Updates on Ibrutinib

DISCLOSURE INFORMATION

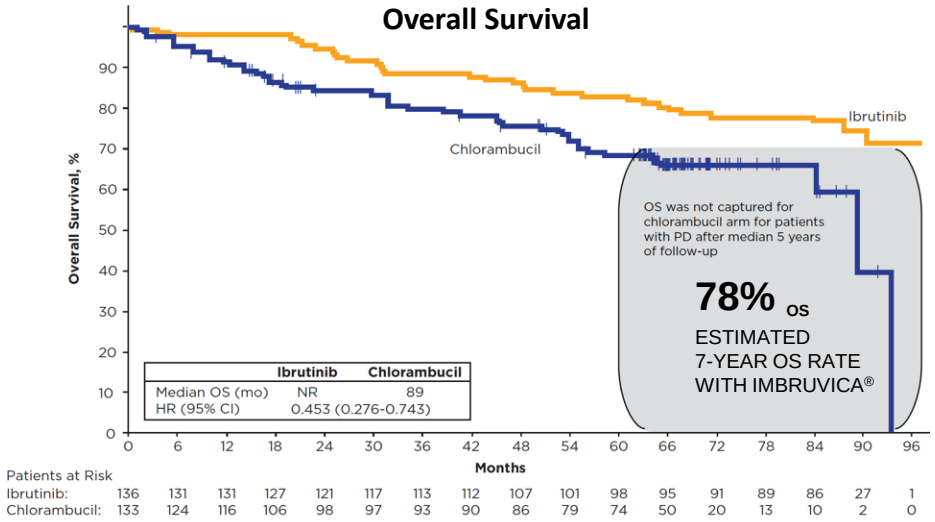
SUSAN O'BRIEN, MD

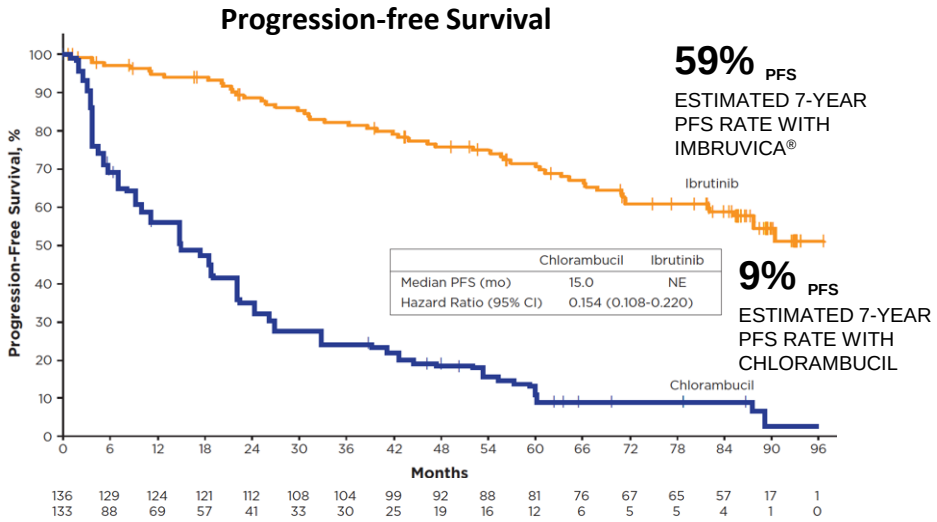
I have the following financial relationships to disclose:

Sponsor/Company	Affiliation(s)
AbbVie	Consultant
Acerta	Research Support
Alexion	Consultant
Amgen	Consultant
Aptose Biosciences Inc.	Consultant
Astellas	Consultant
Autolus	Consultant
Bristol Myers Squibb	Consultant
Caribou	Research Support
Celgene	Consultant
DynaMed	Consultant
Eli Lilly and Company	Consultant
Gilead	Consultant/Research Support
GlaxoSmithKline	Consultant
Janssen Oncology	Consultant
Johnson and Johnson	Consultant
Juno Therapeutics	Consultant
Kite	Research Support
MEI Pharma, Inc.	Consultant
Merck	Consultant
NOVA Research Company	Consultant
Pfizer	Consultant/Research Support
Pharmacyclics	Consultant/Research Support
Regeneron	Research Support
Sunesis	Consultant/Research Support
TG Therapeutics	Consultant/Research Support
Vaniam Group LLC	Consultant
Verastem	Consultant
Vida Ventures	Consultant

Updated August 2021

Up to 8 Years of Follow-up in RESONATE-2: OS and PFS

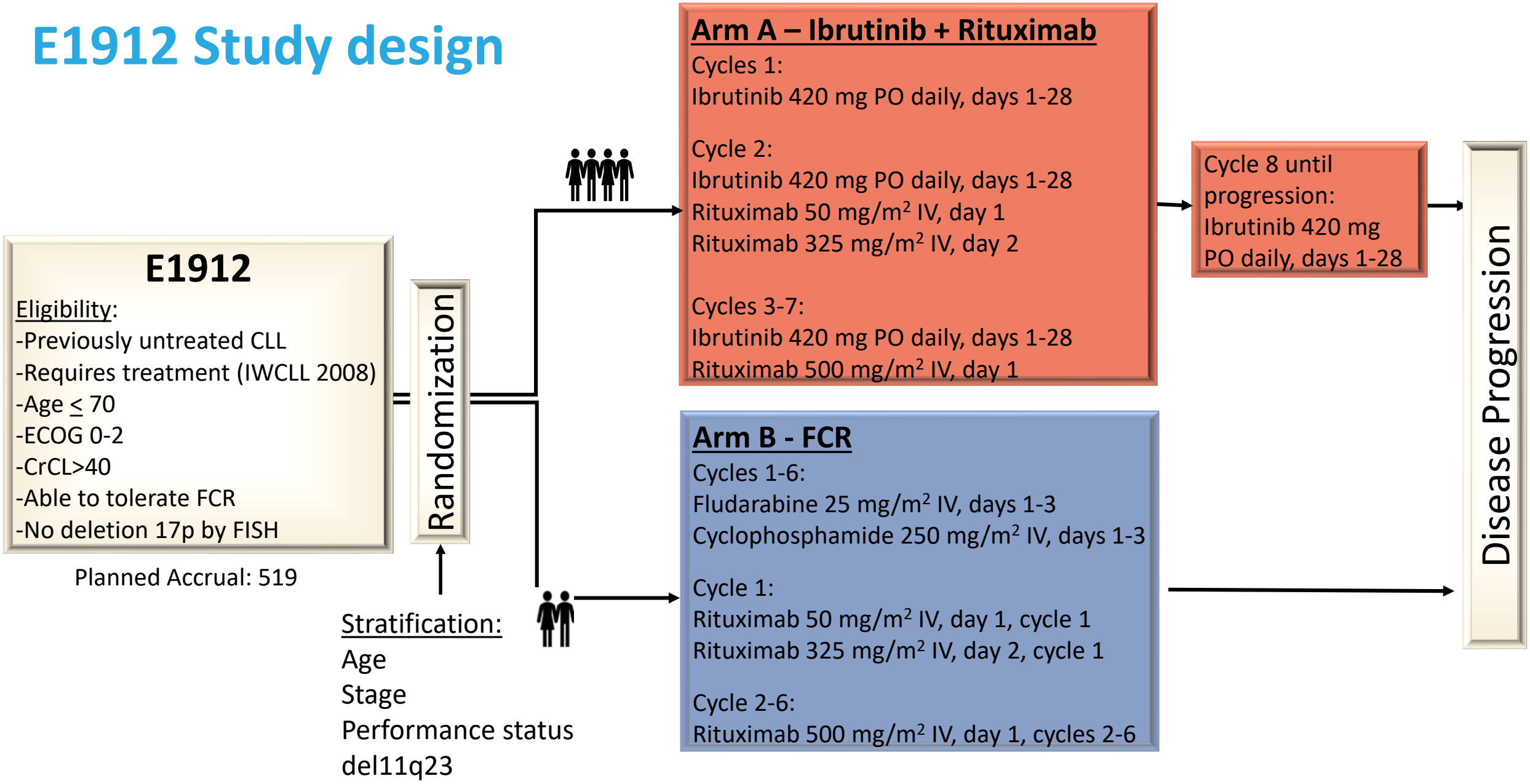




- **78%** taking Ibrutinib were estimated to be alive at 7 years
- **59%** taking Ibrutinib were estimated to be progression-free and alive at 7 years vs 9% of patients taking chlorambucil

1. Barr PM, Owen C, Robak T, et al. Up to 8 years follow-up from RESONATE-2: first-line ibrutinib treatment for patients with chronic lymphocytic leukemia. *Blood Adv*. 2022 Apr 4:bloodadvances.2021006434.doi:10.1182/bloodadvances.2021006434

