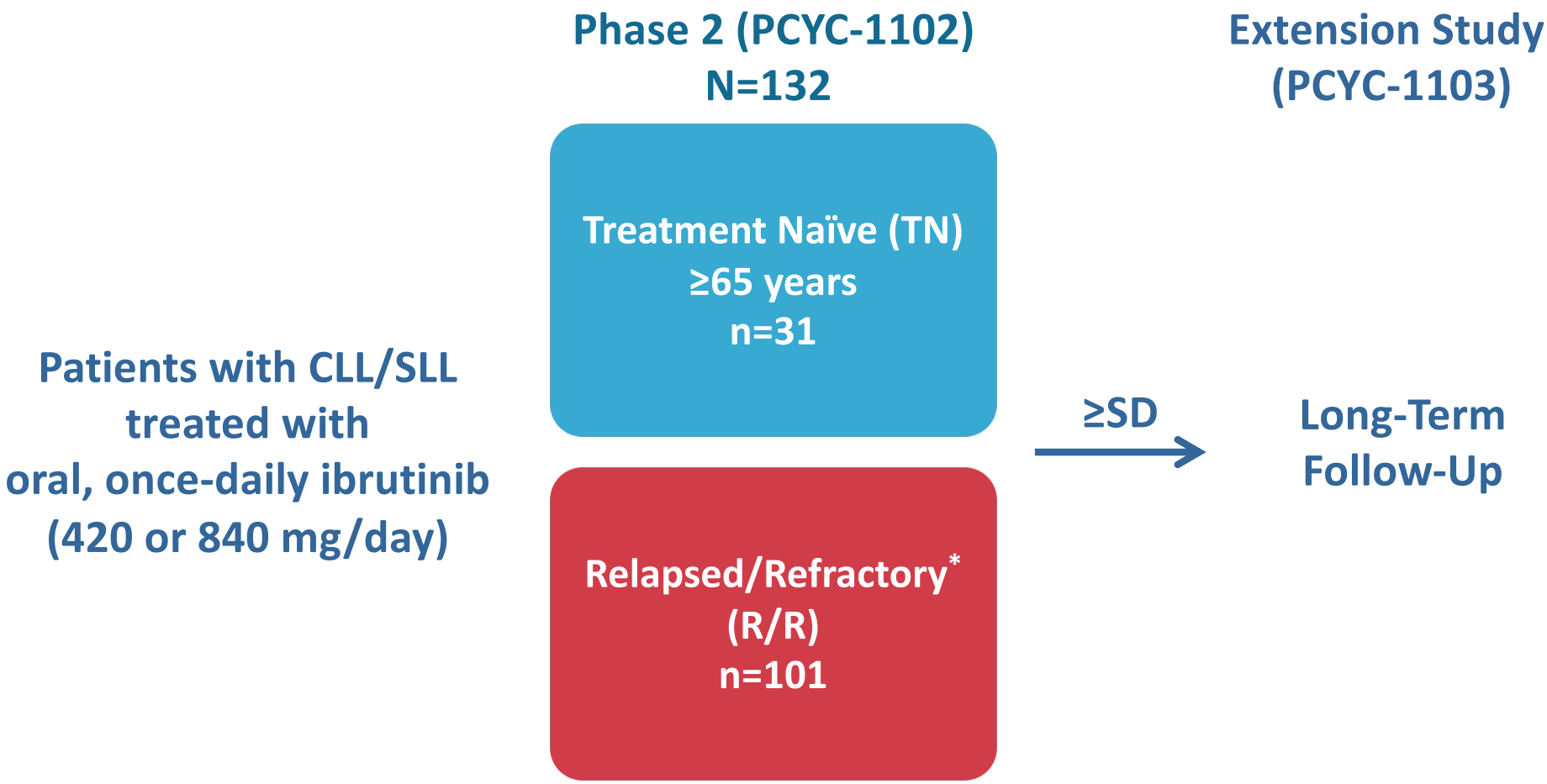
Ibrutinib

Monday November 4, 2019
14:30 – 14:50
Royal Hotel Carlton Bologna

Jan A. Burger
MD Anderson Cancer Center
Houston, Texas, USA

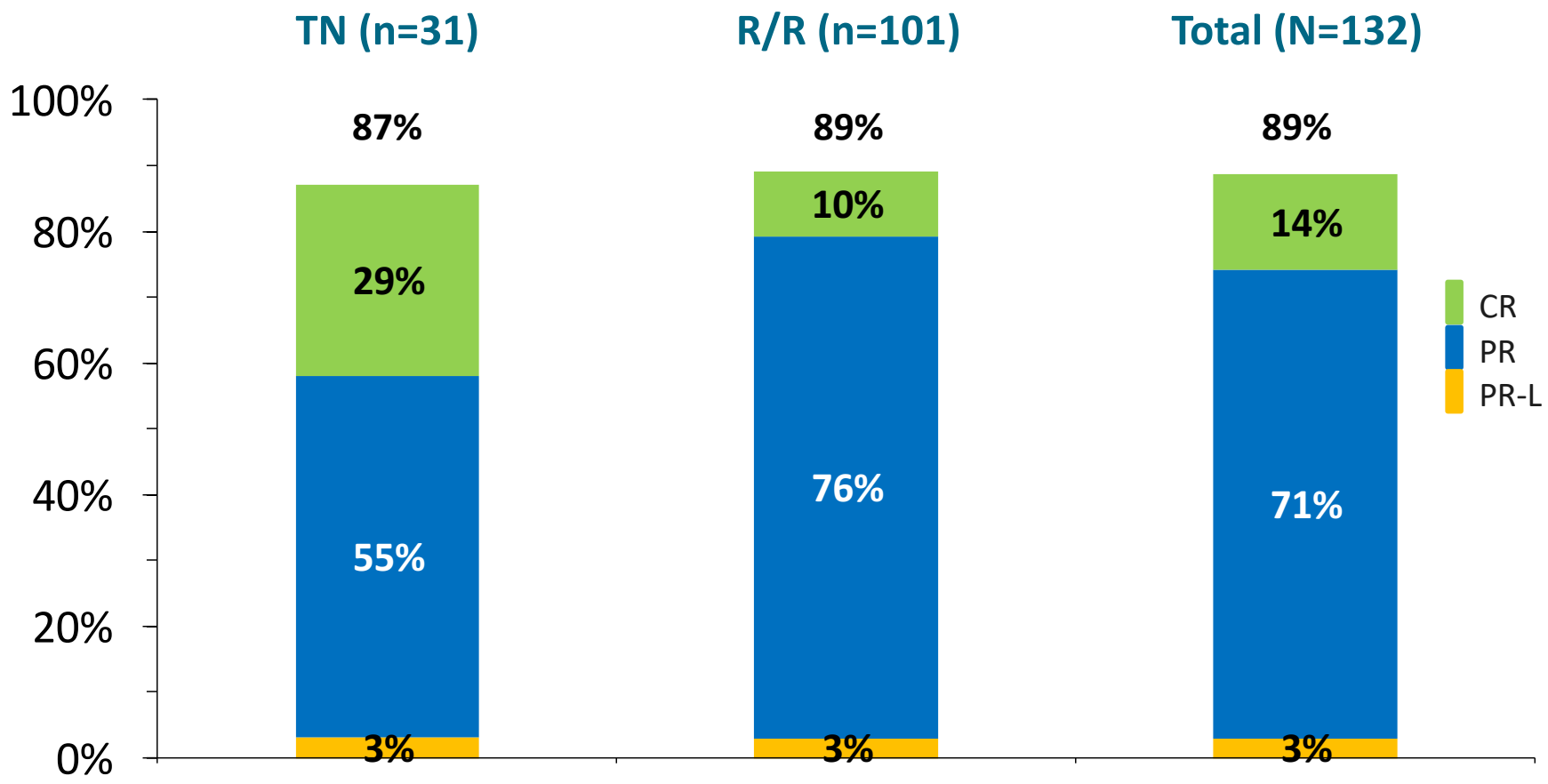
PCYC-1102/1103 Phase 2 Study Design



*R/R includes patients with high-risk CLL/SLL, defined as progression of disease <24 months after initiation of a chemoimmunotherapy regimen or failure to respond

ASH 2016, 1102-03 5-year Update; O'Brien et al.

Best Response



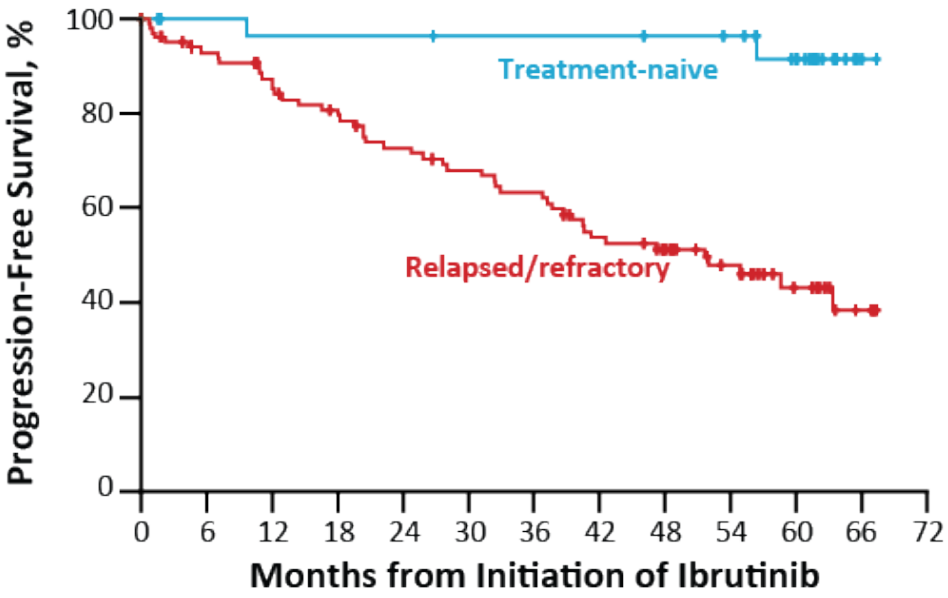
Median DOR, months (range)	NR (0.0+ to 65.5+)	56.8 (0.0+ to 65.5+)	NR (0.0+ to 65.5+)
Median follow-up, months (range)	62 (1 – 67)	49 (1+ – 67)	56 (1+ – 67)

NR, not reached.

