Optimal Therapeutic Strategies for Chronic Lymphocytic Leukemia

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CLL/SLL: Background

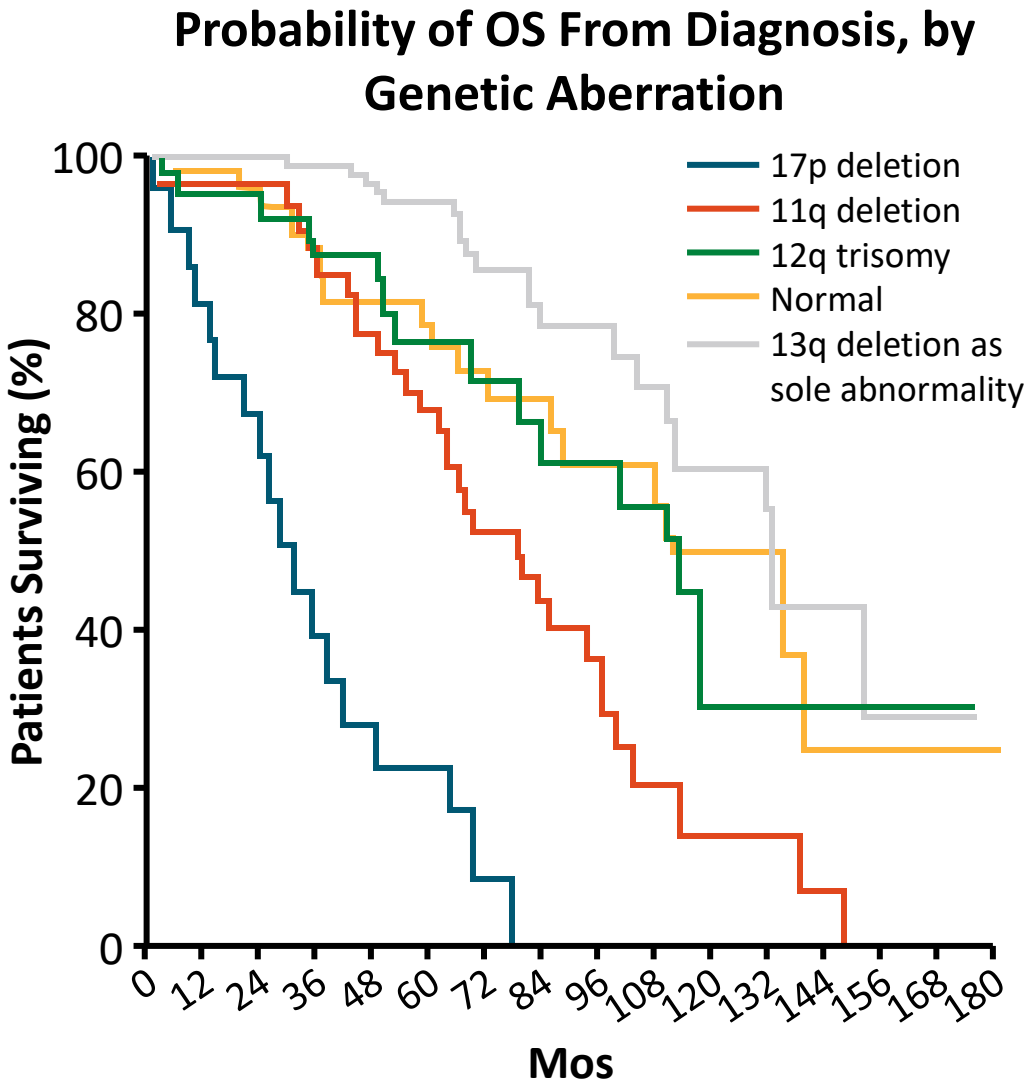
- More than 21,000 estimated new cases in 2020 in the United States[1]
  - 7% of all NHL are CLL/SLL
- Median age at diagnosis: 70 yrs[2]
- SLL and CLL considered the same B-cell malignancy[3]
  - CLL: > 5000 clonal lymphocytes in peripheral blood
  - SLL: presence of lymphadenopathy and/or splenomegaly and < 5000 clonal lymphocytes in peripheral blood
- Historical 5-yr survival: 66% (range: few mos to normal life span)[4]
  - Recent (2009-2015) 5-yr survival: 85%[2]

1. Siegel. CA Cancer J Clin. 2020;70:8. 2. SEER Cancer Stat Facts. Chronic lymphocytic leukemia.
3. American Cancer Society. Chronic lymphocytic leukemia. 4. Nabhan. JAMA. 2014;312:2265.

CLL: Prognostic Value of FISH (Outcomes Prior to Novel Targeted Therapies)

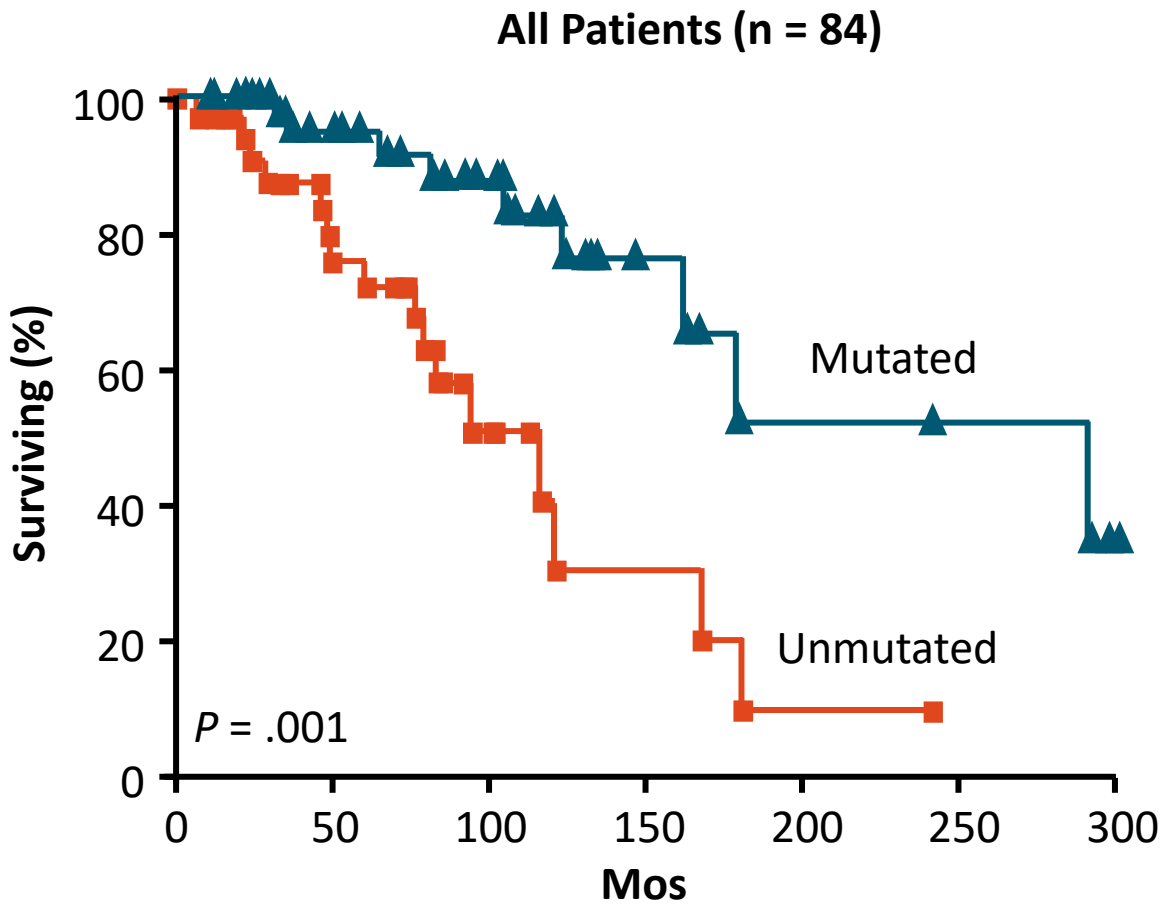
FISH Abnormalities Present in 268/325 Patients (82%)		
Lesion	**%**	**Median OS, Mos**
del(13q)	55	133
del(11q)	18	79
Trisomy 12	16	114
del(17p)	7	32
del(6q)	6	N/A
Normal	18	111

FISH Lesion	Patients With Abnormality, %				
	Dohner et al 1997	Oscier et al 1999	Jarosova et al 2001	Dewald et al 2003	Sindelarava et al 2005
del(13q)	45	36	18	47	54
Trisomy 12	15	15	13	25	16
del(17p)	10	8	11	8	16
del(11q)	20	17	11	15	12



Dohner. NEJM. 2000;343:1910. Dohner. Leukemia. 1997;11(suppl 2):S19. Oscier. Haematologica. 1999;84(suppl EHA-4):88.
Jarosova. Onkologie. 2001;24:60. Dewald. Br J Haematol. 2003;121:287. Sindelárová. Cancer Genet Cytogenet. 2005;160:27.

Survival in CLL According to *IGHV* Mutational Status (Outcomes Prior to Novel Targeted Therapies)



Hamblin. Blood. 1999;94:1848.

Approach to the Patient with Previously Untreated CLL

Chemoimmunotherapy

FCR – fludarabine / cyclophosphamide / rituximab

- Fischer, et al. Blood; 2016
  - Update on CLL8 trial

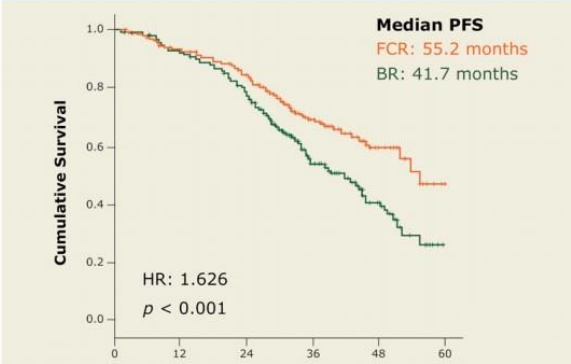
Table 2. PFS and OS in prognostic subgroups

Characteristics	FCR 5-year rate, %	FC 5-year rate, %	HR (95% CI)	*P* value
PFS				
All patients (N = 817)	46.8	25.5	0.59 (0.50-0.69)	<.001
Age				
<65 years (N = 572)	48.3	25.2	0.57 (0.47-0.70)	<.001
≥65 years (N = 245)	43.2	26.1	0.63 (0.47-0.85)	.003
Cytogenetic abnormalities				
17p deletion (N = 51)	15.3	0.0	0.47 (0.25-0.90)	.023
11q deletion (N = 142)	31.4	11.4	0.47 (0.32-0.68)	<.001
Trisomy 12 (N = 61)	61.6	23.7	0.41 (0.20-0.81)	.01
Normal (N = 138)	42.8	37.6	0.83 (0.54-1.26)	.365
13q deletion (N = 224)	63.3	31.0	0.44 (0.31-0.62)	<.001
***IGHV* mutational status**				
UNM (N = 392)	33.1	19.4	0.65 (0.52-0.82)	<.001
MUT (N = 230)	66.6	36.2	0.47 (0.33-0.68)	<.001
OS				
All patients (N = 817)	78.7	66.9	0.68 (0.54-0.89)	.001
Age				
<65 years (N = 572)	80.9	69.2	0.63 (0.47-0.84)	.002
≥65 years (N = 245)	73.9	61.6	0.81 (0.54-1.20)	.288
Sex				
Female (N = 210)	81.3	64.5	0.56 (0.34-0.93)	.003
Male (N = 607)	77.8	67.8	0.71 (0.55-0.93)	<.001
Cytogenetic abnormalities				
17p deletion (N = 51)	36.0	18.2	0.64 (0.32-1.25)	.19
11q deletion (N = 142)	85.8	55.1	0.35 (0.20-0.61)	<.001
Trisomy 12 (N = 61)	91.5	77.4	0.54 (0.19-1.55)	.251
Normal (N = 138)	74.0	81.2	1.31 (0.73-2.35)	.370
13q deletion (N = 224)	87.1	73.1	0.49 (0.28-0.84)	.01

BR – bendamustine / rituximab

- Eichhorst, et al. ASH 2014
  - Update on CLL10 trial

Progression-Free Survival (PFS)



Select Adverse Events

Adverse event	FCR (n = 279)	BR (n = 278)	*p*-value
Neutropenia	84.2%	59.0%	<0.001
Anemia	13.6%	10.4%	0.20
Thrombocytopenia	21.5%	14.4%	0.0
Infection	39.1%	26.8%	<0.001
During therapy (tx) only	22.6%	17.3%	0.1
During first 5 mo after tx	11.8%	3.6%	<0.001
In patients ≤65 years	35.2%	27.5%	0.1
In patients >65 years	47.7%	20.6%	<0.001
Secondary neoplasm*	6.1%	3.6%	0.244

* sAML/MDS: FCR (n = 6); BR (n = 1)

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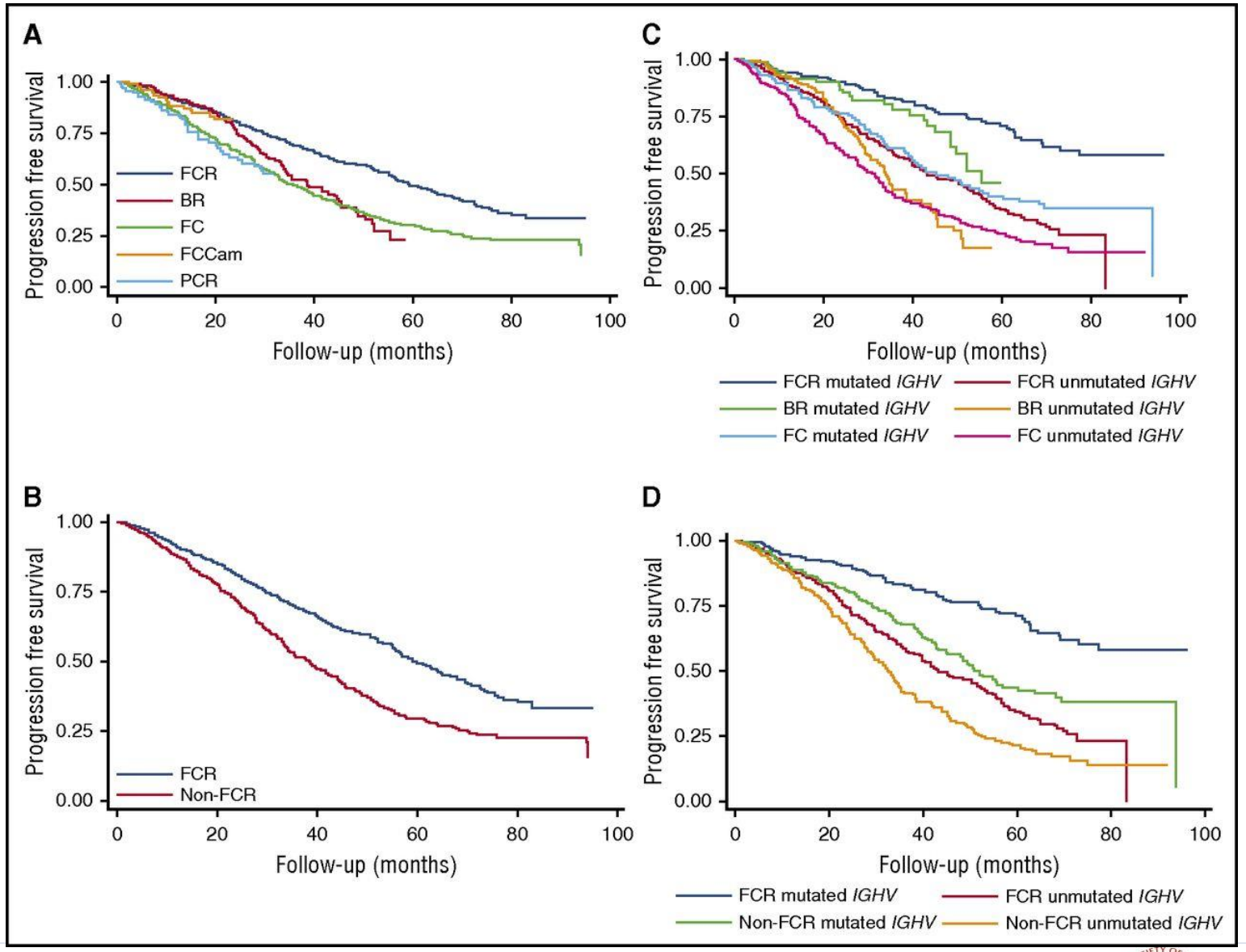
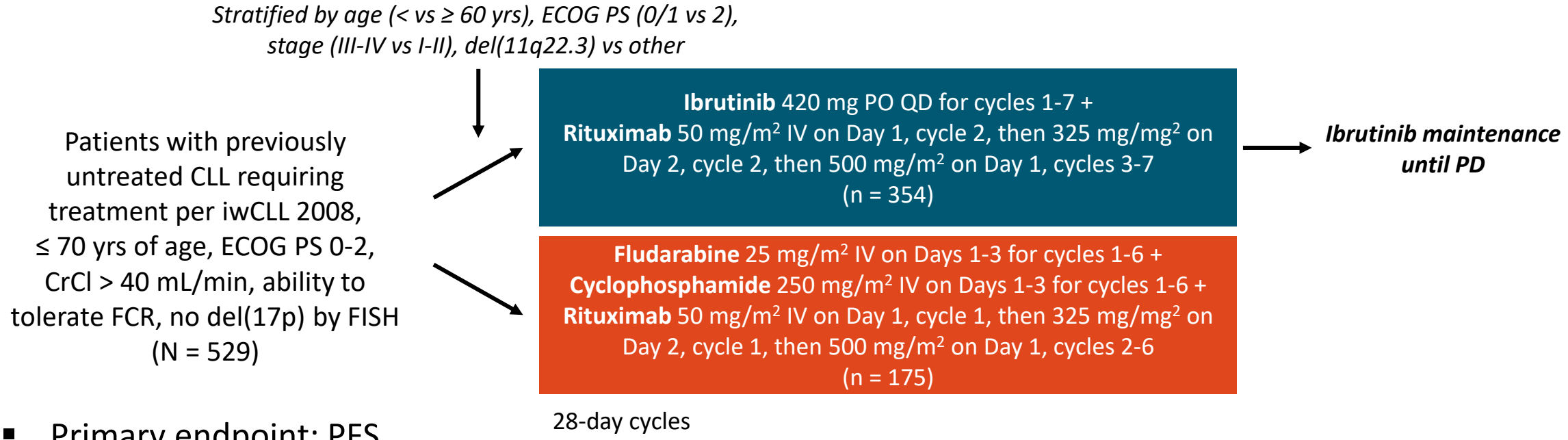
FCR Achieves long-term durable remissions in patients with IGHV-mutated CLL



Chatree Chai-Adisaksopha,Jennifer R. Brown, FCR achieves long-term durable remissions in patients with IGHV-mutated CLL, Blood, 2017, Figure 1.

