Chronic Lymphocytic Leukemia: Where Are We Now and Where Are We Going?

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Disclosure of Conflicts of Interest

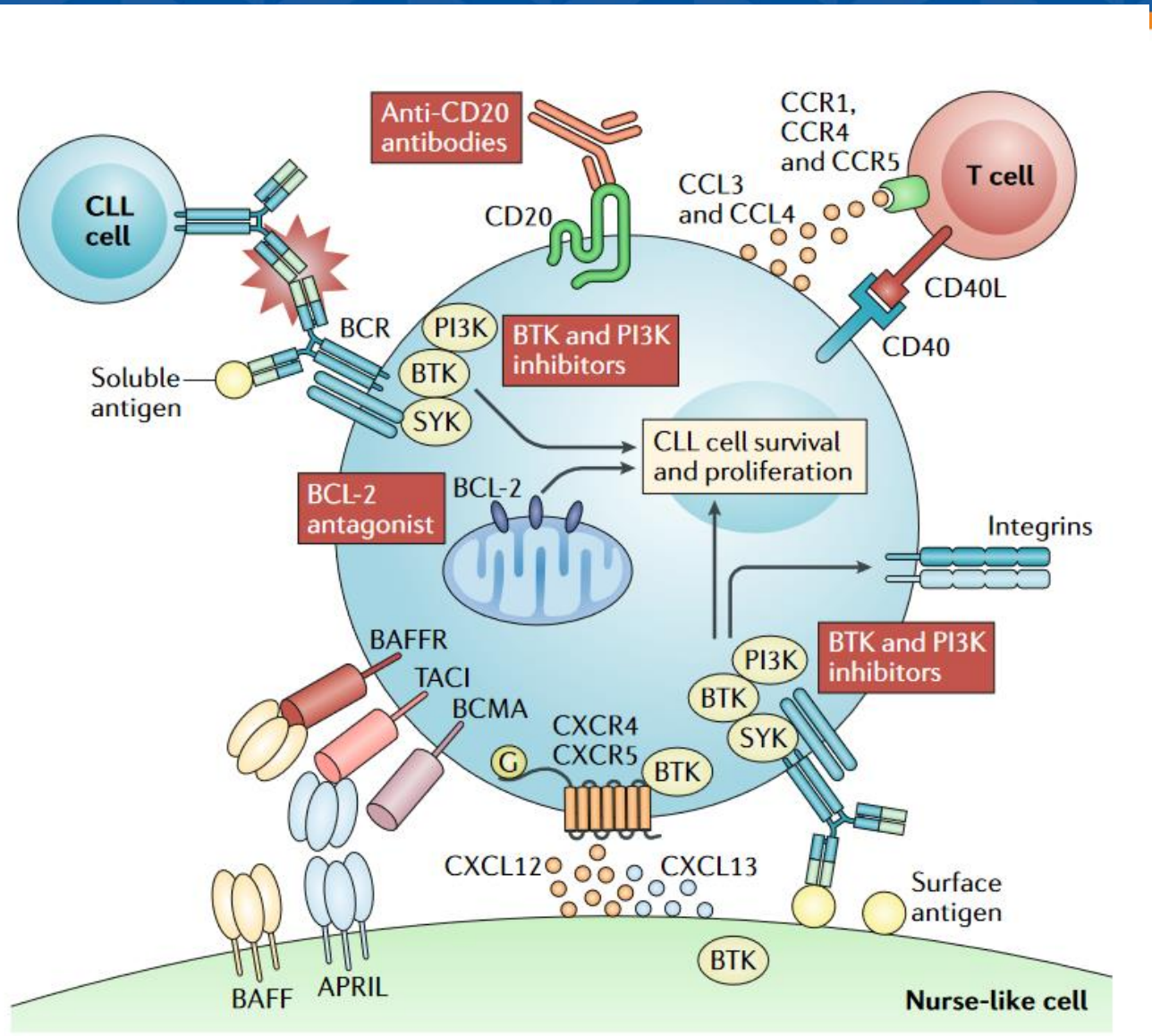
Andrea Sitlinger, MD has the following financial relationships to disclose:

- Consultant – BeiGene, TG Therapeutics
- Speaker – Innate Pharma

Outline

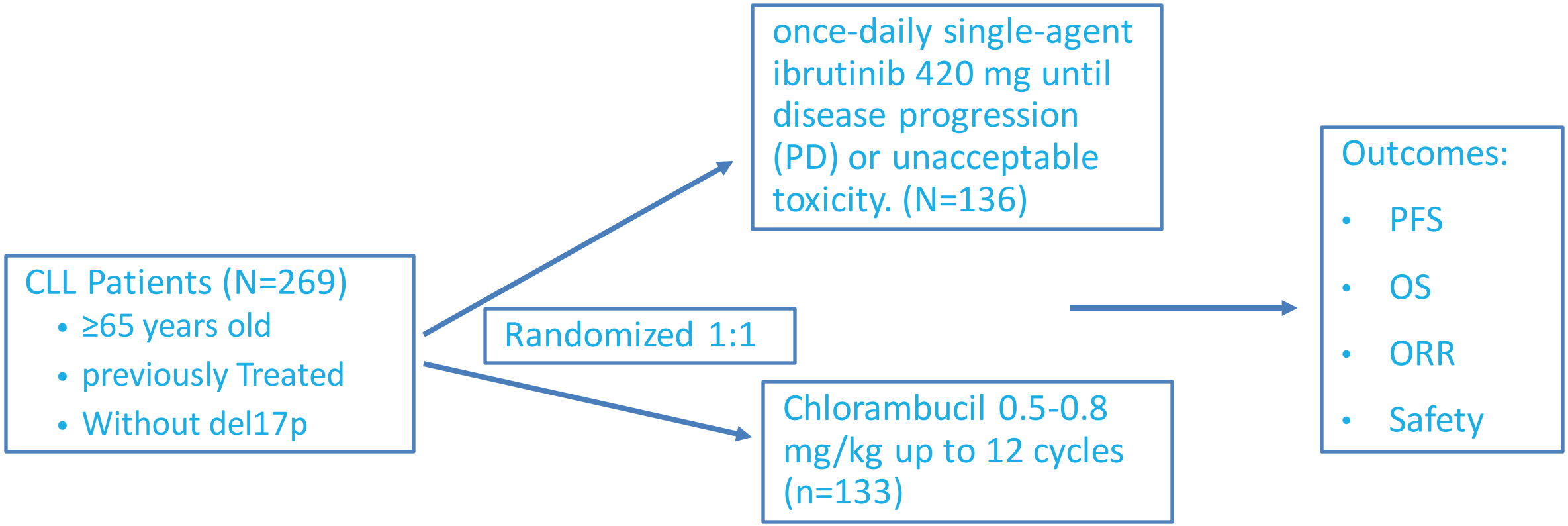
- Where are we now?
  - BTKi Class
  - Venetoclax Based Regimens
- What's Next?