ASH 2016, 1102-03 5-year Update; O'Brien et al.

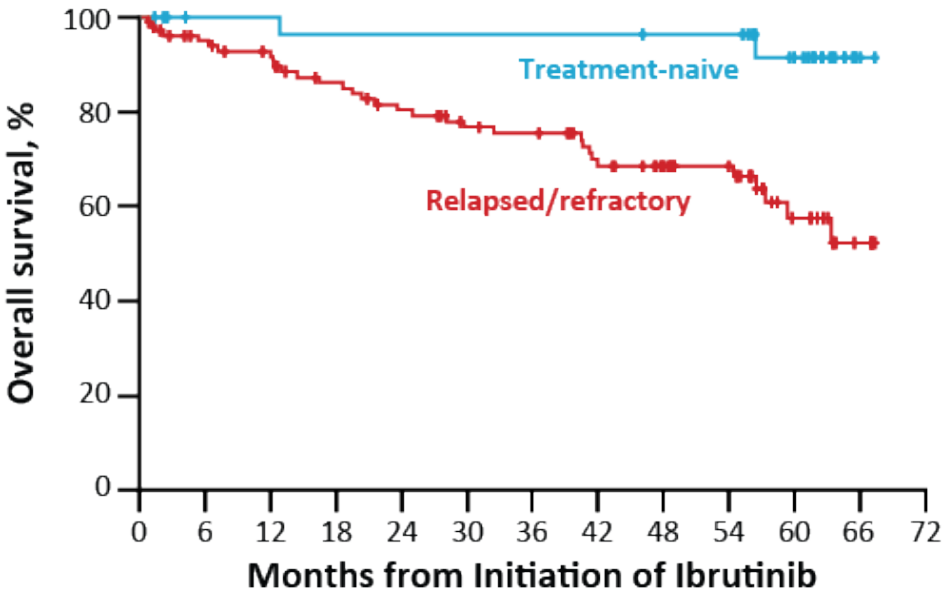
Survival Outcomes: Overall Population

Progression-Free Survival



	Median PFS	5-year PFS
TN (n=31)	NR	92%
R/R (n=101)	52 mo	43%

Overall Survival



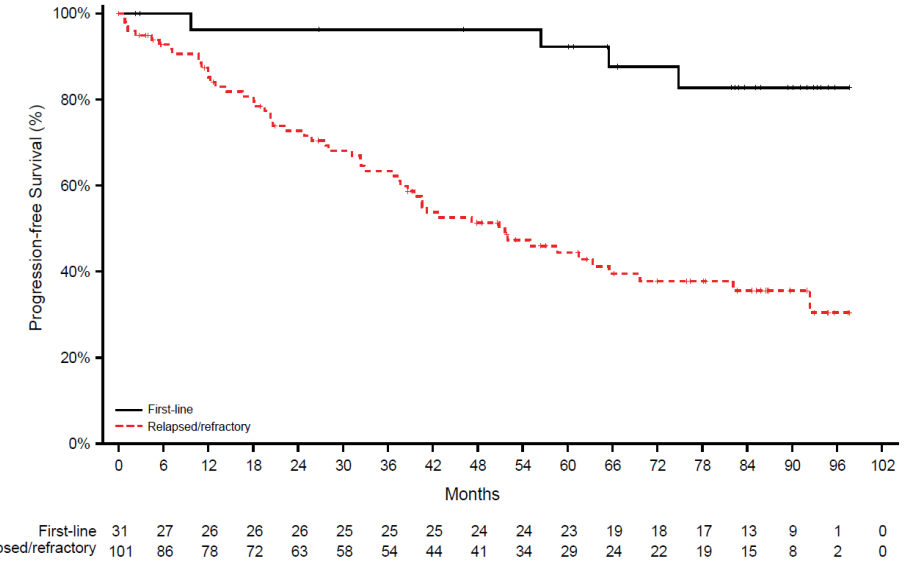
	Median OS	5-year OS
TN (n=31)	NR	92%
R/R (n=101)	NR	57%

NR, not reached.

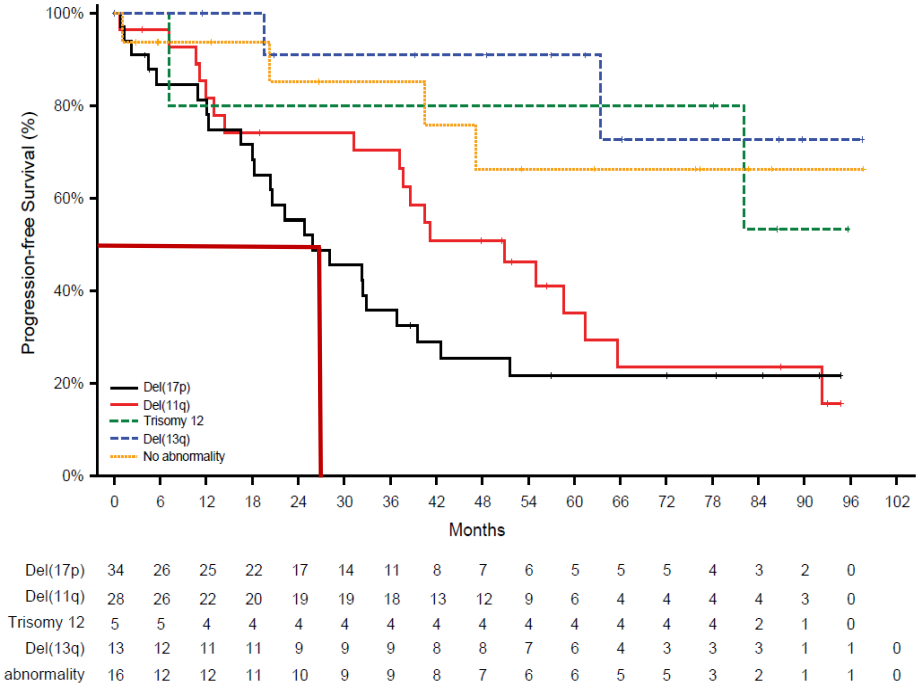
ASH 2016, 1102-03 5-year Update; O'Brien et al.

7-Year Experience With Ibrutinib Monotherapy Survival Outcomes (PCYC 1102/1103)

Progression-Free Survival: TN vs RR



PFS in RR CLL: FISH subgroups



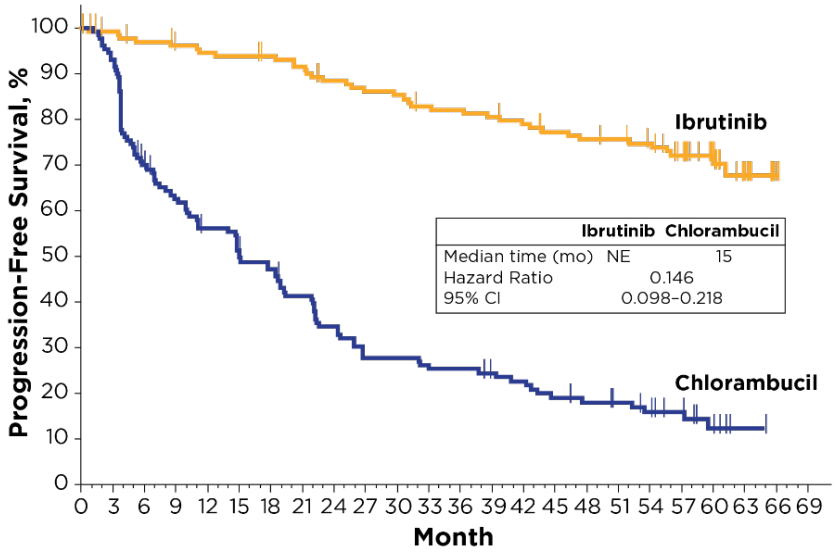
	Median PFS	7-year PFS
TN (n=31)	NR	83%
R/R (n=101)	52 mo	36%

	Median PFS	7-year PFS
Del17p (n=34)	26	22%
Del 11q (n=28)	51	23%
Trisomy 12 (n=5)	NR	53%
Del 13q (n=13)	NR	73%
No abnormality	NR	66%

Byrd et al. 2019, submitted

Ibrutinib PFS and OS Benefit vs Chlorambucil in First-Line CLL/SLL Continues in Long-Term Follow-Up

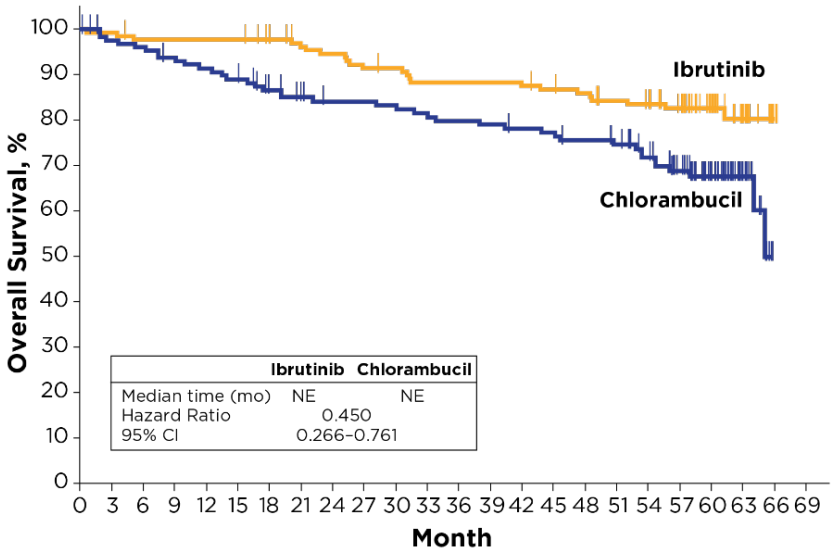
Progression-Free Survival



- At 5 years, 70% of ibrutinib-treated patients and 12% of chlorambucil-treated patients were estimated to be progression-free and alive (HR [95% CI]: 0.146 [0.098–0.218])
  - 21 patients in the ibrutinib arm progressed at any point during follow-up, including patients who had previously discontinued ibrutinib
  - 8/21 patients progressed while actively on ibrutinib

NE, not estimable.

