Chronic Lymphocytic Leukemia

Practical updates in treatment-naïve and relapse disease

Jose D. Sandoval-Sus, MD FACP

Assistant member, Department of Malignant Hematology & Cellular Therapy

Moffitt Cancer Center at Memorial Healthcare System

Pembroke Pines, FL

18th Annual MIAMI CANCER MEETING

JW MARRIOTT MIAMI | MIAMI, FLORIDA

APRIL 1-3, 2022

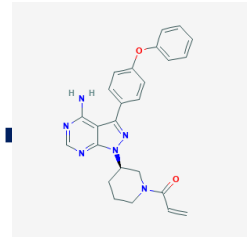
@HemSandoval

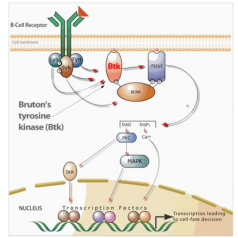
MOFFITT | Memorial Healthcare System

Malignant Hematology & Cellular Therapy

BTKi (single agent) persistent frontline therapies in CLL

With Ibrutinib, everything changed..

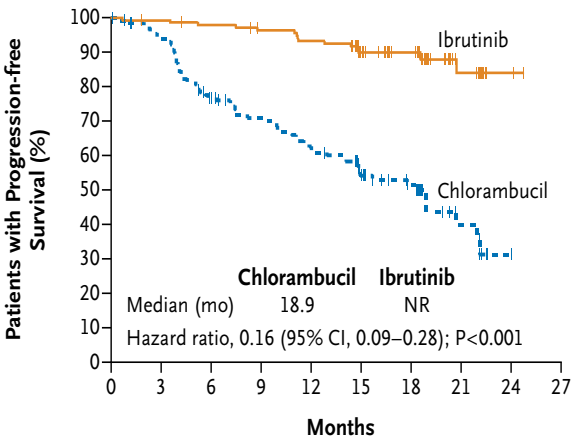


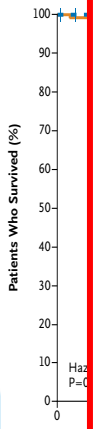


RESONATE-2 c

ATE-2: 5-year f/up

PFS





Subgroup	No. of Patients
All patients	269
Age	
<70 yr	80
≥70 yr	189
Chromosome 11q22.3 deletion	
Yes	54
No	197
IGHV	
Mutated	82
Unmutated	118

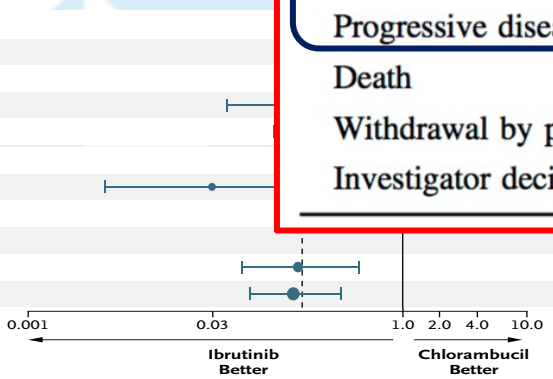
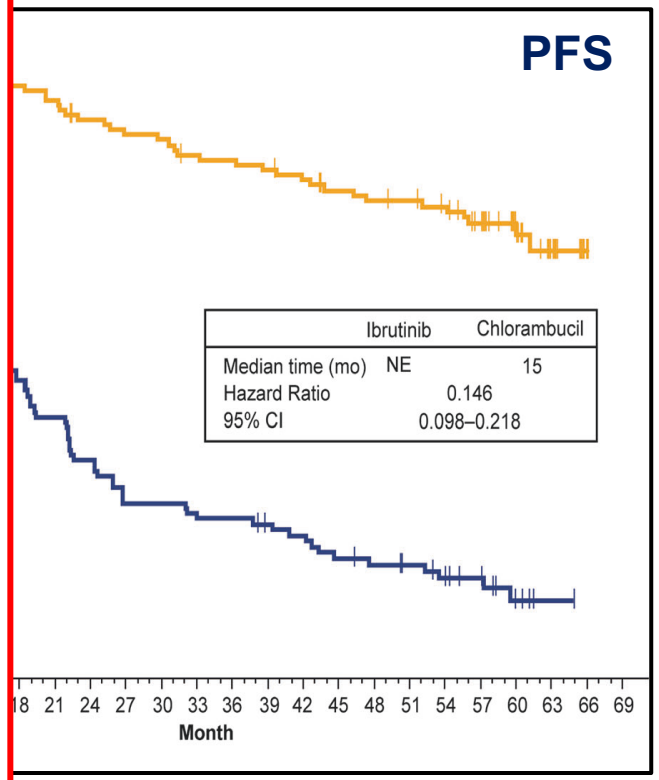


Table 2 Duration of treatment with first-line ibrutinib

	Ibrutinib $n = 136$
Median (range) duration of ibrutinib treatment, months[a]	57.1 (0.7–66.0)
Treatment duration, *n* (%)	
>3 years	99 (73)
>4 years	88 (65)
>5 years	37 (27)
Continuing ibrutinib on study, *n* (%)	79 (58)
Continuing on commercial ibrutinib, *n* (%)	0 (0)
Discontinued ibrutinib, *n* (%)	56 (41)
Adverse event	29 (21)
Progressive disease	8 (6)
Death	8 (6)
Withdrawal by patient	7 (5)
Investigator decision	4 (3)

PFS



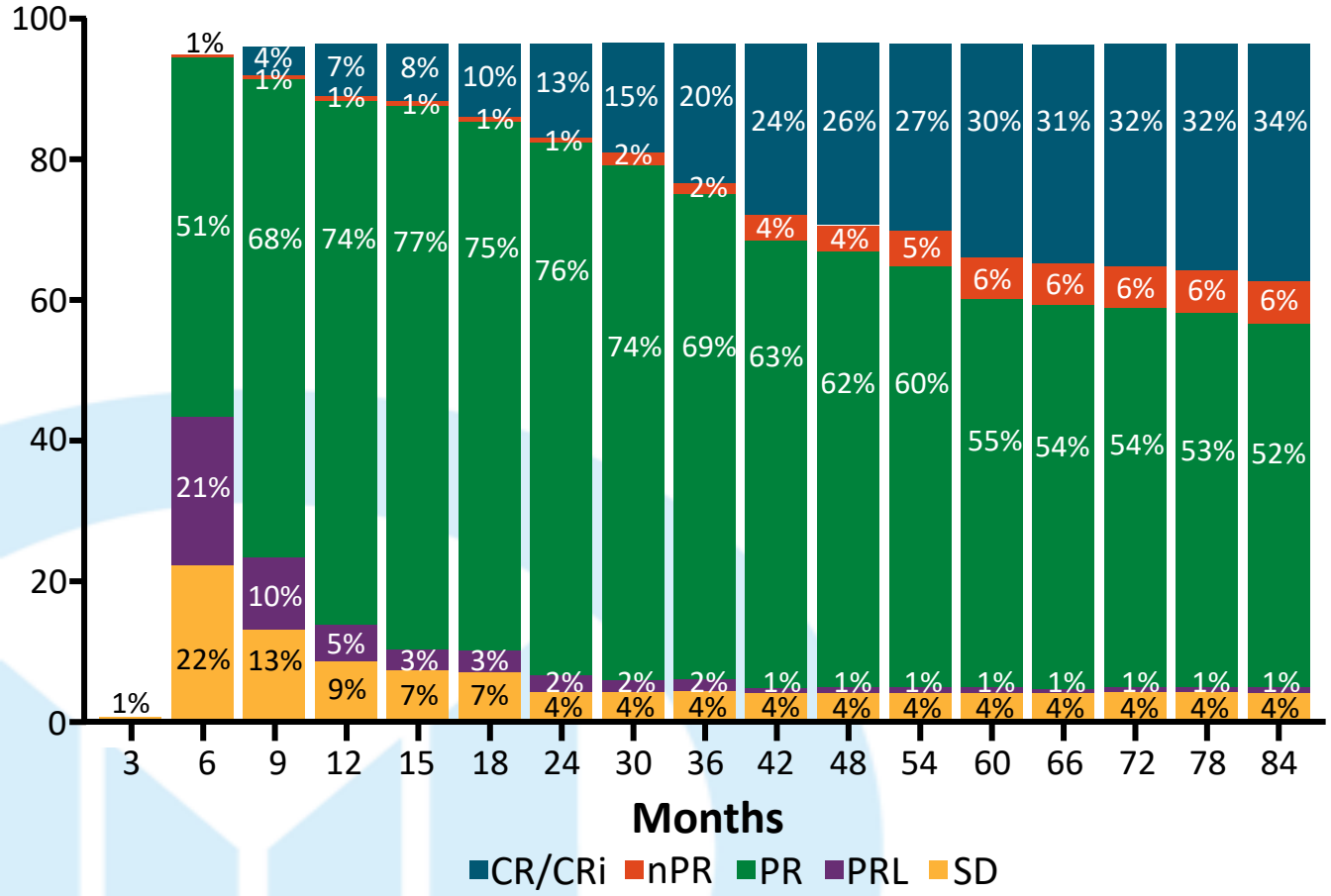
- b vs. 68% for chlorambucil.
- 5 yo OS in high risk CLL (TP53 mut, del11q and/or unmut IGHV): 84% for I Vs. 62% for Chl.

MOFFITT CANCER CENTER

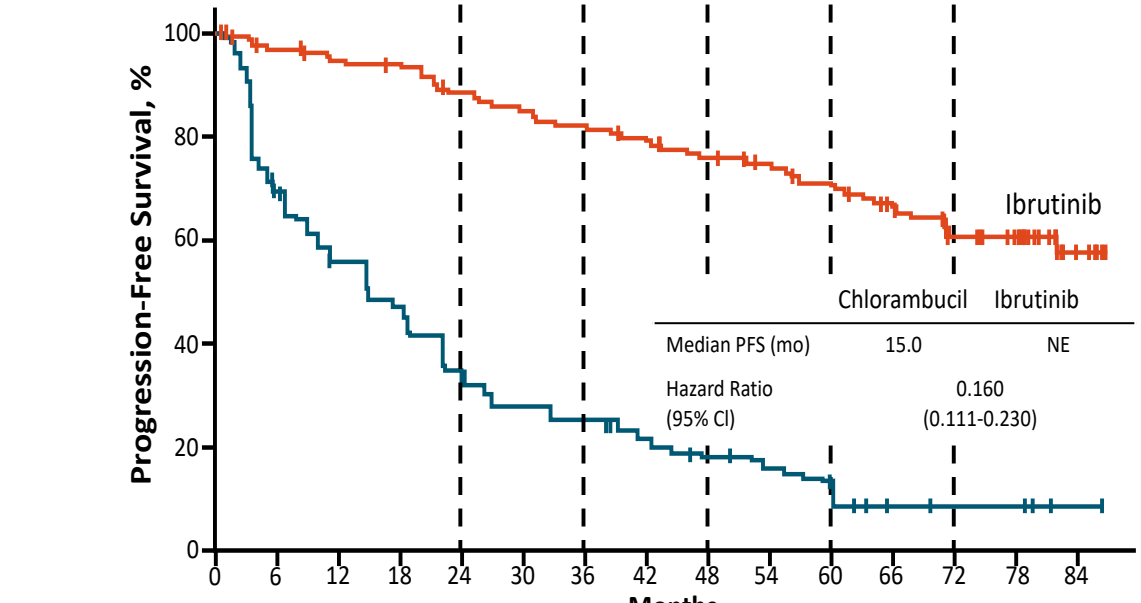
1. Burger JA et al. N Engl J Med 2015;373:2425-37
2. Burger JA. et al. Leukemia 2019 Oct 18.

RESONATE-2: 7-Year Follow-Up of Frontline Ibrutinib in Older CLL/SLL patients

Overall Response Rate (%)



PFS (primary endpoint)



PFS with ibrutinib:

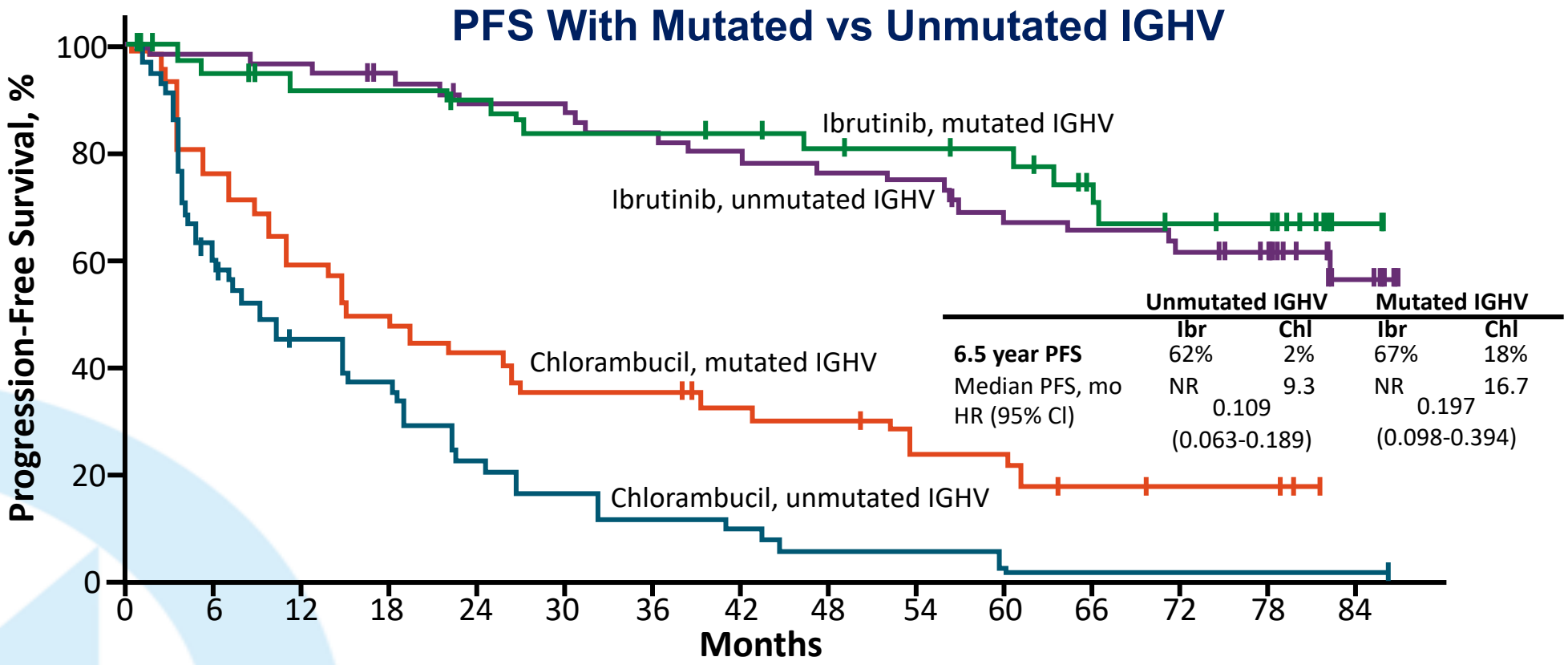
- ✓ 90% at 18 mo
- ✓ 70% at 60 mo
- ✓ **61% at 78 mo (6.5 yo)**

PFS benefit seen across all subgroups

MOFFITT CANCER CENTER

Barr P et al. ASCO 2021. Abstr 7523.

RESONATE-2: 7-Year Follow-Up of Frontline Ibrutinib in Older CLL/SLL patients



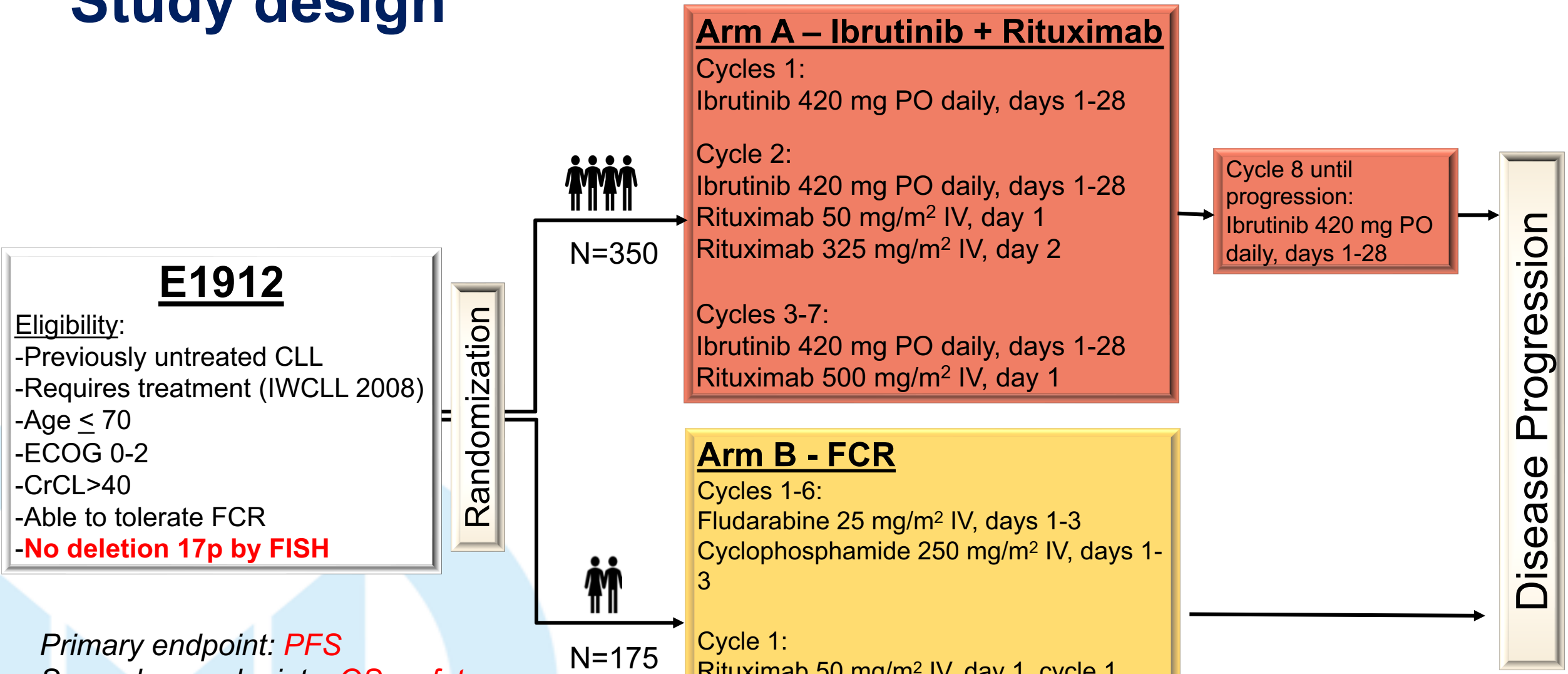
Patients at Risk

Ibrutinib, mutated IGHV:	40	37	34	34	32	30	30	29	27	26	25	20	17	16	4
Ibrutinib, unmutated IGHV:	58	58	56	53	49	48	46	43	42	41	36	35	32	26	8
Chlorambucil, mutated IGHV:	42	42	25	21	18	15	15	12	11	8	8	5	4	4	
Chlorambucil, unmutated IGHV:	60	60	23	19	11	8	6	5	3	3	2	1	1	1	1

MOFFITT CANCER CENTER

Barr P et al. ASCO 2021. Abstr 7523.

Study design



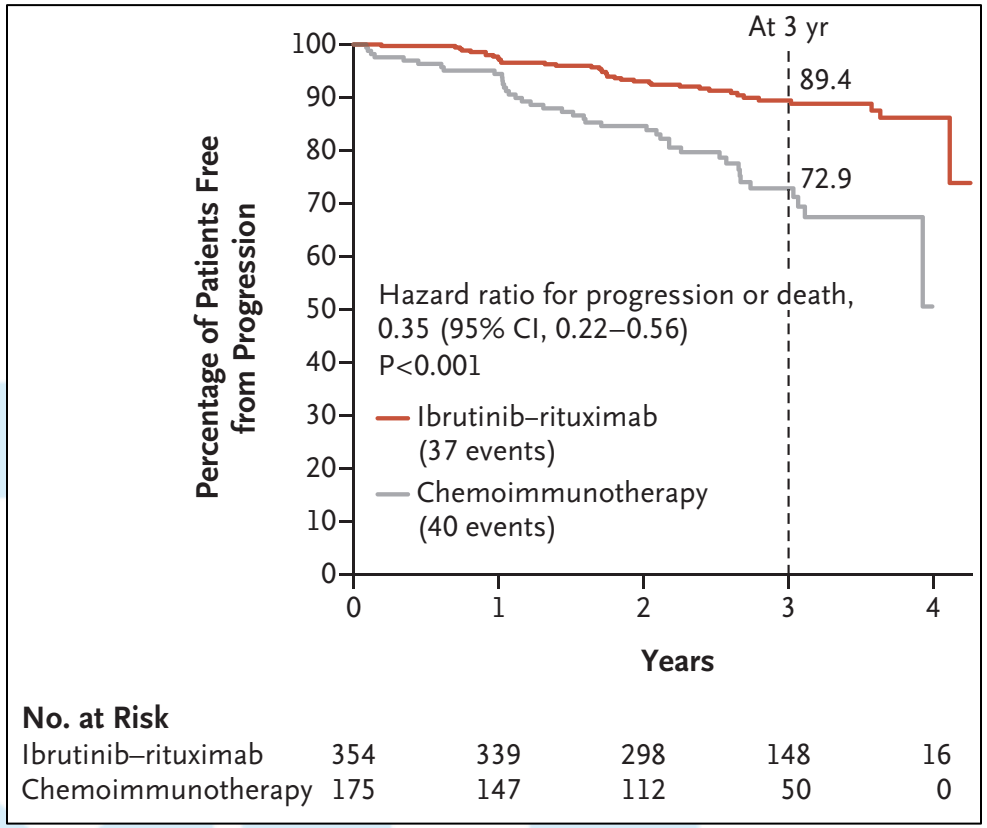
Primary endpoint: PFS
Secondary endpoints: OS, safety
Median follow-up: 33.6 mo (0.5-51.1)

MOFFITT CANCER CENTER

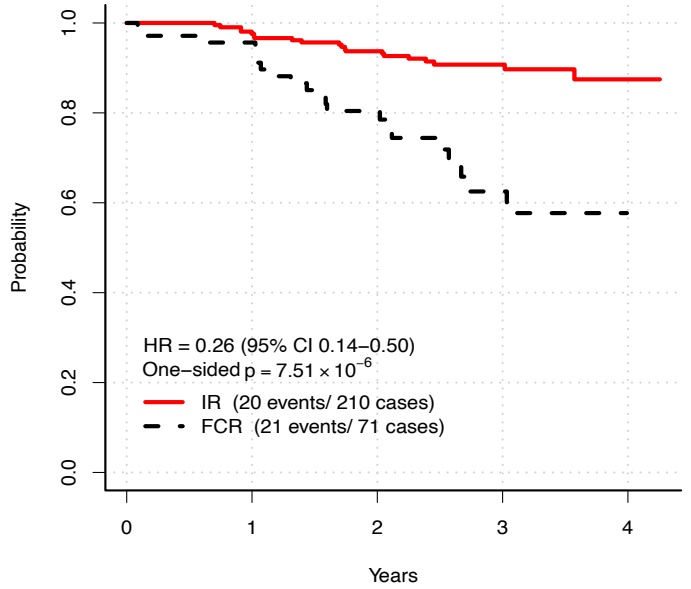
Shanafelt TD et al. N Engl J Med 2019;381:432-43.

Progression Free Survival

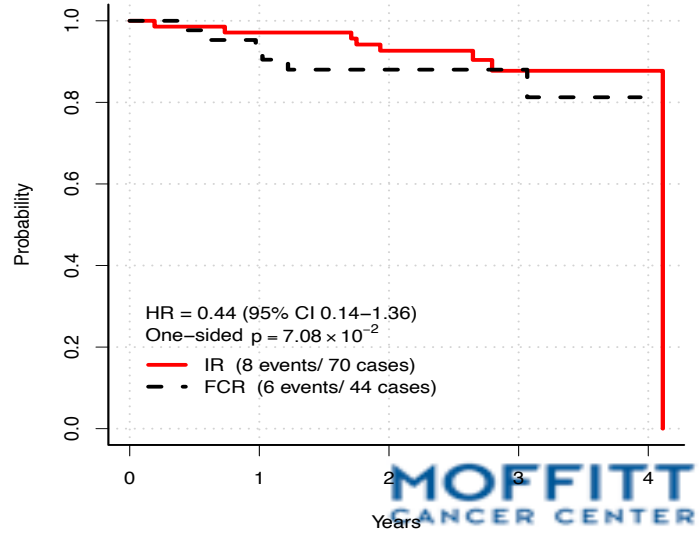
Intent to Treat



IGHV Unmutated



IGHV Mutated



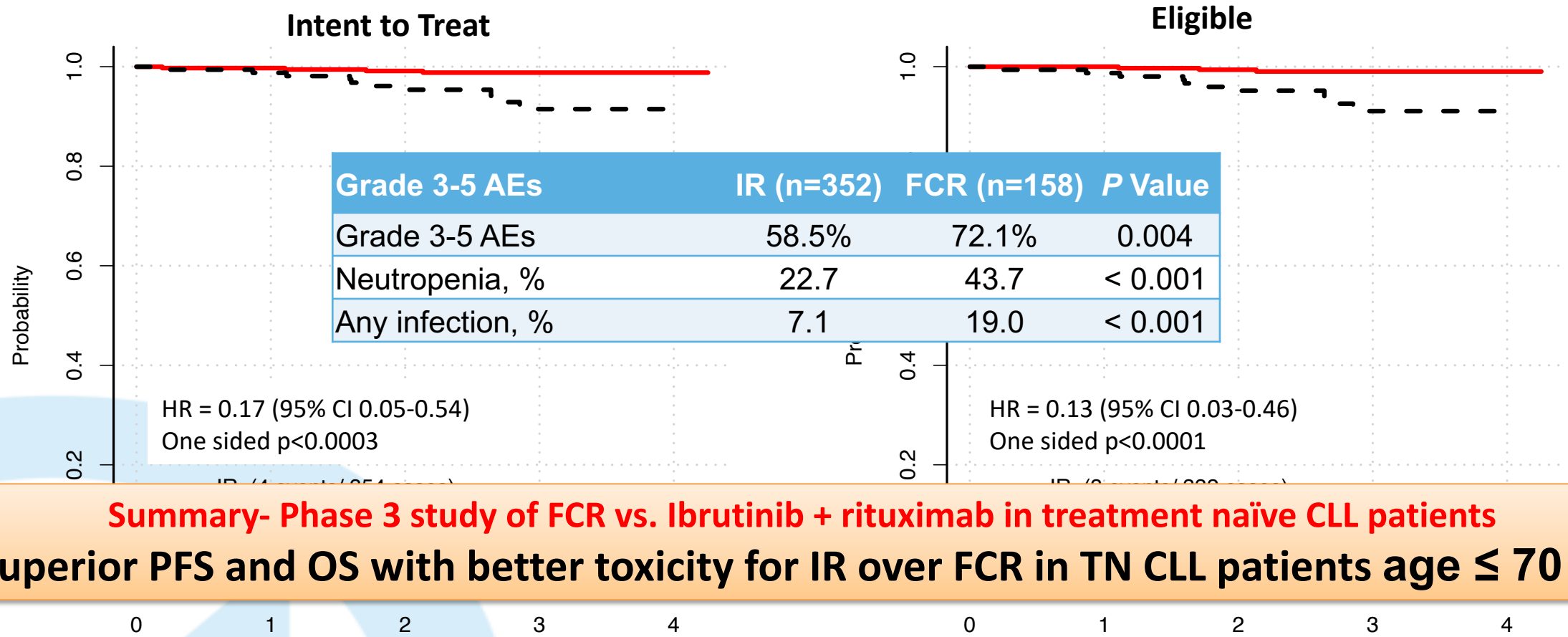
Number at risk

Shanafelt TD et al. N Engl J Med 2019;381:432-43.

