CLL and CML (a lot on the first and not much on the second)

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MOFFITT CANCER CENTER

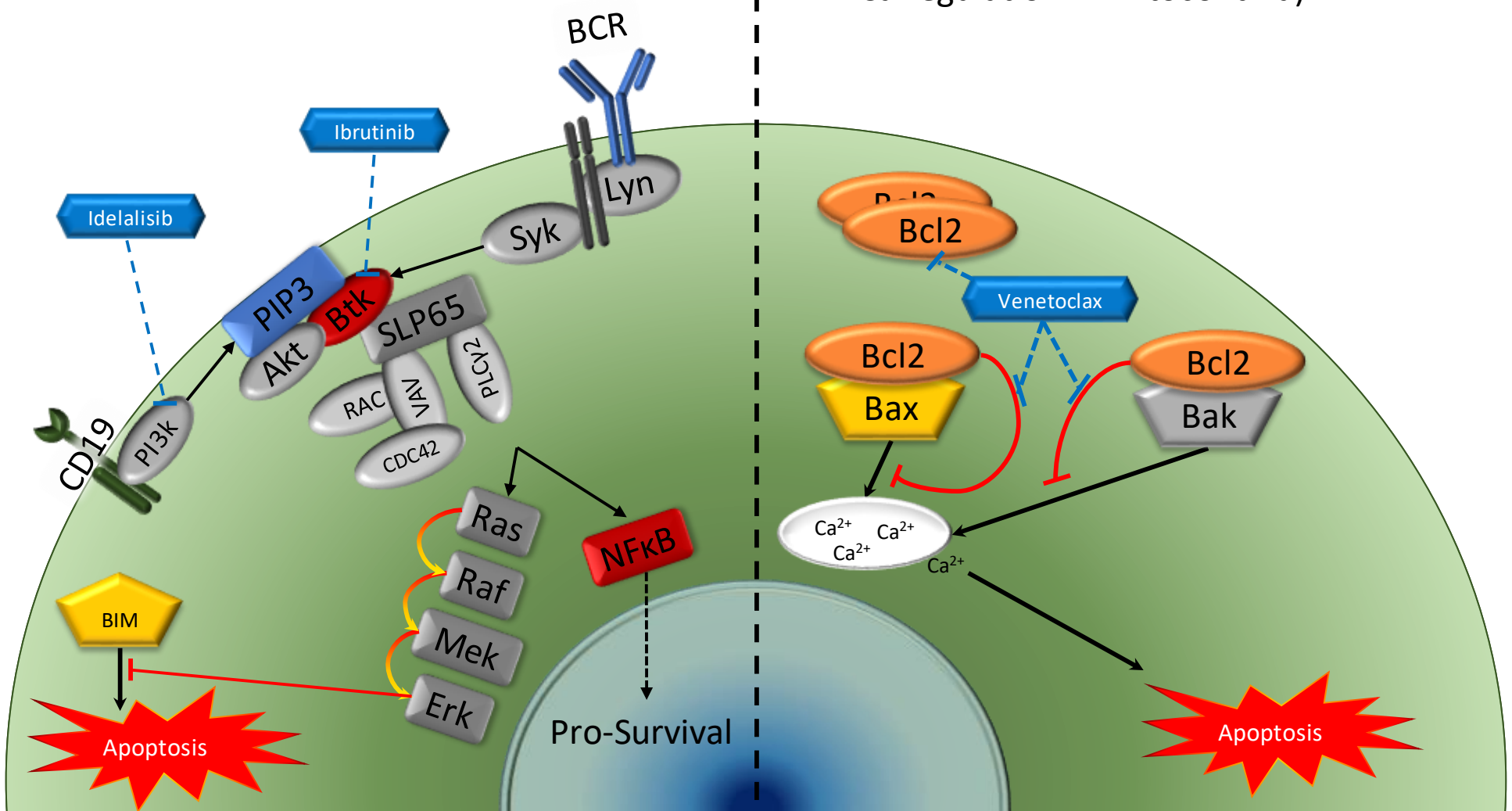
COI

- Janssen/Pharmacyclics: Consulting and speaker bureau.
- Abbvie: Consulting and speaker bureau
- TG Therapeutics: Research funding and consulting.
- Gilead: Speaker bureau
- TEVA: Consulting

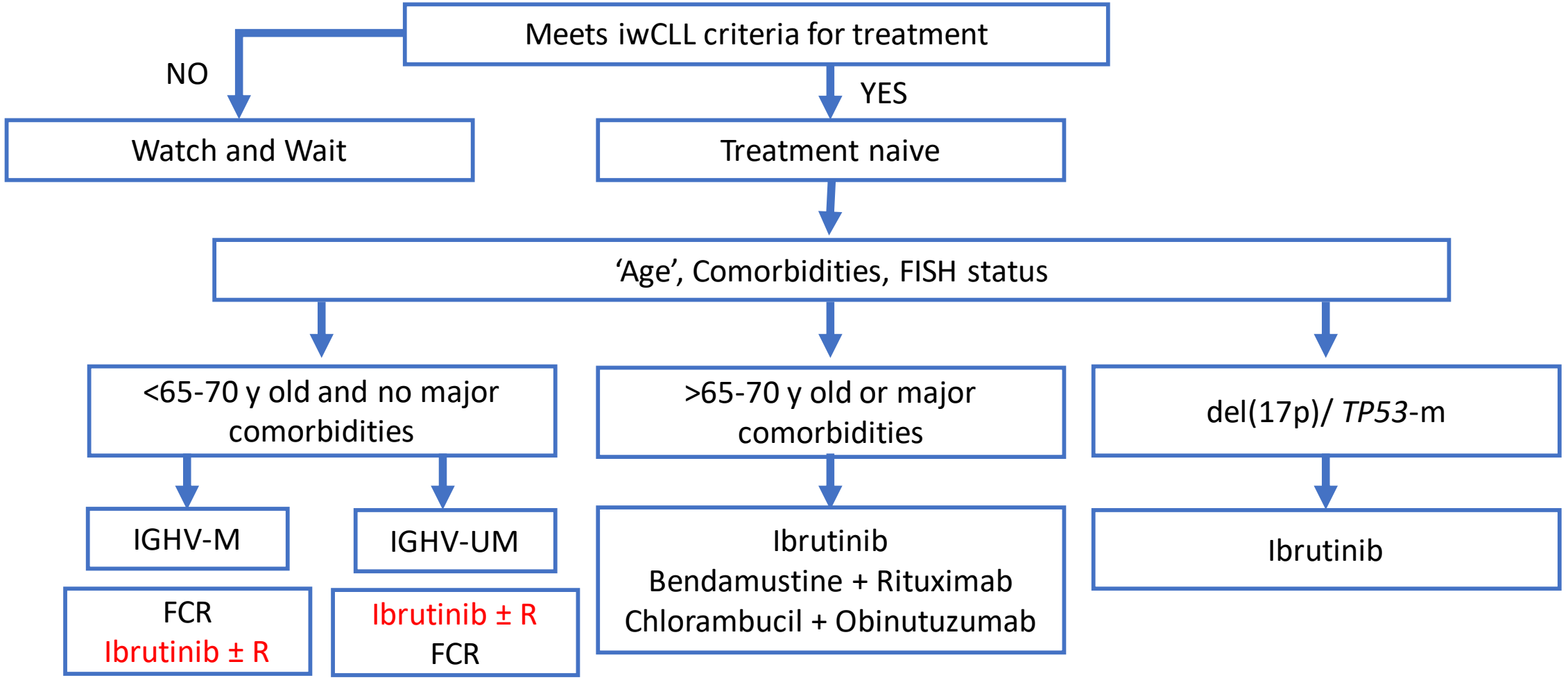
CLL Mechanisms of Survival

Chronic BCR Signaling leads to multiple pathways of survival (anti-apoptotic and pro-survival)

Rampant overexpression of BCL2 leads to dysregulation of pro-apoptotic signal from BAX or BAK via direct binding (alters Ca regulation in Mitocondria)



