Practice Changing for CLL

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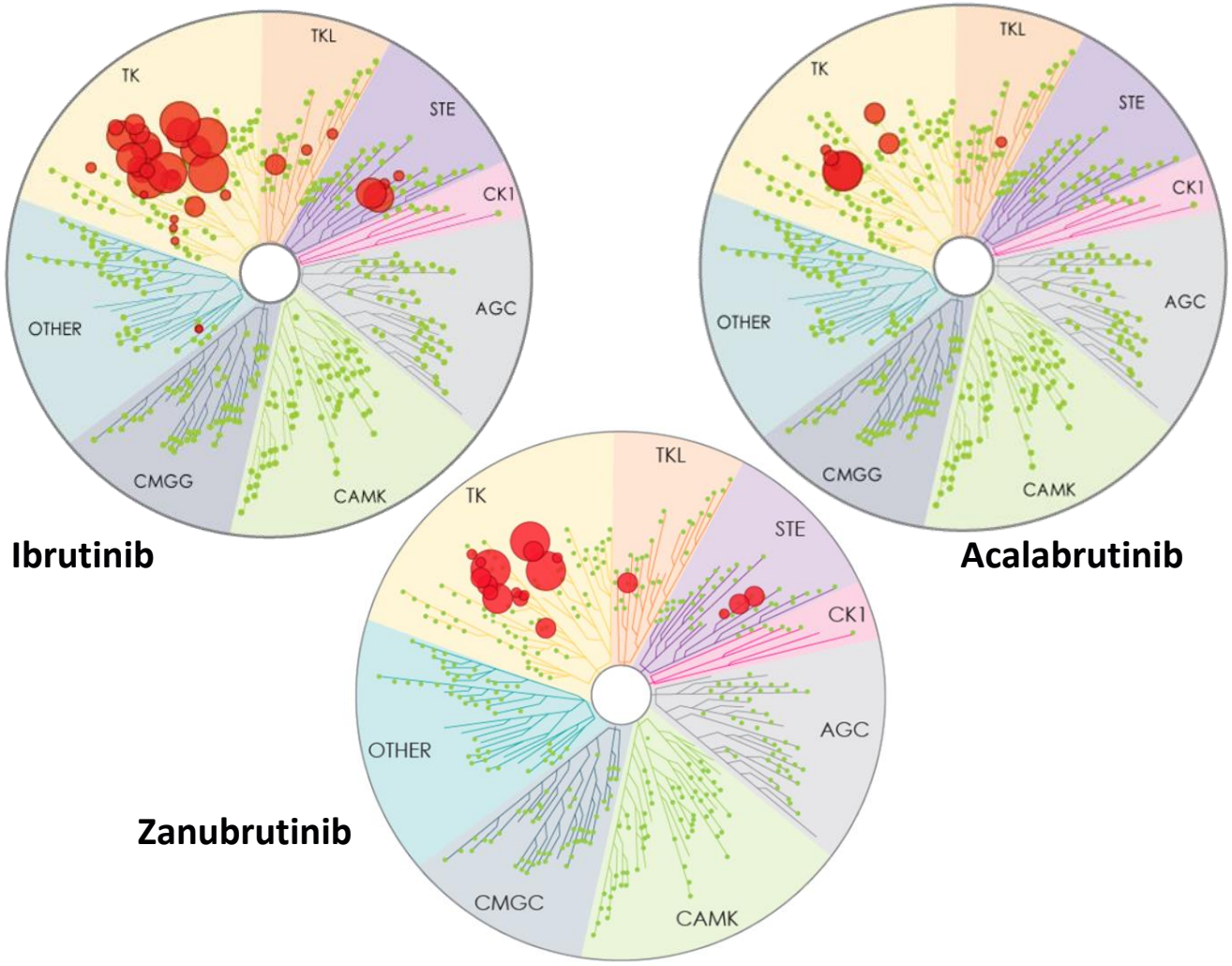
MOFFITT CANCER CENTER

The new era of BTK Inhibitors

Kinase	IC_{50}/EC_{50} (nM) Ibrutinib	Acalabrutinib	Zanubrutinib
BTK	1.5	5.1	0.5
TEC	10	126	44
ITK	4.9	> 1000	50
BMX	0.8	46	1.4
EGFR	5.3	> 1000	21
ERBB4	3.4	16	6.9
JAK3	32	> 1000	1377
BLK	0.1	> 1000	2.5

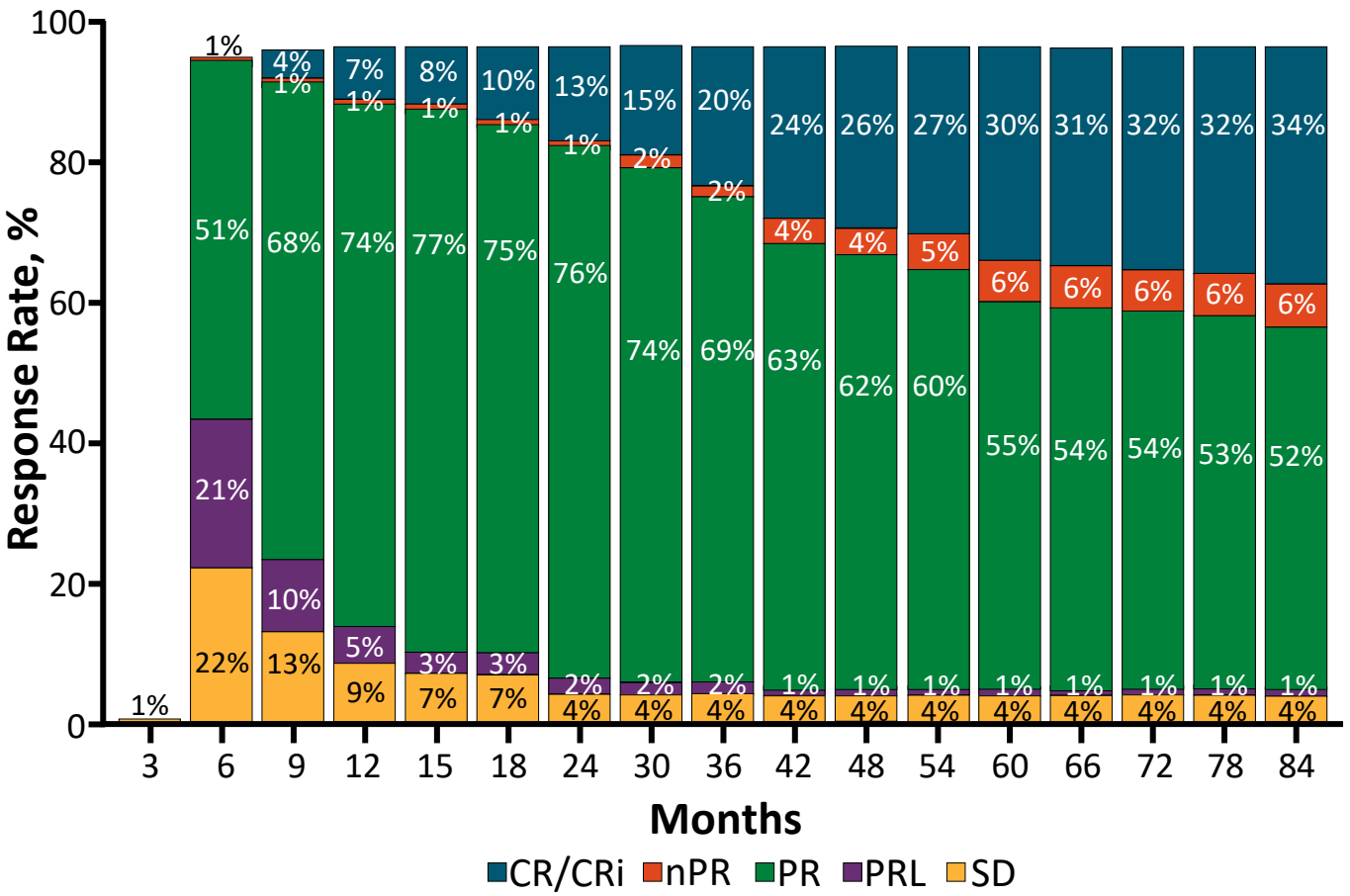
Kinase Selectivity Profiling at 1 μmol/L (in vitro)
Larger red circles represent stronger inhibition



Kaptein. ASH 2018. Abstr 1871.

RESONATE-2: 7-Year Follow-Up - Responses

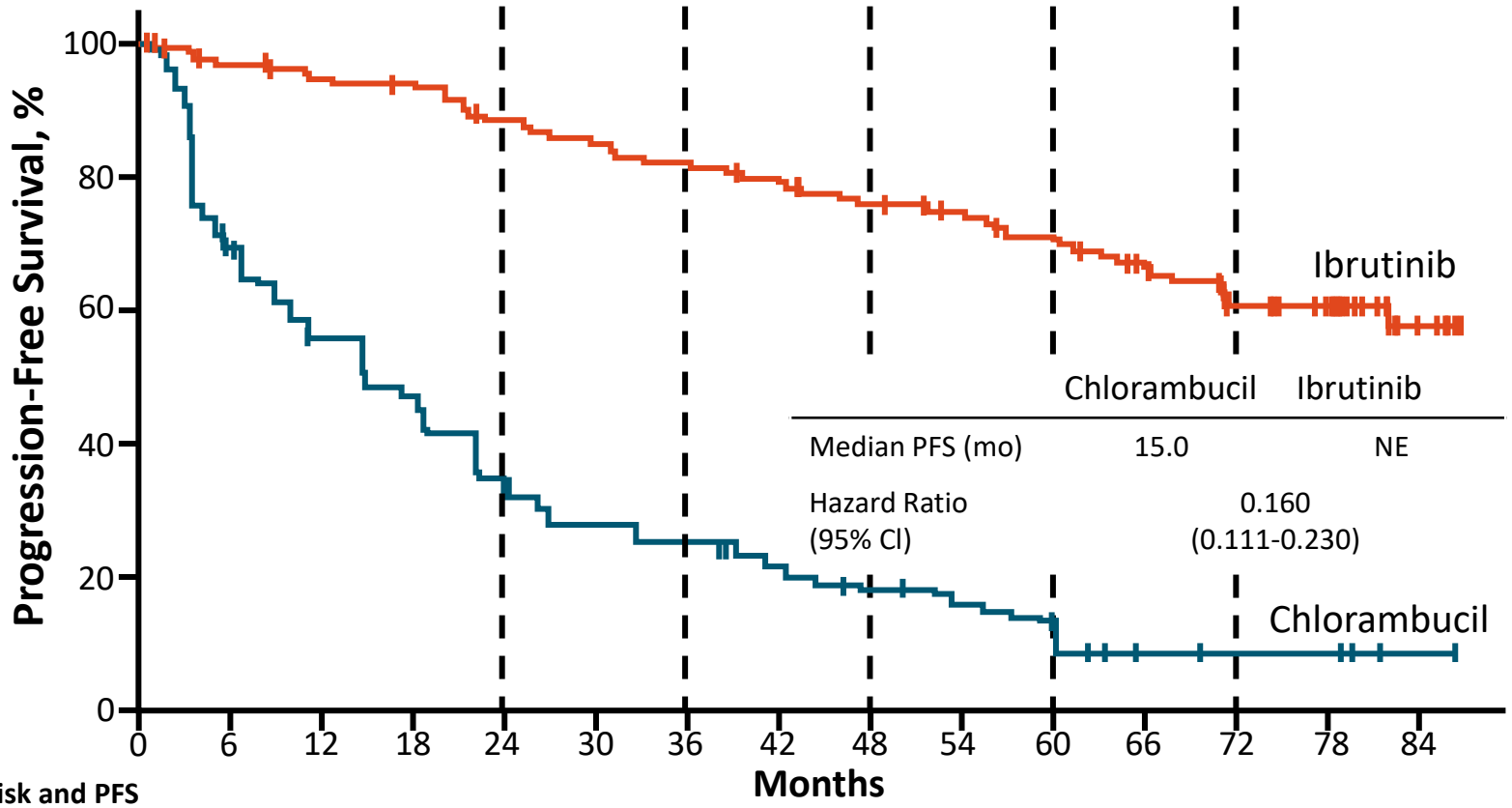
- Open-label, randomized phase III trial of ibrutinib vs chlorambucil in older patients with treatment-naive CLL or SLL (N = 269)
  - Median age: 73 yrs (range: 65-89)
  - Unmutated IGHV in only 48% of ibrutinib arm vs 47% in chlorambucil arm
  - del(17p) excluded



