Chronic Lymphocytic Leukemia: Navigating the Choice and Sequence of Therapy

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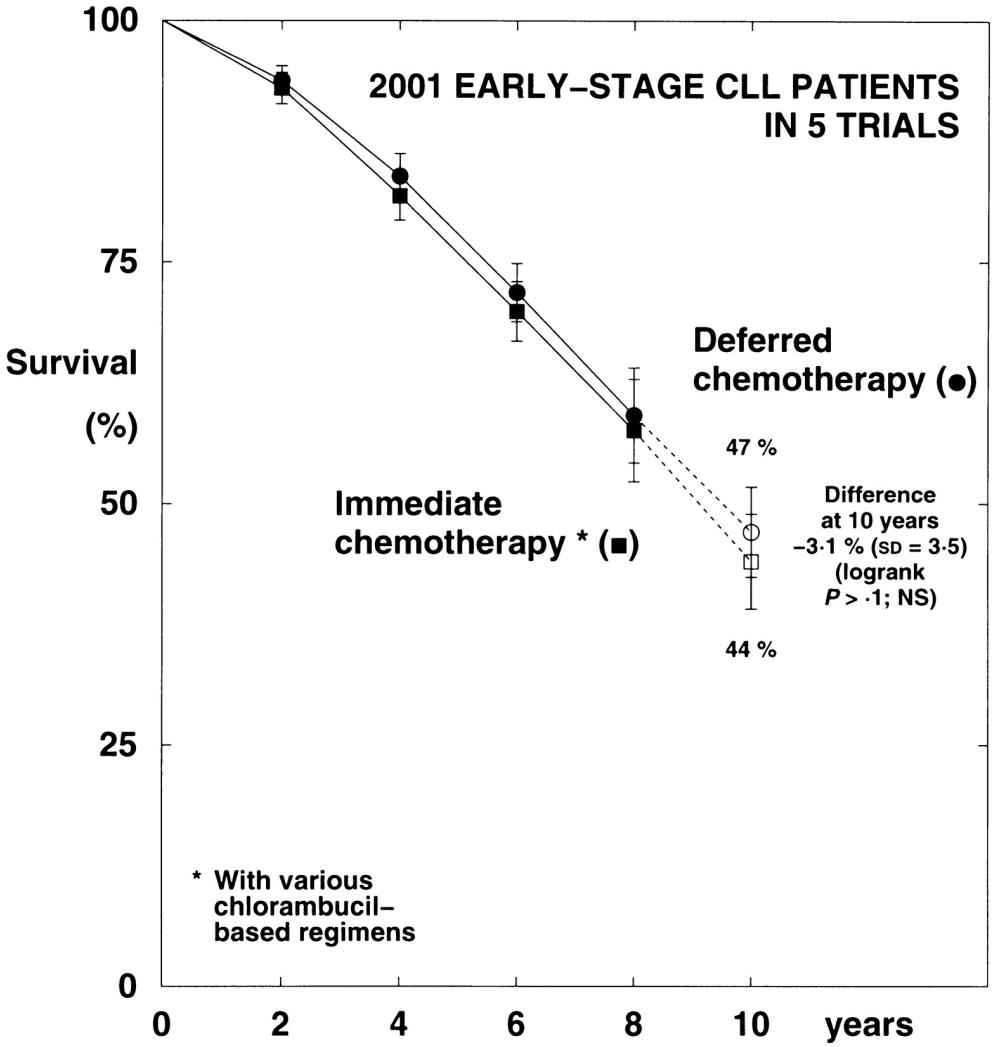
Agenda

- CLL12: Challenging the “Watch and Wait”
- Ibrutinib vs. CIT: Pooled data
- ALPINE study: Ibrutinib vs. Zanubrutinib
- BRUIN study: Pirtobrutinib in R/R CLL
- BTK degraders
- CAPTIVATE study: Ibrutinib + Venetoclax
- CLL13 Trial

“Watch and Wait” is the Standard of Care in Asymptomatic CLL

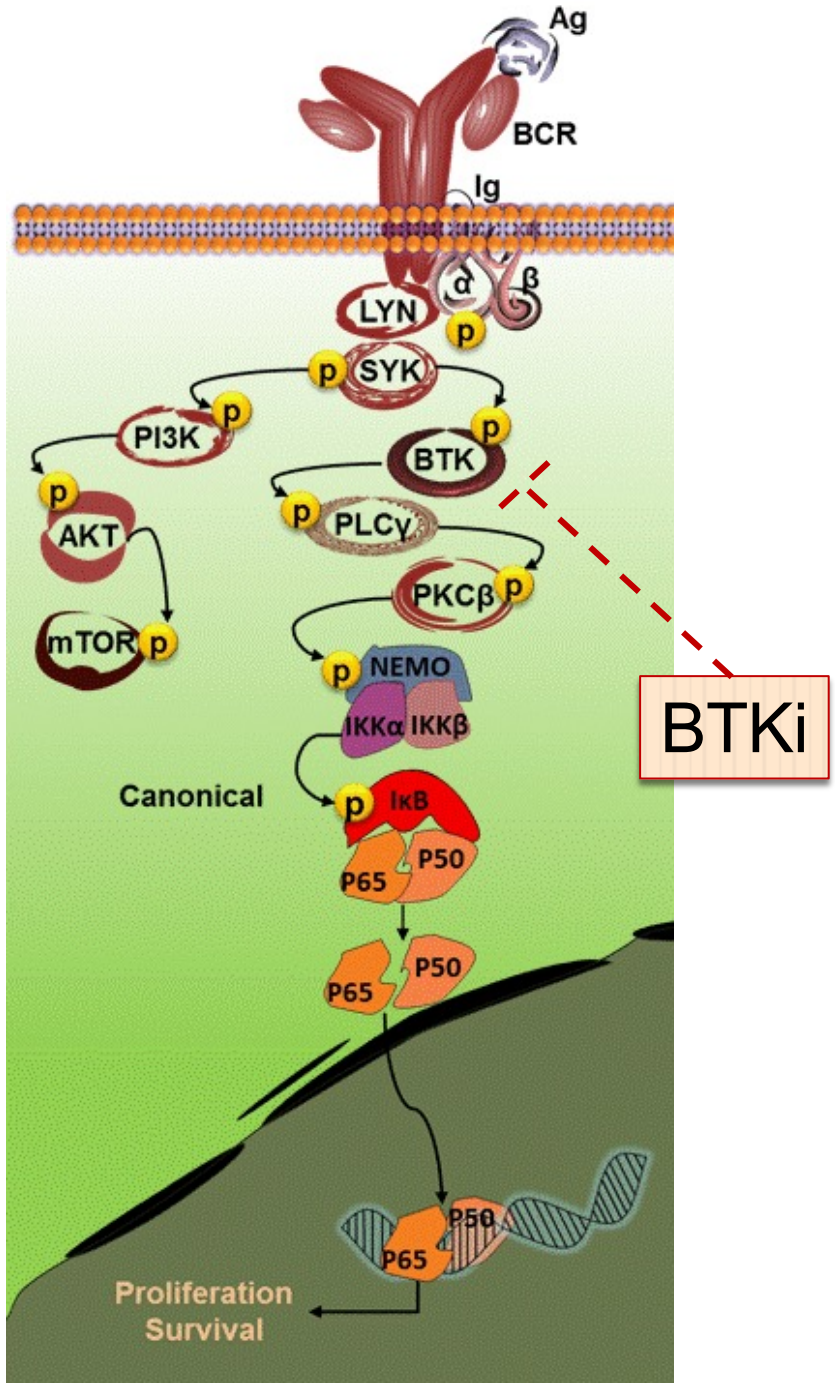


Deaths / person–years					
Immediate	69 / 1894	108 / 1693	102 / 1292	73 / 774	73 / 556
Deferred	62 / 1940	97 / 1737	103 / 1344	77 / 783	82 / 691

- No benefit to early intervention.
- Defer treatment until indications met.
- Up to 1/3 of patients may not require therapy.

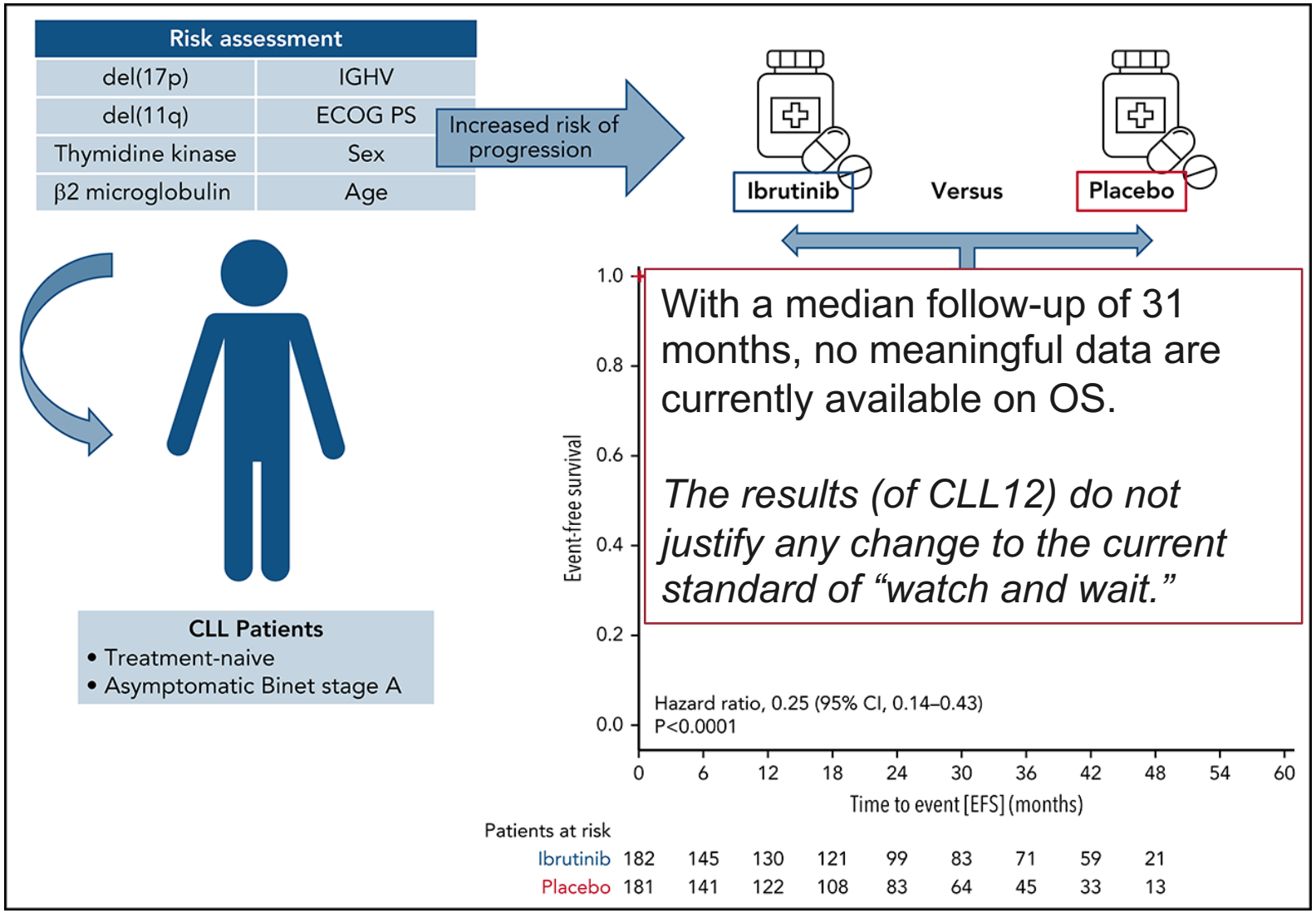
CLL Trialists, JNCI 1999

The B-cell Receptor Pathway



Saba & Wiestner. Curr Opin Hematol. 2014

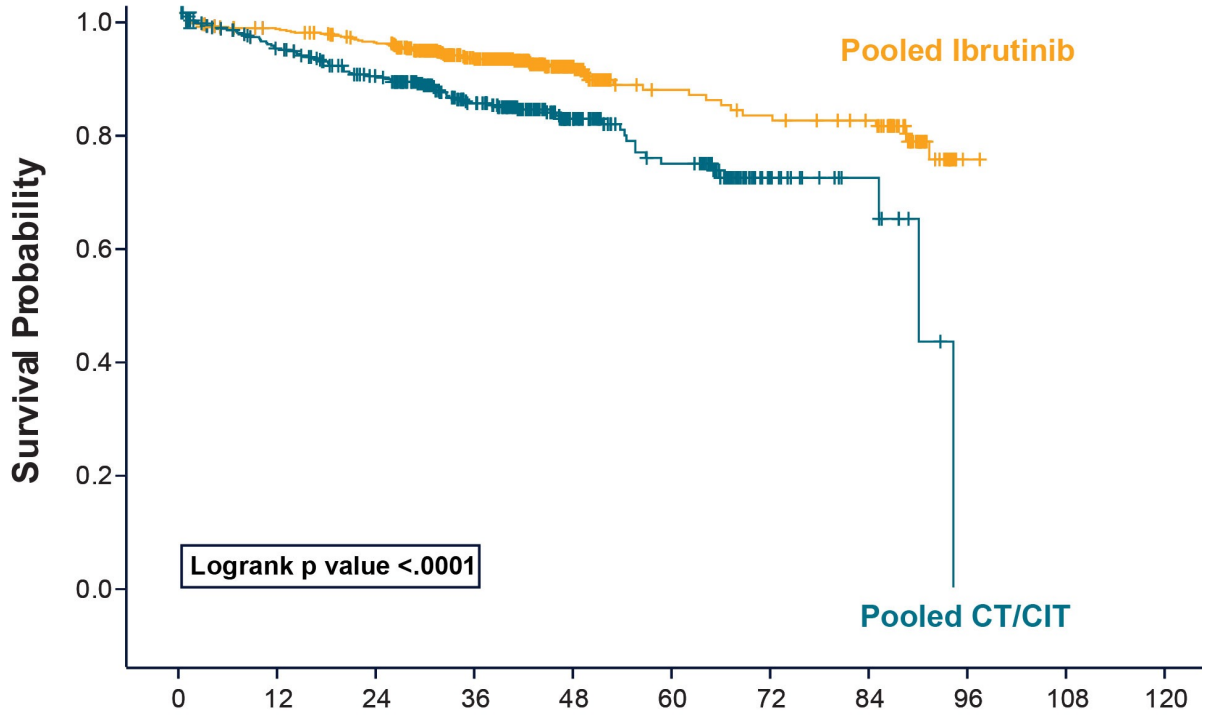
CLL12 trial: ibrutinib vs placebo in early-stage, TN CLL



Langerbeins *et al*. Blood 2022

Ibrutinib Improves OS Compared to CIT in TN CLL

Improved OS for pooled 1L Ibr (603 pts) vs CT/CIT (424 pts) across the 3 ibr studies



With Number of Patients at Risk

Pooled Ibrutinib	603	583	559	396	164	98	91	86	1	0
Pooled CT/CIT	424	379	339	253	108	74	20	10	0	

In this analysis, data was pooled from **RESONATE-2, ECOG-1912, and iLLUMINATE** trials evaluating ibrutinib monotherapy and in combination in **treatment naïve CLL**