E1912 Study design



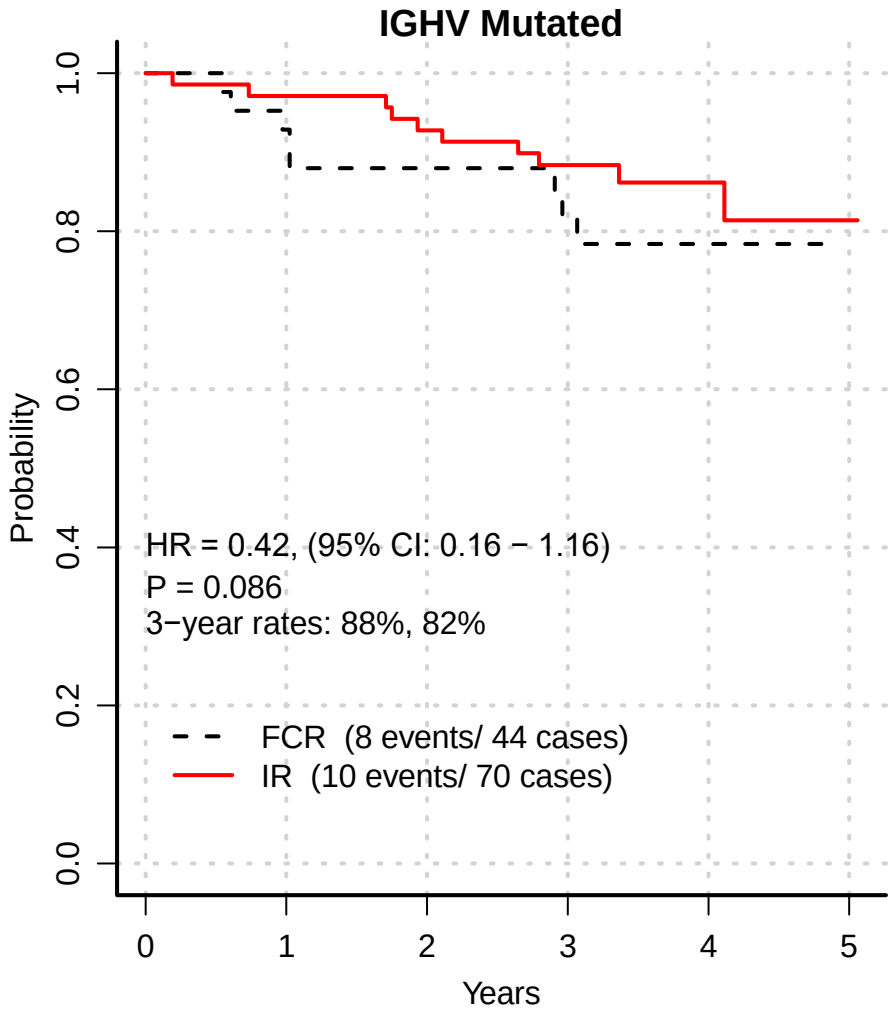
ECOG-ACRIN cancer research group | Reshaping the future of patient care

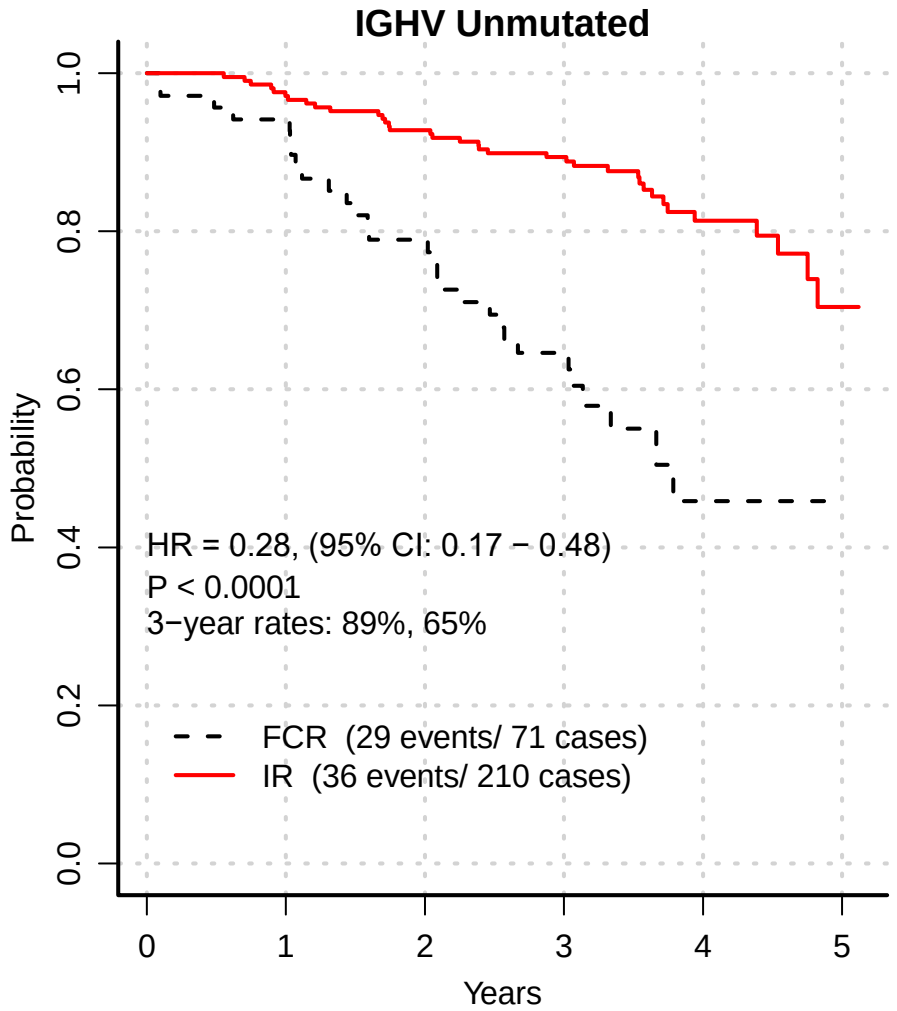
Patient Characteristics Were Well Balanced

Baseline characteristics		IR n=354	FCR n=175	Total
Median age (y)		58	57	58
Age ≥ 60		41.0%	40.0%	40.6%
Female		33.3%	31.4%	32.7%
ECOG = 0		63.8%	62.3%	63.3%
Rai stage 0		3.1%	5.1%	3.8%
Rai stage I-II		52.8%	53.7%	53.1%
Rai stage III-IV		44.1%	41.1%	43.1%
FISH	11q deletion	22.0%	22.3%	22.2%
	Trisomy 12	19.8%	15.4%	18.3%
	13q deletion	34.2%	33.1%	33.8
B2M >3.5 mg/L		51.9%	48.0%	50.6%
IGHV Unmutated*		75.0%	61.7%	71.1%

