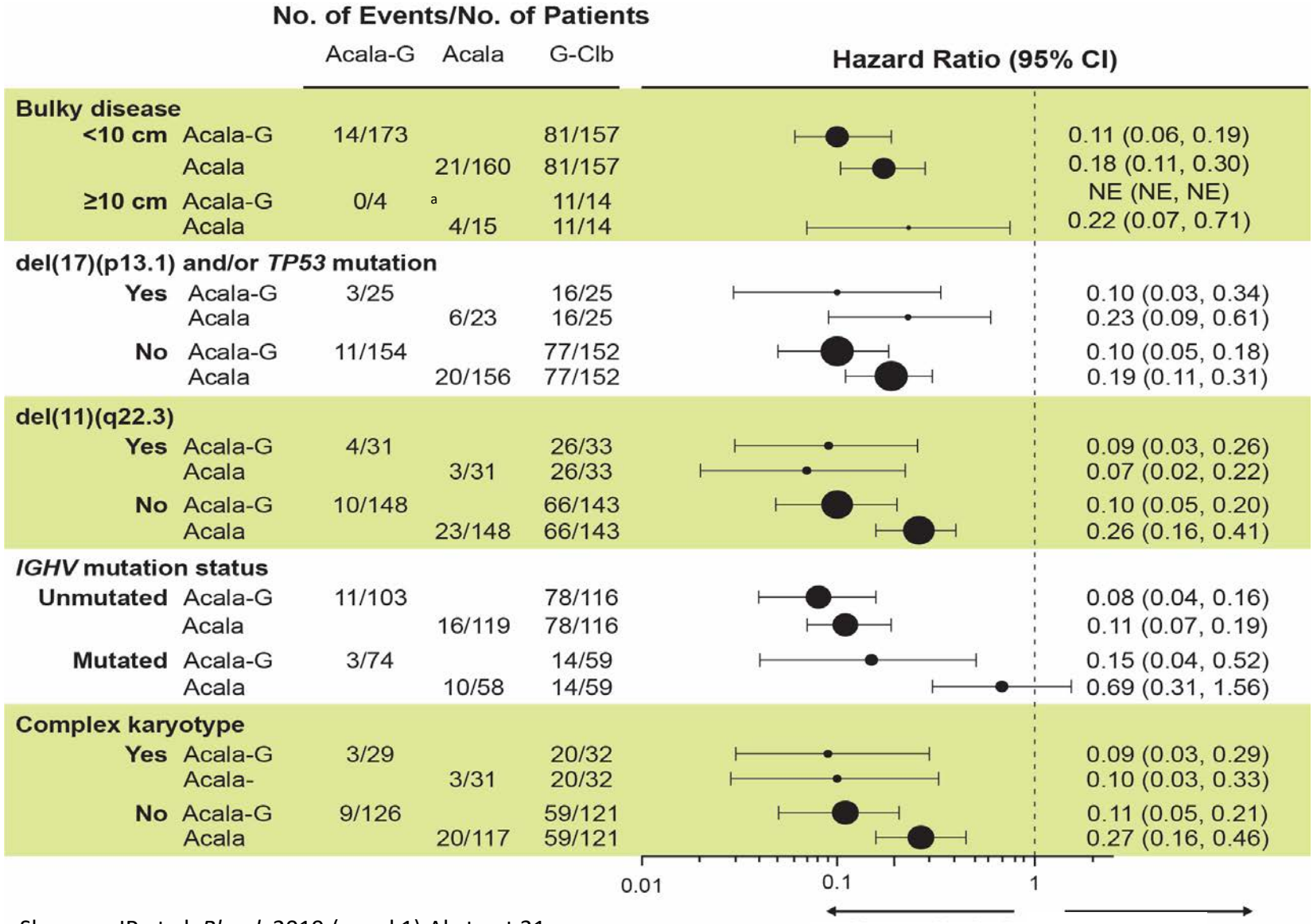
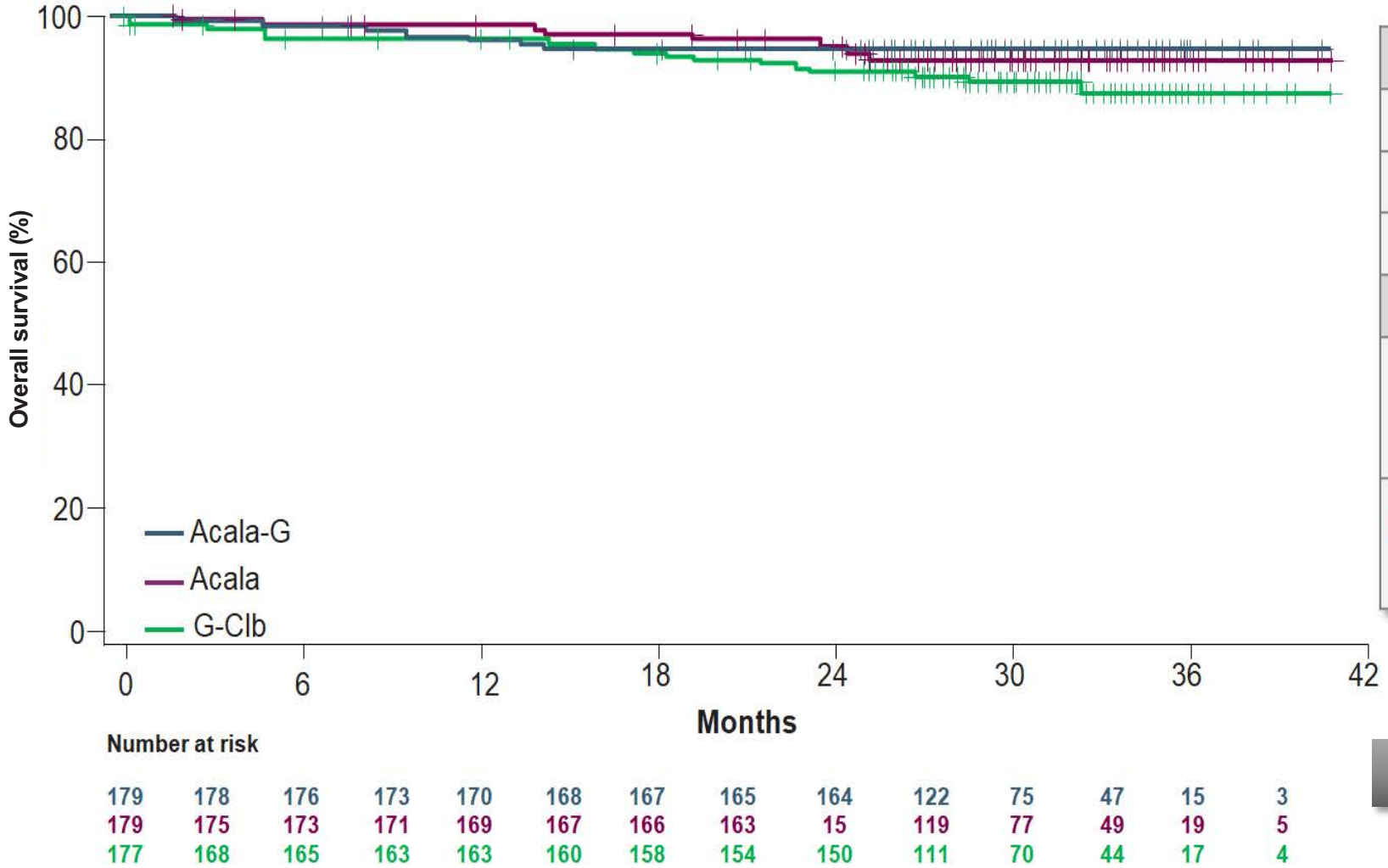
IRC-Assessed PFS Benefit Across Subgroups