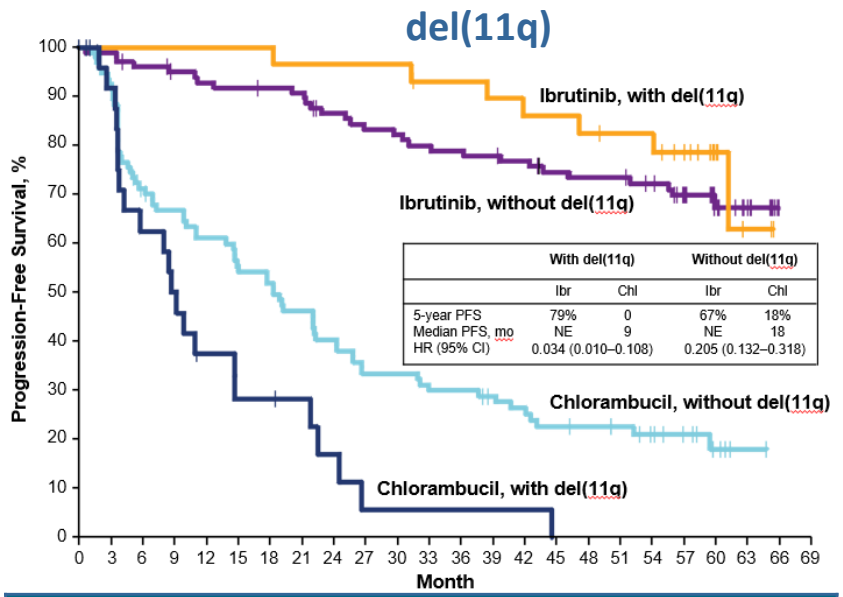
Overall Survival



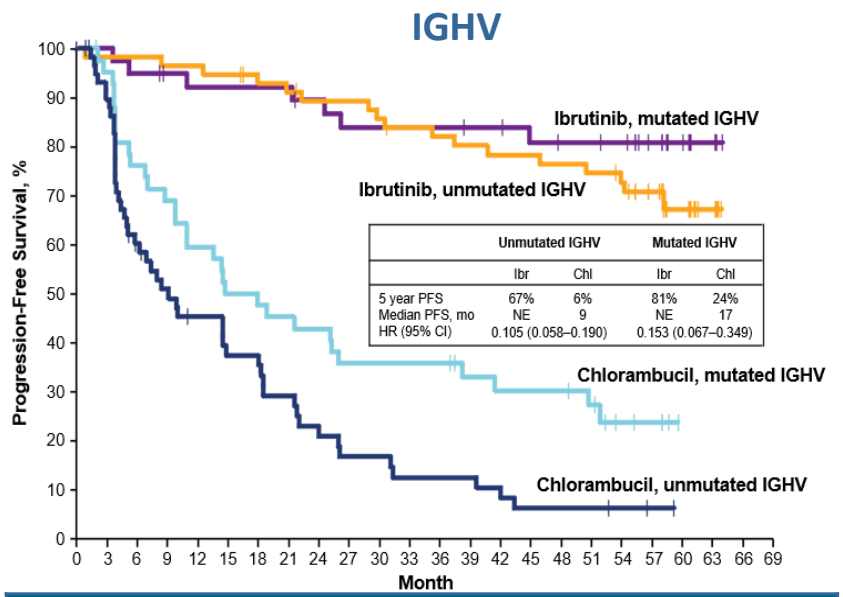
- Improved OS for ibrutinib vs chlorambucil: 5-year estimates, 83% vs 68%; HR (95% CI): 0.450 (0.266–0.761)

iwCLL 2019; RESONATE-2 CLL/SLL; Tedeschi et al.

Ibrutinib PFS Benefit vs Chlorambucil for Patients With del(11q) or Unmutated IGHV



	Ibrutinib	
	With del(11q)	Without del(11q)
5 year PFS	79%	67%
Median PFS, mo	NE	NE
HR (95% CI)	0.719 (0.315–1.642)	

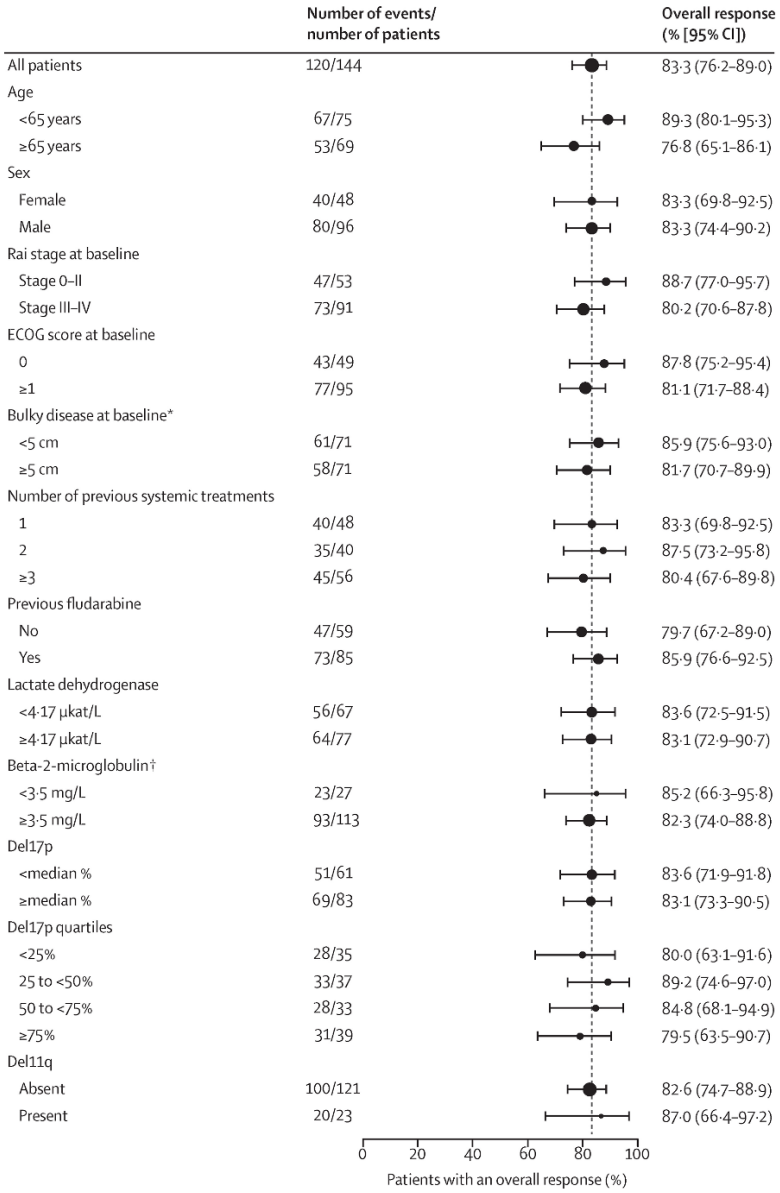


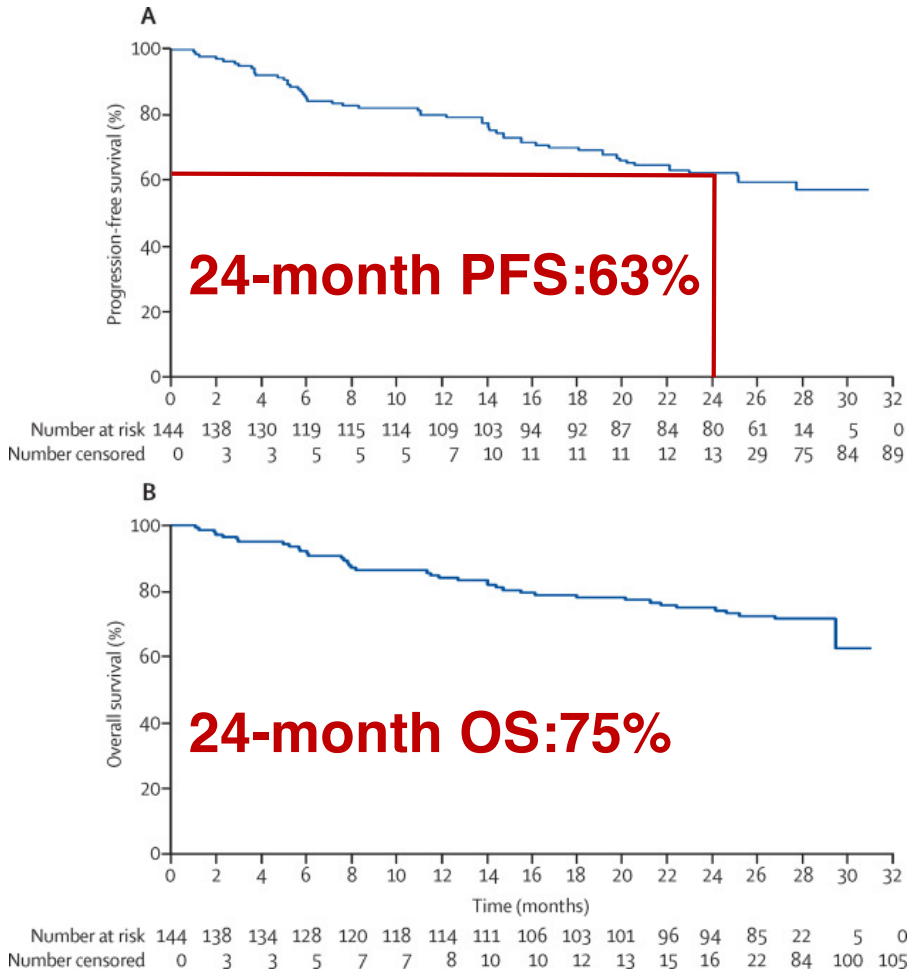
	Ibrutinib	
	Unmutated IGHV	Mutated IGHV
5 year PFS	67%	81%
Median PFS, mo	NE	NE
HR (95% CI)	0.632 (0.262–1.525)	

- Ibrutinib PFS benefit was maintained across all baseline characteristics evaluated, including patients with high-risk genomics (unmutated *IGHV*, del(11q), and/or *TP53* mutation); PFS: HR 0.08 (95% CI: 0.05–0.15); OS: HR 0.37 (95% CI: 0.18–0.74)

iwCLL 2019; RESONATE-2 CLL/SLL; Tedeschi et al.