* Tested in 437 (82%) patients

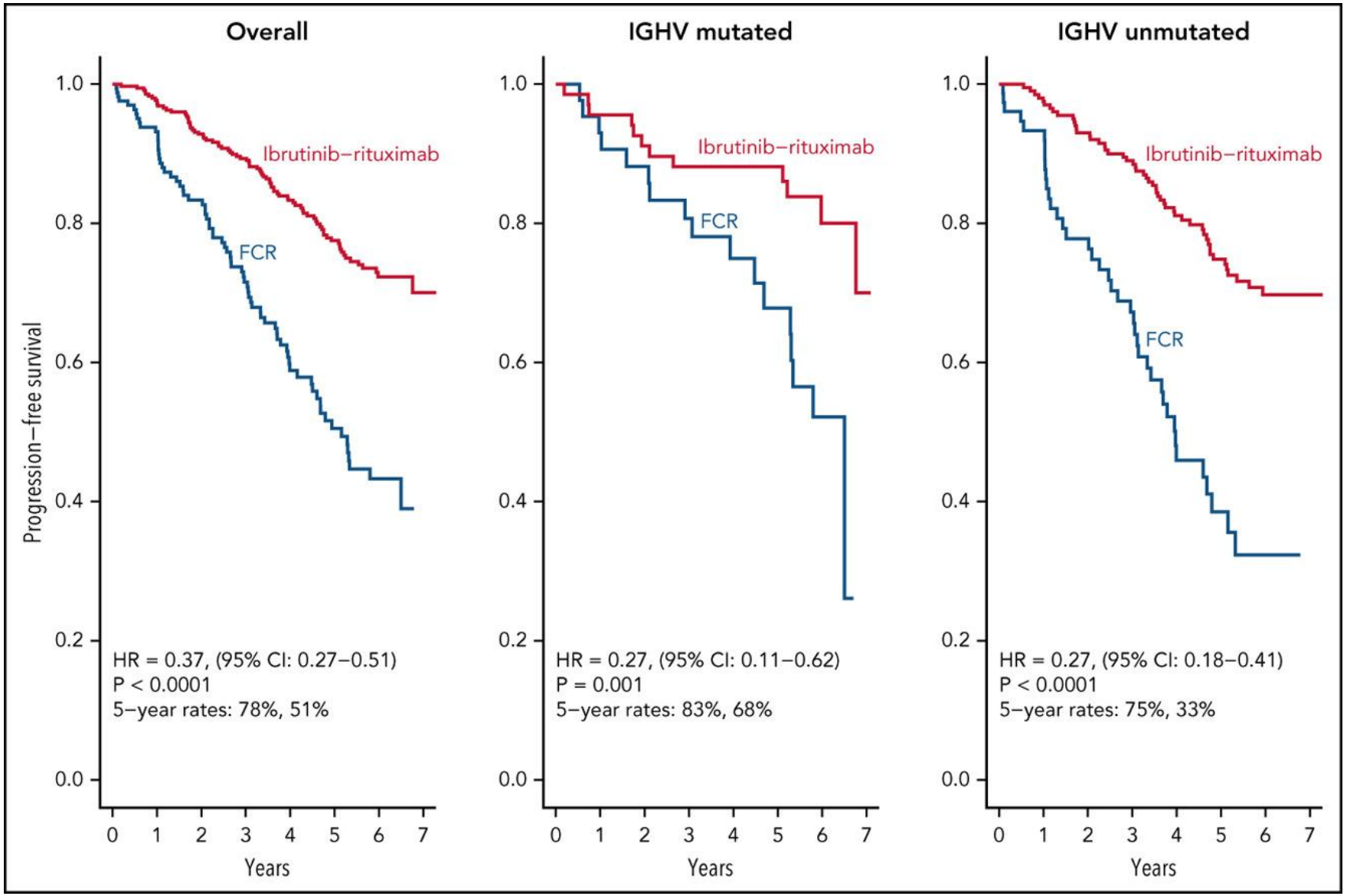
Progression Free Survival: IGHV Status





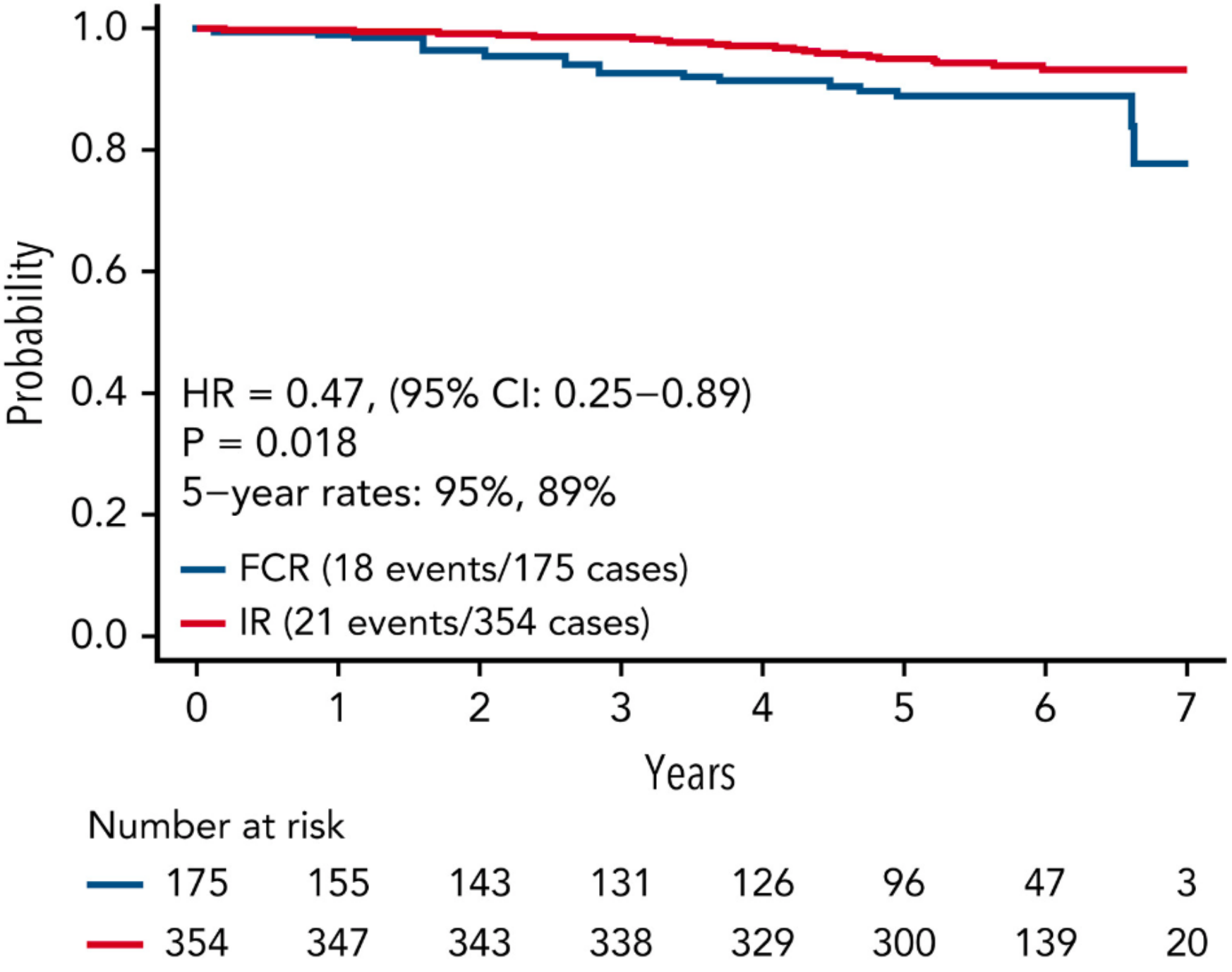
Shanafelt et al ASH 2019

Overall PFS and by IGHV Mutation Status



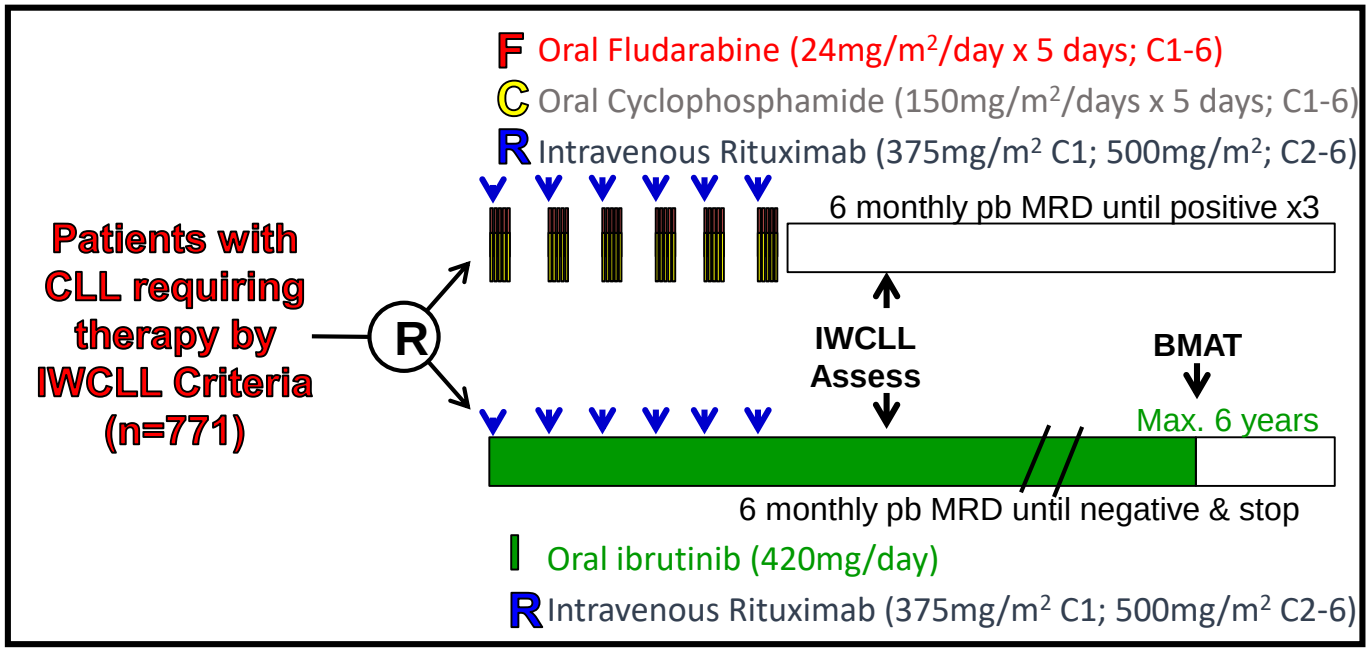
Shanafelt et al Blood July 2022

IR vs FCR Survival



Front-line trial for patients fit for FCR: NCRI *Flair* Trial

Front Line therapy in CLL: Assessment of Ibrutinib plus Rituximab



Primary end-point:
To assess whether IR is superior to FCR in terms of PFS

Key secondary end-points:
Overall survival
Response including MRD
Safety and toxicity

Key Inclusion Criteria:

- Previously untreated CLL requiring therapy by IWCLL criteria
- Considered fit for FCR
- ≤75 years old

Key Exclusion Criteria:
Prior therapy for CLL; History of Richter's transformation; >20% TP53 deletion by FISH; Concomitant warfarin (or equivalent)
Symptomatic cardiac failure or angina

Hillmen *et al.*, Abstract 642, ASH 2021

Baseline Characteristics

Flair

Characteristic		FCR (n=385)	Ibrutinib+ rituximab (n=386)	Total (n=771)
Age	Median (mo)	62	63	62
	>65 years	127 (33.0%)	132 (34.2%)	259 (33.6%)
Gender	Male	282 (73.2%)	283 (73.3%)	565 (73.3%)
Binet stage	Prog A or B	215 (55.8%)	208 (53.9%)	423 (54.9%)
	C	170 (44.2%)	178 (46.1%)	348 (45.1%)
Duration of CLL prior to randomization	Median (mo)	24.7	23.7	24.1
B symptoms	Yes	188 (48.8%)	173 (44.8%)	361 (46.8%)
B2-microglobulin	≥4 mg/l	194 (50.4%)	193 (50%)	387 (50.2%)