Phase III E1912 Trial of Ibrutinib + Rituximab vs FCR in Patients ≤ 70 Yrs of Age With Previously Untreated CLL

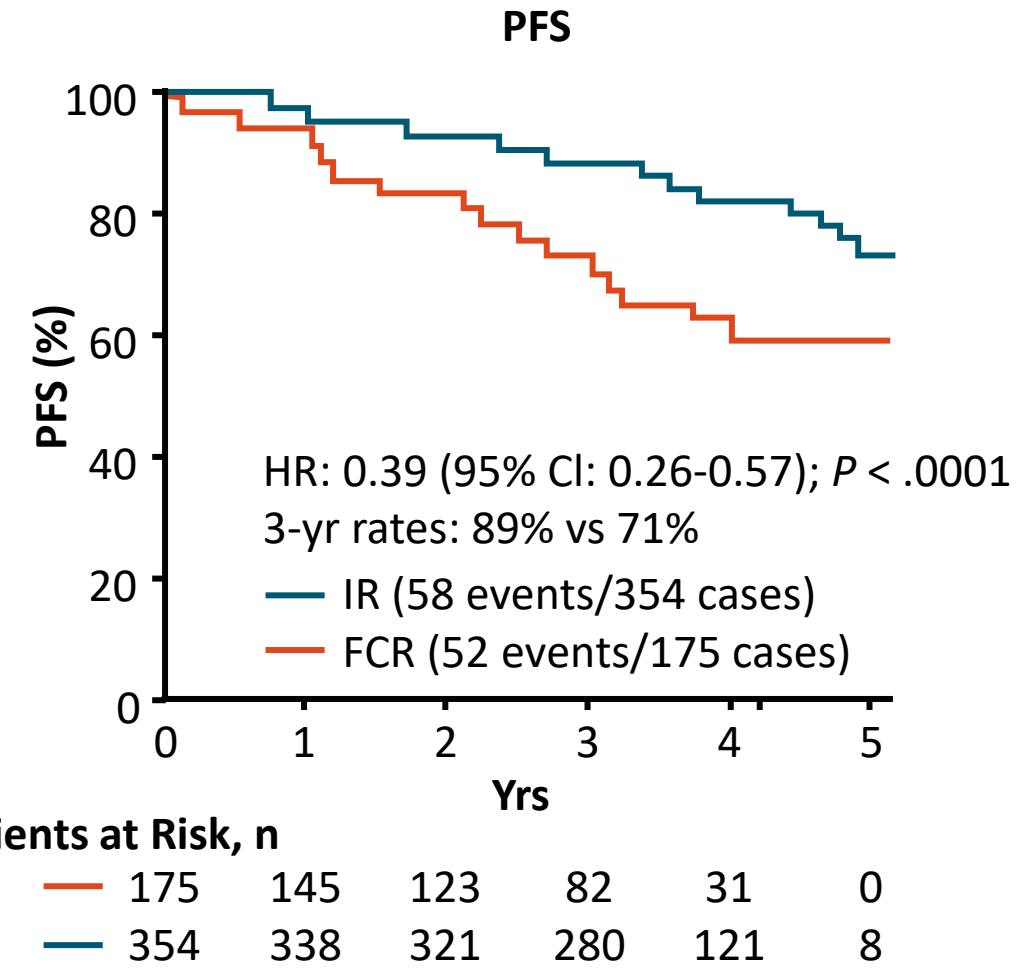
- Primary analysis of randomized, open-label phase III trial (data cutoff: October 24, 2018)

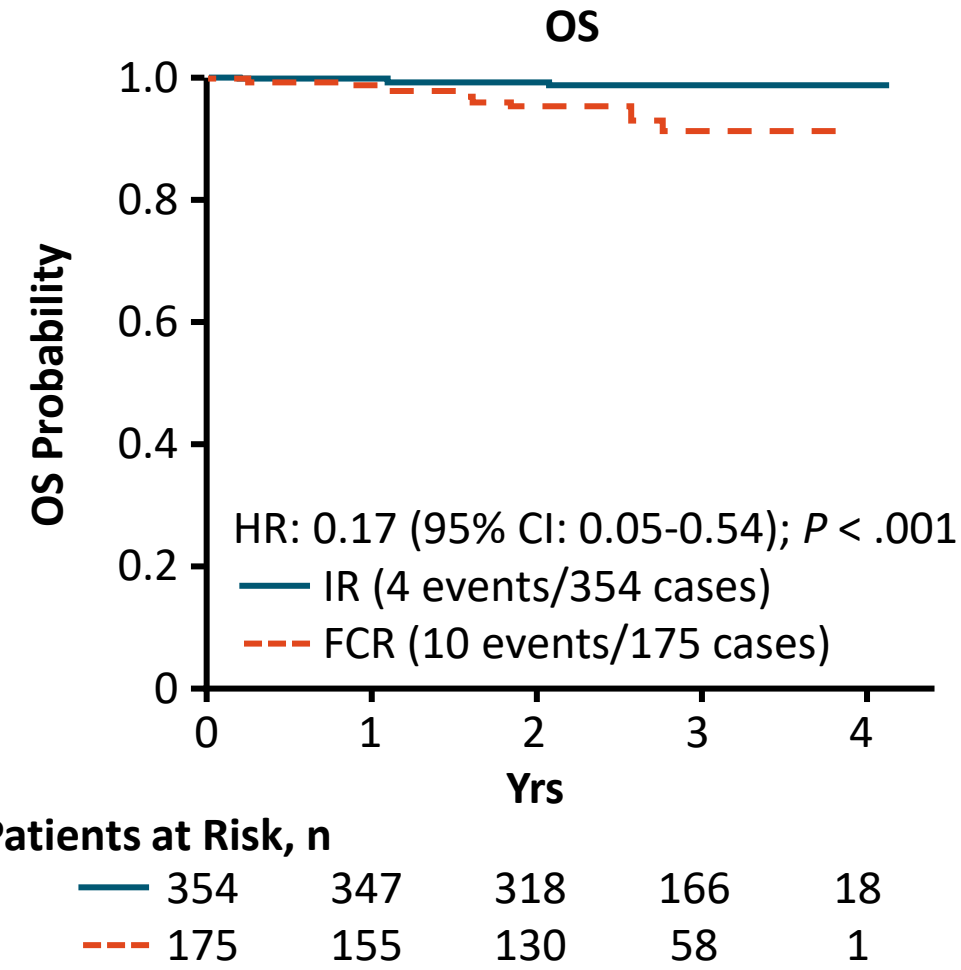


- Primary endpoint: PFS
  - Study has 80% power to detect PFS HR for IR vs FCR of 0.67 using stratified log-rank test, with prespecified boundary of 2.87 for first PFS interim analysis corresponding to 1-sided *P* = .0025
- Secondary endpoints: OS, safety

Shanafelt. NEJM. 2019;381:432. NCT02048813.

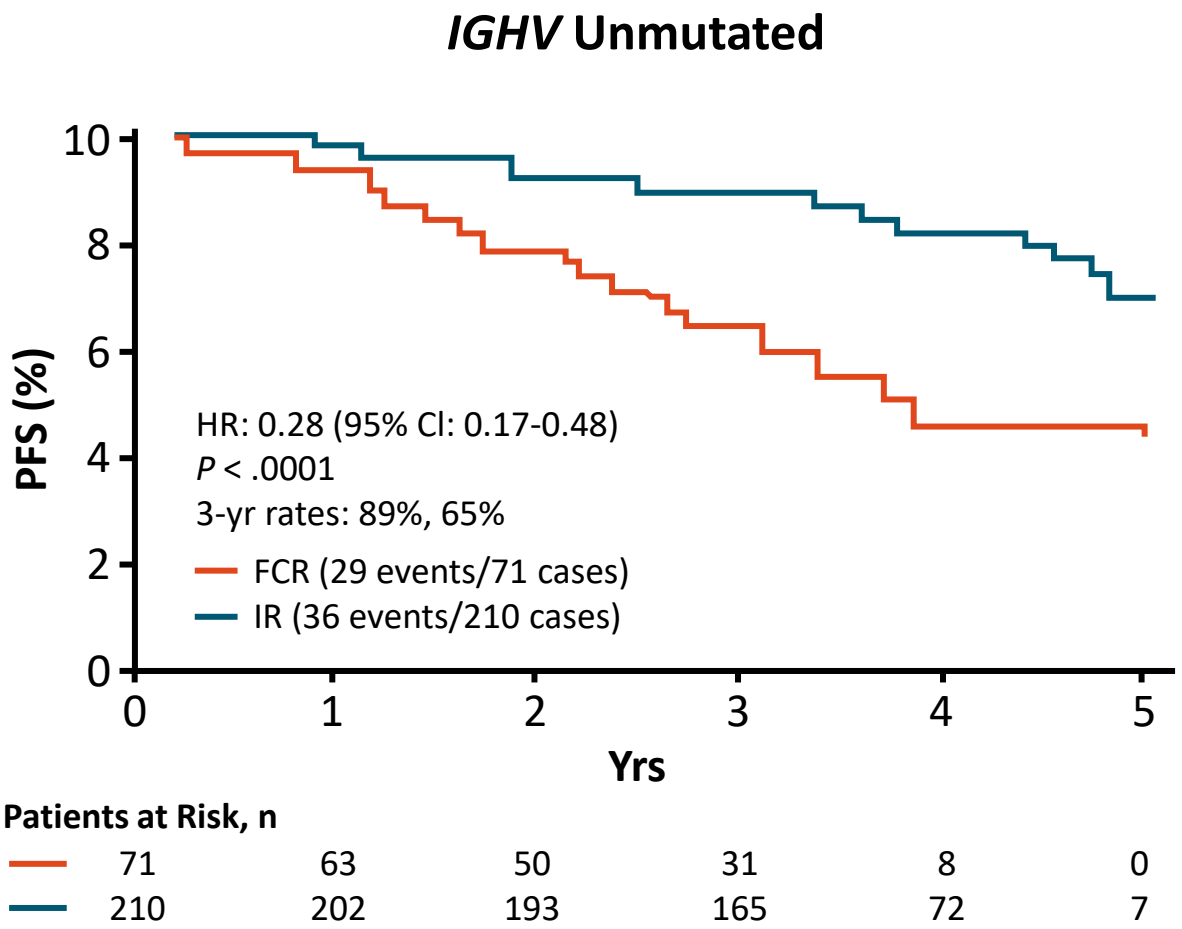
E1912: Updated PFS, OS

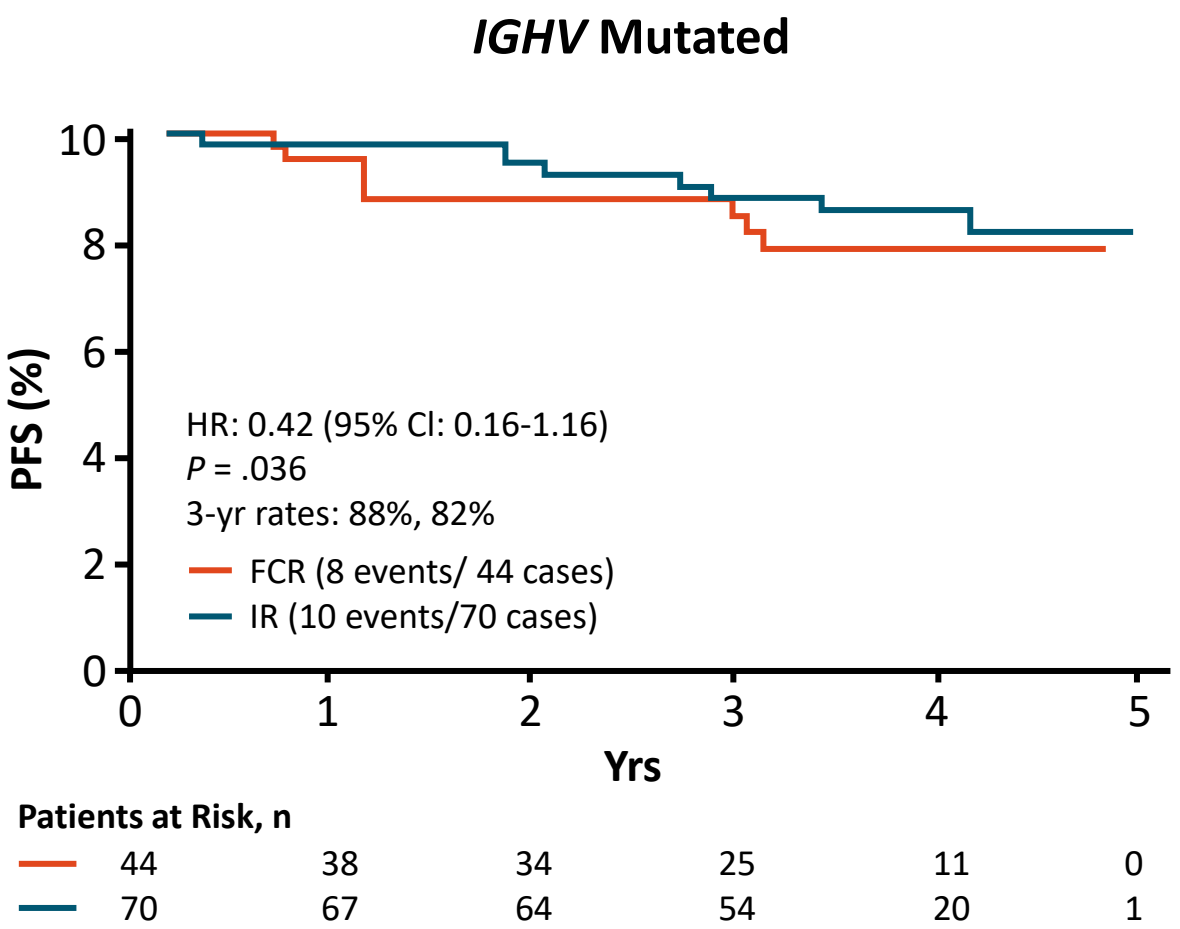




Shanafelt. ASH 2019. Abstr 33.

E1912: Updated PFS by *IGHV* Status



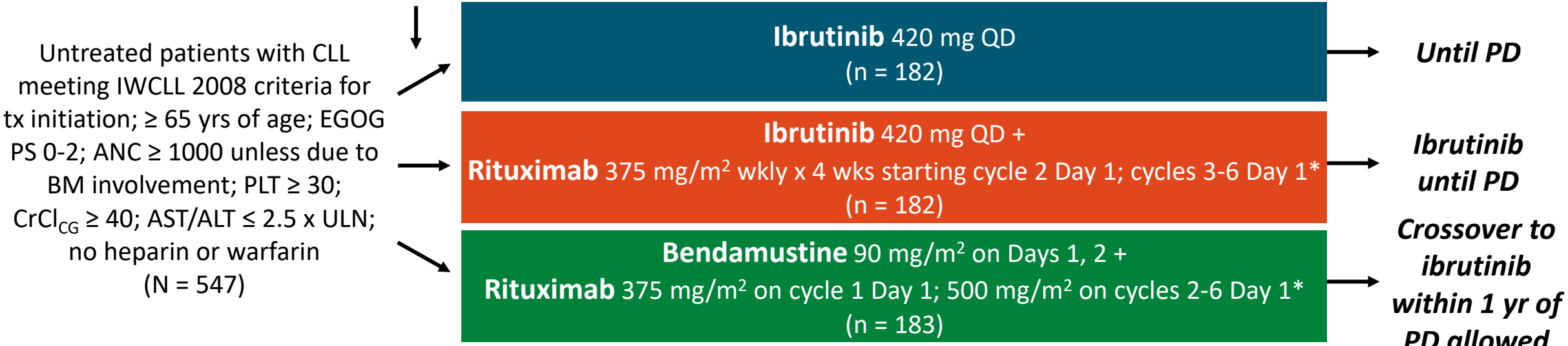


Shanafelt. ASH 2019. Abstr 33.