It’s all about the targets!

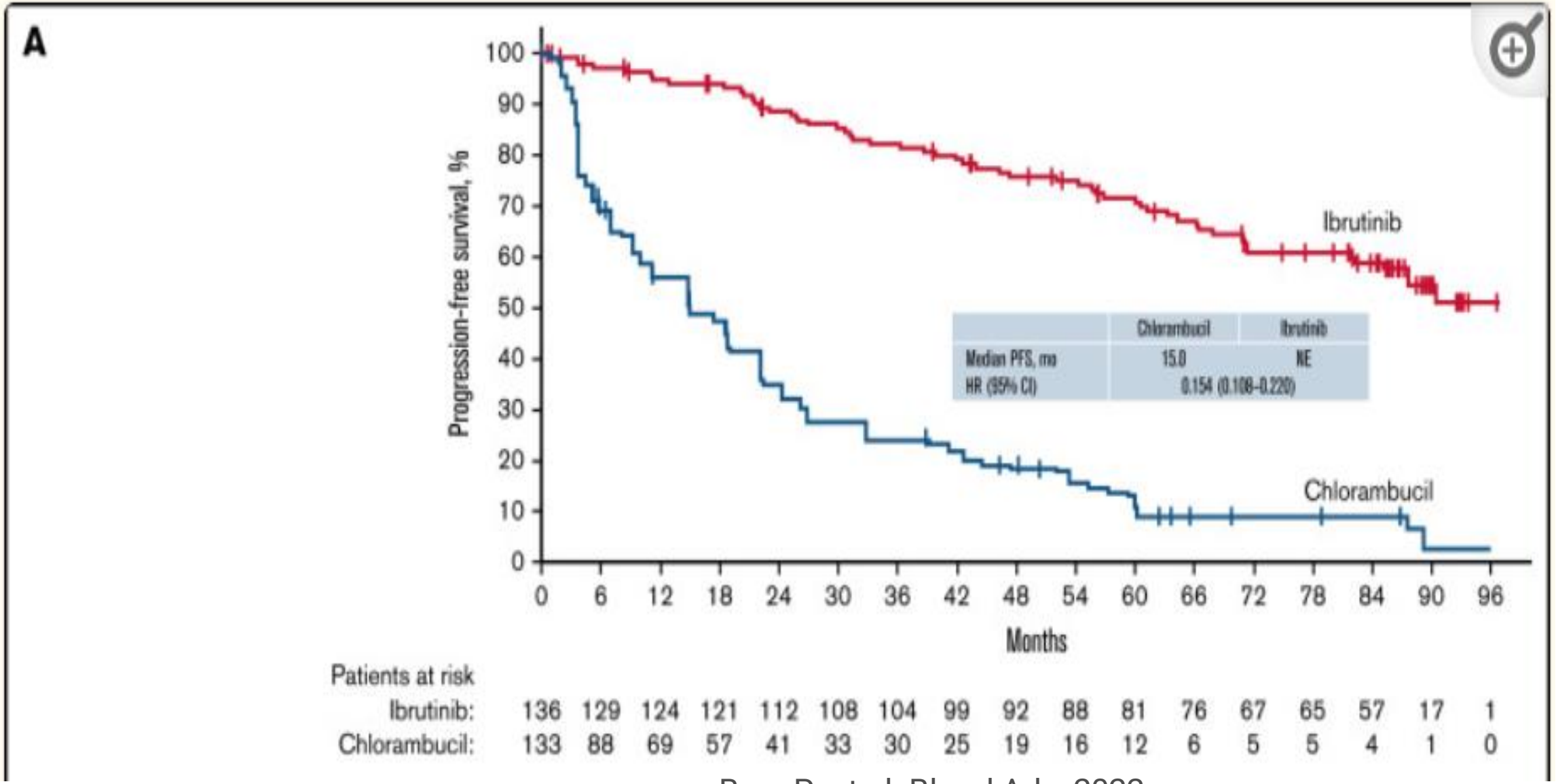


Burger, J.A., O’Brien, S. Evolution of CLL treatment — from chemoimmunotherapy to targeted and individualized therapy. *Nat Rev Clin Oncol* **15,** 510–527 (2018).