Baseline prognostic markers

Flair

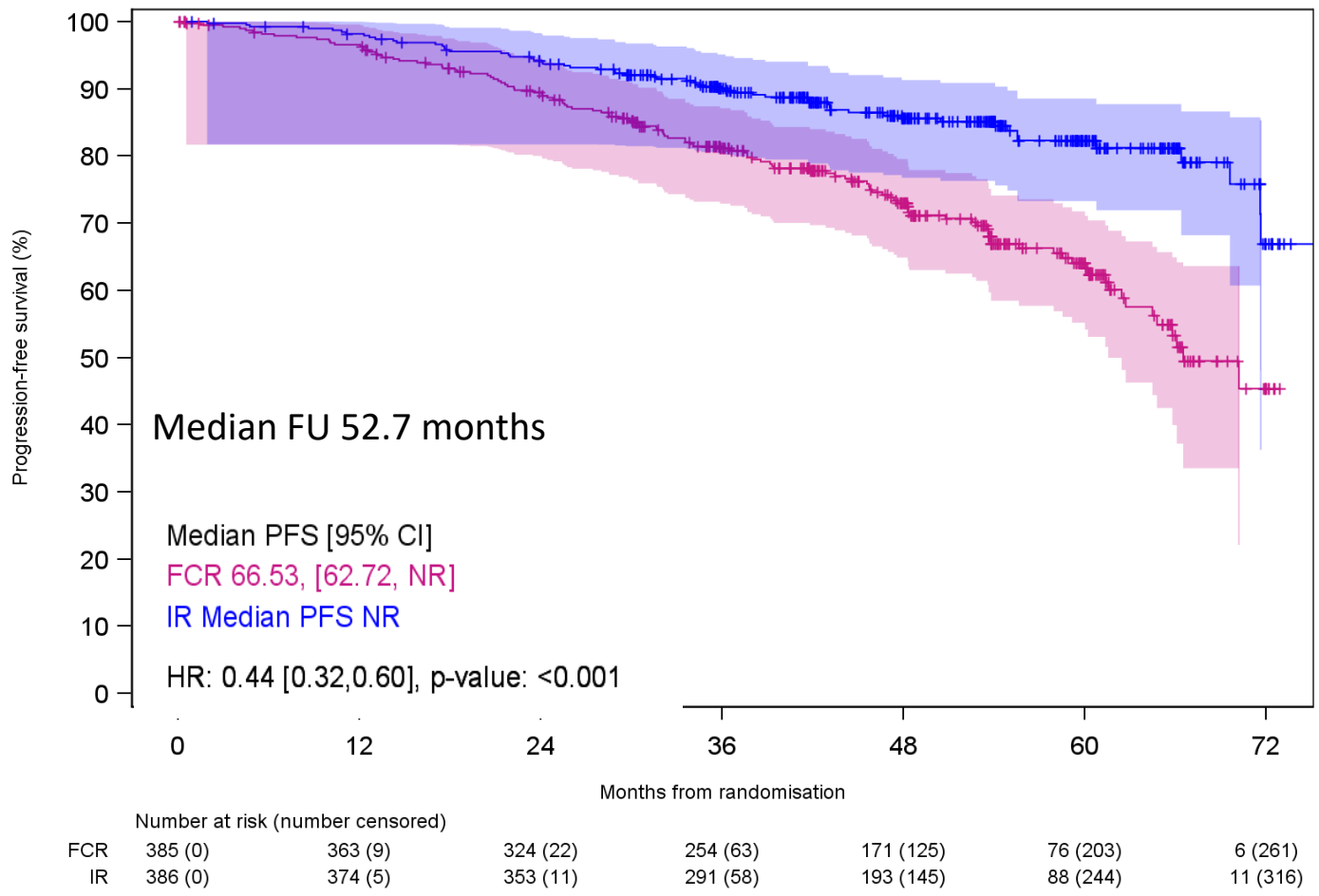
Characteristic		FCR (n=385)	Ibrutinib+rituximab (n=386)	Total (n=771)
IGHV	Mutated (excl subset 2)	146 (37.9%)	148 (38.3%)	294 (38.1%)
	Unmutated (excl subset 2)	194 (50.4%)	194 (50.3%)	388 (50.3%)
	Subset 2	20 (5.2%)	26 (6.7%)	46 (5.9%)
	Not available	25 (6.5%)	18 (4.7%)	43 (5.6%)
FISH Hierarchy	17p deletion*	1 (0.3%)	2 (0.5%)	3 (0.4%)
	11q deletion	63 (16.4%)	56 (14.5%)	119 (15.4%)
	Trisomy 12	49 (12.7%)	46 (11.9%)	95 (12.3%)
	Normal	112 (29.1%)	117 (30.3%)	229 (29.7%)
	13q deletion	131 (34%)	139 (36%)	270 (35%)
	Failed/incomplete	29 (7.6%)	26 (6.7%)	55 (7.1%)

**3 pts with 17p deletion ≥20% by central laboratory (Leeds HMDS)*

Data-lock: 24th May 2021

Hillmen *et al.*, Abstract 642, ASH 20[illegible]

Flair Primary end-point: Progression Free Survival



National Cancer Research Institute

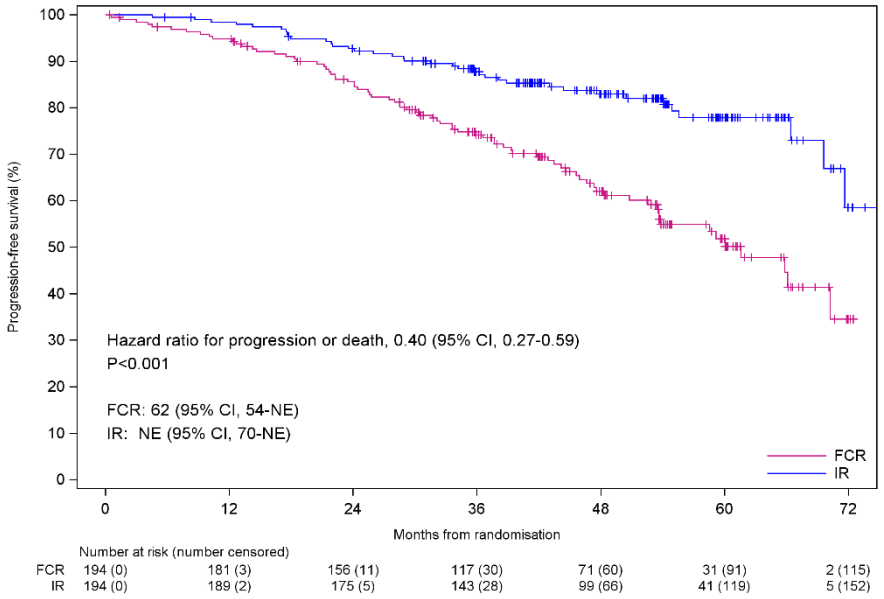
Data-lock: 24th May 2021

Hillmen *et al.,* Abstract 642, ASH 2021

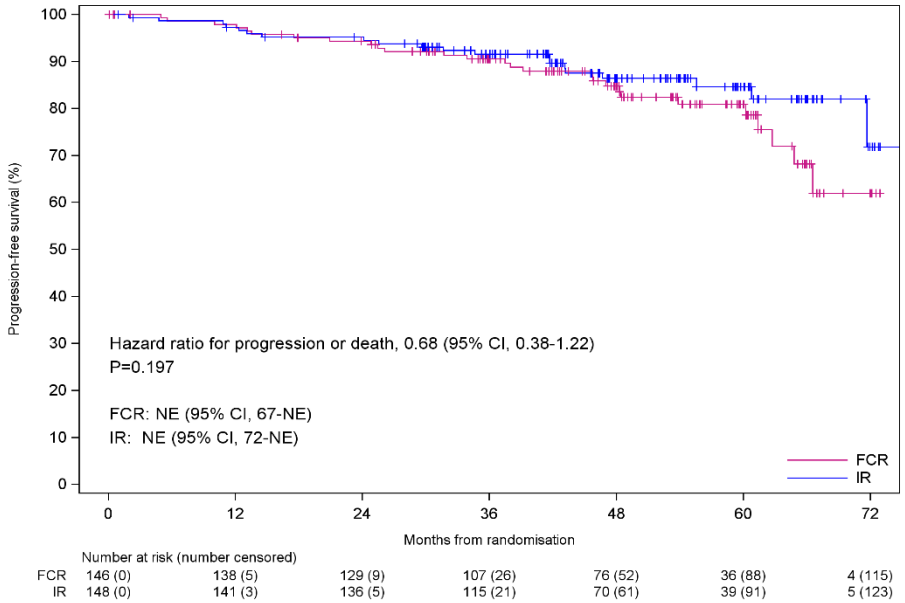
CANCER RESEARCH UK | ctru University of Leeds | LEEDS CLINICAL TRIALS UNIT

PFS by IGHV mutation status

IGHV unmutated excl. Subset 2 CLL (n=388)



IGHV mutated CLL excl. Subset 2 (n=294)

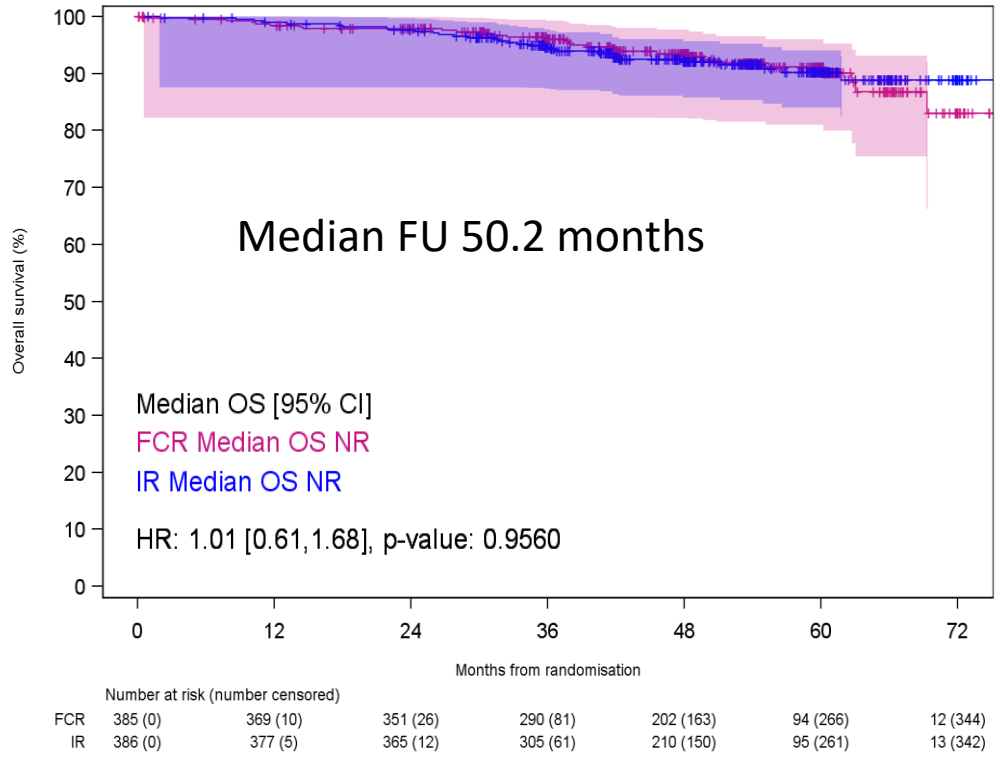


Stereotype Subset 2: n=46 (FCR 20; IR 26) → HR for PD or death 0.32 (95% CI, 0.06-1.76), p=0.191

Data-lock: 24th May 2021

Hillmen *et al.,* Abstract 642, ASH 2021

Flair Overall Survival



Treatment after progression

	FCR (n=56)	IR (n=19)
Therapy for Richter's transformation or Hodgkin's		
CHOP-R (5) or ABVD (1)	4	2
Therapy for relapsed CLL		
BTKi	38	0
Idelalisib + R	1	1
Venetoclax + R	8	5
CIT (FCR/BR/ChlR)	4	10
Rituximab	1	1
Targeted therapy for CLL	**47/52 (90%)**	**6/17 (35%)**

Overall survival historical comparison

Surviving at:	FCR FLAIR (2014-2018)	FCR ADMIRE/ARCTIC (2009-2012)
12 months	98.4%	97.5%
24 months	97.9%	92.9%
36 months	96.4%	86.8%
48 months	94.5%	84.2%

National Cancer Research Institute

Data-lock: 24th May 2021

Hillmen *et al.,* Abstract 642, ASH 2021

CANCER RESEARCH UK | ctru University of Leeds | LEEDS CLINICAL TRIALS UNIT

Causes of death in *Flair*

Cause of death *	FCR (n=29)	IR (n=30)
CLL	4	3
Non-haematological malignancy	4	7
AML/MDS	3	0
ALL	1	0
Richters transformation	3	1
Infections (non-COVID)	6	4
COVID-19	3	3
Haemorrhage	1	2
Cardiac	2	9
Other	2	1
Total	**29**	**30**

Deaths in FCR arm were predominantly secondary haematological malignancies, Richter's transformation and infections.