Ibrutinib in RR CLL with del17p





O'Brien et al. Lancet Oncol 17: 1409-1418, 2016

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Depth and durability of response to ibrutinib in CLL: 5-year follow-up of a phase 2 study

Inhye E. Ahn,[1] Mohammed Z. H. Farooqui,[1] Xin Tian,[2] Janet Valdez,[1] Clare Sun,[1] Susan Soto,[1] Jennifer Lotter,[1] Stephanie Housel,[1,3] Maryalice Stetler-Stevenson,[4] Constance M. Yuan,[4] Irina Maric,[5] Katherine R. Calvo,[5] Pia Nierman,[1] Thomas E. Hughes,[6] Nakhle S. Saba,[1,7] Gerald E. Marti,[1] Stefania Pittaluga,[4] Sarah E. M. Herman,[1] Carsten U. Niemann,[1,8] Lone B. Pedersen,[8] Christian H. Geisler,[8] Richard Childs,[1] Georg Aue,[1] and Adrian Wiestner[1]

Table 1. Baseline characteristics

	All (n = 86)	TP53 cohort (n = 51)	Elderly cohort (n = 35)
Age, median (range), y	66 (33-85)	62 (33-82)	69 (63*-85)
≥65, N (%)	55 (64.0)	21 (41.2)	34 (97.1)*
Sex, N (%)			
Female	36 (41.9)	20 (39.2)	16 (45.7)
Male	50 (58.1)	31 (60.8)	19 (54.3)
Prior treatment status, N (%)			
Treatment-naïve	53 (61.6)	35 (68.6)	18 (51.4)
Relapsed/refractory†	33 (38.4)	16 (31.4)	17 (48.6)
Rai stage, N (%)			
I/II	28 (32.6)	19 (37.3)	9 (25.7)
III/IV	58 (67.4)	32 (62.7)	26 (74.3)
Bulky adenopathy (≥5 cm), N (%)‡	31 (36.0)	19 (37.3)	12 (34.3)
Splenomegaly, N (% evaluable)§	74 (88.1)	44 (88.0)	30 (88.2)
IGHV unmutated, N (%)‖	57 (66.3)	34 (66.7)	23 (65.7)
***TP53* aberration, N (%)**	54 (62.8)	51 (100)	0 (0)
Deletion 17p	50 (58.1)	47 (92.2)	3 (8.6)¶
TP53 mutation	4 (4.7)	4 (7.8)	0 (0)
β2-microglobulin			
Median (range), mg/dL	4·0 (1.7-12.9)	3.9 (1.7-12.3)	4.4 (1.9-12.9)
>4 mg/dL, N (%)	44 (51.2)	24 (47.1)	20 (57.2)

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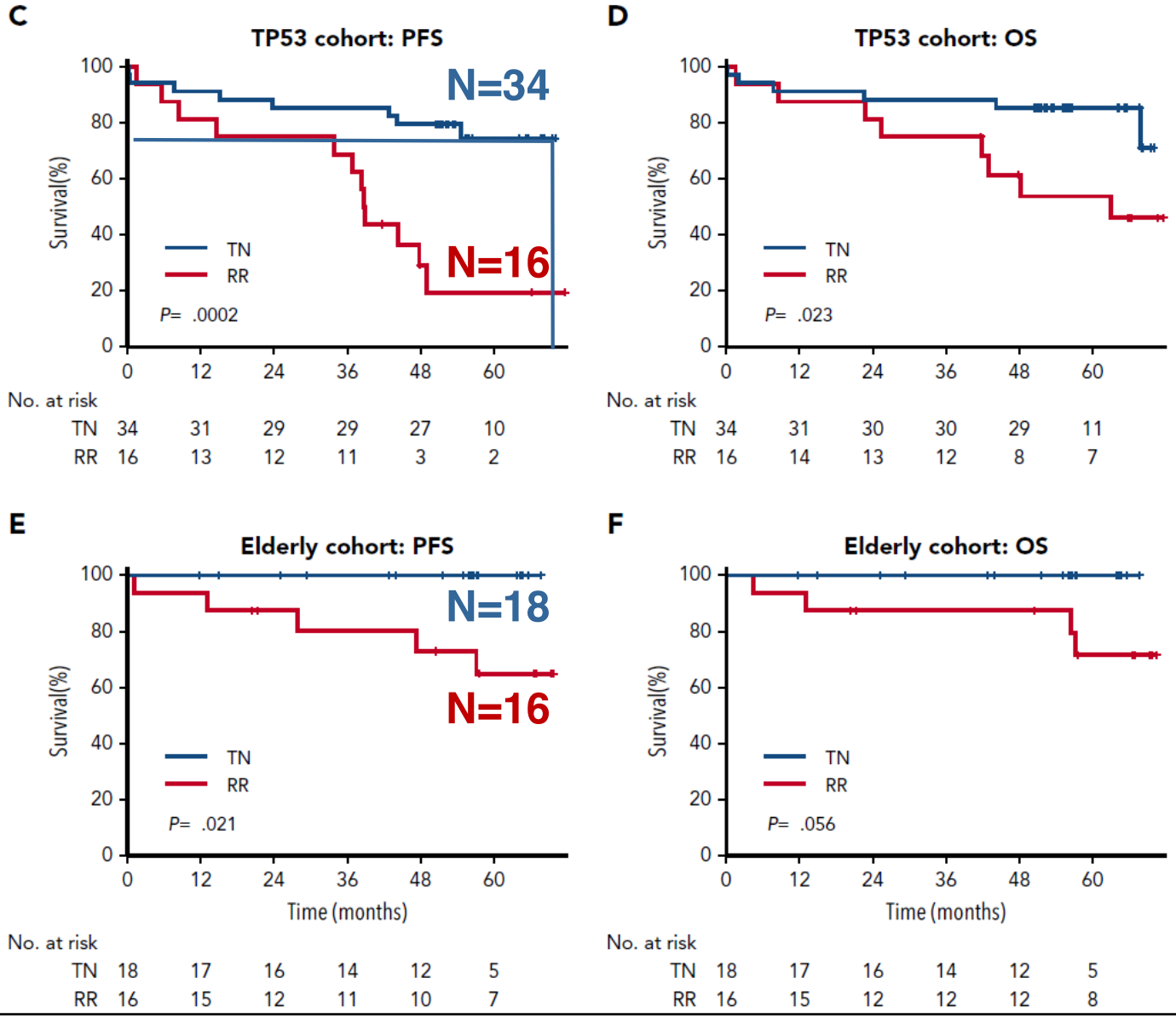
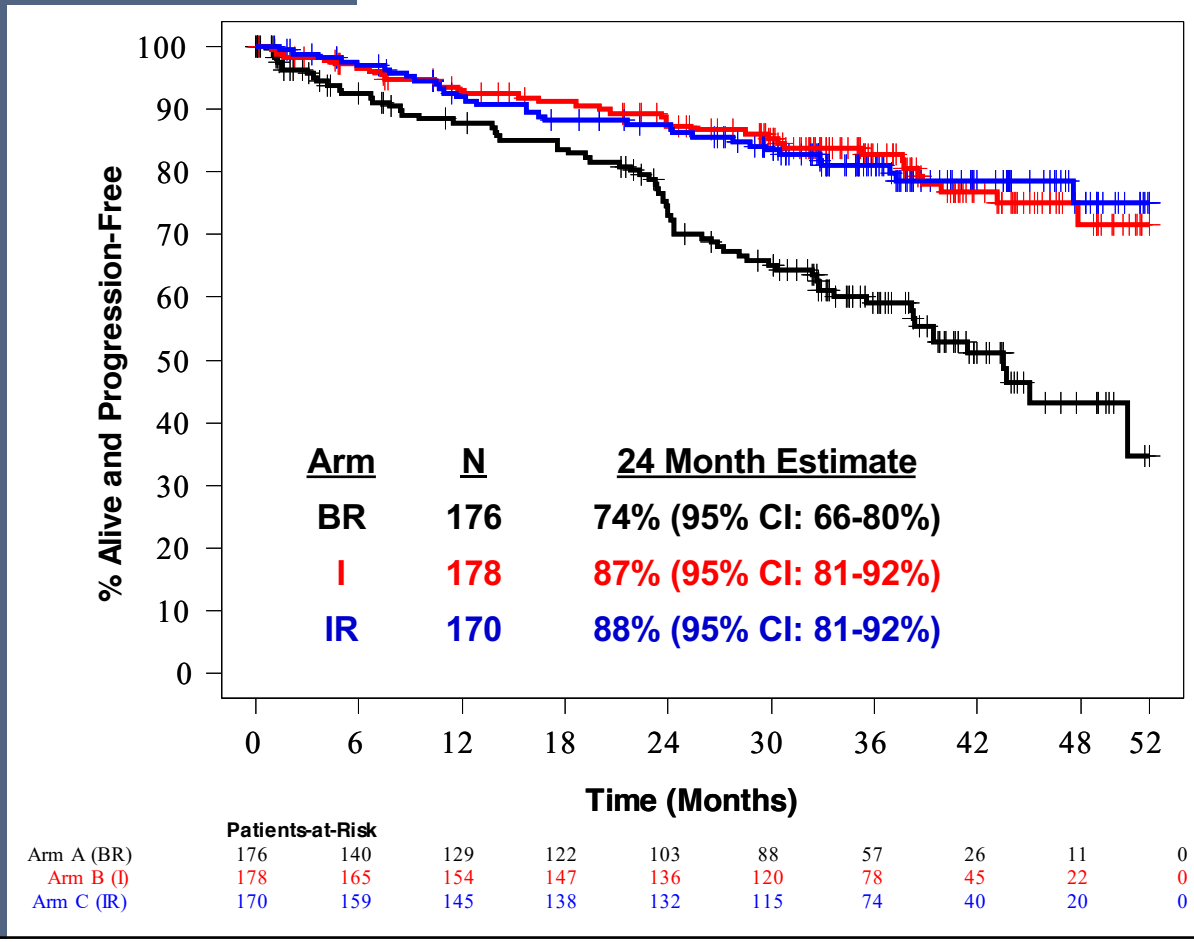