CLL Front Line Treatment Algorithm before ASH 2018



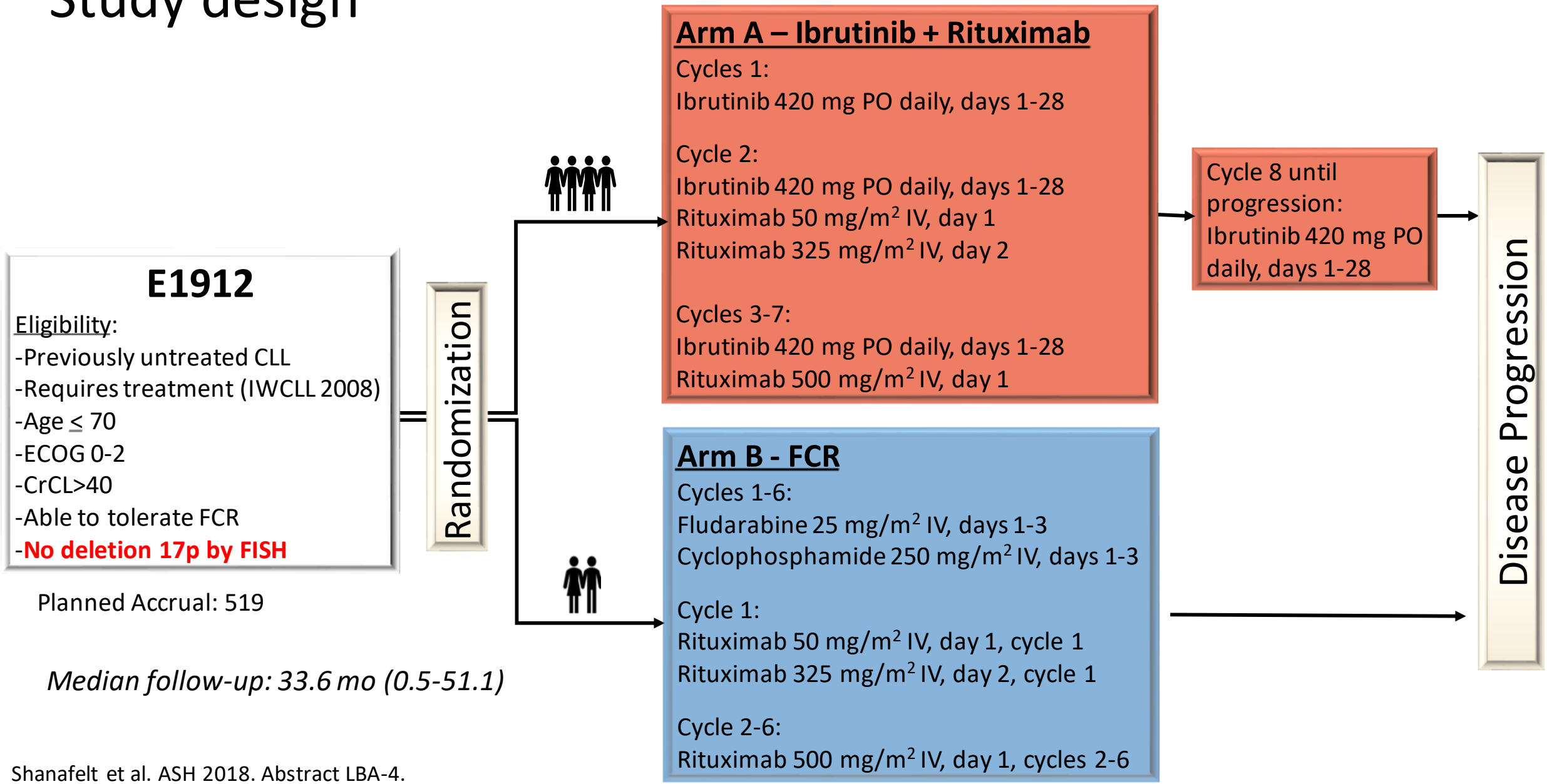
Key questions at ASH 2018

- Is ibrutinib better than standard CIT in front line CLL?
- Does anti-CD20 add any benefit to ibrutinib on front line therapy?
- Is IgHV mutational status a valid marker for therapy stratification?
- Does FCR still have a role in young IgHV mutated patients?
- Will Ibrutinib combinations allow time limited therapy in front line?

Ibrutinib & Rituximab Improves Progression Free and Overall Survival Relative to FCR in Younger Patients with Previously Untreated Chronic Lymphocytic Leukemia (CLL)

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

Study design

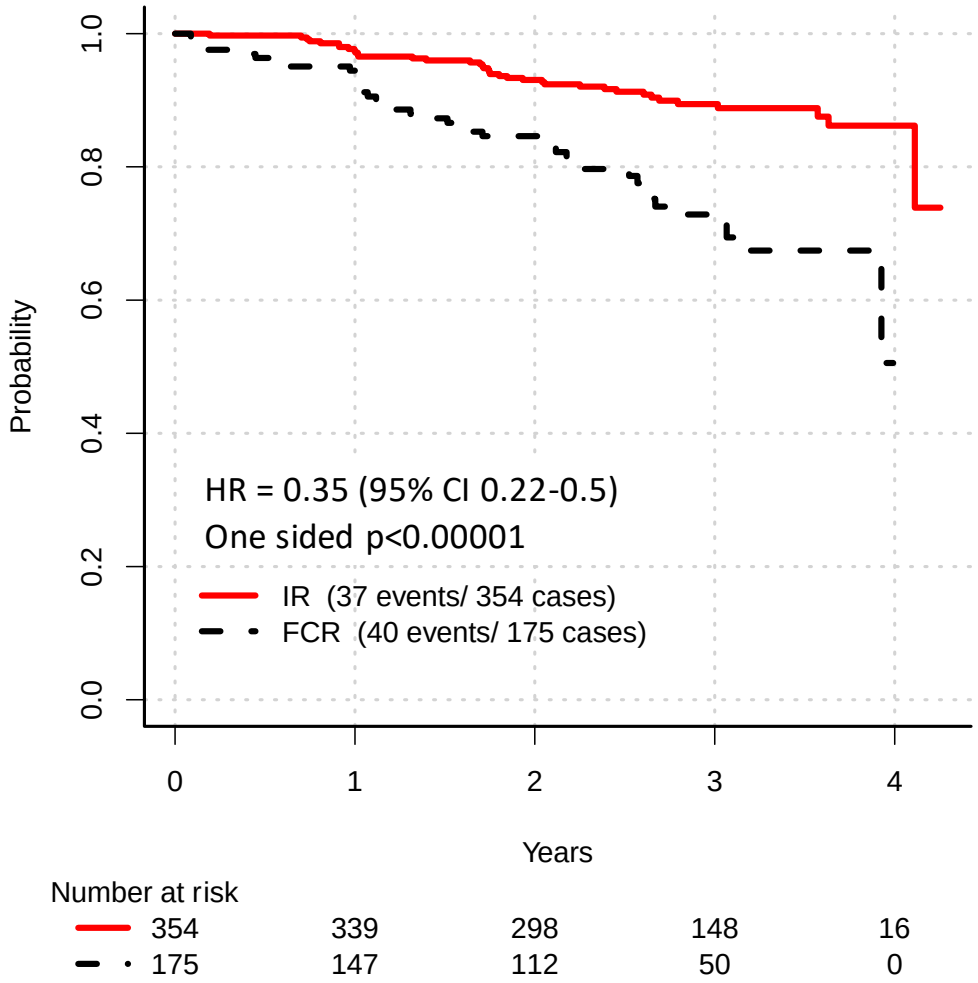


Median follow-up: 33.6 mo (0.5-51.1)

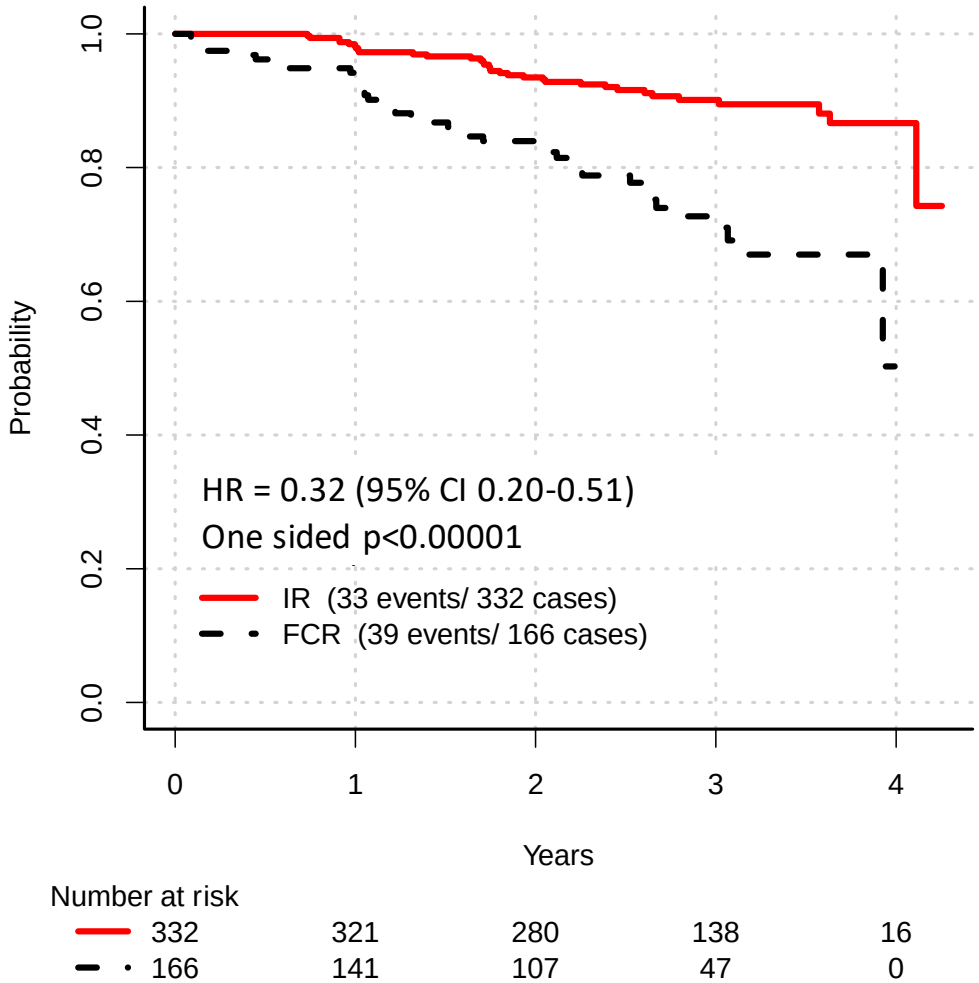
Shanafelt et al. ASH 2018. Abstract LBA-4.