Barr. ASCO 2021.
Ghia EHA21

RESONATE-2: 7-Year Follow-Up - PFS

- PFS with ibrutinib:
  - 90% at 18 mo
  - 70% at 60 mo
  - 61% at 78 mo
- PFS benefit seen across all subgroups

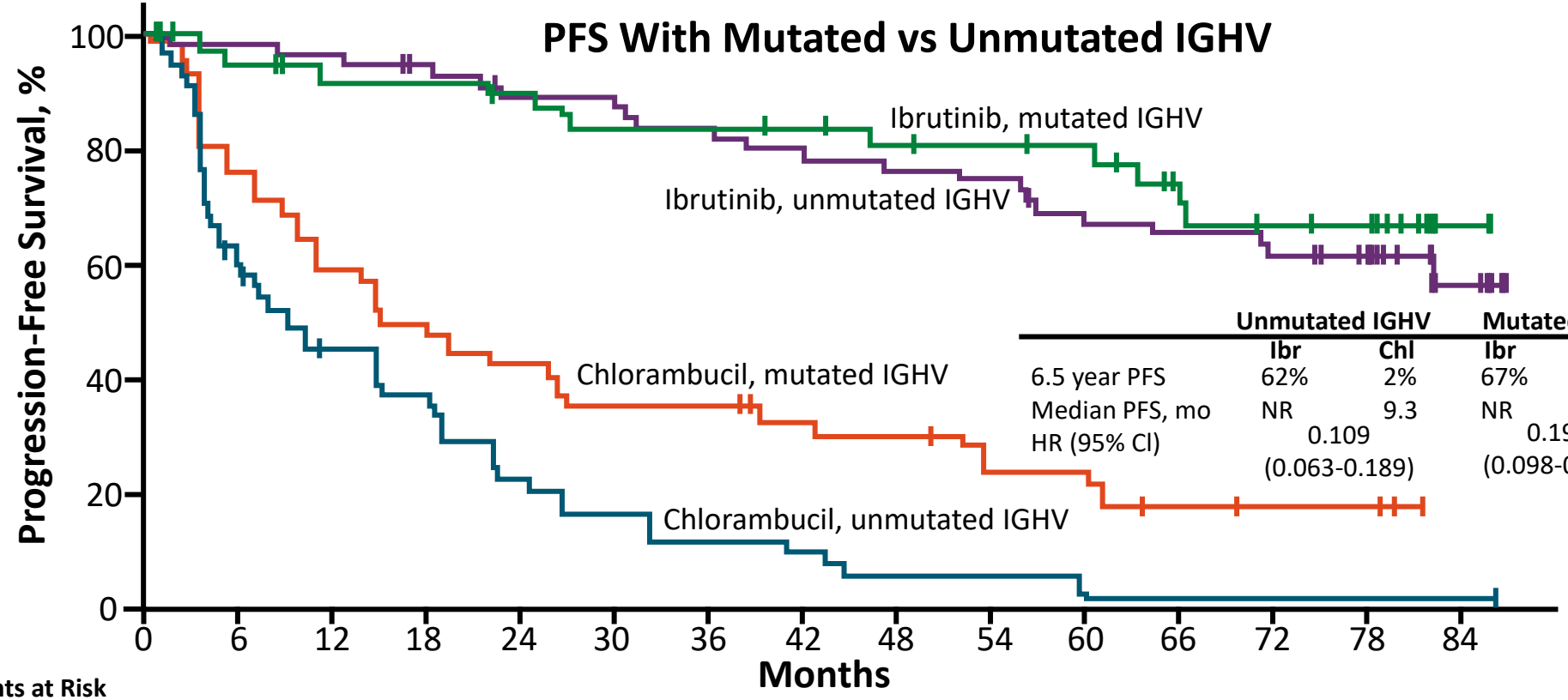


Patients at Risk and PFS

Ibrutinib:	136	129	124	121	112	108	104	99	92	88	81	74	64	56	12
PFS, %:					89		82		76		71		61		
Chlorambucil:	133	88	69	57	41	33	30	25	19	16	12	6	5	5	1
PFS, %:					35		25		18		12		9		

Barr. ASCO 2021.
Ghia EHA21

RESONATE-2: 7-Year Follow-Up



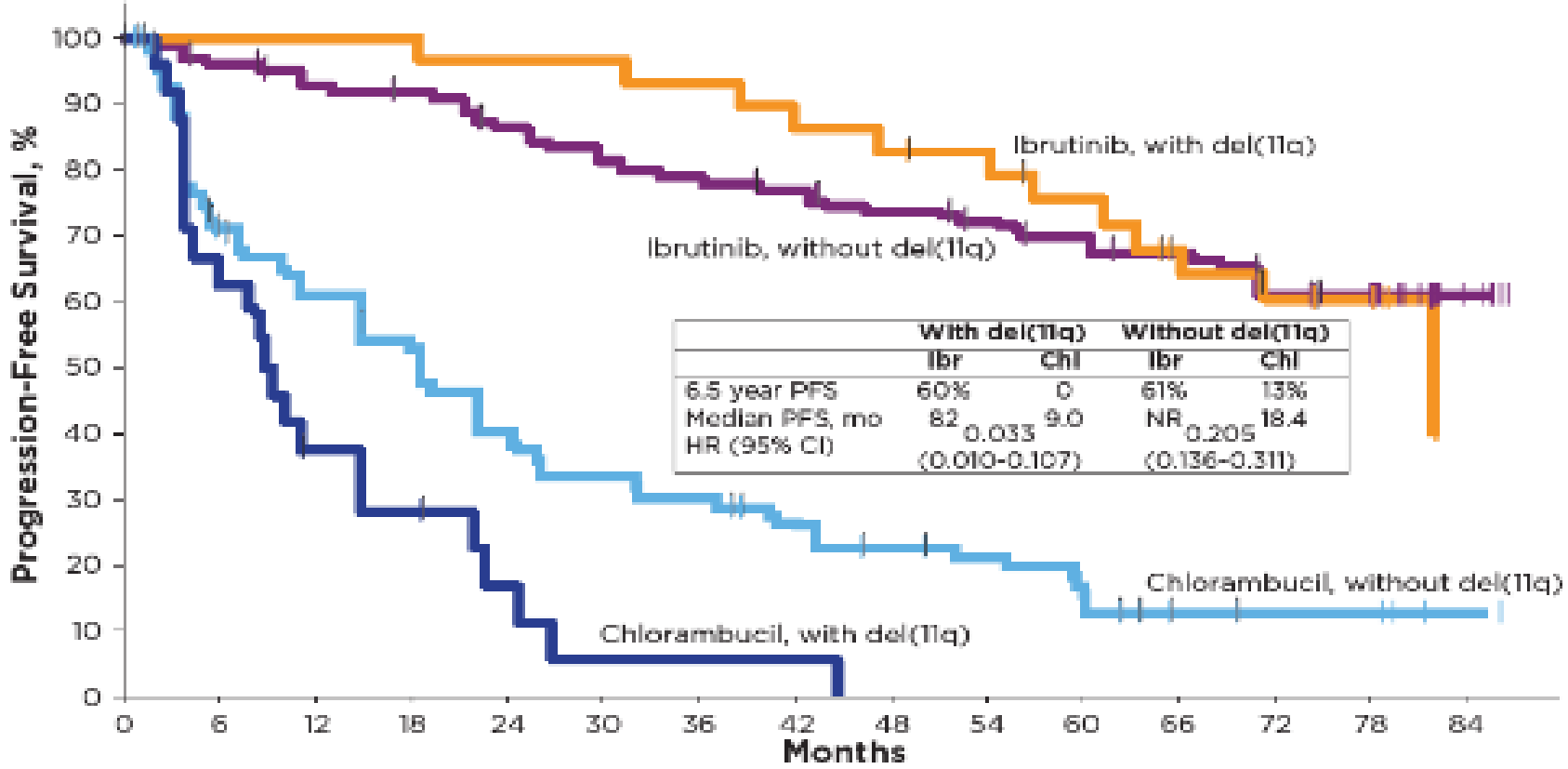
	Unmutated IGHV		Mutated IGHV	
	Ibr	Chl	Ibr	Chl
6.5 year PFS	62%	2%	67%	18%
Median PFS, mo	NR	9.3	NR	16.7
HR (95% CI)	0.109 (0.063-0.189)		0.197 (0.098-0.394)	

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

Barr. ASCO 2021.
Ghia EHA21

RESONATE-2: 7-Year Follow-Up

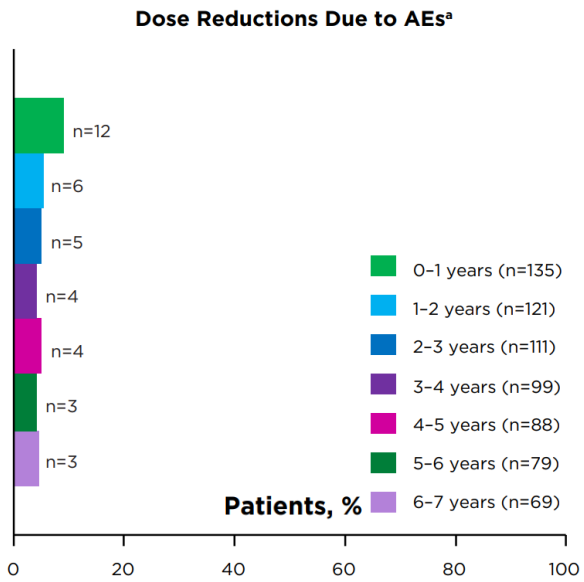


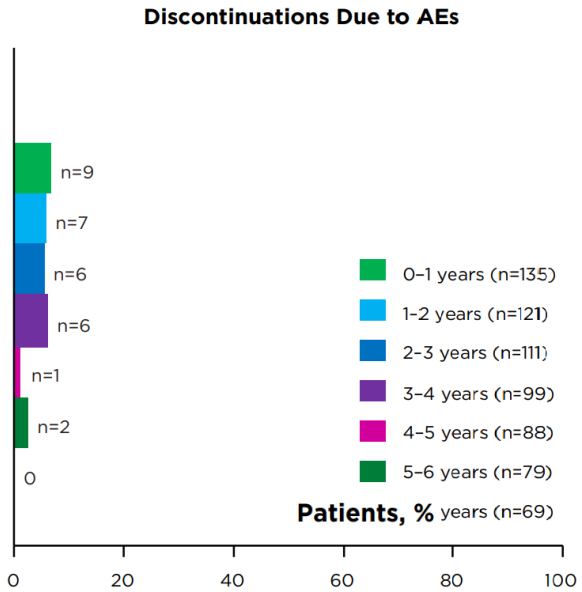
Patients at Risk															
Ibrutinib, without del(11q):	101	94	89	87	80	76	73	70	64	61	57	53	45	41	10
Ibrutinib, with del(11q):	29	29	29	29	28	28	27	25	24	23	20	18	16	13	
Chlorambucil, without del(11q):	96	64	54	45	35	29	26	21	17	15	12	6	5	5	1
Chlorambucil, with del(11q):	25	15	8	6	3	1	1	1							