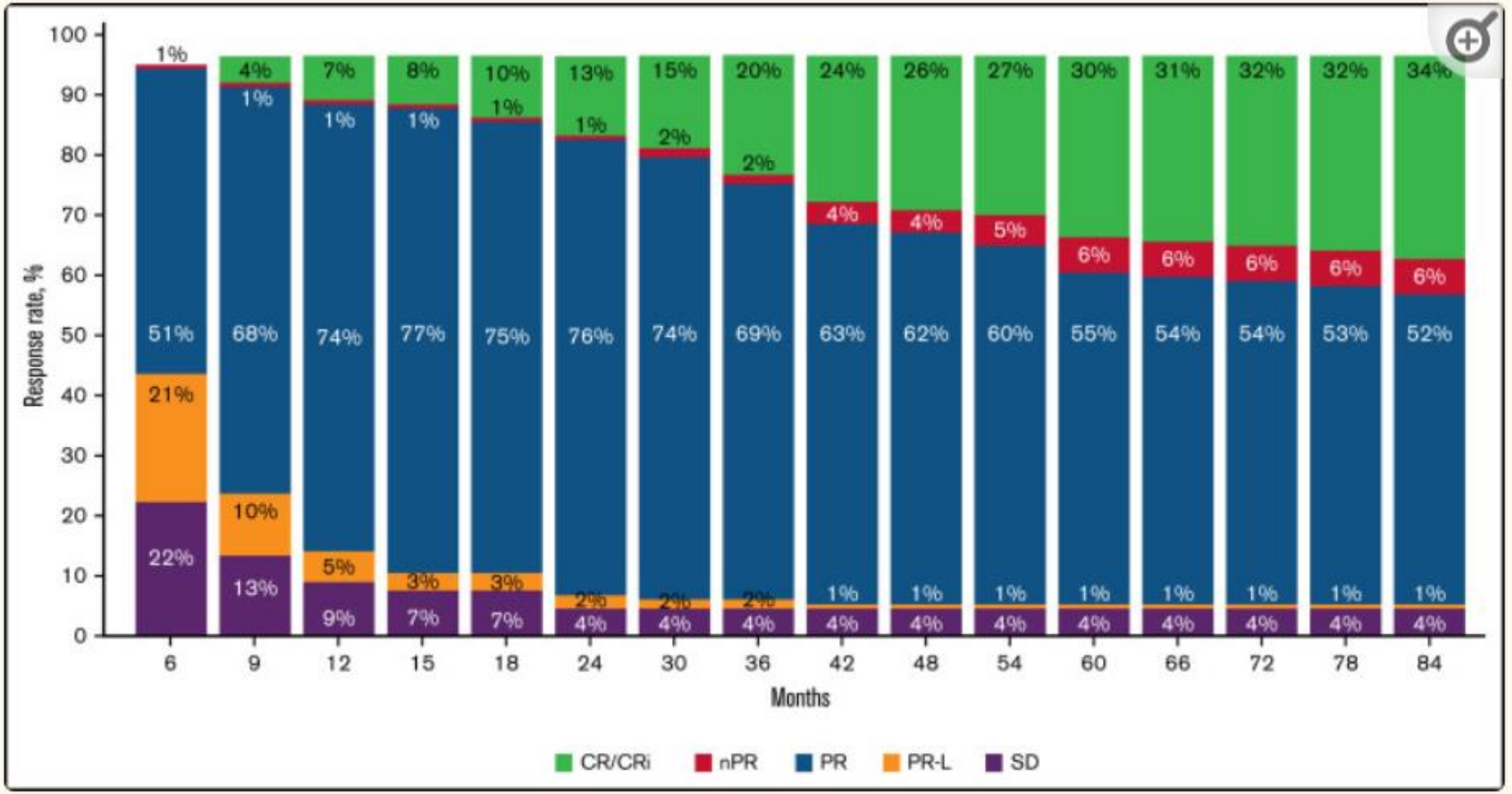
Long Term (up to 8 years) Phase 3 Resonate-2 Follow-Up