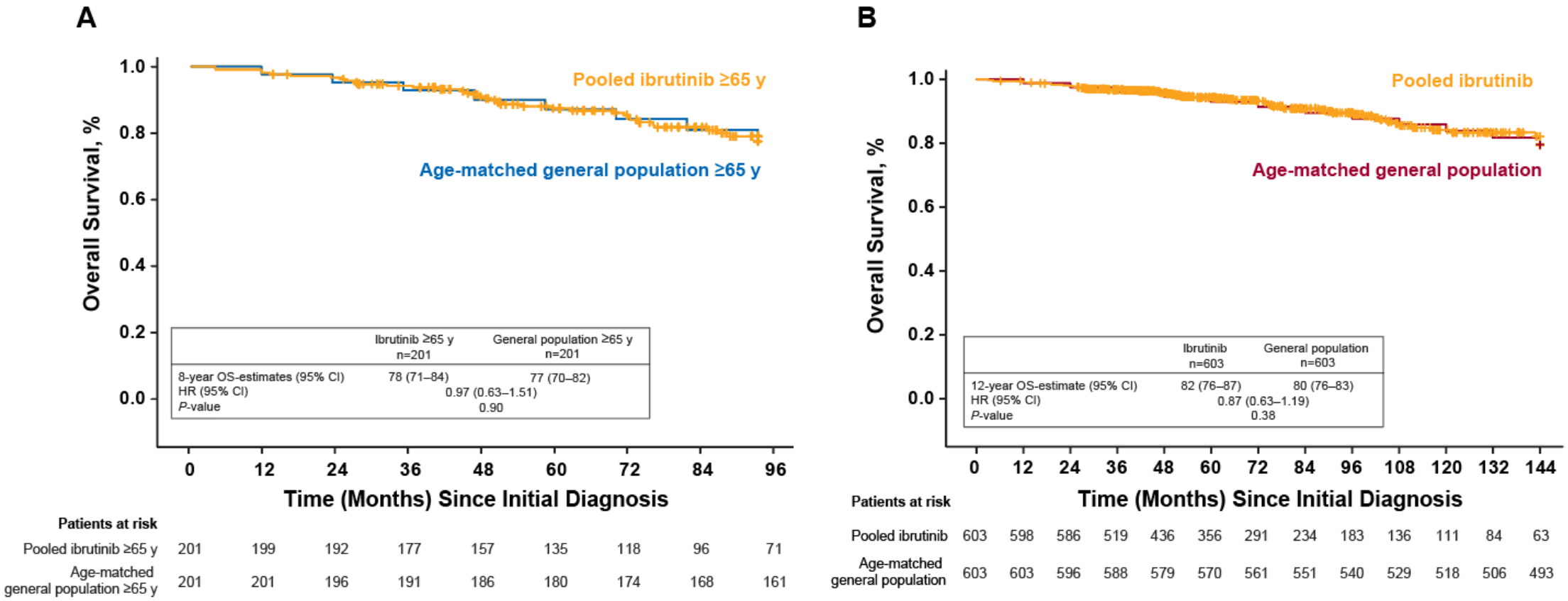
603 treatment naïve patients received ibrutinib. Median age: 63 years.

58.7% Ibr + Ritux	22.6% Ibr monotherapy	18.7% Ibr + Obi

Initiation of ibrutinib in the frontline improved overall survival compared to CIT

Ghia *et al.* ASH 2022; A#1809

Initiating 1L Ibrutinib in Patients with CLL Improves OS to Rates Approximating an Age-Matched Population



Similar OS for Pooled Ibrutinib-Treated Patients ≥65 years (A) All Pooled Ibrutinib-Treated Patients and (B) Age-Matched General US Population

Ghia *et al*. ASH 2022; A#1809

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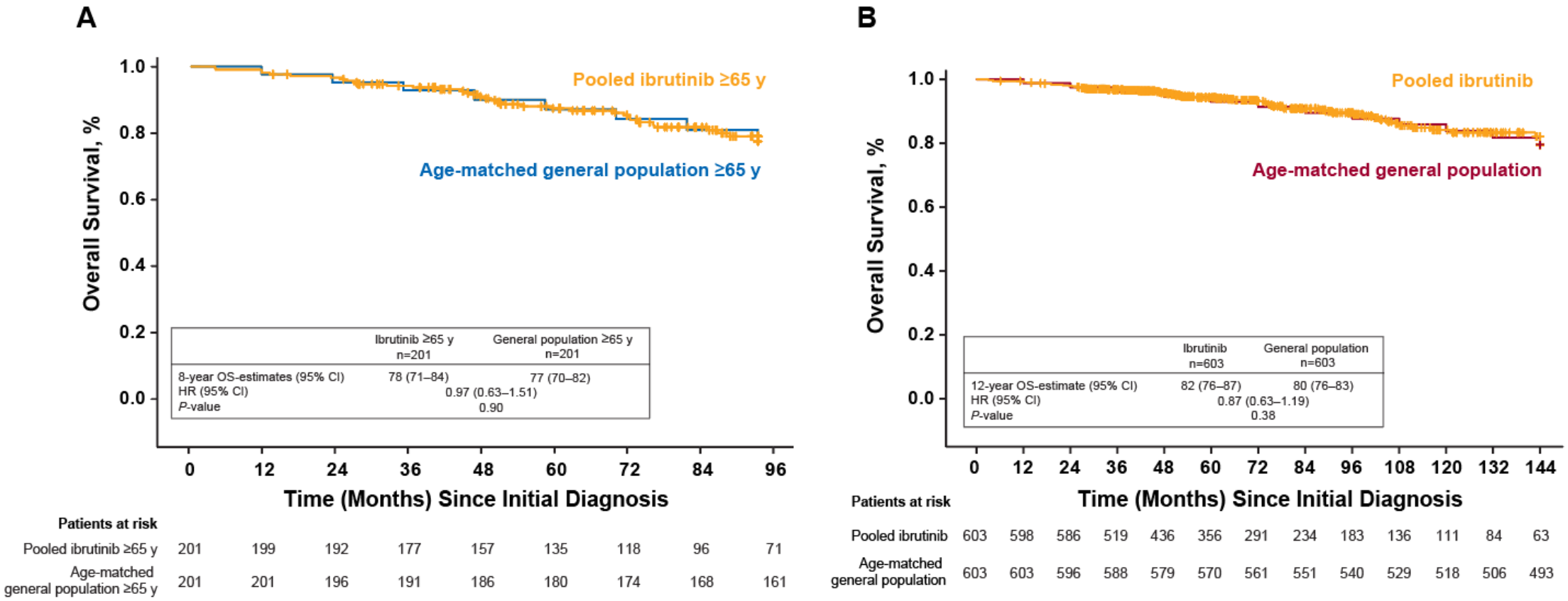
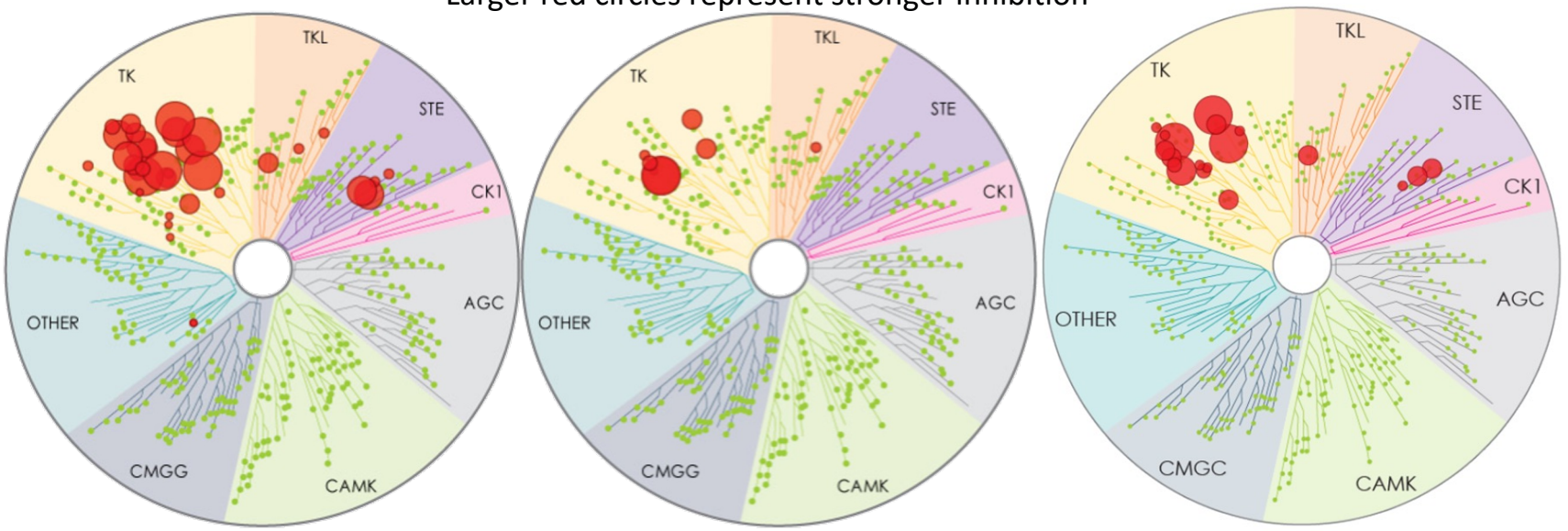


Similar OS for Pooled Ibrutinib-Treated Patients ≥65 years (A) All Pooled Ibrutinib-Treated Patients and (B) Age-Matched General US Population

Ghia *et al*. ASH 2022; A#1809

Kinase Selectivity Profiling at 1 (in vitro)

Larger red circles represent stronger inhibition



Kinase	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

IC50/EC50 (nM)

Kaptein *et al.* ASH 2018

ALPINE: Randomized Phase III, Open Label, Study of Ibrutinib vs. Zanubrutinib in R/R CLL

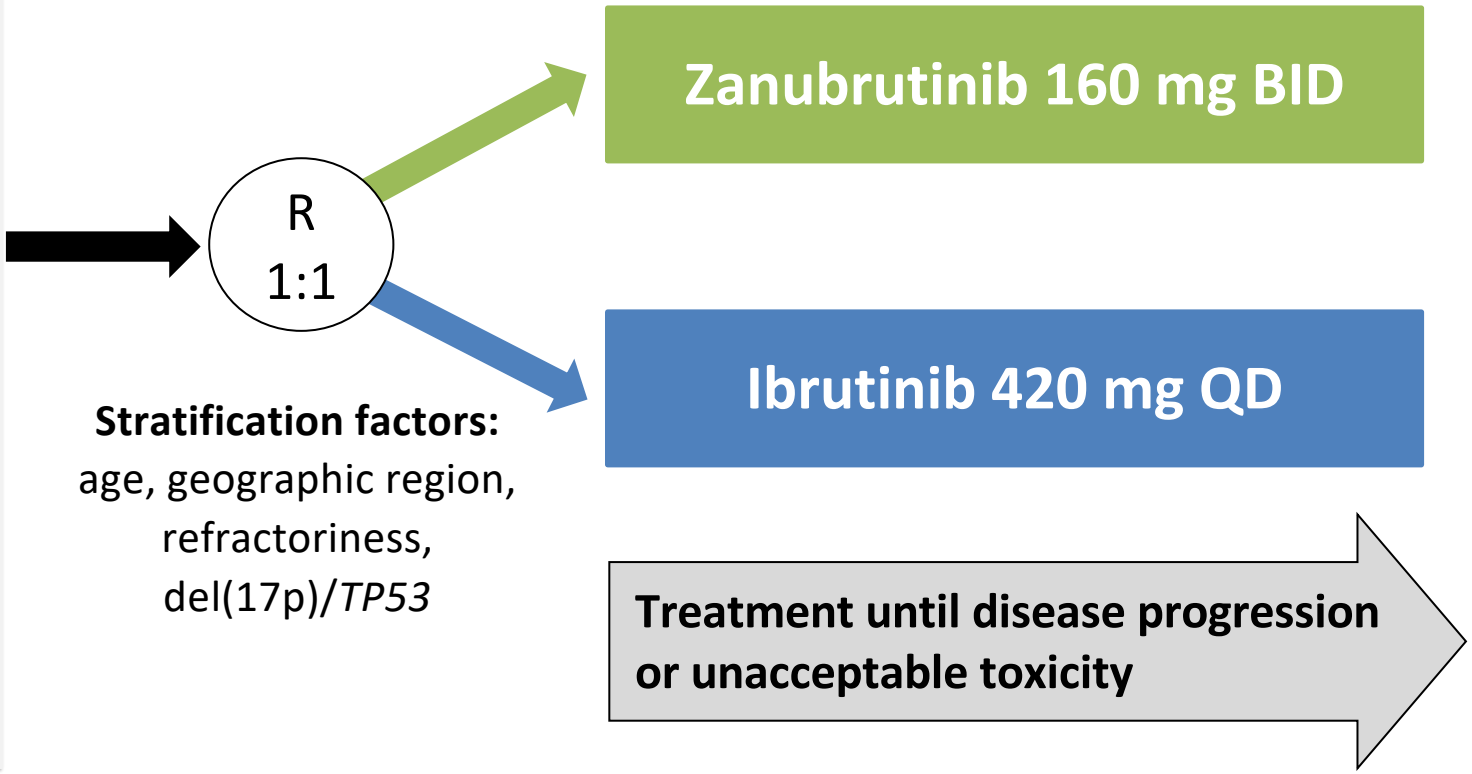
R/R CLL/SLL with ≥ 1 prior treatment
(Planned N=600, Actual N=652)

Key Inclusion Criteria

- R/R to ≥1 prior systemic therapy for CLL/SLL
- Measurable lymphadenopathy by CT or MRI

Key Exclusion Criteria

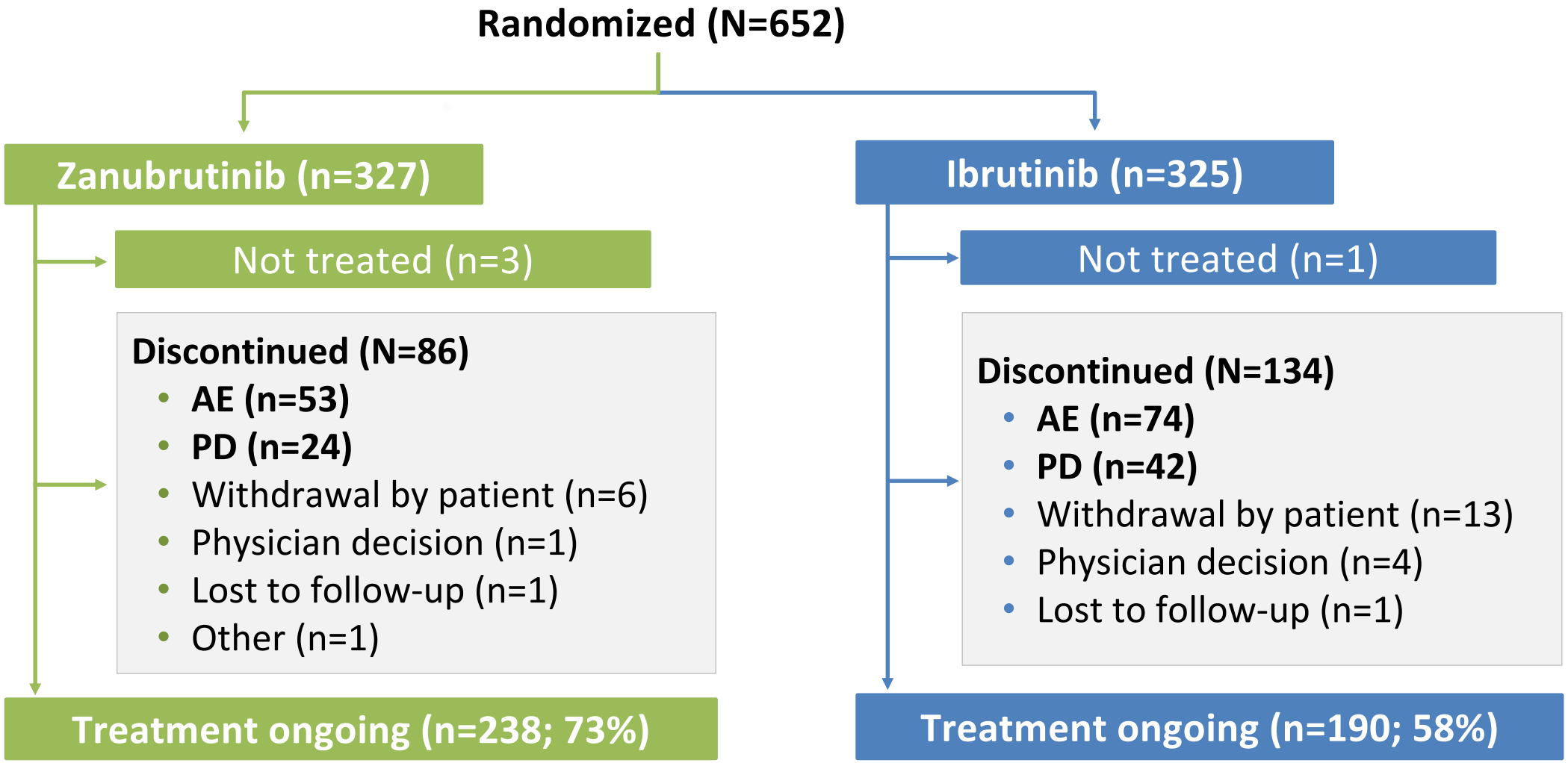
- Prior BTKi therapy
- Treatment with warfarin or other vitamin K antagonists



Primary end point: investigator-assessed ORR.
Key secondary end points: PFS, incidence of atrial fibrillation or flutter, OS, TTTF, DoR.
If noninferiority was established, the superiority of zanubrutinib was assessed and claimed if the two-sided P value was less than 0.05.