Barr. ASCO 2021.
Ghia EHA21

RESONATE-2: 7-Year Follow-Up

- **61% of patients alive and progression-free at 6.5 years**
- **83% of patients alive at 6.5 years**
- **Treatment (with median follow-up of 6.5 years):**
  - 12% of patients on active treatment discontinued for progressive disease
  - 23% discontinued for AEs
  - >50% of patients remained on ibrutinib for ≥6 years
- **Dose adjustments:**
  - 84% of AEs resolved following a dose hold < 7 days
  - 23% of patients had a dose reduction
- **PPI use is common:** 65% of patients were taking medications for acid-related disorders (56% on PPIs)





Barr. ASCO 2021.
Ghia EHA21

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

Phase III trial

Treatment-naive CLL patients ≥ 65 yrs or < 65 yrs with CIRS score > 6 or CrCl < 70 mL/min (N = 535)

Stratified by: del(17p), ECOG PS 0/1 vs 2, geographic region

Acalabrutinib 100 mg PO BID **+ Obinutuzumab*** (n = 179)

Acalabrutinib 100 mg PO BID (n = 179)

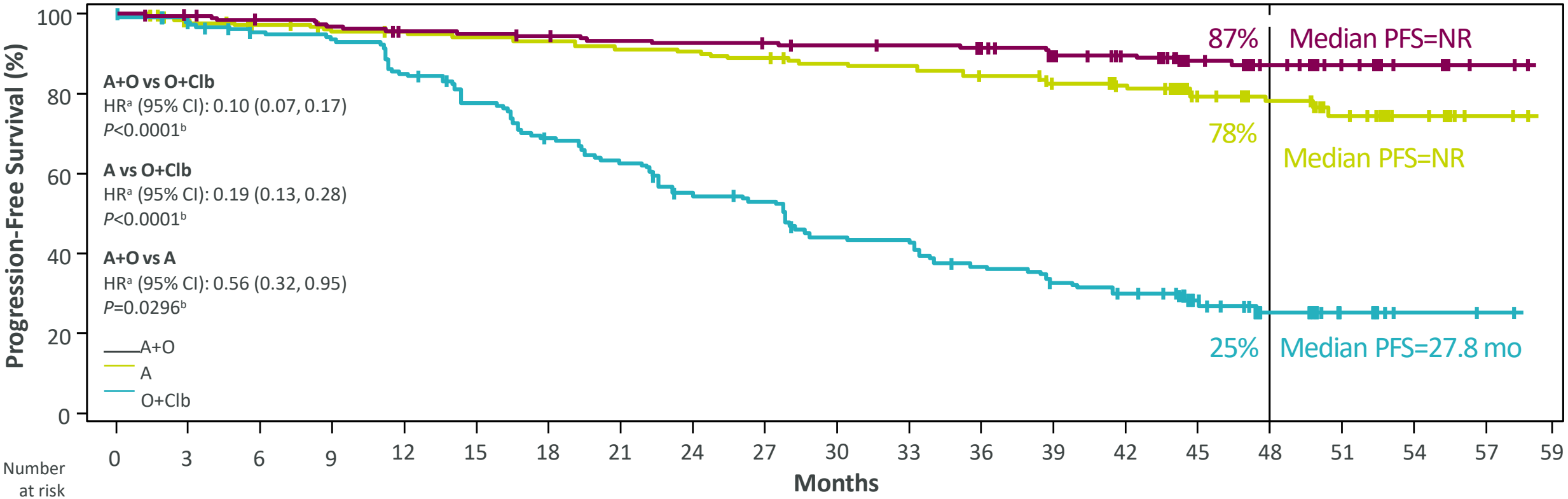
Obinutuzumab* + Chlorambucil 0.5 mg/kg PO D1, 15 (n = 177) → ***Crossover allowed to acalabrutinib after IRC-confirmed progression***

*1000 mg IV on Days 1, 2, 8, 15 of 28-day cycle 1; Day 1 of cycles 2-6.

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

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

Investigator-assessed PFS Overall

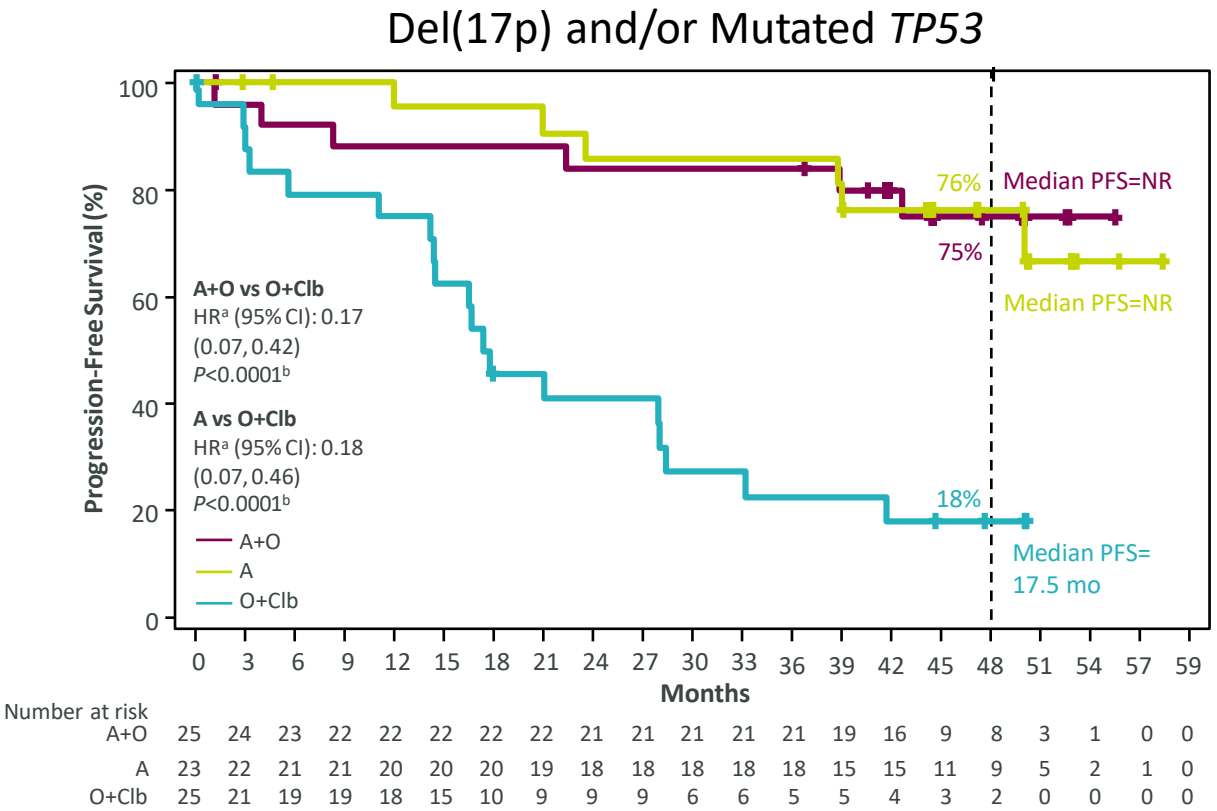


Number at risk	0	3	6	9	12	15	18	21	24	27	30	33	36	39	42	45	48	51	54	57	59
A+O	179	176	171	168	164	163	160	157	156	155	153	152	150	141	132	85	59	33	12	2	0
A	179	167	163	158	156	155	153	150	149	146	142	141	136	130	123	79	61	35	16	4	0
O+Clb	177	163	156	153	139	125	110	100	86	82	67	66	55	48	42	22	13	6	2	1	0

[a]Hazard ratio was based on stratified Cox-Proportional-Hazards model; [b]*P*-value was based on stratified log-rank test.
A, acalabrutinib; CI, confidence interval; Clb, chlorambucil; HR, hazard ratio; NR, not reached; O, obinutuzumab; PFS, progression-free survival.

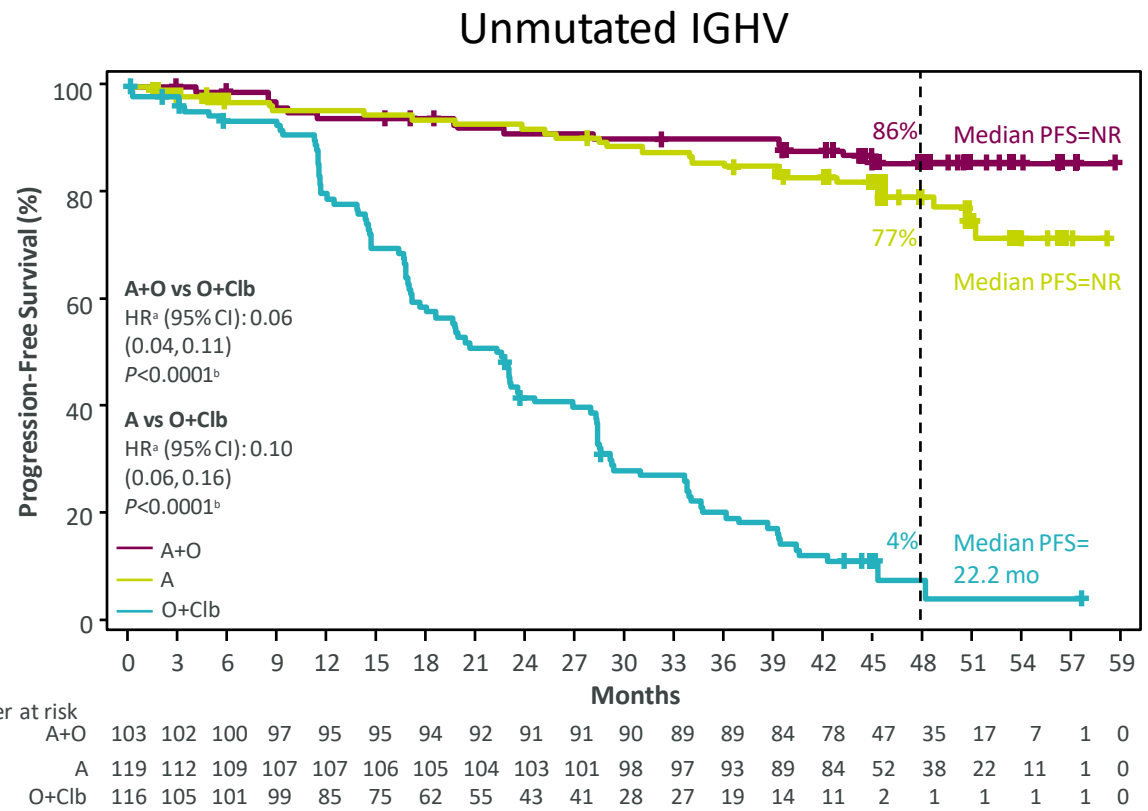
Sharman et al ASCO 2021

Investigator-assessed PFS in Patients With del(17p) and/or Mutated *TP53* OR Unmutated IGHV



Number at risk

	0	3	6	9	12	15	18	21	24	27	30	33	36	39	42	45	48	51	54	57	59
A+O	25	24	23	22	22	22	22	22	21	21	21	21	21	19	16	9	8	3	1	0	0
A	23	22	21	21	20	20	20	19	18	18	18	18	18	15	15	11	9	5	2	1	0
O+Clb	25	21	19	19	18	15	10	9	9	9	6	6	5	5	4	3	2	0	0	0	0