Barr, P. et al. Blood Adv. 2022

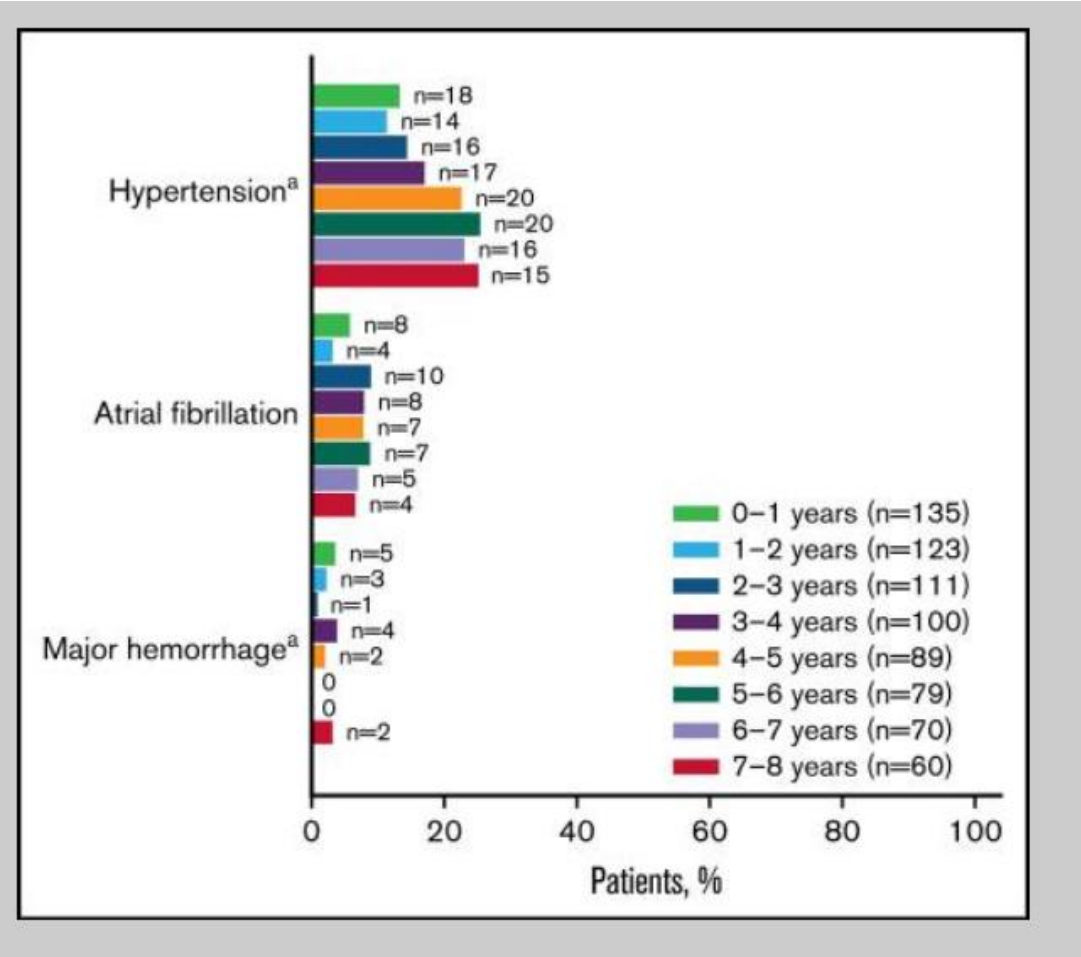


Barr, P. et al. Blood Adv. 2022



Barr, P. et al. Blood Adv. 2022

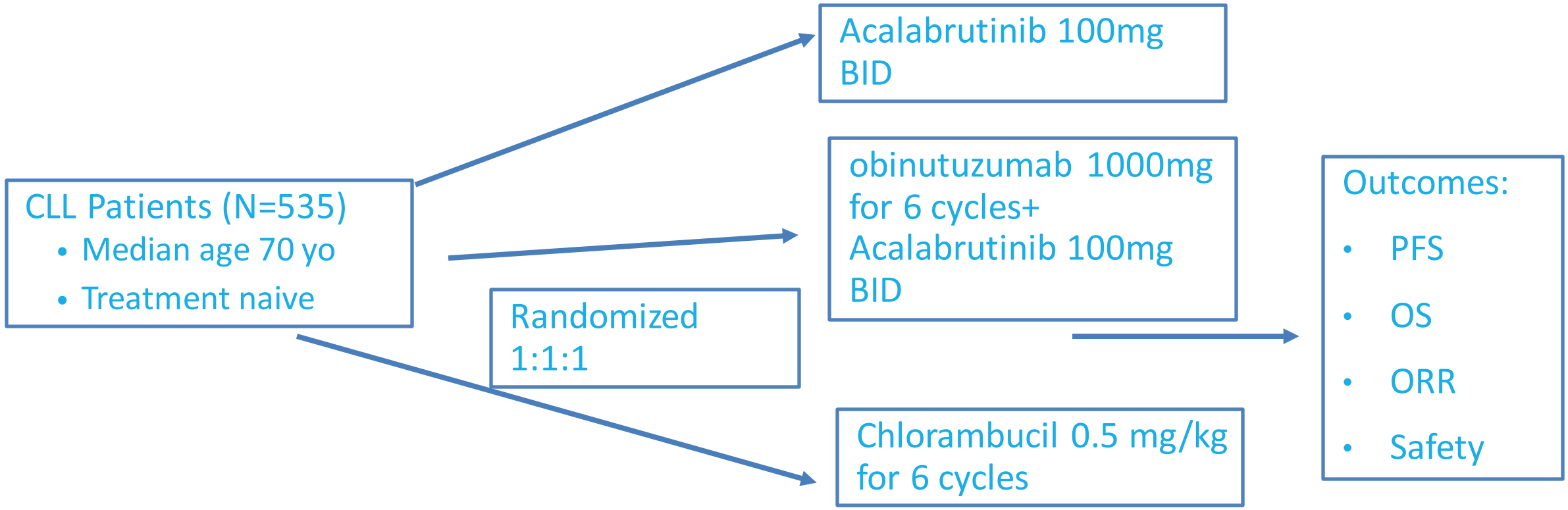
Adverse Events



- Dose Reductions
  - 31 pts due to any-grade AEs
    - 22/31 (71%) had resolution or improvement the AE.
- Discontinuation
  - Primary reason was progressive disease
    - 5–6y: 5%, n=4
    - 6–7y: 6%, n=4
  - Any-grade AEs
    - 5-6 y: 3% , n=2
    - 6–7y: none
- Overall, 47% of pts remain on single-agent ibrutinib.

Barr, P. et al. J Clin Oncol 39, 2021 (suppl 15; abstr 7523)

5 Year Follow-Up ELEVATE-TN



Sharman JP et al. Lancet. 2021

Median Follow-Up 58.2 months

	Progression Free Survival	Estimated 60 month PFS	ORR
Acalabrutinib + Obinutuzumab	**Not reached**	**84%**	**96%**
Acalabrutinib	**Not reached**	**72%**	**90%**
Chlorambucil	27.8 months	21%	83%

In Bold, statistically significant.
Of note, Crossover from O+Clb to A occurred in 72 (41%) patients

J Clin Oncol 40, 2022 (suppl 16; abstr 7539)