Brown et al. NEJM 2022

ALPINE: Patients Disposition



AE, adverse event; PD, progressive disease.

Brown et al. NEJM 2022

Demographics and Disease Characteristics

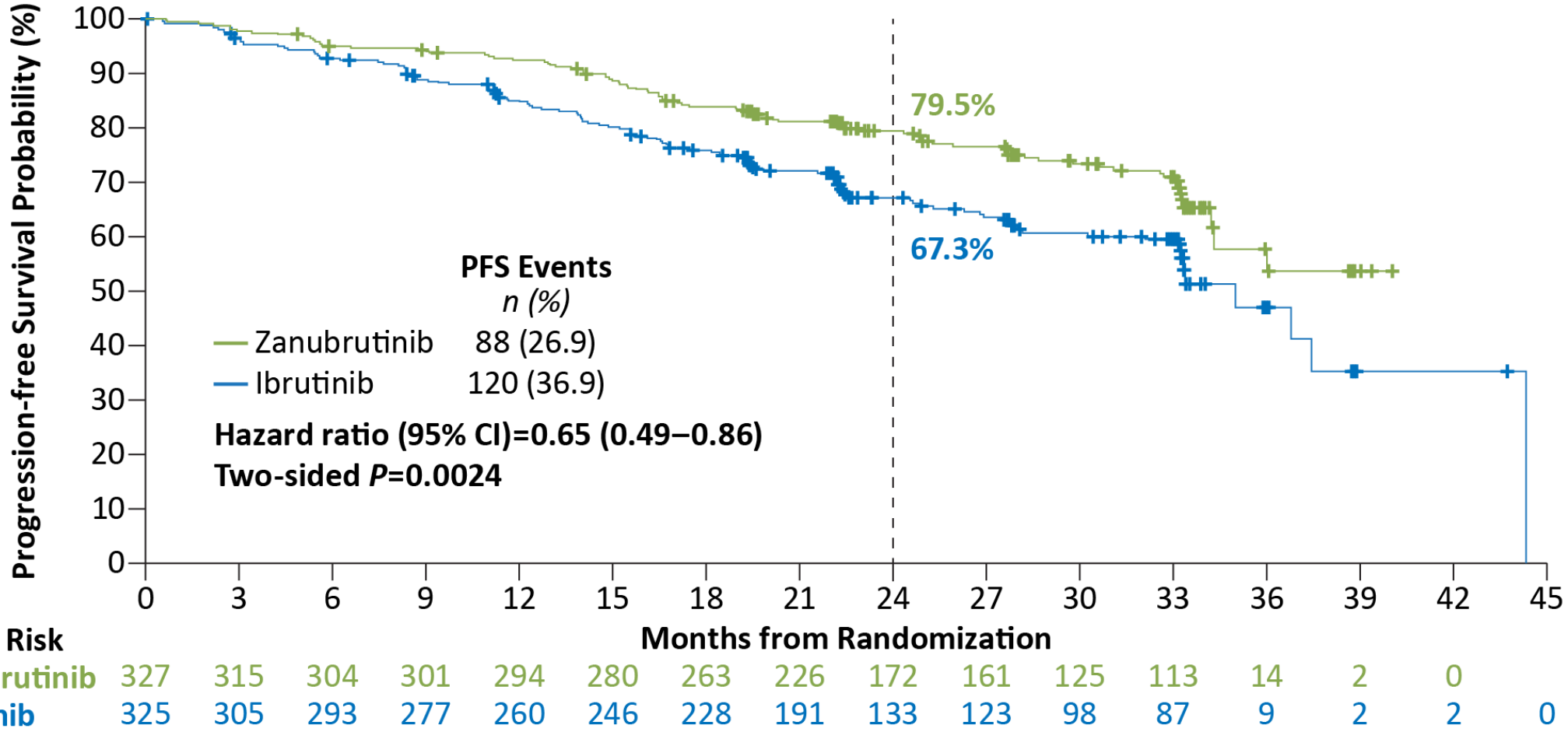
	Zanubrutinib (n=327)	Ibrutinib (n=325)
Age, median (range)	**67 (35-90)**	**68 (35-89)**
≥65 years, n (%)	201 (61.5)	200 (61.5)
Male, n (%)	**213 (65.1)**	**232 (71.4)**
ECOG PS ≥1, n (%)	**198 (60.6)**	**203 (62.5)**
Prior lines of systemic therapy, median (range)	**1 (1-6)**	**1 (1-12)**
>3 prior lines, n (%)	24 (7.3)	30 (9.2)
del(17p) and/or *TP53*^{mut}, n (%)	**75 (22.9)**	**75 (23.1)**
del(17p)	45 (13.8)	50 (15.4)
TP53^{mut} without del(17p)	30 (9.2)	25 (7.7)
del(11q), n (%)	**91 (27.8)**	**88 (27.1)**
IGHV mutational status, n (%)		
Mutated	79 (24.2)	70 (21.5)
Unmutated	**239 (73.1)**	**239 (73.5)**
Complex karyotype*	**56 (17.1)**	**70 (21.5)**
Bulky disease (≥5 cm), n (%)	**145 (44.3)**	**149 (45.8)**

*Complex karyotype is defined as having ≥3 abnormalities.

Brown et al. NEJM 2022

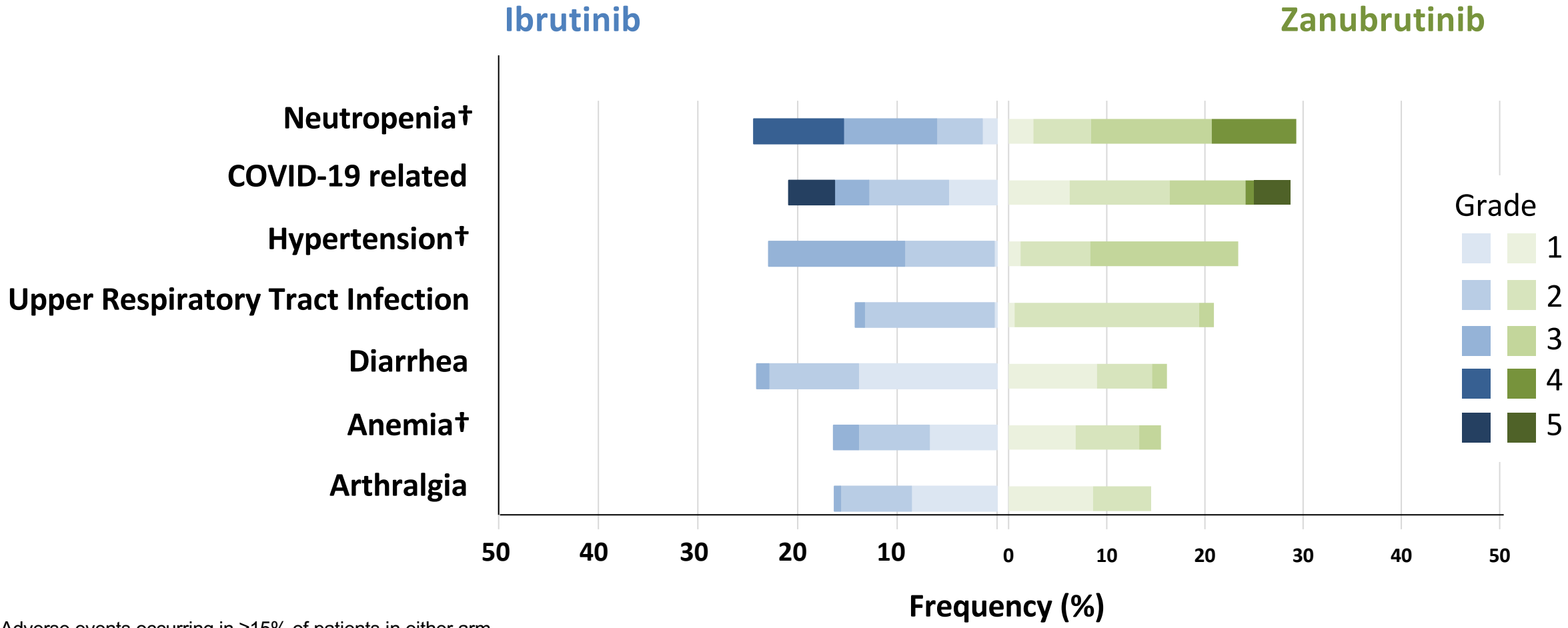
Zanubrutinib PFS by IRC Significantly Superior to Ibrutinib

Median study follow-up of 29.6 months



Brown et al. NEJM 2022

Most Common Adverse Events*

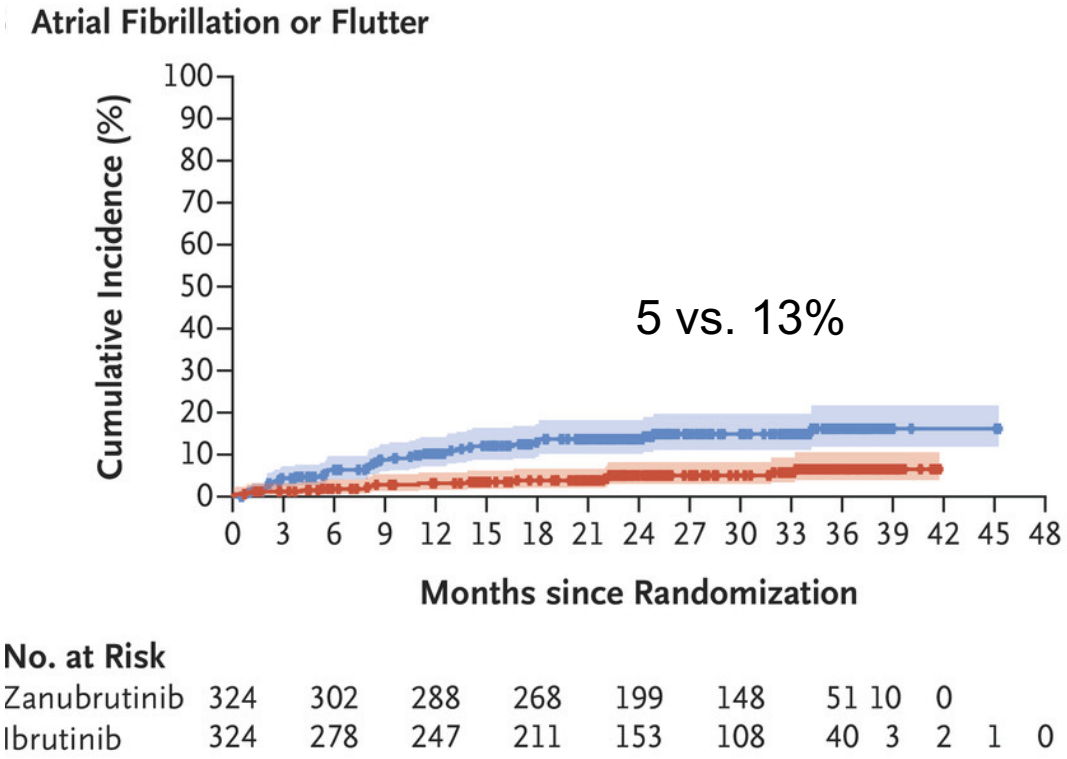


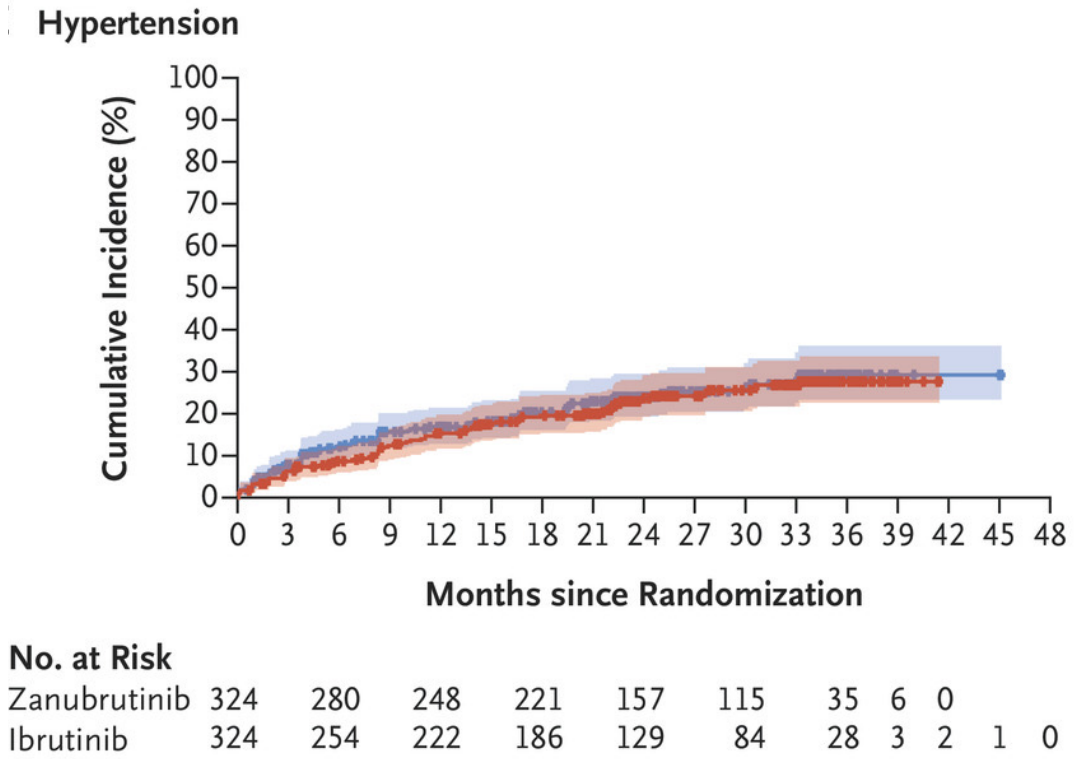
*Adverse events occurring in ≥15% of patients in either arm.
†Pooled terms.