Deaths in IR arm were predominantly CV-related and non-haematological malignancies.

*, Deaths at any time in follow-up

IR vs FCR: Causes of Death

Cause of Death	IR (n=354)	FCR (n=175)
AML	0	3
Cardiac	1	1
CLL	5	6
COVID-19	3	0
Other cancer	5	3
Other cause	2	1
Other medical cause	3	2
Sepsis	1	1
Unknown	1	1
Total	21	18

Other cancer: lung cancer (n=2, IR), brain cancer (n=2, IR), esophagus (IR), colon cancer (n=2, FCR), lung cancer (FCR). Other cause: suicide (IR), accident (IR), drug overdose (FCR). Other medical cause: acute respiratory failure (IR), pancreatitis (IR), stroke (IR), tumor lysis from venetoclax (FCR), GVHD (FCR).

Shanafelt et al Blood July 2022

IBR + VEN: Treatment Schema

	C1	C2	C3	C4-->27
Ibrutinib	420mg daily	420mg daily	420mg daily	420mg daily
Venetoclax	-	-	-	20mg daily 1 week; 50mg daily 1 week; 100mg daily 1 week; 200mg daily 1 week; 400mg daily continuous

Duration of therapy: <u>24 cycles</u> of combination treatment

- **Marrow U-MRD at 24 cycle: Both ibrutinib and venetoclax d/c**
- **Marrow MRD+ at 24 cycle: Both continue for another 1 year**

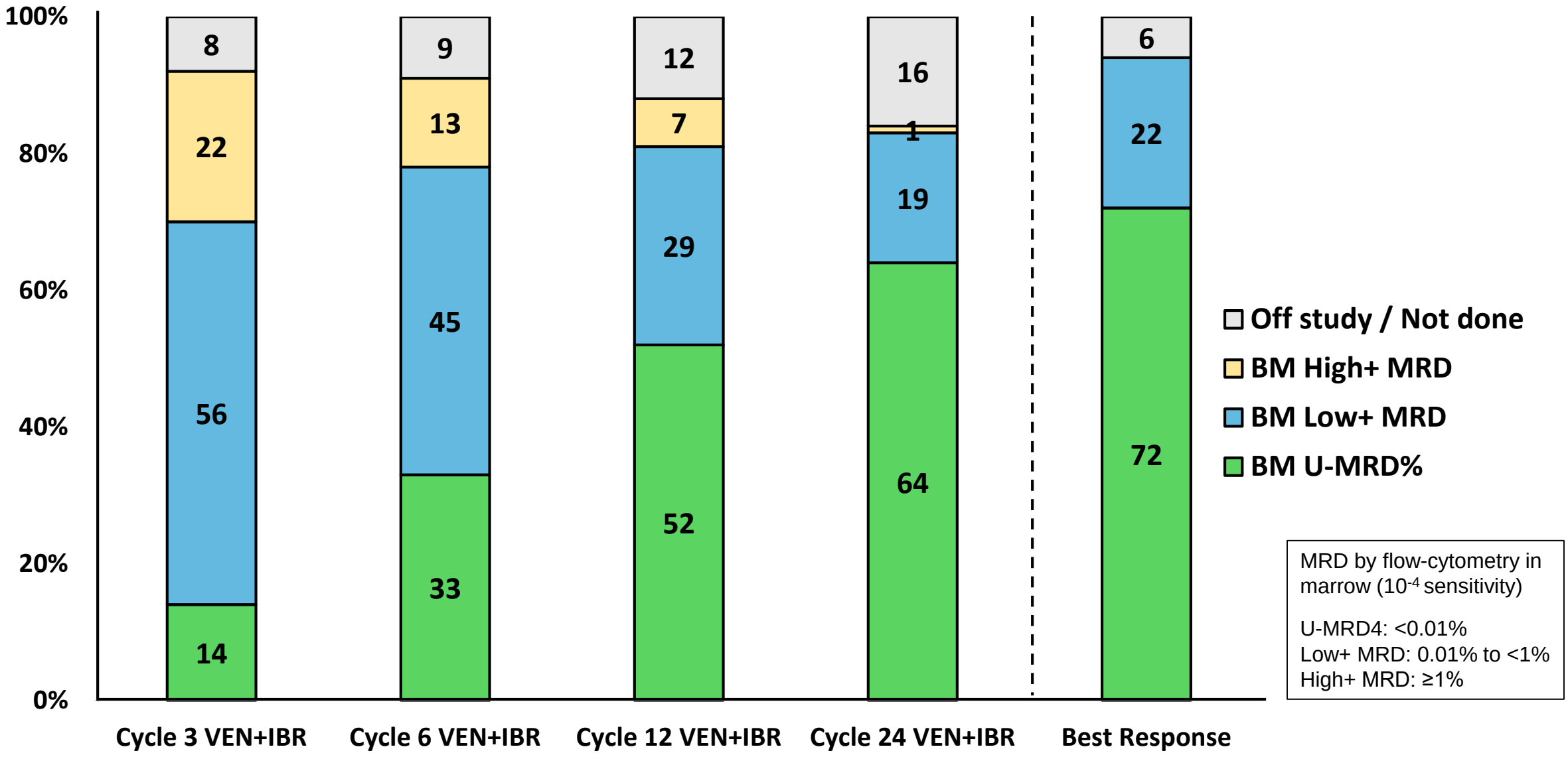
Jain N et al. N Engl J Med. 2019 May 30;380(22):2095-2103.
Jain N et al. JAMA Oncol. 2021 Aug 1;7(8):1213-1219.

Baseline Characteristics (N=120)

Between August 2016 and February 2019, a total of 120 pts were enrolled

		n (%) or median [range]
Age, years		64.5 [26-88]
	≥65	60 (50)
	≥70	35 (29)
Gender, M		87 (73)
ALC, K/µL		76.3 [1.14-366]
PLT, K/µL		140 [28-334]
HGB, g/dL		12.0 [7.7-18.4]
B2M, mg/L		3.6 [1.7-13.7]
FISH	Del(17p)	20 (17)
	Del(11q)	31 (26)
	Trisomy 12	23 (19)
	Negative	19 (16)
	Del(13q)	27 (22)
IGHV status (n=116)	Unmutated	100 (86)
Cytogenetics (n=115)	Complex	15 (13)
Mutations (n=119)	*TP53*	19 (16)
	NOTCH1	35 (29)
	SF3B1	26 (22)
	BIRC3	9 (8)
Del(17p) / *TP53*-m		27 (23)

Marrow MRD Response at Serial Time-Points
Intent-to-Treat (N=120)



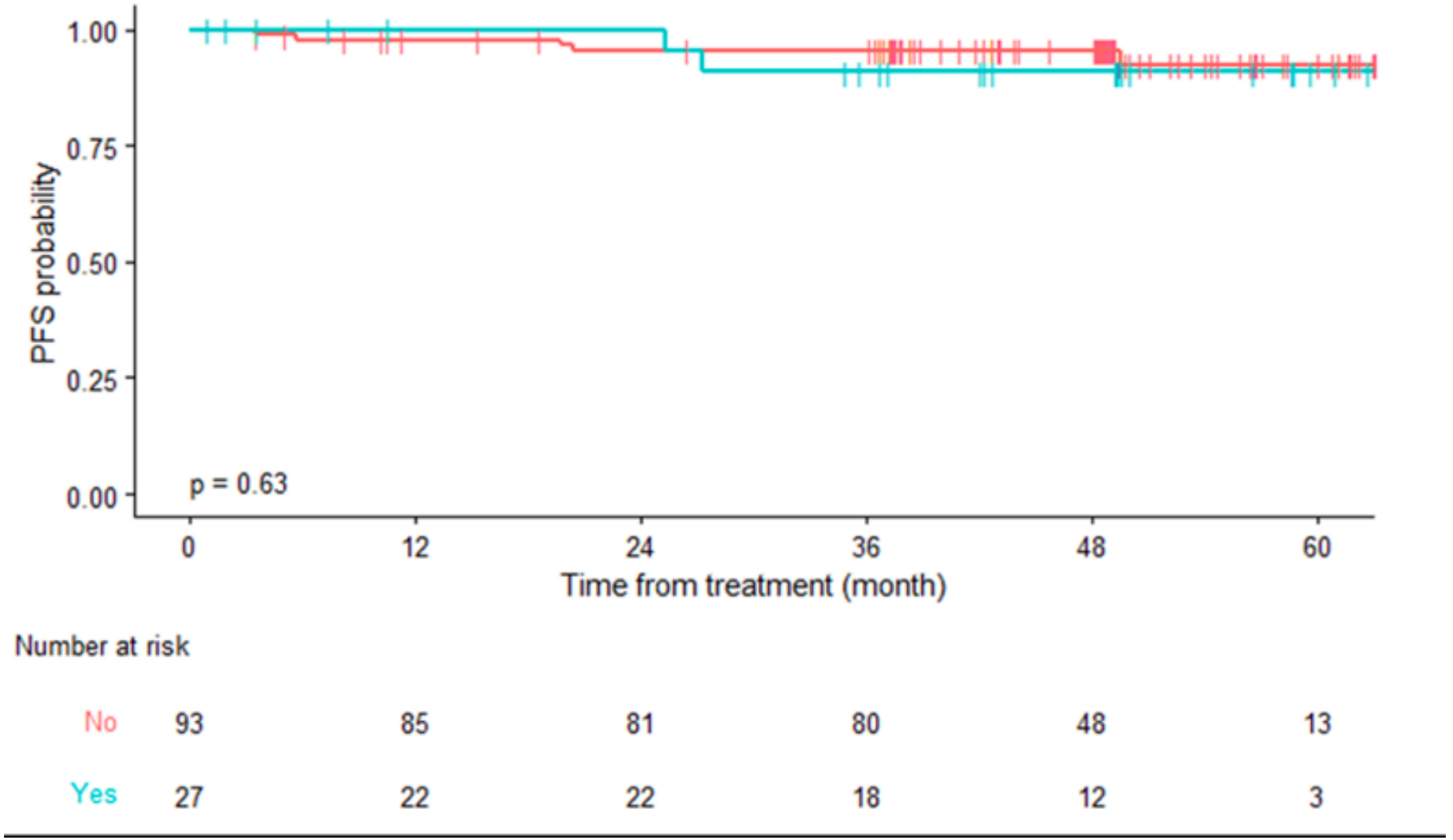
MRD by flow-cytometry in marrow (10^{-4} sensitivity)