Progression Free Survival

Intent to Treat



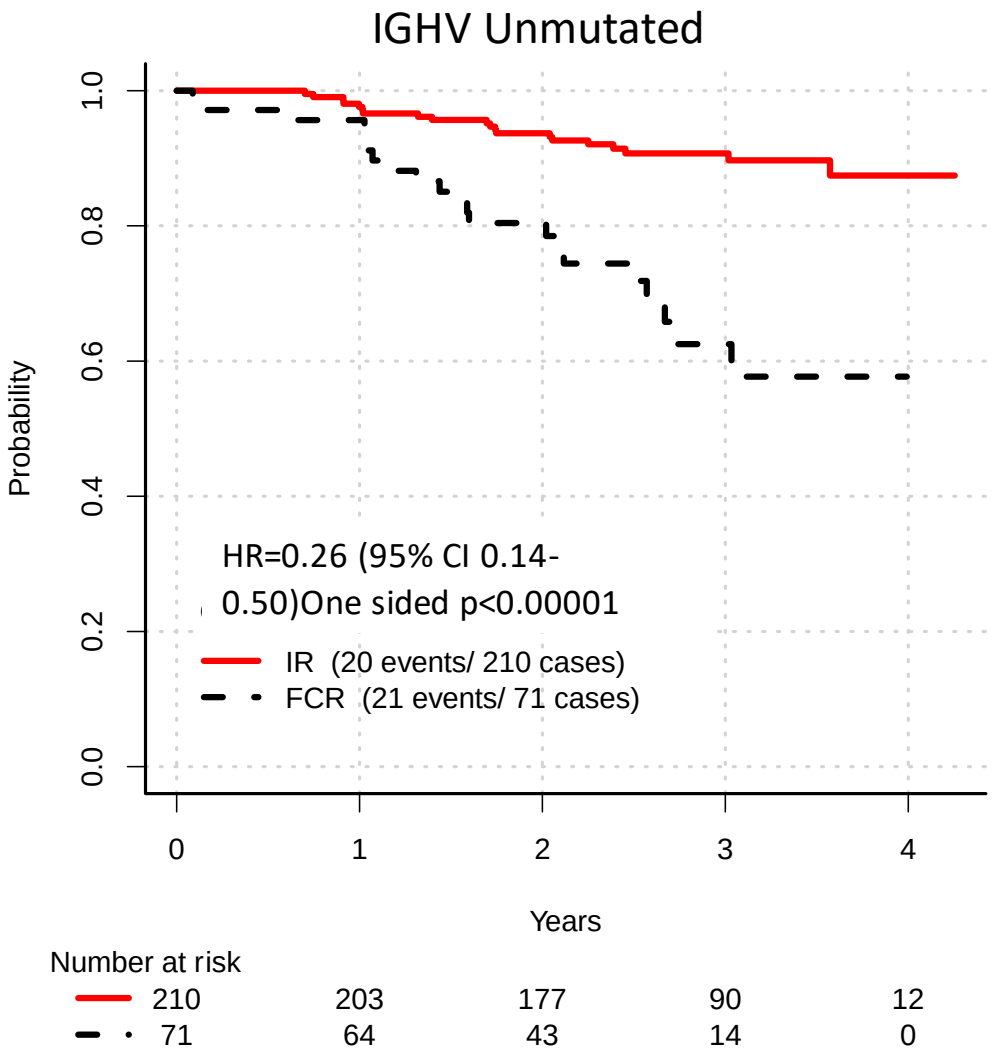
Eligible

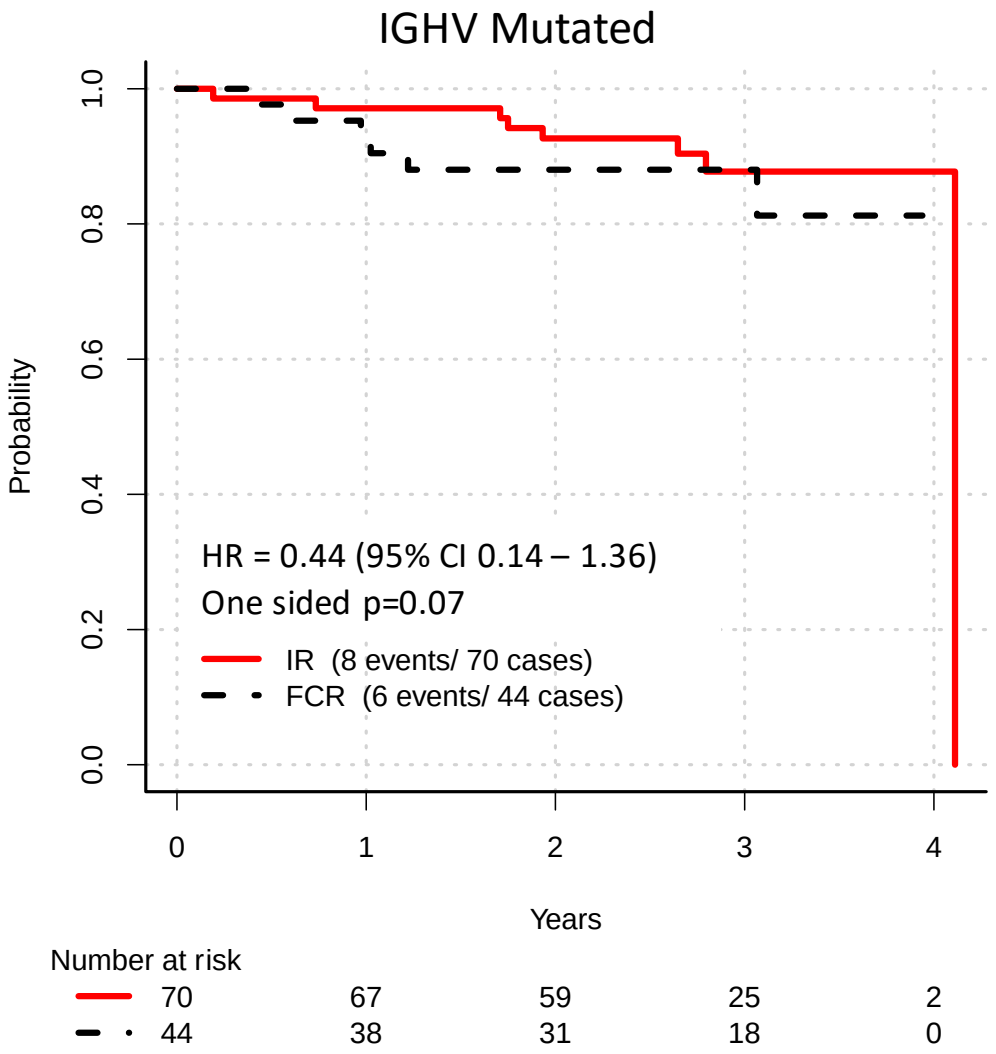


ECOG-ACRIN cancer research group | Reshaping the future of patient care

Shanafelt et al. ASH 2018. Abstract LBA-4. NCT02048813.