A041202: First-line Ibrutinib ± Rituximab vs Bendamustine + Rituximab in CLL/SLL

- Multicenter, randomized, double-blind phase III study (data cutoff: October 4, 2018)

Stratified by Rai stage (high vs intermediate risk), del(11q22.3) or del(17p13.1) (presence vs absence), ZAP-70 methylation (< vs ≥ 20%)



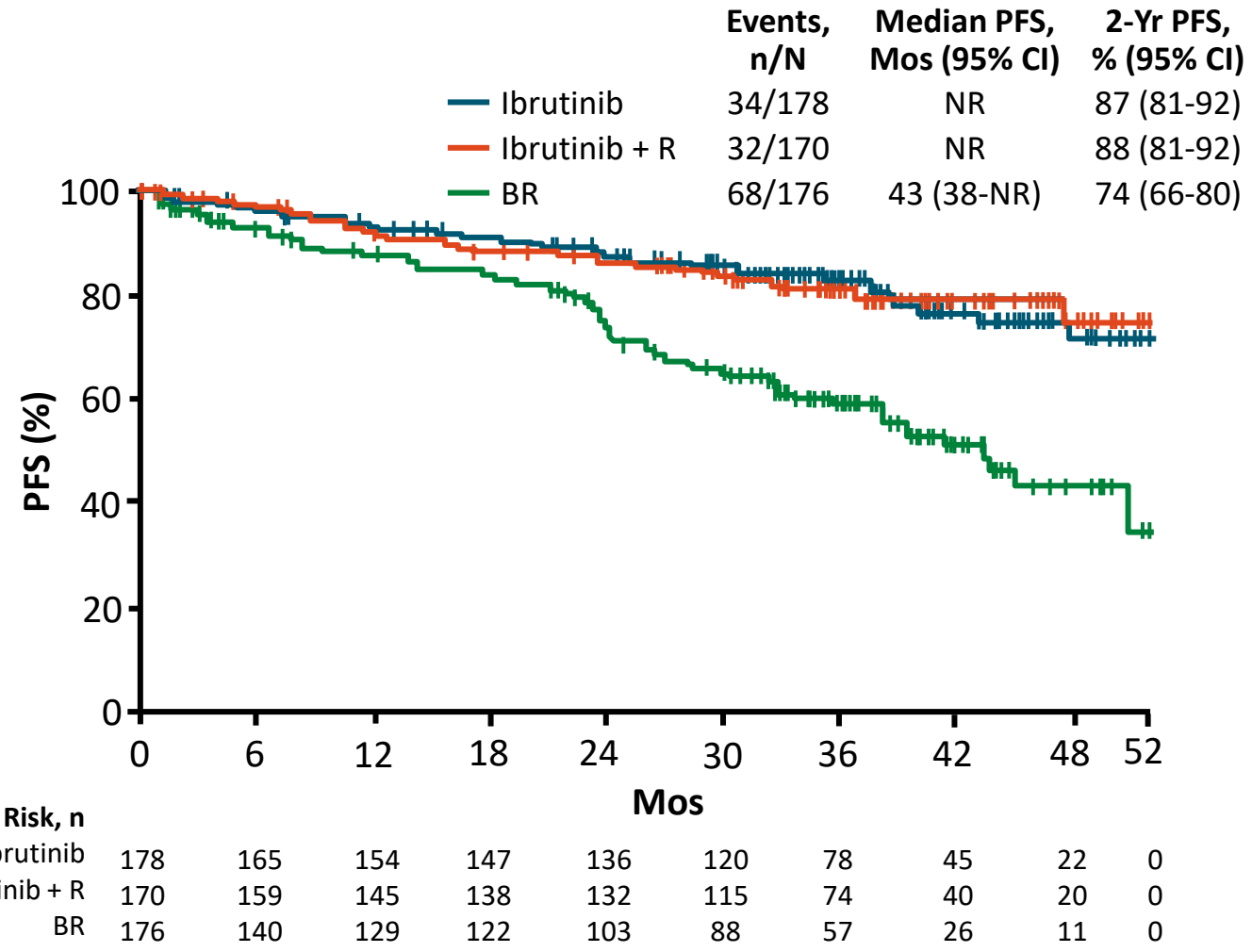
*28-day cycles.

- Primary endpoint: PFS
  - 2 primary comparisons of ibrutinib vs BR and ibrutinib + R vs BR with 90% power to detect HR of 0.586 (estimated 2-yr PFS rates: ibrutinib, 75%; BR, 61%) and overall 1-sided α = 0.025 for each comparison
  - If both primary comparisons significant, third planned comparison of ibrutinib + R vs ibrutinib

Woyach. ASH 2018. Abstr 6. Woyach. NEJM. 2018;379:2517.

A041202: PFS of Eligible Patients* (Primary Endpoint)

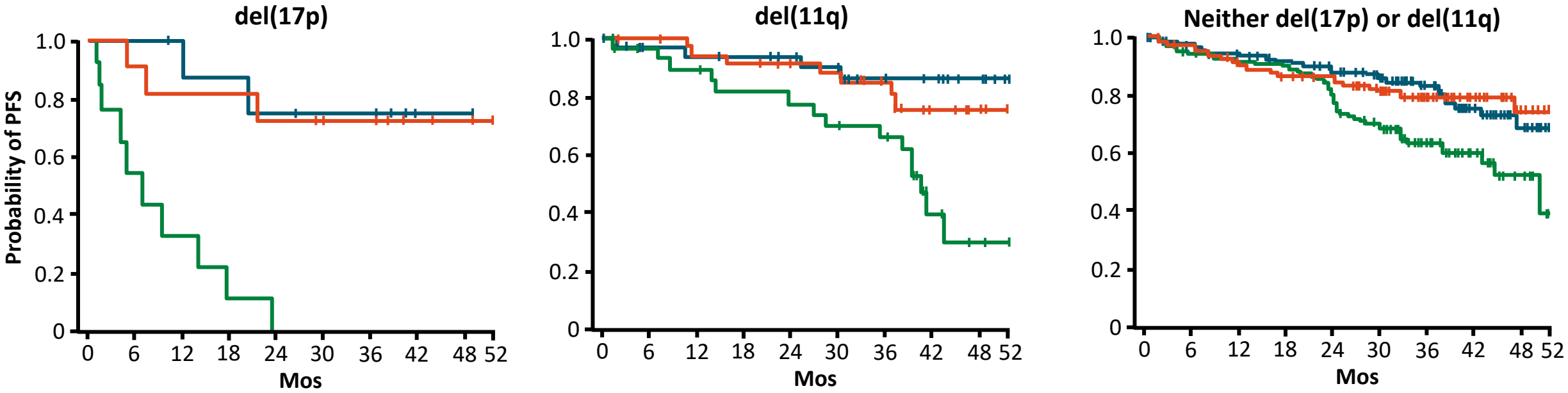
- PFS significantly improved with ibrutinib vs BR and ibrutinib + R vs BR (both 1-sided *P* < .001)
  - HR for ibrutinib vs BR: 0.39 (95% CI: 0.26-0.58)
  - HR for ibrutinib + R vs BR: 0.38 (95% CI: 0.25-0.59)
- No significant difference for ibrutinib + R vs ibrutinib only (1-sided *P* = .49)
  - HR: 1.00 (95% CI: 0.62-1.62)



*524 of 547 randomized patients.

Woyach. NEJM. 2018;379:2517.

A041202: PFS by del(17p) and del(11q) Status



del(17p)	Events, n/N	Median PFS, Mos (95% CI)
Ibrutinib	2/9	NE
Ibrutinib + R	3/11	NE
BR	10/14	7 (4-23)

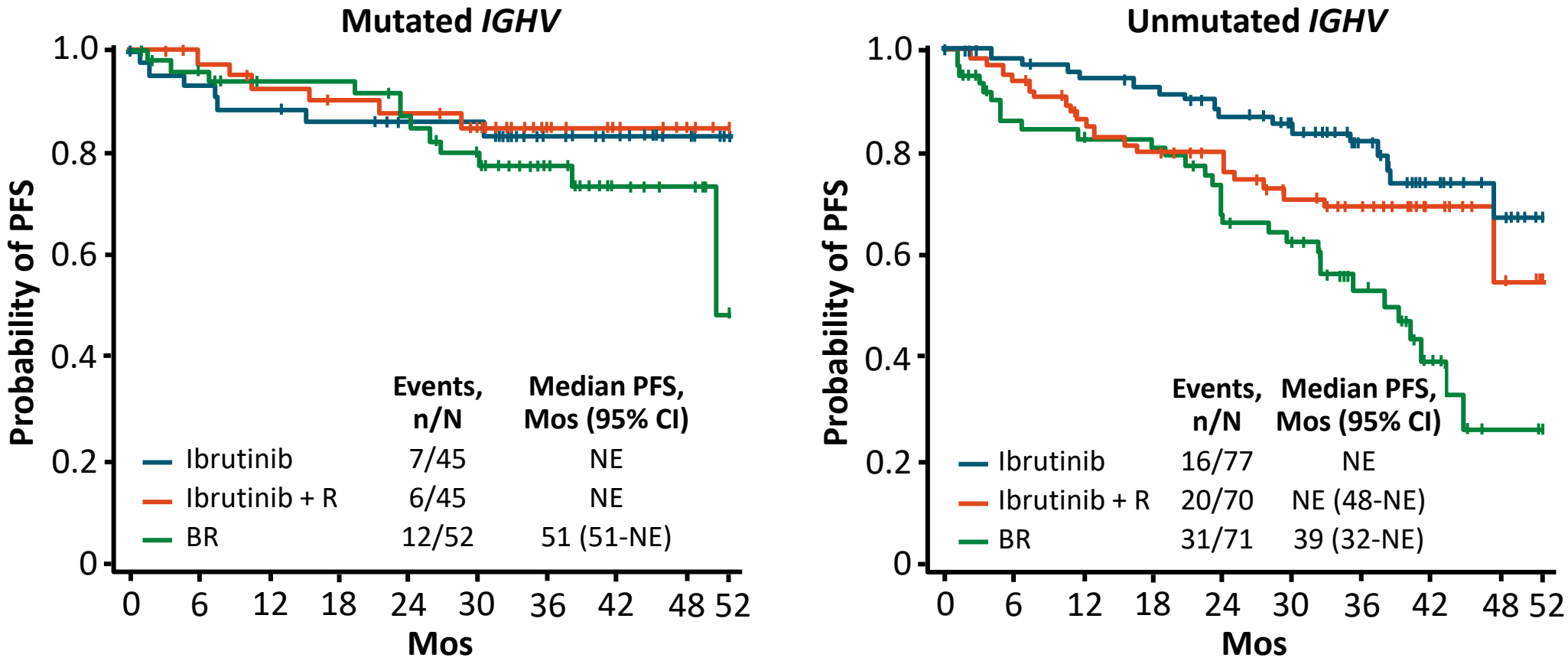
del(11q)	Events, n/N	Median PFS, Mos (95% CI)
Ibrutinib	4/35	NE
Ibrutinib + R	7/37	NE
BR	15/33	41 (36-NE)

Neither del(17p) or del(11q)	Events, n/N	Median PFS, Mos (95% CI)
Ibrutinib	27/137	NE
Ibrutinib + R	25/132	NE
BR	45/134	51 (43-NE)

- PFS benefit with ibrutinib-containing regimens vs BR observed in all cytogenetic factor–related subgroups, with del(17p13.1) being most pronounced

Woyach. NEJM. 2018;379:2517.

A041202: PFS by IGHV Mutation Status



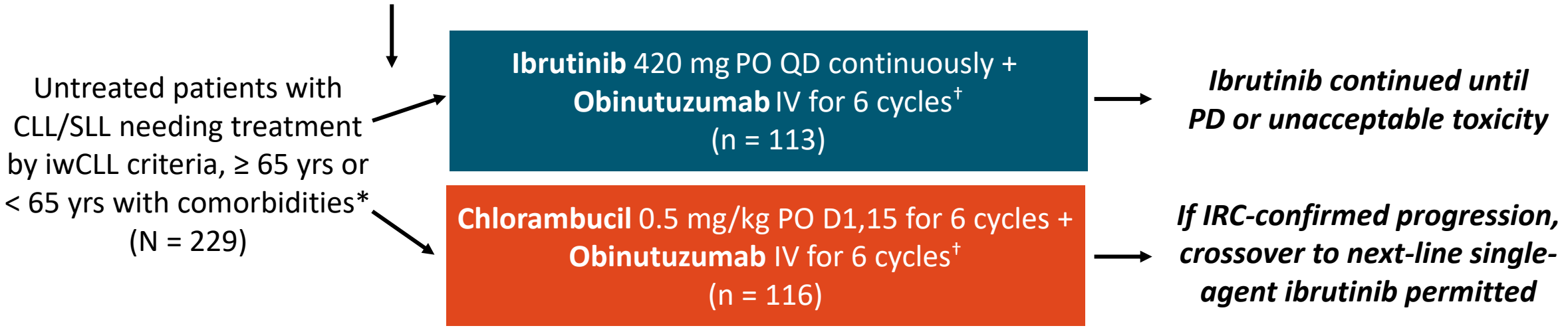
- No significant interaction between *IGHV* mutation status and PFS benefit by regimen
  - Increased PFS among patients with mutated vs unmutated *IGHV* disease (HR: 0.51; 95% CI: 0.32-0.81)

Woyach. NEJM. 2018;379:2517.

iLLUMINATE: First-line Ibrutinib + Obinutuzumab vs Chlorambucil + Obinutuzumab in CLL/SLL

- Randomized, open-label, multicenter phase III trial

Stratified by ECOG PS (0/1 vs 2), del(17p)/del(11q) (+/+ vs +/- vs -/+ vs -/-)



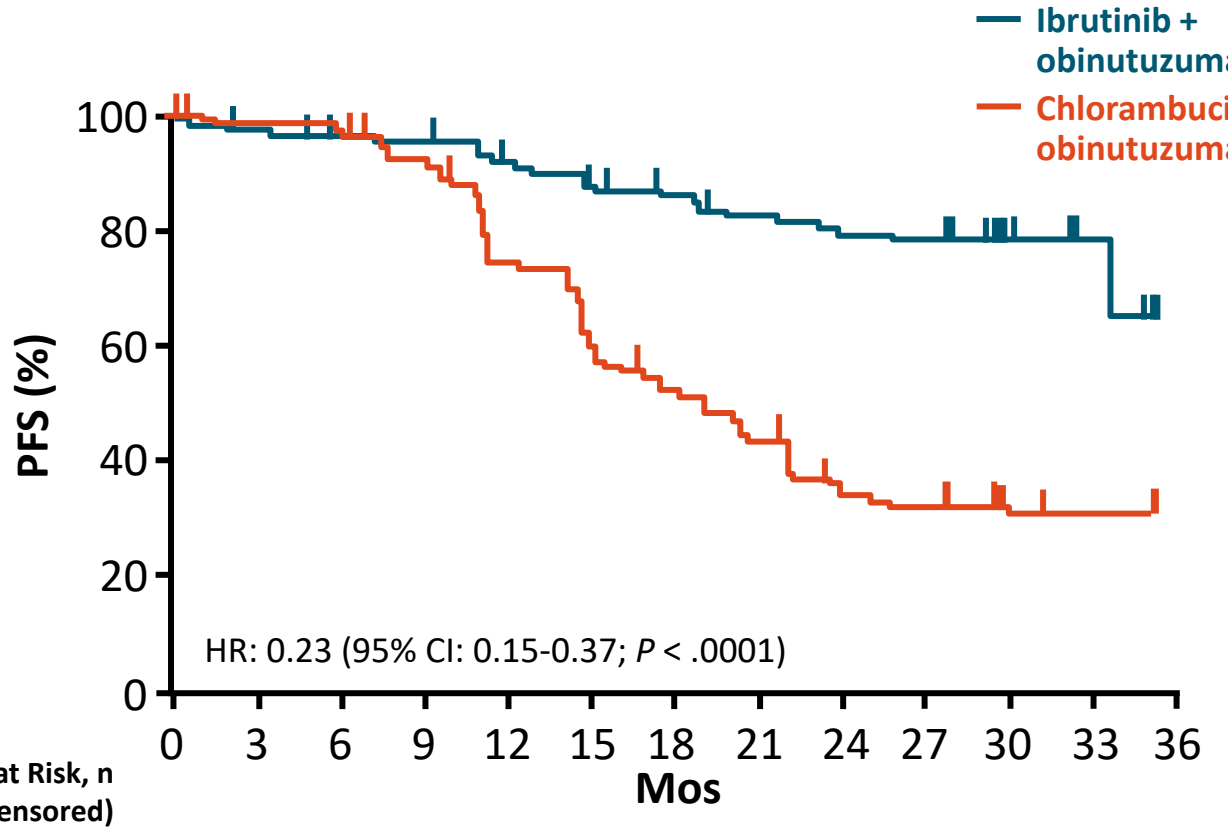
*Cumulative Illness Rating Score > 6, creatinine clearance < 70 mL/min, and/or del(17p)/*TP53* mutation.
†Cycle 1: 100 mg, Days 1; 900 mg, Day 2; 1000 mg, Days 8, 15. Cycle 2-6: 1000 mg, Day 1.