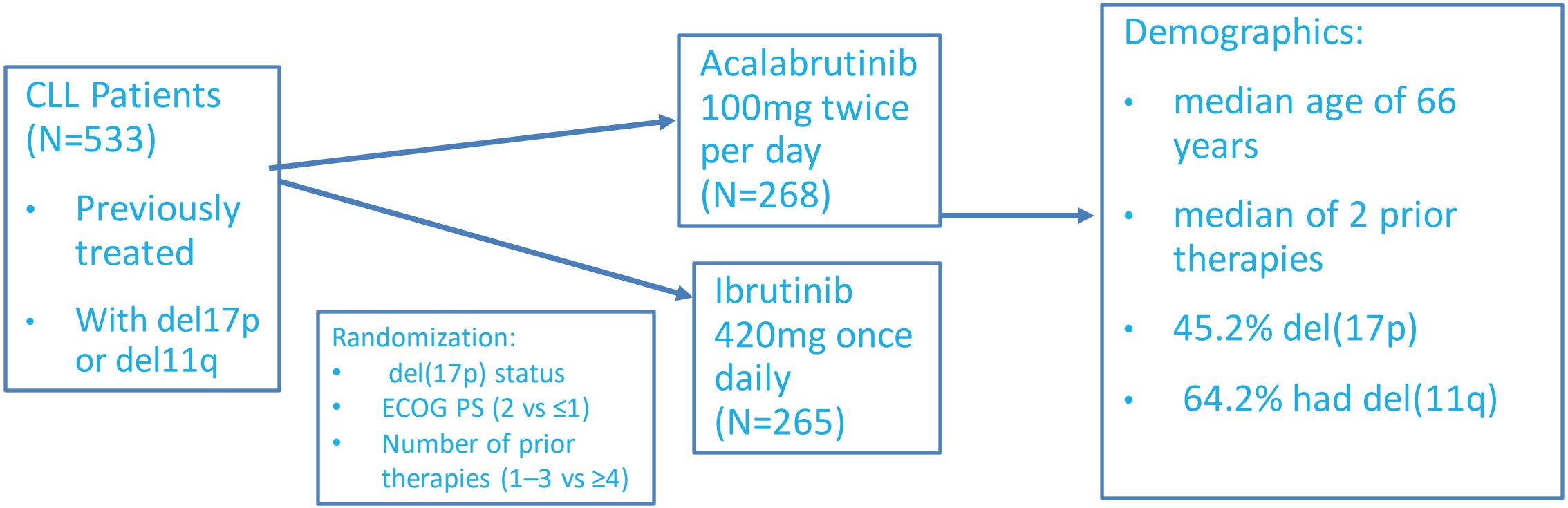
Adverse Events

	A+O (n=178)		A (n=179)		O+Clb (n=169)	
Median treatment exposure (mo)	58.1 (A), 5.5 (O)		58.0		5.6 (O), 5.5 (Clb)	
	Any grade	G≥3	Any grade	G≥3	Any grade	G≥3
Common TEAEs (≥30% of pts), n (%)						
Diarrhea	77 (43.3)	10 (5.6)	76 (42.5)	1 (0.6)	36 (21.3)	3 (1.8)
Headache	72 (40.4)	2 (1.1)	70 (39.1)	2 (1.1)	20 (11.8)	0
Arthralgia	60 (33.7)	4 (2.2)	47 (26.3)	2 (1.1)	10 (5.9)	2 (1.2)
Neutropenia	60 (33.7)	55 (30.9)	22 (12.3)	20 (11.2)	77 (45.6)	71 (42.0)
Nausea	44 (24.7)	0	44 (24.6)	0	53 (31.4)	0
Infusion-related reaction	26 (14.6)	5 (2.8)	1 (0.6)	0	69 (40.8)	10 (5.9)
Selected AEs of interest, n (%)						
Bleeding	88 (49.4)	8 (4.5)	78 (43.6)	6 (3.4)	20 (11.8)	0
Hypertension	17 (9.6)	8 (4.5)	16 (8.9)	7 (3.9)	6 (3.6)	5 (3.0)
Atrial fibrillation	11 (6.2)	2 (1.1)	13 (7.3)	2 (1.1)	1 (0.6)	0

J Clin Oncol 40, 2022 (suppl 16; abstr 7539)

FIRST RESULTS OF A HEAD-TO-HEAD TRIAL OF ACALABRUTINIB VERSUS IBRUTINIB IN PREVIOUSLY TREATED CHRONIC LYMPHOCYTIC LEUKEMIA

- Open label, randomized, noninferiority, phase 3



Hillmen, P. et al. EHA Library. Hillmen P. 06/09/21; 324553; S145

Table. Events of Clinical Interest and Most Common Any-Grade Adverse Events

ECIs	Incidence, n (%)		Exposure-Adjusted Incidence[a]		Exposure-Adjusted Time With Event[b]	
	Acala (n=266)	Ibr (n=263)	Acala (n=266)	Ibr (n=263)	Acala (n=266)	Ibr (n=263)
Cardiac events	64 (24)	79 (30)	1.2	1.9	7.1	13.0
Atrial fibrillation[c]	25 (9)	42 (16)*	0.4	0.7	1.3	3.8
Hypertension[d]	25 (9)	61 (23)*	0.4	1.2	4.1	15.0
Bleeding events[e]	101 (38)	135 (51)*	2.4	3.8	13.7	24.6
Major bleeding events[f]	12 (5)	14 (5)	0.2	0.2	0.1	0.3
Infections[g]	208 (78)	214 (81)	8.9	10.4	14.6	15.6
Other Most Common AEs[h]						
Blood and lymphatic system disorders						
Anemia	58 (22)	49 (19)	1.2	1.2	3.0	1.2
Neutropenia	56 (21)	65 (25)	1.7	1.9	1.4	1.7
Thrombocytopenia	40 (15)	35 (13)	0.8	0.7	1.8	2.5
Gastrointestinal disorders						
Diarrhea	92 (35)	121 (46)*	1.9	2.8	6.7	9.6
Nausea	47 (18)	49 (19)	0.9	0.8	2.9	2.1
Constipation	31 (12)	37 (14)	0.5	0.6	2.0	2.9
Vomiting	28 (11)	36 (14)	0.4	0.5	0.2	0.5
Dyspepsia	10 (4)	32 (12)*	0.1	0.5	1.0	2.4
General disorders and administration site conditions						
Pyrexia	62 (23)	50 (19)	1.1	1.0	0.7	0.4
Fatigue	54 (20)	44 (17)	0.9	0.9	7.4	7.0
Peripheral edema	26 (10)	38 (14)	0.5	0.6	2.9	4.6
Musculoskeletal and connective tissue disorders						
Arthralgia	42 (16)	60 (23)*	0.6	1.3	7.5	10.4
Myalgia	25 (9)	27 (10)	0.4	0.5	3.9	6.6
Back pain	20 (8)	34 (13)*	0.3	0.5	1.9	3.2
Muscle spasms	16 (6)	35 (13)*	0.2	0.7	0.8	10.0
Nervous system disorders						
Headache	92 (35)*	53 (20)	1.8	1.1	7.8	5.4
Dizziness	28 (11)	26 (10)	0.5	0.5	1.2	2.3
Respiratory, thoracic, and mediastinal disorders						
Cough	77 (29)*	56 (21)	1.3	1.1	5.6	4.9
Dyspnea	37 (14)	23 (9)	0.5	0.4	2.7	2.5

*Two-sided p-value <0.05 without multiplicity adjustment, for comparison of incidence based on Barnard's exact test.
[a]Reported as events per 100 person-months. [b]Reported as months with event per 100 person-months. [c]Includes atrial fibrillation and flutter. [d]Includes hypertension, blood pressure increased, and blood pressure systolic increased. [e]Bleeding events occurring in ≥10% of patients in either treatment arm include contusion and epistaxis. [f]Any hemorrhagic event that was serious, grade ≥3, or a CNS hemorrhage (any grade). [g]Infections occurring in ≥10% of patients in either treatment arm include upper respiratory tract infection, pneumonia, bronchitis, nasopharyngitis, and urinary tract infection. [h]AEs occurring in ≥10% of patients in either treatment arm that are not already captured in the ECIs presented.
ECIs, events of clinical interest.