Progression Free Survival: IGHV Status





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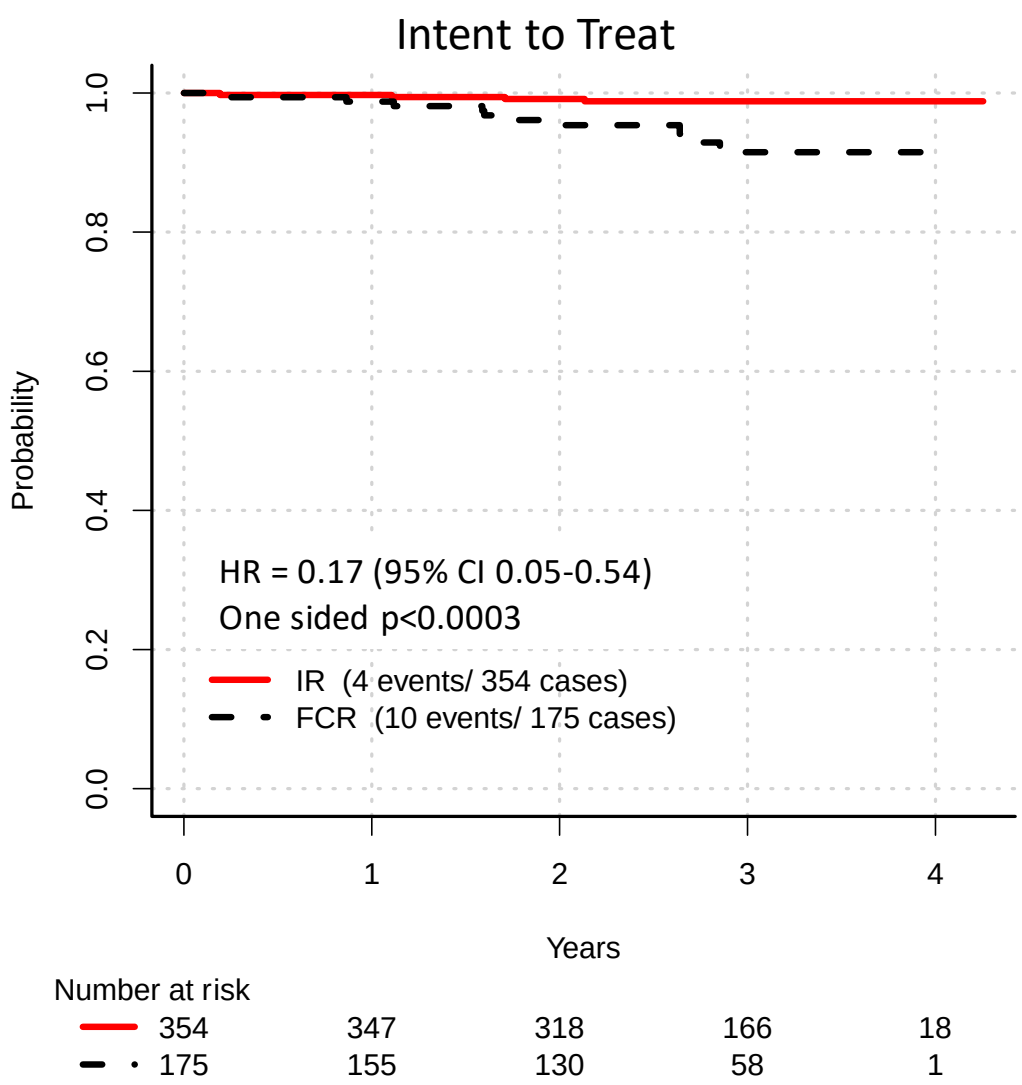
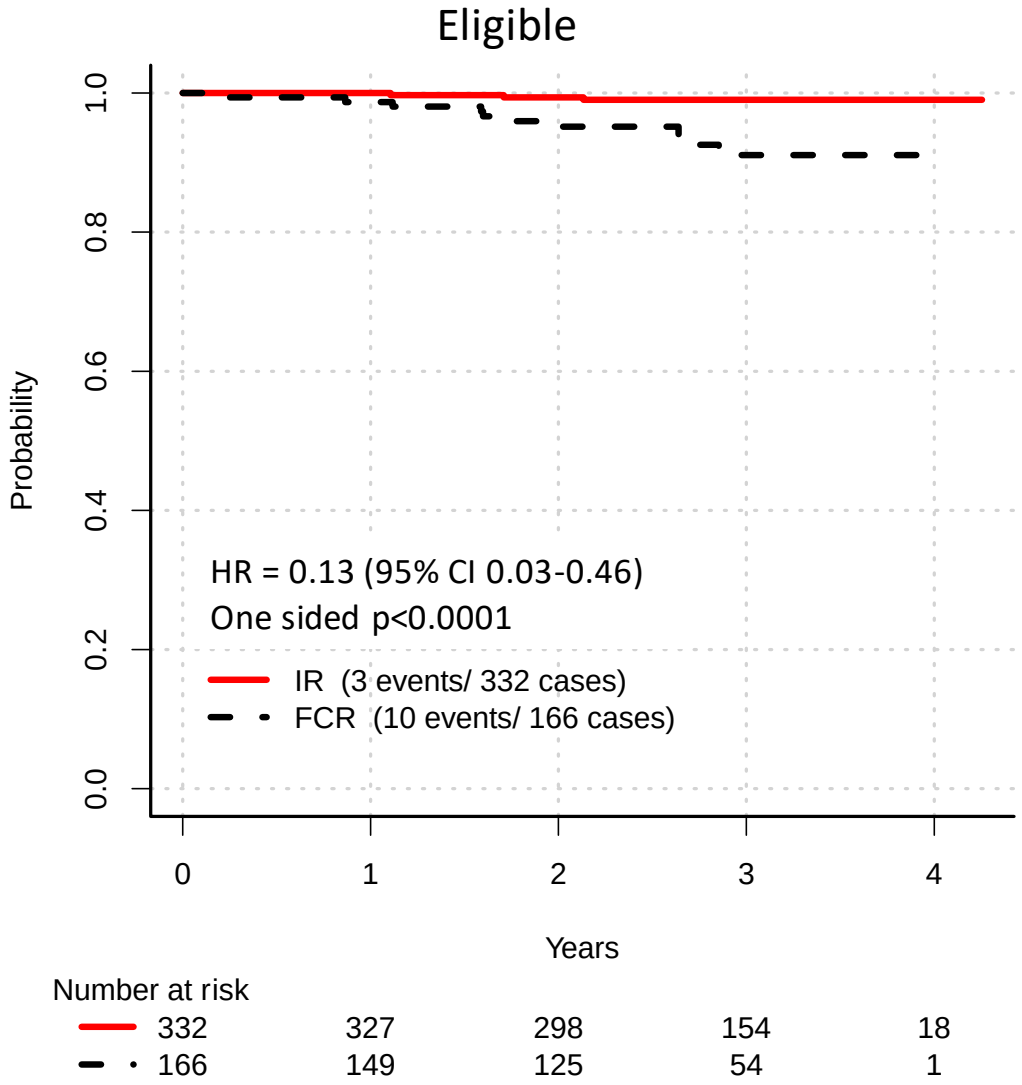
Shanafelt et al. ASH 2018. Abstract LBA-4. NCT02048813.

Overall Survival





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

Shanafelt et al. ASH 2018. Abstract LBA-4. NCT02048813.

Phase 3 Study of IR vs FCR in TN CLL (ECOG-ACRIN E1912)

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
Anemia %	2.6	12.0	<0.001
Thrombocytopenia %	2.9	13.9	<0.001
Any infection, %	7.1	19.0	< 0.001
Atrial fibrillation %	2.9	0.0	0.04
Bleeding %	1.1%	0.0	0.32
Hypertension %	7.4	1.9	0.01
Diarrhea %	2.6	0.6	0.19

Summary

- Superior PFS and OS and improved toxicity for IR over FCR in TN CLL patients age ≤ 70

Shanafelt et al. ASH 2018. Abstract LBA-4.