Brown et al. NEJM 2022

Lower Rates of Cardiac Events with Zanubrutinib

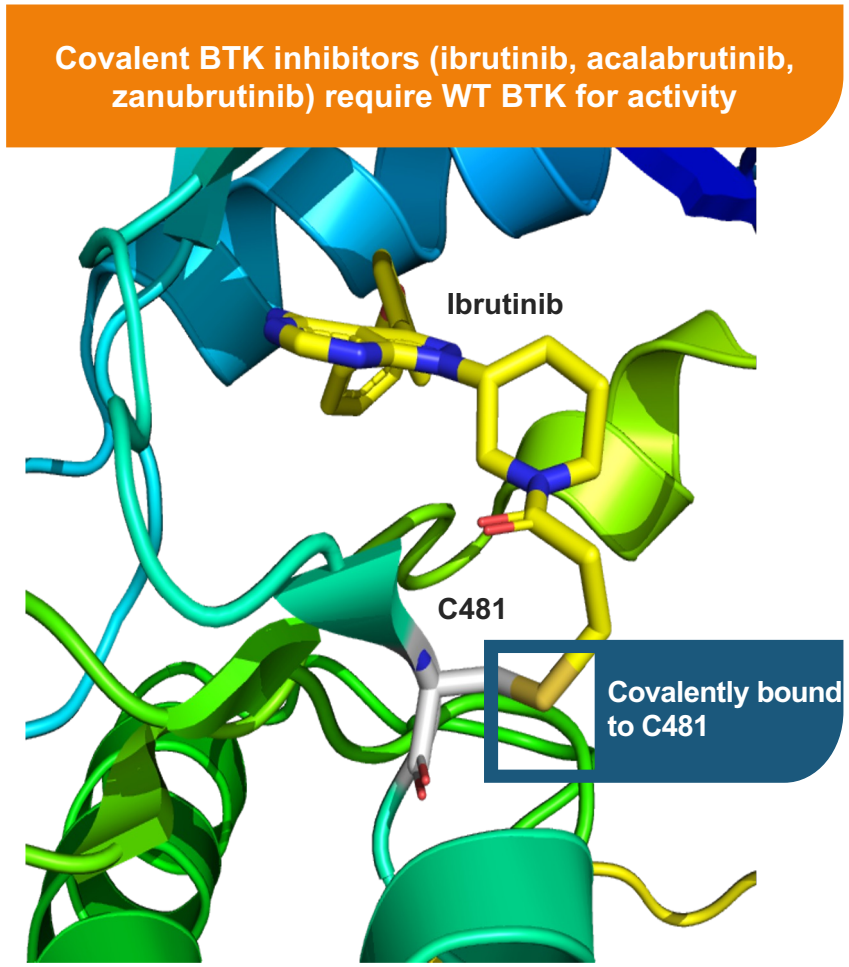
	Zanubrutinib (n=324)	Ibrutinib (n=324)
Cardiac adverse events	69 (21.3%)	96 (29.6%)
Serious cardiac adverse events	6 (1.9%)	25 (7.7%)
Fatal cardiac events	0 (0%)	6 (1.9%)





Brown et al. NEJM 2022

BTKi Resistance Mutations



- Ibrutinib, acalabrutinib, and zanubrutinib require covalent binding at the C481 locus for their mechanism of action.
- C481S mutations are common to all covalent BTKi and confer resistance to BTK inhibition.
- Patients who progress on a covalent BTKi **should not be switched** to an alternative **covalent** BTKi because of this common resistance mechanism.

Extended Follow-up from the Phase 1/2 BRUIN Study

LOXO-305 is a non-covalent BTK inhibitor that is potent against both WT and C481-mutant BTK

Low rates of Grade ≥3 TEAEs:

- HTN: 3%
- Hemorrhage: 2%
- A-Fib: 1%
- Discontinuation for AE: 2%

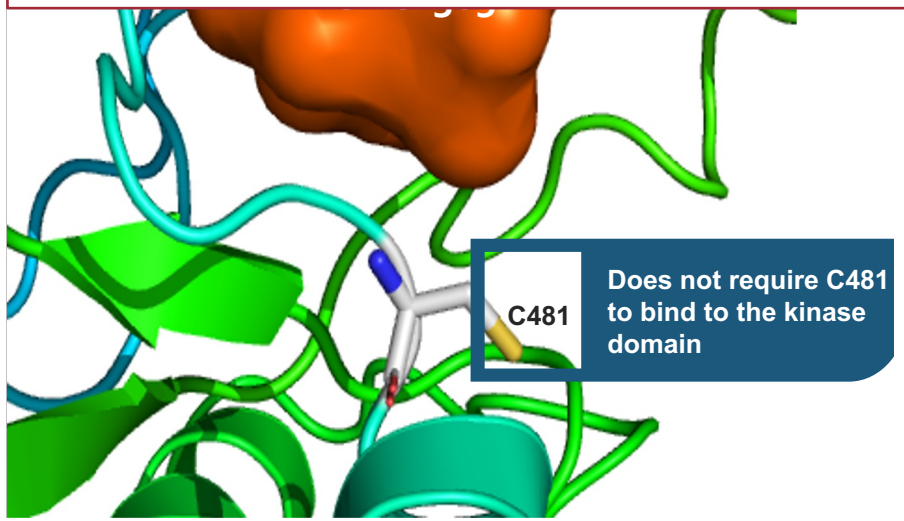
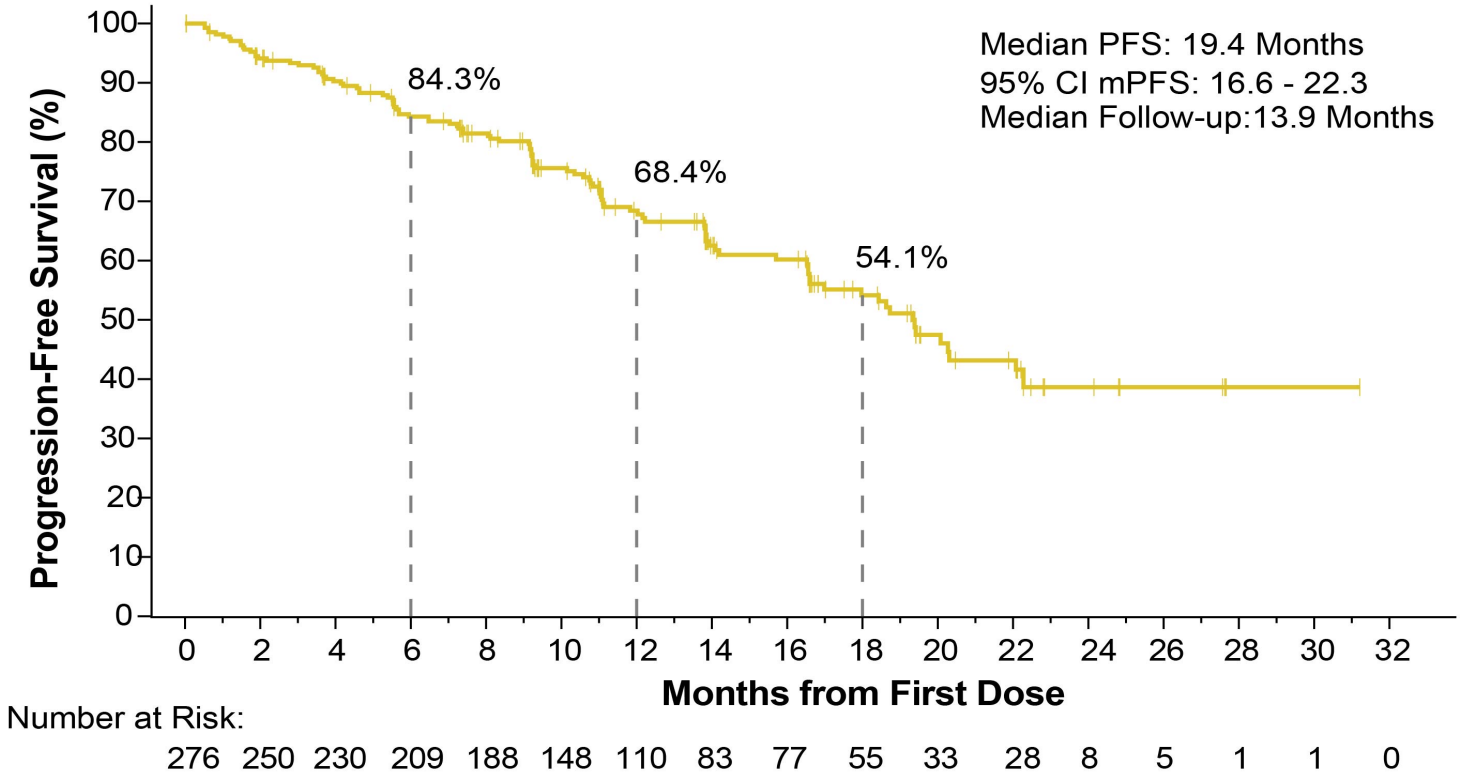
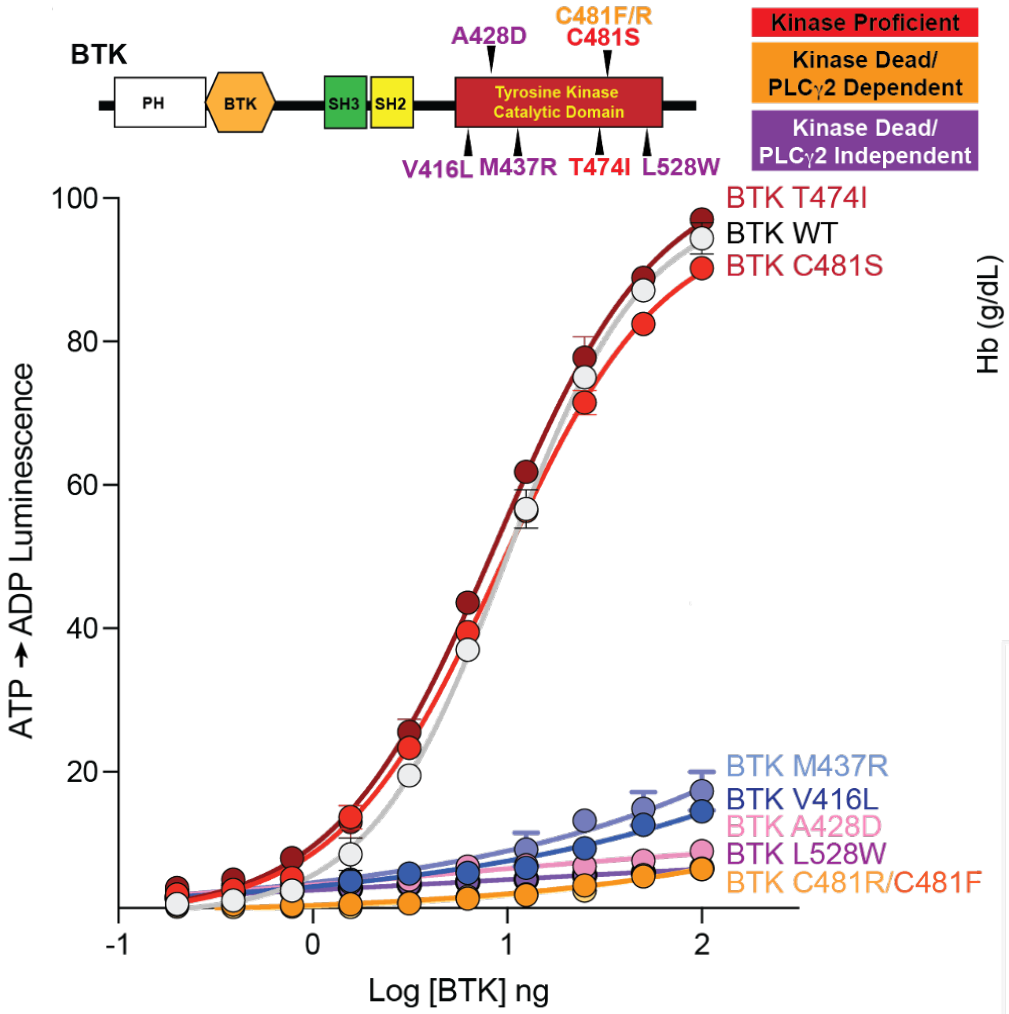


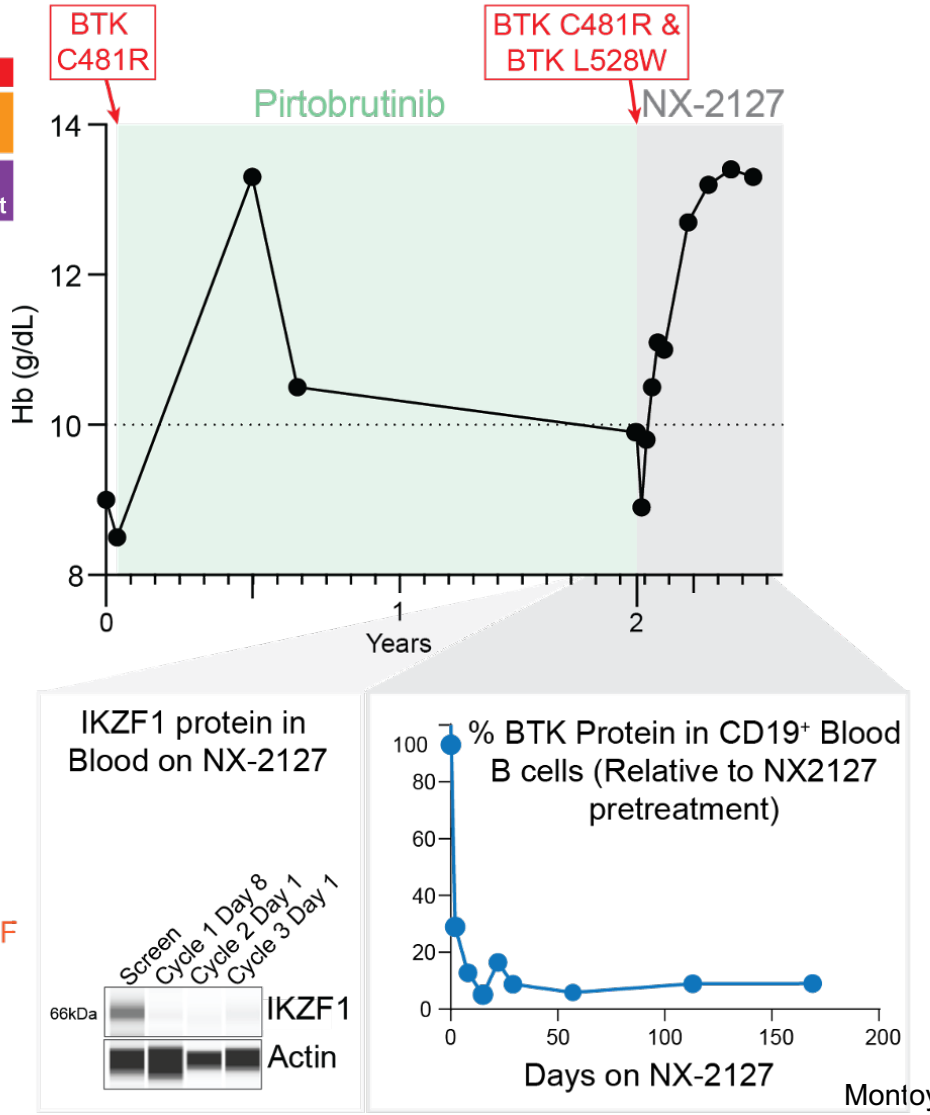
Figure. Progression-free survival in covalent BTKi pre-treated CLL/SLL