Sharman JP et al. *Blood.* 2019;(suppl 1):Abstract 31.
NE, not estimable

Courtesy of Paul M Barr, MD

ELEVATE-TN: Overall Survival



Deaths	N (%)
Acala-G	9 (5.0)
Acala	11 (6.1)
G-Clb	17 (9.6)
Hazard ratio (95% CI)	
Acala-G vs G-Clb	**0.47** (0.21, 1.06) p=0.0577
Acalabrutinib vs G-Clb	**0.60** (0.28, 1.27) p=0.1556

Median follow-up of 28 months

Sharman JP et al. *Blood.* 2019;(suppl 1):Abstract 31.

Courtesy of Paul M Barr, MD

Most Common AEs (≥15% Patients) in Any Treatment Arm

AEs, n (%)	Acala-G N=178		Acalabrutinib N=179		G-Clb N=169	
	Any	Grade ≥3	Any	Grade ≥3	Any	Grade ≥3
Headache	71 (39.9)	2 (1.1)	66 (36.9)	2 (1.1)	20 (11.8)	0
Diarrhea	69 (38.8)	8 (4.5)	62 (34.6)	1 (0.6)	36 (21.3)	3 (1.8)
Neutropenia	56 (31.5)	53 (29.8)	19 (10.6)	17 (9.5)	76 (45.0)	70 (41.4)
Fatigue	50 (28.1)	3 (1.7)	33 (18.4)	2 (1.1)	29 (17.2)	1 (0.6)
Contusion	42 (23.6)	0	27 (15.1)	0	7 (4.1)	7 (4.1)
Arthralgia	39 (21.9)	2 (1.1)	28 (15.6)	1 (0.6)	8 (4.7)	2 (1.2)
Cough	39 (21.9)	0	33 (18.4)	1 (0.6)	15 (8.9)	0
URTI	38 (21.3)	4 (2.2)	33 (18.4)	0	14 (8.3)	1 (0.6)
Nausea	36 (20.2)	0	40 (22.3)	0	53 (31.4)	0
Dizziness	32 (18.0)	0	21 (11.7)	0	10 (5.9)	0
IRR	24 (13.5)	4 (2.2)	0	0	67 (39.6)	9 (5.3)
Pyrexia	23 (12.9)	0	12 (6.7)	1 (0.6)	35 (20.7)	1 (0.6)

AEs reported are from the treatment-emergent period (first dose through to 30 days after the last dose of study drug or the first date starting a new CLL therapy, whichever is earliest)
IRR, infusion-related reaction; URTI, upper respiratory tract infection

Courtesy of Paul M Barr, MD

ELEVATE-TN

Events of Clinical Interest for Acalabrutinib

AEs, n (%)	Acala-G N=178		Acalabrutinib N=179		G-Clb N=169	
	Any	Grade ≥3	Any	Grade ≥3	Any	Grade ≥3
Atrial fibrillation	6 (3.4)	1 (0.6)	7 (3.9)	0	1 (0.6)	0
Hypertension	13 (7.3)	5 (2.8)	8 (4.5)	4 (2.2)	6 (3.6)	5 (3.0)
Bleeding	76 (42.7)	3 (1.7)	70 (39.1)	3 (1.7)	20 (11.8)	0
Major bleeding[a]	5 (2.8)	3 (1.7)	3 (1.7)	3 (1.7)	2 (1.2)	0
Infections	123 (69.1)	37 (20.8)	117 (65.4)	25 (14.0)	74 (43.8)	14 (8.3)
Second primary malignancies, excluding NMSC	10 (5.6)	6 (3.4)	5 (2.8)	2 (1.1)	3 (1.8)	2 (1.2)

On November 21, 2019, the FDA approved acalabrutinib for adults with CLL or small lymphocytic lymphoma.

Sharman JP et al. *Blood.* 2019;134(Suppl 1):31.
[a]Defined as any serious or grade ≥3 hemorrhagic event, or any grade hemorrhagic event in the central nervous system

Courtesy of Paul M Barr, MD

Grade 3-5 Treatment-related Adverse Events

BTKi + anti-CD20 arms

Comparing BTKi + anti-CD20 Treated Patients

Adverse Event	IR Arm[3] E1912 n=352	IR Arm[4] Alliance n=181	AG Arm[1] ELEVATE-TN n=179
Median Age	57 yrs	71 yrs	70 yrs
Age range	31-70	65-86	41-88
Median follow up (months)	33	38	28
Infection	5%	19%	21%
Atrial fibrillation (all grades)	3% (7%)	6% (14%)	1% (6%)
Bleeding	1%	4%	2%
Hypertension	18%	34%	3%
% of pts remaining on ibrutinib	79%	64%	79%

1. Sharman et al. Lancet 2020;395:1278-91. 2. Moreno et al. Lancet Onc 2019;20-43-56. 3. Shanafelt TD et al. *Blood.* 2019;(suppl 1):Abstract 33; 4. Woyach JA et al. *N Engl J Med*. 2018;379:2517-2528.