The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Ibrutinib Regimens versus Chemoimmunotherapy in Older Patients with Untreated CLL

J.A. Woyach, A.S. Ruppert, N.A. Heerema, W. Zhao, A.M. Booth, W. Ding, N.L. Bartlett, D.M. Brander, P.M. Barr, K.A. Rogers, S.A. Parikh, S. Coutre, A. Hurria,* J.R. Brown, G. Lozanski, J.S. Blachly, H.G. Ozer, B. Major-Elechi, B. Fruth, S. Nattam, R.A. Larson, H. Erba, M. Litzow, C. Owen, C. Kuzma, J.S. Abramson, R.F. Little, S.E. Smith, R.M. Stone, S.J. Mandrekar, and J.C. Byrd



Pairwise Comparisons

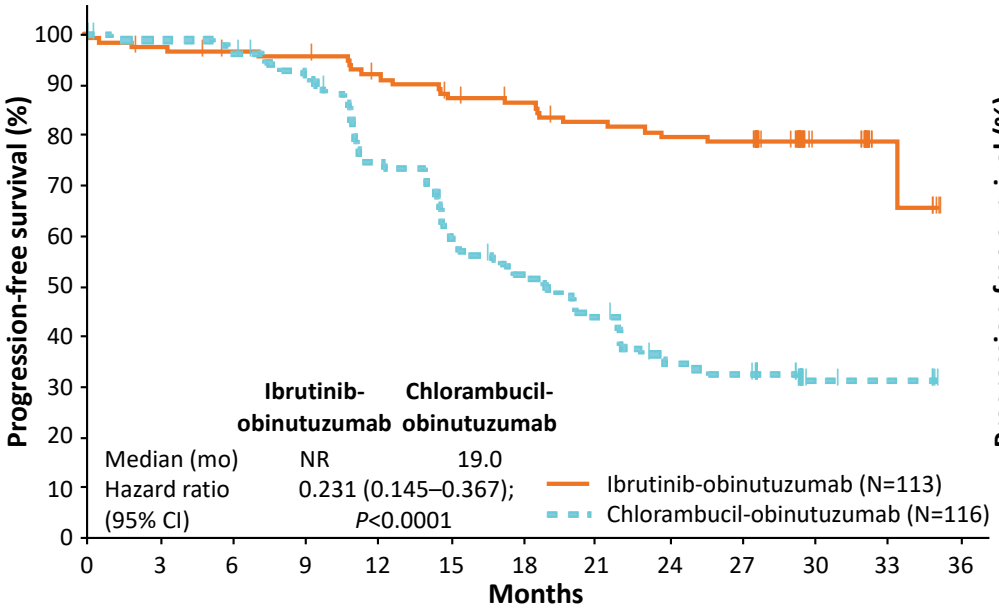
I vs BR:
Hazard Ratio 0.39
95% CI: 0.26-0.58
(1-sided P-value <0.001)

IR vs BR:
Hazard Ratio 0.38
95% CI: 0.25-0.59
(1-sided P-value <0.001)

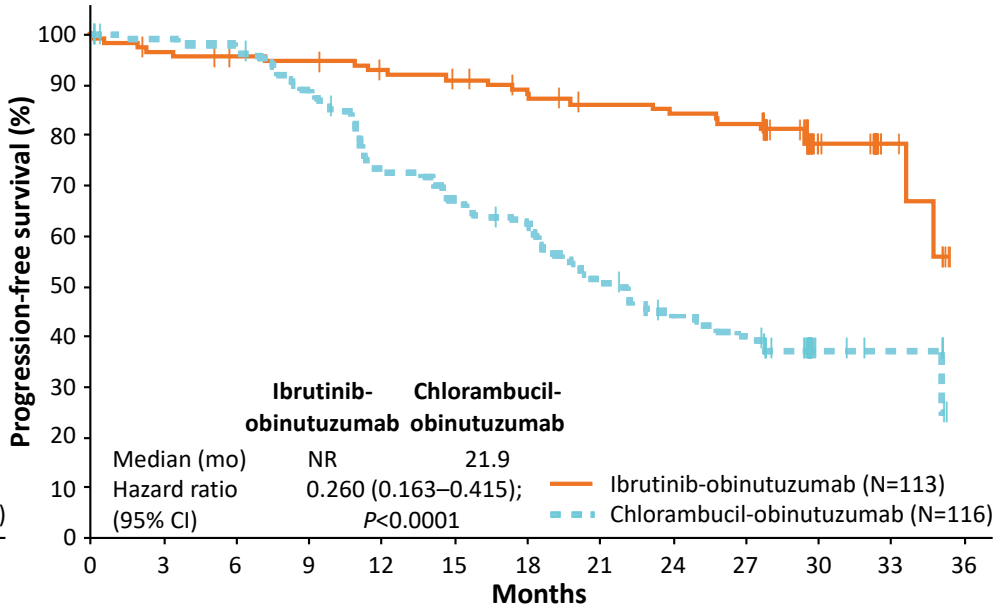
IR vs I:
Hazard Ratio 1.00
95% CI: 0.62-1.62
(1-sided P-value 0.49)