- Primary endpoint: PFS by IRC in ITT population
- Secondary endpoints: PFS in high-risk patients (positive for del[17p] or TP53 mutation, del[11q], or unmutated IGHV), MRD, ORR, OS, IRRs, safety

Moreno. ASH 2018. Abstr 691. Moreno. Lancet Oncol. 2019;20:43.

iLLUMINATE: IRC-Assessed PFS in ITT Population (Primary Endpoint)

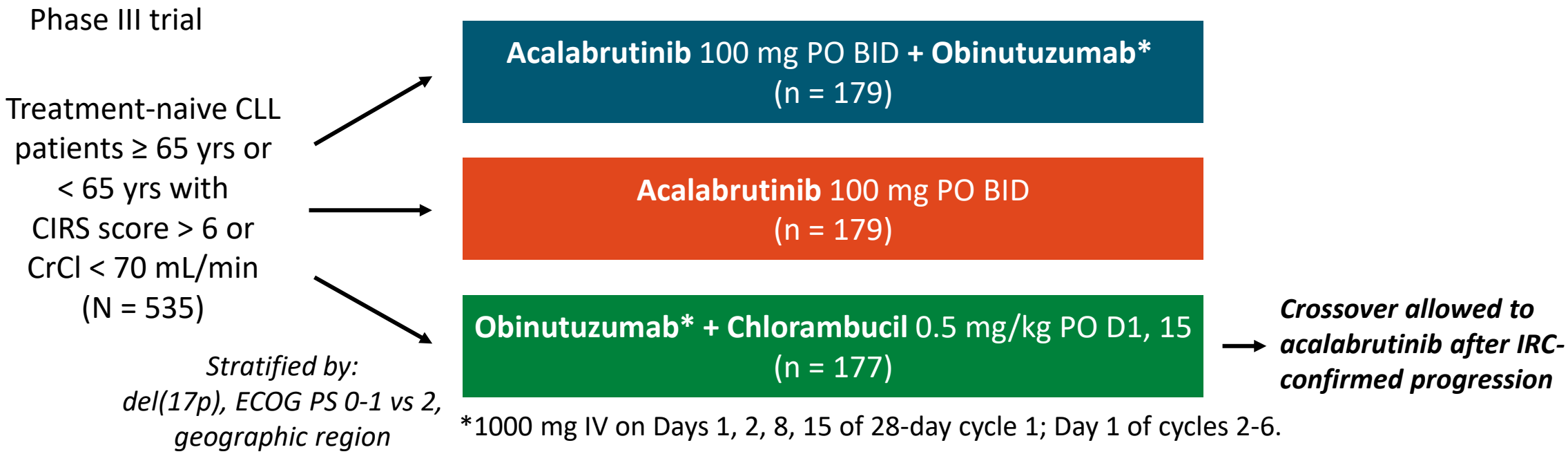
	Patients, n	Median PFS, Mos	30-Mo PFS, % (95% CI)
Ibrutinib + obinutuzumab	113	NR	79 (70-85)
Chlorambucil + obinutuzumab	116	19.0	31 (23-40)



Patients at Risk, n (number censored)													
Ibrutinib + obinutuzumab	113 (0)	109 (1)	106 (3)	105 (3)	99 (5)	94 (6)	90 (8)	85 (9)	82 (9)	82 (9)	28 (62)	6 (84)	0 (89)
Chlorambucil + obinutuzumab	116 (0)	111 (4)	109 (4)	102 (6)	81 (7)	67 (7)	56 (8)	47 (8)	35 (10)	33 (10)	6 (36)	5 (37)	0 (42)

Moreno. Lancet Oncol. 2019;20:43.

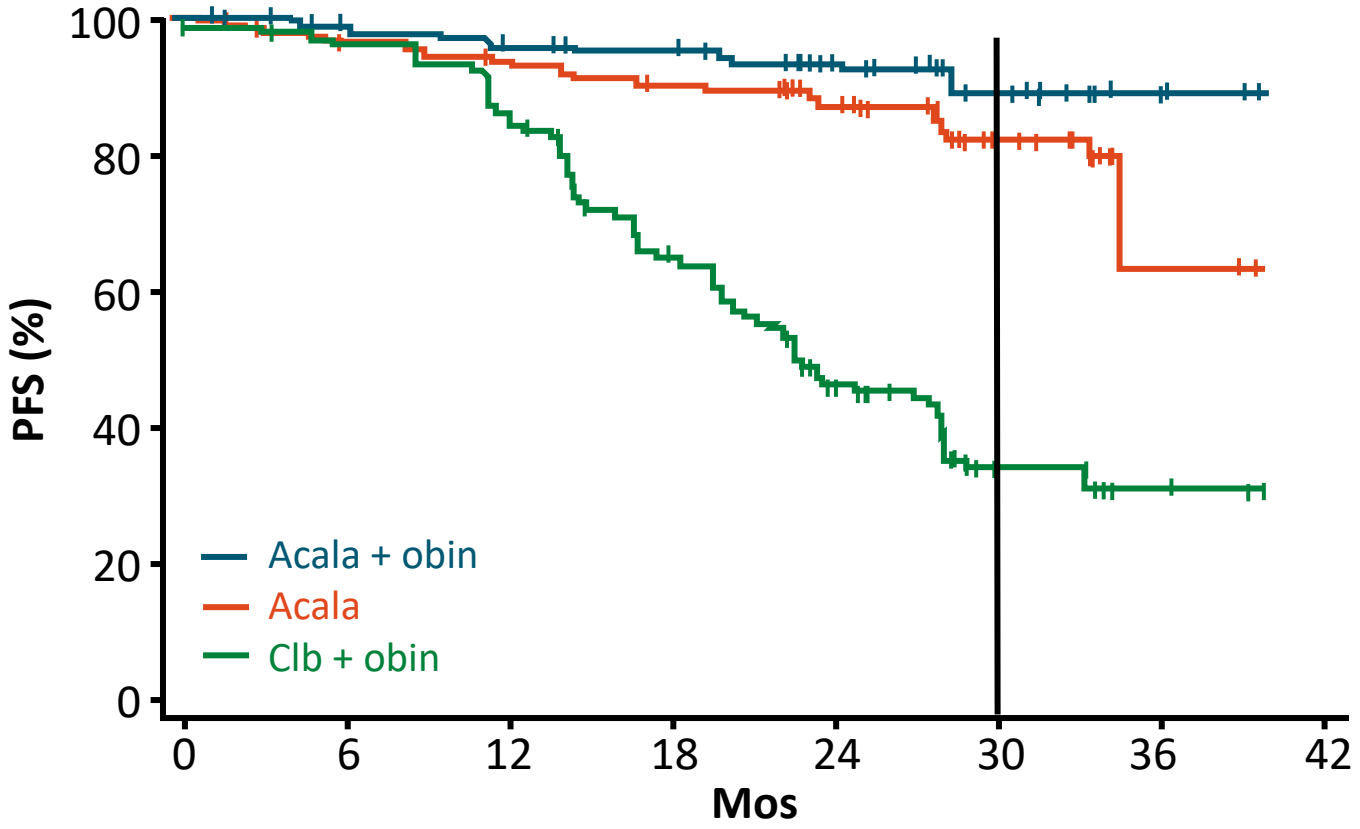
ELEVATE-TN: Acalabrutinib ± Obinutuzumab vs Chlorambucil + Obinutuzumab in Previously Untreated CLL



- Primary endpoint: PFS by IRC of acalabrutinib + obinutuzumab vs obinutuzumab + chlorambucil
- Key secondary endpoints: PFS of acalabrutinib vs obinutuzumab + chlorambucil, ORR by IRC and investigators, time to next treatment, OS, safety

Sharman. Lancet. 2020;395:1278. NCT02475681.

ELEVATE-TN: IRC-Assessed PFS



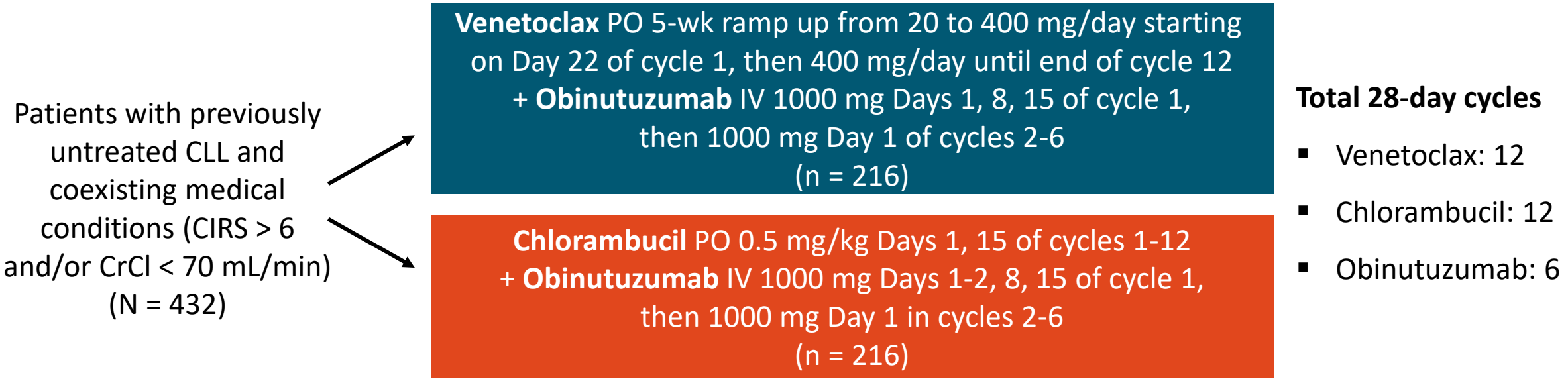
- 30-month PFS estimates
  - Acala + obin: 90%, acala: 82%, Clb + obin: 34%
- 30-month OS estimates
  - Acala + obin: 95%, acala: 94%, Clb + obin: 90%

Outcome	Acalabrutinib + Obinutuzumab	Acalabrutinib	Obinutuzumab + Chlorambucil
Median PFS, mos	Not reached	Not reached	22.6
▪ HR vs acala (95% CI)	0.49 (0.26-0.95)	--	--
▪ HR vs obin/clb (95% CI)	0.10 (0.6-0.17); *P* < .0001	0.20 (0.13-0.30); *P* < .0001	--

Sharman. Lancet. 2020;395:1278.

CLL14: First-line Obinutuzumab + Venetoclax or Chlorambucil in CLL With Coexisting Medical Conditions

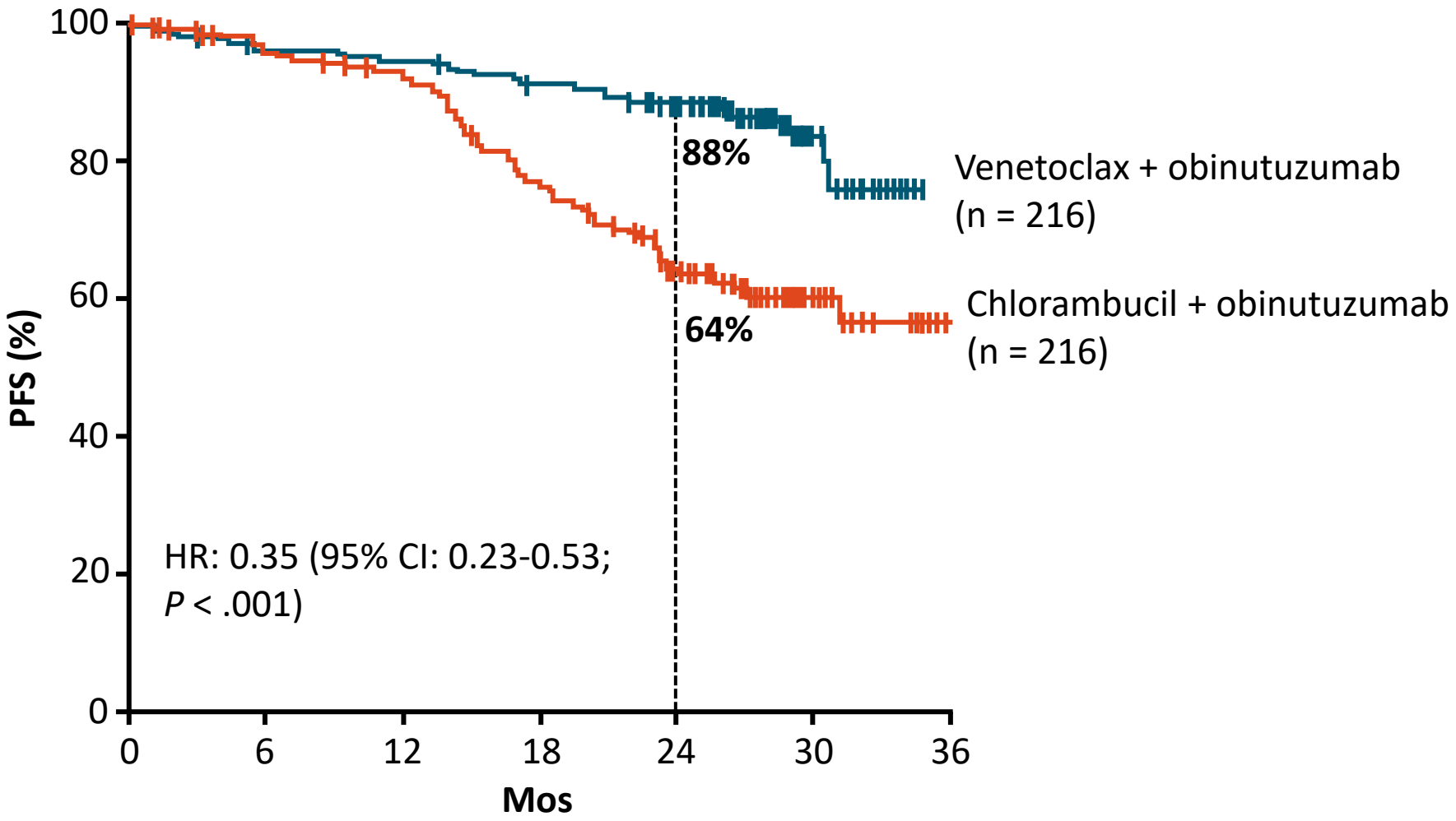
- Open-label, multicenter, randomized phase III trial



- Primary endpoint: investigator-assessed PFS
- Secondary endpoints: IRC-assessed PFS, ORR, MRD negativity, OS, safety

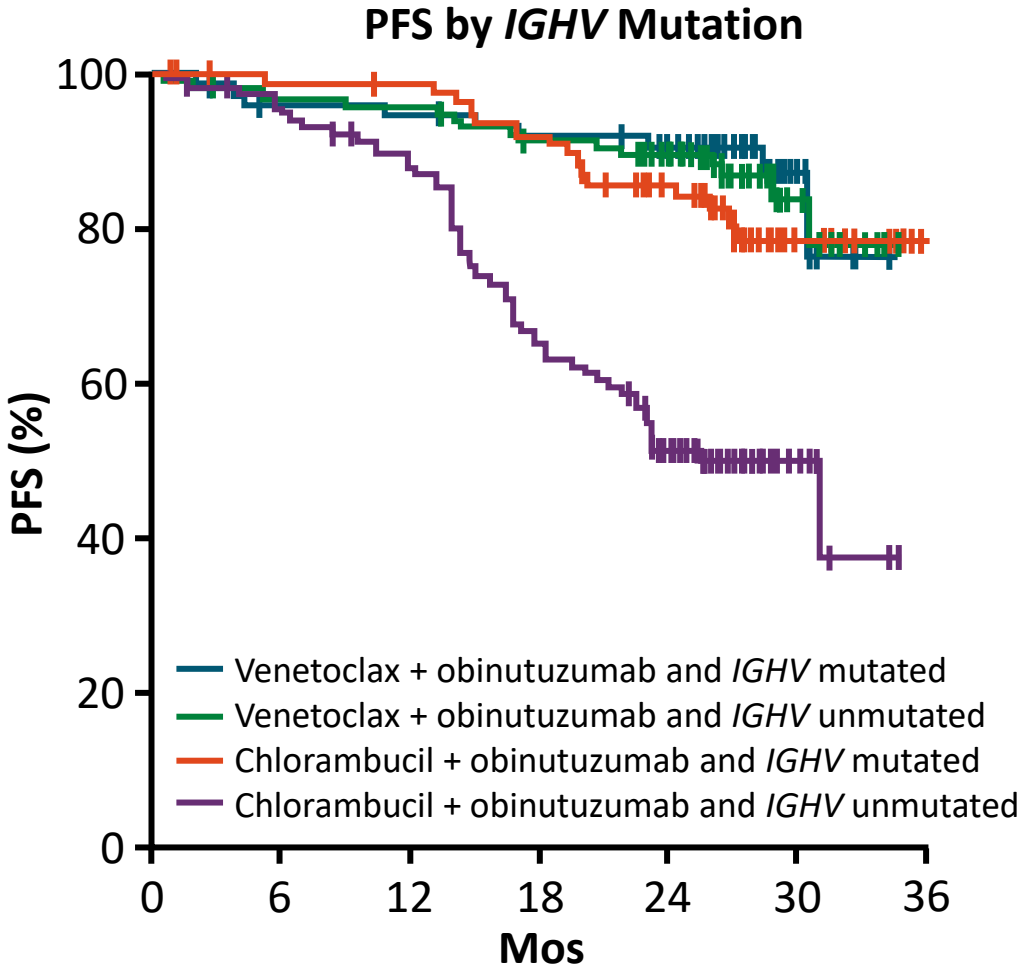
Fischer. ASCO 2019. Abstr 7502. Fischer. NEJM. 2019;380:2225. NCT02242942.