Mato *et al.* ASH 2022, A#961

Not All BTK Mutations Are Equal: Concept of Kinase-Dead BTK





Montoya *et al.* ASH 2022, A#750

A First-in-Human Trial of NX-2127, a BTK Degrader, in R/R CLL and B-Cell Malignancies

R/R CLL (N=17)
≥ 2 prior line of therapy (median 6),
100% post BTKi, 77% post Ven

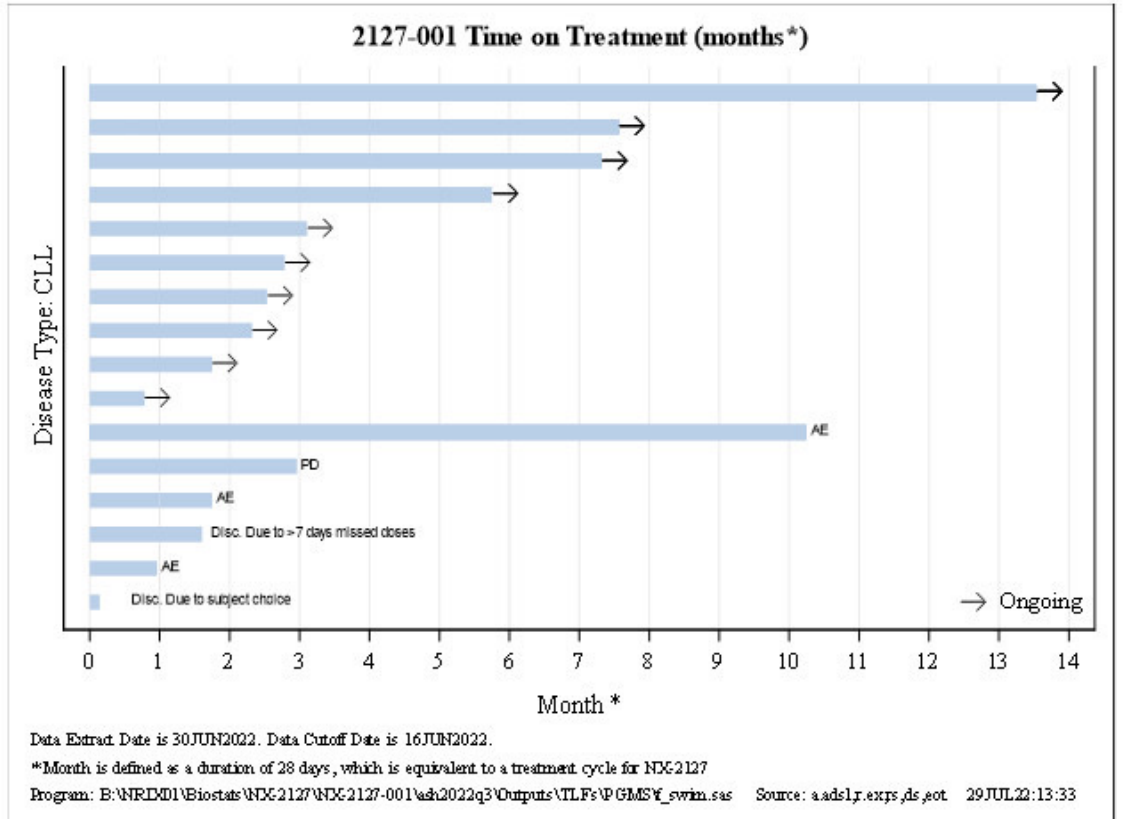
NX-2127
Dose escalation: 100, 200, 300 mg orally daily

Tolerability, Safety, Preliminary Efficacy

Table 1. Summary of treatment-emergent adverse events (TEAEs) occurring in >15% of all patients (including patients with CLL and NHL)

Preferred Term	All Grades (N=26)	Grade ≥ 3 (N=26)	Grade ≥ 3 Related (N=26)
Any AE	25 (96%)	15 (58%)	12 (46%)
Fatigue	16 (62%)	0 (0%)	0 (0%)
Neutrophil Count Decrease	10 (39%)	9 (35%)	9 (35%)
Anemia	7 (27%)	4 (15%)	2 (8%)
Contusion	7 (27%)	0 (0%)	0 (0%)
Hypertension	7 (27%)	1 (4%)	1 (4%)
Dyspnoea	5 (19%)	1 (4%)	0 (0%)
Pruritis	5 (19%)	0 (0%)	0 (0%)
Rash maculo-papular	5 (19%)	0 (0%)	0 (0%)
Blood creatinine increased	4 (15%)	0 (0%)	0 (0%)
COVID-19	4 (15%)	1 (4%)	0 (0%)
Diarrhea	4 (15%)	0 (0%)	0 (0%)
Petechiae	4 (15%)	0 (0%)	0 (0%)
Platelet count decreased	4 (15%)	1 (4%)	0 (0%)

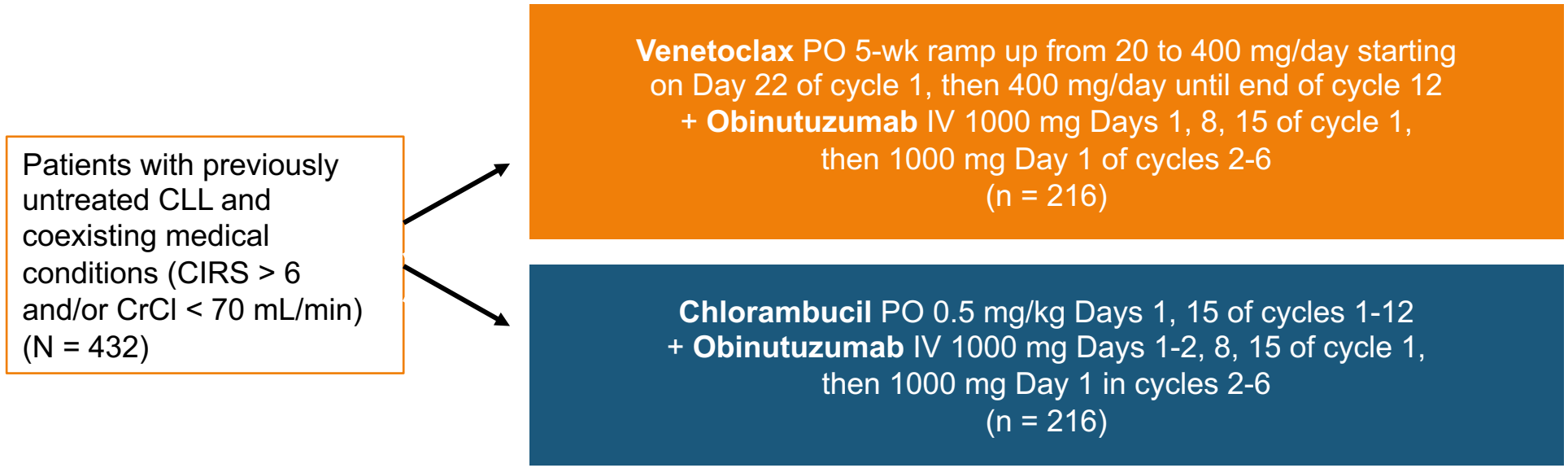
Figure 1. CLL patient disposition



Mato et al. ASH 2022, A#965

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

- Open-label, multicenter, randomized phase III trial



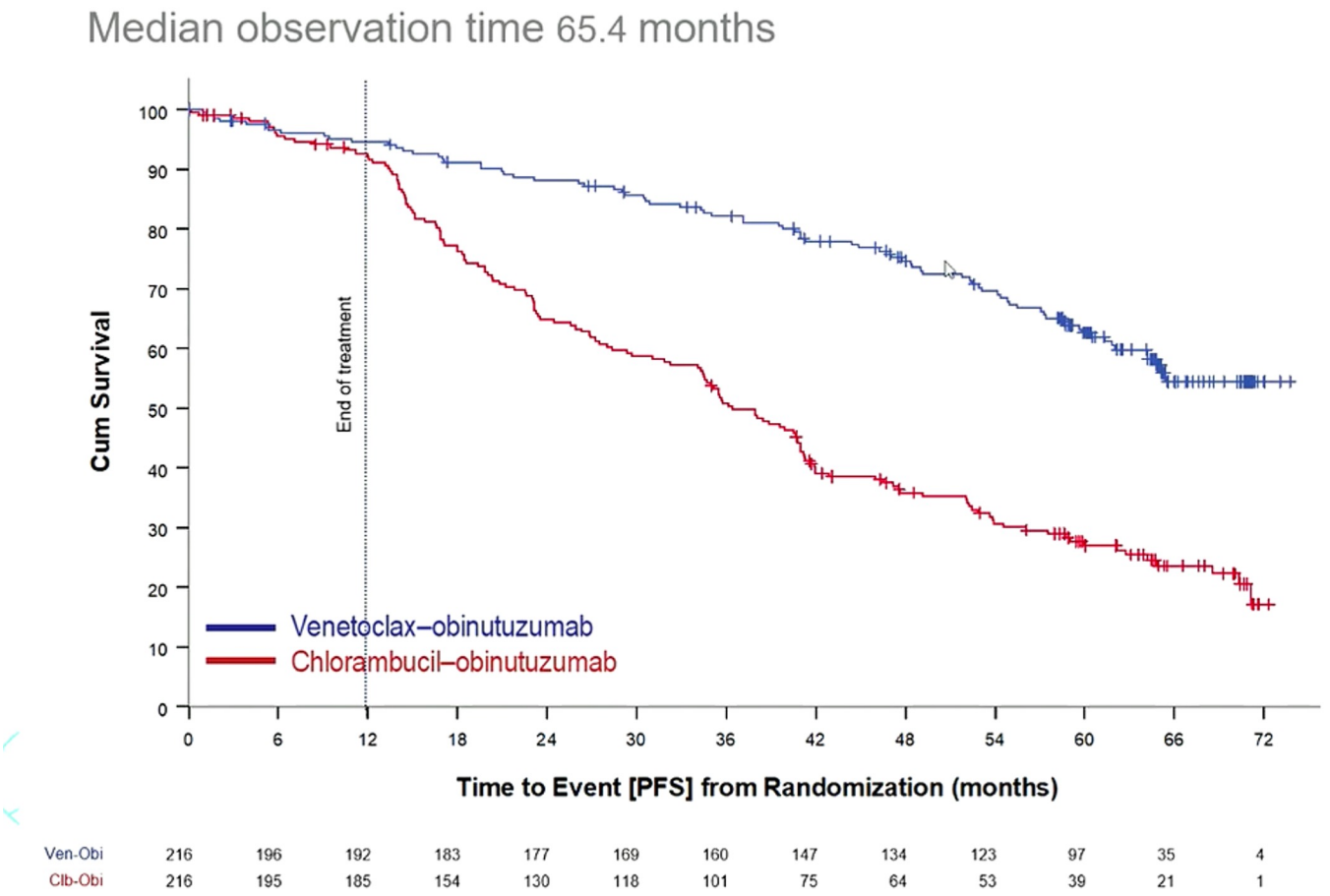
Total 28-day cycles

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

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

Fischer *et al.* NEJM 2019; Al-Sawaf *et al.* Lancet Oncol 2020; Al-Sawaf *et al.* EHA 2021; Burger *et al.* NEJM 2020

CLL14: PFS



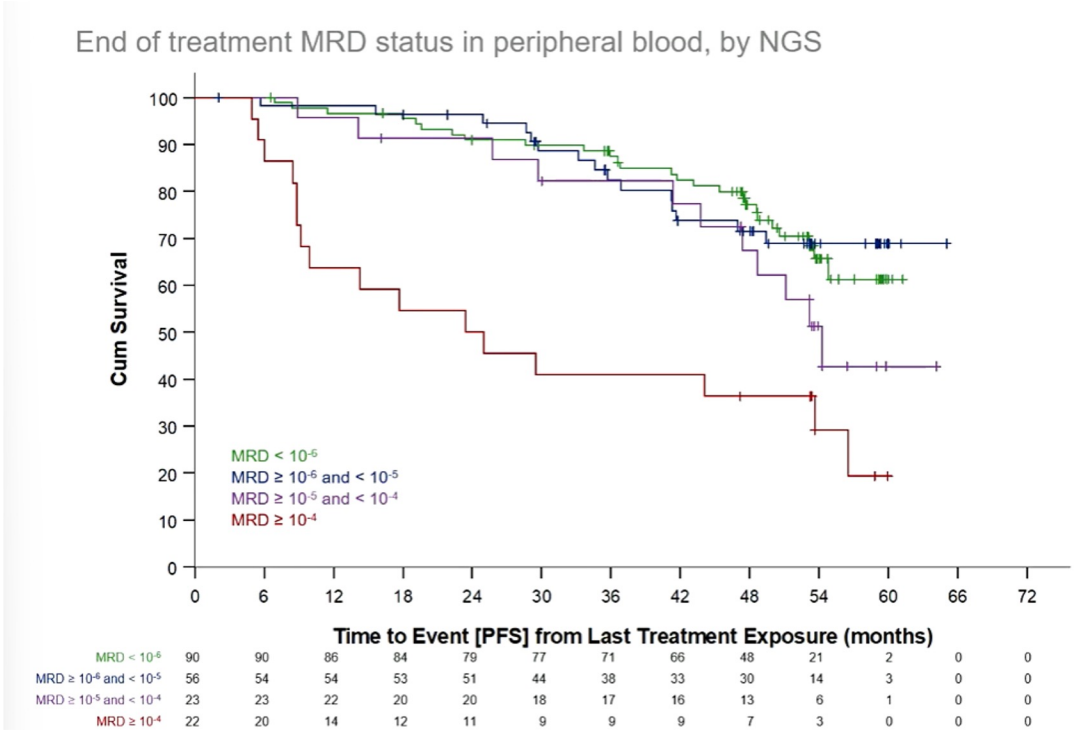
Median PFS
Ven-Obi: not reached
Clb-Obi: 36.4 months

5-year PFS rate
Ven-Obi: 62.6%
Clb-Obi: 27.0%

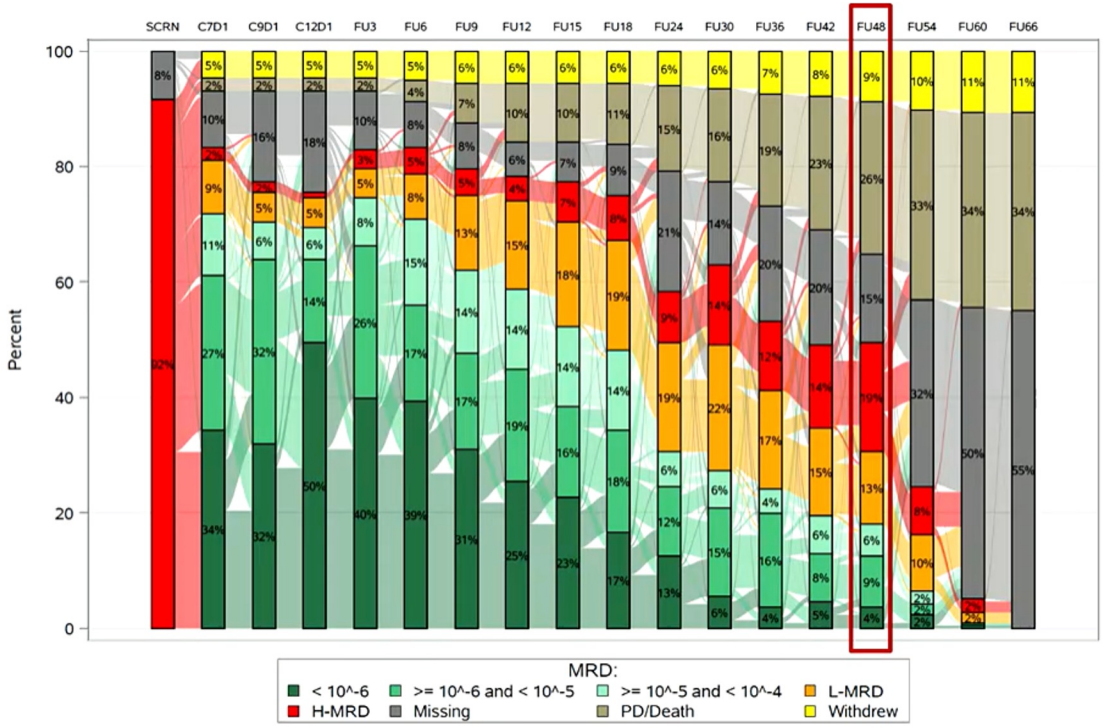
HR 0.35, 95% CI [0.26-0.46]
P<0.0001

Fischer *et al.* NEJM 2019; Al-Sawaf *et al.* Lancet Oncol 2020; Al-Sawaf *et al.* EHA 2021; Burger *et al.* NEJM 2020