ECOG-ACRIN cancer research group
Reshaping the future of patient care

MOFFITT CANCER CENTER

Overall Survival



Grade 3-5 AEs	IR (n=352)	FCR (n=158)	*P* Value
Grade 3-5 AEs	58.5%	72.1%	0.004
Neutropenia, %	22.7	43.7	< 0.001
Any infection, %	7.1	19.0	< 0.001

Summary- Phase 3 study of FCR vs. Ibrutinib + rituximab in treatment naïve CLL patients

Superior PFS and OS with better toxicity for IR over FCR in TN CLL patients age ≤ 70 yo

ECOG-ACRIN cancer research group
Reshaping the future of patient care

MOFFITT CANCER CENTER

Shanafelt TD et al. N Engl J Med 2019;381:432-43.

E1912 Update: PFS and OS

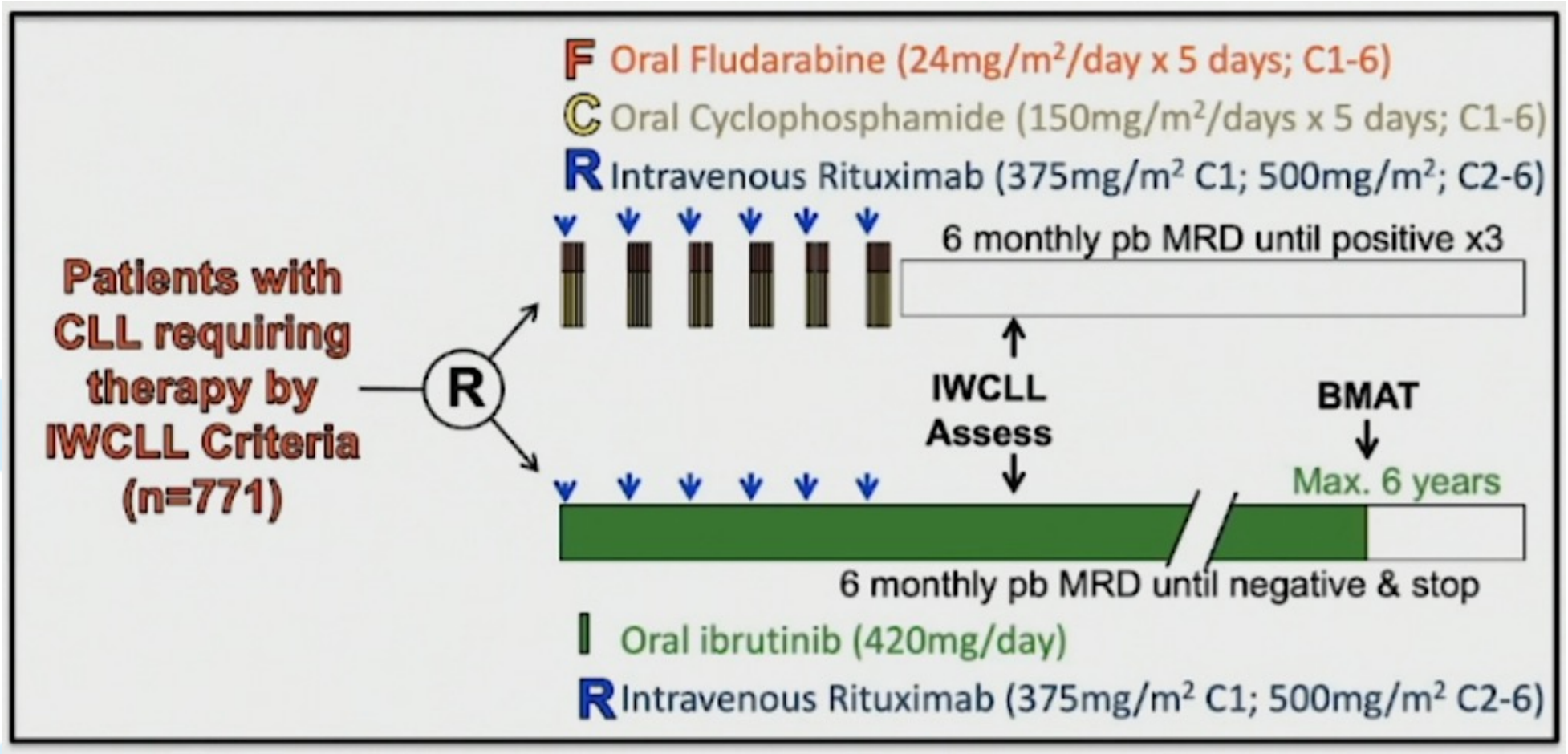
Outcome	I+R (N=354)	FCR (N=175)	HR (95% CI)	*P* Value
PFS (all patients)				
▪ Events	58	52	0.39 (0.26-0.57)	< .0001
▪ 3-yr PFS, %	89	71		
PFS (*IGHV* mutated)				
▪ Events/cases, n	10/70	8/44	0.42 (0.16-1.16)	.086
▪ 3-yr PFS, %	88	82		
PFS (*IGHV* unmutated)				
▪ Events/cases, n	36/210	29/71	0.28 (0.17-0.48)	< .0001
▪ 3-yr PFS, %	89	65		
OS (all patients)				
▪ Events	11	12	0.34 (0.15-0.79)	.009
▪ 3-yr OS, %	99	93		

- ✓ Median follow-up 48 months
- ✓ *TP53* mutation present in 9% of patients receiving ibrutinib + rituximab vs 3% of patients receiving FCR

MOFFITT CANCER CENTER

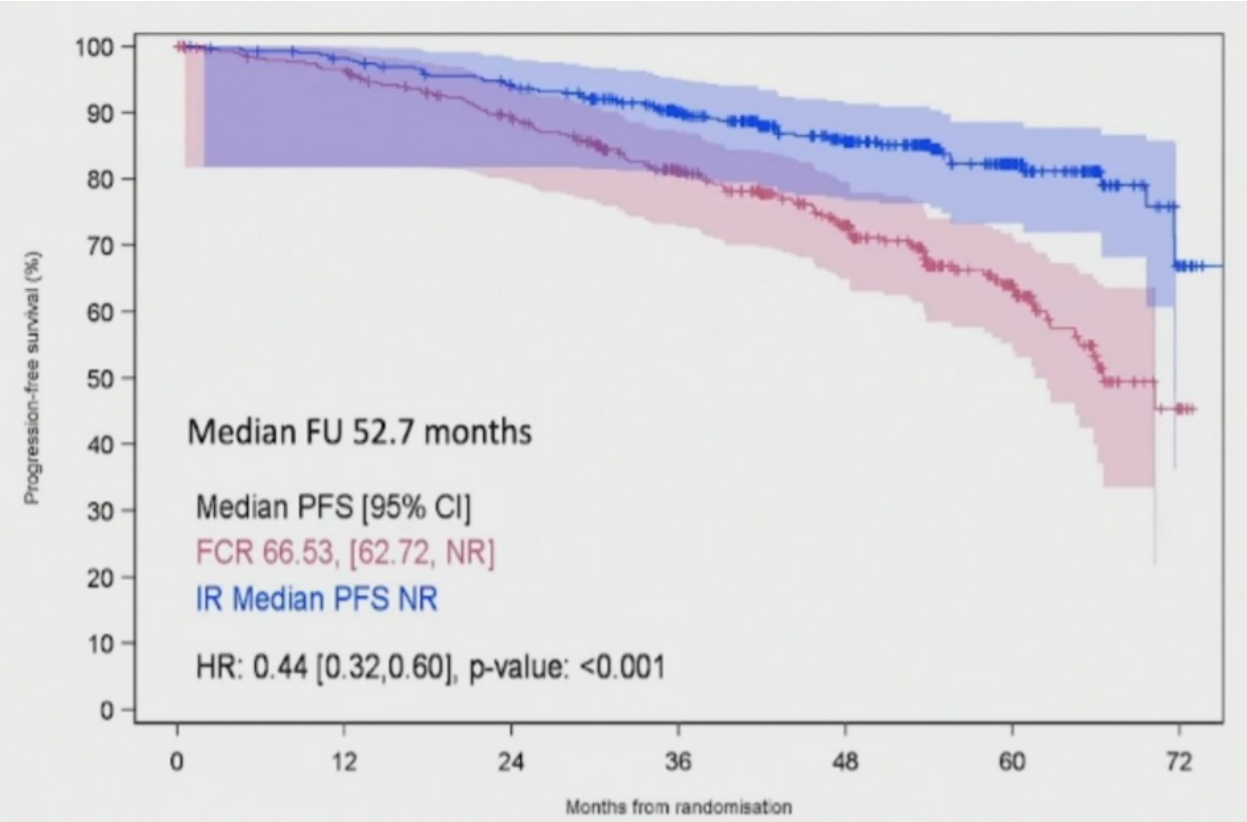
Shanafelt. ASH 2019. Abstr 33.

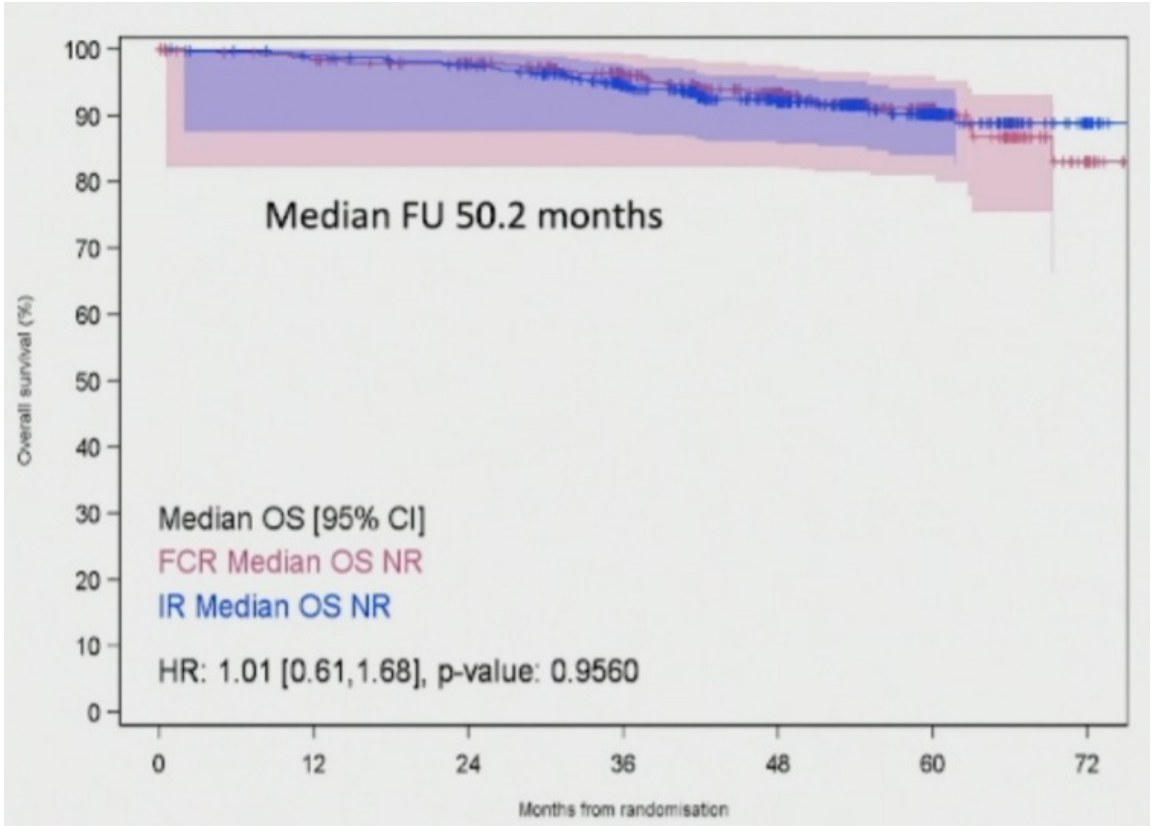
UK Flair Study: IR vs FCR



Hillmen P et al. ASH 2021

UK Flair Study: IR vs FCR





MOFFITT CANCER CENTER

Hillmen P et al. ASH 2021

Phase 3 Study of Ibrutinib ± Rituximab vs BR in TN CLL. (ALLIANCE A041202)

Key eligibility criteria

- Age ≥ 65 y and ECOG PS 0-2
- Treatment naive, symptomatic CLL
- CrCl ≥ 40 mL/min; AST/ALT ≤2.5xULN
- Include 17p/TP53

Patients stratified by:

- High vs intermediate risk Rai stage
- <20% vs ≥20% Zap-70 methylation (centrally performed)
- Presence vs absence del(17p) or del(11q) by FISH

Randomization: 1:1:1

Arm 1: BR (n=183)

n=30 crossover from BR to Ibr

Arm 2: Ibrutinib (n=182)

Arm 3: Ibrutinib + Rituximab (n=182)

Primary endpoints: PFS
Secondary endpoints: OS, TTP, DOR. Proportion achieving MRD negativity, Biopsy proven CR, Toxicity

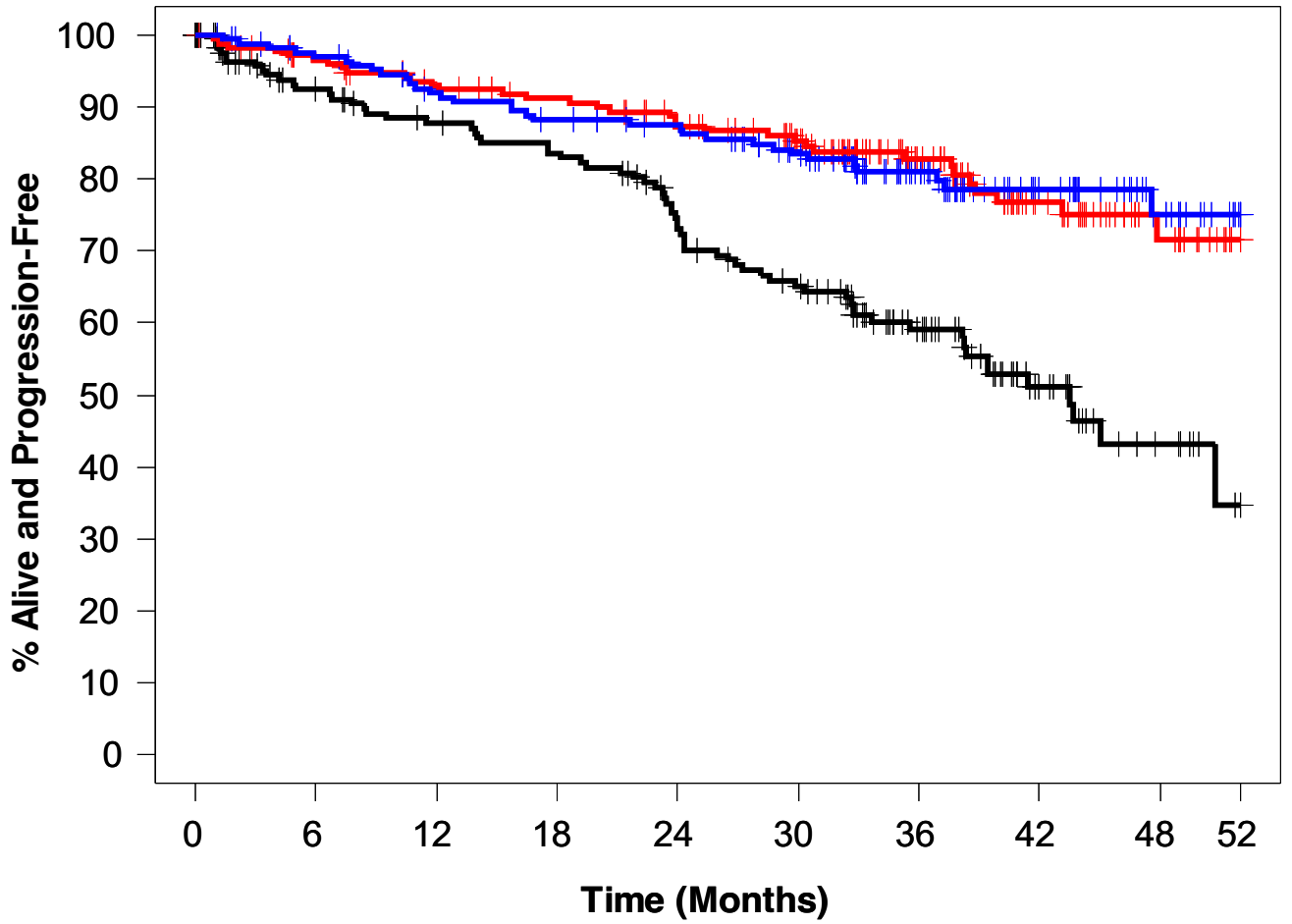
Patient Characteristics	All Patients (N = 547)
Median age, y (range)	71 (65-89)
ECOG PS 0-1	97%
FISH characteristics	
del(17p)	6%
del(11q)[a]	19%
TP53 mutation	10%
Complex karyotype	29%
Zap-70 unmethylated	53%
IGVH unmutated (n=360)	61%

ALLIANCE FOR CLINICAL TRIALS IN ONCOLOGY

MOFFITT CANCER CENTER

Phase 3 Study of Ibrutinib ± Rituximab vs BR in TN CLL

PFS



Patients-at-Risk										
Arm A (BR)	176	140	129	122	103	88	57	26	11	0
Arm B (I)	178	165	154	147	136	120	78	45	22	0
Arm C (IR)	170	159	145	138	132	115	74	40	20	0

Pairwise comparisons

Ibrutinib vs BR
HR: 0.39 (95% CI: 0.26-0.58)
(1-sided p value <0.001)

IbruRitux vs BR
HR: 0.38 (95% CI: 0.25-0.59)
(1-sided p value <0.001)

IbruRitux vs Ibrutinib
HR: 1.00 (95% CI: 0.62-1.62)
(1-sided p value 0.49)

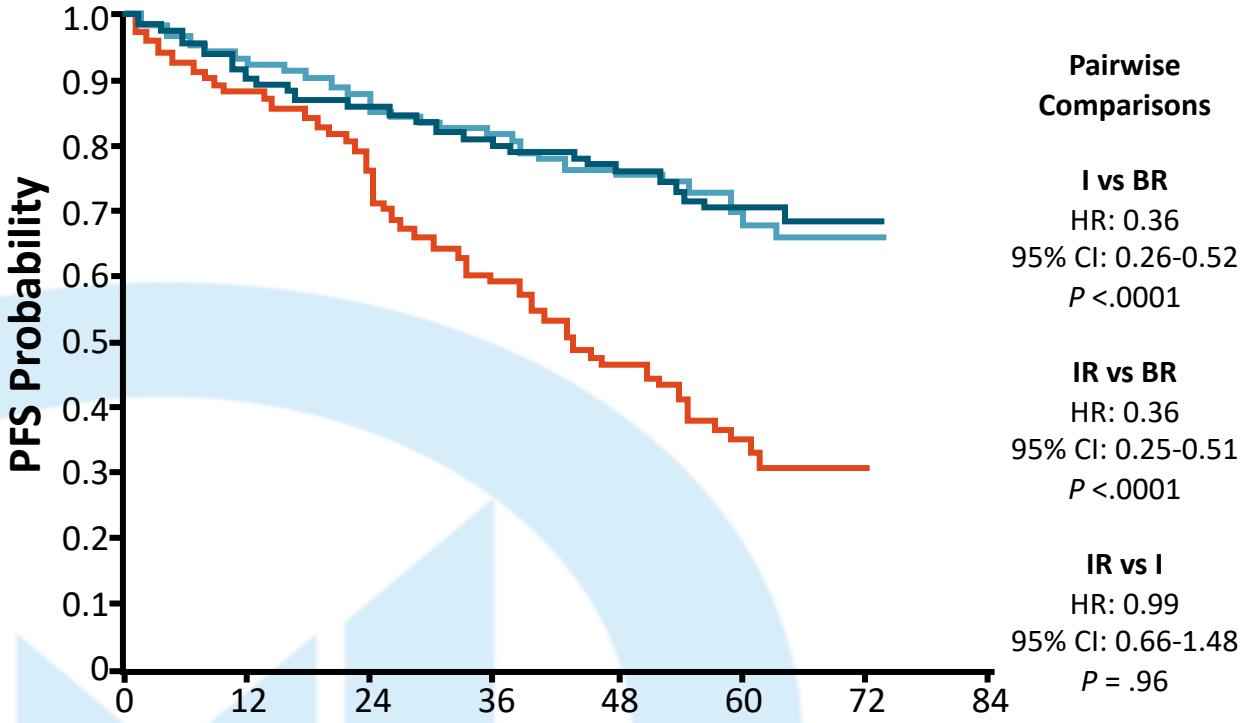
MOFFITT CANCER CENTER

Woyach JA et al. N Engl J Med 2018;379:2517-28.

Phase 3 Study of Ibrutinib ± Rituximab vs BR in TN CLL: Long term follow up

4-year PFS

Arm	Events/Total	Time Point	PFS Est. (95% CI)	Time Point	PFS Est. (95% CI)
BR	94/183	24 mo	0.75 (0.67-0.81)	48 mo	0.47 (0.39-0.55)
Ibru	48/182	24 mo	0.87 (0.80-0.91)	48 mo	0.76 (0.69-0.82)
Ibru + ritux	47/185	24 mo	0.87(0.81-0.91)	48 mo	0.76 (0.69-0.82)



Pairwise Comparisons

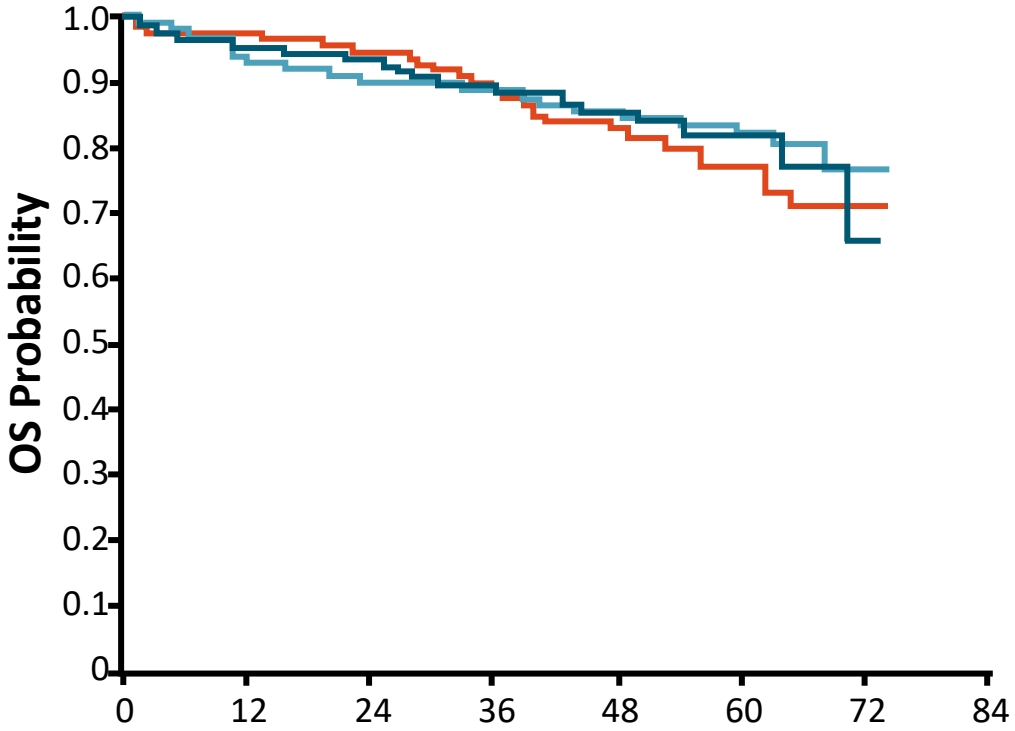
I vs BR
HR: 0.36
95% CI: 0.26-0.52
P <.0001

IR vs BR
HR: 0.36
95% CI: 0.25-0.51
P <.0001

IR vs I
HR: 0.99
95% CI: 0.66-1.48
P = .96

2-year OS

Arm	Events/Total	Time Point	OS Est. (95% CI)
BR	38/183	24 mo	0.95 (0.90-0.97)
Ibru	31/182	24 mo	0.90 (0.85-0.94)
Ibru + ritux	33/182	24 mo	0.94 (0.89-0.97)

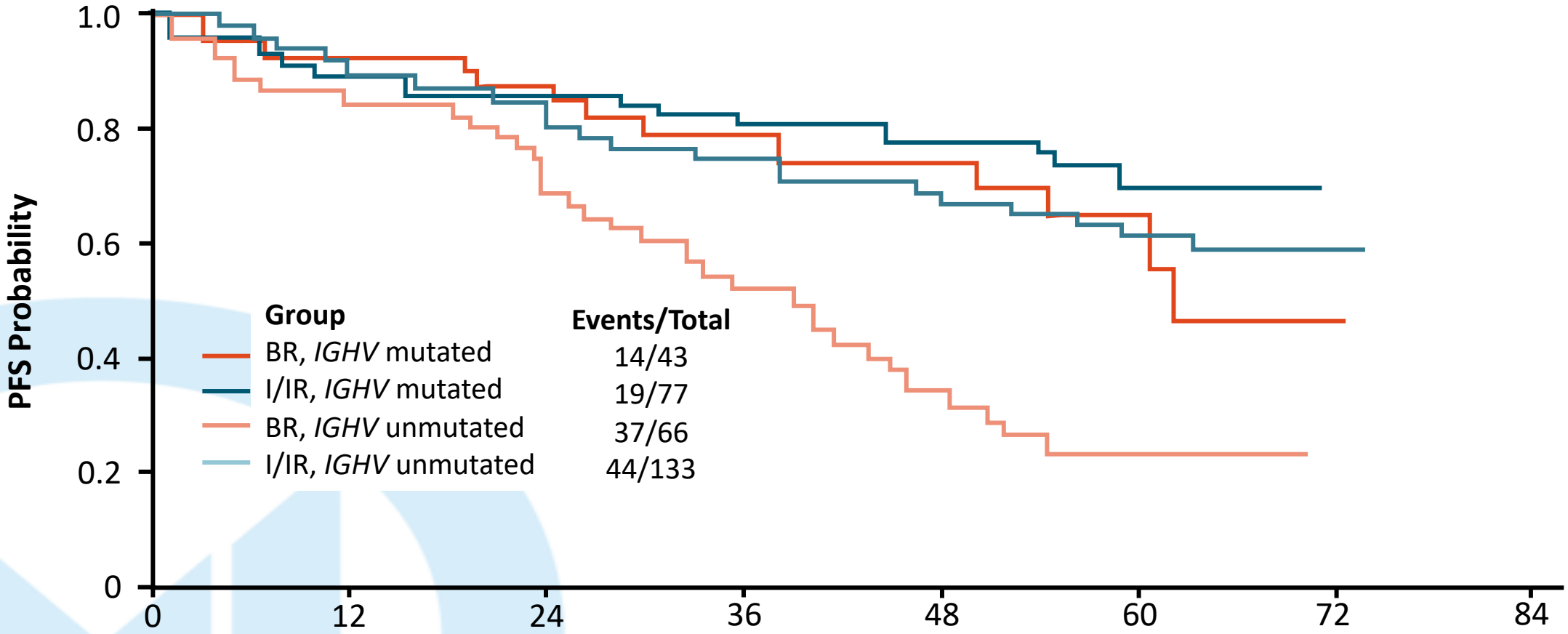


MOFFITT CANCER CENTER

Woyach JA et al. Blood. 2021;138, Abstr 639 (suppl 1).

Phase 3 Study of Ibrutinib ± Rituximab vs BR in TN CLL

PFS by IGHV Mutation Status



MOFFITT CANCER CENTER

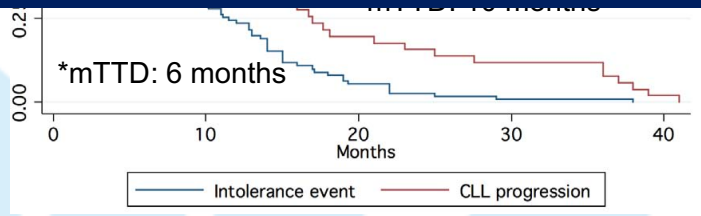
Woyach JA et al. Blood. 2021;138, Abstr 639 (suppl 1).