Figure 1. Cumulative Incidence of Atrial Fibrillation/Flutter in Patients Without a Prior History

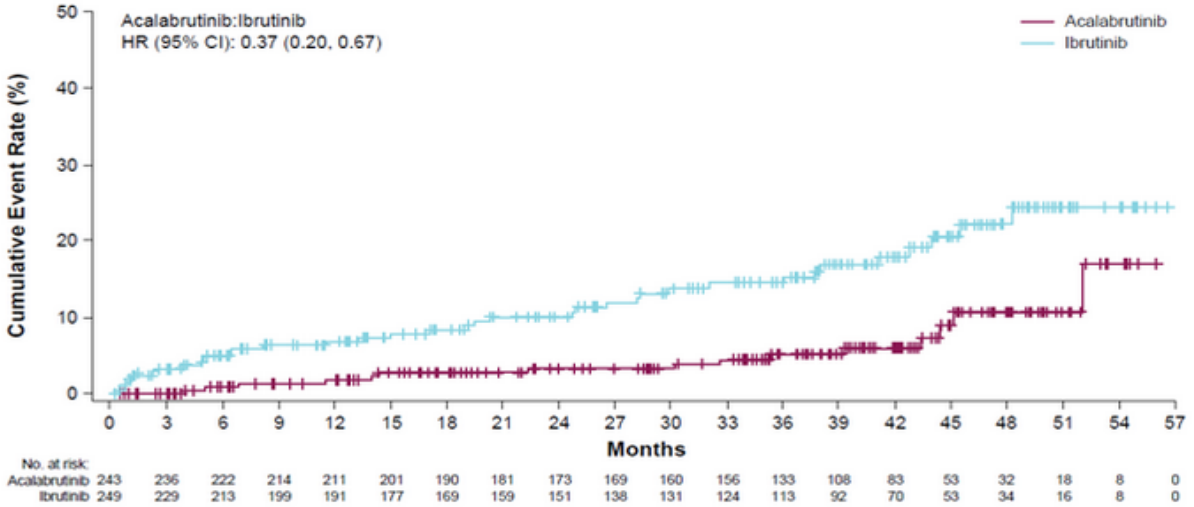
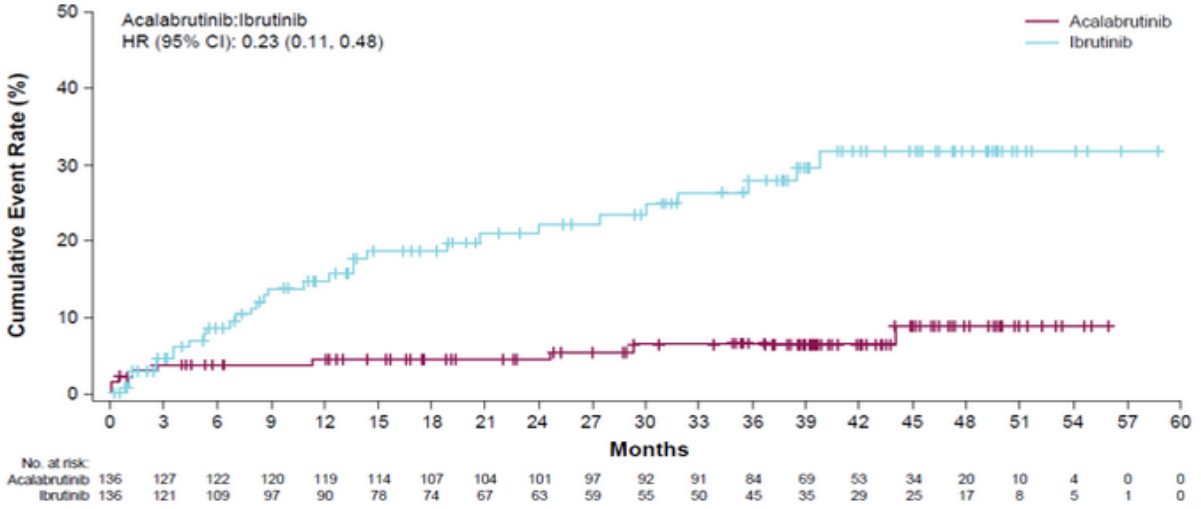


Figure 2. Cumulative Incidence of Hypertension in Patients Without a Prior History



Blood (2021) 138 (Supplement 1): 3721.

Adverse Events

Table. Selected events of clinical interest

	Acalabrutinib (n=266)		Ibrutinib (n=263)	
Events, n (%)	Any grade	Grade ≥3	Any grade	Grade ≥3
Cardiac events	64 (24.1)	23 (8.6)	79 (30.0)	25 (9.5)
Atrial fibrillation[a]	25 (9.4)	13 (4.9)	42 (16.0)	10 (3.8)
Ventricular tachyarrhythmias	0	0	1 (0.4)	1 (0.4)
Hypertension[b]	25 (9.4)	11 (4.1)	61 (23.2)	24 (9.1)
Bleeding events	101 (38.0)	10 (3.8)	135 (51.3)	12 (4.6)
Major bleeding events[c]	12 (4.5)	10 (3.8)	14 (5.3)	12 (4.6)
Infections	208 (78.2)	82 (30.8)	214 (81.4)	79 (30.0)
Second primary malignancies excluding non-melanoma skin cancers	24 (9.0)	16 (6.0)	20 (7.6)	14 (5.3)

[a]Includes preferred terms of atrial fibrillation and atrial flutter.