CLL14: EOT MRD, and MRD Dynamics



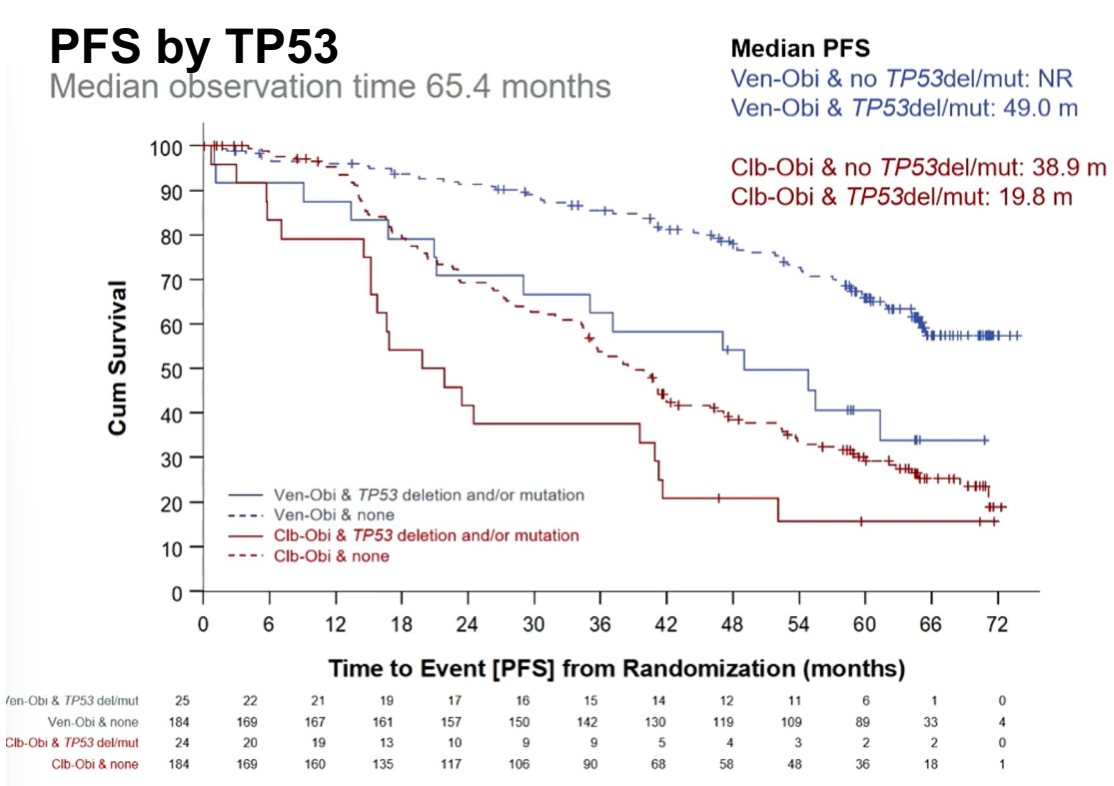
Depths of remission beyond 10^{-4} correlates with long-term PFS

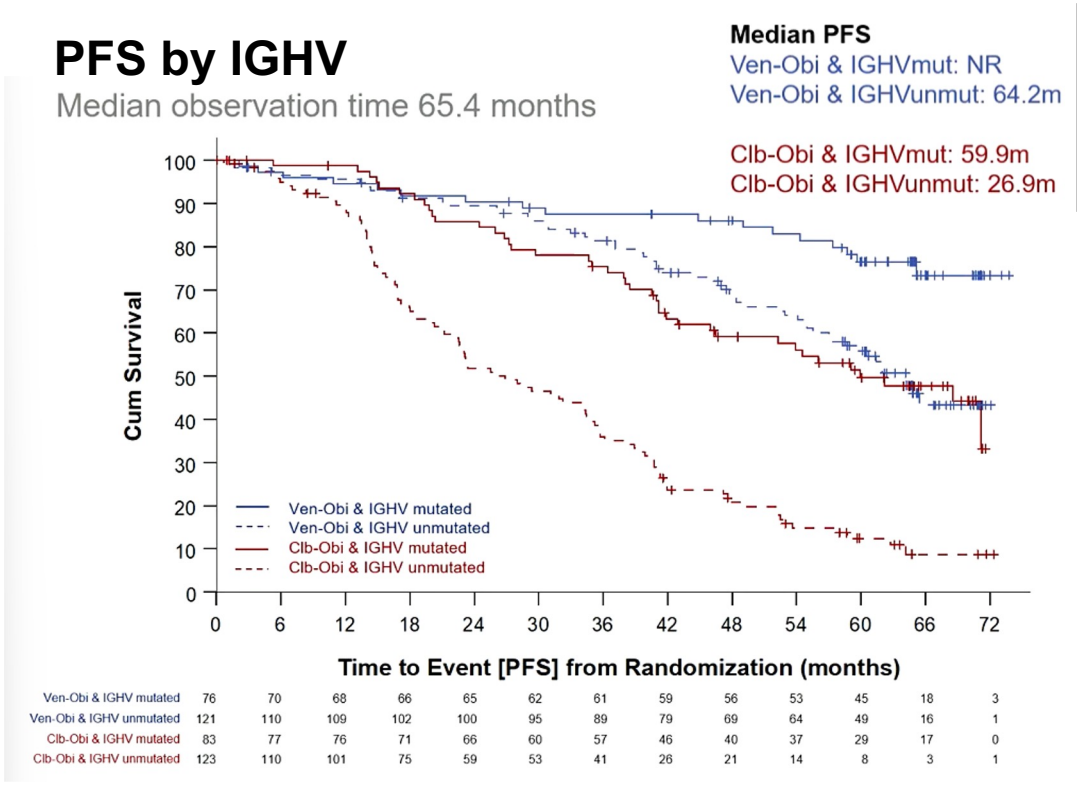


39 (18.1%) of patients had sustained MRD $<10^{-4}$ after 4 years

Fischer *et al.* NEJM 2019; Al-Sawaf *et al.* Lancet Oncol 2020; Al-Sawaf *et al.* EHA 2021; Burger *et al.* NEJM 2020

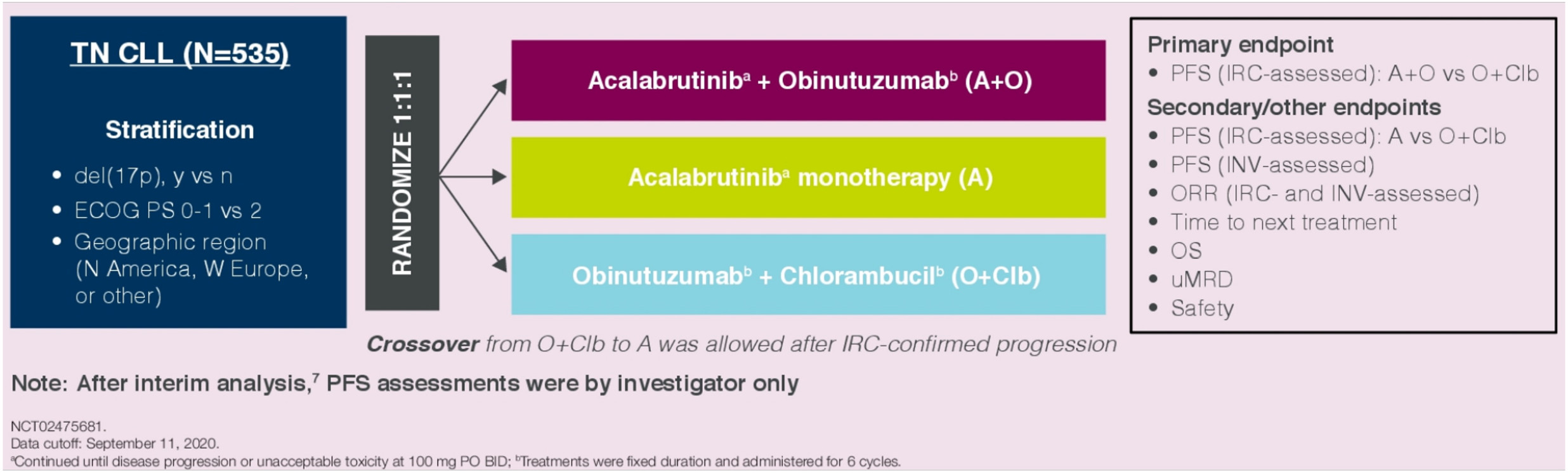
CLL14: PFS by TP53 and IGHV status





Fischer *et al.* NEJM 2019; Al-Sawaf *et al.* Lancet Oncol 2020; Al-Sawaf *et al.* EHA 2021; Burger *et al.* NEJM 2020

ELEVATE TN: Randomized Phase III Trial in TN CLL

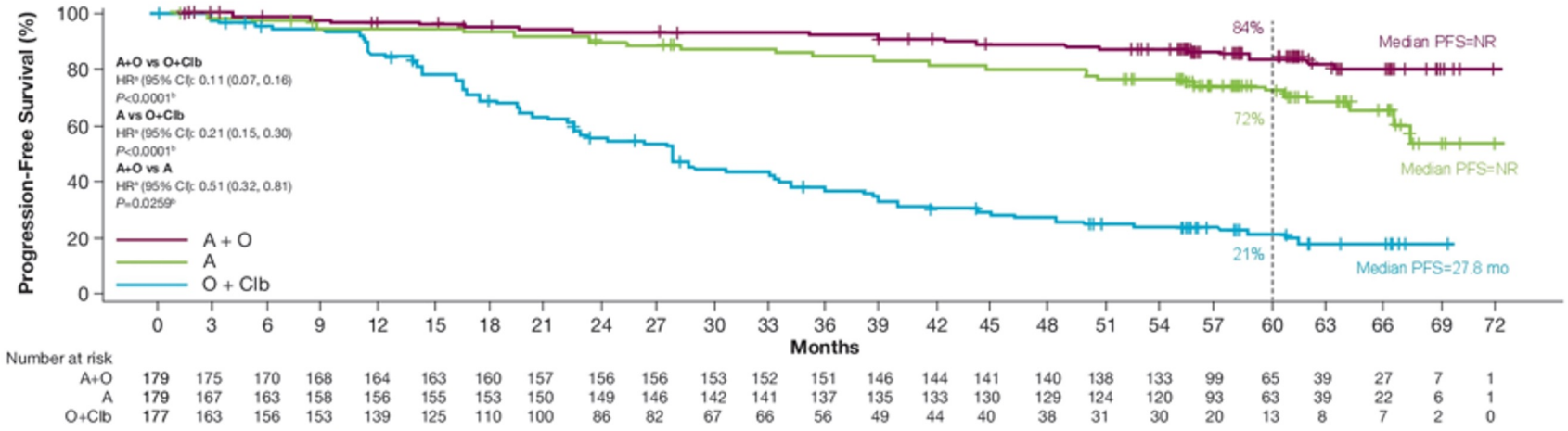


NCT02475681.
Data cutoff: September 11, 2020.
[a]Continued until disease progression or unacceptable toxicity at 100 mg PO BID; [b]Treatments were fixed duration and administered for 6 cycles.

Sharman *et al.* ASCO 2022

ACALABRUTINIB - ELEVATE-TN: IRC-Assessed PFS

A. Investigator-assessed PFS

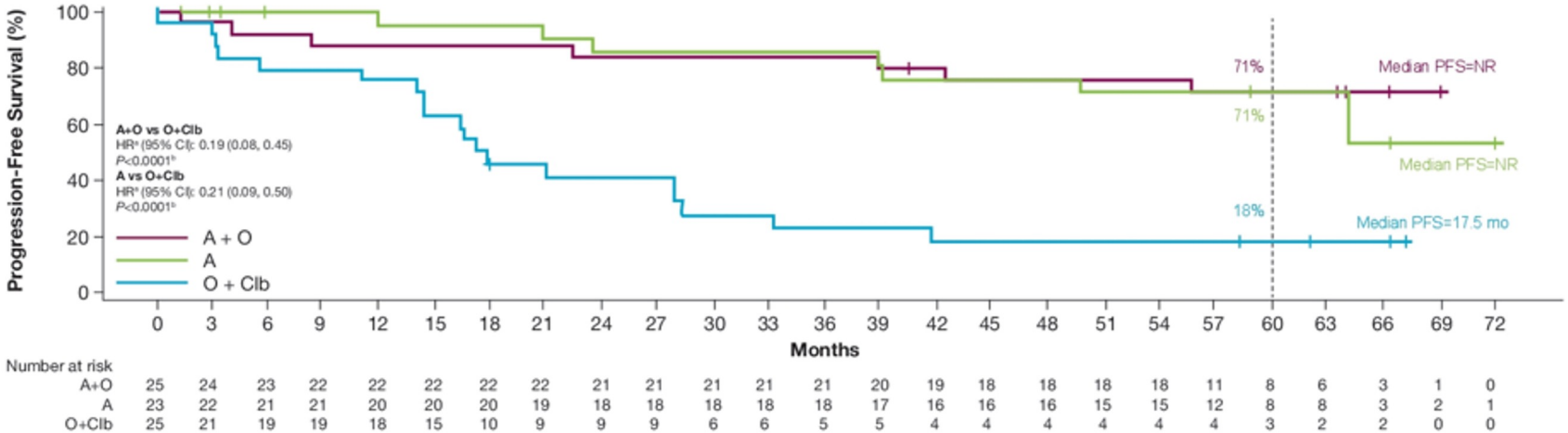


Number at risk

A+O	179	175	170	168	164	163	160	157	156	156	153	152	151	146	144	141	140	138	133	99	65	39	27	7	1
A	179	167	163	158	156	155	153	150	149	146	142	141	137	135	133	130	129	124	120	93	63	39	22	6	1
O+Clb	177	163	156	153	139	125	110	100	86	82	67	66	56	49	44	40	38	31	30	20	13	8	7	2	0

[a]Hazard ratio based on Cox proportional-hazard model stratified by 17p deletion status (yes vs no based on interactive voice/web response system). [b]P-value based on log-rank test stratified by 17p deletion status (yes vs no based on interactive voice/web response system).