Toxicities and outcomes of 621 ibrutinib-treated chronic lymphocytic leukemia patients in the United States: a real-world analysis

haematologica
Journal of the European Hematology Association
Owned & published by the Ferrata Storti Foundation

Concerns with long term treatment with Ibrutinib:

- ✓Arterial hypertension (increases overtime)
- ✓Important cardiovascular adverse events (elderly pts)
- ✓Low grade but ongoing mild to moderate AEs:
  - Myalgias and arthralgias
  - Diarrhea
  - Skin rashes, nail changes.
- ✓ Increase bleeding
- ✓ Financial toxicity (ongoing costly therapy)



*mTTD: median time to discontinuation

- A. fib (25%)
- Rash (16.5%)

✓ Discontinuation rate in PIII trials: **10%**

MOFFITT CANCER CENTER

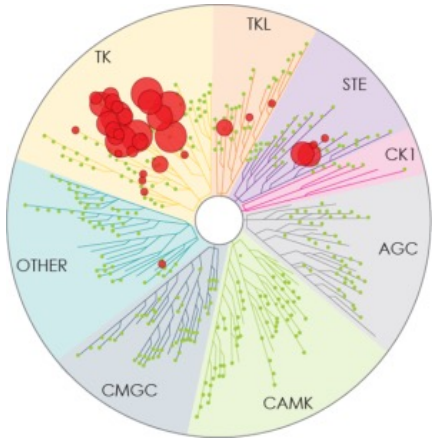
Mato A et al. Haematologica May 2018 103: 874-879

Approved Bruton tyrosine kinase inhibitors (BTKi) for the treatment CLL

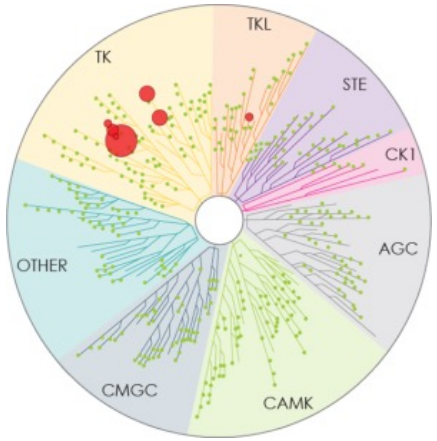
BTKi Kinome profiling

(Kinase selectivity profiling at 1 μM)

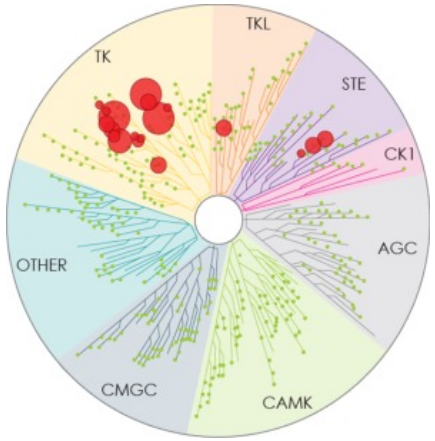
Ibrutinib



Acalabrutinib



Zanubrutinib



Kinase Inhibition IC_{50} $(nM)^2$

Kinase	Ibrutinib	Acalabrutinib	Zanubrutinib
BTK	1.5	5.1	0.3
TEC	10	126	2.0
ITK	4.9	>1,000	56
BMX	0.8	46	0.6
TXK	2.0	368	3.0
EGFR	5.3	>1,000	2.6
ERBB2	6.4	~1,000	530
ERBB4	3.4	16	1.6
BLK	0.1	>1,000	1.1
JAK3	32	>1,000	580

MOFFITT CANCER CENTER

Brown J. Hematology Am Soc Hematol Educ Program 2018 Nov 30;2018(1).

Phase 3 ELEVATE-TN: Acalabrutinib in Treatment-Naïve CLL

N = 535 randomized

- Patients with treatment-naïve CLL per iwCLL criteria, aged ≥65 y or <65 y with coexisting conditions (CIRS score >6, creatinine clearance <70 mL/min)

R

- **Obinutuzumab + chlorambucil** (N= 177)
- **Acalabrutinib + obinutuzumab** (N= 179)
- **Acalabrutinib monotherapy** (N= 179)

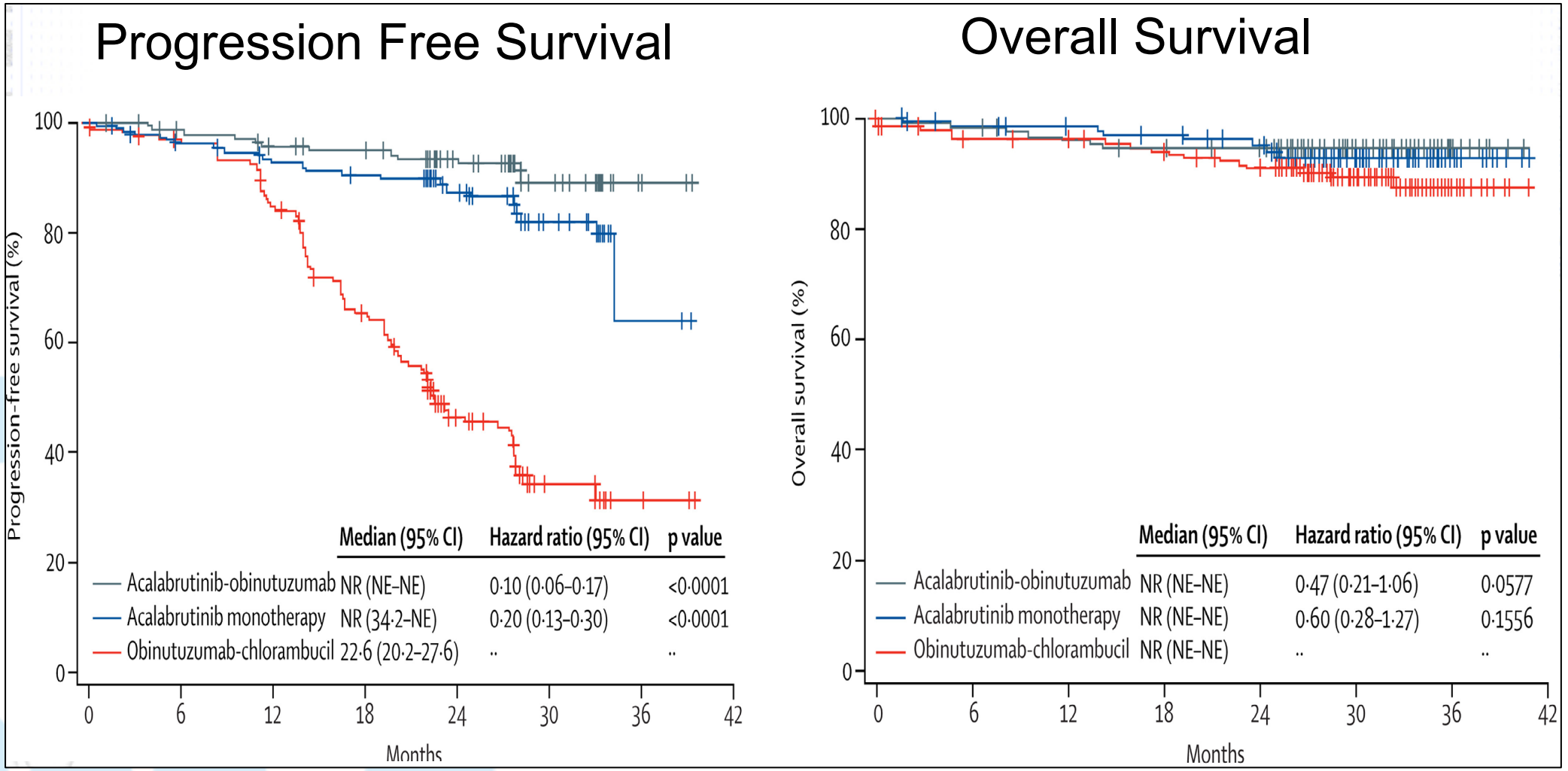
- **Primary endpoint:** PFS
- **Patient demographics and typical of other initial Rx studies**

- **Acalabrutinib:** 100 mg twice daily continuously
- **Obinutuzumab:** 1,000 mg on d 1, 2, 8, and 15 of cycle 2, and d 1 of subsequent cycles
- **Chlorambucil:** 0.5 mg/kg on d 1 and 15 of each cycle

MOFFITT CANCER CENTER

Sharman JP et al. Lancet 2020; 395: 1278-91

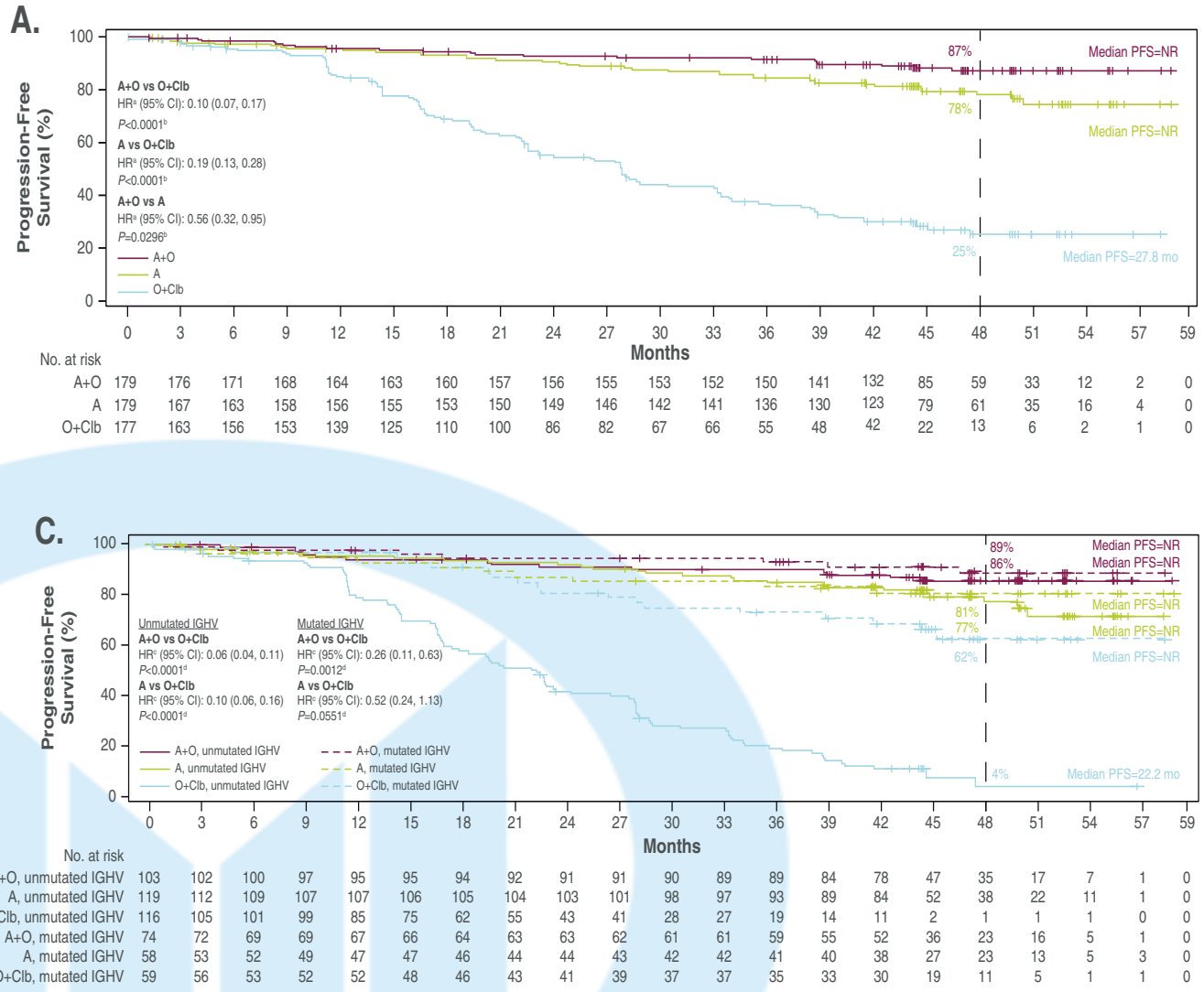
Phase 3 ELEVATE TN trial: Outcomes



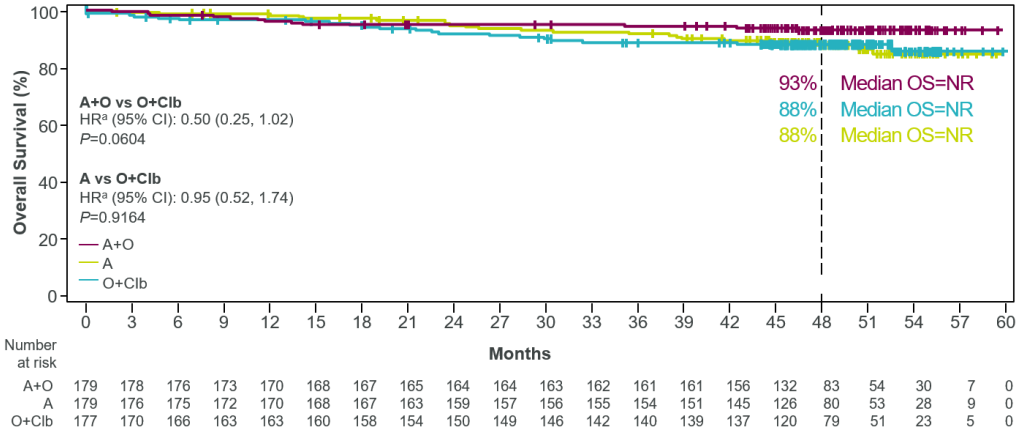
MOFFITT CANCER CENTER

Sharman JP et al. Lancet 2020; 395: 1278-91

Phase 3 ELEVATE TN trial
Efficacy and safety 4-year-follow up



Overall Survival



MOFFITT CANCER CENTER

Sharman JP et a. Leukemia. 2022 Jan 1.doi: 10.1038/s41375-021-01485

Phase 3 ELEVATE TN trial
Efficacy and safety 4-year-follow up

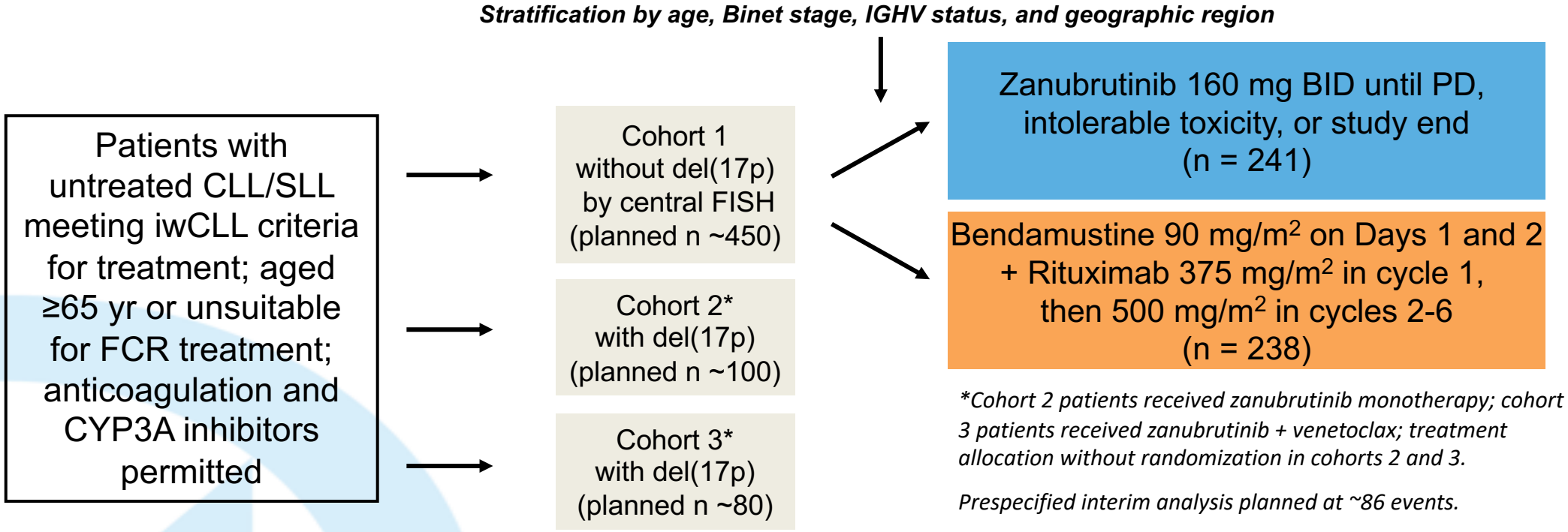
	A + O (*n* = 178)		A (*n* = 179)		O + Clb (*n* = 169)	
Treatment exposure, median (range), months	46.6 (2.3–58.6)		45.7 (0.3–59.3)		5.6 (0.9–7.4)	
Common AEs (in ≥ 25% of patients [any grade] in any group), *n* (%)						
	Any grade	Grade ≥3	Any grade	Grade ≥3	Any grade	Grade ≥3
Diarrhea	73 (41.0)	9 (5.1)	72 (40.2)	1 (0.6)	36 (21.3)	3 (1.8)
Headache	71 (39.9)	2 (1.1)	68 (38.0)	2 (1.1)	20 (11.8)	0
Neutropenia	60 (33.7)	55 (30.9)	22 (12.3)	20 (11.2)	76 (45.0)	70 (41.4)
Fatigue	50 (28.1)	4 (2.2)	39 (21.8)	2 (1.1)	30 (17.8)	2 (1.2)
Arthralgia	47 (26.4)	2 (1.1)	35 (19.6)	2 (1.1)	8 (4.7)	2 (1.2)
Cough	46 (25.8)	1 (0.6)	40 (22.3)	1 (0.6)	15 (8.9)	0
URTI	44 (24.7)	4 (2.2)	46 (25.7)	0	16 (9.5)	1 (0.6)
Nausea	41 (23.0)	0	41 (22.9)	0	53 (31.4)	0
IRR	25 (14.0)	5 (2.8)	0	0	68 (40.2)	10 (5.9)
Selected events of clinical interest, *n* (%)						
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/flutter	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)
Excluding NMS	15 (8.4)	10 (5.6)	11 (6.1)	4 (2.2)	3 (1.8)	2 (1.2)

MOFFITT CANCER CENTER

Sharman JP et a. Leukemia. 2022 Jan 1.doi: 10.1038/s41375-021-01485

Phase 3 Randomized Study of Zanubrutinib vs Bendamustine + Rituximab in Patients With Treatment-Naive CLL/SLL

SEQUOIA Trial



**Cohort 2 patients received zanubrutinib monotherapy; cohort 3 patients received zanubrutinib + venetoclax; treatment allocation without randomization in cohorts 2 and 3.*

Prespecified interim analysis planned at ~86 events.

- Multicenter, multicohort, open-label, part-randomized phase III trial.
- Primary endpoint (cohort 1): IRC-assessed PFS
- Secondary endpoints (cohort 1): investigator-assessed PFS, ORR, OS, safety

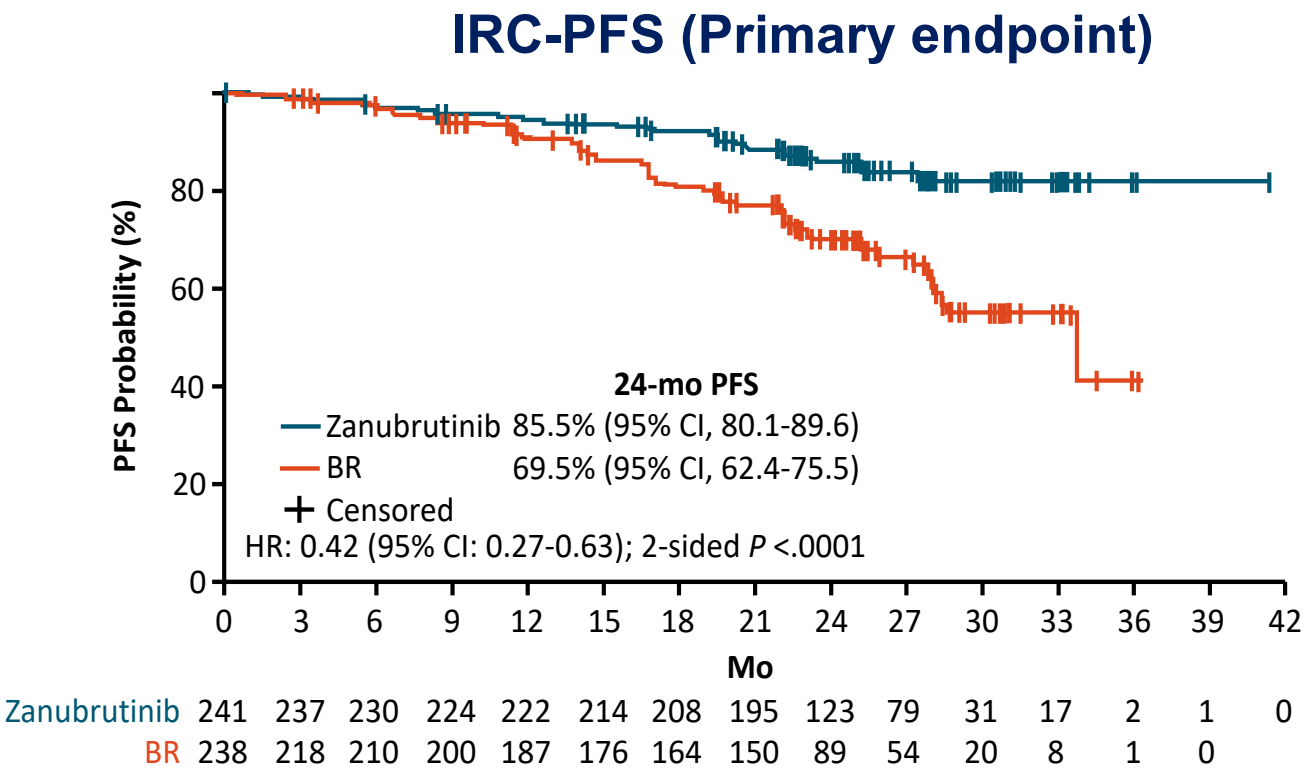
MOFFITT CANCER CENTER

Tam C et al. Blood. 2021;138, Abstr 396 (suppl 1).

SEQUOIA Trial (Cohort 1)

Baseline characteristics

Characteristic	Zanubrutinib (n = 241)	Bendamustine + Rituximab (n = 238)
Median age, yr (IQR)	70 (66-75)	70 (66-74)
Aged ≥65 yr, n (%)	196 (81.3)	192 (80.7)
Male, n (%)	154 (63.9)	144 (60.5)
ECOG PS 2, n (%)	15 (6.2)	20 (8.4)
Region, n (%)		
▪ North America	34 (14.1)	28 (11.8)
▪ Europe	174 (72.2)	172 (72.3)
▪ Asia/Pacific	33 (13.7)	38 (16.0)
Binet stage C*	70 (29.0)	70 (29.4)
Bulky disease ≥5 cm	69 (28.6)	73 (30.7)
Cytopenia†	102 (42.3)	109 (45.8)
del(11q)	43 (17.8)	46 (19.3)
TP53 mutation	15/232 (6.5)	13/223 (5.8)
Unmutated *IGHV* gene	125/234 (53.4)	121/231 (52.4)

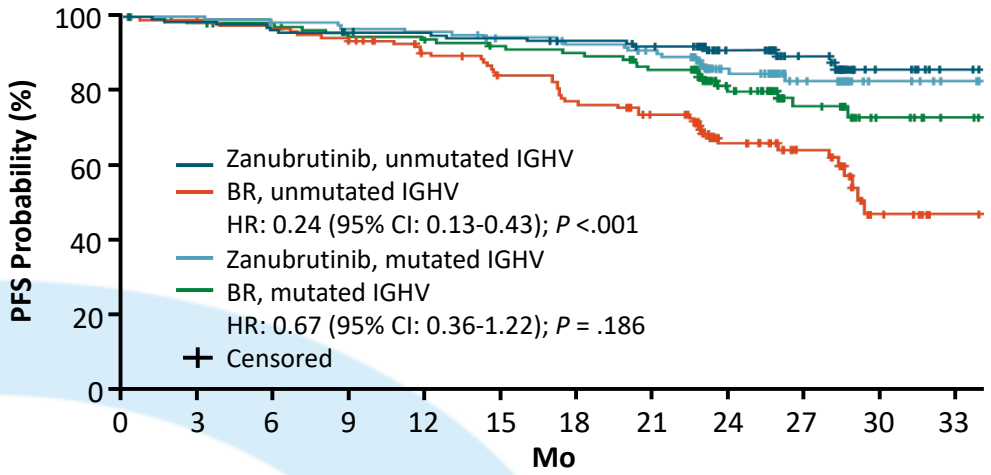


MOFFITT CANCER CENTER

Tam C et al. Blood. 2021;138, Abstr 396 (suppl 1).

SEQUOIA Trial (Cohort 1)

IRC-PFS based on IGHV mutational status



Zanubrutinib - Unmutated	125	121	117	114	113	112	109	104	68	44	14	6
BR - Unmutated	121	110	106	100	90	82	73	65	39	25	6	1
Zanubrutinib - Mutated	109	109	106	104	103	97	94	88	53	33	15	10
BR - Mutated	110	101	98	94	91	88	86	80	47	27	14	7

- **Median f/up: 26 months**
- **Median PFS was better with Zanu vs. BR in nearly all subgroups:**
  - ✓ Bulky disease (HR, 0.52; 95% CI, 0.27-0.97)
  - ✓ Unmutated *IGHV* (HR, 0.24; 95% CI, 0.24-0.43)
  - ✓ Del(11q) (HR, 0.21; 95% CI, 0.09- 0.50)
- OS is the same for both groups

- **Zanu had a more favorable safety profile vs. BR:**
  - ✓ Fewer grade ≥ 3 AEs: 53% vs 80%.
  - ✓ Fewer serious AEs: 37% vs 50%.
  - ✓ Fewer dose reductions due to AEs: 8% vs 37%
  - ✓ Fewer Tx discontinuations: 8% vs 14%

MOFFITT CANCER CENTER

Tam C et al. Blood. 2021;138, Abstr 396 (suppl 1).

SEQUOIA Trial (Cohort 1)
Common Adverse Events (AEs)

AEs in ≥12% of Patients, n (%)	Zanubrutinib (n = 240)*		Bendamustine + Rituximab (n = 227)*	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3
Contusion	46 (19.2)	0 (0.0)	8 (3.5)	0 (0.0)
Upper respiratory tract infection	41 (17.1)	2 (0.8)	27 (11.9)	2 (0.9)
Neutropenia	37 (15.4)	27 (11.3)	129 (56.8)	116 (51.1)
Diarrhea	33 (13.8)	0 (0.0)	30 (13.2)	4 (1.8)
Arthralgia	32 (13.3)	2 (0.8)	20 (8.8)	1 (0.4)
Fatigue	28 (11.7)	3 (1.3)	36 (15.9)	2 (0.9)
Rash	26 (10.8)	0 (0.0)	44 (19.4)	6 (2.6)
Constipation	24 (10.0)	1 (0.4)	43 (18.9)	0 (0.0)
Nausea	24 (10.0)	0 (0.0)	74 (32.6)	3 (1.3)
Pyrexia	17 (7.1)	0 (0.0)	60 (26.4)	8 (3.5)
Vomiting	17 (7.1)	0 (0.0)	33 (14.5)	3 (1.3)
Anemia	11 (4.6)	1 (0.4)	43 (18.9)	4 (1.8)
Thrombocytopenia	9 (3.8)	4 (1.7)	31 (13.7)	16 (7.0)

MOFFITT CANCER CENTER

Tam C et al. Blood. 2021;138, Abstr 396 (suppl 1).