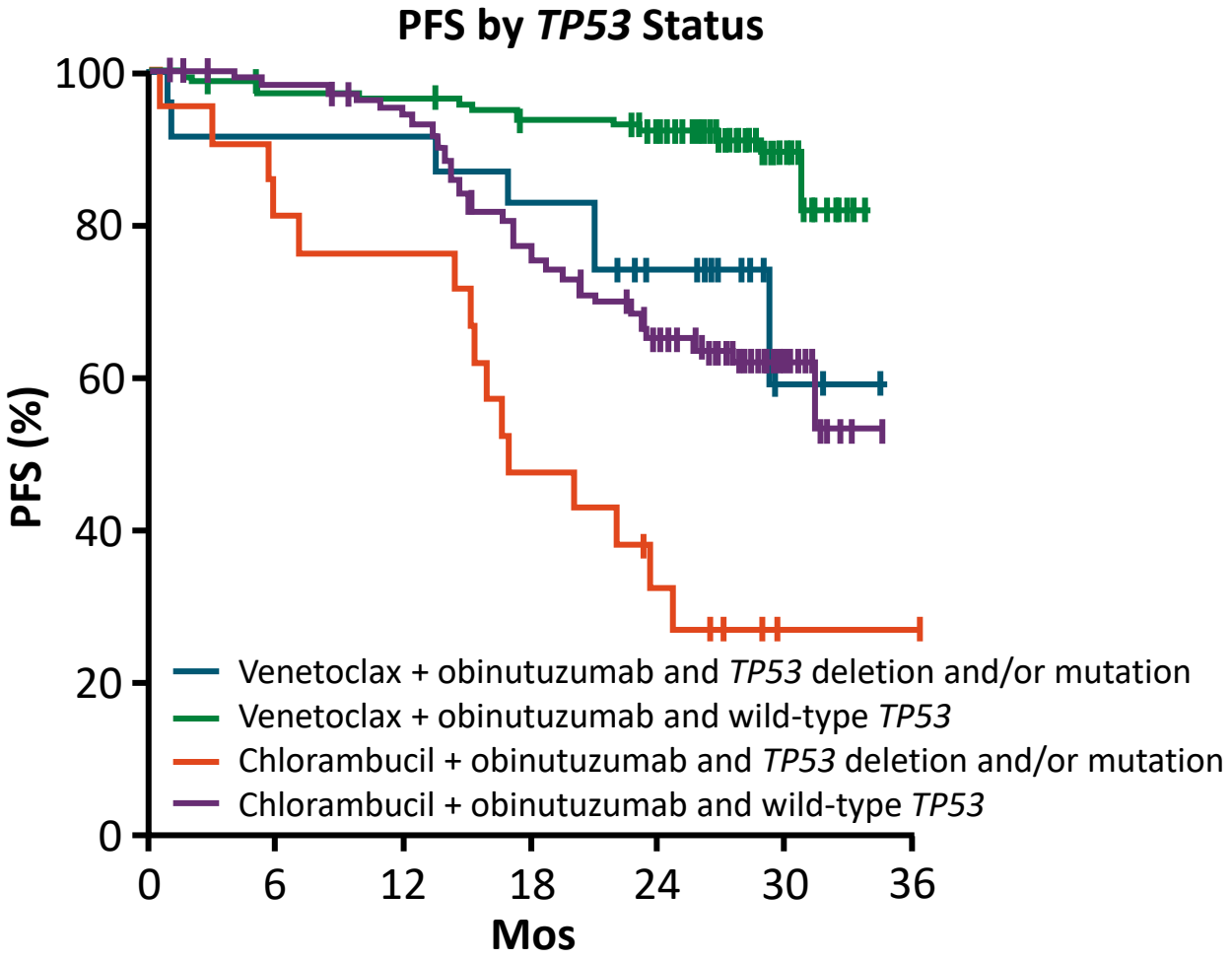
CLL14: Investigator-Assessed PFS (Primary Endpoint)



Fischer. ASCO 2019. Abstr 7502. Fischer. NEJM. 2019;380:2225.

CLL14: PFS by *IGHV* Mutation and *TP53* Status





Fischer. ASCO 2019. Abstr 7502. Fischer. NEJM. 2019;380:2225.

CLL14: MRD Negativity

MRD Status,* %	Venetoclax + Obinutuzumab (n = 216)	Chlorambucil + Obinutuzumab (n = 216)	*P* Value
Peripheral blood			
▪ Negative ($< 10^{-4}$)	76	35	< .001
▪ Negative ($< 10^{-4}$) in CR	42	14	< .001
Bone marrow			
▪ Negative ($< 10^{-4}$)	57	17	< .001
▪ Negative ($< 10^{-4}$) in CR	34	11	< .001

*MRD status assessed by ASO-PCR 3 mos after completion of treatment.

MRD Status,† %	Venetoclax + Obinutuzumab (n = 216)	Chlorambucil + Obinutuzumab (n = 216)
$< 10^{-6}$	42	7
$\geq 10^{-6}$ and $< 10^{-5}$	26	13
$\geq 10^{-5}$ and $< 10^{-4}$	11	14
$\geq 10^{-4}$ and $< 10^{-2}$	6	23
$\geq 10^{-2}$	5	29
No sample/ not evaluable	12	14

†MRD status assessed by NGS in peripheral blood 3 mos after completion of treatment.

- MRD negativity ($< 10^{-4}$) with venetoclax + obinutuzumab occurred early and was durable

Fischer. ASCO 2019. Abstr 7502. Fischer. NEJM. 2019;380:2225.

CLL14: Safety

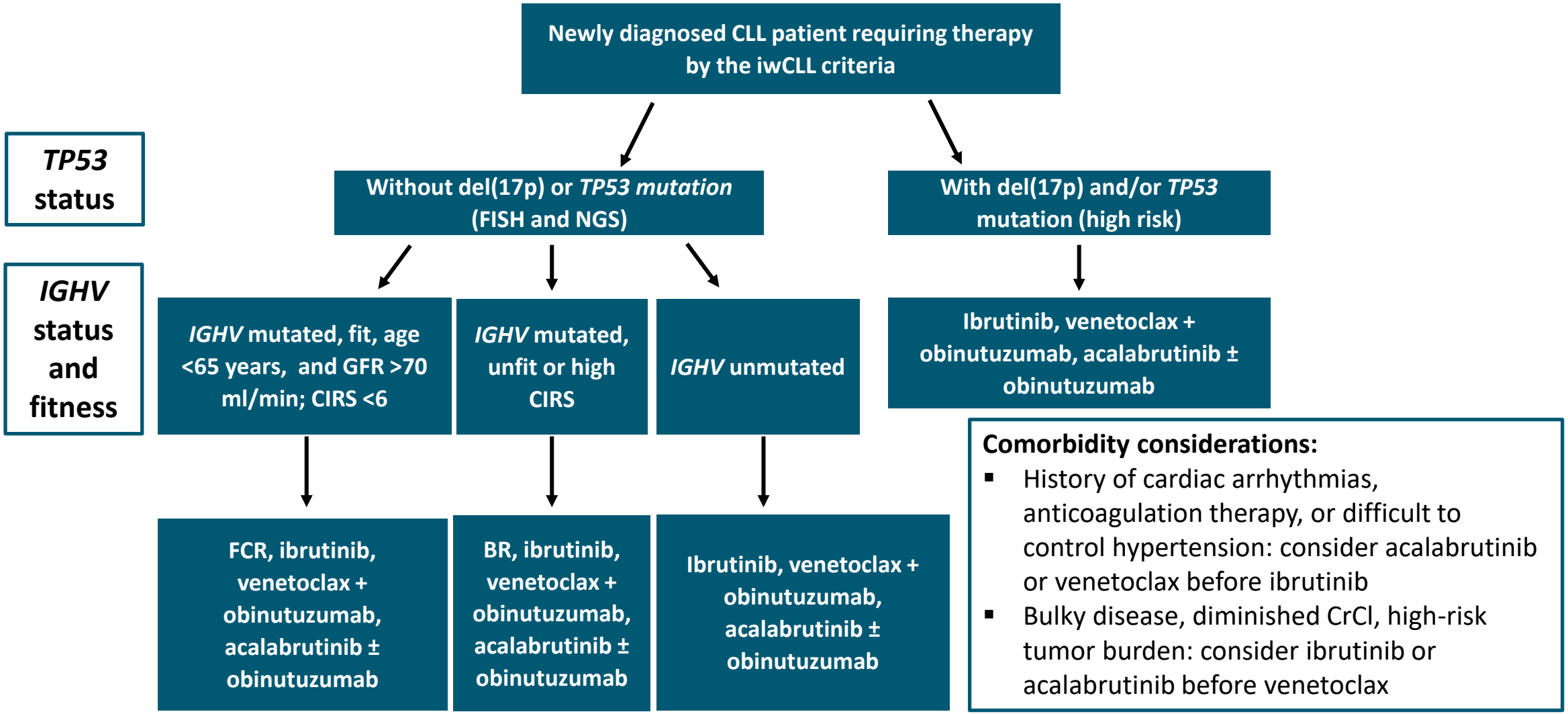
Grade 3/4 AE, %	Venetoclax + Obinutuzumab (n = 212)	Chlorambucil + Obinutuzumab (n = 214)
Hematologic AEs	60	55
▪ Neutropenia	53	48
▪ Thrombocytopenia	14	15
▪ Anemia	8	7
▪ Febrile neutropenia	5	4
Injury, poisoning, procedural complications	12	14
▪ Infusion-related reaction	9	10
Infections and infestations	18	15
▪ Pneumonia	4	4
Metabolism, nutrition disorders*	12	6

*P = .02

Grade 5 AE, n (%)	Venetoclax + Obinutuzumab (n = 212)	Chlorambucil + Obinutuzumab (n = 214)
Total events	16 (8)	8 (4)
Events during therapy	5 (2)	4 (2)
▪ Infections and infestations	4 (2)	3 (1)
▪ Neoplasms	1 (< 1)	1 (< 1)
Events after therapy completion	11 (5)	4 (2)
▪ Cardiac disorders	3 (1)	1 (< 1)
▪ Infections and infestations	4 (2)	0
▪ Neoplasms	2 (< 1)	2 (< 1)
▪ Other reasons	2 (< 1)	1 (< 1)

Fischer. ASCO 2019. Abstr 7502. Fischer. NEJM. 2019;380:2225.

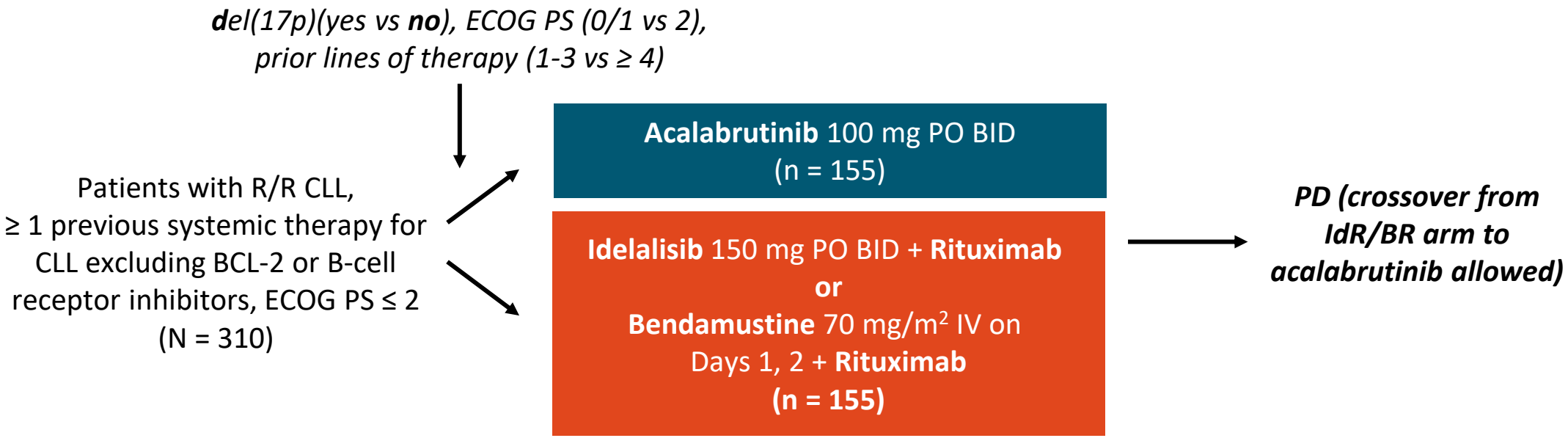
Treatment Algorithm for Newly Diagnosed CLL



Management of Previously Treated CLL

ASCEND: Acalabrutinib vs Idelalisib + Rituximab or BR in Previously Treated CLL

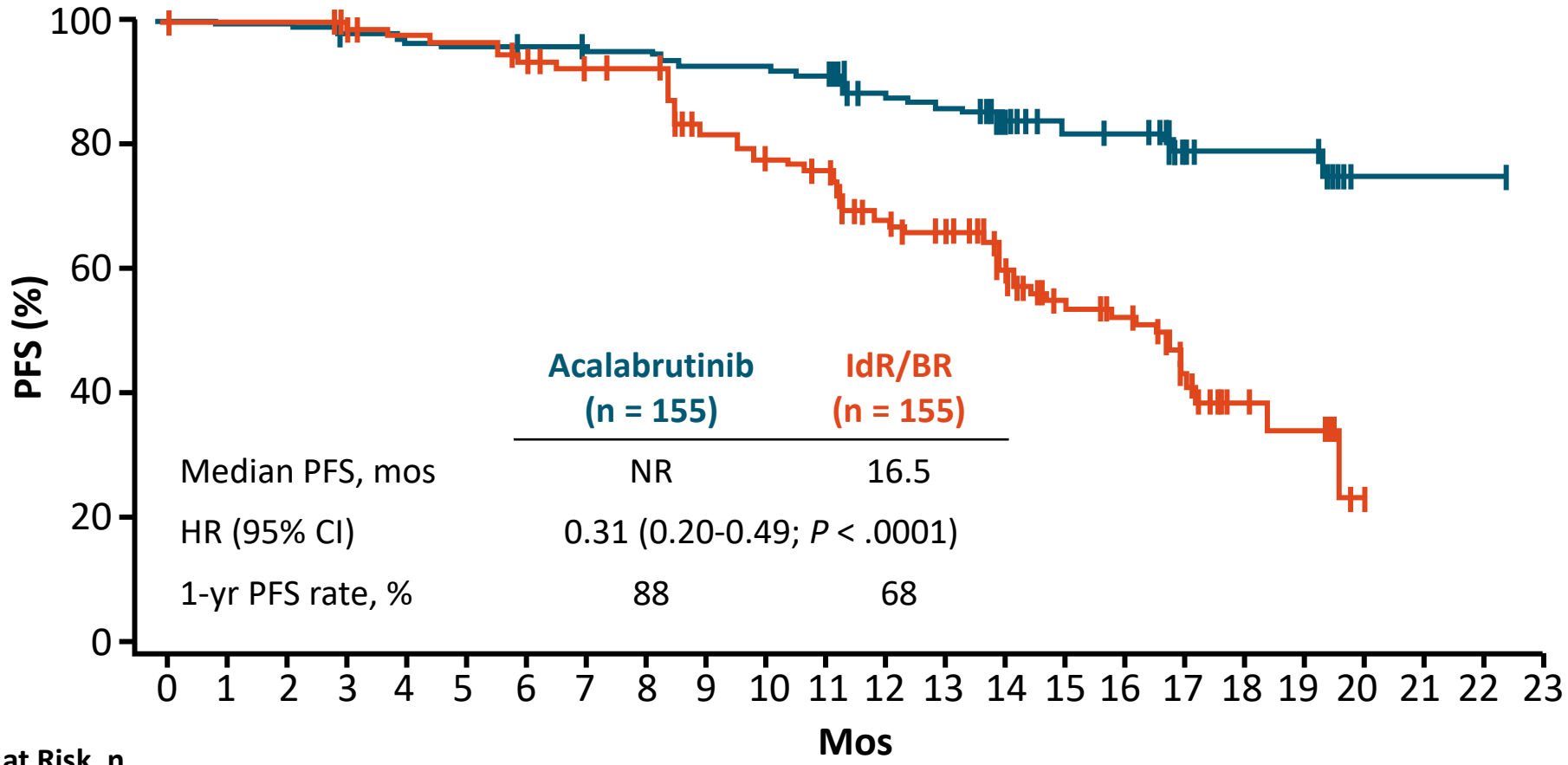
- International, randomized, open-label phase III trial



- Primary endpoints: PFS per IRC
- Secondary endpoints: ORR, DoR, PFS per investigator, OS
- Interim analysis planned after ≈ 79 PFS events

Ghia. EHA 2019. Abstr LB2606. NCT02970318.