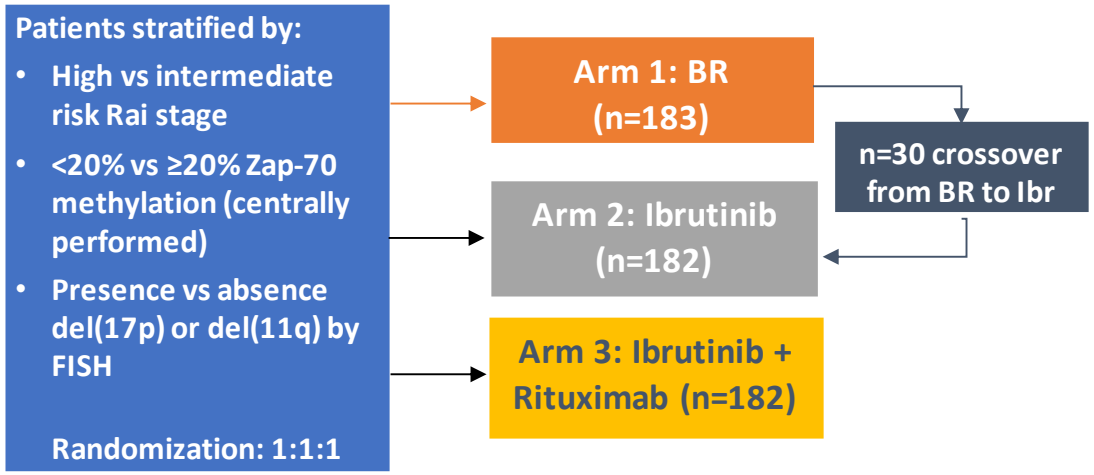
Ibrutinib alone or in combination with rituximab produces superior progression free survival (PFS) compared with bendamustine plus rituximab in untreated older patients with chronic lymphocytic leukemia (CLL): Results of Alliance North American Intergroup Study A041202

Jennifer A. Woyach, Amy S. Ruppert, Nyla Heerema, Weiqiang Zhao, Allison M Booth, Wei Ding, Nancy L. Bartlett, Danielle M Brander, Paul M Barr, Kerry A Rogers, Sameer Parikh, Steven Coutre, Arti Hurria, Gerard Lozanski, Sreenivasa Nattam, Richard A. Larson, Harry Erba, Mark Litzow, Carolyn Owen, James Atkins, Jeremy Abramson, Rich Little, Scott E. Smith, Richard M. Stone, Sumithra Mandrekar, John C. Byrd

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

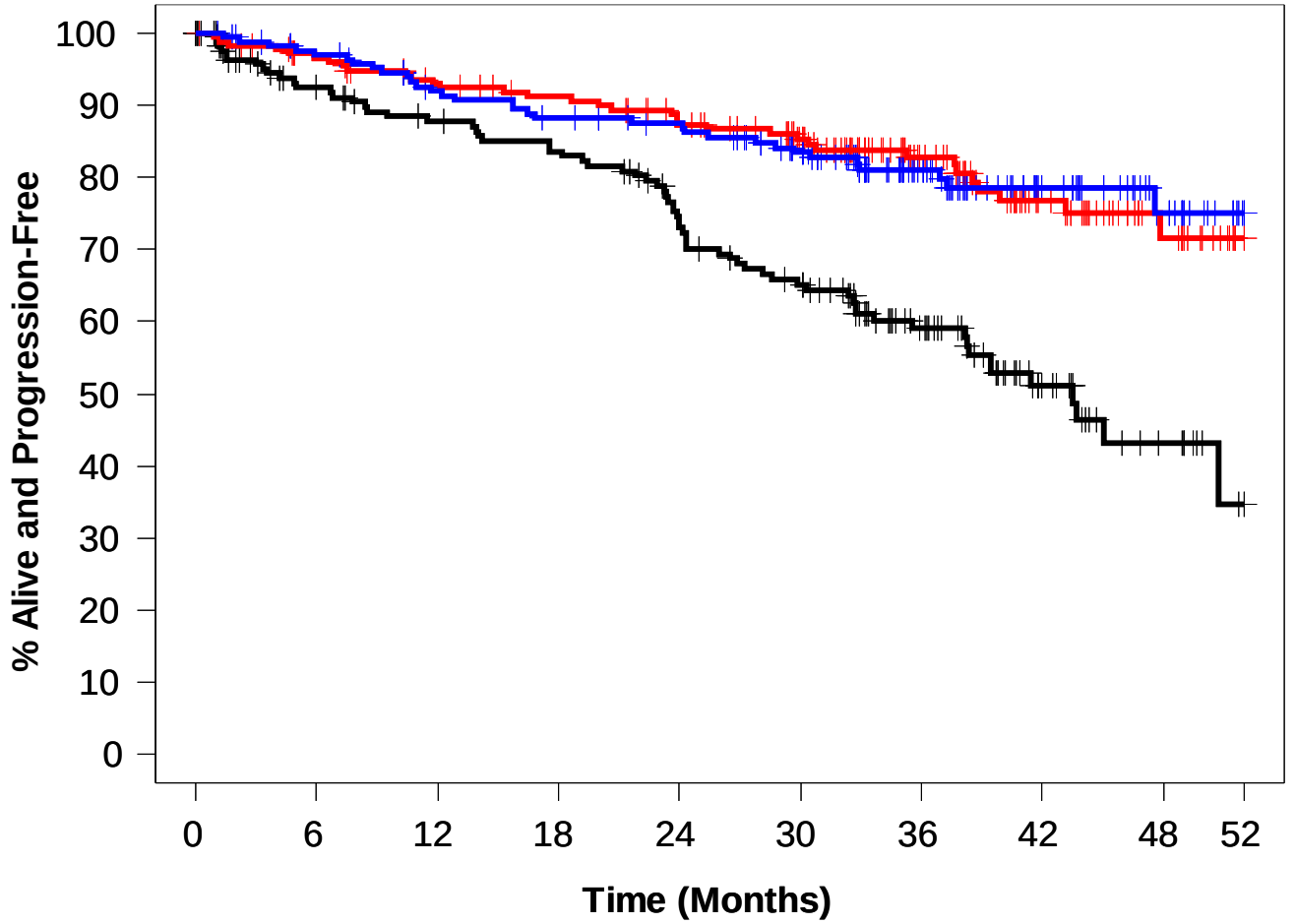


Primary endpoints: PFS
Secondary endpoints: OS, TTP, DOR. Proportion achieving MRD negativity, Biopsy proven CR, Toxicity

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%

Data cutoff: October 4, 2018.
Woyach (Coutre) et al. ASH 2018. Abstract 6.
https://clinicaltrials.gov/ct2/show/NCT01886872.

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



Pairwise comparisons

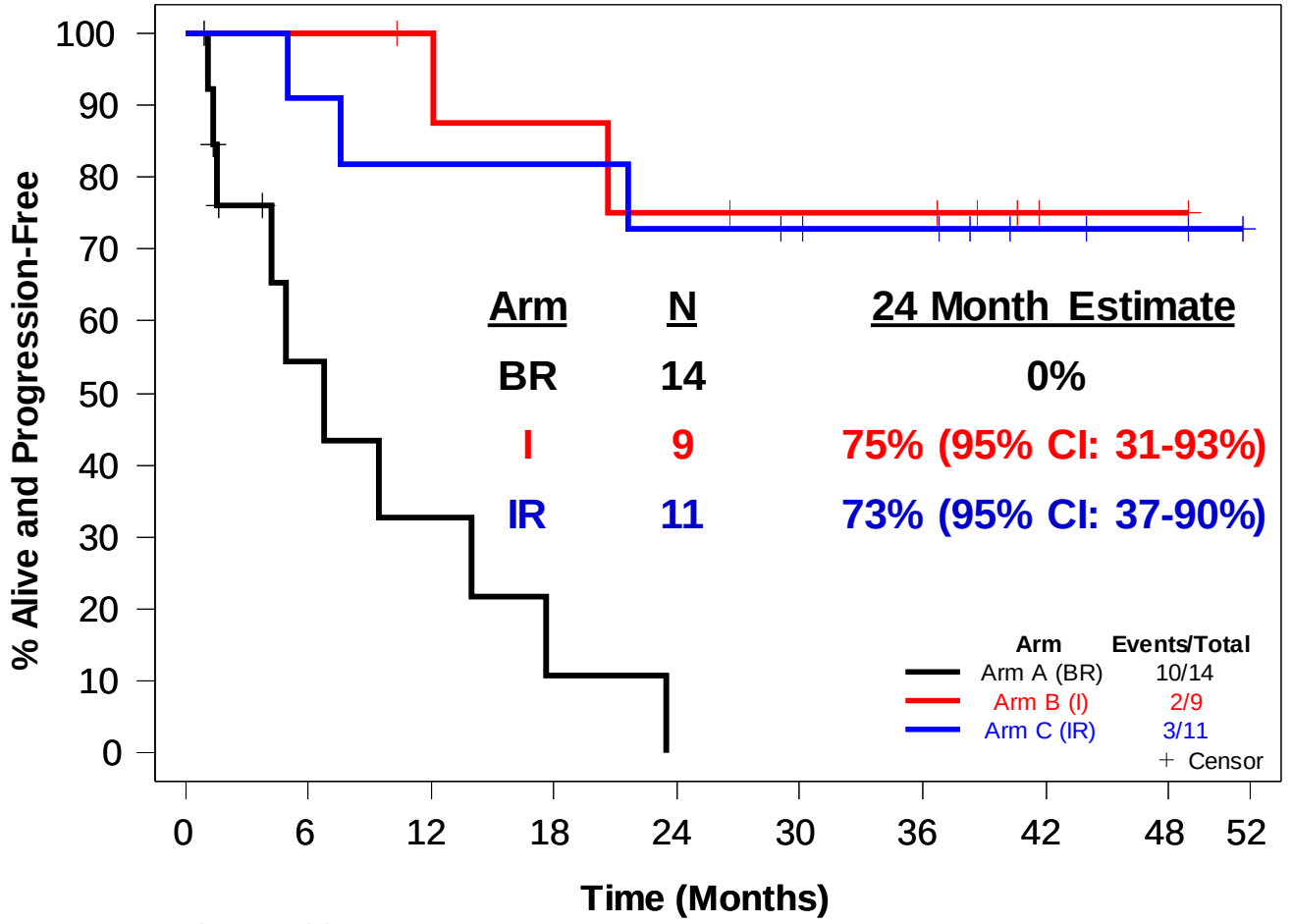
I vs BR
HR: 0.39 (95% CI: 0.26-0.58)
(1-sided p value <0.001)