Number at risk

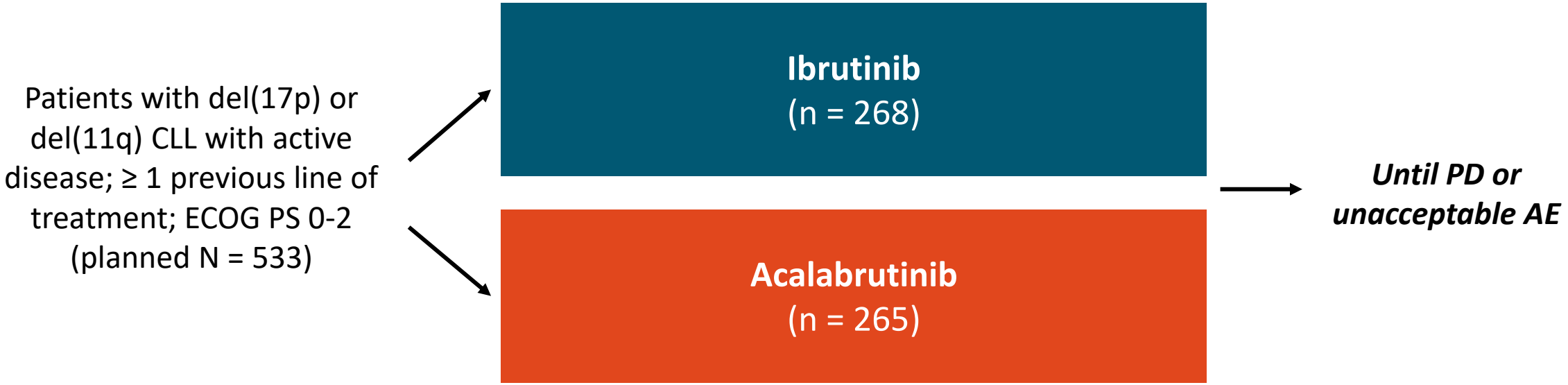
	0	3	6	9	12	15	18	21	24	27	30	33	36	39	42	45	48	51	54	57	59
A+O	103	102	100	97	95	95	94	92	91	91	90	89	89	84	78	47	35	17	7	1	0
A	119	112	109	107	107	106	105	104	103	101	98	97	93	89	84	52	38	22	11	1	0
O+Clb	116	105	101	99	85	75	62	55	43	41	28	27	19	14	11	2	1	1	1	1	0

[a]Hazard ratio was based on unstratified Cox-Proportional-Hazards model. [b]*P*-value was based on unstratified log-rank test.
A, acalabrutinib; CI, confidence interval; Clb, chlorambucil; HR, hazard ratio; IGHV, immunoglobulin heavy chain variable region; NR, not reached; O, obinutuzumab; PFS, progression-free survival.

Sharman et al ASCO 2021

ELEVATE-RR: Ibrutinib vs Acalabrutinib in Patients With High-Risk Relapsed/Refractory CLL

- Final analysis of randomized, multicenter, open-label, noninferiority phase III trial

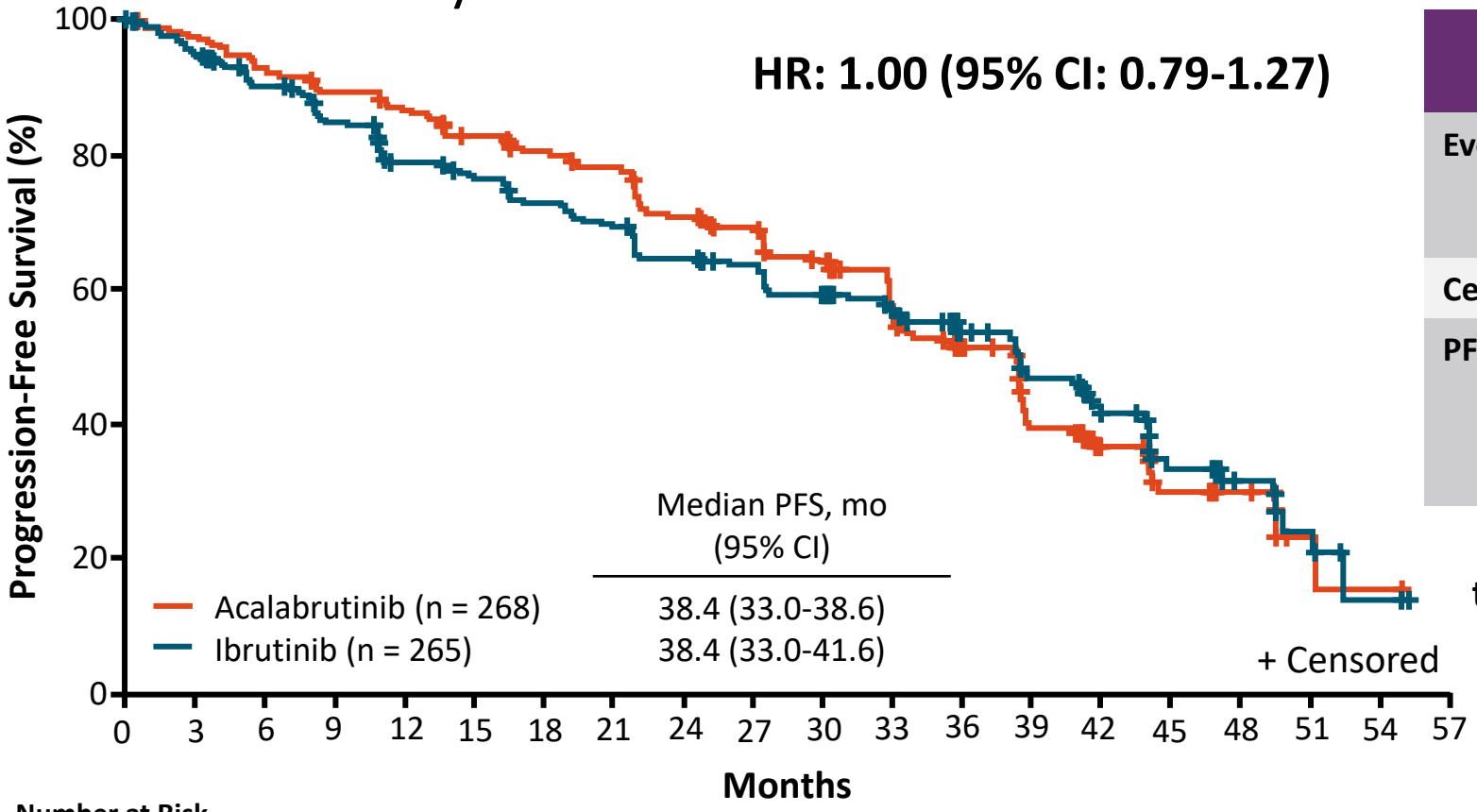


- Primary endpoint: PFS
- Secondary endpoints: OS; incidence of treatment-emergent AEs, atrial fibrillation; Richter's transformation; grade ≥3 infections
- FPI October 2015 – LPI November 2017 (25 mo)
- Final analysis: 279 IRC PFS events, data cutoff 9/2020

Byrd. ASCO 2021. Abstr 7500.

ELEVATE-RR: Noninferiority Met on IRC-Assessed PFS

- Noninferiority met on IRC-assessed PFS



Number at Risk

Acalabrutinib	268	250	235	227	219	207	200	193	173	163	148	110	84	59	31	21	13	3	1	0
Ibrutinib	265	240	221	205	186	178	168	160	148	142	130	108	81	66	41	26	15	8	2	0

Median follow-up: 41 months

	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)

Noninferiority achieved if upper bound of the 95% CI of HR is less than the prespecified NI margin of 1.429

Byrd. ASCO 2021. Abstr 7500.

ELEVATE-RR: Adverse events

- *Initial safety results*
  - **Atrial fibrillation significantly less common with acalabrutinib (*P* = .023)**
    - Acalabrutinib: 9.4%
    - Ibrutinib: 16.0%
  - Grade ≥3 infection and Richter transformation comparable between arms (~30% and ~4.5%, respectively)
- Any-grade AEs in ≥20%
  - Less common with acalabrutinib: hypertension, arthralgia, diarrhea, cardiac, hypertension, bleeding
  - More common with acalabrutinib: headache, cough
- Fewer discontinuations with acalabrutinib: 14.7% vs 21.3% with ibrutinib

Byrd. ASCO 2021. Abstr 7500.

ALPINE: Ibrutinib vs Zanubrutinib in Patients With Relapsed/Refractory CLL

- Ongoing randomized, multicenter phase III trial

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)

Ibrutinib 420 mg PO QD

Zanubrutinib 160 mg PO BID

Until PD or unacceptable AE

- Primary endpoint: ORR
- Secondary endpoints: PFS, DoR, OS; safety, patient-assessed QoL

Hillmen et al. EHA 2021.

ORR by Investigator Assessment

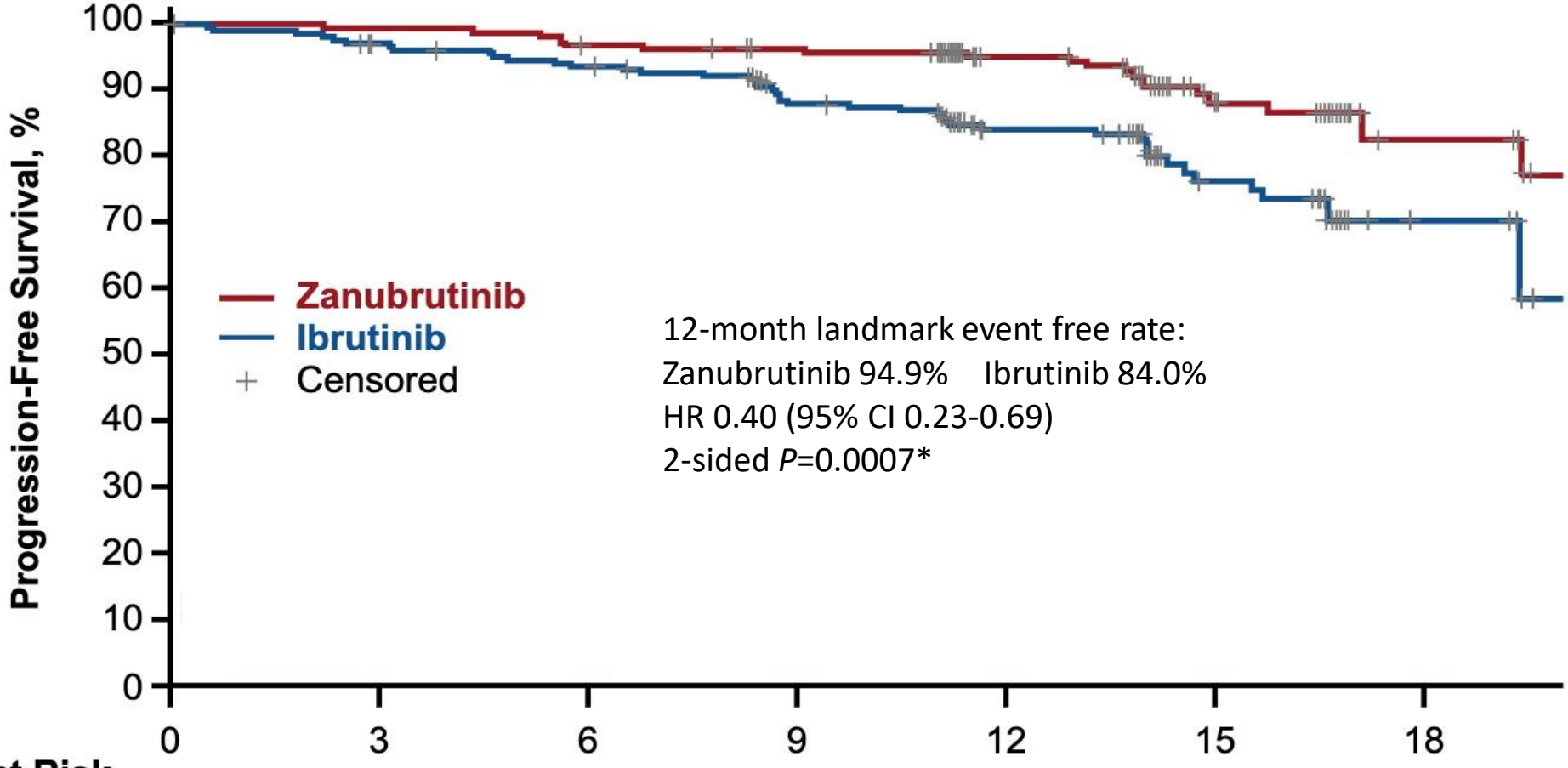
	Zanubrutinib (n=207), n (%)	Ibrutinib (n=208), n (%)
Primary endpoint:	162 (**78.3**) 95% CI: 72.0, 83.7	130 (**62.5**) 95% CI: 55.5, 69.1
ORR (PR+CR)	Superiority 2-sided *P*=0.0006 compared with pre-specified alpha of 0.0099	
CR/CRi	4 (1.9)	3 (1.4)
nPR	1 (0.5)	0
PR	157 (75.8)	127 (61.1)
ORR (PR-L+PR+CR)	*183 (88.4)*	*169 (81.3)*
PR-L	21 (10.1)	39 (18.8)
SD	17 (8.2)	28 (13.5)
PD	1 (0.5)	2 (1.0)
Discontinued or new therapy prior to 1st assessment	6 (2.9)	9 (4.3)

	del(17p) (n=24), n (%)	del(17p) (n=26), n (%)
ORR (PR+CR)	20 (83.3)	14 (53.8)