U-MRD4: <0.01%
Low+ MRD: 0.01% to <1%
High+ MRD: ≥1%

IBR + VEN: PFS by TP53 Status (N = 120)

4 year PFS 94.5%;

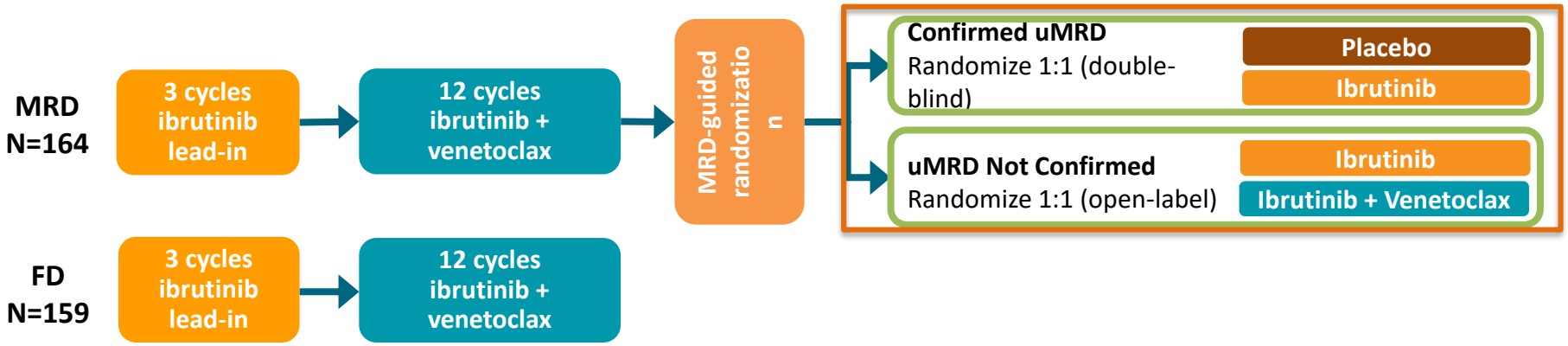
90.9% TP53 aberrant vs 95.5%



Jain et al ASH 2002 Abstract # 95

Phase 2 CAPTIVATE Study

- CAPTIVATE (PCYC-1142) is an international, multicenter phase 2 study evaluating first-line treatment with 3 cycles of ibrutinib followed by 12 cycles of combined ibrutinib + venetoclax with 2 cohorts: MRD and FD

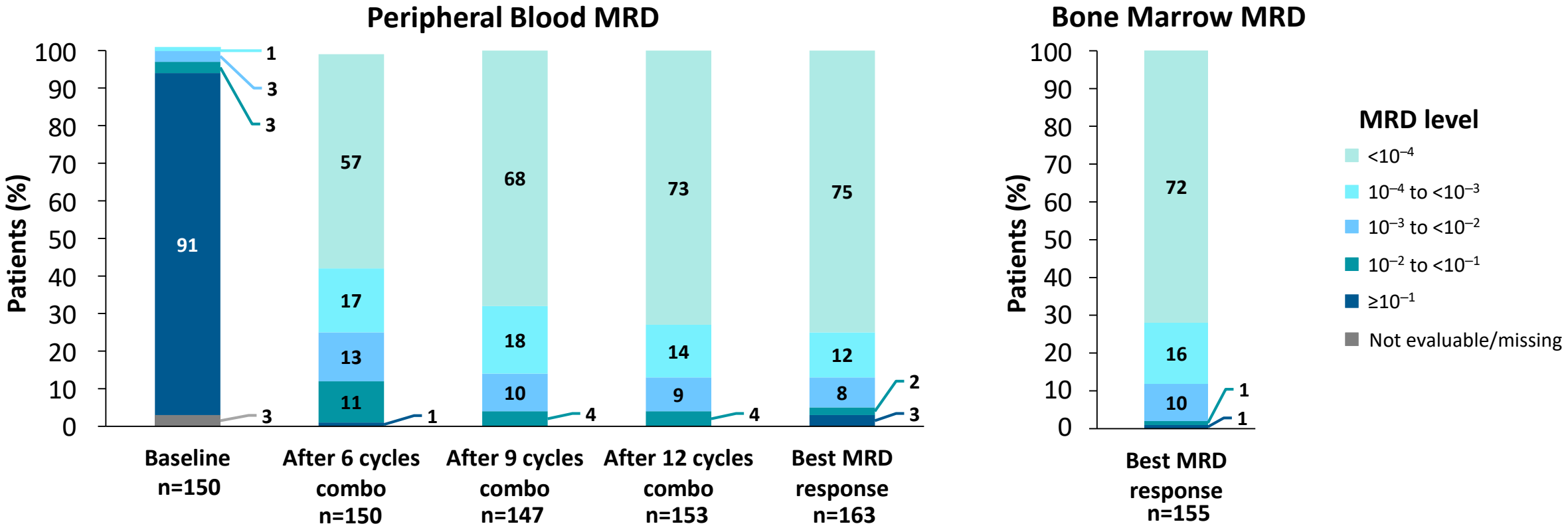


- Primary analyses of both cohorts have been previously reported[1,2]
- Presented are updated results from the MRD cohort, with median time on study: 38.2 months (range, 15.0–47.9)
  - Median postrandomization follow-up: 24.0 months (range, 5.8–33.1)

2 MRD, minimal residual disease; FD, fixed-duration.
9 1. Wierda WG et al. ASH 2020. Abstract #123. 2. Ghia P et al. ASCO 2021. Abstract #7501.

ASH 2021, CAPTIVATE-MRD; Ghia et al.

CAPTIVATE: A PHASE 2 STUDY OF IBRUTINIB + VENETOCLAX IN 1L CLL

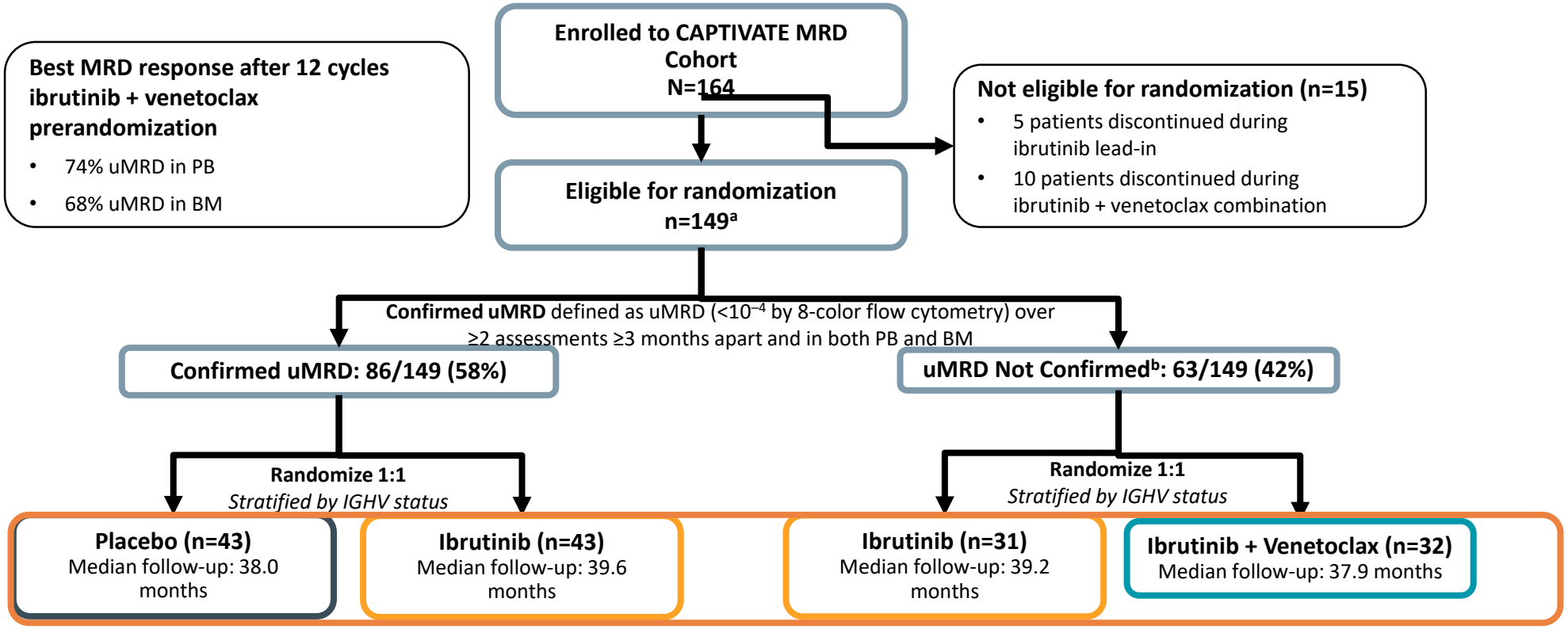


Proportion of patients with undetectable MRD in peripheral blood increased over the 12 cycles of combination therapy

[a]BM MRD assessment was scheduled after completion of 12 cycles of combination treatment.