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

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

Woyach et al., ASH 2018, abstract 6

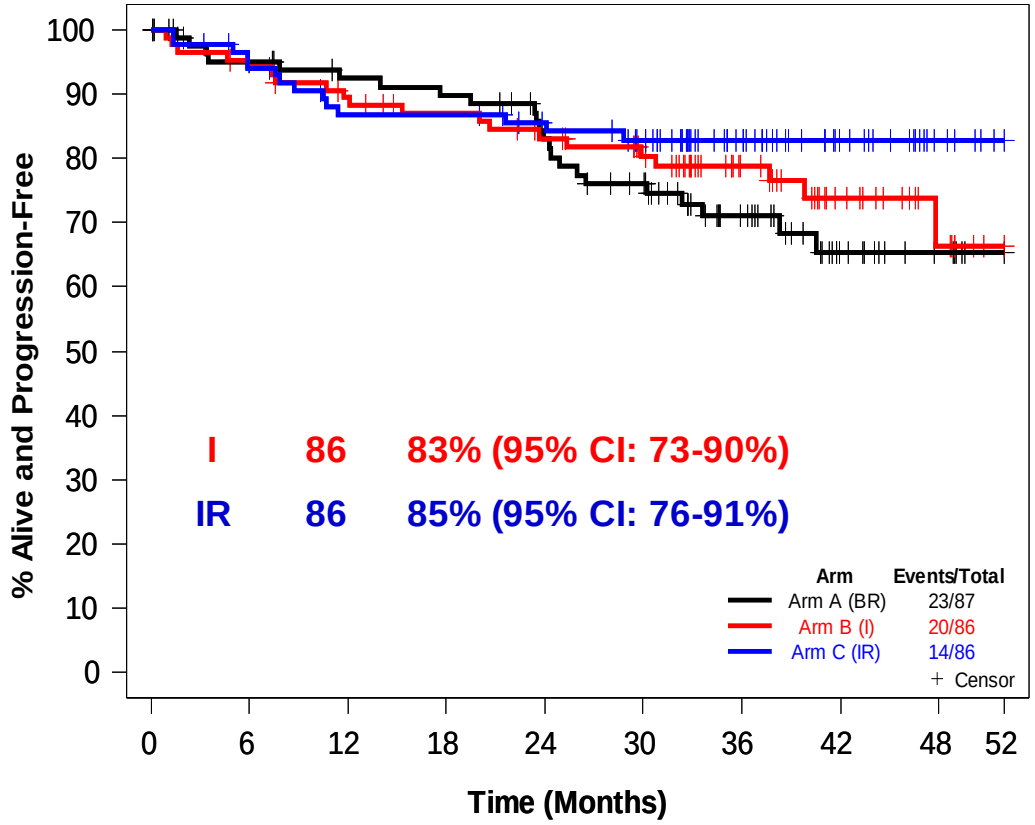
Del (17p13.1) Subgroup: Progression Free Survival Intention-to-Treat Patient Population



Patients-at-Risk										
Arm A (BR)	14	5	3	1	0					
Arm B (I)	9	9	8	7	6	5	5	1	1	0
Arm C (IR)	11	10	9	9	8	7	6	3	2	0

IGVH mutated & Zap-70 methylated Subgroups PFS Intention-to-Treat Patient Population

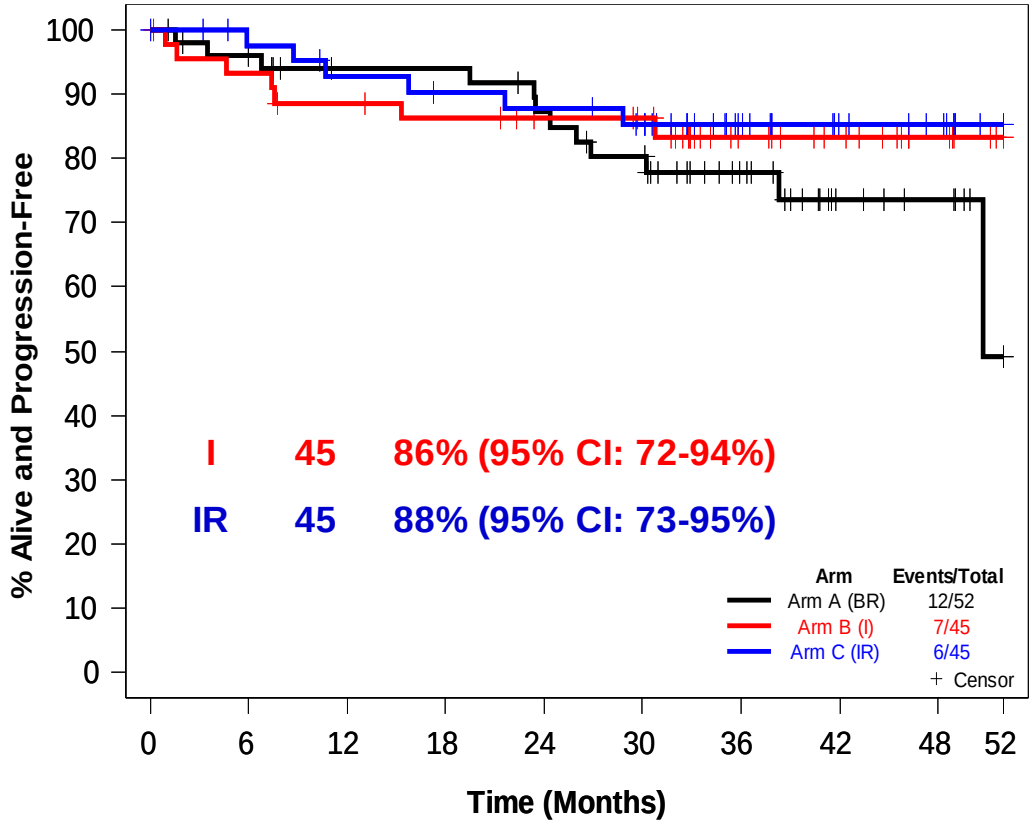
Zap-70 Methylated



Patients-at-Risk

Arm A (BR)	87	75	70	68	60	52	33	15	7	0
Arm B (I)	86	80	74	69	64	56	35	20	9	0
Arm C (IR)	86	79	70	70	65	59	37	18	6	0