SEQUOIA Trial (Cohort 1)

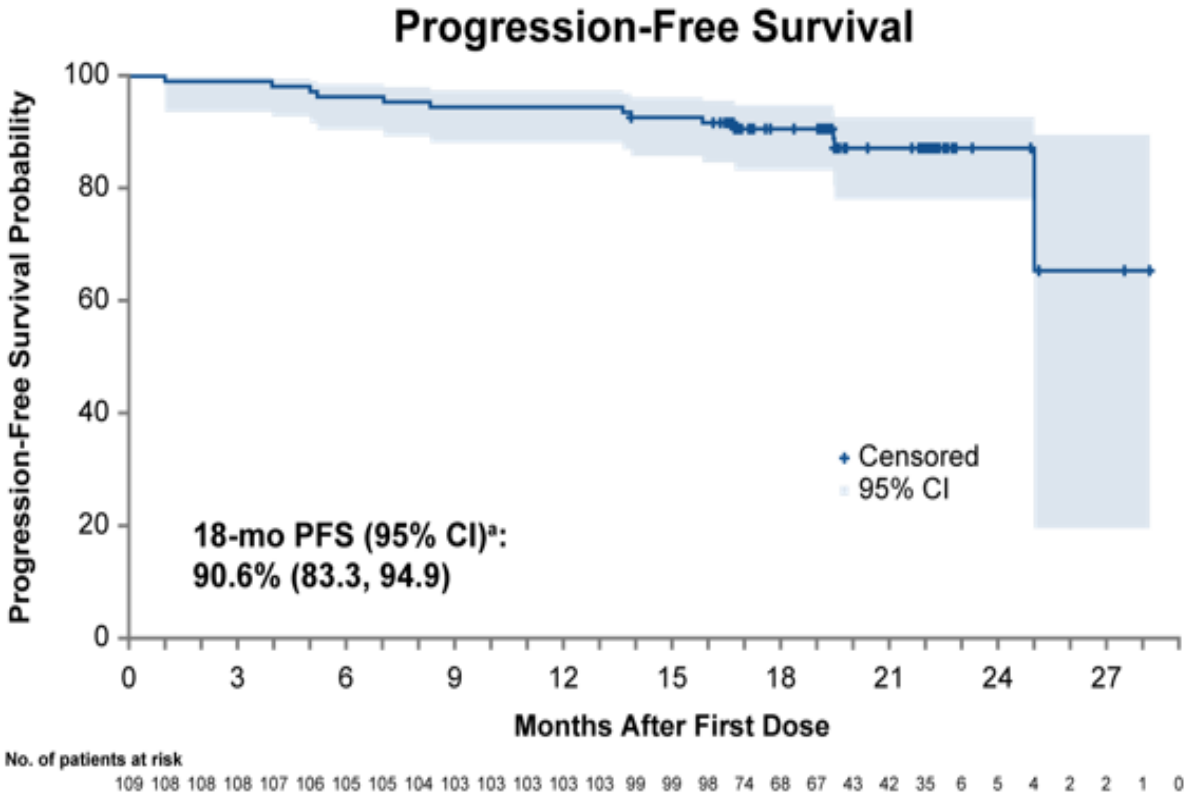
AEs of interest

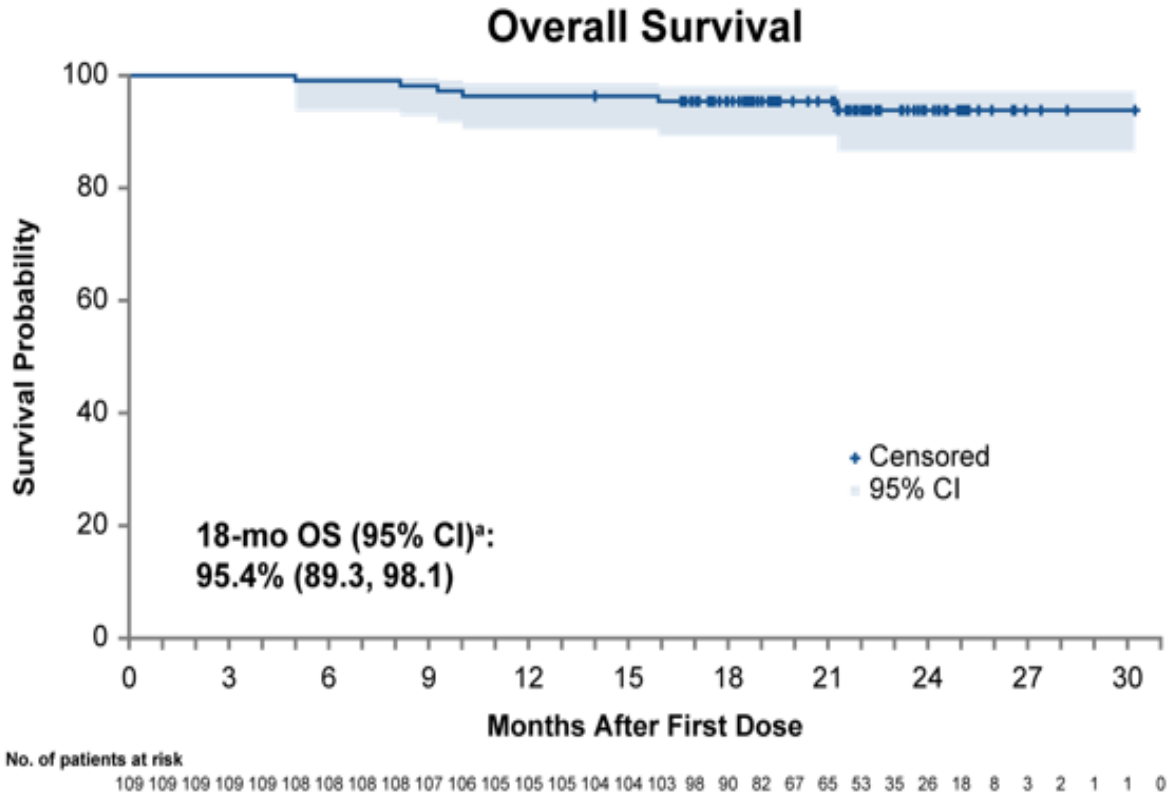
AEs, n (%)	Zanubrutinib (n = 240)*		Bendamustine + Rituximab (n = 227)*	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3
Anemia	11 (4.6)	1 (0.4)	44 (19.4)	4 (1.8)
Neutropenia	38 (15.8)	28 (11.7)	129 (56.8)	116 (51.1)
Thrombocytopenia	11 (4.6)	5 (2.1)	40 (17.6)	18 (7.9)
Arthralgia	32 (13.3)	2 (0.8)	20 (8.8)	1 (0.4)
Atrial fibrillation	8 (3.3)	1 (0.4)	6 (2.6)	3 (1.3)
Bleeding	108 (45.0)	9 (3.8)	25 (11.0)	4 (1.8)
▪ Major bleeding	12 (5.0)	9 (3.8)	4 (1.8)	4 (1.8)
Diarrhea	33 (13.8)	2 (0.8)	31 (13.7)	5 (2.2)
Hypertension	34 (14.2)	15 (6.3)	24 (10.6)	11 (4.8)
Infections	149 (62.1)	39 (16.3)	127 (55.9)	43 (18.9)
Myalgia	9 (3.8)	0 (0.0)	3 (1.3)	0 (0.0)
Other cancers	31 (12.9)	17 (7.1)	20 (8.8)	7 (3.1)
▪ Dermatologic	16 (6.7)	2 (0.8)	10 (4.4)	2 (0.9)

MOFFITT CANCER CENTER

Tam C et al. Blood. 2021;138, Abstr 396 (suppl 1).

SEQUOIA (Cohort 2): IRC-Assessed PFS in Patients With del(17p)





MOFFITT CANCER CENTER

Tam C et al. Blood. 2021;138, Abstr 396 (suppl 1).

Combined (time limited frontline therapies) in CLL

Venetoclax plus Obinutuzumab

MOFFITT CANCER CENTER

ORIGINAL ARTICLE

Venetoclax and Obinutuzumab in Patients with CLL and Coexisting Conditions

K. Fischer, O. Al-Sawaf, J. Bahlo, A.-M. Fink, M. Tandon, M. Dixon, S. Robrecht, S. Warburton, K. Humphrey, O. Samoylova, A.M. Liberati, J. Pinilla-Ibarz, S. Opat,

- Open-label, multicenter, randomized phase III trial

Patients with previously untreated CLL and coexisting medical conditions (CIRS > 6 and/or CrCl < 70 mL/min) (N = 432)

→ **Venetoclax** PO 5-wk ramp up from 20 to 400 mg/day starting on Day 22 of cycle 1, then 400 mg/day until end of cycle 12 **+ Obinutuzumab** IV 1000 mg Days 1, 8, 15 of cycle 1,* then 1000 mg Day 1 of cycles 2-6 (n = 216)

→ **Chlorambucil** PO 0.5 mg/kg Days 1, 15 of cycles 1-12 **+ Obinutuzumab** IV 1000 mg Days 1-2, 8, 15 of cycle 1,* then 1000 mg Day 1 in cycles 2-6 (n = 216)

Total 28-day cycles

- Venetoclax: 12
- Chlorambucil: 12
- Obinutuzumab: 6

*Obinutuzumab could also be administered at 100 mg on Day 1, 900 mg on Day 2, and then 1000 mg on Days 8 and 15 of cycle 1.

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

MOFFITT CANCER CENTER

Fischer. K et al. NEJM. 2019;380:2225-36

CLL14: Patient Demographics

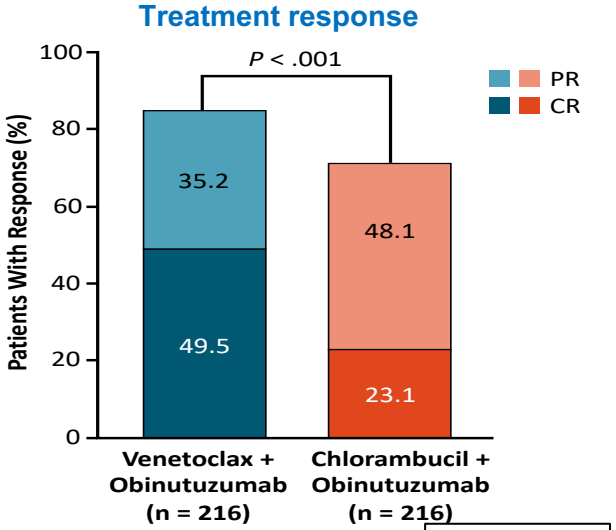
Characteristic	Venetoclax + Obinutuzumab (n = 216)	Chlorambucil + Obinutuzumab (n = 216)
Median age, yrs	72	72
Binet stage A/B/C, %	21/36/43	20/37/43
Median total CIRS score	9	8
Median CrCl, mL/min	65.2	67.5
TLS risk category low/int/high, %	13/64/22	12/68/20
IGHV unmutated, %	61	59
TP53 deleted and/or mutated, %	12	12
Cytogenetics, %		
▪ del(17p)	9	7
▪ del(11q)	18	20
▪ Trisomy 12	18	21
▪ No abnormalities	25	22
▪ del(13q) alone	31	31

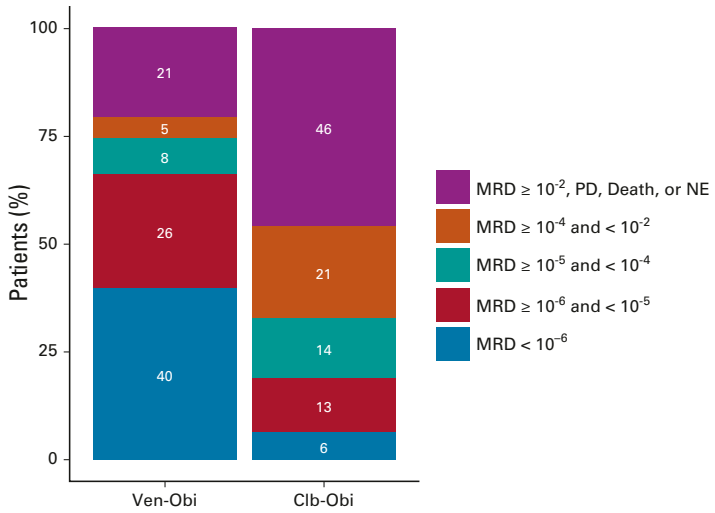
- There were no significant differences between the groups at baseline.
- Scores on the Cumulative Illness Rating Scale (CIRS) range from 0 to 56, with higher scores indicating more impaired function of organ systems.

Fischer. K et al. NEJM. 2019;380:2225-36

ORR and measurable residual disease (MRD) in CLL14

Updated follow up

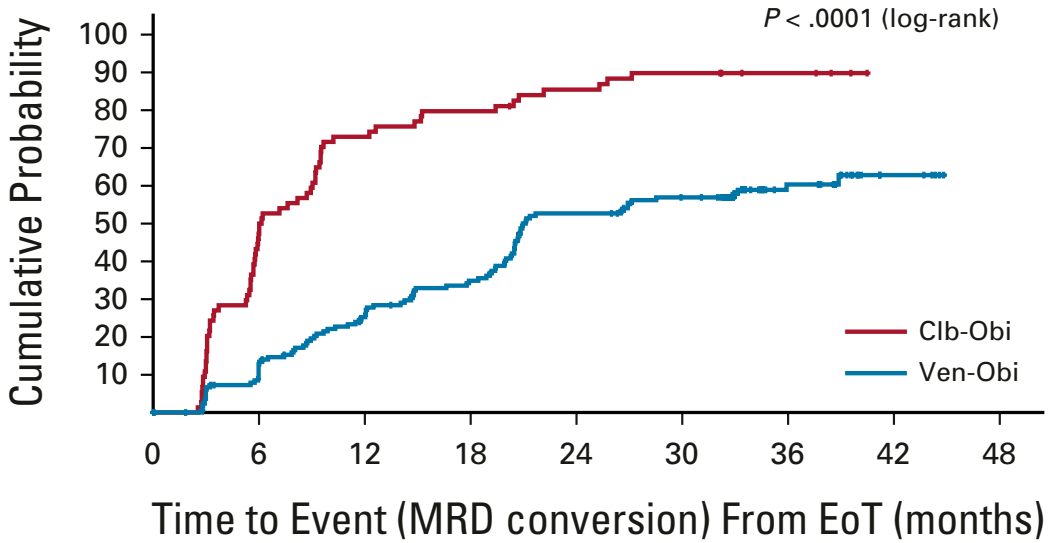




75.5% PB
59.9% BM

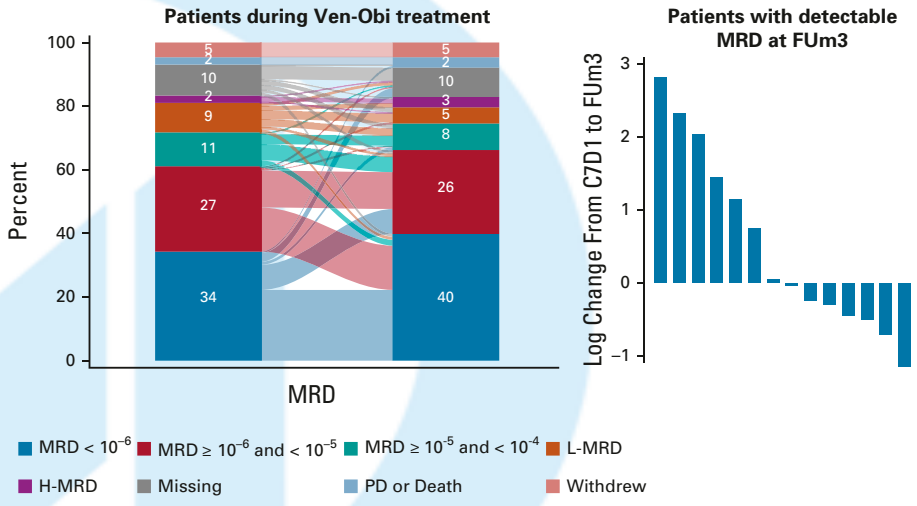
MRD - status
(3 months s/p Tx)
P = <0.001

35.2% PB
17.1% BM



No. at risk:

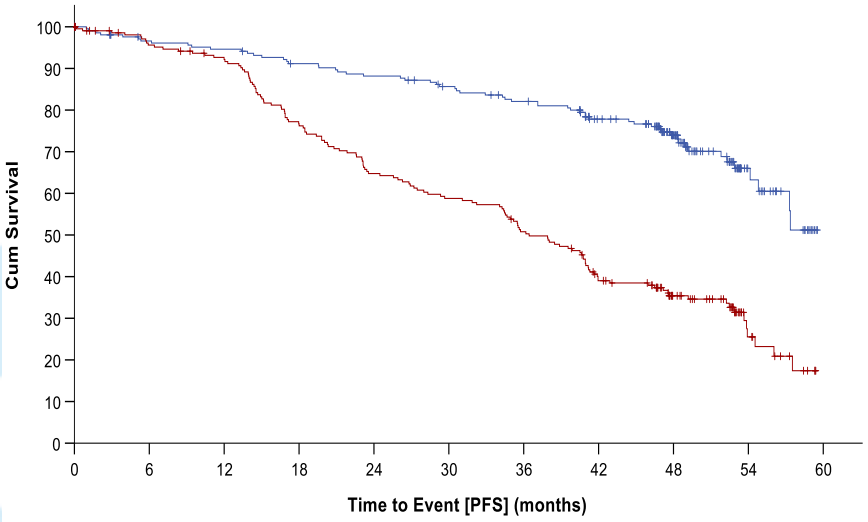
Ven–Obi	169	142	118	100	71	59	28	5	0
Clb–Obi	74	39	20	15	10	7	4	0	0



1. Fischer. K et al. NEJM. 2019;380:2225-36
2. Al-Sawaf O et al. J Clin Oncol. 2021 39:4049-4060

CLL14 (time limited therapy):
Venetoclax + Obi Vs. Obi + Chlorambucil
Updated follow up

PFS



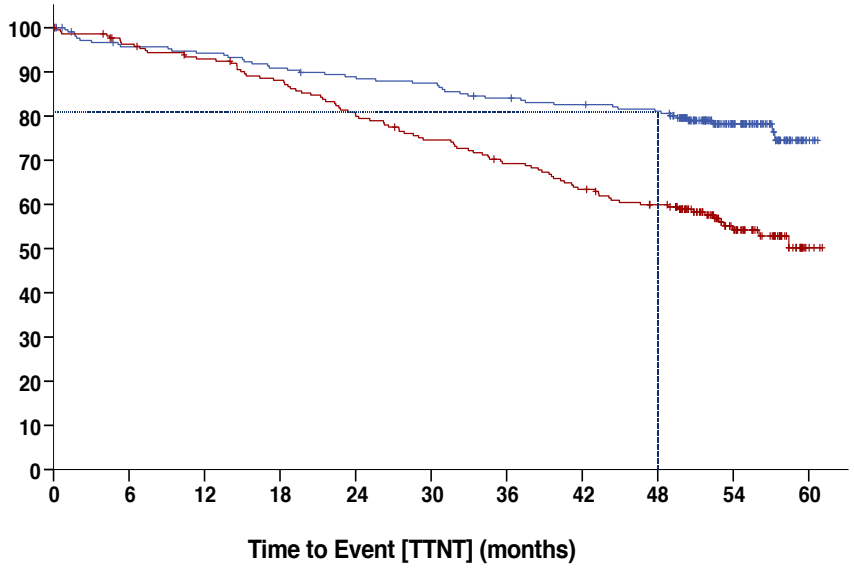
Median PFS
Ven-Obi: not reached
Clb-Obi: 36.4 months

4-year PFS rate
Ven-Obi: 74.0%
Clb-Obi: 35.4%

HR 0.33, 95% CI [0.25-0.45]
P<0.0001

Median follow-up
52.4 mos

Time to next treatment (TTNT)



Median TTNT
Ven-Obi: not reached
Clb-Obi: not reached

4-year TTNT rate
Ven-Obi: 81.08%
Clb-Obi: 59.9%

Next anti-leukemic therapy:
Ven-Obi: 35 PDs – 17 NLT
Clb-Obi: 122 PDs – 70 NLT

HR 0.46, 95% CI [0.32-0.65]
P<0.0001

Median f/up 52.4 months

All patients have been off study treatment for at least 3 years

MOFFITT CANCER CENTER

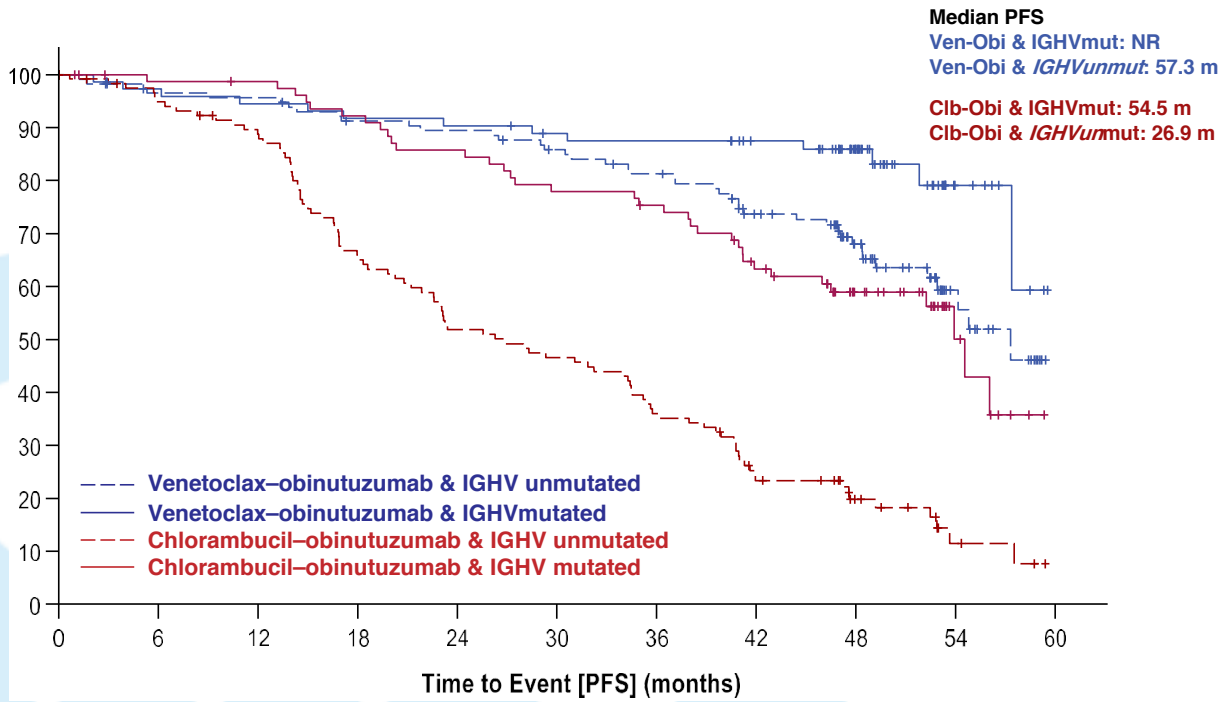
Al-Sawaf O et al. J Clin Oncol. 2021 39:4049-4060

CLL14 (time limited therapy):

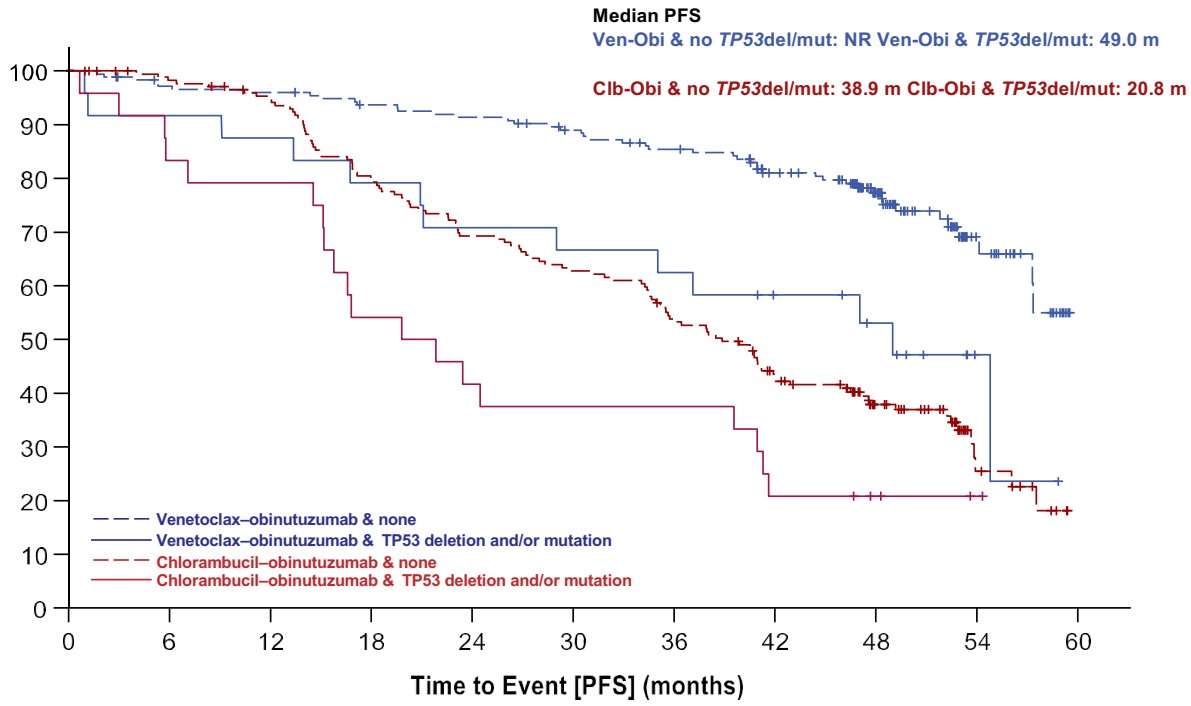
Venetoclax + Obi Vs. Obi + Chlorambucil

Updated follow up

PFS by IgHV status



PFS by TP53 status



Median f/up 52.4 months

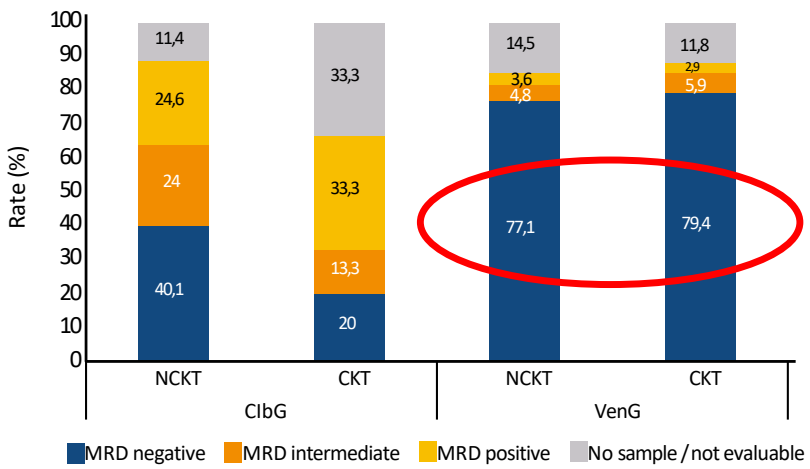
All patients have been off study treatment for at least 3 years