B. Investigator-assessed PFS in Patients With del(17p) and/or Mutated *TP53*

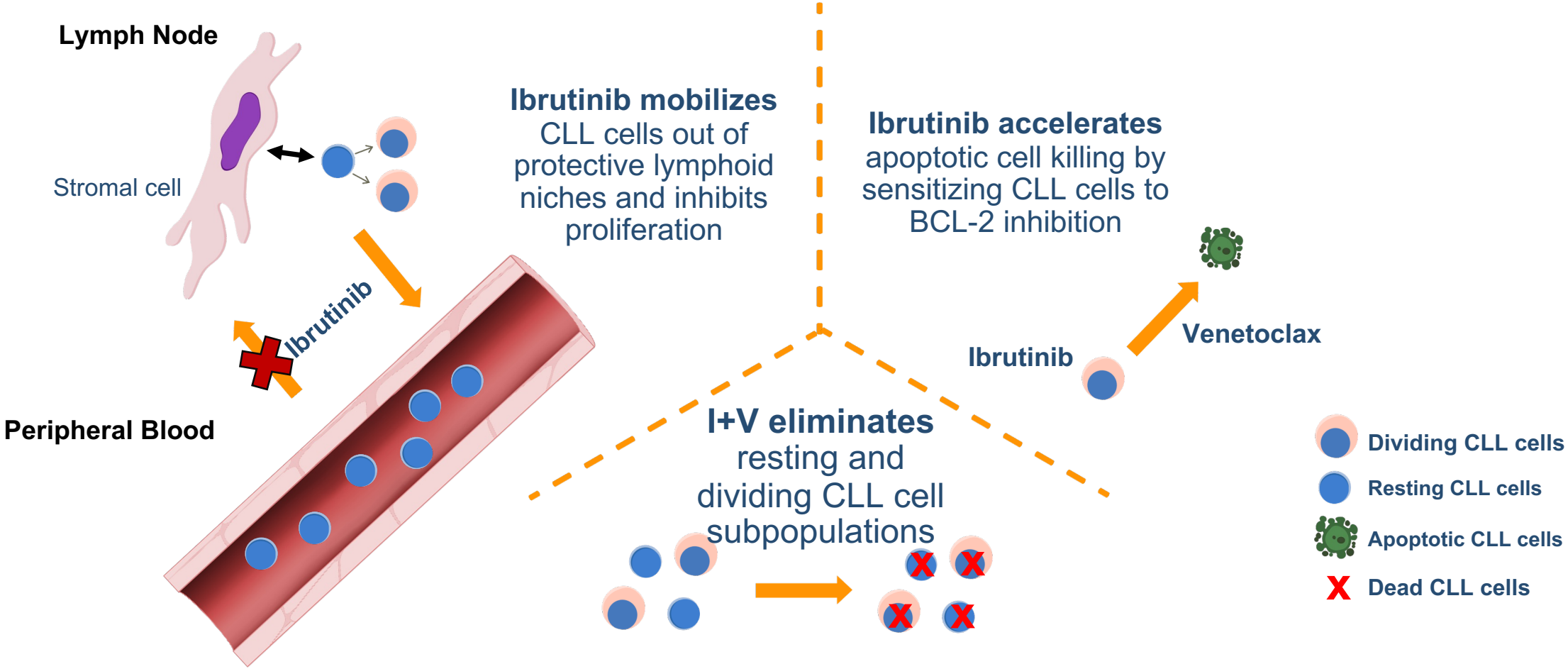


Number at risk

A+O	25	24	23	22	22	22	22	22	21	21	21	21	21	20	19	18	18	18	18	11	8	6	3	1	0
A	23	22	21	21	20	20	20	19	18	18	18	18	18	17	16	16	16	15	15	12	8	8	3	2	1
O+Clb	25	21	19	19	18	15	10	9	9	9	6	6	5	5	4	4	4	4	4	4	3	2	2	0	0

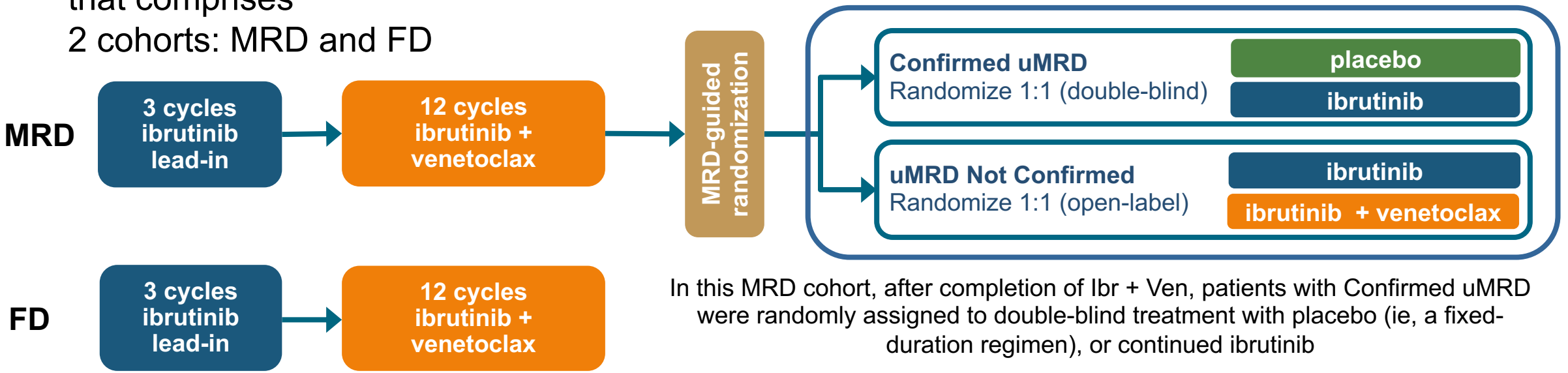
Sharman *et al.* ASCO 2022

BTKi + BCL2i Have Distinct and Synergistic Mechanisms of Action



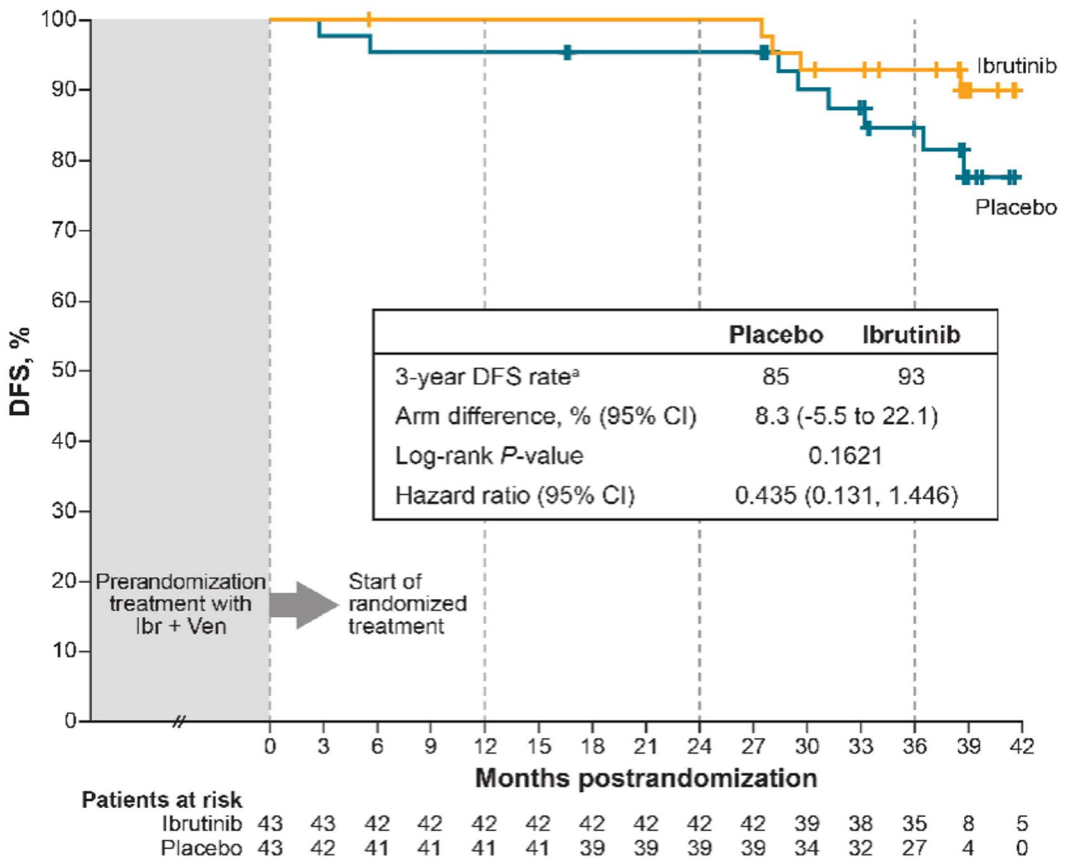
Phase 2 CAPTIVATE Study

- 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

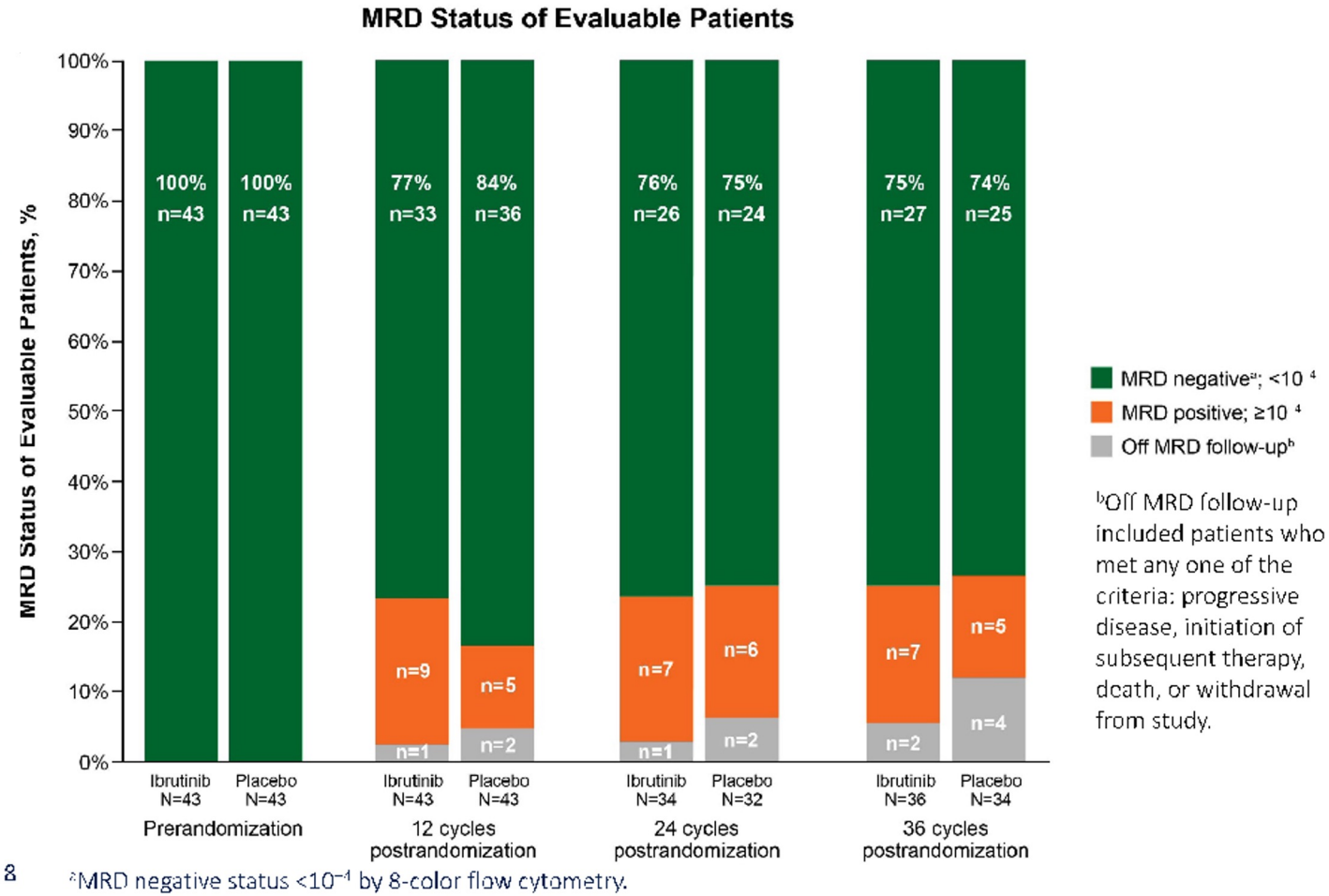


In this MRD cohort, after completion of Ibr + Ven, patients with Confirmed uMRD were randomly assigned to double-blind treatment with placebo (ie, a fixed-duration regimen), or continued ibrutinib

uMRD Rates Were Sustained 3 Years Post-randomization to Placebo vs Continued Ibrutinib



	Placebo	Ibrutinib
3-year DFS rate[a]	85	93
Arm difference, % (95% CI)	8.3 (-5.5 to 22.1)	
Log-rank *P*-value	0.1621	
Hazard ratio (95% CI)	0.435 (0.131, 1.446)	

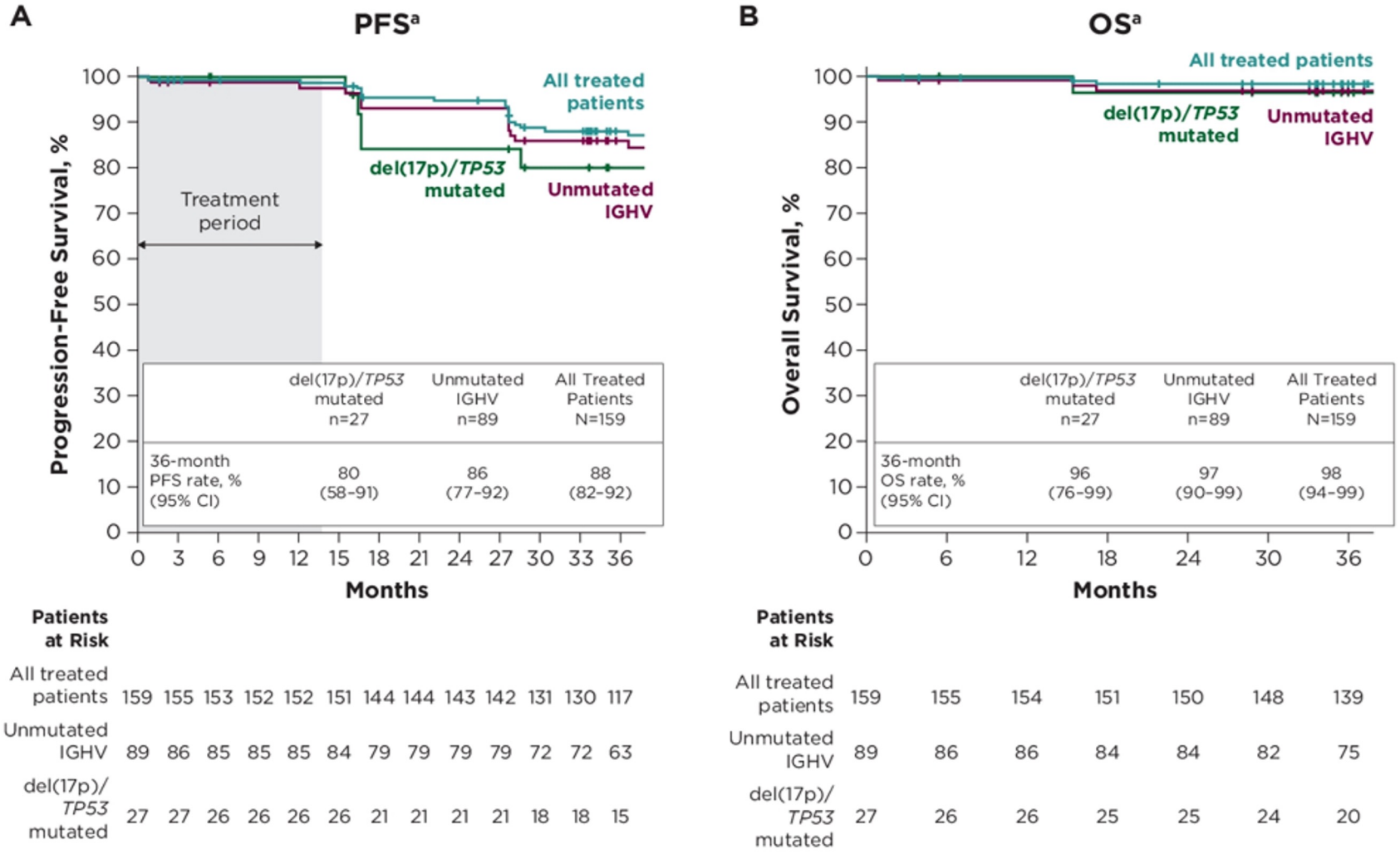


[b]Off MRD follow-up included patients who met any one of the criteria: progressive disease, initiation of subsequent therapy, death, or withdrawal from study.