IGVH Mutated

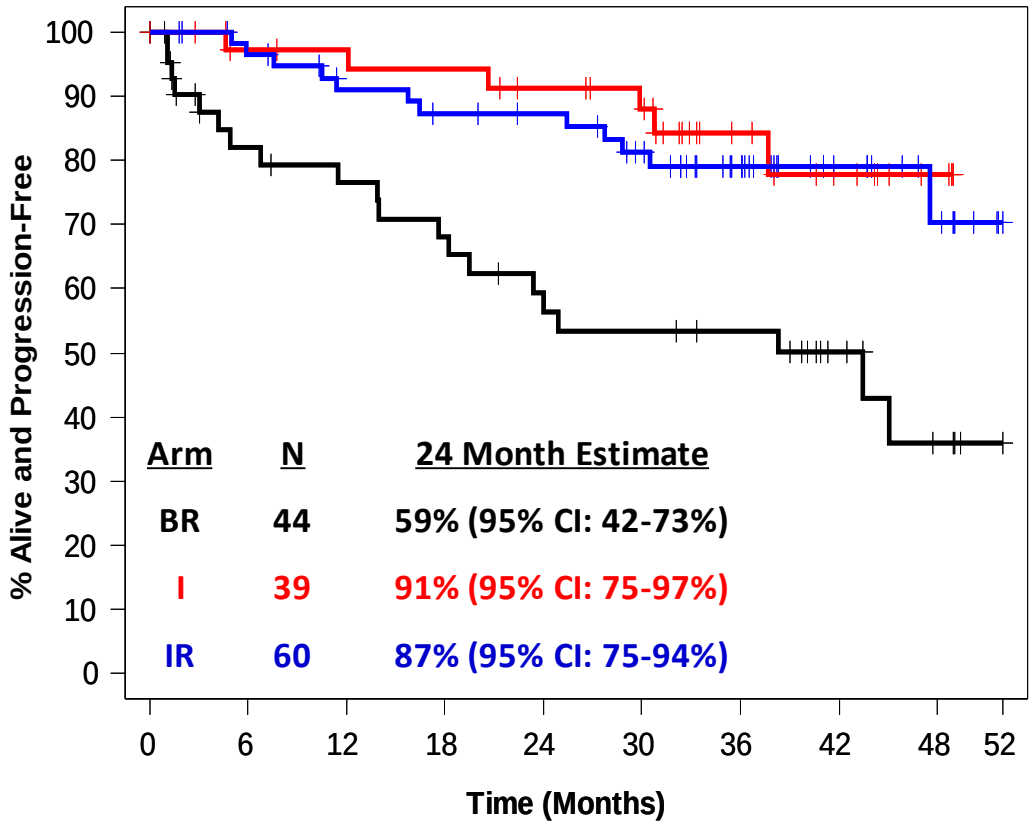


Patients-at-Risk

Arm A (BR)	52	47	42	42	38	34	22	10	7	0
Arm B (I)	45	41	38	36	33	31	18	13	6	0
Arm C (IR)	45	41	38	36	35	32	18	10	7	0

Complex Karyotype Subgroups: Progression Free Survival Intention-to-Treat Patient Population

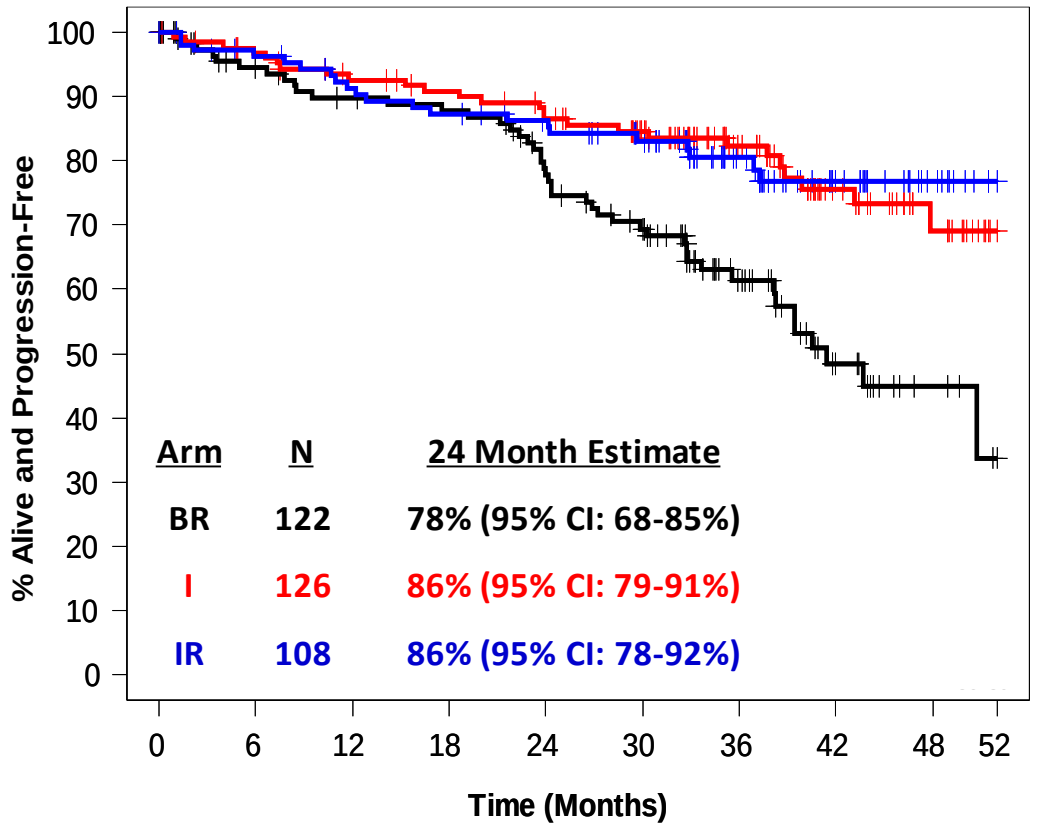
Complex Karyotype



Patients-at-Risk

Arm A (BR)	44	30	27	24	20	18	16	9	4	0
Arm B (I)	39	34	33	32	29	26	14	9	4	0
Arm C (IR)	60	55	49	46	44	38	27	14	8	0

Not Complex Karyotype



Patients-at-Risk

Arm A (BR)	122	100	93	90	76	64	37	16	6	0
Arm B (I)	126	118	109	104	97	85	58	33	17	0
Arm C (IR)	108	100	92	88	83	74	46	24	10	0

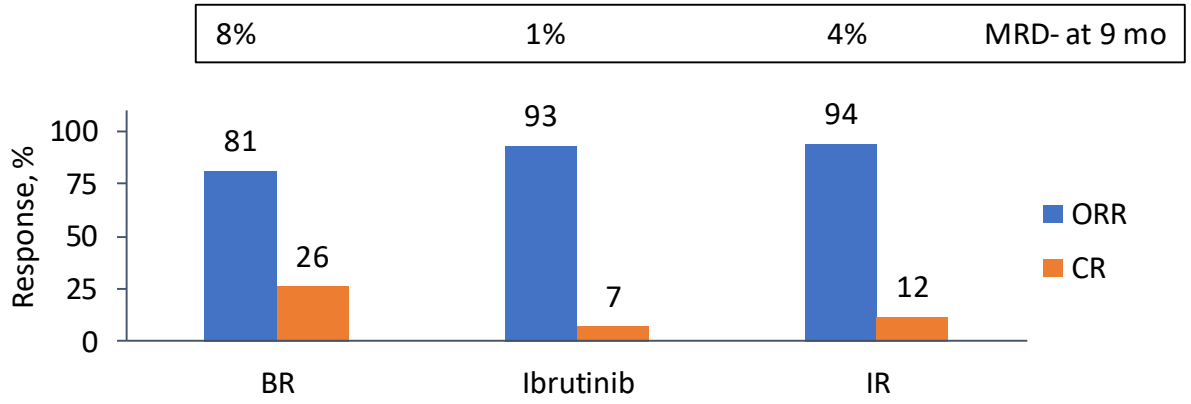
Phase 3 Study of Ibrutinib ± Rituximab vs BR in TN CLL (ALLIANCE A041202)

Median follow-up: 38 months

Outcomes	BR	Ibr	Ibr + R
2-y PFS, % (95% CI)	**74 (66-80)** (n=176)	**87 (81-92)** (n=178)	**88 (81-92)** (n=170)
For del(17p)	0 (n=14)	75 (31-93) (n=9)	73 (37-90) (n=11)
For complex karyotype	59 (42-73) (n=44)	91 (75-97) (n=39)	87 (75-94) (n=60)
ZAP-70 methylated	83 (72-90) (n=87)	83 (73-90) (n=86)	85 (76-91) (n=86)
IGVH mutated (unmutated not shown)	87 (74-94) (n=52)	86 (72-94) (n=45)	88 (73-95) (n=45)
2-y OS, % (95% CI)	**95 (91-98)** (n=183)	**90 (85-94)** (n=183)	**94 (89-97)** (n=182)

Pairwise comparisons for PFS: HR (95% CI); *P* value

- Ibrutinib vs BR 0.39 (0.26-0.58); *P*<0.001
- IR vs BR 0.38 (0.25-0.59); *P*<0.001
- IR vs Ibrutinib 1.00 (0.62-1.62); *P*=0.49



Grade ≥ 3 AEs	BR (n=176)	Ibr (n=180)	IR (n=181)	*P* Value
Hematologic, %	61	41	38	<0.001
Nohematologic AEs, %	63	74	74	0.04
Death during treatment + 30 d, n (%)	2 (1)	13 (7)	13 (7)	-
Deaths during treatment + 30 d, up to 6 cycles, n (%)	2 (1)	3 (2)	6 (3)	-

Summary

- **Ibrutinib ± rituximab significantly prolonged PFS and improved safety vs BR in older patients with CLL**
- **Rituxiab does not improve PFS over ibrutinib alone**
- **Ibrutinib use requires close monitoring of AEs in older patients**

Data cutoff: October 4, 2018. Woyach et al. ASH 2018. Abstract 6.