Superior Progression-Free Survival with Ibrutinib-Obinutuzumab

IRC Assessment



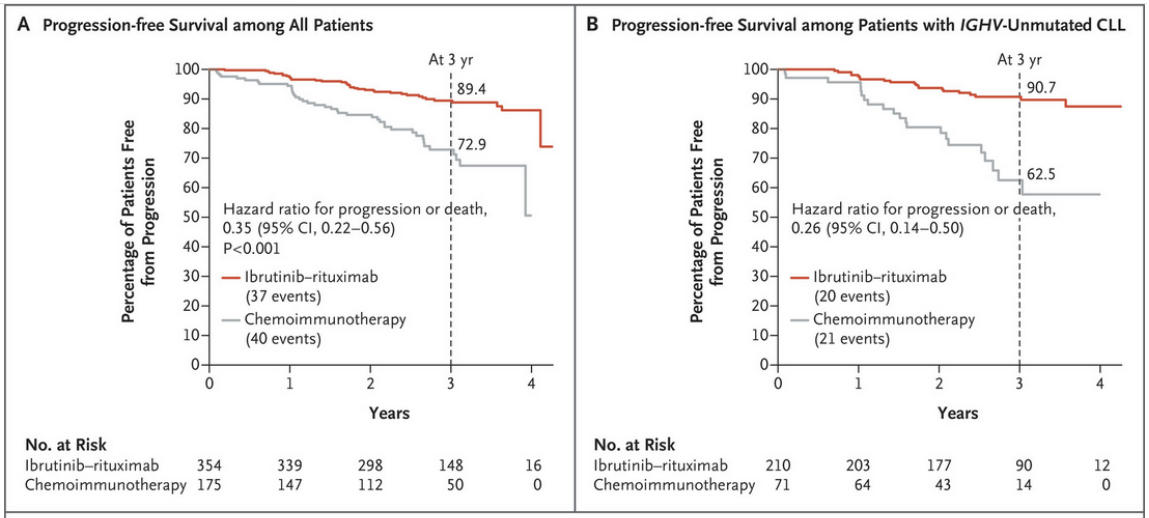
INV Assessment

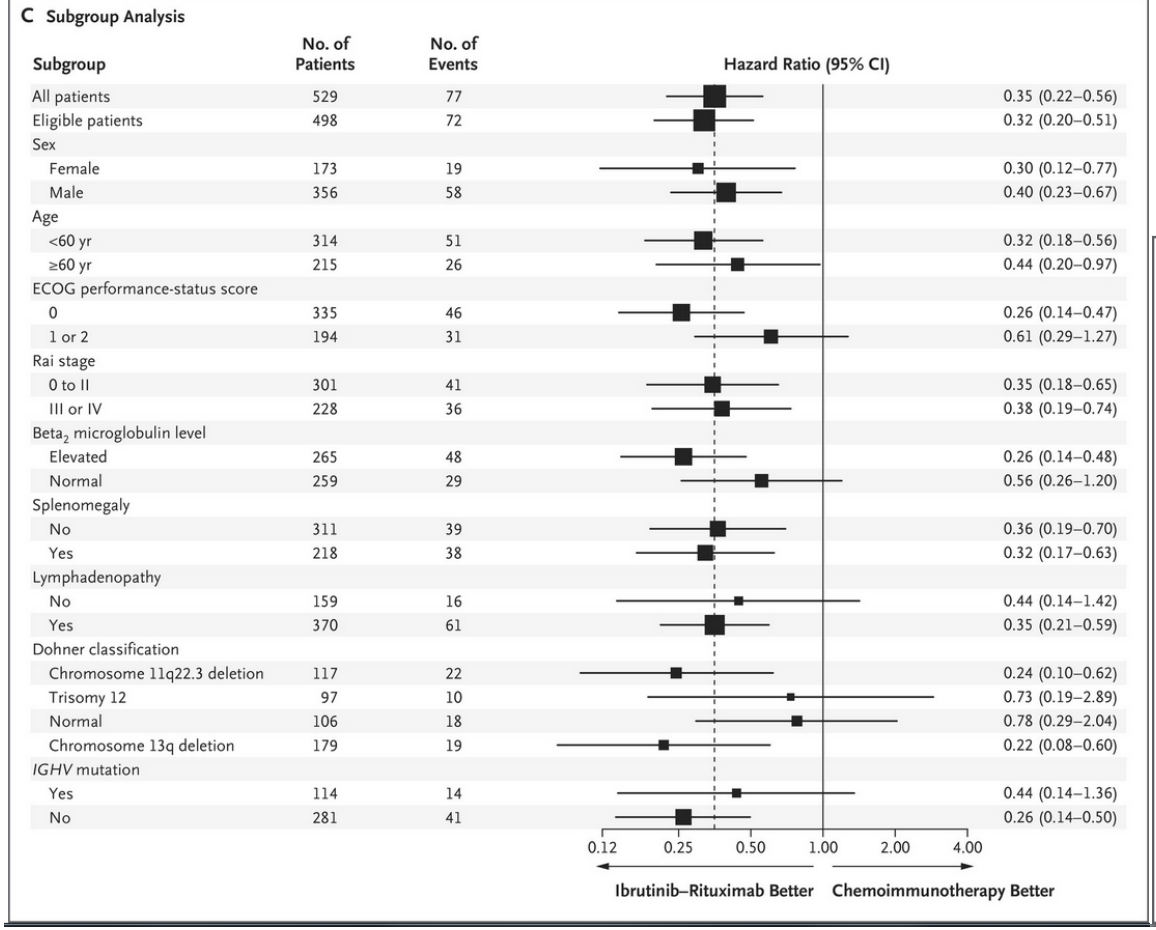


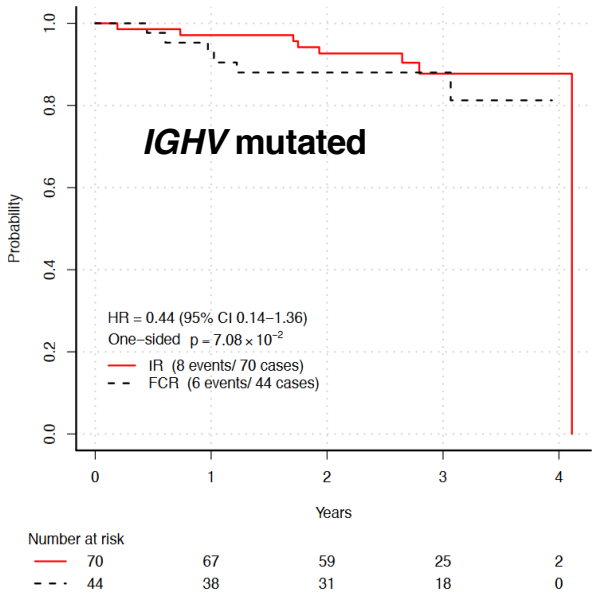
- Median follow-up, 31.3 months (range, 0.2–36.9)
- Estimated PFS at 30 months: 79% with ibrutinib-obinutuzumab vs. 31% with chlorambucil-obinutuzumab
- Even after excluding patients with del(17p): 74% reduction in risk of progression or death with ibrutinib-obinutuzumab

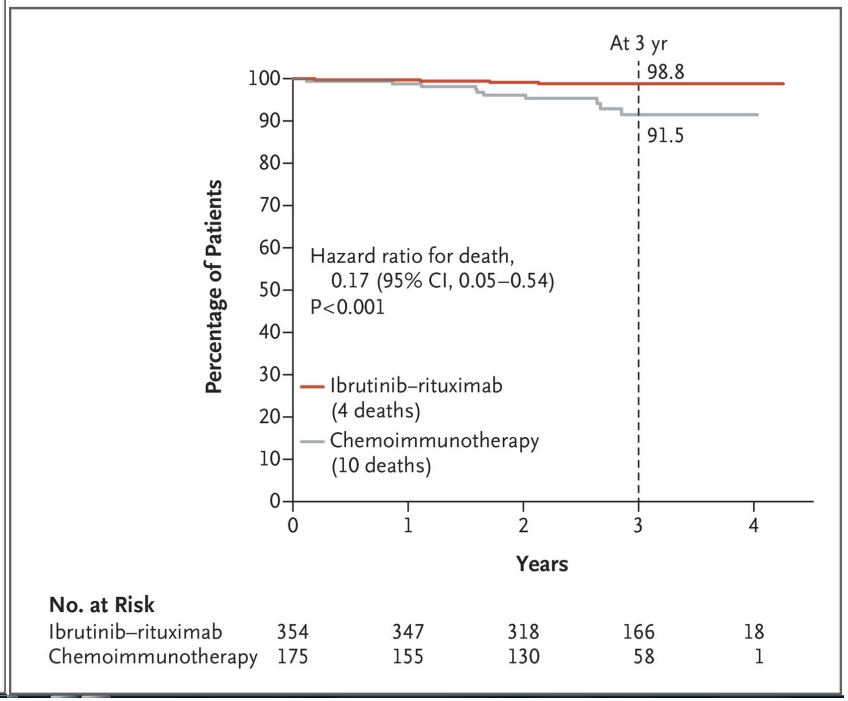
INV, investigator; NR, not reached.

Moreno et al; ASH2018, Abstract 691



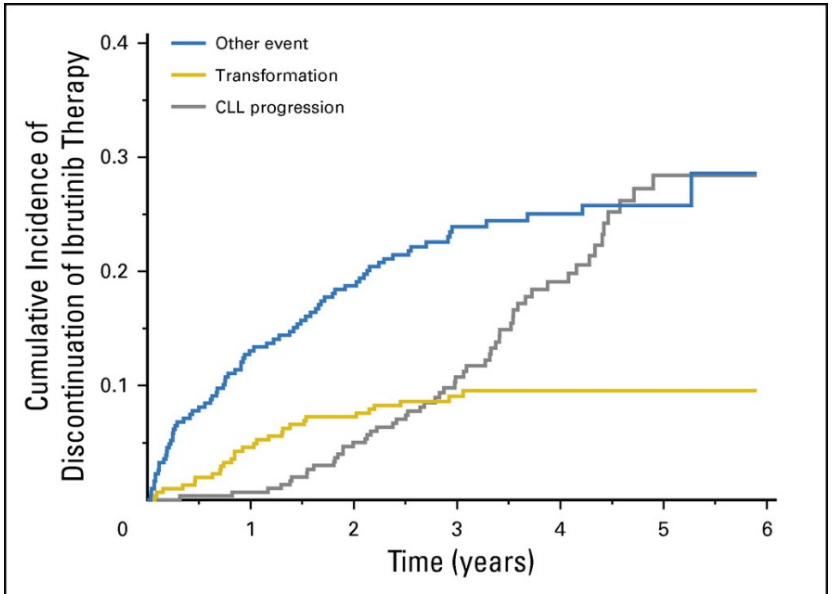






Shanafelt et al; NEJM 381(5):432-443, 08-2019

IBRUTINIB DISCONTINUATION AND RESISTANCE: OSU DATA



Cumulative Incidence Estimates (95% CI)	At 2 Years	At 3 Years	At 4 Years
CLL progression	5.0% (2.5% to 7.5%)	10.8% (7.1% to 14.4%)	19.1% (13.9% to 24.3%)
Transformation	7.3% (4.3% to 10.2%)	9.1% (5.8% to 12.4%)	9.6% (6.2% to 13.0%)
Other event	18.7% (14.3% to 23.1%)	23.9% (19.0% to 28.8%)	25.0% (20.0% to 30.1%)

Woyach JA, JCO 2017

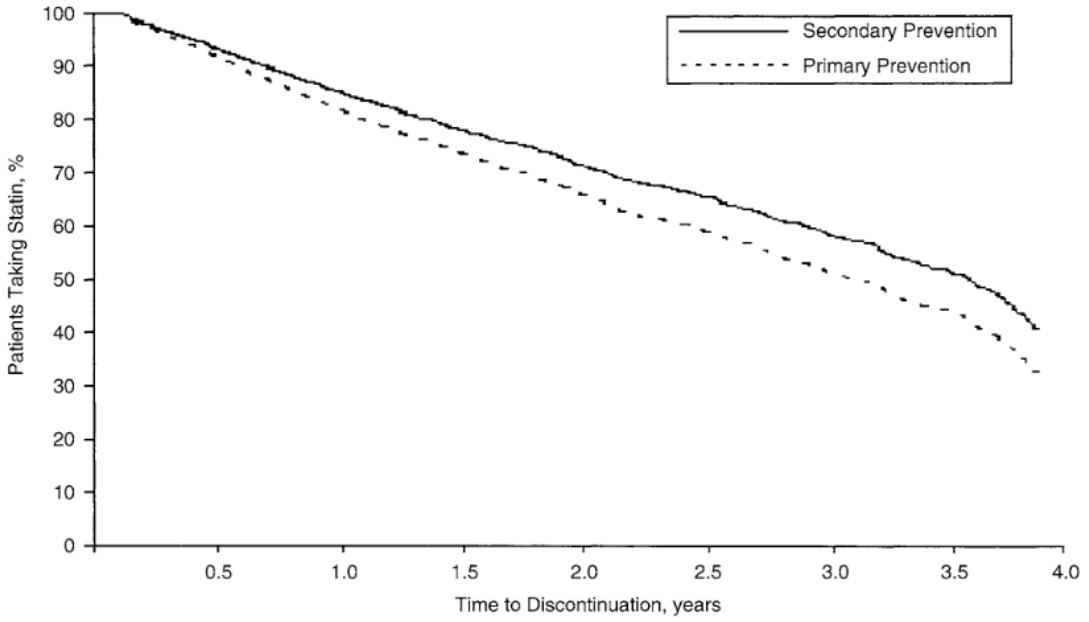


FIGURE 1. Survival curves for discontinuation of statin therapy by prevention category. Adjusted for all available covariates. The median time to discontinuation was 3.7 years for secondary prevention and 3.4 years for primary prevention.