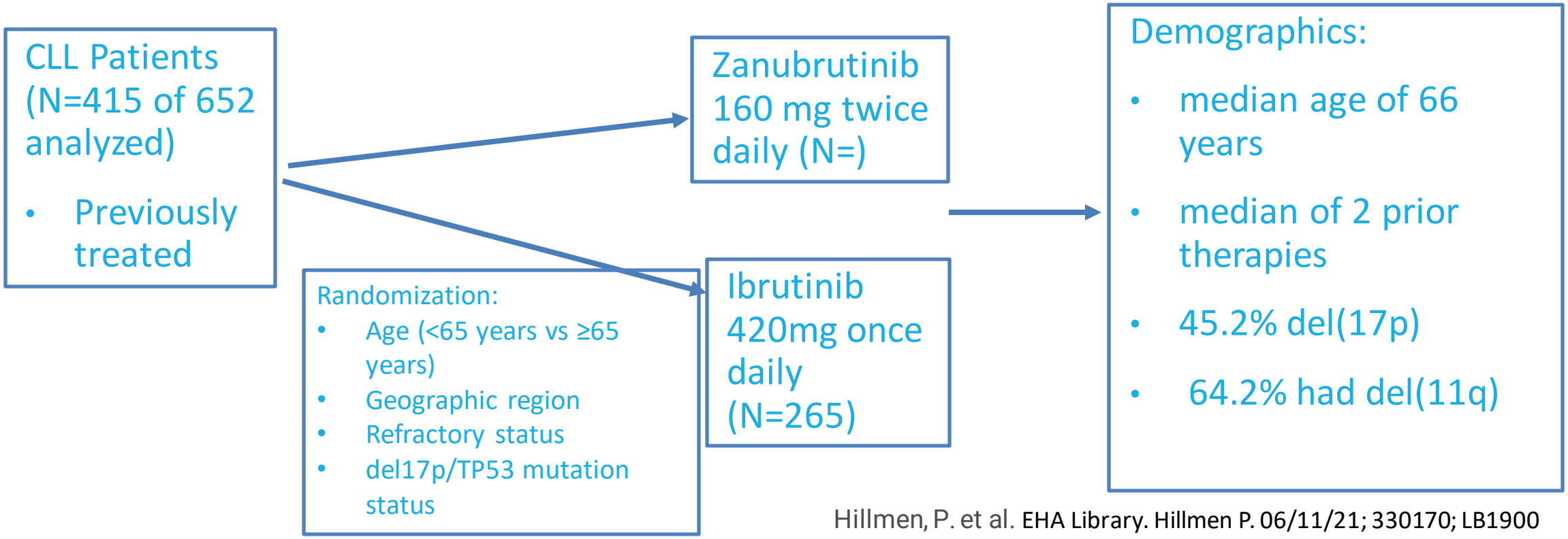
Adverse Events occurring in Greater than 20% of Patients		
Adverse Event	Acalabrutinib	Ibrutinib
Hypertension	9.4%	23.2%
Arthralgia	15.8%	22.8%
Diarrhea	34.6%	46.0%
Headache	34.6%	20.2%
Cough	28.9%	21.3%

Adverse events led to treatment discontinuation in 14.7% of acalabrutinib-treated patients compared with 21.3% of ibrutinib-treated patients.

Hillmen, P. et al. EHA Library. Hillmen P. 06/09/21; 324553; S145

ALPINE – Zanubrutinib vs Ibrutinib

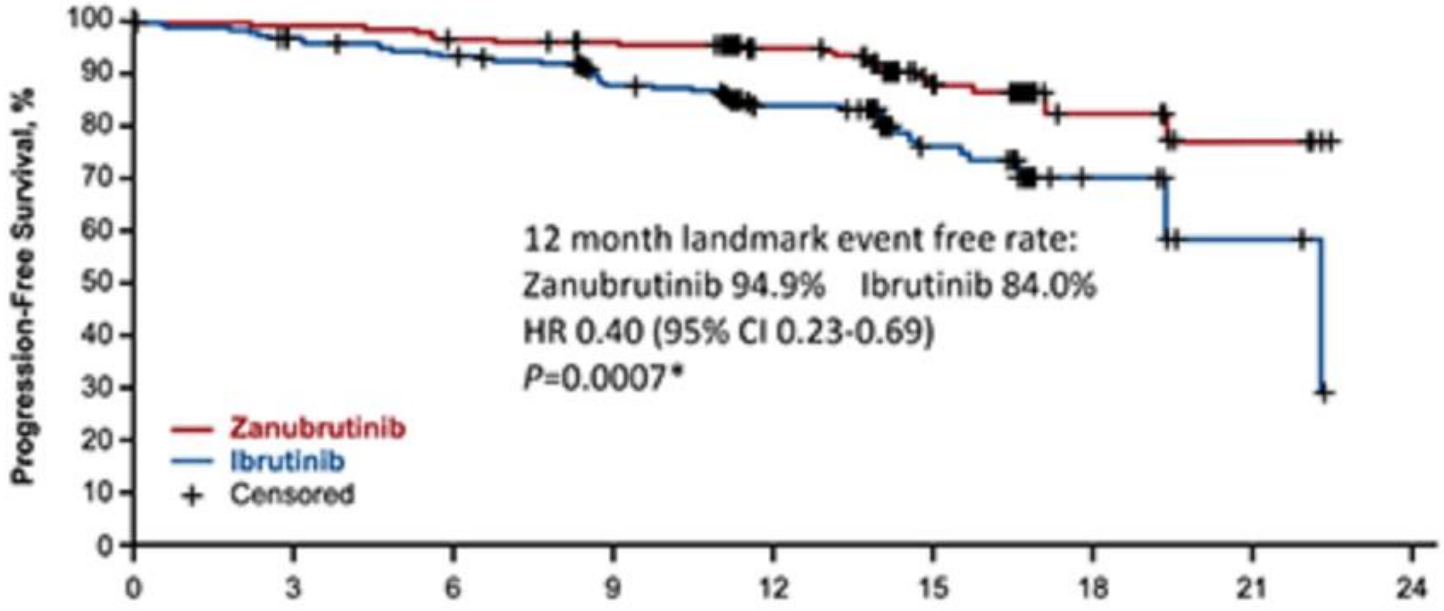
- Randomized, phase 3 study. This was the pre-planned interim analysis scheduled approximately 12 mo after the first 415 out of 652 patients were enrolled.