Ibrutinib + Obinutuzumab Versus Chlorambucil + Obinutuzumab as First-Line Treatment in Patients With Chronic Lymphocytic Leukemia or Small Lymphocytic Lymphoma (CLL/SLL): Results From Phase 3 iLLUMINATE

Carol Moreno, MD, PhD[1]; Richard Greil, MD[2]; Fatih Demirkan, MD[3]; Alessandra Tedeschi, MD[4]; Bertrand Anz, MD[5]; Loree Larratt, MD[6]; Martin Simkovic, MD, PhD[7]; Olga Samoilova, MD[8]; Jan Novak, MD, PhD[9]; Dina Ben-Yehuda, MD[10]; Vladimir Strugov, MD[11]; Devinder Gill, MD, MRCP, FRCPath[12]; John G. Gribben, MD, DSc, FRCP, FRCPath, FMedSci[13]; Emily Hsu, PhD[14]; Cathy Zhou, MS[14]; Fong Clow, ScD[14]; Danelle F. James, MD, MAS[14]; Lori Styles, MD[14]; Ian W. Flinn, MD, PhD[15]

Phase 3 iLLUMINATE Study of Ibrutinib-G vs Clb-G in Patients With TN CLL/SLL

Key eligibility criteria

- **Age ≥65 years of age or < 65 years old with ≥1 coexisting condition (CIRS score > 6, CrCl < 70 mL/min, and/or del(17p) or *TP53* mutation)**

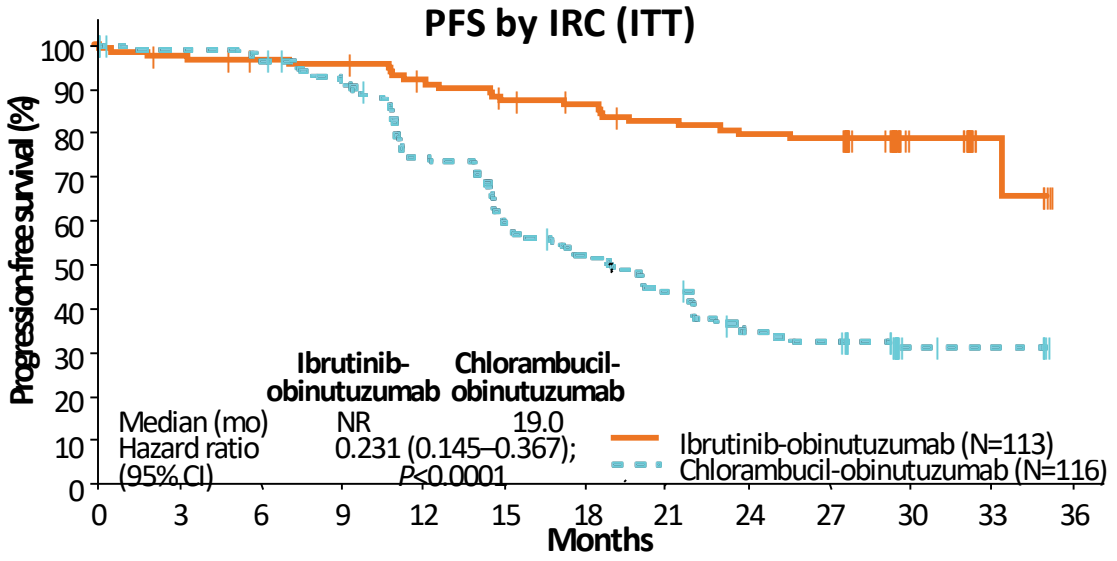
RANDOMIZED

Ibr-G (n = 113)
Ibr 420 mg/d continuously
G 1000 mg, d1/2 (split), 8, and 15 c1, then d1 (6 cycles)

Clb-G[a] (n = 116)
Clb 0.5 mg/kg, d1 and 15 (6 cycles)
G 1000 mg, days 1/2 (split), 8, and 15 c1, then d1 (6 cycles)

[a]Patients with PD on Clb-G could cross over Ibr monotherapy as next-line therapy (n=46).

Primary endpoints: PFS (IRC)
Secondary endpoints: PFS in high-risk patients, MRD, ORR, OS, safety, infusion-related reactions



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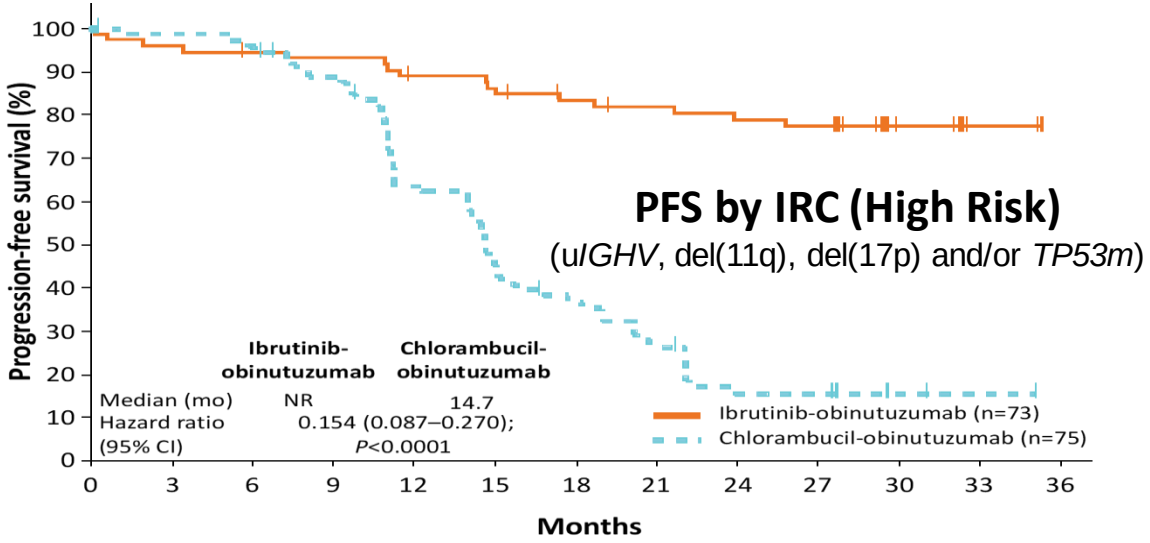

Moreno et al. ASH 2018. Abstract 691.

Phase 3 iLLUMINATE Study of Ibrutinib-G vs Clb-G in Patients With TN CLL/SLL

Outcomes, %	Ibr-G (n=113)	Clb-G (n=116)	HR (95% CI)	*P* value
Median IRC-assessed PFS, mo 30 mo PFS rate, %	NR 79	19.0 31	0.231 (0.145-0.367)	<0.0001
Median INV-assessed PFS, mo	NR	21.9	0.260 (0.163-0.415)	<0.0001
Median PFS in high-risk (del (17p)/*TP53* mutation, del (11q), and/or unmutated *IGHV)* , mo	NR	14.7	0.154 (0.087-0.27)	<0.0001
30-mo OS rate, %	86	85		
Response, %				
IRC (INV)-assessed ORR	88 (91)	73 (81)		
IRC (INV) CR/CRi	19 (41)	8 (16)		
Undetectable MRD in BM/PB ($<10^{-4}$)	35	25		

- In non-del(17p): 74% reduction in risk of PD or death with I+G
- In unmutated IGHV without del(17p): 85% improvement in PFS vs G-Clb
- 40% of Clb-G pts received single-agent Ibr as second-line therapy

AEs Overall	Ibr-G (n=113)	Clb-G (n=116)
Median duration of treatment, months (range)	29.3 (0.10–36.6)	5.1 (0.03–6.7)
Most common grade ≥3 AEs		
Any	77 %	72 %
Neutropenia	36 %	46 %
Thrombocytopenia	19 %	10 %
Pneumonia	7 %	4 %
Atrial fibrillation	5 %	0 %
Febrile neutropenia	4 %	6 %
Anemia	4 %	8 %
Hypertension	4 %	3 %
Neutrophils decreased	4 %	0 %
Infusion-related reaction	2 %	8 %

Summary

- **Ibr-G demonstrated improved PFS vs Clb-G irrespective of high-risk genomic features**
- **ORR, CR, and undetectable MRD were also higher with Ibr-G vs G-Clb**
- **Ibr-G demonstrated tolerability with no new safety signals, and represents effective chemotherapy-free regimen for firstline CLL/SLL**

Moreno et al. ASH 2018. Abstract 691.