ASCEND: PFS by IRC Review (Primary Endpoint)



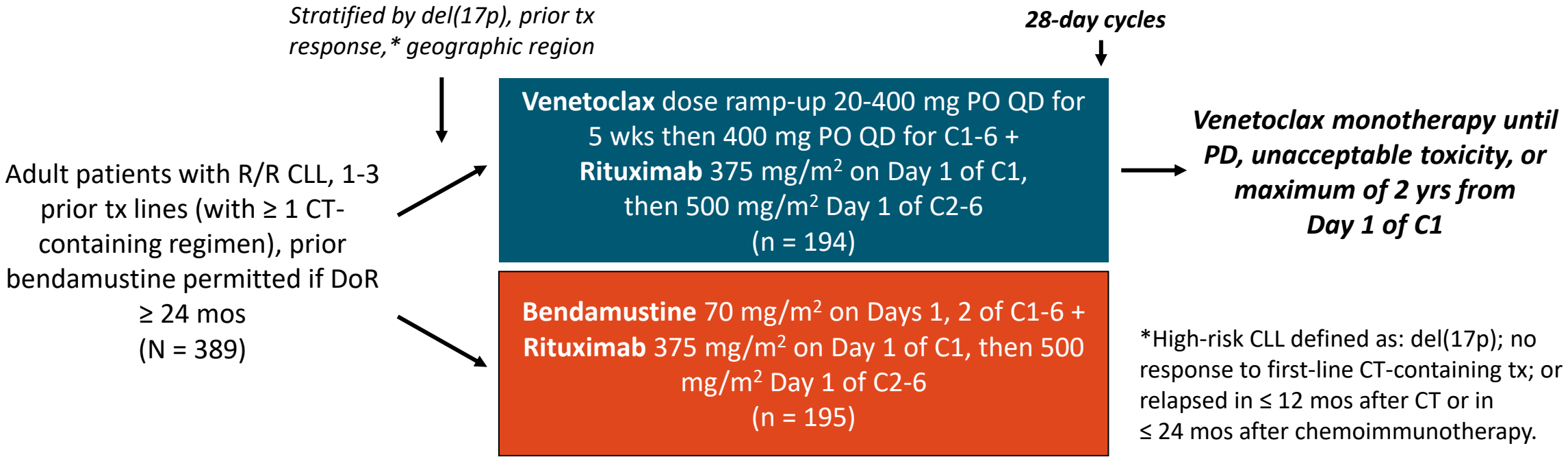
Patients at Risk, n

Acalabrutinib	155	153	153	149	147	146	145	143	143	139	139	137	118	116	73	61	60	25	21	21	1	1	1	0
IdR/BR	155	150	150	146	144	142	136	130	129	112	105	101	82	77	56	44	39	18	10	8	0			

Ghia. EHA 2019. Abstr LB2606.

MURANO: Venetoclax + Rituximab vs BR in Previously Treated CLL/SLL

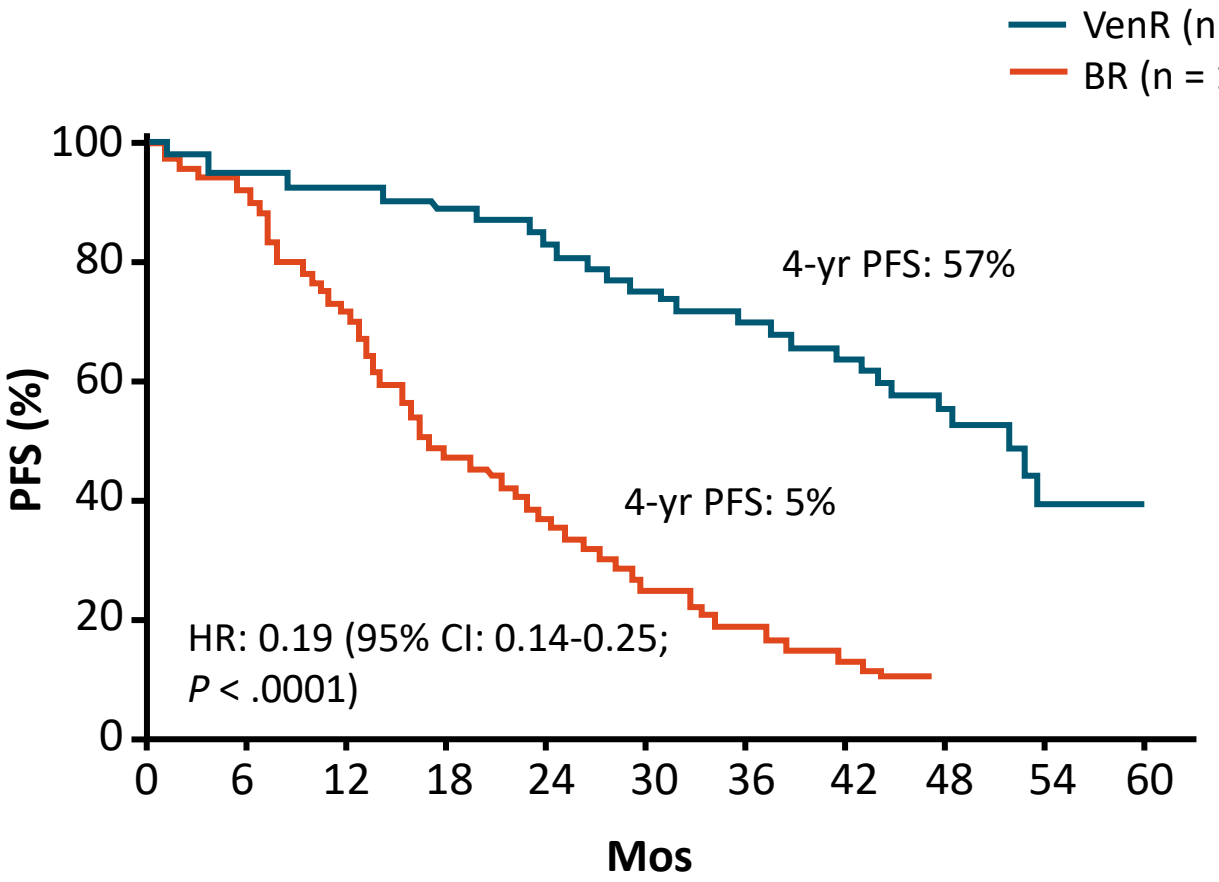
- Multicenter, randomized, open-label phase III trial

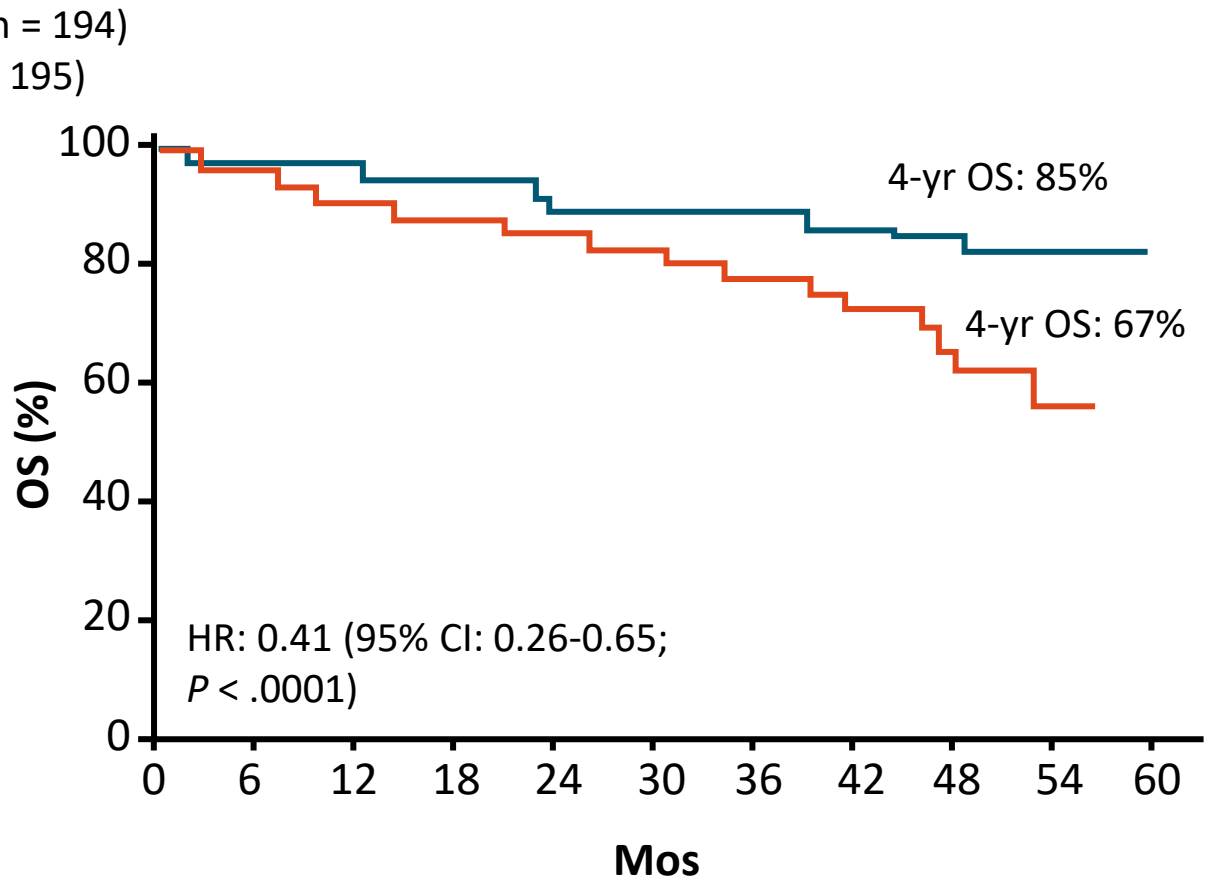


- Primary endpoint: investigator-assessed PFS
- Secondary endpoints: IRC-assessed PFS and MRD negativity, IRC-assessed CR → ORR → OS, safety

Seymour. NEJM 2018; 378:1107. NCT02005471.

MURANO: Updated PFS and OS

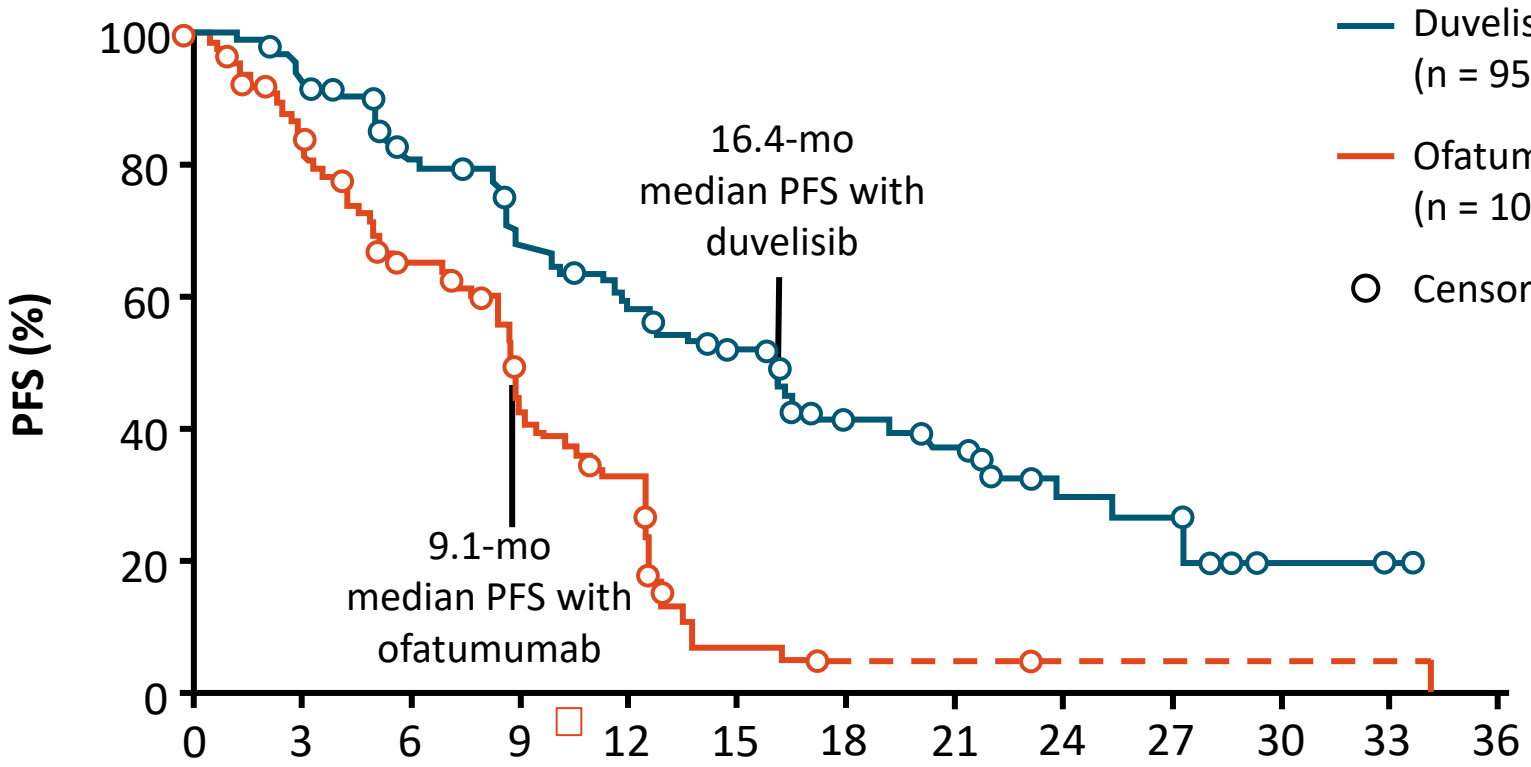




- Median follow-up: 48.0 mos

Seymour. ASH 2019. Abstr 355.

Phase III DUO Trial of Duvelisib vs Ofatumumab in R/R CLL: PFS

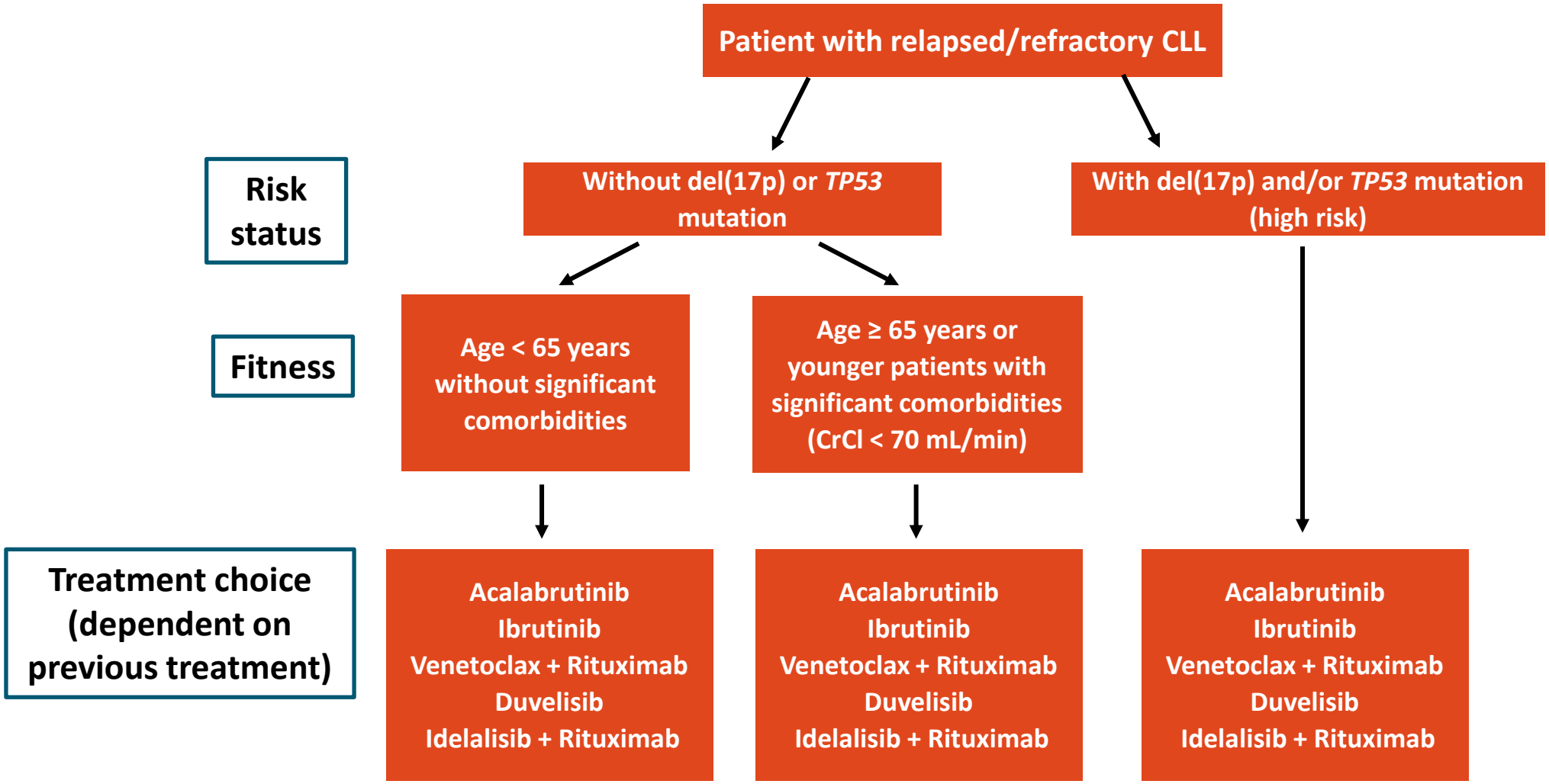


Patients at Risk, n													
Duvelisib	95	88	69	60	50	39	23	19	11	9	2	2	0
Ofatumumab	101	78	52	39	22	4	2	2	1	1	1	1	0