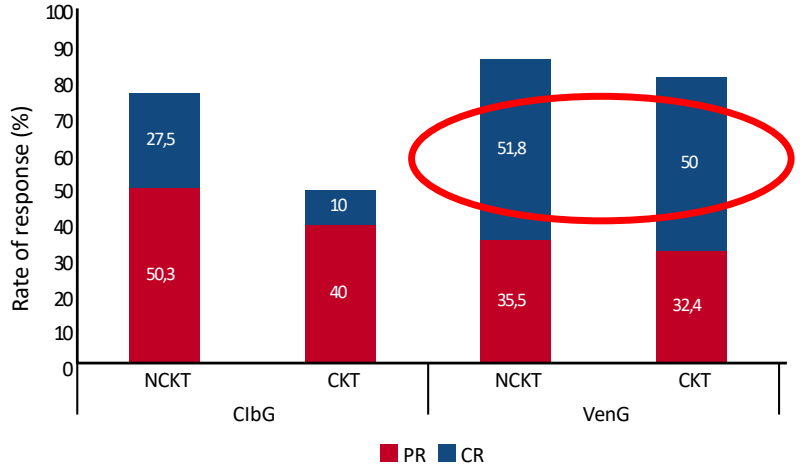
MOFFITT CANCER CENTER

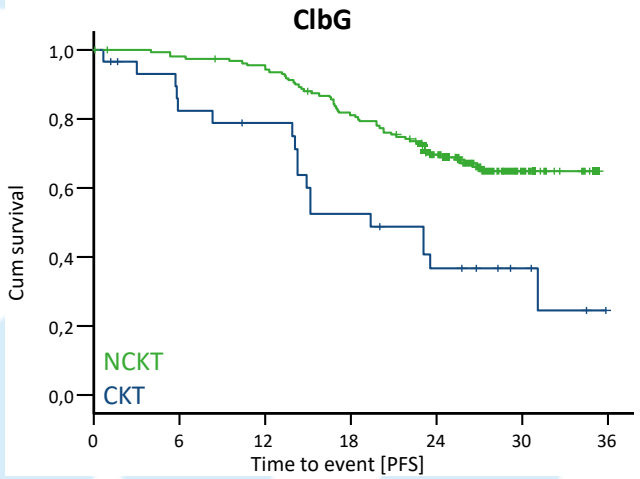
Al-Sawaf O et al. J Clin Oncol. 2021 39:4049-4060

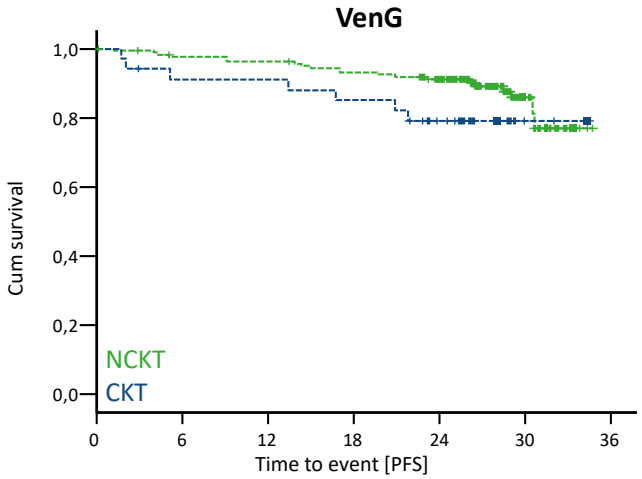
CLL14 (time limited therapy):
Venetoclax + Obi Vs. Obi + Chlorambucil
Updated follow up

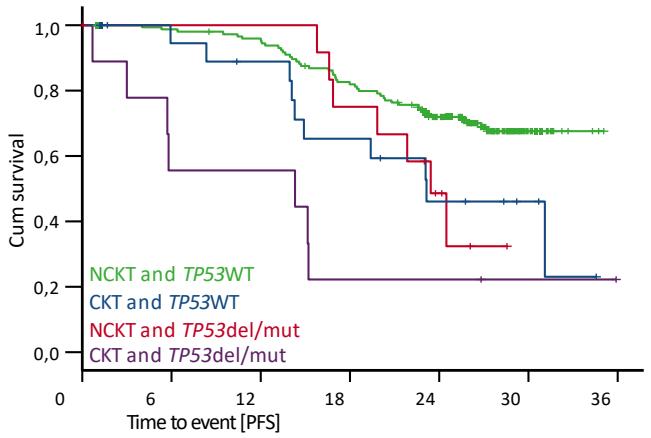
Complex Karyotype is Not Prognostic with VenG









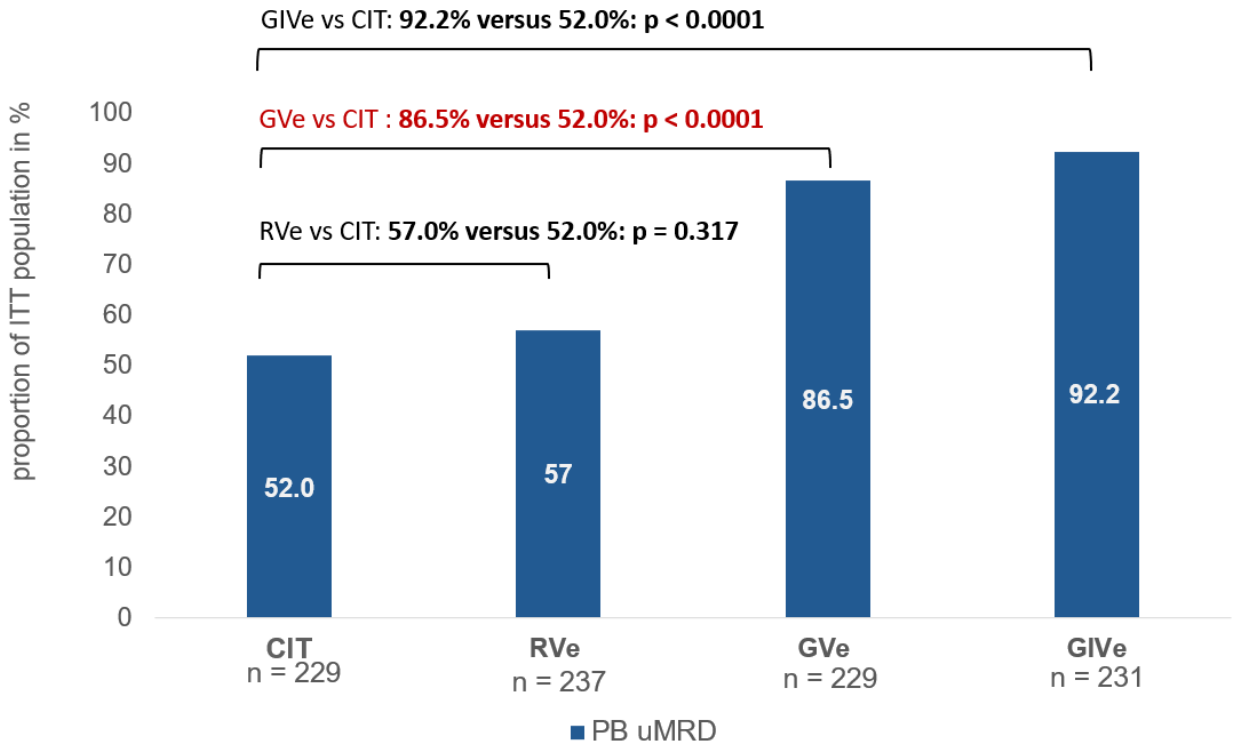


Al-Sawaf O et al. J Clin Oncol. 2021 39:4049-4060

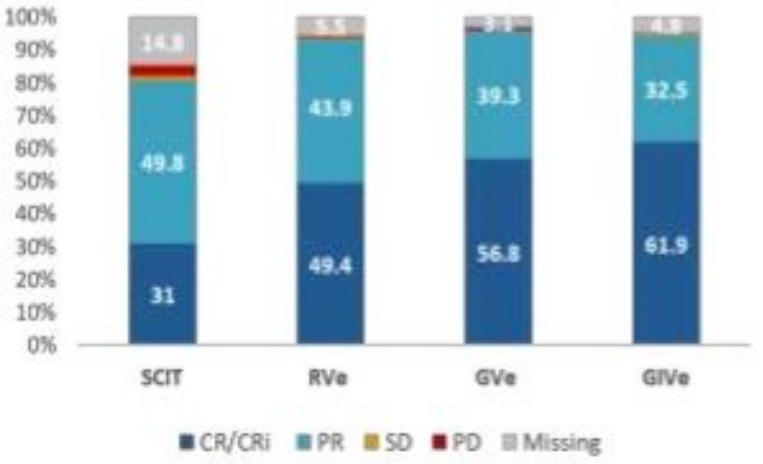
Randomized Phase 3 Study of Venetoclax-Based Time-Limited Combination Treatments vs Standard Chemoimmunotherapy in Frontline CLL Fit Patients

GAIA (CLL13) trial

CLL13 Coprimary Endpoint: MRD by Flow on peripheral blood



Response rates at Month 15



	CIT	RVe	GVe	GIVe
Adverse Event	Arm 1 (%)	Arm 2 (%)	Arm 3 (%)	Arm 4 (%)
Febrile Neutropenia	11.1	4.2	3.1	7.8
Infections	19.9	11.4	14.0	22.1
Tumor Lysis Syndrome	4.2	10.1	8.8	6.5

- CIT (Arm 1): Chemoimmunotherapy (FCR and BR)
- RVe (Arm 2): Rituximab + Venetoclax
- GVe (Arm 3): Obinutuzumab + Venetoclax
- GIVe (Arm 4): Obinutuzumab + Ibrutinib + Venetoclax

MOFFITT CANCER CENTER

Eichhorst B et al. ASH abstract 71. *Blood*. 2021;138(suppl 1)

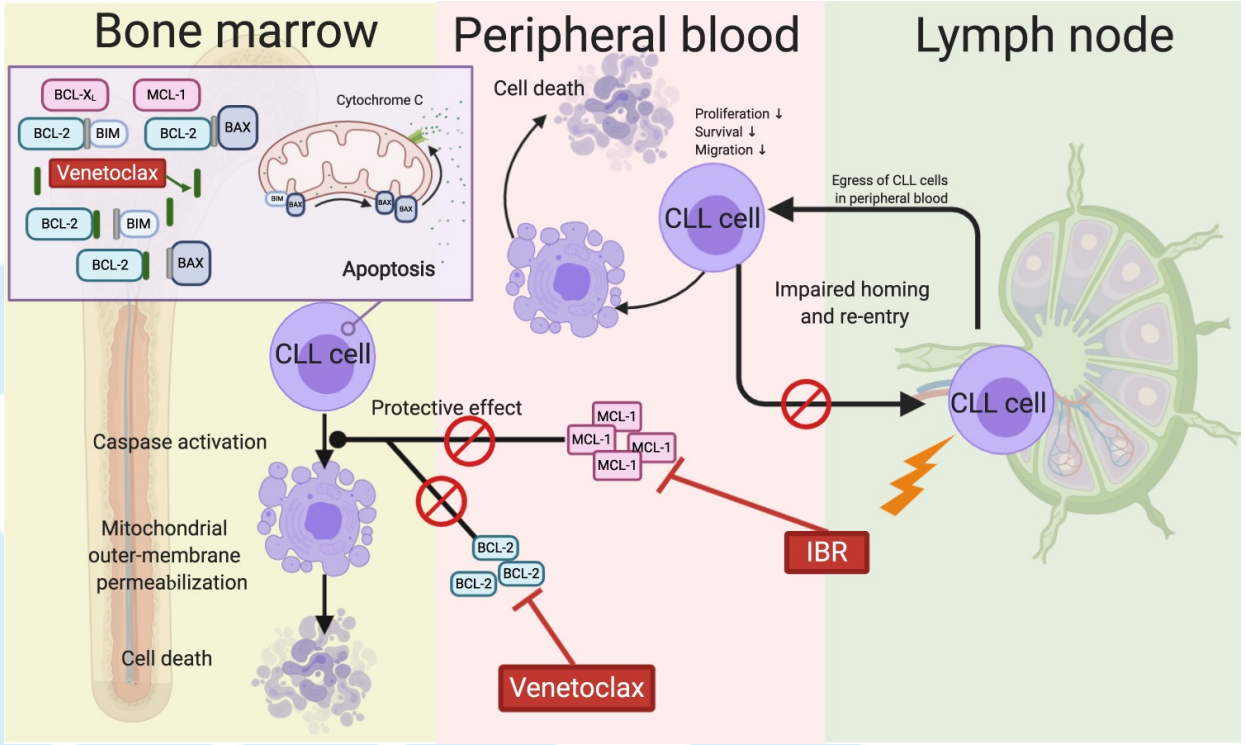
Combined (time limited frontline therapies) in CLL

Ibrutinib plus Venetoclax (Ibru+Ven)

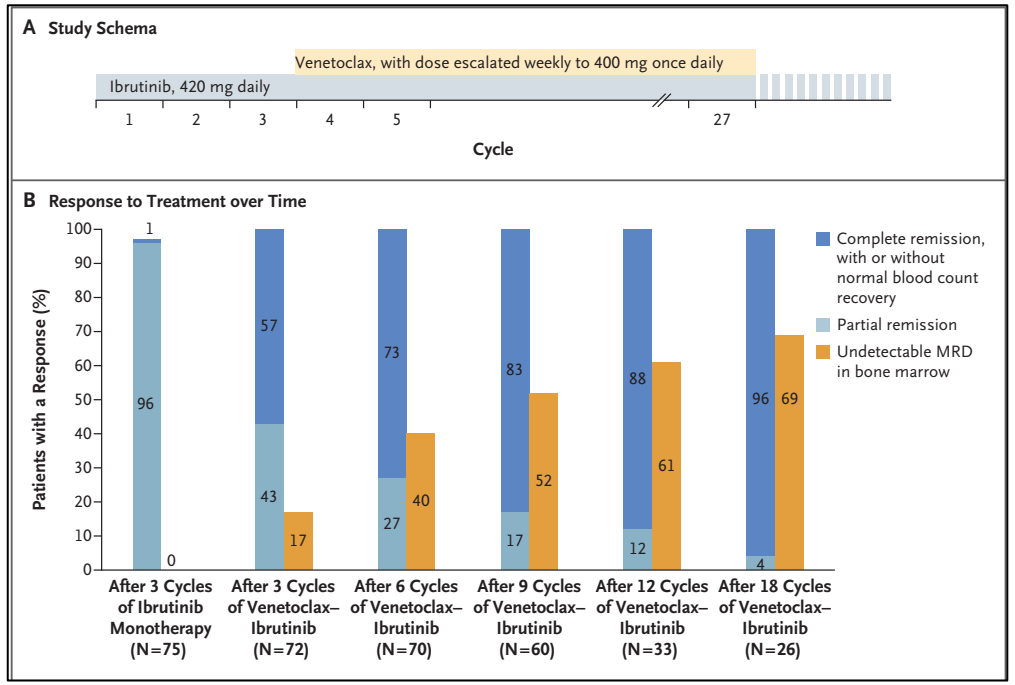
The NEW ENGLAND JOURNAL of MEDICINE
ESTABLISHED IN 1812 MAY 30, 2019 VOL. 380 NO. 22

Ibrutinib and Venetoclax for First-Line Treatment of CLL

Why Ibru + Ven?



Treatment Naïve CLL + High Risk:
At least 1 of: del(17p), *TP53* mut, del(11q), unmutated *IGHV*, age > 65 yrs **(N=80)**

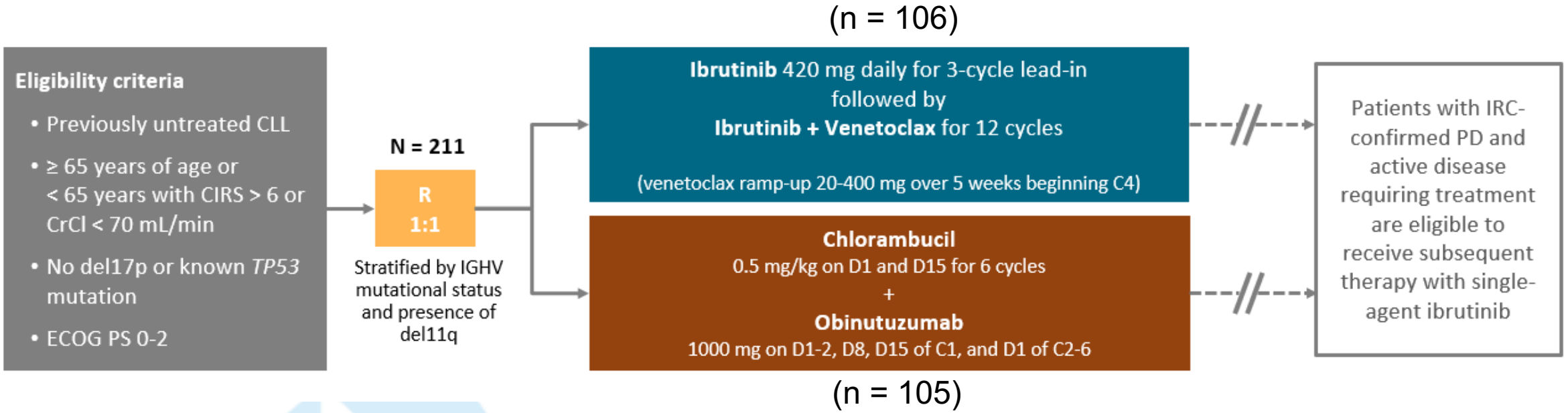


MOFFITT CANCER CENTER

Timofeeva N, Gandhi V. Blood Cancer J. 2021 Apr 29;11(4):79
Jain N et al. N Engl J Med 2019;380:2095-103.

Phase 3 RCT of fixed duration ibrutinib + venetoclax vs G-Clb in previously untreated CLL

GLOW study



- Primary endpoint: PFS by IRC

-Secondary endpoints:

uMRD in BM, CR per IRC, OS, safety

Median follow-up: 34.1 months

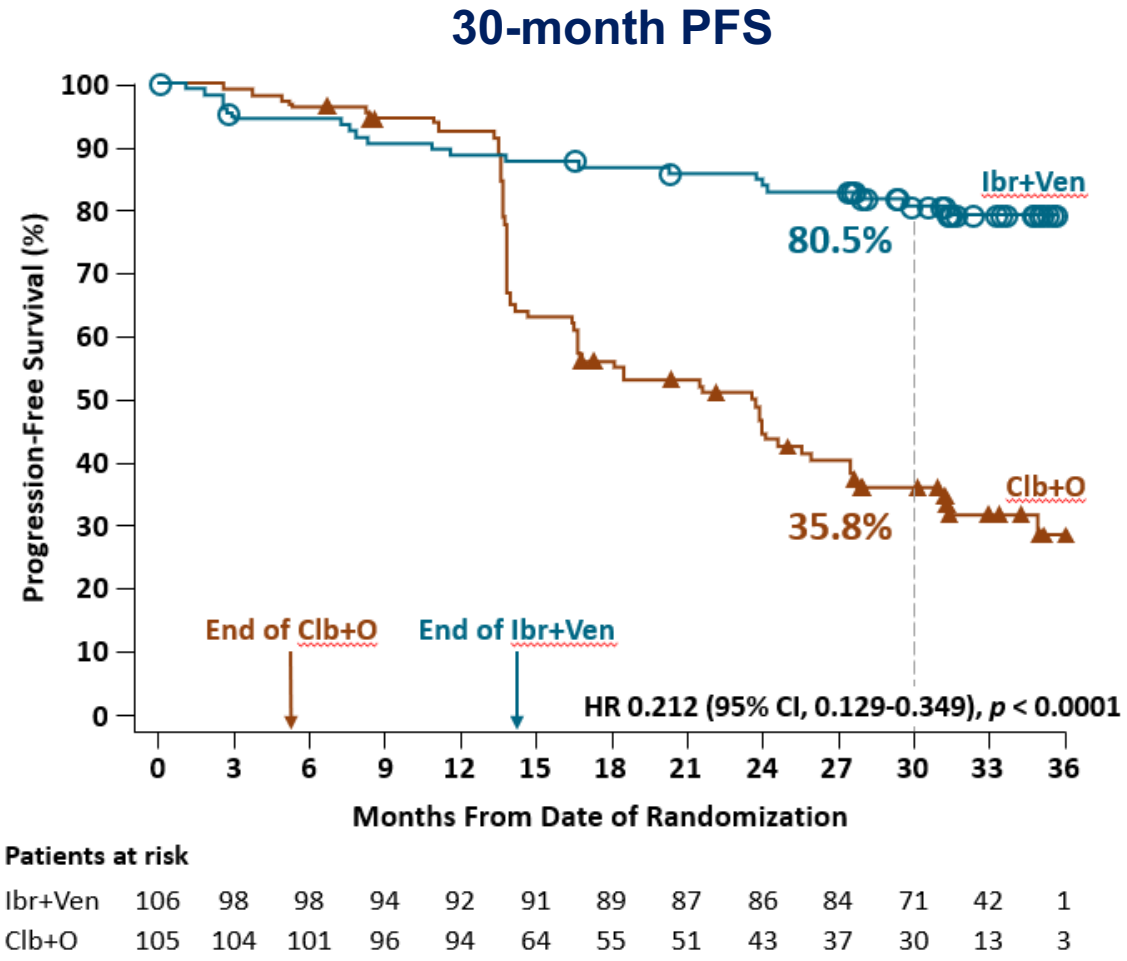
- Current MRD analysis: uMRD at $<10^{-4}$ and $<10^{-5}$ by NGS
- PB/BM concordance calculated for patients with evaluable data at EOT+3

MOFFITT CANCER CENTER

Munir T et al. Blood.2021;138 Abstr 396 (suppl 1).

Phase 3 RCT of fixed duration ibrutinib + venetoclax vs G-Clb in previously untreated CLL

GLOW study



uMRD rates ($<10^{-4}$) on BM and PB

uMRD at EOT+3, %	Ibr + Ven (n = 106)	Clb + O (n = 105)	*P* Value
$<10^{-4}$			
▪ BM	51.9	17.1	<.0001
▪ PB	54.7	39.0	.0259
▪ BM/PB concordance	92.9	43.6	

MOFFITT CANCER CENTER

Munir T et al. Blood.2021;138 Abstr 396 (suppl 1).

uMRD rates ($<10^{-4}$) on BM for Ibru+Ven vs. Clb+O across prespecified subgroups

Characteristic, %	Ibr + Ven	Clb + O	RR
Bulky disease (≥5 cm)			
No	50.0	19.4	2.58
Yes	56.1	13.2	4.26
Elevated BL LDH			
No	53.5	13.0	4.13
Yes	48.6	21.6	2.25
IGHV			
Mutated	44.4	18.5	2.40
Unmutated	58.2	14.8	3.93
Del11q			
No	50.0	18.4	2.72
Yes	60.0	11.1	5.40

- 5 of 7 patients (71.4%) with mutated *TP53* achieved uMRD $<10^{-5}$ in both BM and PB with Ibr + Ven.

MRD Dynamics Posttreatment

uMRD Dynamics From EOT+3 to EOT+12	Ibr + Ven	Clb + O
Sustained uMRD $<10^{-4}$, % (n/N)	84.5 (49/58)	29.3 (12/41)
Sustained uMRD $<10^{-5}$, % (n/N)	80.4 (37/46)	26.3 (5/19)
Decrease in uMRD $<10^{-4}$ rate, %	6	27

- uMRD in PB better sustained with Ibr + Ven vs Clb + O from EOT+3 to EOT+12.
- Patients treated with Ibr+Ven with detectable MRD $\geq 10^{-4}$ at EOT+3 less likely to:
  - ✓ Convert to PD at EOT+12 vs patients treated with Clb+O
  - ✓ Have increasing levels of detectable MRD at EOD+12 vs patients treated with Clb+O

MOFFITT CANCER CENTER

Munir T et al. Blood.2021;138 Abstr 396 (suppl 1).

Phase 3 RCT of fixed duration ibrutinib + venetoclax vs G-Clb in previously untreated CLL

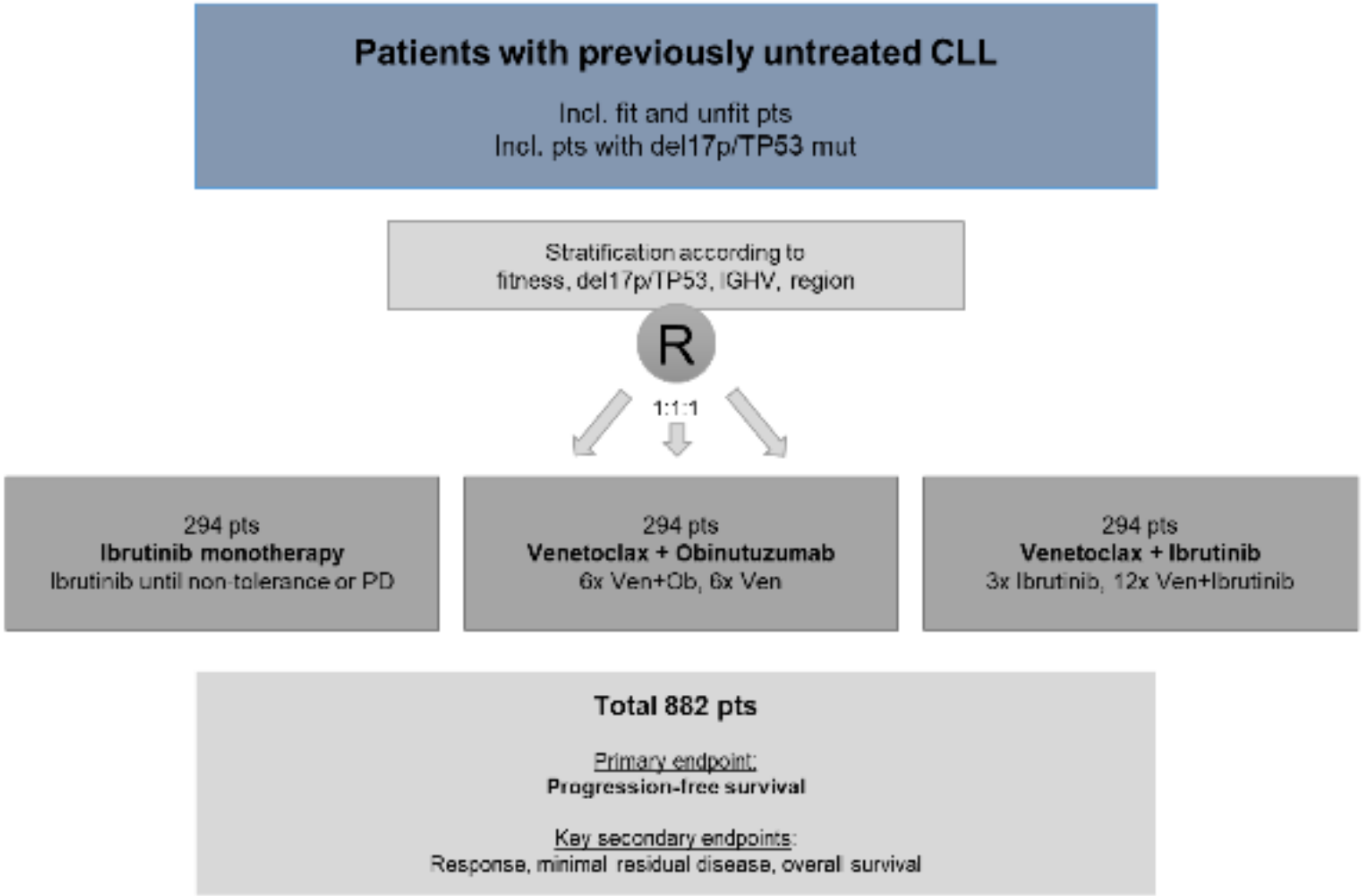
GLOW study

Grade 3 or Higher AEs in ≥5% of Patients

	I+V (N = 106)	Clb+O (N = 105)
Median exposure, mos (range)	13.8 (0.7-19.5)	5.1 (1.8-7.9)
Any, %	75.5	69.5
Neutropenia[a]	34.9	49.5
Infections[b]	17.0	11.4
Thrombocytopenia	5.7	20.0
Diarrhea	10.4	1.0
Hypertension	7.5	1.9
Atrial fibrillation	6.6	0
Hyponatremia	5.7	0
TLS	0	5.7

Munir T et al. Blood.2021;138 Abstr 396 (suppl 1).