ASH 2019, CAPTIVATE-MRD; Tam et al.

MRD Cohort: Patient Disposition and Randomization (cont.)



BM, bone marrow; PB, peripheral blood.
[a]Includes 1 patient who discontinued venetoclax but completed planned treatment with ibrutinib. [b]Did not meet criteria for uMRD because of detectable MRD in PB and/or BM *or* undetectable MRD in PB that was not confirmed at consecutive assessments.

ASH 2021, CAPTIVATE-MRD; Ghia et al.

Most Patients Had High-Risk Disease Features

Placeholder for Video

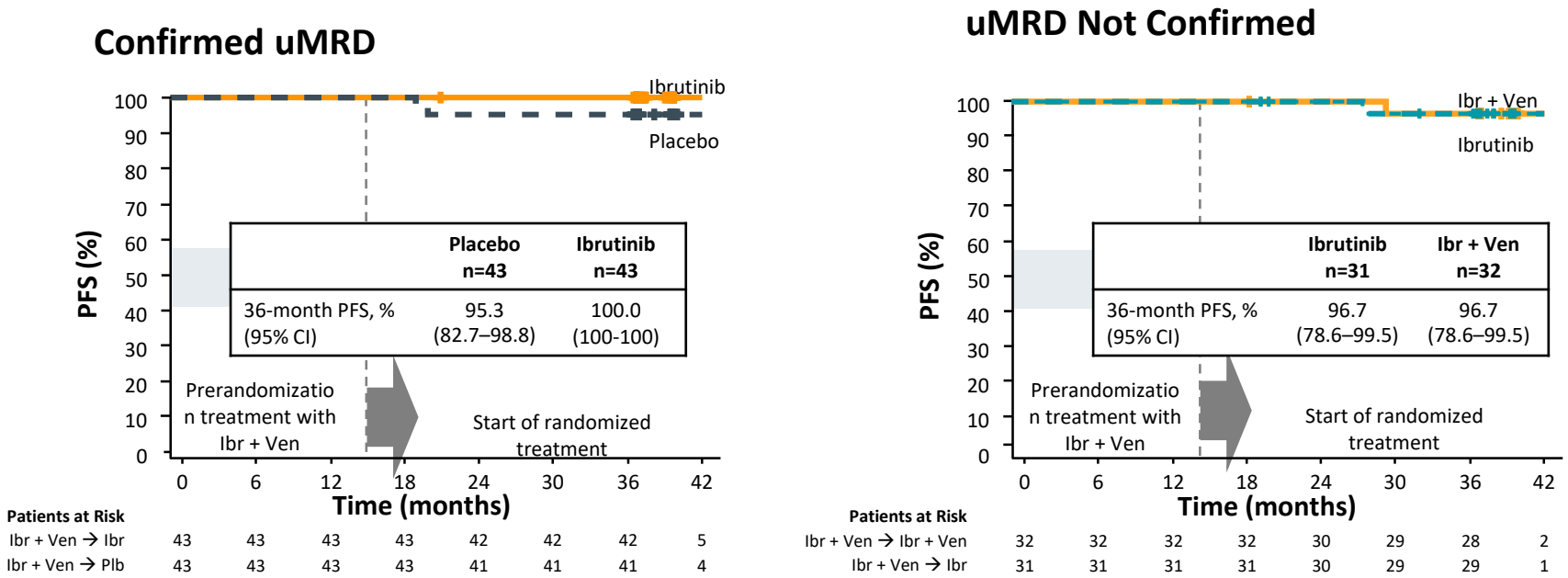
Characteristic	All Treated Population N=164	Confirmed uMRD (n=86)		uMRD Not Confirmed (n=63)	
		Placebo n=43	Ibrutinib n=43	Ibrutinib n=31	Ibrutinib + Venetoclax n=32
Median age (range), year	58 (28–69)	61 (43–69)	56 (34–69)	58 (28–69)	56 (37–69)
Rai stage III/IV disease, n (%)	53 (32)	15 (35)	8 (19)	14 (45)	11 (34)
High-risk features, n (%)					
del(17p)/*TP53* mutation	32 (20)	2 (5)	13 (30)	5 (16)	8 (25)
del(11q)[a]	28 (17)	8 (19)	10 (23)	3 (10)	2 (6)
Complex karyotype[b]	31 (19)	4 (9)	13 (30)	5 (16)	4 (13)
Unmutated IGHV	99 (60)	30 (70)	30 (70)	14 (45)	15 (47)
Any cytopenia, n (%)	59 (36)	19 (44)	6 (14)	13 (42)	14 (44)
ANC ≤1.5 × 10^9/L	14 (9)	5 (12)	0	2 (6)	4 (13)
Hemoglobin ≤11 g/dL	35 (21)	14 (33)	2 (5)	9 (29)	7 (22)
Platelets ≤100 × 10^9/L	30 (18)	4 (9)	4 (9)	9 (29)	9 (28)
Lymph node diameter, n (%)					
≥5 cm	53 (32)	18 (42)	10 (23)	7 (23)	11 (34)
Median ALC × 10^9/L (range)	56 (1–419)	53 (1–235)	56 (2–256)	85 (1–342)	87 (3–419)
ALC ≥25 × 10^9/L, n (%)	125 (76)	32 (74)	34 (79)	25 (81)	24 (75)

ALC, absolute lymphocyte count; ANC, absolute neutrophil count.

[a]Without del(17p) per Dohner hierarchy. [b]Defined as ≥3 abnormalities by CpG-stimulated cytogenetics.

ASH 2021, CAPTIVATE-MRD; Ghia et al.

3-Year PFS Rates Were ≥95% Across All Randomized Arms



Median follow-up = 38 months

- With an additional year of follow-up since the primary analysis, only 1 new PFS event occurred on study; a patient in the uMRD Not Confirmed ibrutinib arm who had PD after 42 months
- 36-month OS was 99% overall (97%–100% across randomized treatment arms)

ASH 2021, CAPTIVATE-MRD; Ghia et al.

PFS, progression-free survival; Plb, placebo. Tick marks indicate patients with censored data.

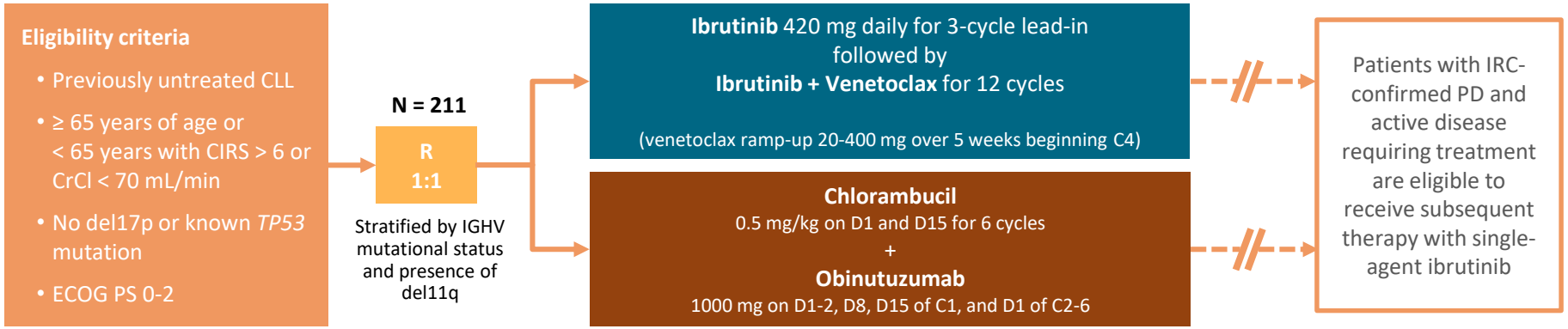
CAPTIVATE MRD Undetectable Cohort Randomized to Ibrutinib or Placebo: Efficacy Outcomes

Efficacy outcomes, % (95% CI)	All treated PBO (N=43)	All treated Ibr (N=43)	High-risk[a] PBO (N=6)	High-risk[a] Ibr (N=20)
DFS (3-y)	85 (69–93)	93 (80–98)	100 (100–100)	95 (70–99)
PFS (4-y)	88 (74–95)	95 (82–99)	100 (100–100)	95 (70–99)
OS (4-y)	100 (100–100)	98 (84–100)	100 (100–100)	100 (100–100)

High risk defined as del(17p), TP53 mutation or complex karyotype

Allan et al ASH 2022 Abstract # 92

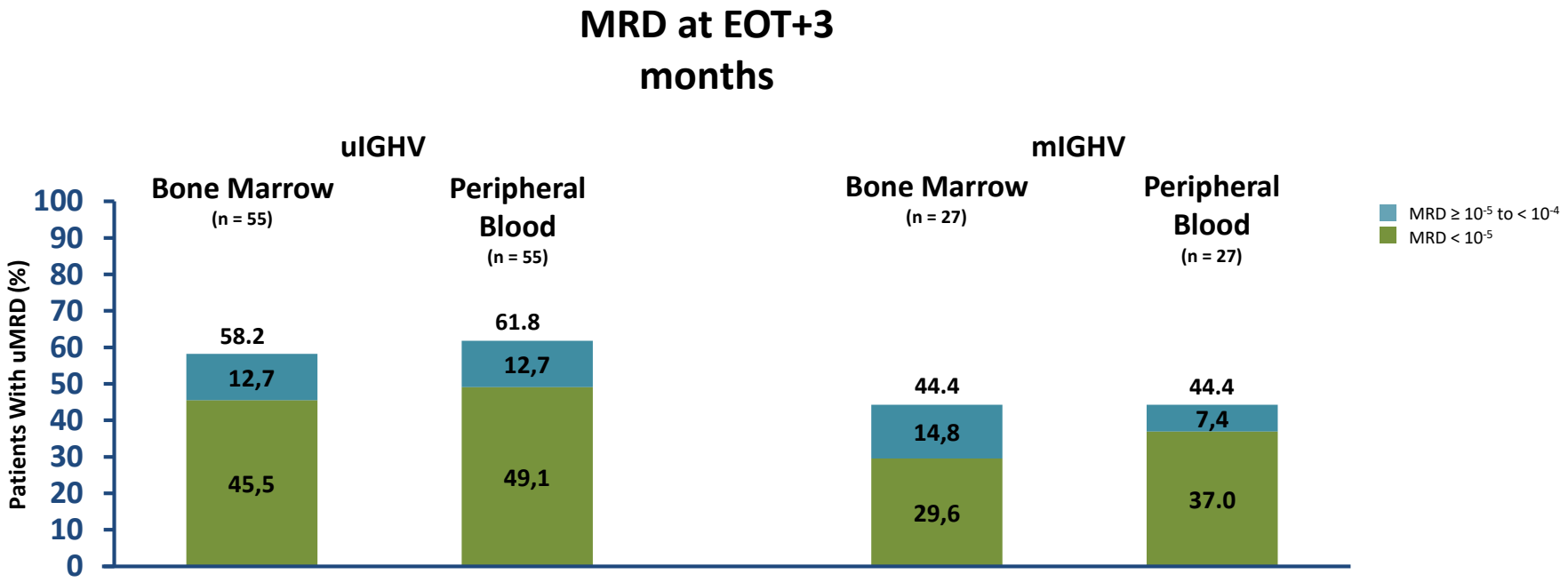
Phase 3 GLOW Study Design (NCT03462719)