- Duvelisib met its primary endpoint of PFS in the DUO subpopulation

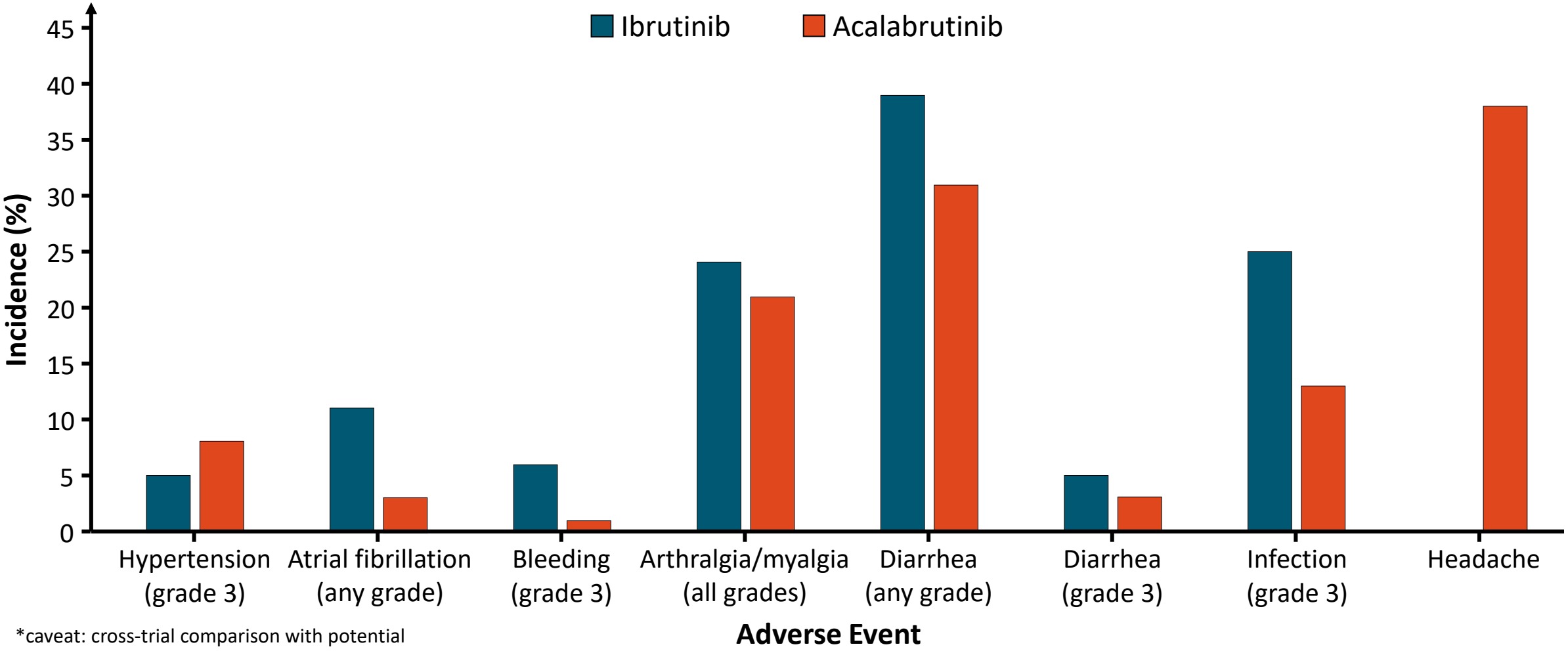
Duvelisib PI.

Treatment Algorithm for Relapsed/Refractory CLL



Targeted Agents-Adverse Event Management

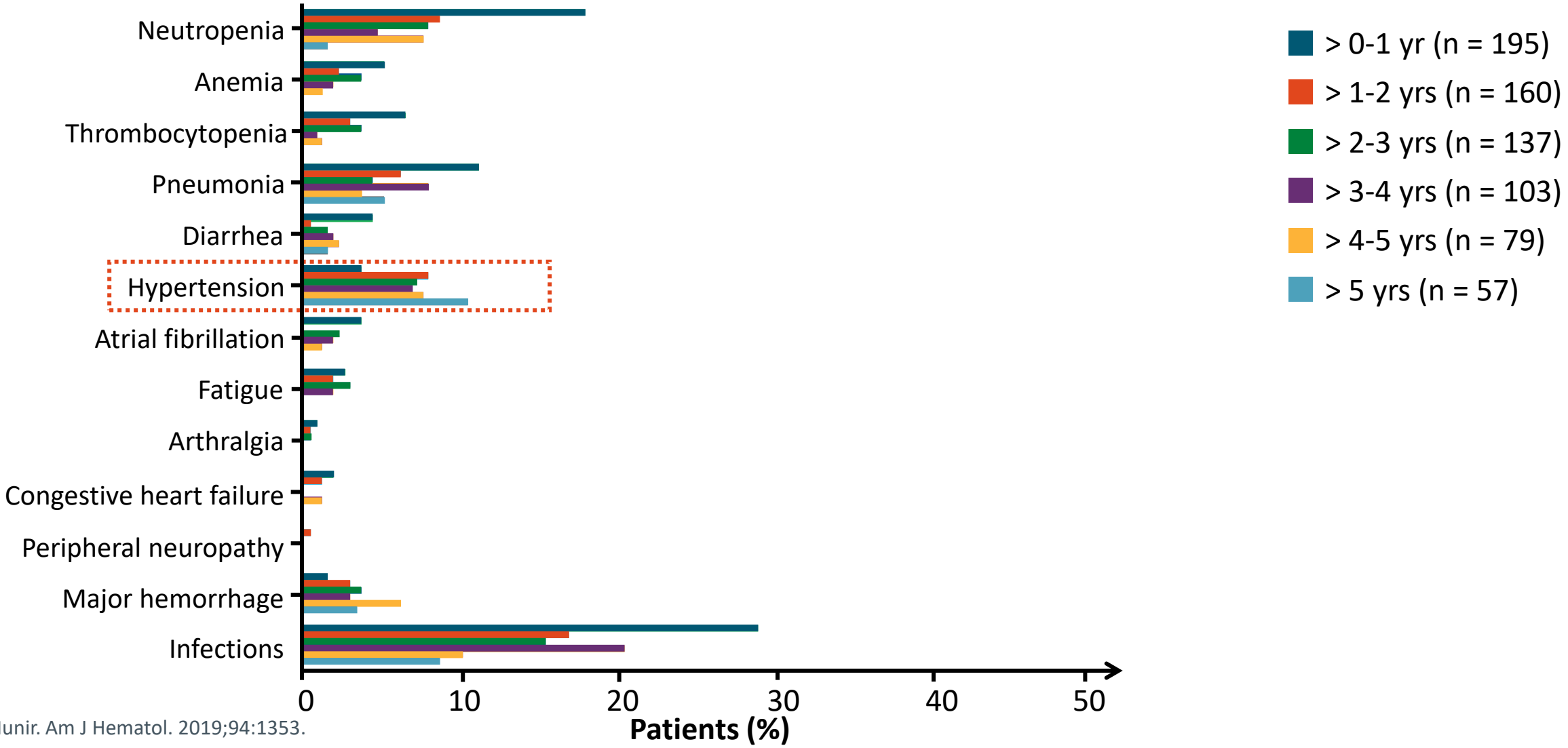
BTK Inhibitors in CLL: Select Adverse Events Across Pivotal Trials*



*caveat: cross-trial comparison with potential differences in patient population and trial design

Rule. Haematologica. 2019;104:e211. Tam. ICML 2019. Abstr 191. Wang. Lancet. 2018;391:659. Ibrutinib PI. Acalabrutinib PI. Zanubrutinib PI.

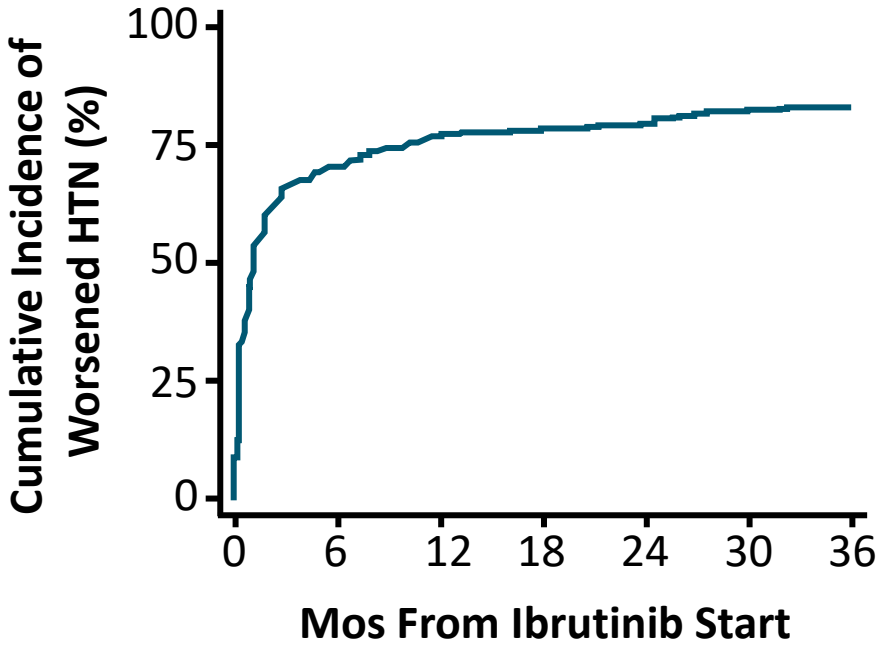
Ibrutinib: Prevalence of Select Grade ≥ 3 Adverse Events Over Time



Munir. Am J Hematol. 2019;94:1353.

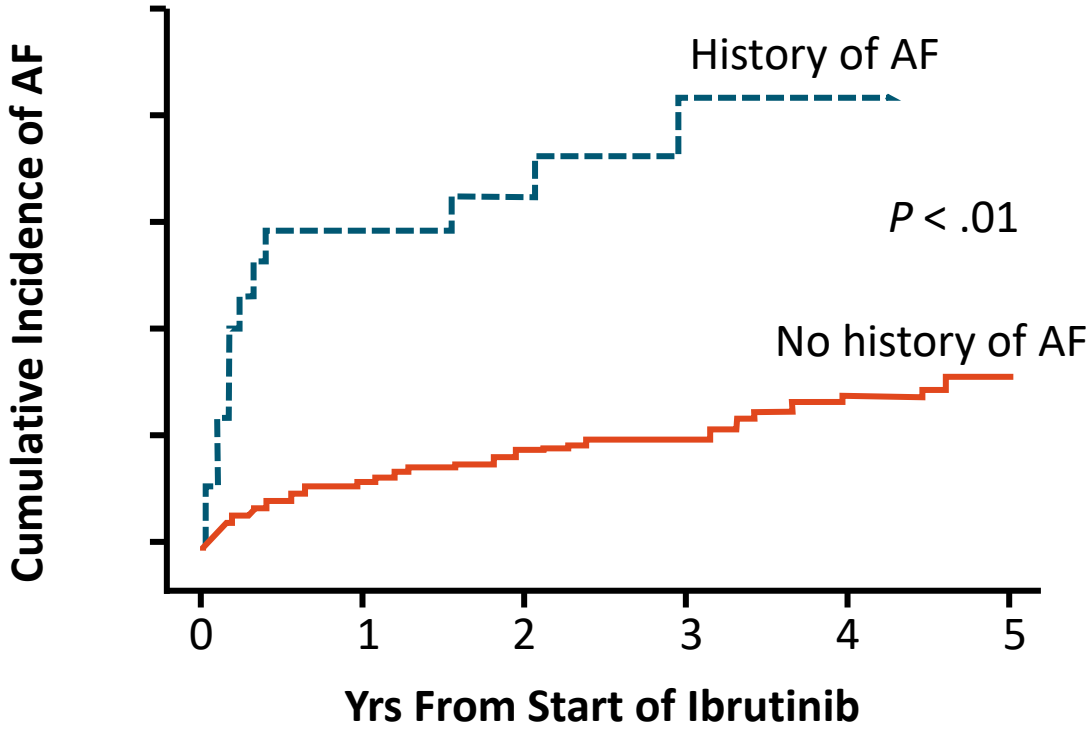
Hypertension and Atrial Fibrillation on Ibrutinib

Cumulative Incidence of Hypertension During Ibrutinib[1]



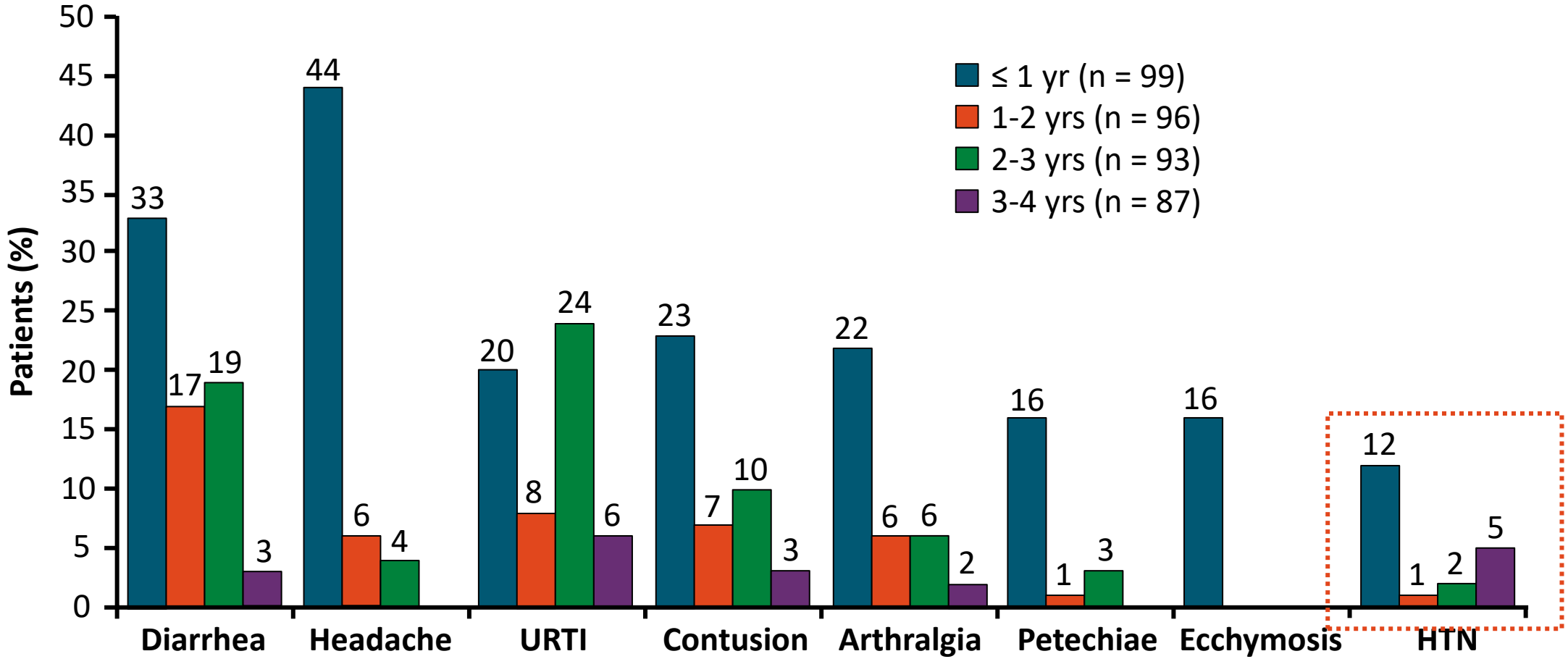
Time to 50% cumulative incidence: 1.1 mos
Median follow-up: 29.3 mos

Impact of Atrial Fibrillation History With Ibrutinib[2]



1. Dickerson. Blood. 2019;134:1919. 2. Wiczer. Blood Adv. 2017;1:1739.

Acalabrutinib in CLL (ACE-CL-001): Select AEs Over Time



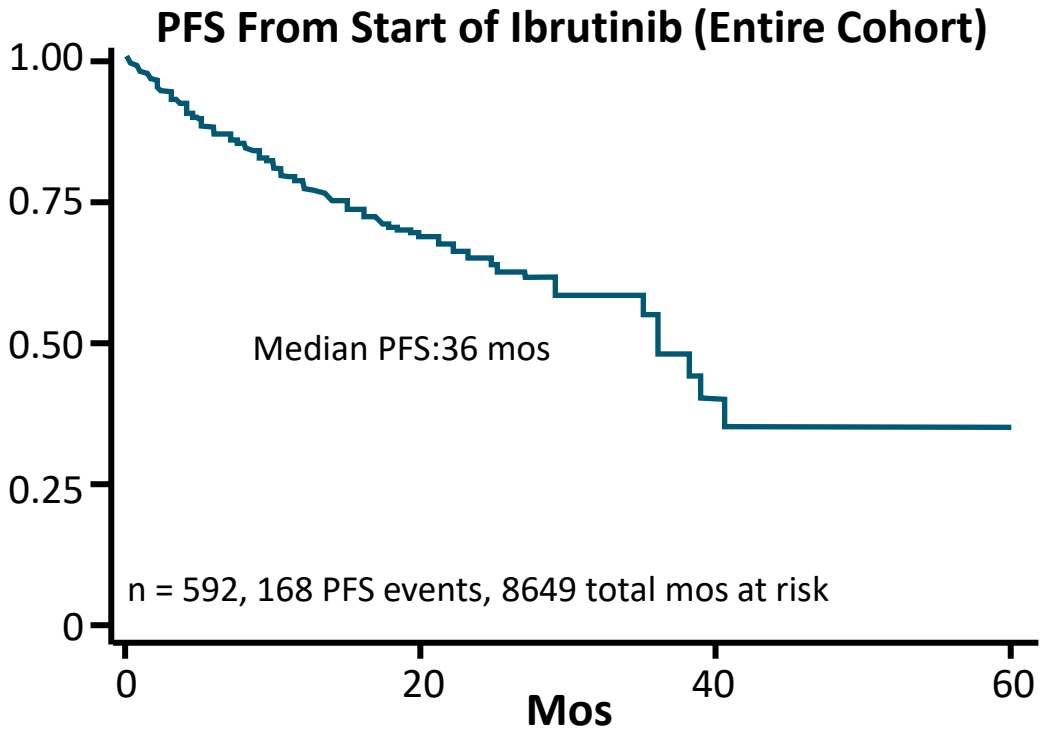
- In general, AEs more common in first yr of acalabrutinib treatment

Byrd. ASH 2018. Abstr 692.