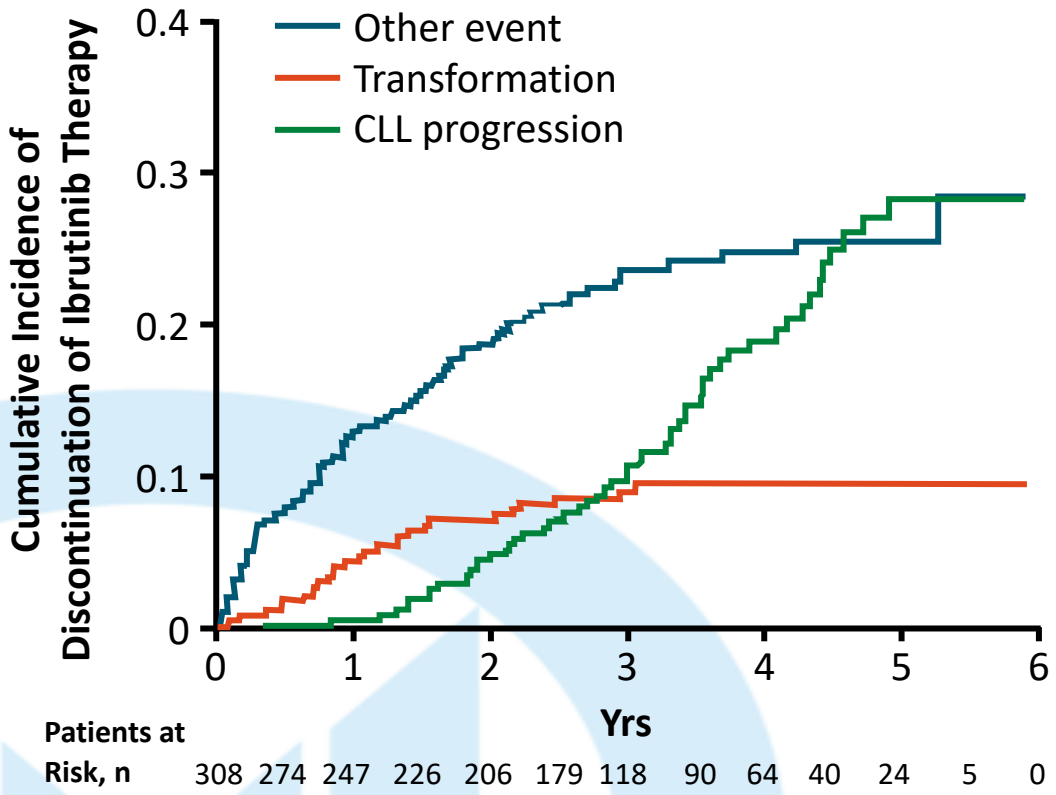
CLL 17



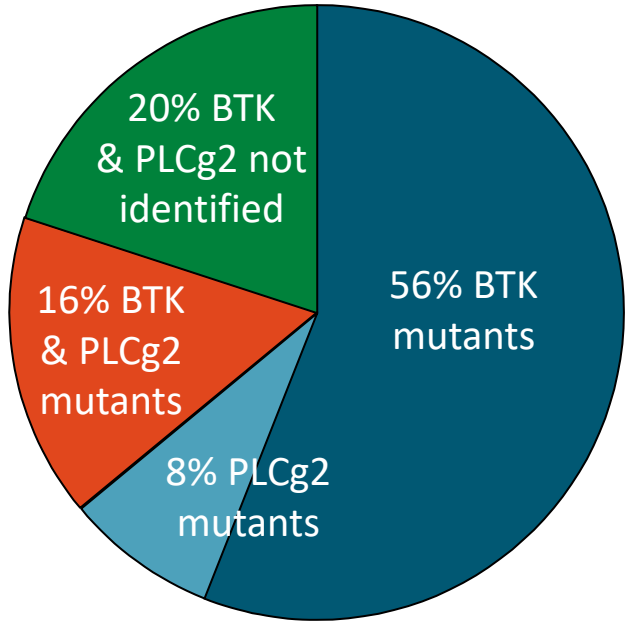
Hallek M, SOHO meeting 2020

Relapse/Refractory (R/R) CLL

Ibrutinib Discontinuation from 4 Sequential Studies[1]



Ibrutinib Acquired Resistance in Patients With Progressive CLL[2]



- Frontline ibrutinib d/c rate at 5 yrs: 41%[1]
- R/R predicted ibrutinib d/c rate at 5 yrs: 53.7% (4 sequential studies)[7]
- Appearance of BTK C481 mutations dominant reason for progressive CLL after covalent BTKi[1-8]
- BTK C481 mutations prevent covalent BTKi from effective target inhibition[1-6]

1. Woyach. JCO. 2017;35:1437. 2. Lampson. Expert Rev Hematol. 2018;11:185. 3. Woyach. NEJM. 2016;374:323. 4. Byrd. NEJM. 2016;374:323. 5. Xu. Blood. 2017;129:2519. 6. Hershkovitz-Rokah. Br. J. Haematol. 2018;181;306. 7. Burger. Leukemia. 2020;34:787. 8. Woyach. ASH 2019. Abstr 642.

ELEVATE-RR (Acalabrutinib vs. Ibrutinib in R/R CLL)

Phase 3, Randomized, Non-Inferiority Open-Label trial

Previously treated CLL patients (N=533)

Must have ≥1 of the following:
del(17p) or del(11q) by central laboratory testing

R (1:1)

(n=268)

Acalabrutinib (100 mg PO Q12hrs)[a]

(n=265)

Ibrutinib (420 mg PO Q24hrs)[a]

Primary endpoint

Non-inferiority on IRC assessed PFS[b]

Secondary endpoints (hierarchical order)

- **Incidence of any grade atrial fibrillation/flutter**
- **Incidence of grade ≥3 infections**
- **Incidence of Richter's transformation**
- **OS**

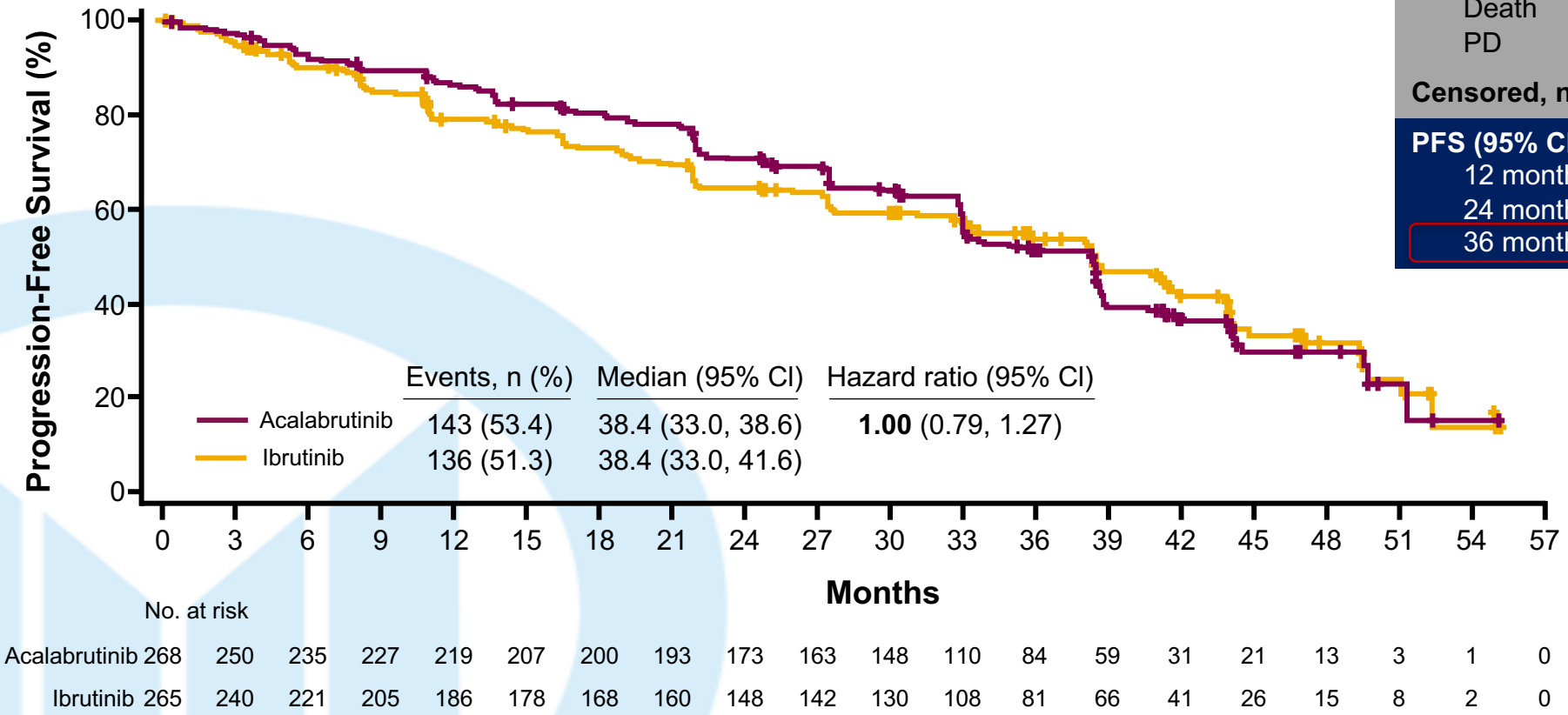
Stratification:
- del (17p) status (yes or no)
- ECOG PS (2 vs ≤1)
- Number of prior therapies (1-3 vs ≥4)

Key exclusion criteria: Known CNS lymphoma or leukemia, significant cardiovascular disease ≤6 months before screening, Hx of bleeding diathesis, requiring or receiving anticoagulation with warfarin or equivalent vitamin K antagonists within 7 days of first dose of study drug, History of stroke or intracranial hemorrhage, Prior exposure to ibrutinib, BCR inhibitor or a BCL-2 inhibitor.

Byrd JC et al. ASCO Virtual Annual Meeting; June 4-8, 2021.

Primary Endpoint: IRC-Assessed PFS

- At a median follow-up of 40.9 months (range 0.0–59.1), acalabrutinib was non-inferior to ibrutinib with a median PFS of 38.4 months in both arms (HR: 1.00; 95% CI 0.79–1.27)



	Acalabrutinib (n = 268)	Ibrutinib (n = 265)
Events, n (%)	143 (53.4)	136 (51.3)
Death	22 (8.2)	28 (10.6)
PD	121 (45.1)	108 (40.8)
Censored, n (%)	125 (46.6)	129 (48.7)
PFS (95% CI), %		
12 months	86.7 (81.8-90.3)	78.8 (73.1-83.4)
24 months	70.9 (64.8-76.1)	64.5 (58.1-70.2)
36 months	51.4 (44.7-57.8)	53.8 (47.0-60.1)

MOFFITT CANCER CENTER

Events, n (%)	Any grade		Grade ≥3	
	Acalabrutinib (n=266)	Ibrutinib (n=263)	Acalabrutinib (n=266)	Ibrutinib (n=263)
Cardiac events	64 (24.1)	79 (30.0)	23 (8.6)	25 (9.5)
Atrial fibrillation[a]*	25 (9.4)	**42 (16.0)**	13 (4.9)	10 (3.8)
Ventricular arrythmias[b]	0	3 (1.1)	0	1 (0.4)
Bleeding events*	101 (38.0)	**135 (51.3)**	10 (3.8)	12 (4.6)
Major bleeding events[c]	12 (4.5)	14 (5.3)	10 (3.8)	12 (4.6)
Hypertension[d]*	25 (9.4)	**61 (23.2)**	11 (4.1)	**24 (9.1)**
Infections[e]	208 (78.2)	214 (81.4)	82 (30.8)	79 (30.0)
ILD/pneumonitis*	7 (2.6)	**17 (6.5)**	1 (0.4)	2 (0.8)
SPMs excluding NMSC	24 (9.0)	20 (7.6)	16 (6.0)	14 (5.3)

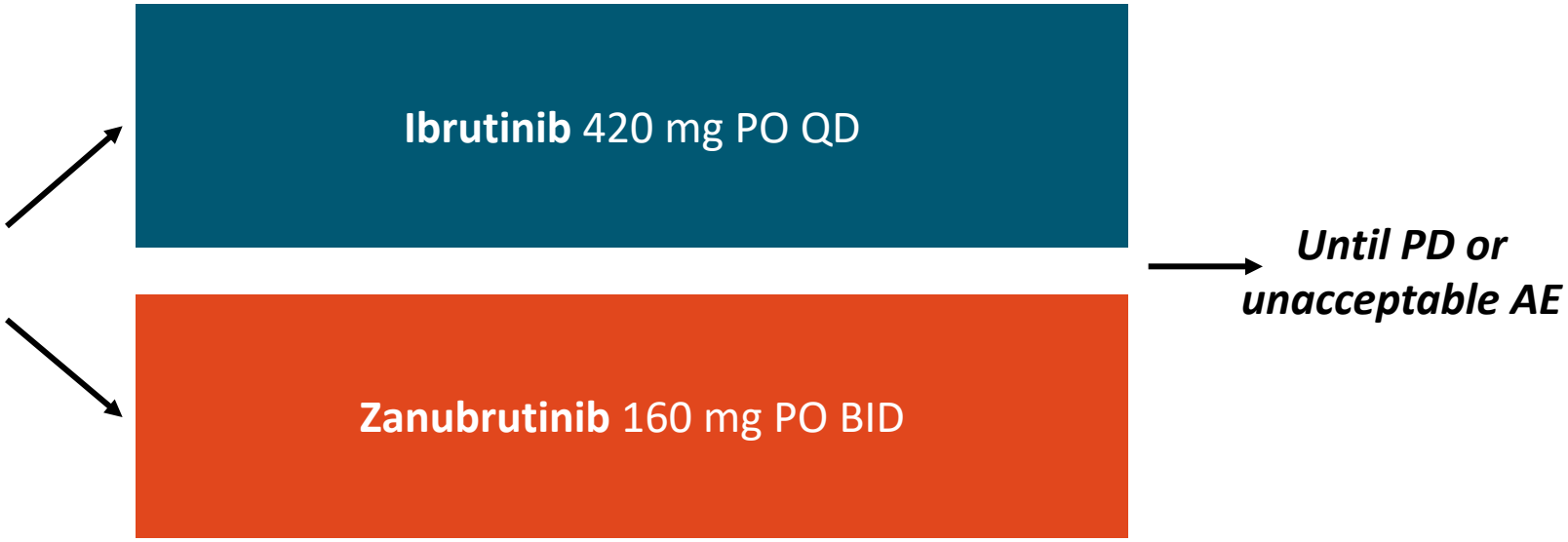
CANCER CENTER

Byrd JC et al.ASCO Virtual Annual Meeting; June 4-8, 2021.

Phase 3 Randomized Study of Zanubrutinib vs. Ibrutinib in Patients with R/R CLL/SLL

ALPINE study

Patients with CLL that meets 2008 iwCLL criteria for treatment; relapsed or refractory to ≥ 1 previous line of treatment; ECOG PS 0-2; adequate organ function; no clinically significant cardiac disease (planned N = 400)



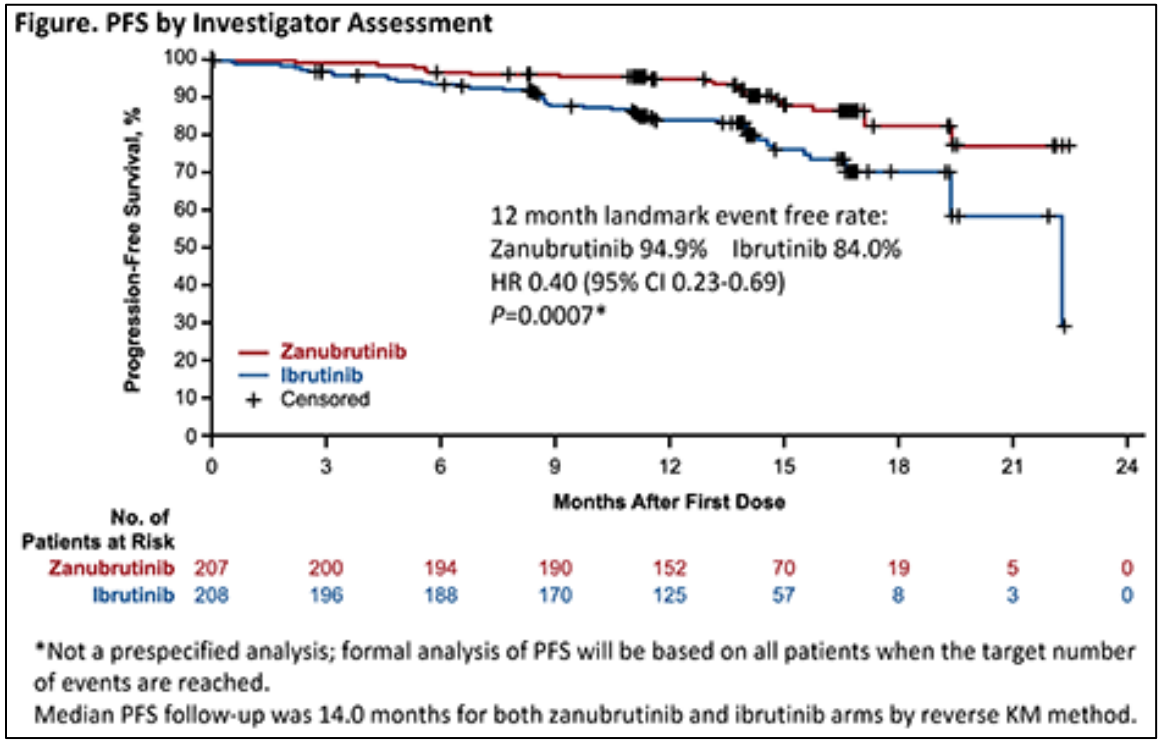
- **Ongoing randomized, multicenter phase III trial**
- **Primary endpoint:** ORR (Not by IRC)
- Secondary endpoints: PFS, DoR, OS; safety, patient-assessed QoL

MOFFITT CANCER CENTER

Hillmen. EHA 2021. Abstr LB1900. NCT02477696.

ALPINE Study: Response rates and Investigator assessed PFS *(Interim results)*

Outcome, % (95% CI)	Zanubrutinib (n = 207)	Ibrutinib (n = 208)	*P* Value
Efficacy			
ORR (Invest.-Assessed)	78.3 (72.0-83.7)	62.5 (55.5-69.1)	.0006
ORR (IRC- assessed)	76.3	64.4	.0121
ORR in del(17p)	83.3	53.8	NR
12-mo PFS	94.9	84.0	.0007
	HR = 0.40 (0.23 – 0.69)		

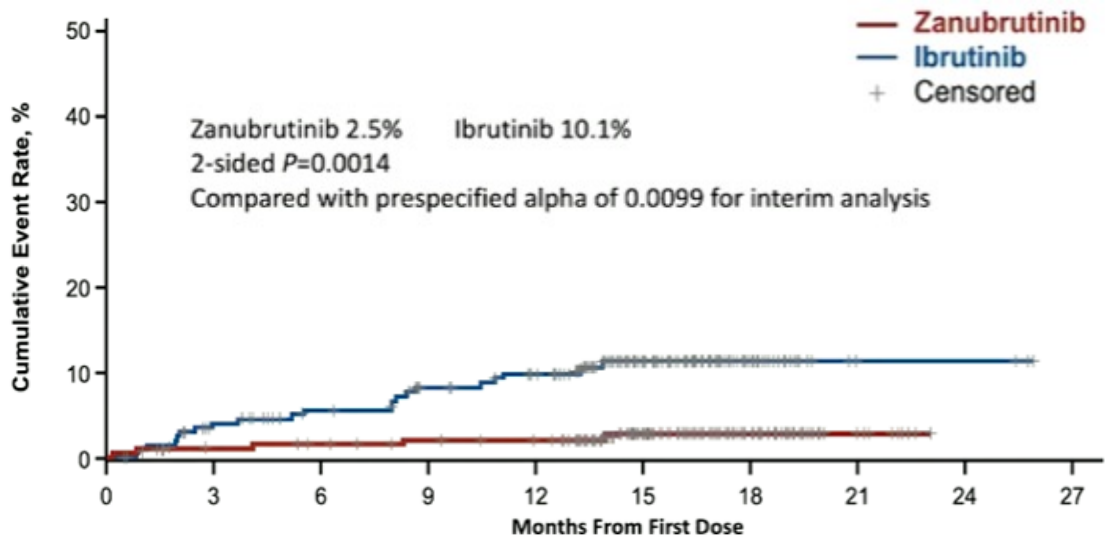


MOFFITT CANCER CENTER

Hillmen. EHA 2021. Abstr LB1900. NCT02477696.

ALPINE Study: Adverse events of special interest *(Interim results)*

Select AEs, any grade %	Zanubrutinib (n = 207)	Ibrutinib (n = 208)
Afib or flutter (key secondary point *p=.0014*)	2.5	10.1
Cardiac disorders	13.7	25.1
Hemorrhage	35.8	36.2
Major hemorrhage	2.9	3.9
Hypertension	16.7	16.4
Infections	59.8	63.3
Neutropenia	28.4	21.7
Secondary primary malignancies	8.3	6.3
Skin cancers	3.4	4.8
Thrombocytopenia	9.3	12.6



MOFFITT CANCER CENTER

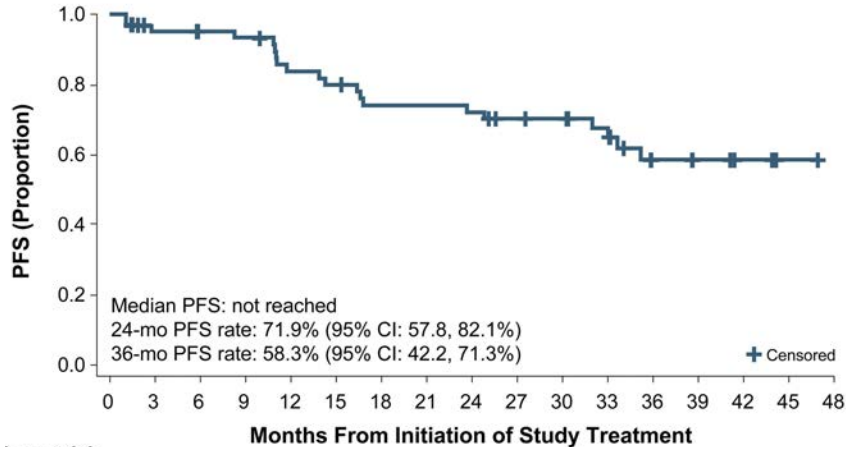
Hillmen. EHA 2021. Abstr LB1900. NCT02477696.

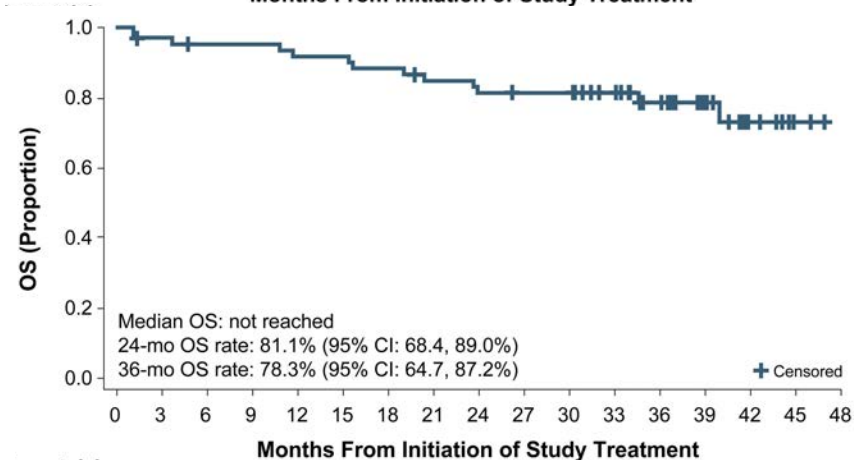
Phase II study of acalabrutinib in ibrutinib-intolerant patients with relapsed/refractory chronic lymphocytic leukemia

Characteristic	N=60
Age in years, median (range)	69.5 (43-88)
Men, n (%)	38 (63)
ECOG PS ≤1, n (%)	58 (97)
Number of prior systemic therapies, n (%)	
1	14 (23)
2	18 (30)
3	11 (18)
≥4	17 (28)
β2-microglobulin >3 mg/L, n/N (%)	46/58 (79)
Genetic risk features, n/N (%)	
Unmutated *IGHV*	46/58 (79)
del(11q)[a]	14/60 (23)
del(17p)[a]	17/60 (28)
Rai stage III-IV, n (%)	31 (52)
Lymph nodes ≥5 cm, n (%)	19 (32)
Laboratory values, median (range)	
Lymphocyte count, 10^9/L	12.3 (0.9-172.4)
Neutrophil count, 10^9/L	3.3 (0.4-20.1)
Hemoglobin, g/dL	12.2 (7.5-17.3)
Platelet count, 10^9/L	117.5 (37-350)

- Pts with R/R CLL in need of therapy that were intolerant to Ibrutinib patients with disease activity received acalabrutinib; med 2 prior tx (range 1-10)

At median follow-up of 34.6 mo,
48% of patients remain on acalabrutinib





MOFFITT CANCER CENTER

Rogers K et al. Hematologica 2021;106(9):2364-2373

Ibrutinib-tolerance adverse events and recurrence after acalabrutinib treatment

Adverse event	Number of patients with ibrutinib intolerance[a]	Acalabrutinib experience for same patients			
		Total	Lower grade	Same grade	Higher grade
Atrial fibrillation	16[b]	2	2	0	0
Diarrhea	7	5	3	2	0
Rash	7	3	3	0	0
Bleeding[c,d]	6	5	3	2	0
Arthralgia	7[e]	2	1	1	0
Total	41	24	18	6	1

[a]Among 60 patients meeting the study enrollment criteria, 41 patients had a medical history of one or more (43 events in total) of the following categories of ibrutinib-intolerance events: atrial fibrillation, diarrhea, rash, bleeding, or arthralgia. [b]Includes patients with atrial flutter (n=2). [c]Events categorized as bleeding included ecchymosis, hemorrhage, epistaxis, contusion, hematuria, and subdural hematoma. [d]All but one patient experienced a different type of bleeding event with acalabrutinib compared with ibrutinib treatment. [e]Includes one patient with arthritis.