- **Study primary endpoint:** PFS as assessed by IRC
- **Current MRD analysis:**
  - MRD evaluated via NGS and reported with cutoffs of < 10^{-4} and < 10^{-5} (not all samples had sufficient cell yield to be analyzed at < 10^{-6}). NGS analysis not yet available beyond EOT+12 time point
  - PB/BM concordance calculated for patients with uMRD in PB at EOT+3 who had a paired BM sample
  - PFS results updated with 34.1 months of follow-up

BM, bone marrow; C, cycle (28 days); CIRS, Cumulative Illness Rating Scale score; CrCl, creatinine clearance; D, day; ECOG PS, Eastern Cooperative Oncology Group performance status; EOT, end of treatment; EOT+3,
3 months after EOT; EOT+12, 12 months after EOT; IRC, independent review committee; NGS, next-generation sequencing; PB, peripheral blood; PD, progressive disease; R, randomization; uMRD, undetectable minimal residual disease.

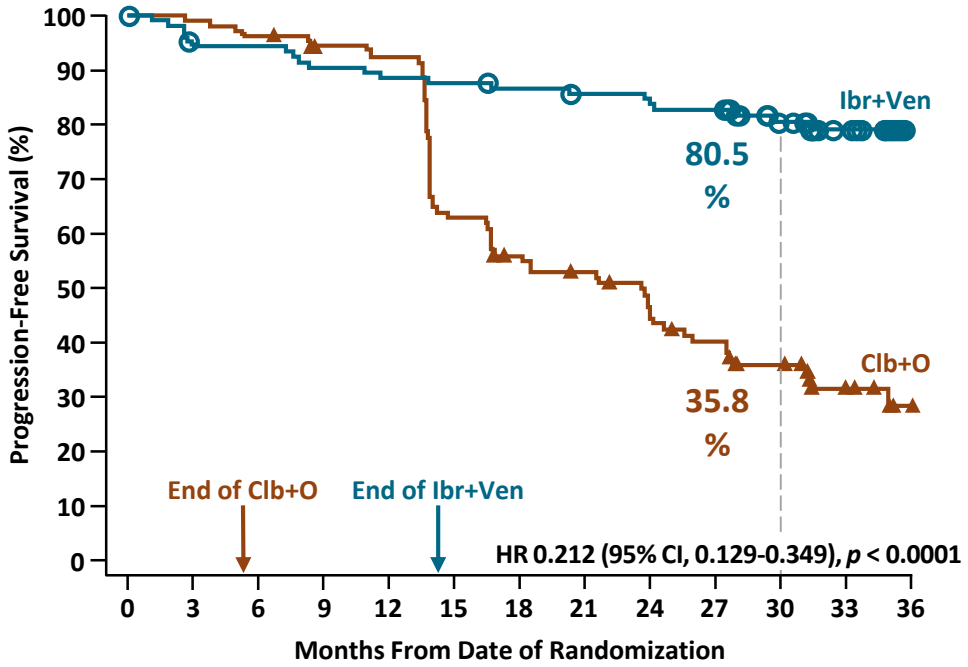
Ibr+Ven: uMRD Rates Were High in BM and PB for Patients With uIGHV CLL



- With Ibr+Ven, depth of MRD response was similar in BM and PB for patients with uIGHV CLL
- Among patients with mutated *TP53*, 5 of 7 achieved uMRD < 10^{-5} in both BM and PB with Ibr+Ven

Patients with IGHV status not available (n = 24): 45.8% (BM) and 50.0% (PB) had uMRD < 10^{-4}.
MRD results by next-generation sequencing at EOT+3.
BM, bone marrow; EOT, end of treatment; mIGHV, mutated IGHV; PB, peripheral blood; uIGHV, unmutated IGHV.

Superior Progression-Free Survival With Ibr+Ven vs Clb+O Was Maintained With Median 34.1 Months of Follow-up



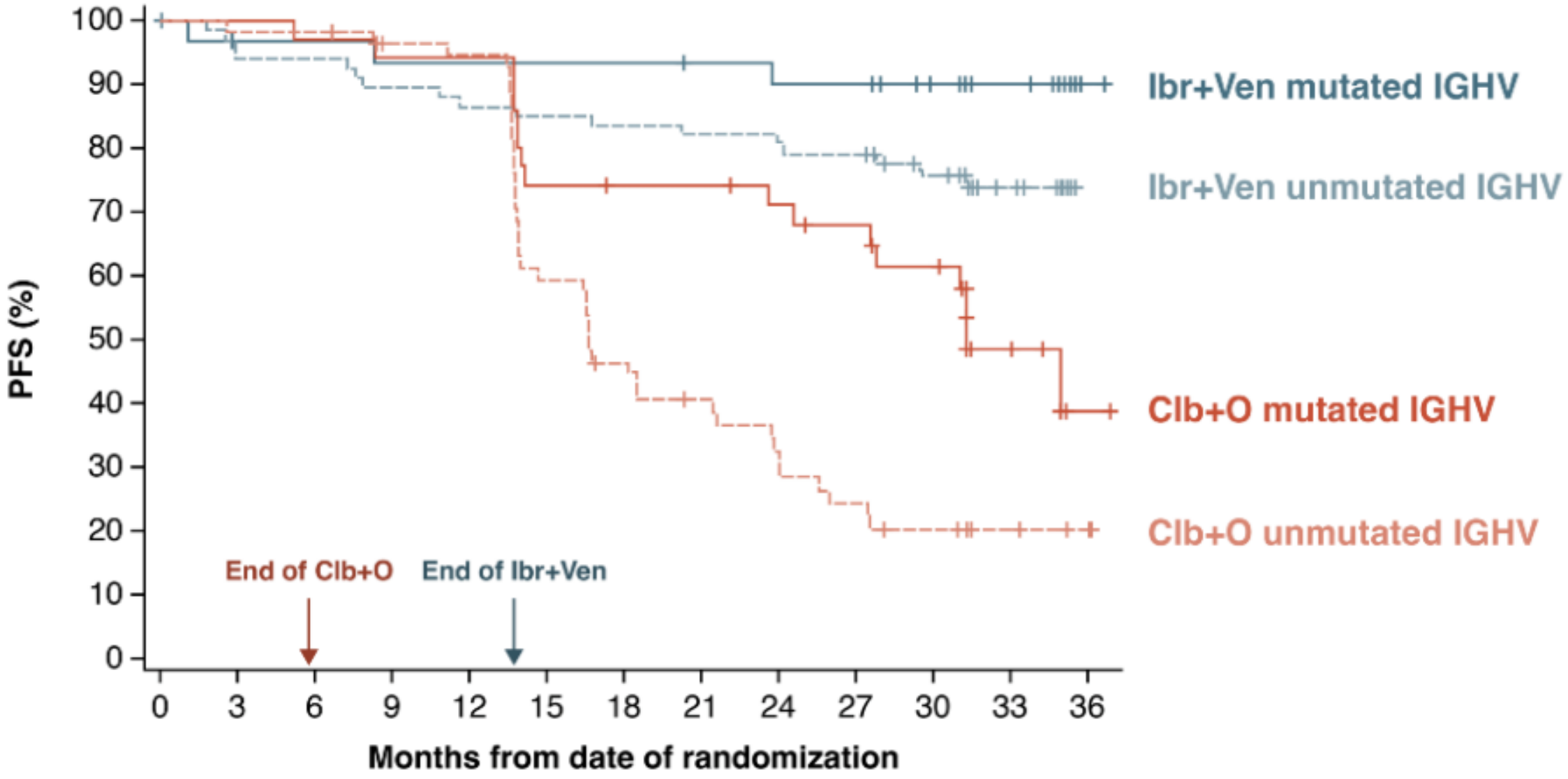
Patients at risk

Ibr+Ven	106	98	98	94	92	91	89	87	86	84	71	42	1
Clb+O	105	104	101	96	94	64	55	51	43	37	30	13	3

CI, confidence interval; HR, hazard ratio; OS, overall survival.

- IRC-assessed PFS for Ibr+Ven was superior to Clb+O at primary analysis (median 27.7 months of follow-up)
  - HR 0.216 (95% CI, 0.131-0.357; $p < 0.0001$)
- **With median follow-up of 34.1 months:**
  - IRC-assessed PFS remained superior for Ibr+Ven (HR 0.212, 95% CI, 0.129-0.349; $p < 0.0001$)
  - 30-month PFS: 80.5% for Ibr+Ven vs 35.8% for Clb+O
  - Overall survival HR 0.76 (95% CI, 0.35-1.64), with 11 deaths for Ibr+Ven vs 16 for Clb+O

GLOW: PFS by IGHV Status



Niemann et al ASH 2022 Abstract # 93