CR, complete response; CRi, complete response with incomplete bone marrow recovery; D/C, discontinuation; DOR, duration of response; NE, not evaluable;

Hillmen et al. EHA 2021.

PFS by Investigator Assessment



Patients at Risk							
Zanubrutinib	207	200	194	190	152	70	19
Ibrutinib	208	196	188	170	125	57	8

Hillmen et al. EHA 2021.

Safety Summary

Safety Analysis Population	Zanubrutinib (n=204) n (%)	Ibrutinib (n=207) n (%)
Any AE	195 (95.6)	205 (99.0)
[illegible]	114 (55.9)	106 (51.2)
Serious AEs	56 (27.5)	67 (32.4)
Fatal AEs	8 (3.9)	12 (5.8)
AEs leading to dose reduction	23 (11.3)	25 (12.1)
AEs leading to dose interruption	81 (39.7)	84 (40.6)
AEs leading to treatment discontinuation	16 (7.8)	27 (13.0)

Hillmen et al. EHA 2021.

Additional AEs of Special Interest

Safety Analysis Population	Zanubrutinib (n=204), n (%)		Ibrutinib (n=207), n (%)	
	Any Grade	≥ Grade 3	Any Grade	≥ Grade 3
Cardiac disorders[a]	28 (13.7)	5 (2.5)	52 (25.1)	14 (6.8)
Atrial fibrillation and flutter (key 2º endpoint)	**5 (2.5)**	**2 (1.0)**	**21 (10.1)**	**4 (1.9)**
Hemorrhage	73 (35.8)	6 (2.9)	75 (36.2)	6 (2.9)
Major hemorrhage[b]	6 (2.9)	6 (2.9)	8 (3.9)	6 (2.9)
Hypertension	34 (16.7)	22 (10.8)	34 (16.4)	22 (10.6)
Infections	122 (59.8)	26 (12.7)	131 (63.3)	37 (17.9)
Neutropenia[c]	58 (28.4)	38 (18.6)	45 (21.7)	31 (15.0)
Thrombocytopenia[c]	19 (9.3)	7 (3.4)	26 (12.6)	7 (3.4)
Secondary primary malignancies	17 (8.3)	10 (4.9)	13 (6.3)	4 (1.9)
Skin cancers	7 (3.4)	3 (1.5)	10 (4.8)	2 (1.0)

Hillmen et al. EHA 2021.

Coming back to the old Treatment Paradigm in CLL: MRD negative

- **Bcl2 inhibitors**

MRD Negativity (Cure)

- Goal of therapy: **disease eradication**
  - High CR rates
  - **MRD negative**
  - Long PFS
- Targets the pathogenic cause of CLL (elimination of malignant clone)
- Finite treatment course

- **BCR inhibitors**

Preservation of Response and Amelioration of Symptoms (Treat to Progression)

- Goal of therapy: **disease control**
  - Long PFS
  - Duration of response
- Sustained PRs as best response (or SD)

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

- 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)

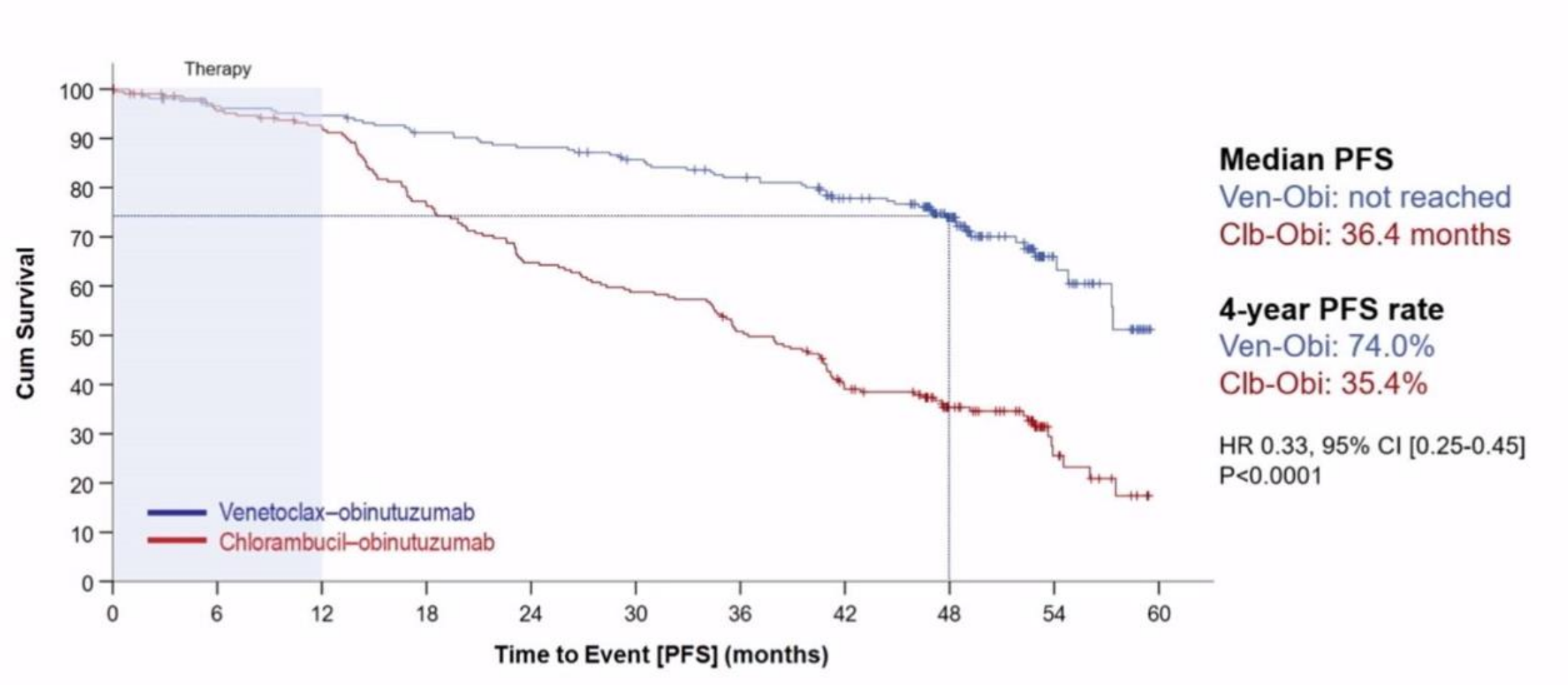
Total 28-day cycles

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

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

Fischer. NEJM. 2019;380:2225. Al-Sawaf. Lancet Oncol. 2020;21:1188.

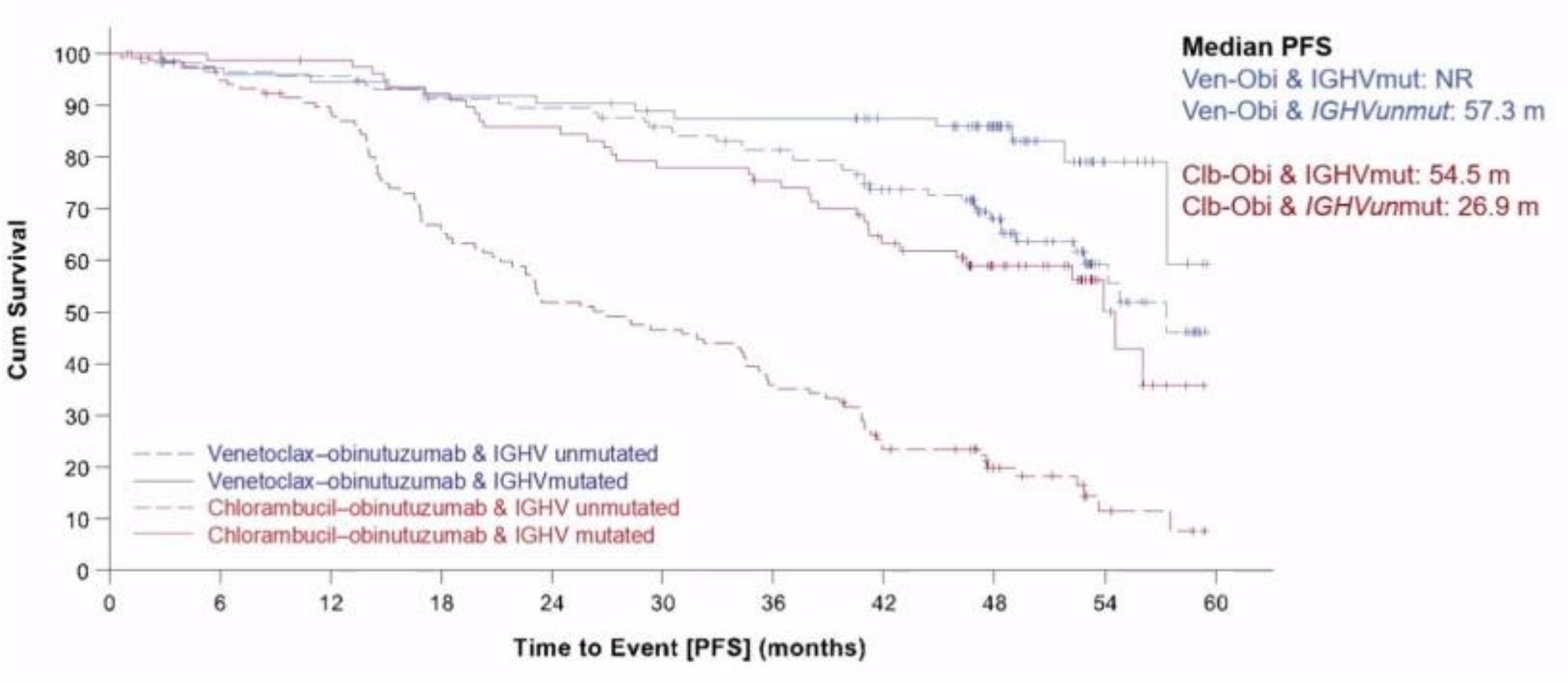
CLL14: PFS (V+G vs C+G)



Median follow-up 52.4 months.