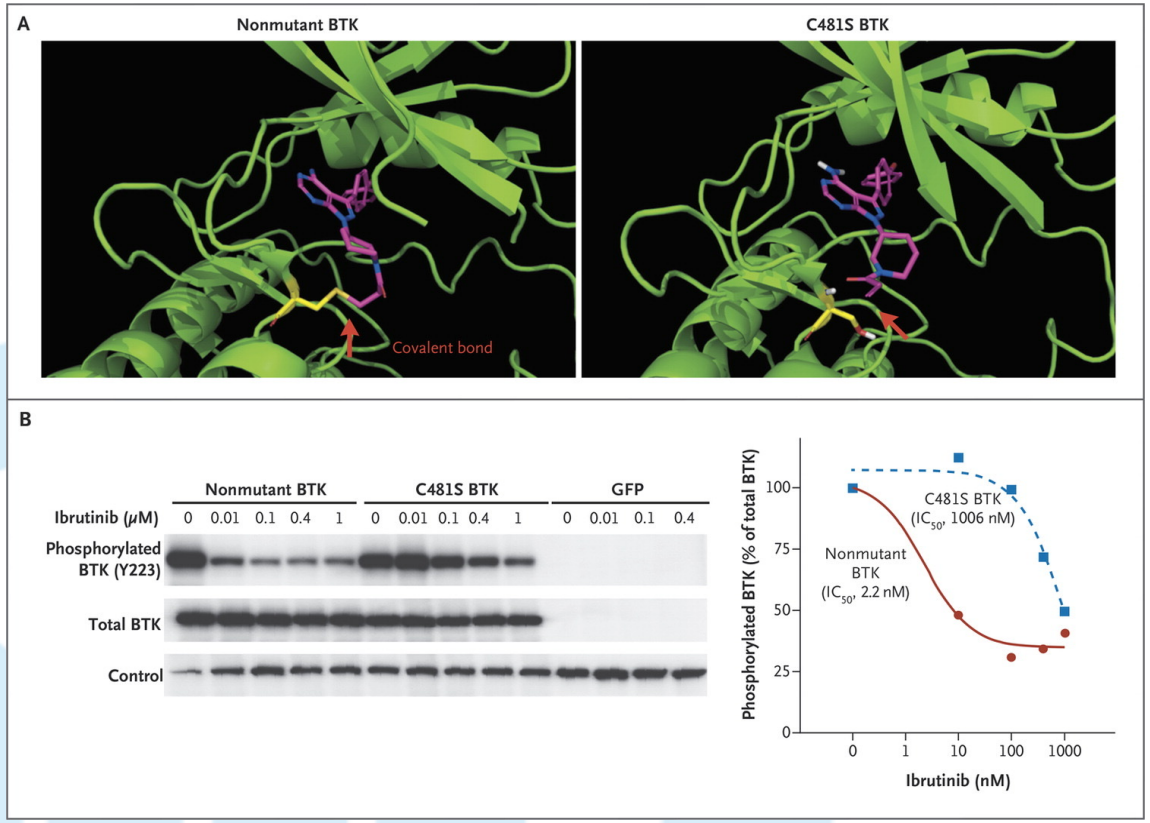
- Acalabrutinib is well tolerated in patients with Ibrutinib intolerance

MOFFITT CANCER CENTER

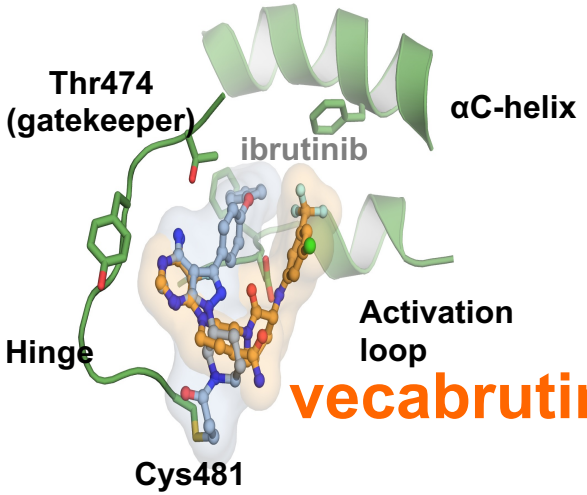
Rogers K et al. Hematologica 2021;106(9):2364-2373

Tackling BTK resistance = 3rd generation BTK inhibitors

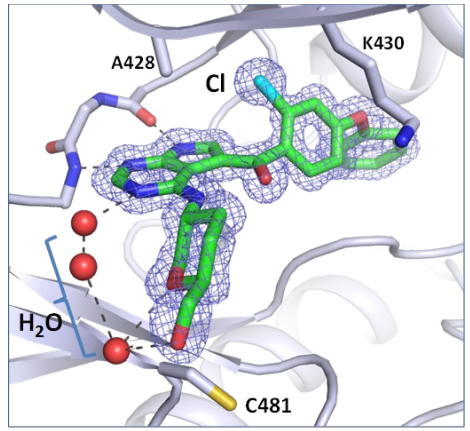
Effect of C481S Mutation of Bruton's Tyrosine Kinase (BTK) on Ibrutinib Binding



Furman RR et al. N Engl J Med 2014;370:2352-2354.



ARQ-531



LOXO-305

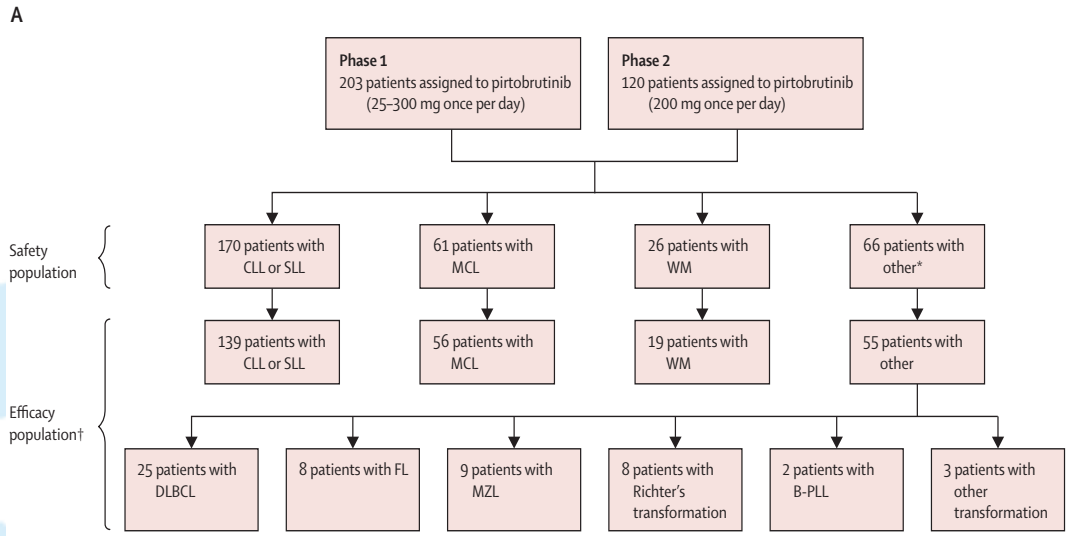
- Reversible inhibition of BTK
- Occupies the ATP binding pocket – non C481.
- Orally bioavailable DUAL INHIBITORS of both wild type and C481S mutated BTK

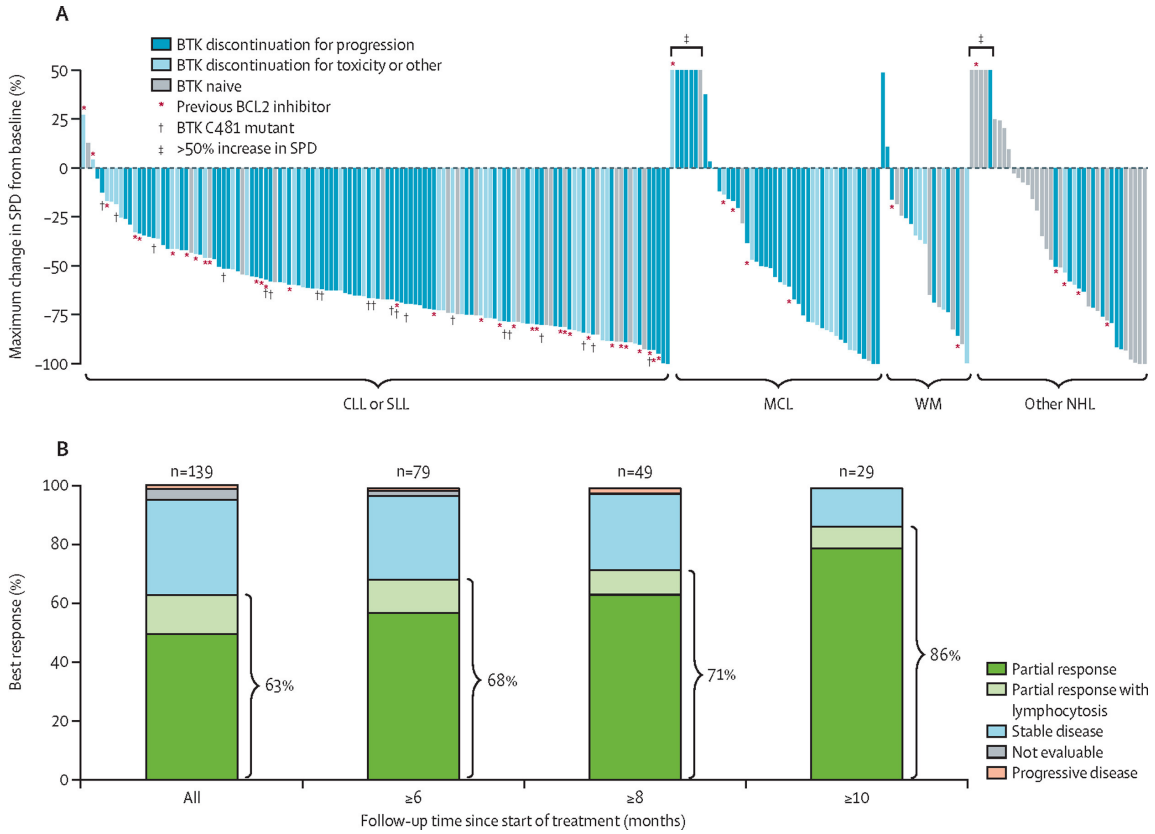
MOFFITT CANCER CENTER

Reiff et al, Cancer Discovery, 2018

Pirtobrutinib in relapsed or refractory B-cell malignancies (BRUIN): a phase 1/2 study

Anthony R Mato, Nirav N Shah, Wojciech Jurczak, Chan Y Cheah, John M Pagel, Jennifer A Woyach, Bita Fakhri, Toby A Eyre, Nicole Lamanna, Manish R Patel, Alvaro Alencar, Ewa Lech-Maranda, William G Wierda, Catherine C Coombs, James N Gerson, Paolo Ghia, Steven Le Gouill, David John Lewis, Suchitra Sundaram, Jonathon B Cohen, Ian W Flinn, Constantine S Tam, Minal A Barve, Bryone Kuss, Justin Taylor, Omar Abdel-Wahab, Stephen J Schuster, M Lia Palomba, Katharine L Lewis, Lindsey E Roeker, Matthew S Davids, Xuan Ni Tan, Timothy S Fenske, Johan Wallin, Donald E Tsai, Nora C Ku, Edward Zhu, Jessica Chen, Ming Yin, Binoj Nair, Kevin Ebata, Narasimha Marella, Jennifer R Brown, Michael Wang

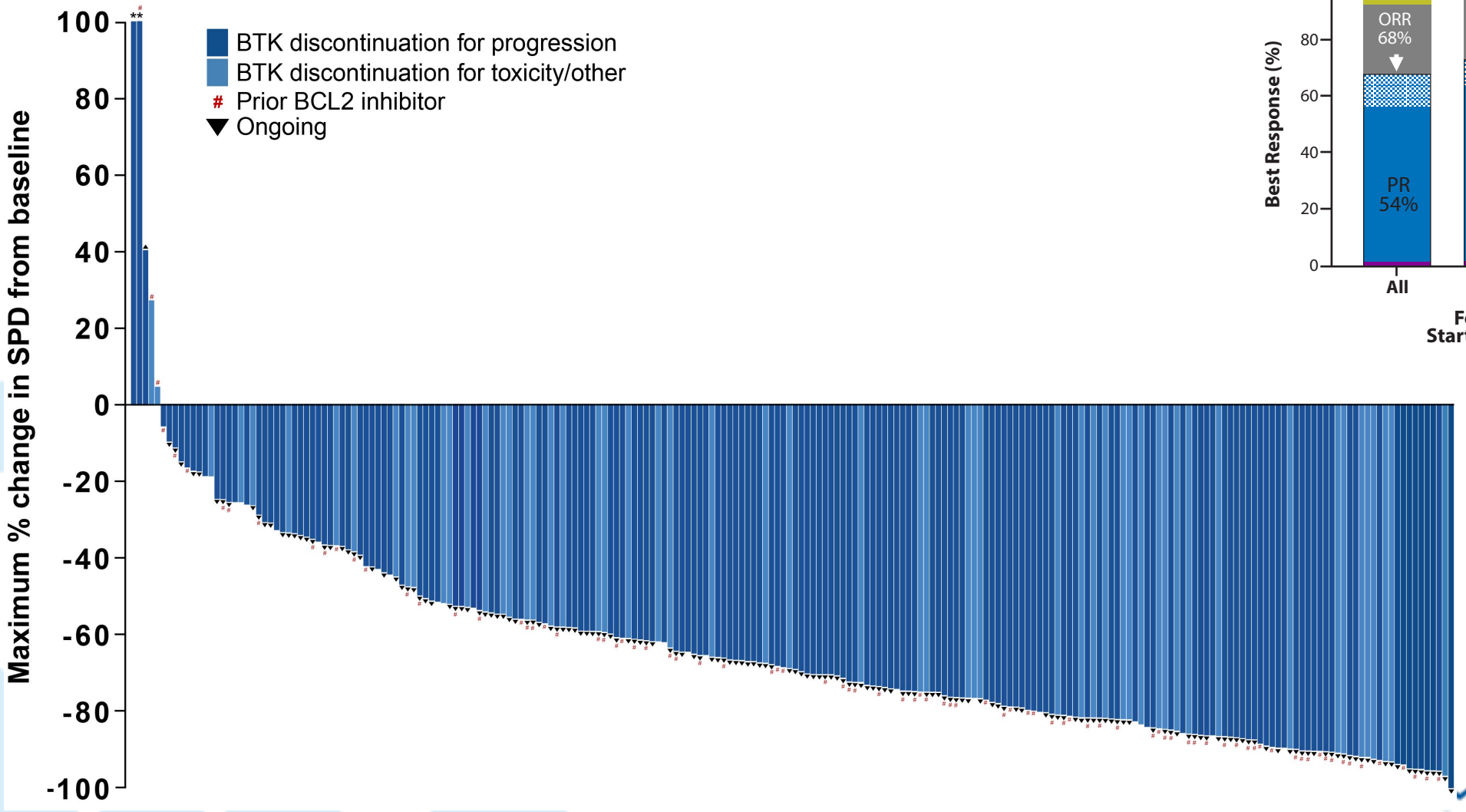


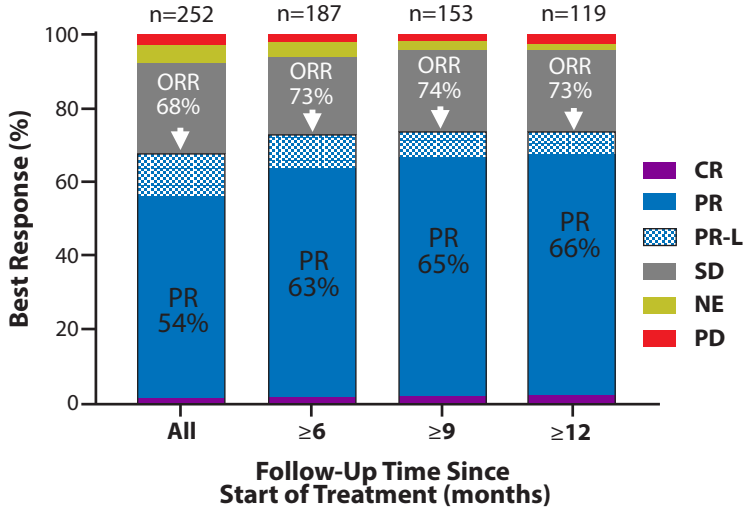


MOFFITT CANCER CENTER

Mato AR et al. Lancet 2021;397(10277):892-901. .

Pirtobrutinib Efficacy in BTK Pre-treated CLL/SLL Patients





MOFFITT CANCER CENTER

Mato AR et al. ASH 2021;Abstract 391.

Pirtobrutinib Efficacy in BTK Pre-treated CLL/SLL Patients

	All doses and patients (n=618)							
	Treatment-emergent AEs, (≥15%), %						Treatment-related AEs, %	
Adverse Event	Grade 1	Grade 2	Grade 3	Grade 4	Any Grade		Grades 3/4	Any Grade
Fatigue	13%	8%	1%	-	23%		1%	9%
Diarrhea	15%	4%	<1%	<1%	19%		<1%	8%
Neutropenia[a]	1%	2%	8%	6%	18%		8%	10%
Contusion	15%	2%	-	-	17%		-	12%
AEs of special interest[b]								
Bruising[c]	20%	2%	-	-	22%		-	15%
Rash[d]	9%	2%	<1%	-	11%		<1%	5%
Arthralgia	8%	3%	<1%	-	11%		-	3%
Hemorrhage[e]	5%	2%	1%[g]	-	8%		<1%	2%
Hypertension	1%	4%	2%	-	7%		<1%	2%
Atrial fibrillation/flutter[f]	-	1%	<1%	<1%	2%[h]		-	<1%

- **No DLTs reported and MTD not reached**
- **96% of patients received ≥1 pirtobrutinib dose at or above RP2D of 200 mg daily**
- **1% (n=6) of patients permanently discontinued due to treatment-related AEs**

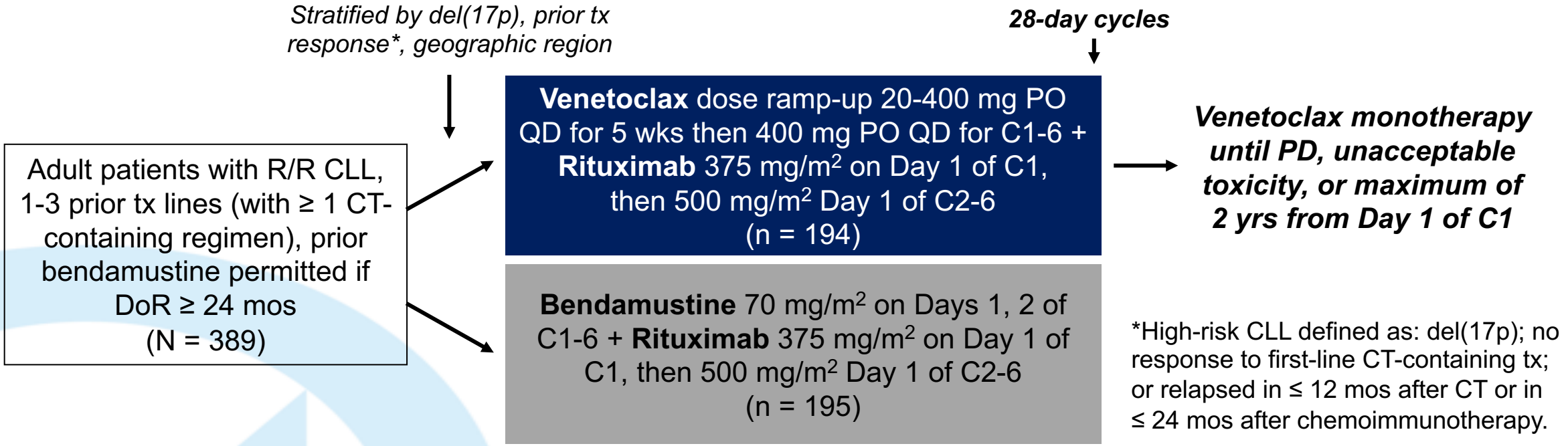
MOFFITT CANCER CENTER

Mato AR et al. ASH 2021;Abstract 391.

Venetoclax + Rituximab vs BR in previously treated CLL/SLL patients

MURANO Study

- **Multicenter, randomized, open-label phase III trial**



*High-risk CLL defined as: del(17p); no response to first-line CT-containing tx; or relapsed in ≤ 12 mos after CT or in ≤ 24 mos after chemoimmunotherapy.

Primary endpoint:

- Investigator-assessed PFS

Secondary endpoints:

- IRC-assessed PFS and MRD negativity,

- IRC-assessed CR → ORR → OS (hierarchical testing), safety

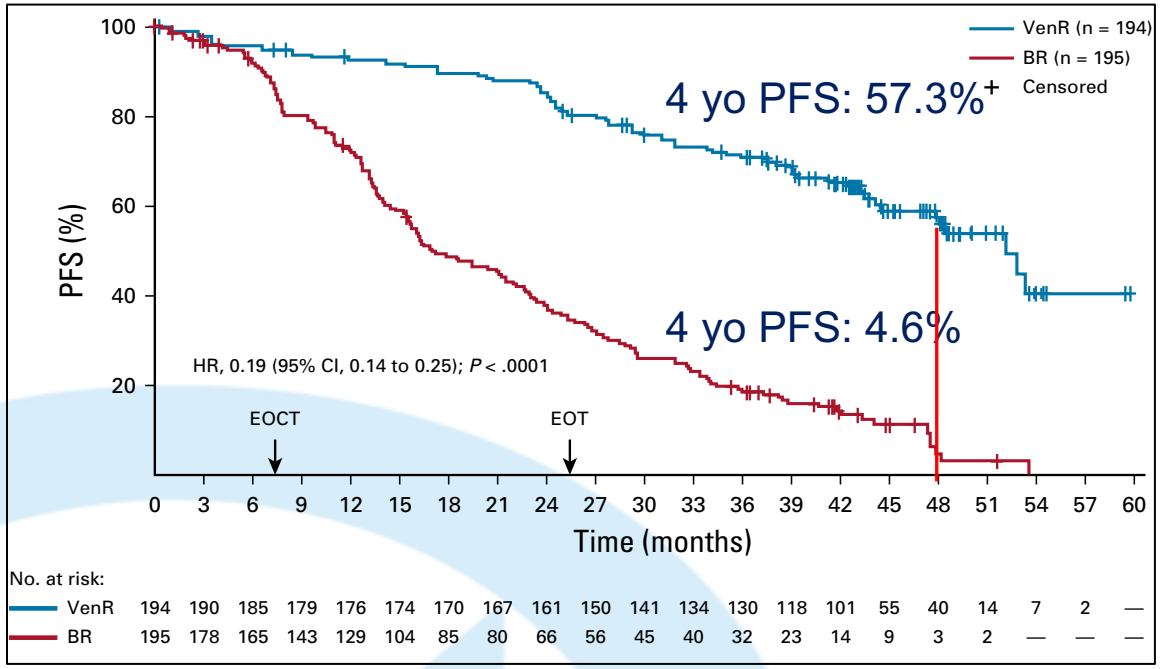
MOFFITT CANCER CENTER

Seymour JF et al. . NEJM 2018; 378:1107.
Kater A et al. J Clin Oncol 2020; 38:4042-4054.

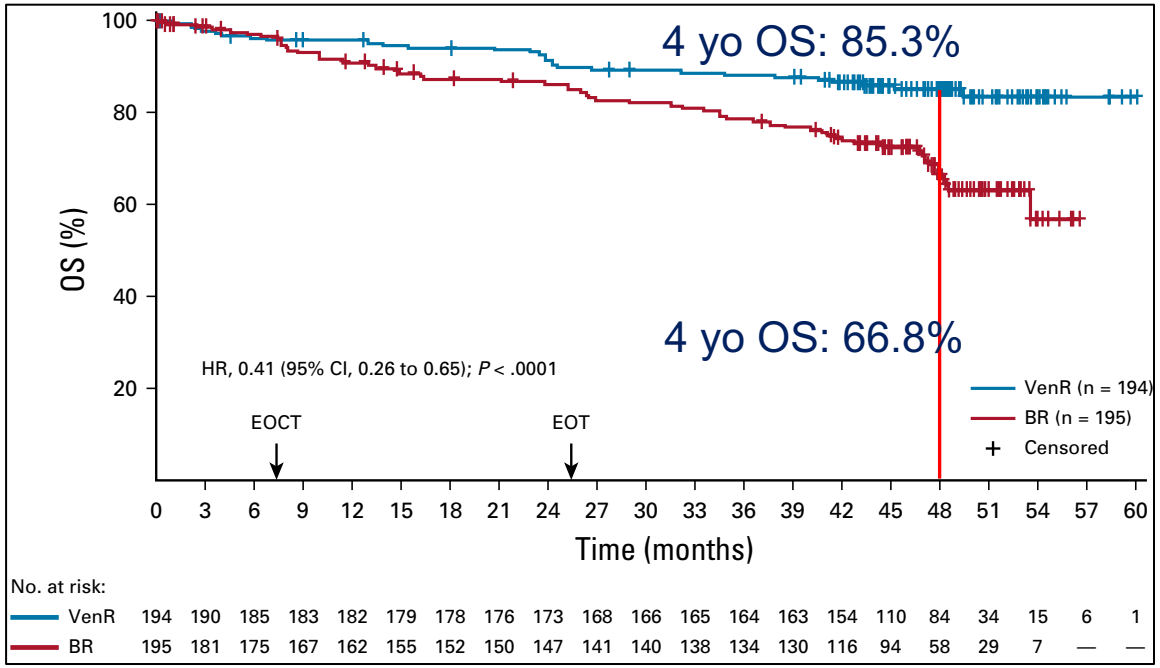
MURANO trial: 4 year follow up

(Includes impact of genomic complexity and mutations)

PFS



OS



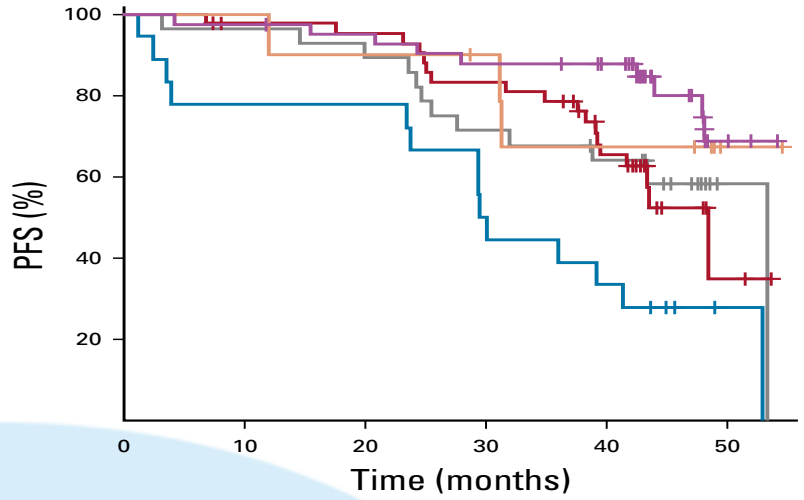
MOFFITT CANCER CENTER

Kater A et al. J Clin Oncol 2020; 38:4042-4054.

MURANO trial: 4 year follow up

Impact of cytogenetics in CLL outcomes

PFS on the VenR based on cytogenetics

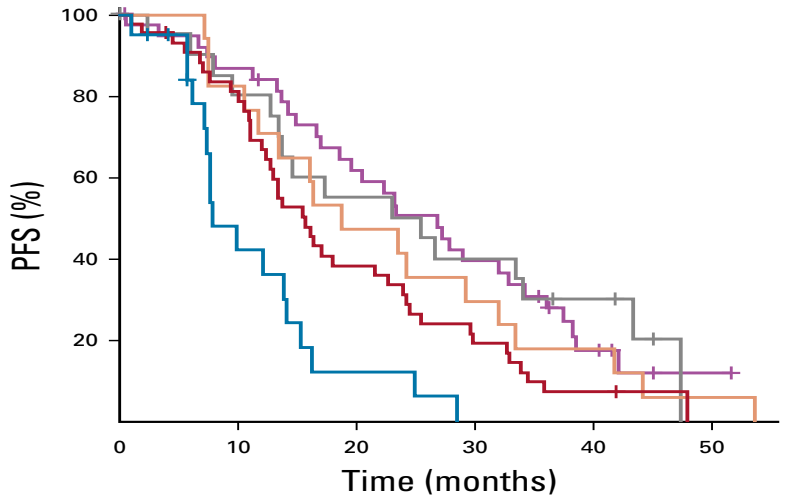


No. at risk:

del(17p)	18	14	14	9	6	1
del(11q)	44	41	40	35	24	2
Trisomy 12	10	10	9	8	6	1
del(13q)	42	41	39	36	33	4
Other	28	27	25	20	17	1

	del(11q)	Trisomy 12	del(13q)	Other
del(17p)	HR, 0.41 (95% CI, 0.2 to 0.83) *P* = .014	HR, 0.28 (95% CI, 0.08 to 0.98) *P* = .046	HR, 0.18 (95% CI, 0.078 to 0.42) *P* = .000082	HR, 0.41 (95% CI, 0.18 to 0.9) *P* = .027
del(11q)	—	HR, 0.61 (95% CI, 0.17 to 2.1) *P* = .43	HR, 0.41 (95% CI, 0.18 to 0.91) *P* = .028	HR, 1 (95% CI, 0.48 to 2.1) *P* = .99
Trisomy 12	—	—	HR, 0.72 (95% CI, 0.2 to 2.7) *P* = .63	HR, 1.6 (95% CI, 0.45 to 5.8) *P* = .46
del(13q)	—	—	—	HR, 2.4 (95% CI, 1 to 5.7) *P* = .049

PFS on the BR based on cytogenetics



No. at risk:

del(17p)	22	7	2	0	0	0
del(11q)	45	33	16	8	2	0
Trisomy 12	17	14	8	5	3	1
del(13q)	41	32	22	14	5	1
Other	21	16	11	8	5	0

	del(11q)	Trisomy 12	del(13q)	Other
del(17p)	HR, 0.44 (95% CI, 0.24 to 0.8) *P* = .0074	HR, 0.32 (95% CI, 0.15 to 0.7) *P* = .0042	HR, 0.23 (95% CI, 0.12 to 0.45) *P* = .00002	HR, 0.28 (95% CI, 0.13 to 0.61) *P* = .0012
del(11q)	—	HR, 0.76 (95% CI, 0.42 to 1.4) *P* = .36	HR, 0.55 (95% CI, 0.34 to 0.9) *P* = .016	HR, 0.58 (95% CI, 0.32 to 1.1) *P* = .076
Trisomy 12	—	—	HR, 0.79 (95% CI, 0.43 to 1.4) *P* = .44	HR, 0.76 (95% CI, 0.38 to 1.5) *P* = .44
del(13q)	—	—	—	HR, 0.96 (95% CI, 0.52 to 1.8) *P* = .89

MOFFITT CANCER CENTER

Kater A et al. J Clin Oncol 2020; 38:4042-4054.