Ellis, J.J. et al. J GEN INTERN MED (2004) 19: 638

Toxicities and outcomes of 621 ibrutinib-treated CLL patients in the US: a real-world analysis

- At a median follow-up of 17 months (range 1-60 months), 42% of patients discontinued ibrutinib
- Median time to ibrutinib discontinuation was 7 months (range, 0.1–41)

Table 2. Reasons for Ibrutinib Discontinuation

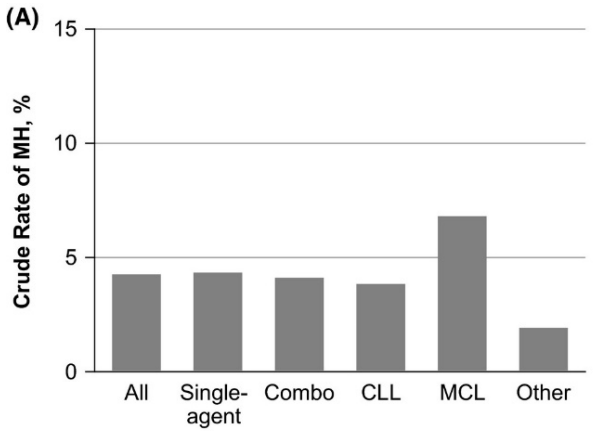
Reason for ibrutinib discontinuation	Ibrutinib in front-line n=19	Ibrutinib in relapse n=231
Toxicity	63.1% (n=12)	50.2% (n=116)
CLL progression	15.8% (n=3)	20.9% (n=49)
Other/unrelated death	5.3% (n=1)	12.1% (n=28)
Physician or patient preference	10.5% (n=2)	6.7% (n=15)
RT DLBCL	5.3% (n=1)	4.6% (n=10)
Stem cell transplantation/CAR T-cell	0	3.3% (n=8)
Financial concerns	0	0.8% (n=2)
Secondary malignancy	0	0.8% (n=2)
RT Hodgkin Lymphoma	0	0.4% (n=1)

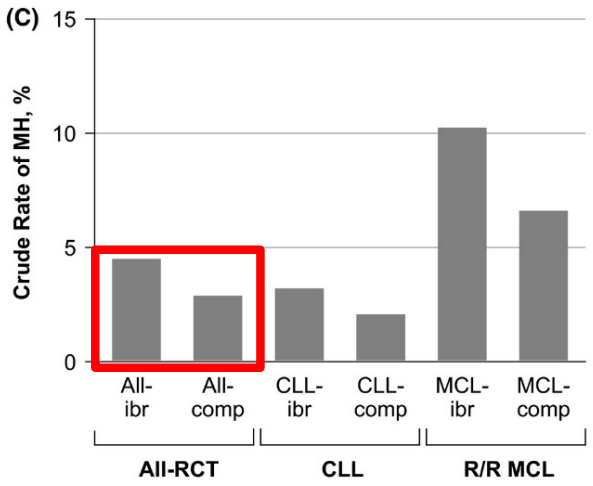
Table 2 Abbreviations: CLL (Chronic Lymphocytic Leukemia); RT DLBCL (Richter's Transformation Diffuse Large B Cell Lymphoma); CAR T-cell (Chimeric Antigen Receptor T-cell); RT (Richter's Transformation)

Mato A, Haematologica 2018

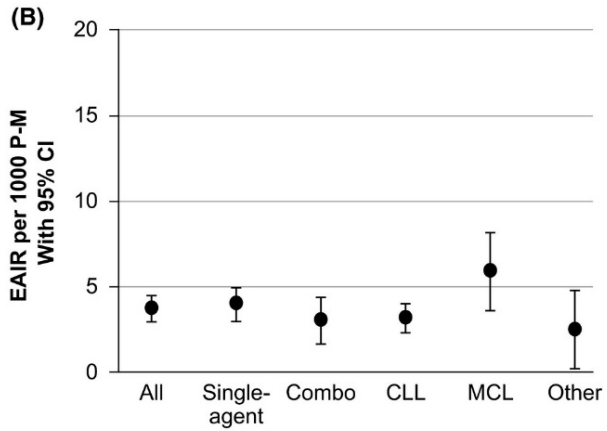
Bleeding in ibrutinib-treated patients: pooled data from 1768 patients

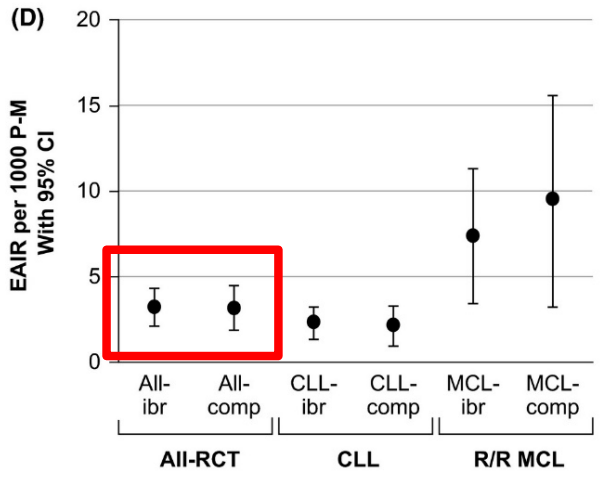
Crude rate of major hemorrhage





Exposure-adjusted incidence rates (EAIR)



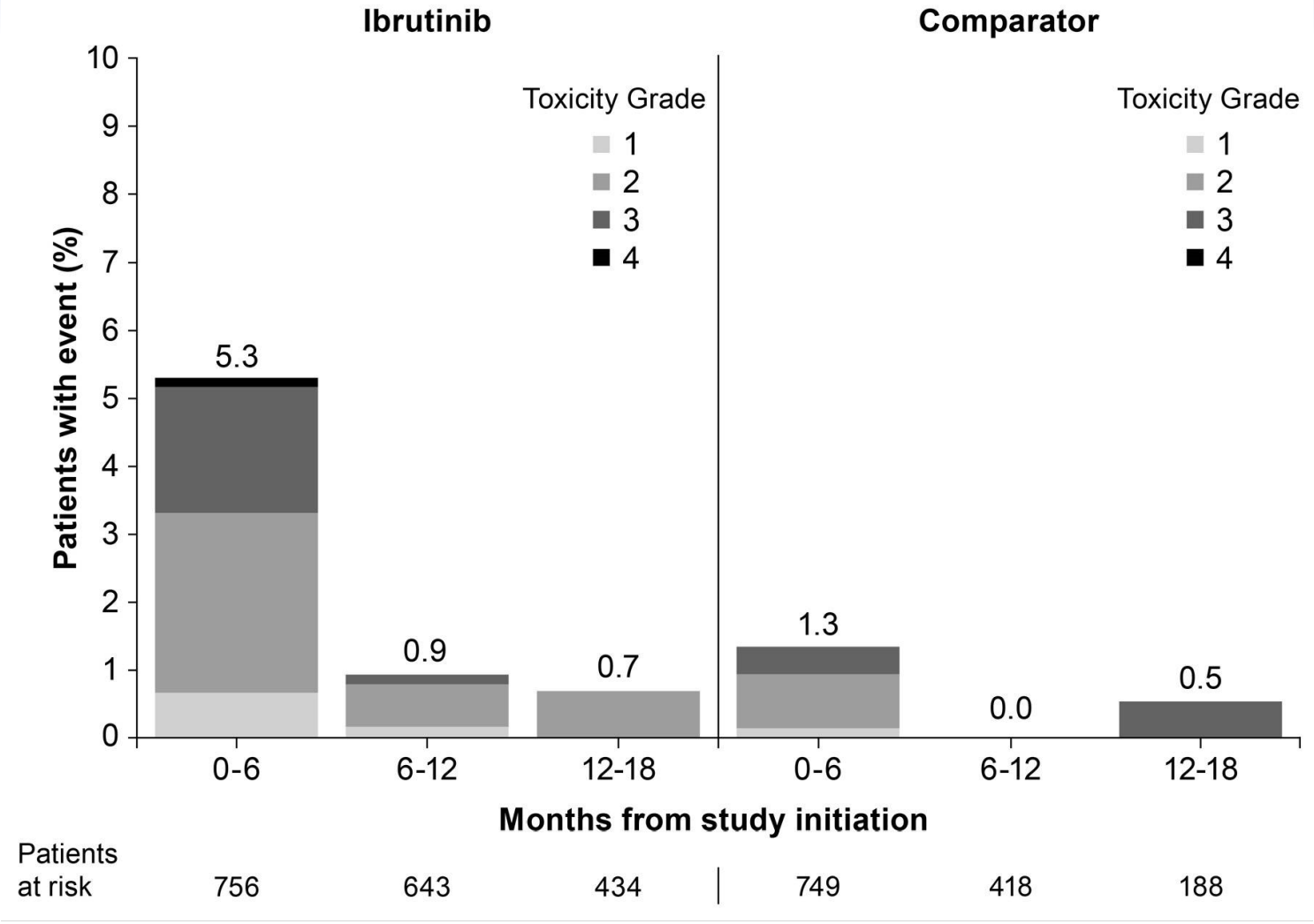


- **Low-grade bleeding** in 36% of patients
- **Major hemorrhage** (MH) in 4.1% of patients
- 1% of patients discontinue ibrutinib because of MH
- Moderate associations between anticoagulant/anti-platelet (AC/AP) use and risk of MH in ibrutinib- and comparator-treated patients

Mechanism: Ibrutinib inhibits platelet aggregation due to inhibition of BTK and TEC in glycoprotein VI collagen-activated pathway

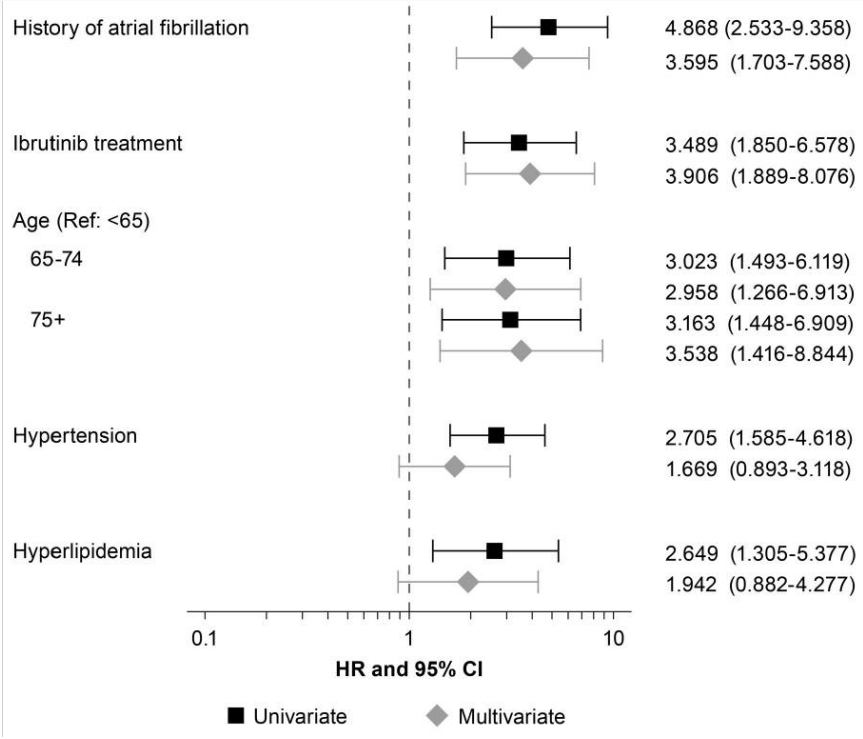
Brown JR Br J Haematol 184(4):558-569, 2019