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Courtesy of Paul M Barr, MD

Young Fit Patients: Factors to Consider

Indefinite therapy

- Favors acalabrutinib
  - Convenience (avoids early monitoring with venetoclax)
  - PFS benefit with anti-CD20 addition
  - Less side effects (arrhythmias, hypertension, arthralgias, rash)
- Favors ibrutinib
  - Longer follow-up and more phase III data
  - More data supporting efficacy of venetoclax after ibrutinib vs little data on the reverse
  - Convenience (once daily)
  - Compatible with PPI/H2 inhibitors

Time limited therapy

- Favors venetoclax + anti-CD20
  - High CR and undetectable MRD
  - Avoid selection pressure for resistance
  - Fewer long-term side effects
- Favors FCR
  - 60% of mutated IGHV patients plateau on PFS curve
  - Less cost

Courtesy of Paul M Barr, MD

Randomized Front Line Studies for Fit Patients

Future upfront therapy for CLL

- EA9161: Ibrutinib/Venetoclax/Obinu vs. Ibrutinib/Obinu (<70 yrs)
- CLL13 (GAIA): FCR/BR vs. Venetoclax/Obinu vs. Venetoclax/Ritux vs. Ibrutinib/Venetoclax/Obinu (Fit pts)
- CLL17: Venetoclax/Obinu vs. Ibrutinib/Venetoclax vs. Ibrutinib (Fit pts)
- ACE-CL-311: FCR/BR vs. Acalabrutinib/Venetoclax vs. Acalabrutinib/Venetoclax/Obinu vs. FCR (Fit pts)

Jain et al. ASCO 2017 #7522, Davids et al. Lancet Haem 2019;6:E419-E428, Tam et al. *Blood* (2019) 134 (Supplement_1): 35, ClinicalTrials.gov: NCT03701282, ClinicalTrials.gov: NCT04608318, ClinicalTrials.gov: NCT03836261

Courtesy of Paul M Barr, MD

Case 1

- 55-year-old male c/o fatigue for 1.5 years
  - Police officer, exercises daily
- Low testosterone identified in 2016, referred to urology for replacement. CBC performed.
- CBC
  - ALC 74,000/uL, confirmed CLL
  - Hgb 16 g/dL
  - Platelets 164,000/uL
- Risk factor testing at diagnosis demonstrated mutated IGHV genes and del(13q).
- Diffuse lymphadenopathy on exam

	WBC	ALC	Hgb	PLT
2/2016	79K	74K	16.2	164K
4/2016	72K	68K	15.6	128K
7/2016	84K	77K	14.3	147K

- Enrolled on ECOG-E1912
  - CTs with diffuse ~2-3cm lymphadenopathy
  - Bone marrow 60% involvement by CLL
  - Randomized to Ibrutinib/Rituximab
- Oral sensitivity, diarrhea, GI upset/reflux, muscle cramping, HTN
  - Probiotics, tonic water, dose hold
  - Loperamide daily, PPI, antihypertensive
- 11/2017
  - CTs: near resolution of lymphadenopathy
  - Marrow: 2% involvement by CLL
- Ibrutinib dose reduction 280mg 2/2019, 140mg 6/2020
  - Improved muscle cramping and diarrhea

	WBC	ALC	Hgb	PLT
11/2016	9K	4K	15.1	123K
11/2017	7K	2K	15.7	134K
9/2020	5K	2K	16.4	163K

Courtesy of Paul M Barr, MD

Case 2

- 58-year-old male diagnosed with CLL in 2014 in the setting of a minimal lymphocytosis
- In 2015, he developed isolated thrombocytopenia. Platelet nadir of 27,000/uL.
  - Treated with prednisone for ITP
- Recurrent thrombocytopenia in 2017
  - Additional prednisone
  - Rituximab x 4 doses
- Recurrent thrombocytopenia in 2018
  - BM biopsy with 20% CLL involvement, normal megakaryocytes, no evidence of MDS
  - Prednisone
  - Rituximab for 2 years
- Recurrent thrombocytopenia 9/2020
  - Referred for help with management
- Now 64 years old
- HTN, obesity, obstructive sleep apnea, renal insufficiency
- Received dexamethasone x 4 days

	WBC	ALC	Hgb	PLT
9/15/2020	41K	40K	13.8	9K
9/22/2020	13K	3K	13.0	88K
9/29/2020	12K	2K	13.6	60K

- IGHV unmutated, del 13q
- Started on acalabrutinib 10/2020
  - Last platelet count 112,000/uL

Courtesy of Paul M Barr, MD