Ibrutinib Intolerance in the "Real World"

- Multicenter, retrospective analysis of patients with CLL treated in clinics and clinical trials (N = 616)

Discontinuation rate: 42% after median follow-up of 17 mos



Reasons for Discontinuation (%)	
Frontline	Relapsed
Arthralgias (42.0)	Atrial fibrillation (12.3)
Atrial fibrillation (25.0)	Infection (11.0)
Rash (16.0)	Pneumonitis (10.0)
	Bleeding (9.0)
	Diarrhea (7.0)

Mato. Haematologica. 2018;103:874.

Adverse Events and Suggested Management of Ibrutinib

Ibrutinib

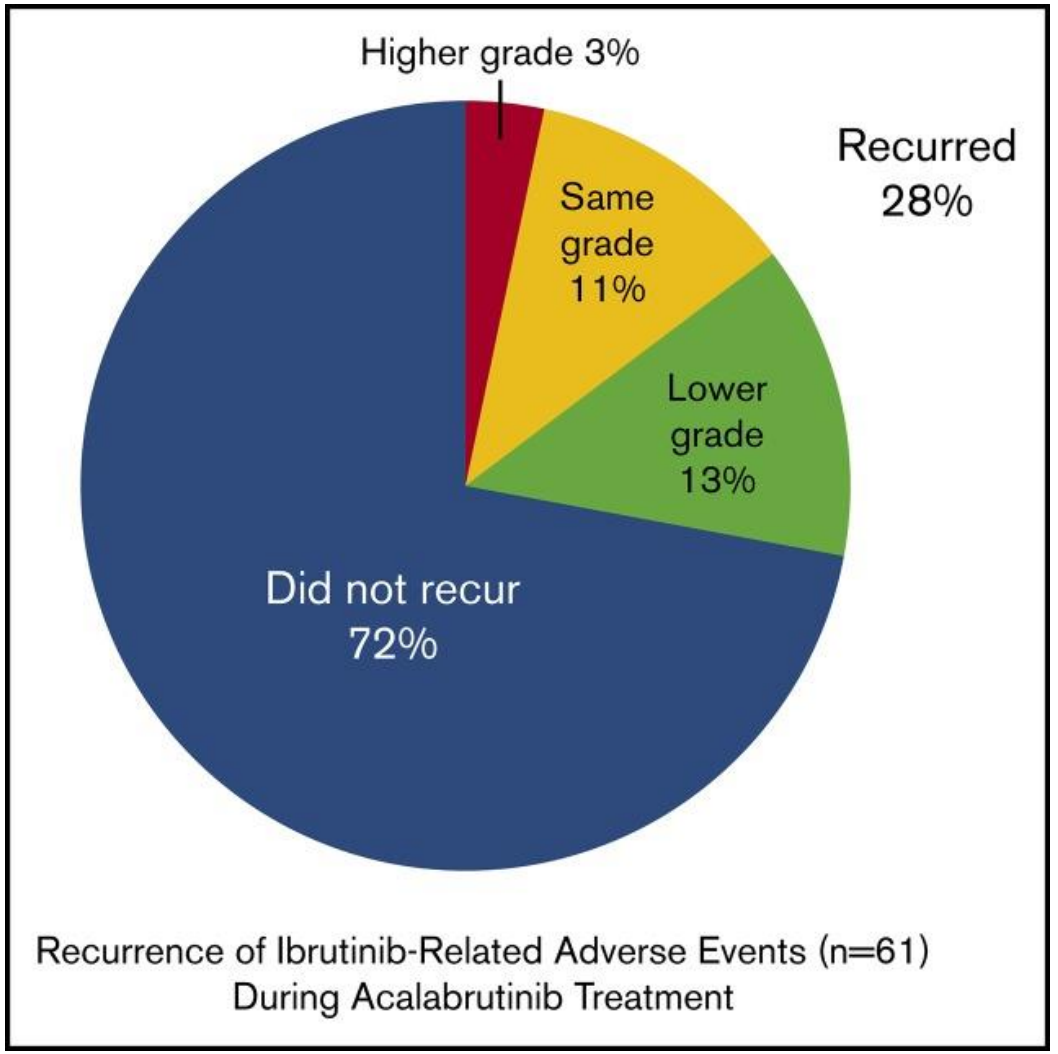
- Muscle cramps
  - Magnesium and calcium tablets, stretching
- Hypertension
  - Standard management, discontinue if 2-3 meds required
- Arthralgias/myalgias
  - Acetaminophen, prednisone, discontinue
- Leg lymphedema
  - Discontinue
- Fatigue
  - Reduce dose/discontinue

- For patients who experience grade 3/4 nonhematologic AEs, ibrutinib should be held until resolution to baseline or grade 1
- Once resolved, ibrutinib can be restarted at the **starting dose** (420 mg QD for CLL or WM; 560 mg QD for MCL and MZL) **for the first occurrence** or can be **dose reduced by 140 mg per recurrence**
  - If the AE recurs for a fourth time, ibrutinib should be discontinued

Ibrutinib PI.

Acalabrutinib in CLL (ACE-CL-001): Results in Ibrutinib-Intolerant Cohort

- N = 33 heavily pretreated patients with CLL treated with acalabrutinib
  - 23 remained on acalabrutinib at median of 19 mos on treatment
  - No acalabrutinib dose reductions
- 61 ibrutinib-related AEs associated with intolerance at study entry
  - No recurrence: 72%
  - Recurrence at lower grade than with acalabrutinib: 13%
- ORR: 76%
- Median PFS: not reached
  - 1-yr PFS rate: 83.4%



Recurrence of Ibrutinib-Related Adverse Events (n=61) During Acalabrutinib Treatment

Awan. Blood Adv. 2019;3:1553.

Atrial Fibrillation With BTK Inhibitors: Tips for Management

Mechanism

- Dose dependent (possibly off-target cardiac PI3K inhibition; BTK and TEC also implicated)

Management

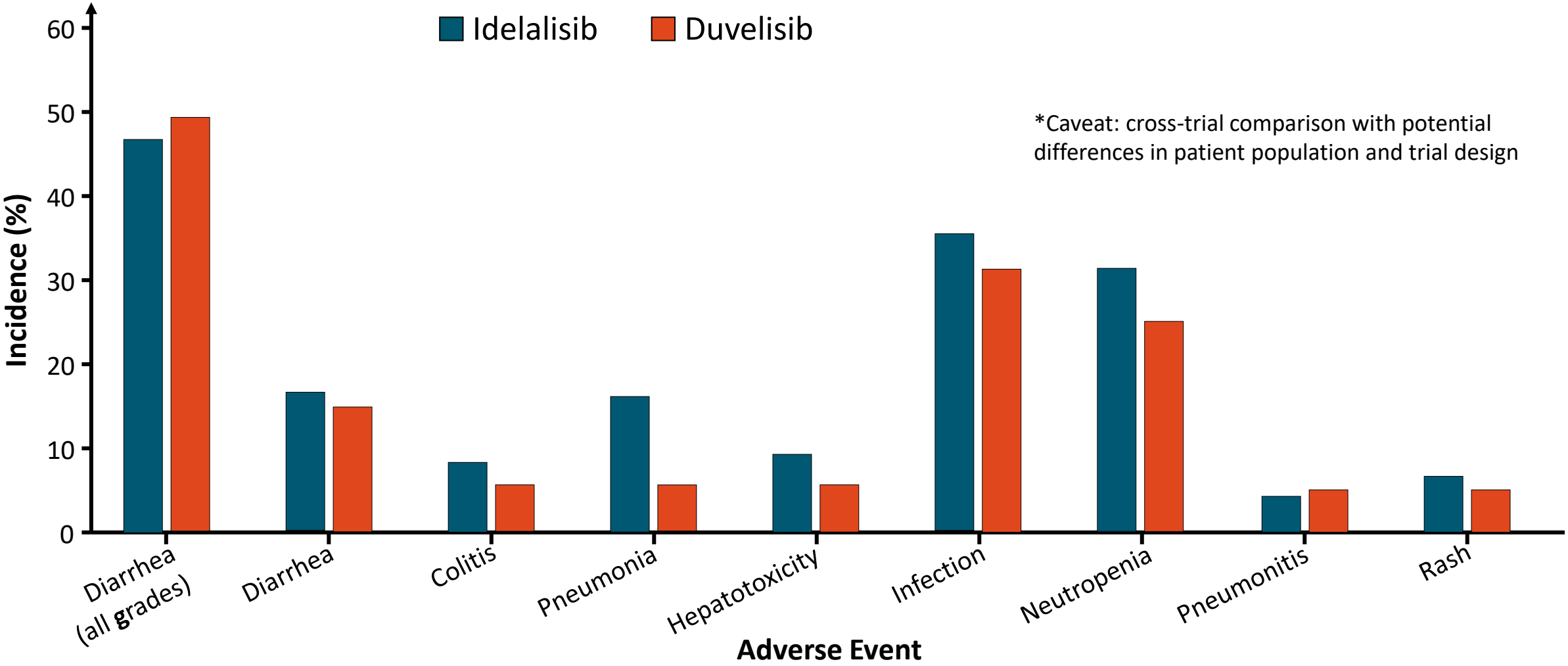
- Rate control (beta-blocker preferred as verapamil and diltiazem are CYP inhibitors)
  - Monitor digoxin level if used with P-gp inhibitor (see later table)
- Rhythm control (careful selection due to drug interactions)
- Controllable A fib: continue therapy (some consider switching to alternative BTKi)
- Uncontrollable A fib: consider alternative therapy

Anticoagulation

- Calculate $CHA2DS_2$-VASc score
- 2+: consider anticoagulation (avoid warfarin)

Stephens. Blood. 2019;133:1298. de Weerdt. Haematologica. 2017;102:1629. McMullen. Blood. 2014;124:3829. Ibrutinib PI.

PI3K Inhibitors: Select Grade ≥ 3 Adverse Events Across Pivotal Trials*



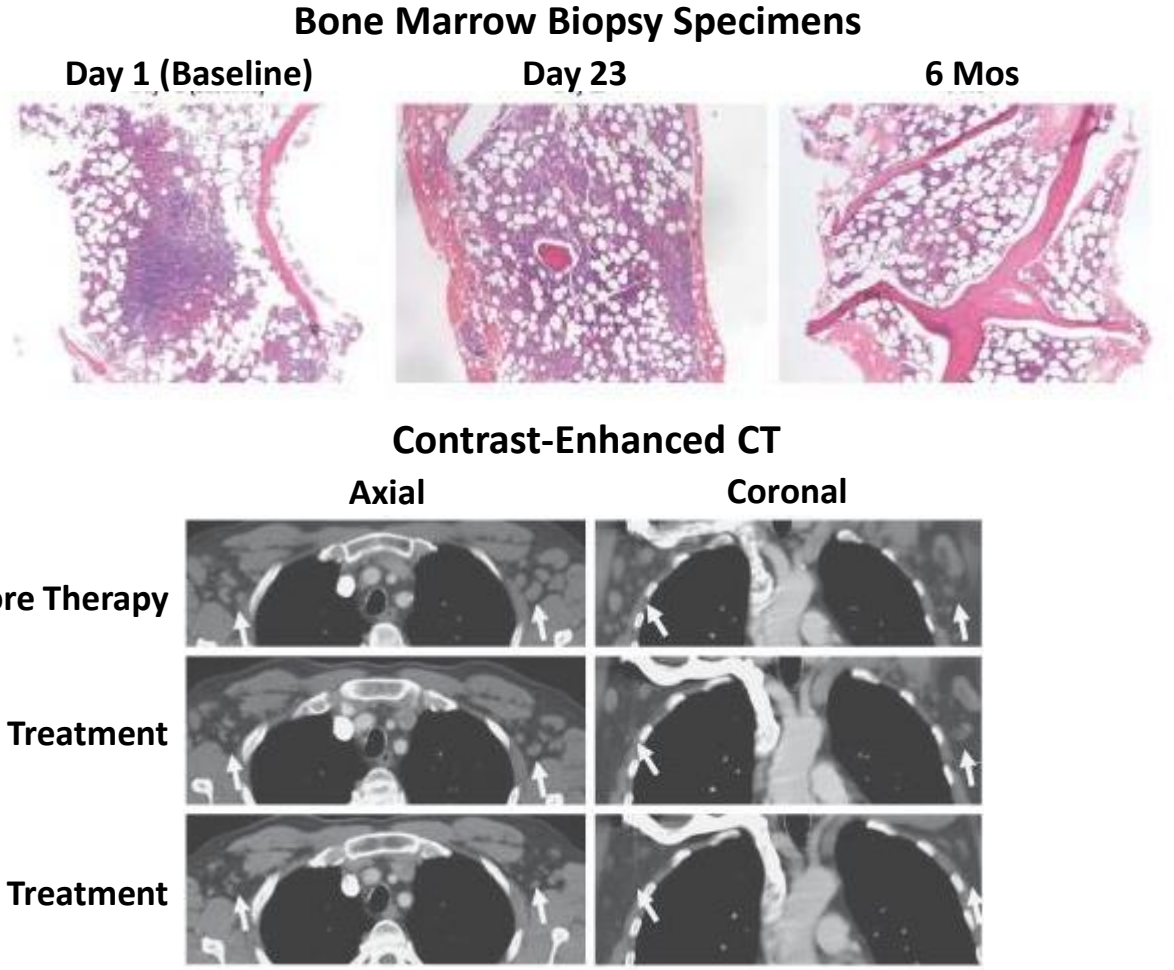
Gopal. NEJM. 2014;370:1008. Dreyling. JCO. 2017;35:3898. Flinn. JCO. 2019;37:912.

Future Directions

Chimeric Antigen Receptor T-Cell Therapy

- 2011: first case report of successful CAR T-cell therapy in CLL[1]
- Since then, multiple reports of sustained remissions after CAR T-cell therapy[2]
- Ibrutinib + anti-CD19 CAR T-cell therapy associated with 89% CR rate in CLL[3]
- In pts with R/R CLL previously treated with ibrutinib (39% received venetoclax), anti-CD19 CAR T-cell therapy induced rapid and durable responses[4]
  - ORR: 82% (CR/CRi: 46%)
  - MRD negativity rate (10^{-4}): 75% in peripheral blood and 65% in bone marrow

Case Report: CAR T-Cell Therapy in CLL[1]



1. Porter. NEJM. 2011;365:725. 2. Turtle. JCO. 2017;35:3010.
3. Gill. ASCO 2017. Abstr 7509. 4. Siddiqi. ASH 2019. Abstr 503.

Conclusions

- Novel targeted agents are eclipsing chemoimmunotherapy both in patients with newly diagnosed and relapsed CLL
- Initial therapy options include acalabrutinib ± obinutuzumab, ibrutinib, and venetoclax + obinutuzumab
- Therapy options for relapsed CLL include acalabrutinib, ibrutinib, venetoclax + rituximab, duvelisib, and idelalisib + rituximab
- Ongoing investigation is exploring novel agents and multitargeted combination regimens with the goal of MRD eradication
- CAR T-cells are showing early promise as a potential future option for high-risk relapsed/refractory disease