MURANO trial: 5 year follow up

PFS & OS

Outcome	VenR (n = 194)	BR (n = 195)
Median PFS, mos	53.6	17.0
5-yr PFS, %	37.8	Not evaluable
▪ HR (95% CI)	0.19 (0.15-0.26)	
▪ *P* value	< 0.0001	
Median OS, mos	Not evaluable	Not evaluable
5-yr OS, %	82.1	62.2
▪ HR (95% CI)	0.40 (0.26-0.62)	
▪ *P* value	< 0.0001	

PFS and OS according to uMRD status at EOT with VenR

Category	PFS Since EOT, % (95% CI)		HR (95% CI)
	24 Mos	36 Mos	
uMRD ($< 10^{-4}$) (n = 83)	85.4 (77.4-93.4)	61.3 (47.3-75.2)	vs low-MRD+: 0.40 (0.18-0.91); *P* = .0246 vs high-MRD+: 0.02 (< 0.01-0.18); *P* < .0001

Category	OS Since EOT, % (95% CI)		HR
	24 Mos	36 Mos	
uMRD ($< 10^{-4}$) (n = 83)	98.8 (96.4-100.0)	95.3 (90.0-100.0)	HR: NS
MRD ($\geq 10^{-4}$) (n = 35)	88.6 (78.0-99.1)	85.0 (72.8-97.2)	*P* = NS

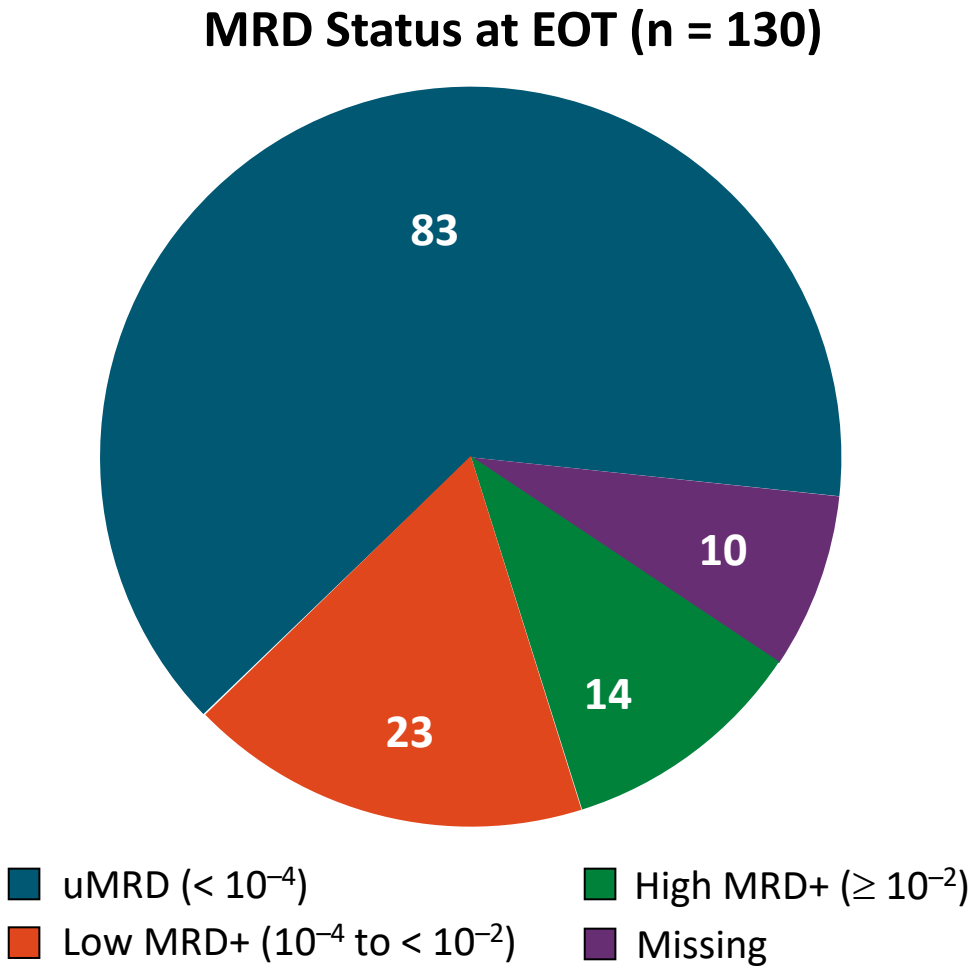
CANCER CENTER

Kater A et al. ASH 2021. Abstr 125.

MURANO trial: 5 year follow up

Among 83 patients with uMRD at EOT:

- 32 (38.6%) sustained uMRD.
- 28 (33.7%) had MRD conversion without. PD
- 19 (22.9%) had MRD conversion with PD.
- Median time from MRD conversion to PD: 25.2 mos (95% CI: 19.4-30.4).



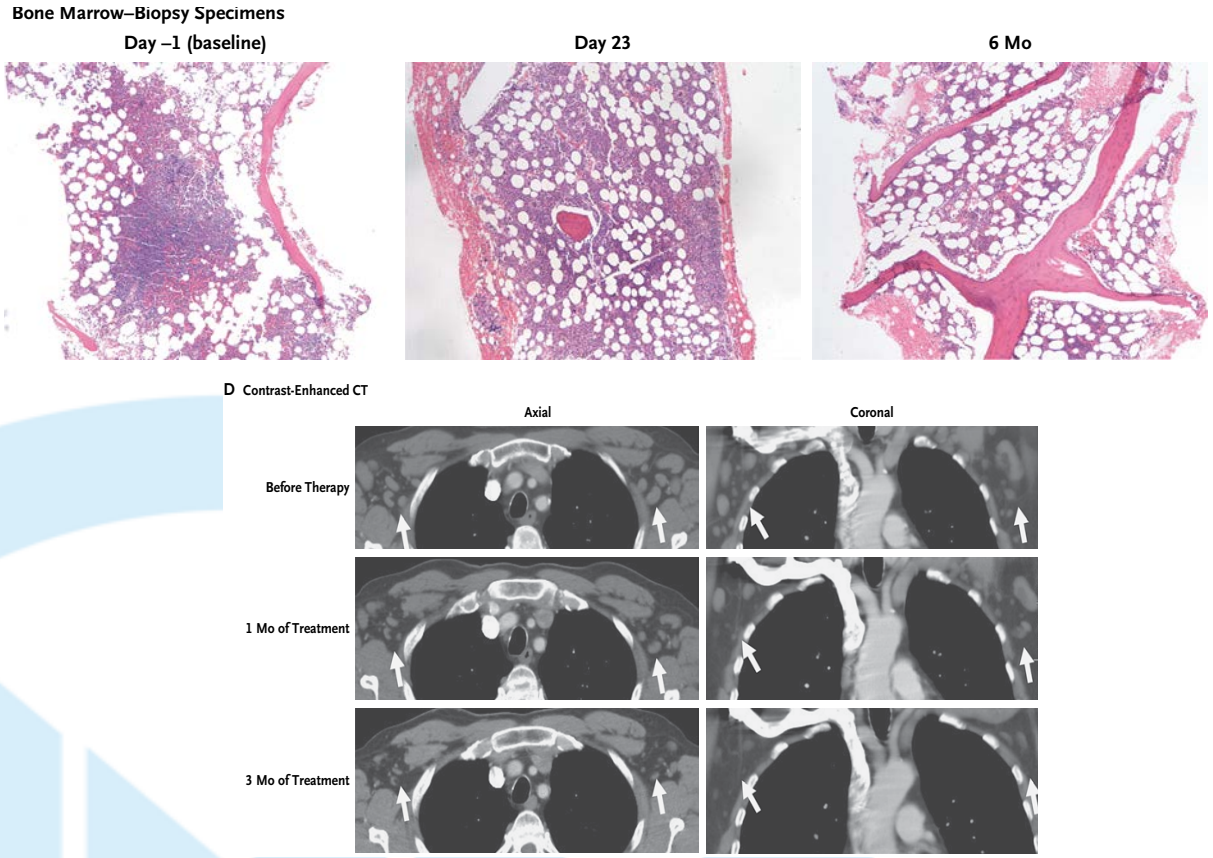
MOFFITT CANCER CENTER

Kater A et al. ASH 2021. Abstr 125.

BRIEF REPORT

Chimeric Antigen Receptor–Modified T Cells in Chronic Lymphoid Leukemia

David L. Porter, M.D., Bruce L. Levine, Ph.D., Michael Kalos, Ph.D., Adam Bagg, M.D., and Carl H. June, M.D.



Article

Decade-long leukaemia remissions with persistence of CD4+ CAR T cells

https://doi.org/10.1038/s41586-021-04390-6
Received: 7 May 2021
Accepted: 29 December 2021
Published online: 02 February 2022
Check for updates

J. Joseph Melenhorst[1,2,3,4,5,15,16]✉, Gregory M. Chen[6,15], Meng Wang[1,2,3,14], David L. Porter[3,7,15], Changya Chen[8,9], McKensie A. Collins[1,2,3,10], Peng Gao[8,9], Shovik Bandyopadhyay[10], Hongxing Sun[1,2,3], Ziran Zhao[1,2,3], Stefan Lundh[1,2,3], Iulian Pruteanu-Malinici[11], Christopher L. Nobles[12], Sayantan Maji[1,2,3], Noelle V. Frey[3], Saar I. Gill[3], Lifeng Tian[1,3], Irina Kulikovskaya[1,2,3], Minnal Gupta[1,2,3], David E. Ambrose[1,2,3], Megan M. Davis[1,2,3], Joseph A. Fraietta[1,2,3,12], Jennifer L. Brogdon[11], Regina M. Young[1,2,3], Anne Chew[1,2,3], Bruce L. Levine[1,2,3], Donald L. Siegel[1,2,13], Cécile Alanio[4,5,14], E. John Wherry[4,5,14], Frederic D. Bushman[12], Simon F. Lacey[1,2,3], Kai Tan[2,4,6,9,10,16]✉ & Carl H. June[1,2,3,4,5,16]✉

Cancer

First patients of pioneering CAR T-cell therapy 'cured of cancer'

Cancer-killing cells still present 10 years on, with results suggesting therapy is a cure for certain blood cancers

Linda Geddes *Science correspondent*

Wed 2 Feb 2022 11.00 EST

Doug Olson still has cancer-killing cells 10 years after infusion. Photograph: AP

Two of the first human patients to be treated with a revolutionary therapy that engineers immune cells to target specific types of cancer still possess cancer-killing cells a decade later with no sign of their illness returning.

The finding suggests CAR T-cell therapy constitutes a "cure" for certain blood cancers, although adapting it to treat solid tumours is proving more challenging.

Porter DL et al. N Engl J Med 2011;365:725-33.
Melenhorst JJ et al. *Nature* 2022;[Online ahead of print].
https://www.theguardian.com/society/2022/feb/02/first-patients-pioneering-car-t-cell-therapy-cured-of-cancer

MOFFITT CANCER CENTER

JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

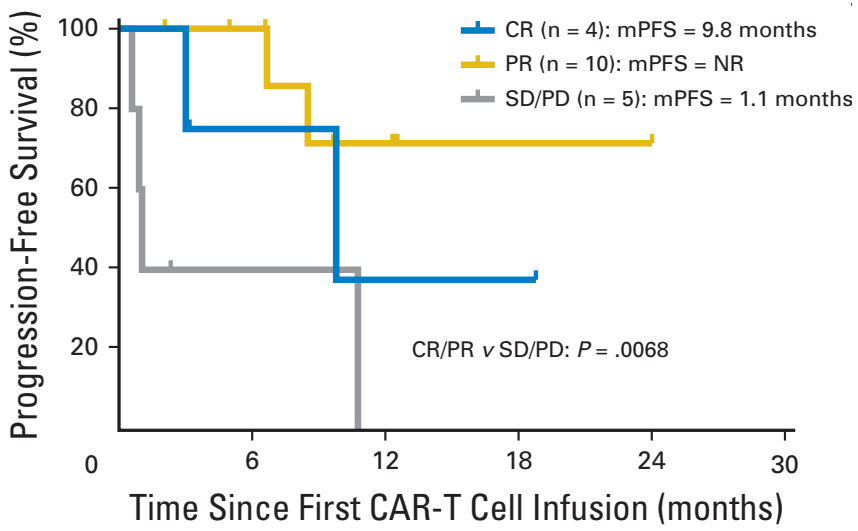
Durable Molecular Remissions in Chronic Lymphocytic Leukemia Treated With CD19-Specific Chimeric Antigen Receptor–Modified T Cells After Failure of Ibrutinib

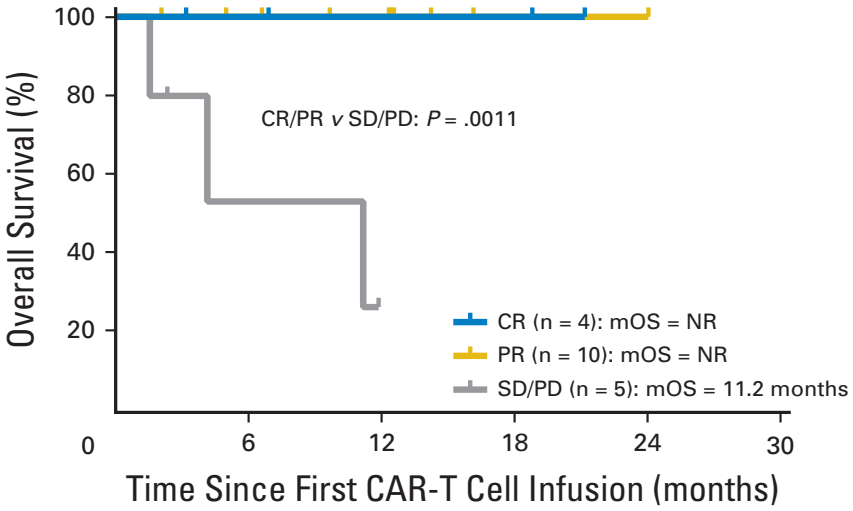
Cameron J. Turtle, Kevin A. Hay, Laïla-Aïcha Hanafi, Daniel Li, Sindhu Cherian, Xueyan Chen, Brent Wood, Arletta Lozanski, John C. Byrd, Shelly Heimfeld, Stanley R. Riddell, and David G. Maloney

Patient characteristics

No.	Histology	Age (years)	Prior Therapies (No.)	Progression on Ibrutinib	Intolerant to Ibrutinib	Time on Ibrutinib (months)	Venetoclax	Complex Karyotype	Del 17p
1	CLL/Richter's	65	9	Yes	No	12	No	No	Yes
2	CLL/PLL	54	3	No	No	0.75	No	Yes	Yes
3	CLL/Richter's	64	9	Yes	No	10	No	No	Yes
4	CLL	59	7	No	Yes	1	No	Yes	No
5	CLL	55	7	Yes	No	17	Refractory	Yes	No
6	CLL	61	6	Yes	No	11	No	No	Yes
7	CLL	63	7	No	No	3	Refractory	No	Yes
8	CLL	62	5	Yes	No	14	No	Yes	Yes
9	CLL	53	5	Yes	No	13	No	Yes	Yes
10	CLL/Richter's	68	4	Yes	No	16	No	Yes	No
11	CLL	53	5	Yes	No	34	No	Yes	Yes
12	CLL	70	5	No	Yes	5	No	No	Yes
13	CLL/Richter's	47	3	Yes	No	13	No	No	Yes
14	CLL/IPCs	40	4	Yes	No	14	No	Yes	Yes
15	CLL	73	3	Yes	No	4	No	No	Yes
16	CLL	61	4	No	Yes	0.75	No	Yes	No
17	SLL/Richter's	70	6	Yes	No	8	No	No	No
18	CLL	58	7	Yes	No	26	Refractory	Yes	No
19	CLL	50	6	Yes	No	22	Refractory	Yes	Yes
20	CLL	64	5	Yes	No	19	No	Yes	No
21	CLL/IPCs	53	5	Yes	No	39	No	Yes	No
22	CLL	62	7	Yes	No	9	Refractory	Yes	No
23	CLL	66	4	Yes	No	26	No	Yes	No
24	CLL	58	7	Yes	No	19	Refractory	Yes	Yes

RT/PLL =6 (25%) **N=19 (79%)** **N=6 (25%)** **N=16 (66%)** **N=14 (58%)**





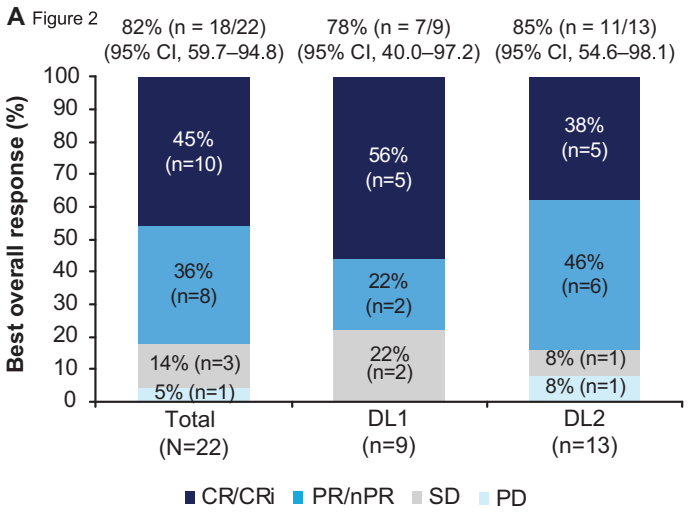
MOFFITT CANCER CENTER

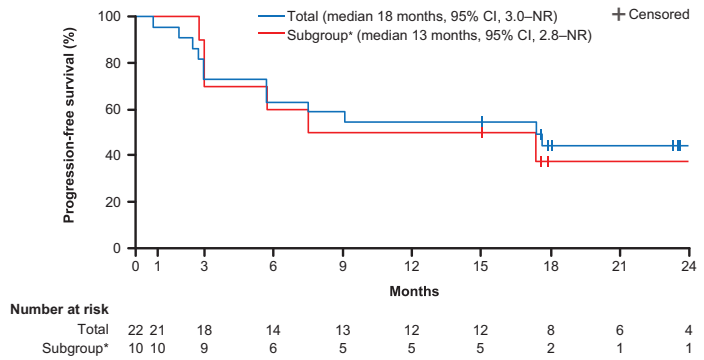
Turtle C et al. J Clin Oncol 35:3010-3020.

Phase 1 TRANSCEND CLL 004 study of lisocabtagene maraleucel in pts with R/R CLL/SLL

Characteristic	All patients (n = 23)
Age, y	66 (50-80)
High-risk features, any	19 (83)
del17p	8 (35)
mutated TP53	14 (61)
unmutated IGHV	8 (35)
complex karyotype	11 (48)
Lines of prior therapy	4 (2 – 11)
prior CIT	20 (87)
prior ibrutinib	23 (100)
prior venetoclax	15 (65)

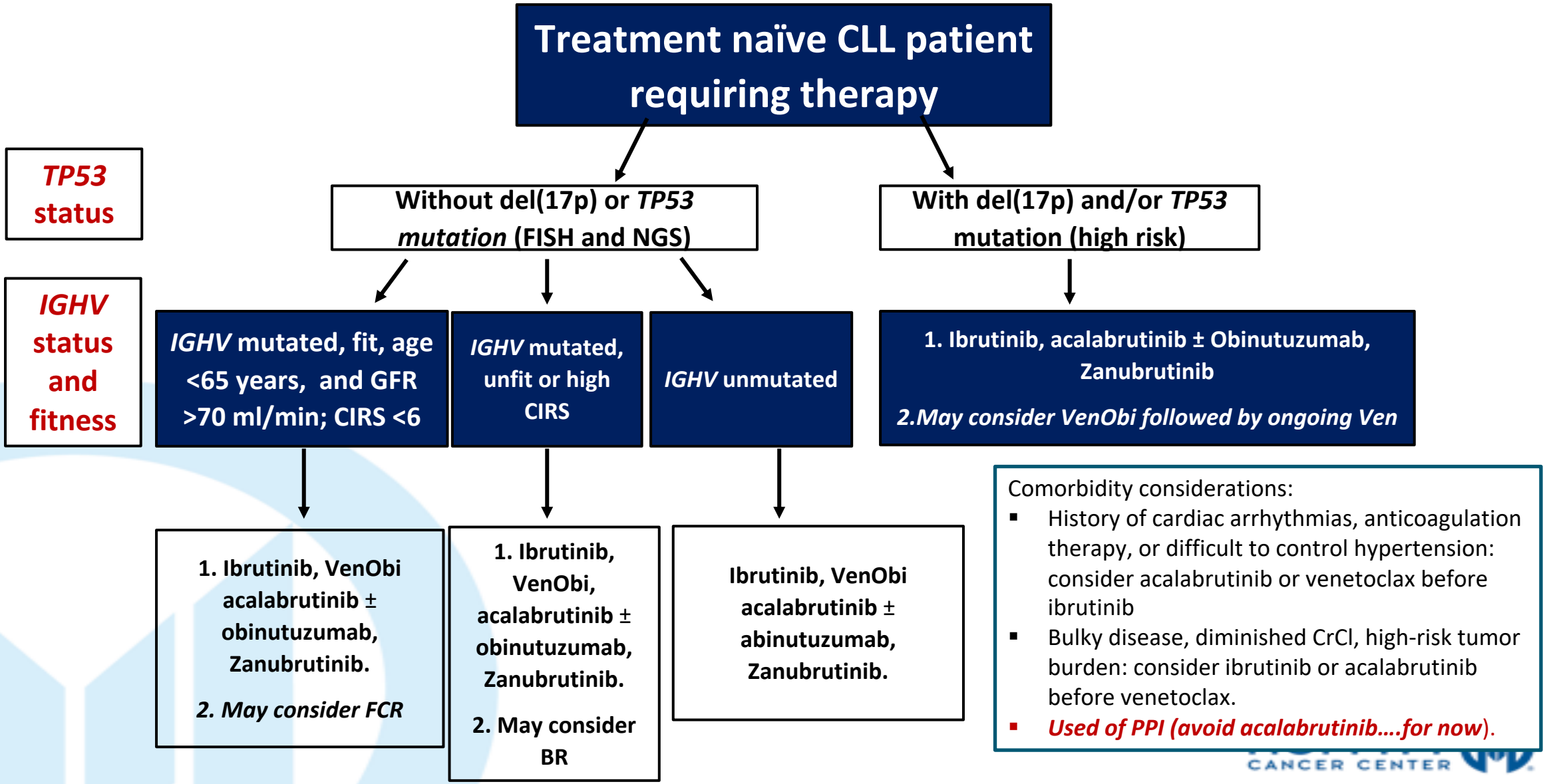
	All patients (N = 23)	Dose level 1 (n = 9)	Dose level 2 (n = 14)
Patients with CRS			
Any grade	17 (74)	7 (78)	10 (71)
Grade 1	7 (30)	3 (33)	4 (29)
Grade 2	8 (35)	4 (44)	4 (29)
Grade 3	2 (9)	0	2 (14)
Grade 4	0	0	0
Grade 5	0	0	0
Time to CRS onset, days	3 (1–10)	7 (1–10)	2 (1–10)
Time to CRS resolution, days	12 (2–50)	6 (2–30)	12.5 (2–50)
Patients with NEs*			
Any grade	9 (39)	2 (22)	7 (50)
Grade 1	0	0	0
Grade 2	4 (17)	0	4 (29)
Grade 3†	4 (17)	2 (22)	2 (14)
Grade 4†	1 (4)	0	1 (7)
Grade 5	0	0	0
Tocilizumab and/or corticosteroid use			
Tocilizumab only	6 (26)	3 (33)	3 (21)
Corticosteroids only	1 (4)	0	1 (7)
Both tocilizumab and corticosteroids	8 (35)	2 (22)	6 (43)
Tocilizumab and/or corticosteroids	15 (65)	5 (56)	10 (71)





MOFFITT CANCER CENTER

Siddiqi T et al. Blood 2021; blood.2021011895 [Online ahead of print].


Treatment naïve CLL patient requiring therapy
TP53 status
Without del(17p) or TP53 mutation (FISH and NGS)
With del(17p) and/or TP53 mutation (high risk)
IGHV status and fitness
IGHV mutated, fit, age <65 years, and GFR >70 ml/min; CIRS <6
IGHV mutated, unfit or high CIRS
IGHV unmutated
1. Ibrutinib, acalabrutinib ± Obinutuzumab, Zanubrutinib
2.May consider VenObi followed by ongoing Ven
1. Ibrutinib, VenObi acalabrutinib ± obinutuzumab, Zanubrutinib.
2. May consider FCR
1. Ibrutinib, VenObi, acalabrutinib ± obinutuzumab, Zanubrutinib.
2. May consider BR
Ibrutinib, VenObi acalabrutinib ± abinutuzumab, Zanubrutinib.
Comorbidity considerations:
History of cardiac arrhythmias, anticoagulation therapy, or difficult to control hypertension: consider acalabrutinib or venetoclax before ibrutinib
Bulky disease, diminished CrCl, high-risk tumor burden: consider ibrutinib or acalabrutinib before venetoclax.
Used of PPI (avoid acalabrutinib….for now).

Treatment of R/R CLL patient *requiring* therapy

Patient's factors:

- Co-morbidities,
- Medications (e.g., anticoagulants, anti-arrhytmics, PPIs, etc),
- Tx preferences.

Disease factors:

- Cytogenetics (Karyotype/FISH)
- Molecular (NGS)
  - ✓ Resistance mutations (BTKi vs. Ven)

Frontline therapy:

- BTKi (intolerance vs. progression)
- BCL2i (intolerance vs. progression)
- CIT
- Duration of response

BTKi +/- Anti-CD20 Mab

Progression on BTKi

1. Ven+Rituximab.
2. Venetoclax monoTx

Consider Clinical trial.

1.Consider clinical trial
2. PI3K inh +/- Anti-CD20 Mab
3. CAR-T Vs. AlloHCT

Intolerance to BTKi

1. Different covalent BTKi
2. Non-covalent BTKi if known mut.

Consider Clinical trial.

1. Ven+Rituximab.
2. Venetoclax monoTx

Consider Clinical trial.

1. Ven+Rituximab.
2. Venetoclax monoTx

Consider Clinical trial.

1. Different covalent BTKi
2. Non-covalent BTKi if known mut.

Consider Clinical trial.

1.Consider clinical trial
2. PI3K inh +/- Anti-CD20 Mab
3. CAR-T Vs. AlloHCT

Ven+Obi

Intolerance

BTKi

Consider Ven-based re-treatment
- Consider Clinical trial.

Progression s/p Tx

- Ven-based Tx.
- Consider Clinical trial.

BTKi

Progression on Tx

BTKi

- Ven-based Tx.
- Consider Clinical trial.

1.Consider clinical trial
2. PI3K inh +/- Anti-CD20 Mab
3. CAR-T Vs. AlloHCT

Thank you very much to:

- All the patients and caregivers.
- All our RN, ARNPs, PharmD and others.
- All my mentors.

MOFFITT | Memorial Healthcare System
Malignant Hematology & Cellular Therapy

Email: jose.sandoval@moffiitt.org; **jsandovalsus@mhs.net**

MOFFITT CANCER CENTER