Atrial fibrillation in ibrutinib-treated patients: pooled data from 1505 patients



Brown JR & Burger JA Haematologica102: 1796, 2017

Atrial fibrillation in ibrutinib-treated patients: risk factors and management



Risk factors associated with *de novo* AF (Shanafelt risk score)

- **Older age**
- **Male gender**
- **Valvular heart disease**
- **Arterial hypertension**

	Ibrutinib (n=49)		Comparator (n=12)	
	n (%)	Median duration while on study (range), weeks	n (%)	Median duration while on study (range), weeks
Beta blockers or alpha blockers	41 (83.7)	54.4 (0.1-194.4)	9 (75.0)	57.9 (0.4-114.4)
Diuretics	23 (46.9)	39.9 (0.1-148.6)	8 (66.7)	3.1 (0.3-21.6)
ACE inhibitors	19 (38.8)	56.7 (4.6-143.0)	5 (41.7)	6.3 (0.6-104.0)
Calcium channel blockers	16 (32.7)	28.7 (0.1-80.3)	3 (25.0)	6.0 (0.1-10.4)
Antiarrhythmic	25 (51.0)	9.1 (0.1-66.1)	7 (58.3)	20.9 (0.1-77.1)
Digoxin	13 (26.5)	1.3 (0.1-19.7)	1 (8.3)	0.1 (0.1-0.1)
Lipid-lowering medications, statins, and antidiabetics	22 (44.9)	59.5 (0.1-114.3)	5 (41.7)	10.0 (4.1-152.1)
Antiplatelets				
Aspirin	23 (46.9)	50.3 (2.1-103.9)	4 (33.3)	4.4 (2.0-61.0)
Antiplatelets other than aspirin	10 (20.4)	18.1 (0.1-74.9)	0	0
Anticoagulants				
Low-molecular-weight heparin	25 (51.0)	4.3 (0.1-50.4)	7 (58.3)	2.4 (0.9-45.1)
Novel oral anticoagulants	12 (24.5)	40.9 (2.3-99.1)	1 (8.3)	87.3 (87.3-87.3)
Vitamin K antagonists	7 (14.3)	13.0 (0.3-55.0)	2 (16.7)	4.1 (2.1-6.0)
Other	8 (16.3)	0.4 (0.1-76.1)	1 (8.3)	67.6 (67.6-67.6)

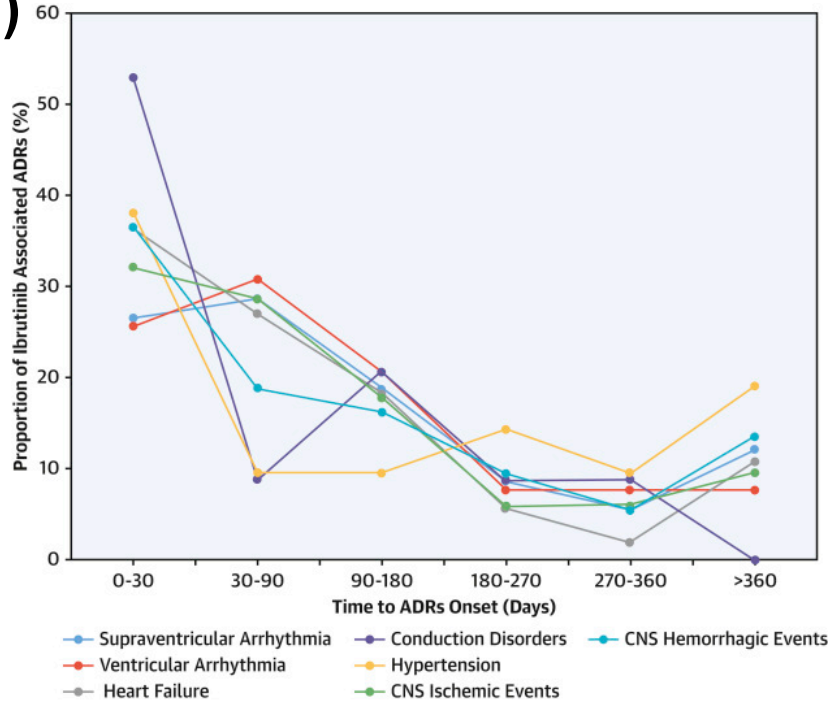
ACE, angiotensin-converting-enzyme; AF, atrial fibrillation.

Brown JR Haematologica102: 1796, 2017

Cardiovascular Toxicities Associated With Ibrutinib

- Data based on VigiBase (International pharmaco-vigilance database) and disproportionality analysis using reporting odds ratios (ROR)
- 13,572 Ibrutinib individual case safety report (ICSR)
- Study identified **303 ibrutinib-associated cardiovascular deaths**

- **Supraventricular arrhythmias (ROR: 23.1)**
- **Heart failure (ROR: 3.5; 95%)**
- **Ventricular arrhythmias (ROR: 4.7)**
- **Conduction disorders (ROR: 3.5)**
- **CNS hemorrhagic events (ROR: 3.7)**
- **CNS ischemic events (ROR: 2.2)**
- **Hypertension (ROR: 1.7)**



Salem JE J AM Coll Cardiol 2019 74(13):1667-78

Ibrutinib studies with reported sudden deaths/cardiac arrests

Studies*	No. of Patients	Median time on therapy (months)	Age (y)		No. of sudden deaths/cardiac arrests in ibrutinib arm	Incidence per 100 000 patient-years (95% CI)
			Median	Range		
OSU experience: NCT01105247, NCT01217749, NCT01589302, NCT01578707 (RESONATE)	308	20	65	26-91	1	194.8 (4.9-1085.4)
NCT01722487 (RESONATE-2)	135	17.4	73	65-89	2	1021.7 (123.7-3690.8)
MDACC experience: NCT01105247, NCT01520519, NCT01752426, NCT01578707 (RESONATE)	127	13	61	36-83	2	1453.7 (176.1-5252.1)
NCT01500733 (Phase 2 NHLBI)	51	24†	62	33-82	1	980.4 (24.8-5462.4)
Swedish Compassionate Use	95	10.2†	69	42-86	1	1238.4 (31.4-6899.9)
NCT01611090 (HELIOS)	287	14.7	64	31-86	3	853.3 (176.0-2493.7)

The weighted average of the incidence rates was **788 events per 100 000 person-years**.
In comparison, rates of sudden cardiac death for 65-year-olds are in the range of **200 to 400 events** per 100 000 person-years

Ibrutinib and fungal infections

- In CNS lymphoma, 39% of patients treated with ibrutinib plus steroids developed aspergillosis
- Potential mechanism: inhibitory BTK-related effects on macrophages, suppressing phagocytosis of aspergillus
- In CLL or MCL, incidence of Aspergilloses much lower than in CNS lymphoma
- Predominant sites of infection: lungs, CNS
- Early onset fungal infection after start of ibrutinib therapy characteristic
- anti-fungal prophylaxis is not warranted for the general population of ibrutinib-treated patients,
- Particular attention and close follow-up, especially during the first months of therapy, recommended for patients with high-risk, such as concomitant corticosteroid use, higher number of prior therapies, diabetes, or liver disease

National Comprehensive Cancer Network®

NCCN Guidelines for CLL frontline therapy (non-del17p)

SUGGESTED TREATMENT REGIMENS[a,b,c,d]
CLL/SLL without del(17p)/*TP53* mutation
(alphabetical by category)

FIRST-LINE THERAPY		
Frail patient with significant comorbidity (not able to tolerate purine analogs) OR Patients age ≥65 y and younger patients with significant comorbidities	Preferred regimens • Ibrutinib[e] (category 1) • Venetoclax[e,f] + obinutuzumab	Other recommended regimens • Bendamustine (70 mg/m² in cycle 1 with escalation to 90 mg/m² if tolerated) + anti-CD20 monoclonal antibody[d,g] (Not recommended for frail patients) • Chlorambucil + anti-CD20 monoclonal antibody[g,h] • High-dose methylprednisolone (HDMP) + rituximab (category 2B) • Ibrutinib[e] + obinutuzumab (category 2B) • Obinutuzumab (category 2B) • Chlorambucil (category 3) • Rituximab (category 3)
Patients age <65 y without significant comorbidities	Preferred regimens • Ibrutinib[e] (category 1)	Other recommended regimens • Bendamustine + anti-CD20 monoclonal antibody[d,g,i] • FCR (fludarabine,[j] cyclophosphamide, rituximab)[i,k,l] • FR (fludarabine,[j] rituximab)[k,m] • HDMP + rituximab (category 2B) • Ibrutinib[e] + rituximab (category 2B) • Venetoclax[e,f] + obinutuzumab (category 2B) • PCR (pentostatin, cyclophosphamide, rituximab) (category 3)

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) Version 5.2019

NCCN Guidelines for CLL frontline therapy Version 5.2019 (del17p)

SUGGESTED TREATMENT REGIMENS[a,b,c,d]
CLL/SLL with del(17p)/*TP53* mutation
(alphabetical by category)

FIRST-LINE THERAPY	
Preferred regimens	**Other recommended regimens**
• Ibrutinib[e] • Venetoclax[e,f] + obinutuzumab	• Alemtuzumab[q] ± rituximab • HDMP + rituximab • Obinutuzumab

Summary

- Ibrutinib has replaced CIT for many CLL patients
- Long-term therapy and toxicities remain a challenge
- Resistance mostly an issue in high-risk patients (del17p, multiple prior therapies)
- Limited duration therapy may help to reduce the risk for toxicities and resistance

Thank-
you!

Dept. of Leukemia, MDACC

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