Al-Sawaf O et al. EHA 2021 abstract S146.

CLL14 Genetic Markers and Outcome: PFS and *IGHV* Mutation Status

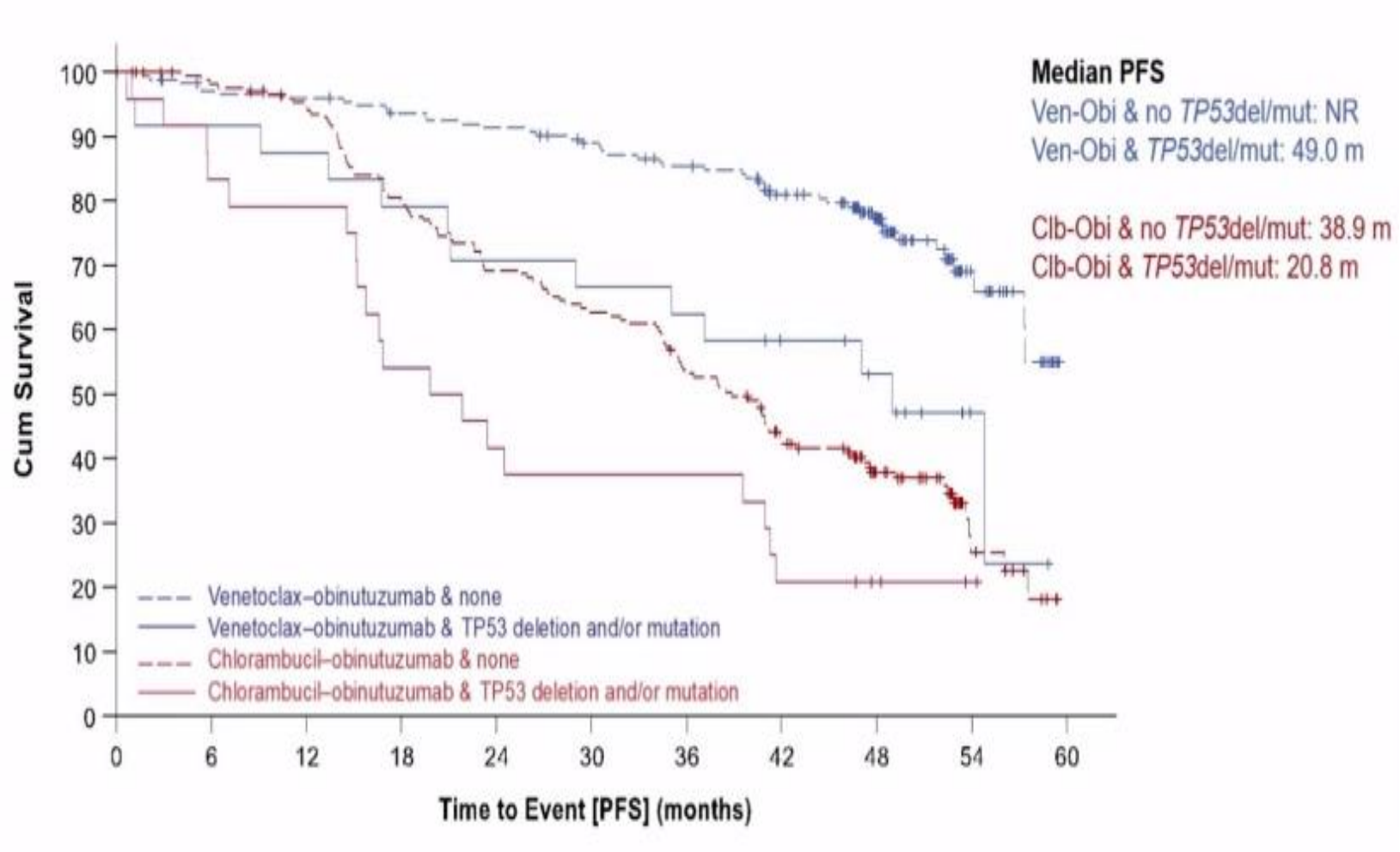


Median follow-up 52.4 months.

Al-Sawaf O et al. EHA 2021 abstract S146.

Tausch E et al. EHA 2021 abstract S144.

CLL14 Genetic Markers and Outcome: PFS and *TP53* Status



Median follow-up 52.4 months.

Al-Sawaf O et al. EHA 2021 abstract S146.

Tausch E et al. EHA 2021 abstract S144.

The Very New Changing Treatment Paradigm in CLL

- **Bcl2 inhibitors+ BCRi**

MRD Negativity (Cure)

- Goal of therapy: **disease eradication**
  - High CR rates
  - MRD negative
  - Long PFS
- Targets the pathogenic cause of CLL (elimination of malignant clone)
- Finite treatment course

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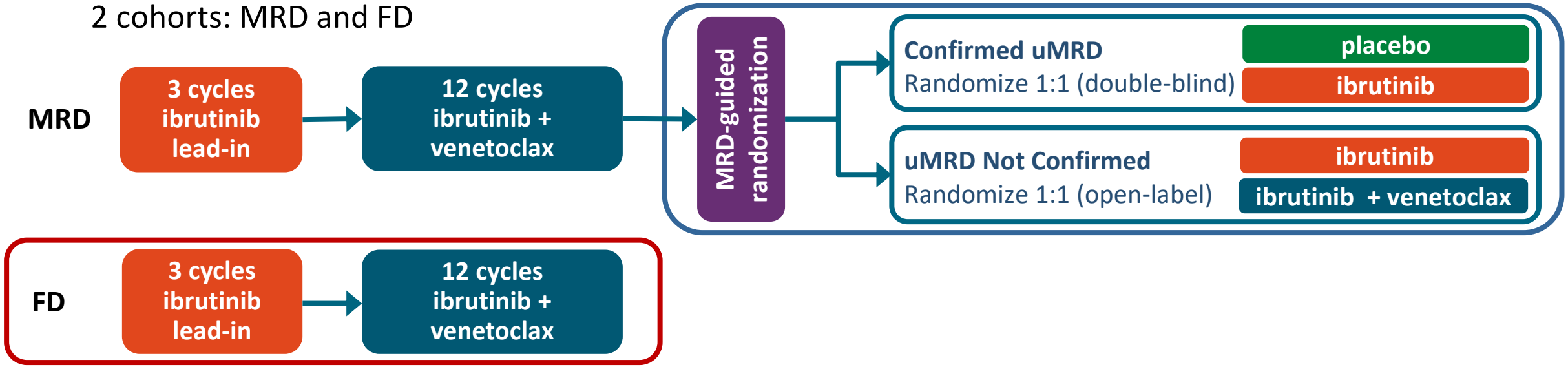
- Sustained PRs as best response (or SD)

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 that comprises 2 cohorts: MRD and FD

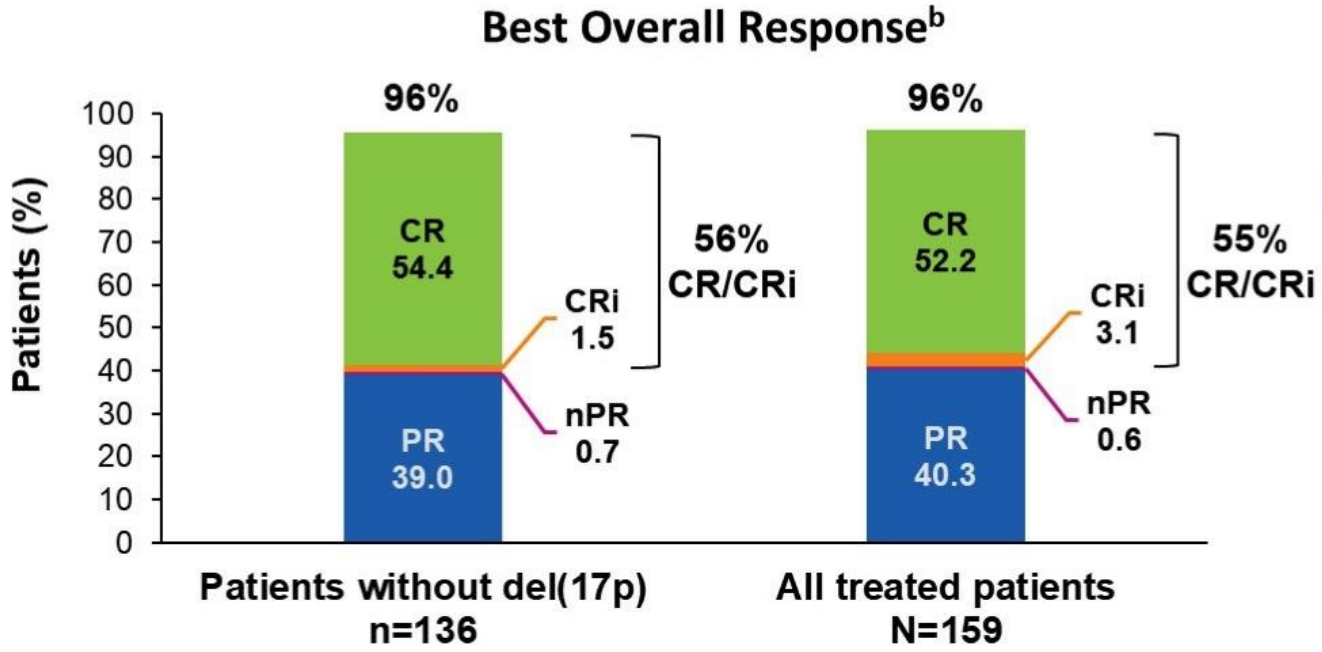


- Results from the MRD cohort demonstrated uMRD in more than two-thirds of patients treated with 12 cycles of ibrutinib + venetoclax (PB, 75%; BM, 68%), and 30-month PFS rates of ≥95% irrespective of subsequent MRD-guided randomized treatment[1]

- Primary analysis results from the FD cohort of CAPTIVATE are presented

Ghia et al . ASCO 2021. Allen et al EHA21

CAPTIVATE Fixed-Dose Cohort: primary endpoint of CR rate



DOCR ≥12 cycles n/N (%)	66/76 (87)	78/88 (89)*

*After achieving CR[a], 9 patients with <1 year of follow-up were not evaluable; 1 patient died 7 months after CR and completion of therapy.