[a]MRD negative status $<10^{-4}$ by 8-color flow cytometry.

Allen *et al.* ASH 2022, A#92

Phase 2 CAPTIVATE Study, Fixed-Duration Cohort



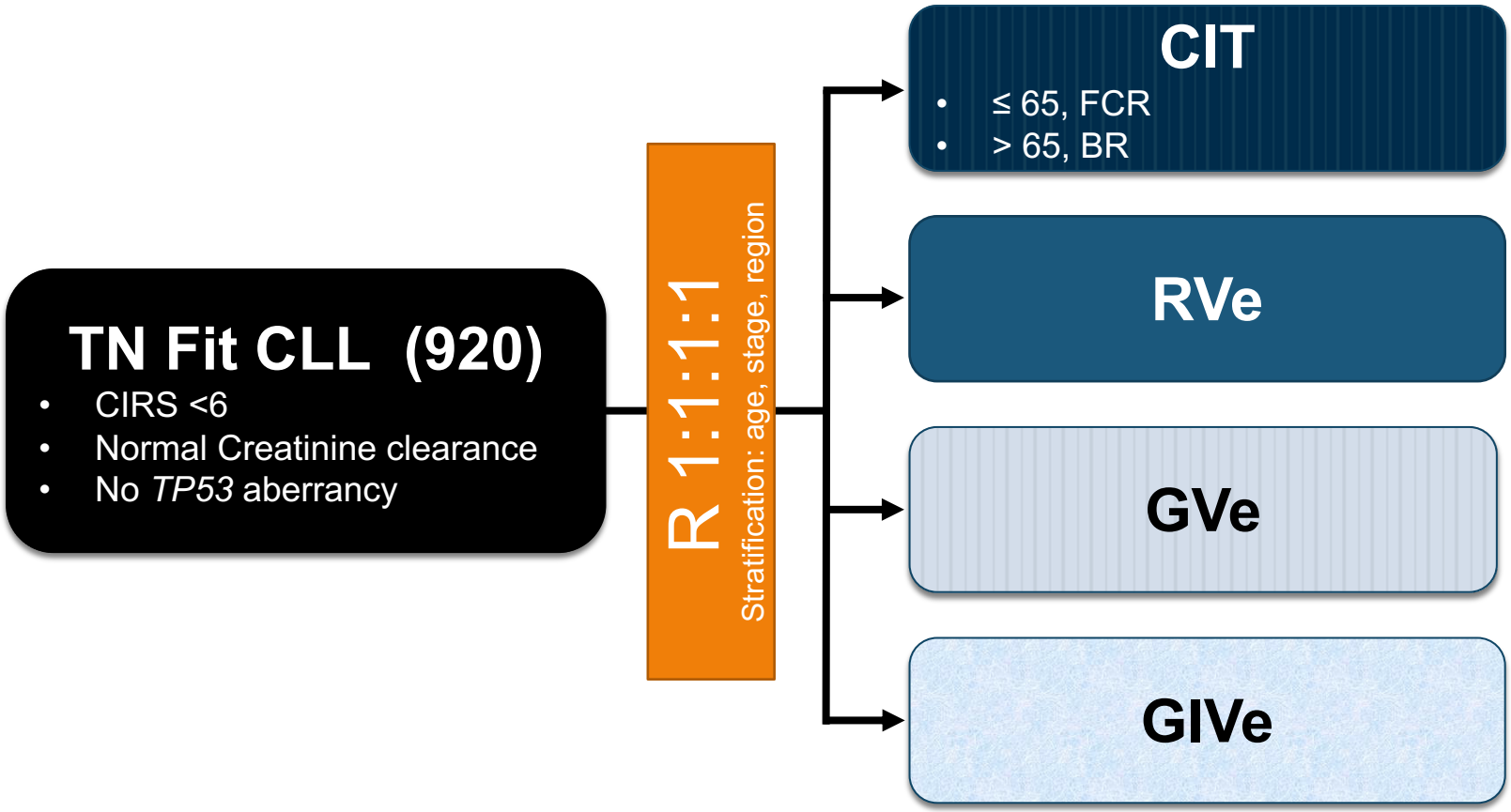
- The estimated 36-mo PFS rate was 88%
  - Similar rates in patients with del(17p)/*TP53* mutated (80%) or unmutated IGHV (86%)
- The estimated 36-mo OS rate was 98%
  - Similar rates in patients with del(17p)/*TP53* mutated (96%) or unmutated IGHV (97%)

[a]*Due to rapid enrollment in the study, the number of patients at risk drops substantially between 36 and 39 months. The Kaplan-Meier curves have therefore been truncated at 38 months due to instability of the curves.*

Wierda *et al.* ASCO 2022

CLL13 trial: A randomized Phase III Trial

First-Line Venetoclax Combinations in TN CLL



Primary endpoints:

- MRD4 at 15 months
- PFS

Secondary endpoints:

- ORR/CR
- OS
- TTNT
- QoL

Rituximab 375 (500) mg/m² iv c 1-6 (before chemo)
Fludarabine 25 mg/m² iv c 1-6 d 1-3
Cyclophosphamide 250 mg/m² iv c 1-6 d 1-3
(or) Bendamustine 90 mg/m² c 1-6 d1,2

Obinutuzumab 1000 mg iv (c1 d1(2)/8/15, c2-6 d1)
Ibrutinib d 1-MRD-/PD 420 mg po daily for up to 36 month *or* until MRD negativity is achieved,
Venetoclax c1 d 22- c12 d28 400 mg po daily (ramp-up)

Rituximab 375 (500) mg/m² iv (c1 – 6, d1)
Venetoclax c1 d22 – c12 d28 400 mg po daily (ramp-up)

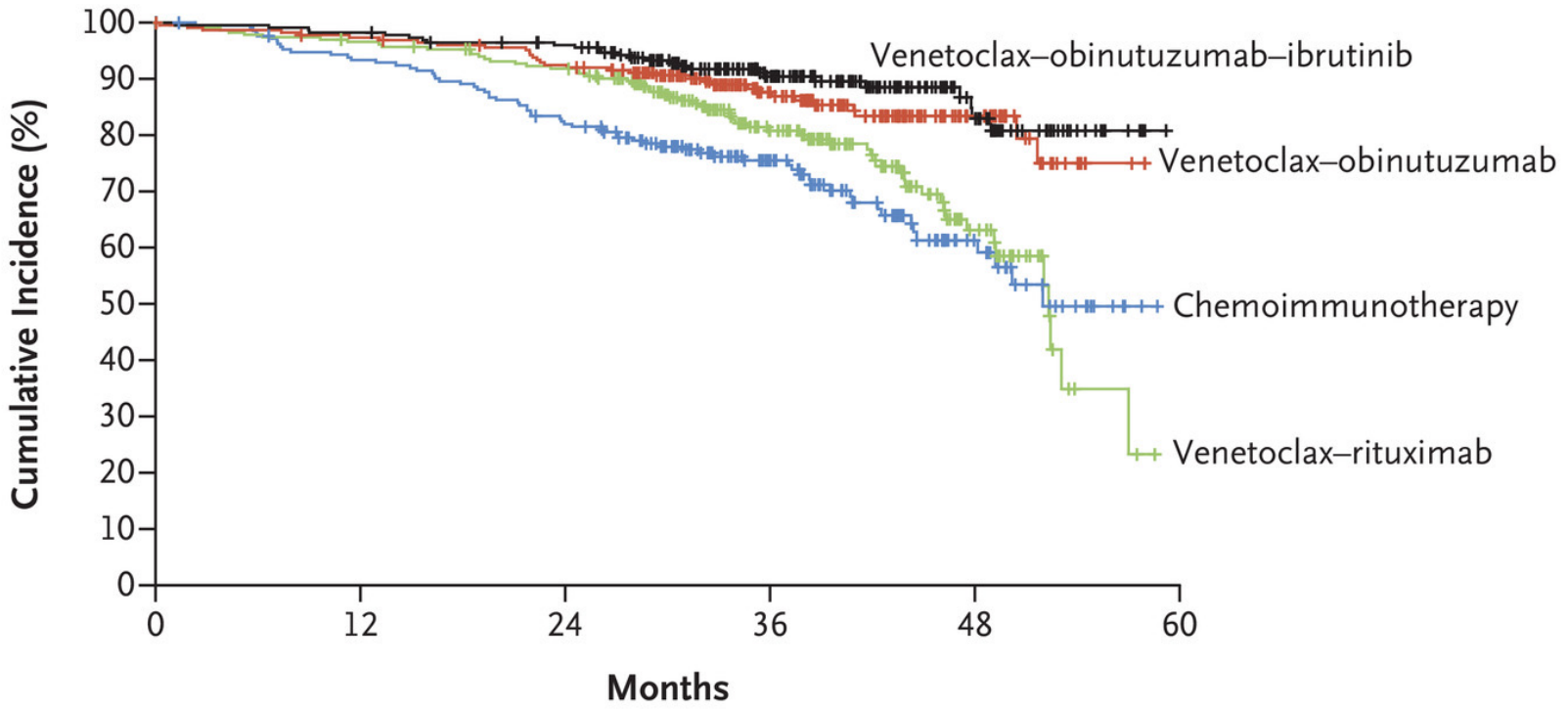
Obinutuzumab 1000 mg iv (c1 d1(2)/8/15, c2-6 d1)
Venetoclax c1 d22 – c12 d28 400 mg po daily (ramp-up)

Eichhorst *et al.* NEJM 2023

CLL13 trial: A randomized Phase III Trial

First-Line Venetoclax Combinations in TN CLL

Progression-free Survival, All Patients



Median follow-up time: 38.8 months

No. at Risk

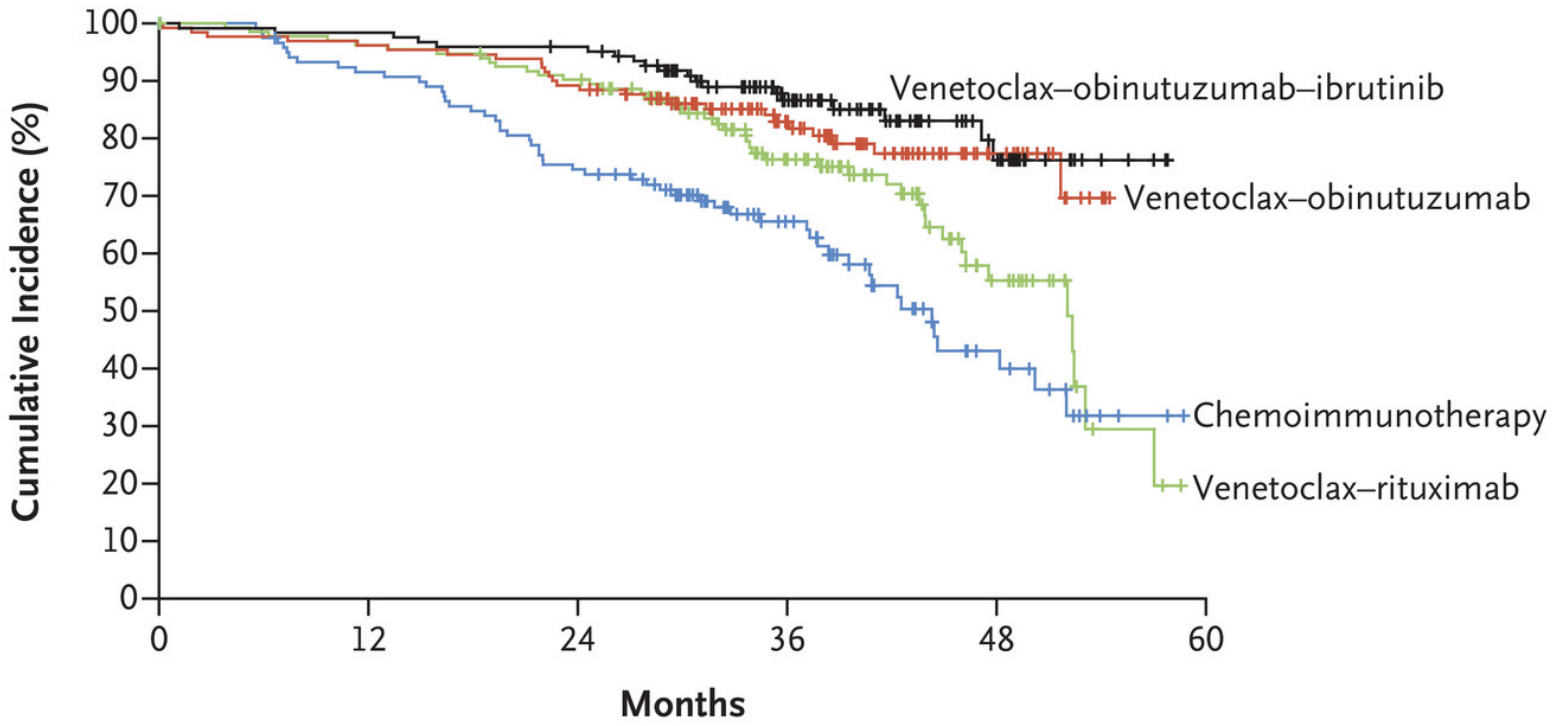
Chemoimmunotherapy	229	197	172	98	28	0
Venetoclax–rituximab	237	226	212	119	32	0
Venetoclax–obinutuzumab	229	221	208	125	42	0
Venetoclax–obinutuzumab–ibrutinib	231	227	217	132	44	0

Eichhorst *et al.* NEJM 2023

CLL13 trial: A randomized Phase III Trial

First-Line Venetoclax Combinations in TN CLL

Progression-free Survival, Patients with Unmutated *IGHV*



Median follow-up time: 38.8 months

No. at Risk

Chemoimmunotherapy	131	108	88	48	14	0
Venetoclax–rituximab	134	128	119	67	20	0
Venetoclax–obinutuzumab	130	125	116	71	21	0
Venetoclax–obinutuzumab–ibrutinib	123	121	117	70	22	0

Eichhorst *et al.* NEJM 2023

Ongoing Phase 3 Trials of Time-Limited Combinations for 1L CLL

Chemo-free versus CIT

- FLAIR: Ven/Ibr vs. Ibr monotherapy vs. FCR
- ACE-CLL-311: Acala/Ven +/- G vs. CIT (BR/FCR)

Chemo-free

- CLL17: Ibr mono (indefinite) vs. Ven/G (12 mo) vs Ven/Ibr (15 mo)

Thank You