- Primary endpoint was met: 56% (95% CI, 48–64) CR rate[a] in patients without del(17p)
  - Significantly excludes 37% minimum rate ($P<0.0001$)
  - Meaningful improvement over 40% rate of historical comparator of FCR in CLL10[1]

Ghia et al . ASCO 2021. Allen et al EHA21

CAPTIVATE Fixed-Dose Cohort: Safety

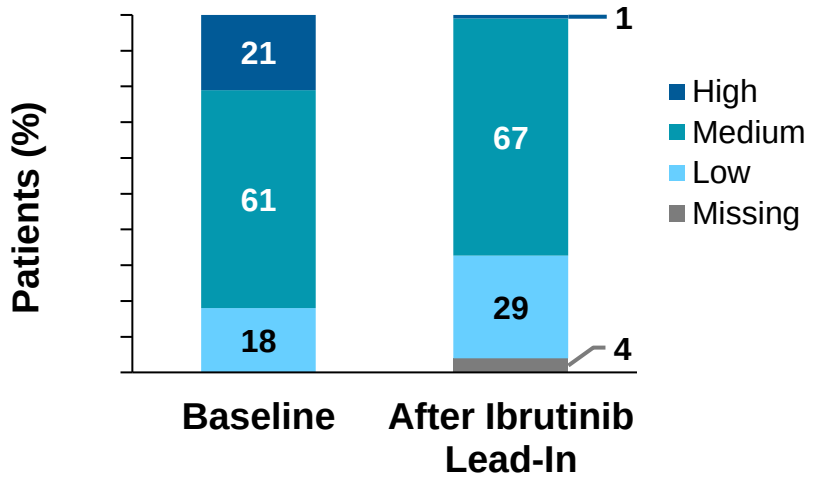
- 92% of patients completed planned 12 cycles of I+V

AEs, n (%)	All treated patients N=159	
Most frequent AEs (≥30%)	**Grade 1/2**	**Any grade**
Diarrhea	94 (59)	99 (62)
Nausea	66 (42)	68 (43)
Neutropenia	14 (9)	66 (42)
Arthralgia	51 (32)	53 (33)
Grade 3/4 AEs (≥5%)	98 (62)	
Neutropenia	52 (33)	
Infections[a]	13 (8)	
Hypertension	9 (6)	
Neutrophil count decreased	8 (5)	
AEs of clinical interest (any grade)		
Atrial fibrillation	7 (4)	
Major hemorrhage[a]	3 (2)	
Any serious AE	36 (23)	
Fatal AEs	1 (1)[b]	

Dose Adjustments

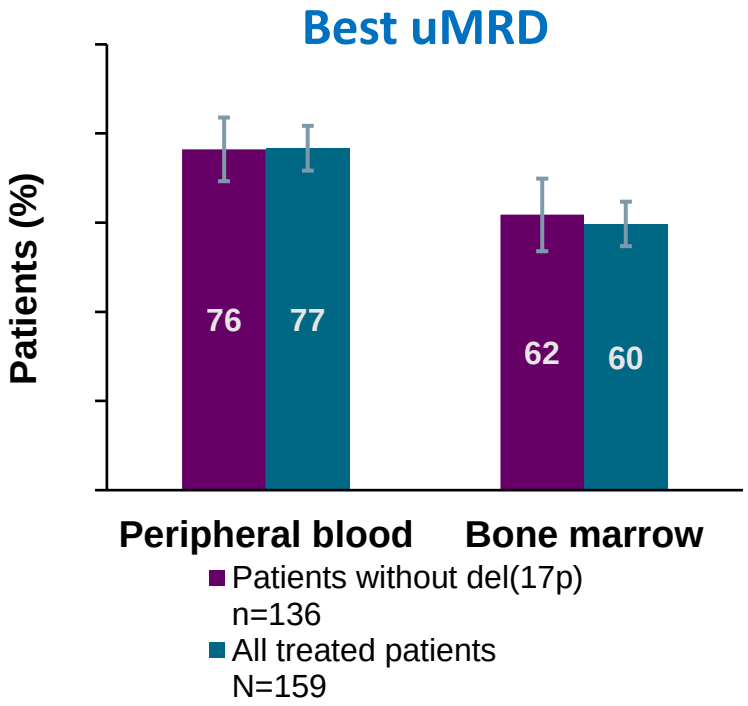
AEs, n (%)	All treated patients N=159
AEs leading to discontinuation	8 (5)
Both ibrutinib and venetoclax	3 (2)[a]
AEs leading to dose reduction	33 (21)
Ibrutinib only	9 (6)
Venetoclax only	18 (11)
Both ibrutinib and venetoclax	6 (4)

Tumor Burden Category for TLS Prophylaxis



Ghia et al . ASCO 2021. Allen et al EHA21

CAPTIVATE Fixed-Dose Cohort: MRD



uMRD rate	PB	BM
Bulky Disease		
Yes	77%	63%
No	77%	59%
IGHV status		
uIGHV	84%	64%
mIGHV	67%	53%

Ghia et al . ASCO 2021. Allen et al EHA21

GLOW: Fixed-Duration Ibrutinib + Venetoclax vs Chlorambucil + Obinutuzumab in Frontline CLL

- International, open-label, randomized phase III trial

Stratified by IGHV status, del(11q) presence

Patients with previously untreated CLL; aged ≥65 yr or <65 yr with CIRS >6 or CrCl <70 mL/min; no del(17p) or known *TP53* mutation; ECOG PS 0-2 (N = 211)

→ **Ibrutinib** 420 mg PO QD x 3 cycles followed by **Ibrutinib** + **Venetoclax*** 12 cycles (n = 106)

→ **Chlorambucil** 0.5 mg/kg on Days 1, 15 x 6 cycles + **Obinutuzumab** 1000 mg on Days 1-2, 8, 15 of cycle 1 and Day 1 of cycles 2-6 (n = 105)

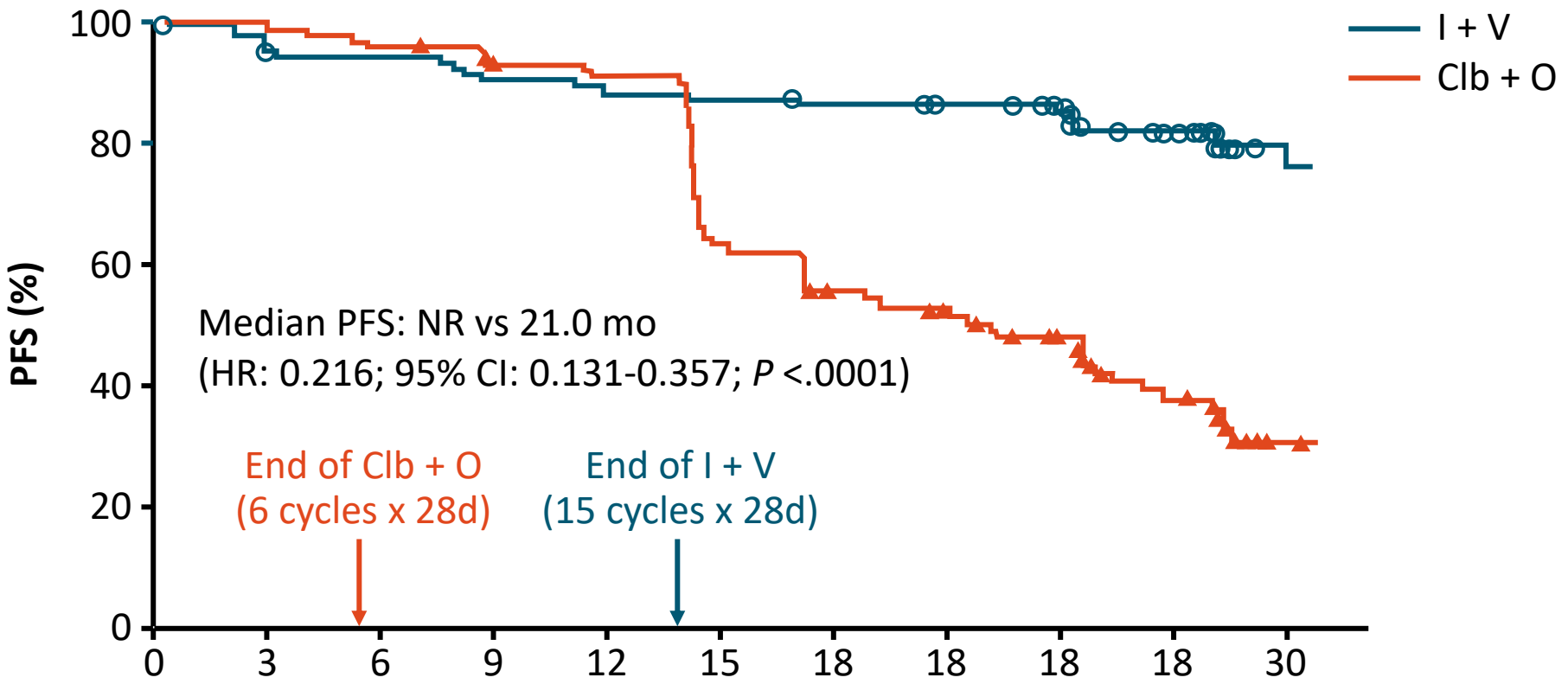
→ *If IRC-confirmed PD and active disease requiring tx, eligible for subsequent single-agent ibrutinib*

*Ramp-up from 20 to 400 mg over 5 wk starting in cycle 4.

- **Primary endpoint:** PFS per IRC
  - 71 PFS events to detect effect size with HR of 0.5 (80% power, 2-sided α = 0.05)
- **Key secondary endpoints:** uMRD in BM, CR rate per IRC, ORR per IRC, OS, safety

Kater et al . EHA 2021.

GLOW: PFS by IRC



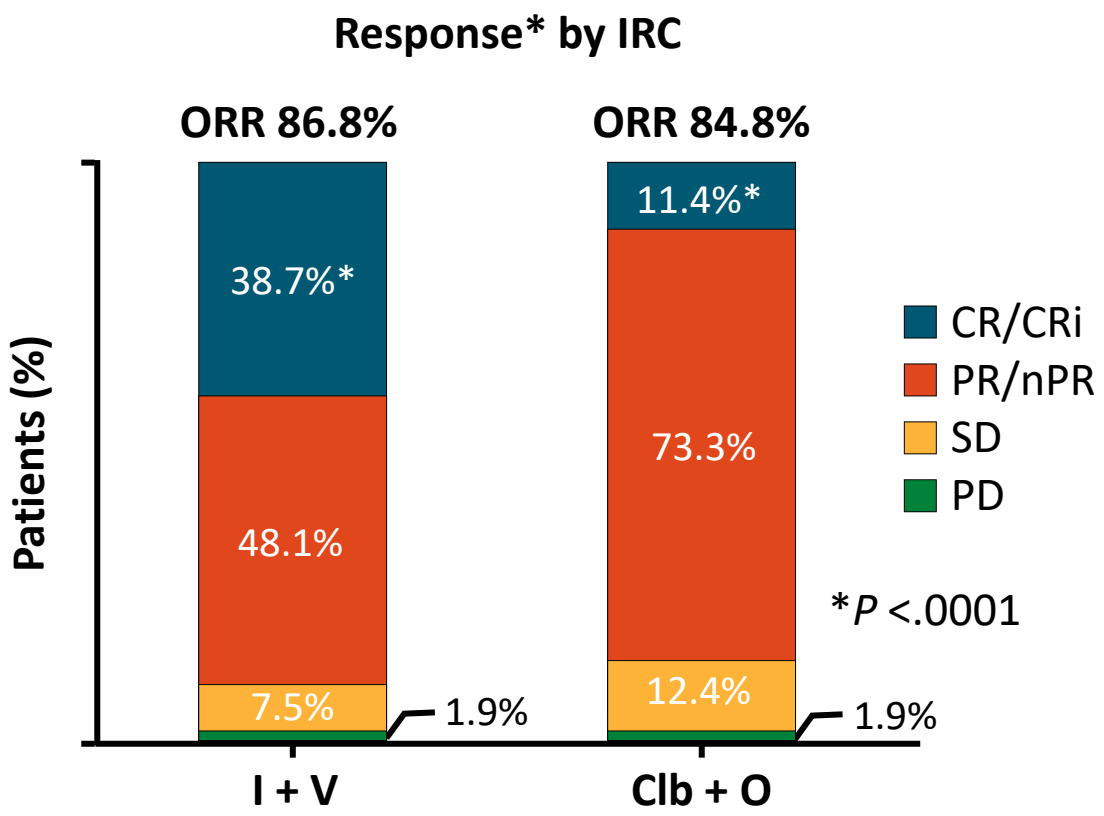
Patients at Risk, n

I + V	106	98	98	94	92	91	89	87	71	59	20
Clb + O	105	104	101	95	93	63	54	47	36	25	6

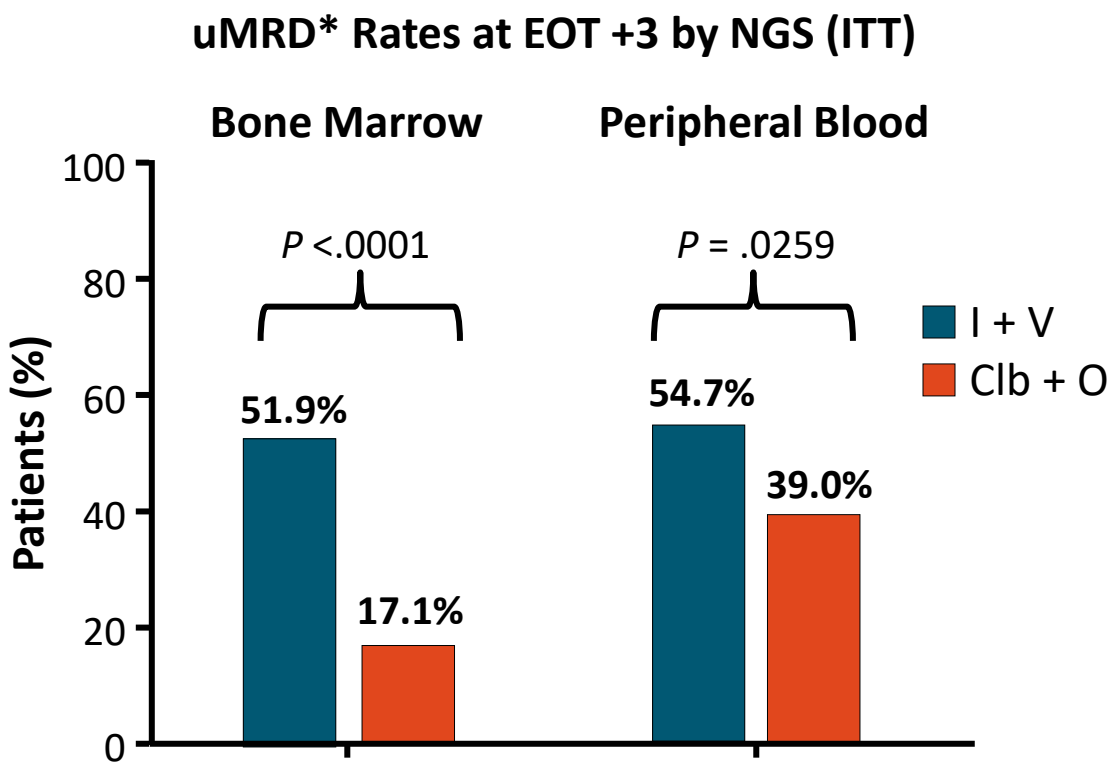
Median follow-up: 27.7 mo

Kater et al . EHA 2021.

GLOW: CR/CRi and uMRD Rates



*90% of responders in the I + V arm sustained response 24 mo after initial response vs 41% in the control arm



*84.5% of I + V patients had sustained PB uMRD vs 29.3% in the control arm; MRD trends were similar when assessed by flow cytometry

Kater et al . EHA 2021.

GLOW: Safety

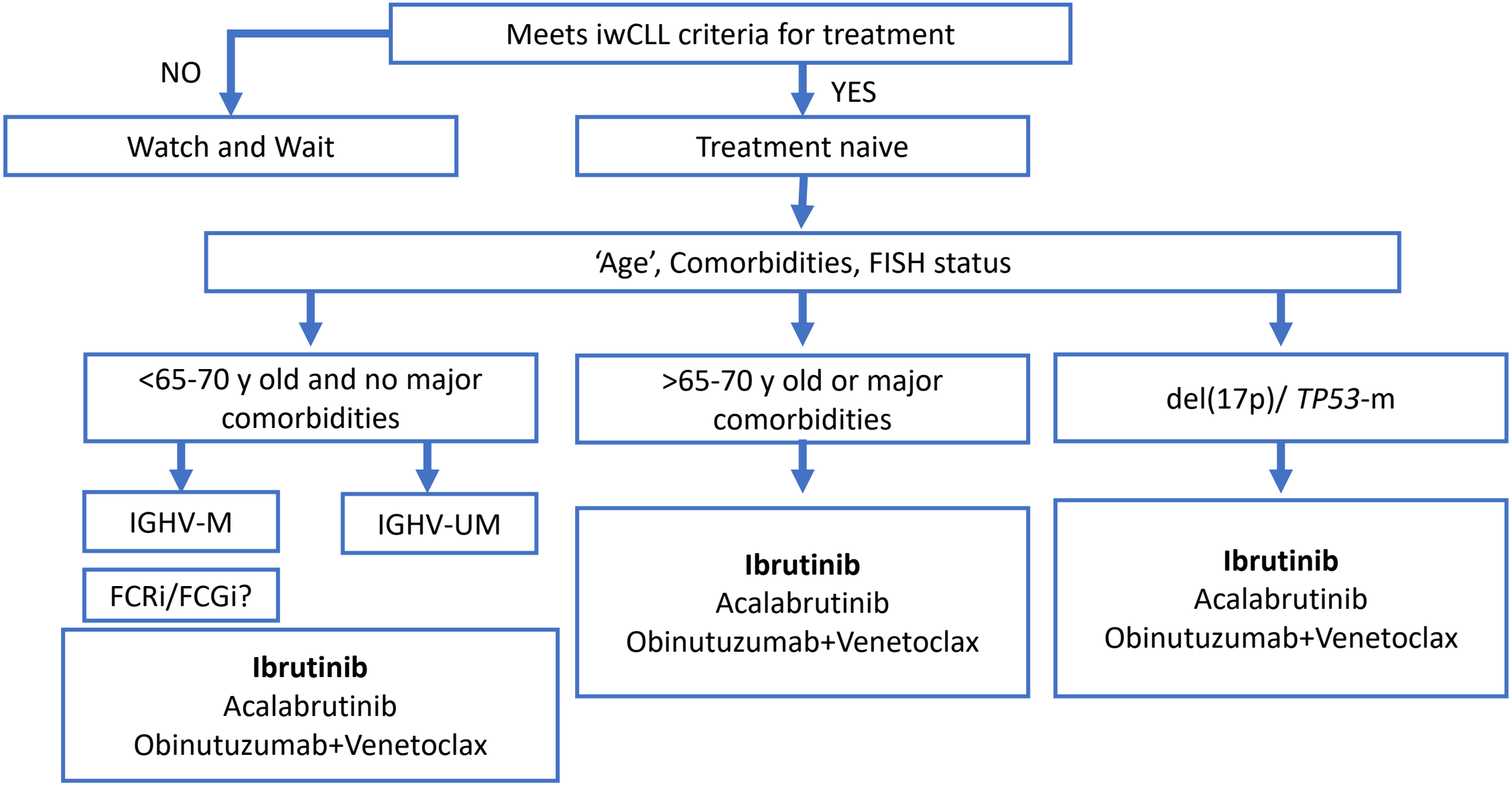
Safety Outcome	Ibrutinib + Venetoclax (n = 106)	Chlorambucil + Obinutuzumab (n = 105)
Median exposure, mo (range)	13.8 (0.7-19.5)	5.1 (1.8-7.9)
Any grade ≥3 AE in ≥5% of patients, %	75.5	69.5
▪ Neutropenia	34.9	49.5
▪ Infections	17.0	11.4
▪ Thrombocytopenia	5.7	20.0
▪ Diarrhea	10.4	1.0
▪ Hypertension	7.5	1.9
▪ Atrial fibrillation	6.6	0
▪ Hyponatremia	5.7	0
▪ TLS	0	5.7

- Grade ≥3 febrile neutropenia observed in 1.9% of I + V arm vs 2.9% of Clb + O arm

- Following the ibrutinib lead-in, <2% of patients determined to be at risk for TLS per high tumor burden
- In the I + V arm, ibrutinib was discontinued due to atrial fibrillation in n = 2 (1.9%)
- Serious AEs in ≥5% of patients for I + V vs Clb + O arms: infections, 12.3% vs 8.6%; atrial fibrillation, 6.6% vs 0%
- Secondary primary malignancies for I + V vs Clb + O arms: 8.5% vs 10.5%
  - Nonmelanoma skin cancer: 3.8% vs 1.9%
  - Other: 4.7% vs 8.6%

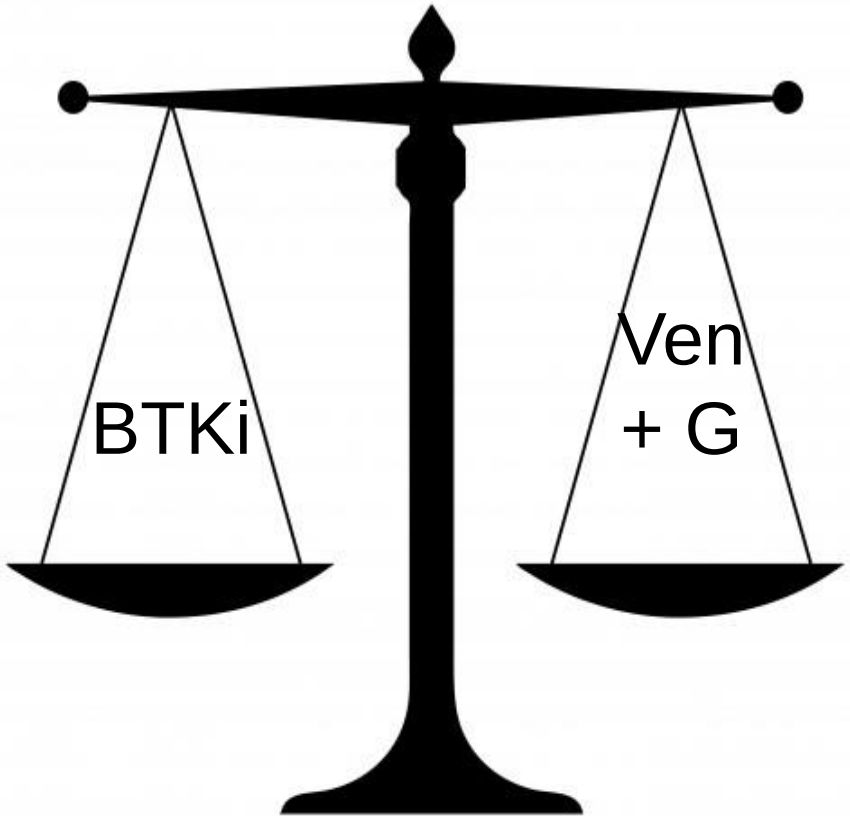
Kater et al . EHA 2021.

CLL Front Line Treatment Algorithm 2021



The alternatives Treatment Paradigm in CLL: Factors to Consider

- Convenience (no infusions, TLS monitoring)
- Long-term efficacy data
- Multiple Phase 3 data
- Data for efficacy of venetoclax at time of ibrutinib progression
- Low progression while on continue therapy.
- Older age.
- Good data on High risk factors.
- LN based disease.
- High financial toxicity
- **Prolong PFS while on therapy**



- Potential for 1-year time-limited therapy
- No known cardiac or bleeding risks
- Less concern with long-term adherence
- Potential for cost-savings if 1 year of therapy is durable
- Less financial toxicity
- Low risk dx
- BM based disease: cytopenias.
- Younger age
- Possibility of retreatment
- **Prolong PFS after MRD negative**

Conclusions

- RESONATE 2 seven years follow up confirm the excellent outcomes of Ibrutinib vs chemoimmunotherapy in 4 phase III trials and has become an excellent front line therapy.
- Acalabrutinib and zanubrutinib offer a new alternative for BTK inhibition with a different side effect profile.
- Obinutuzumab + Venetoclax is now offering a time limited therapy in the front line settings with excellent results and high MRD- status, however high risk patients relapse sooner.
- Ibrutinib+venetoclax shows a new alternative for fixed therapy in the near future with the convenience of oral administration .

Thank you

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