Hillmen, P. et al. EHA Library. Hillmen P. 06/11/21; 330170; LB1900

Alpine

Figure. PFS by Investigator Assessment



No. of Patients at Risk									
Zanubrutinib	207	200	194	190	152	70	19	5	0
Ibrutinib	208	196	188	170	125	57	8	3	0

*Not a prespecified analysis; formal analysis of PFS will be based on all patients when the target number of events are reached.
Median PFS follow-up was 14.0 months for both zanubrutinib and ibrutinib arms by reverse KM method.

Hillmen, P. et al. EHA Library. Hillmen P. 06/11/21; 330170; LB1900

AEs– Zanubrutinib vs Ibrutinib

- Atrial fibrillation/flutter 2.5% vs 10.1% (2-sided *P*=0.0014, compared with pre-specified alpha of 0.0099 for interim analysis)
- Major bleeding: 2.9% vs 3.9%
- Neutropenia 28.4% vs 21.7%
- Grade ≥3 infections 12.7% vs 17.9%

- Adverse events leading to discontinuation (7.8% vs 13.0%) or death (3.9% vs 5.8%) were also lower with zanubrutinib.

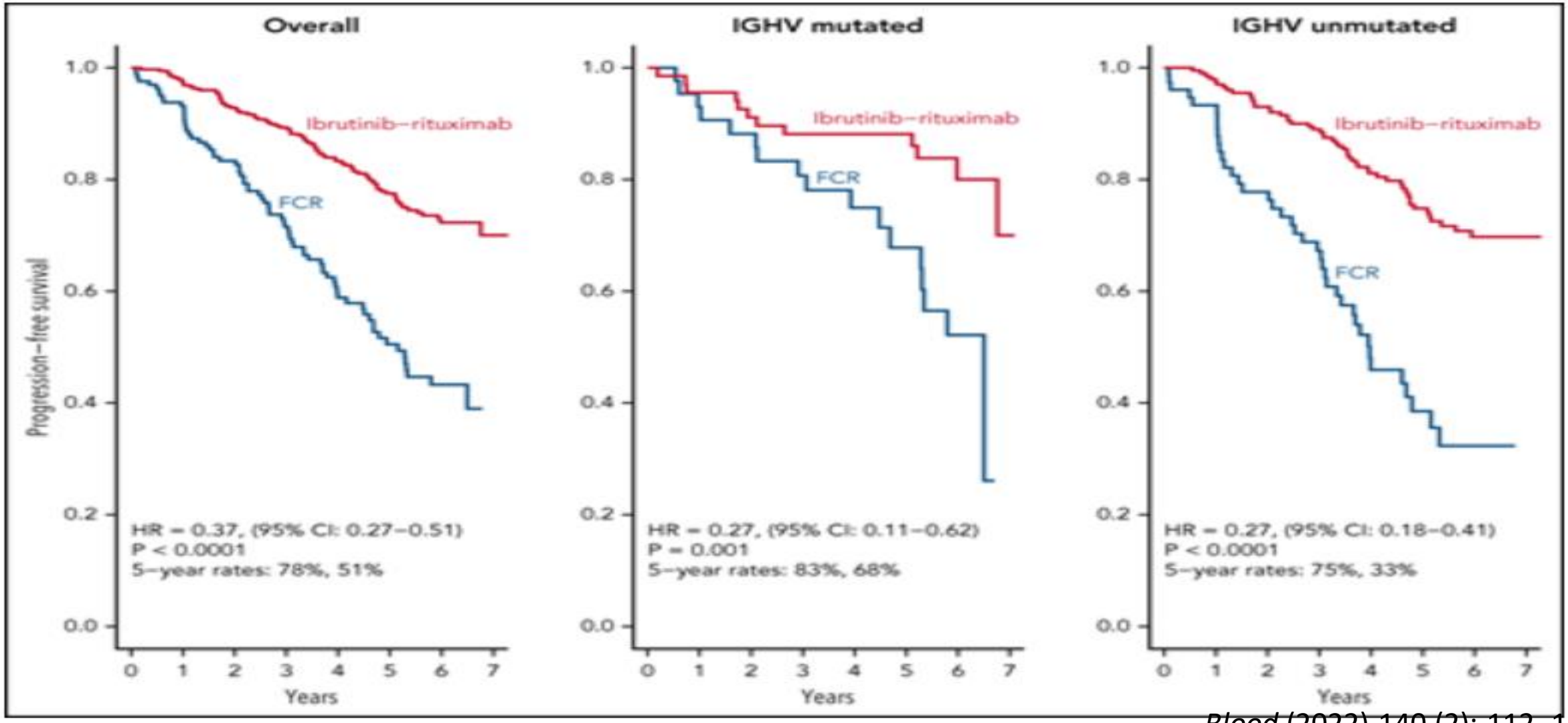
Hillmen, P. et al. EHA Library. Hillmen P. 06/11/21; 330170; LB1900

Bendamustine Rituximab (BR)/Fludarabine Cyclophosphamide Rituximab (FCR) vs BTKi

	Methods	Progression Free Survival
E1912 Trial: FCR vs Ibrutinib + Rituximab	Median follow-up of 6 years 529 treatment naïve patients 70 or younger Randomized 2 to 1 ratio	5 Year PFS: • Total: 78% vs 51% p<0.0001 • IgH unmutated: 75% vs 33% p<0.0001 • IgH mutated: 83% vs 68% p = 0.001
ASCEND: Aclabrutinib vs BR	310 patients were randomly assigned to acalabrutinib monotherapy (n = 155) or investigator's choice (n = 155; I-R, n = 119; B-R, n = 36. -Relapsed setting	median 46.5 mo (acala)/45.3 mo (IdR/BR): • median not reached [NR] vs 16.8 mo; *P*<0.0001 • 42-mo PFS rates were 62% for acala vs 19% for IdR/BR.
Sequoia: Zanubrutinib vs BR vs Idela+Rituximab	479 pts without del(17p) were randomized to zanu (n=241) and BR (n=238)	26.2 month F/Up: • 85.5% (95% CI 80.1%- 89.6%) vs 69.5% (95% CI 62.4%-75.5%)

Blood (2022) 140 (2): 112–120; *Blood* (2022) 140 (2): 112–120. ;*Blood* (2021) 138 (Supplement 1): 396.

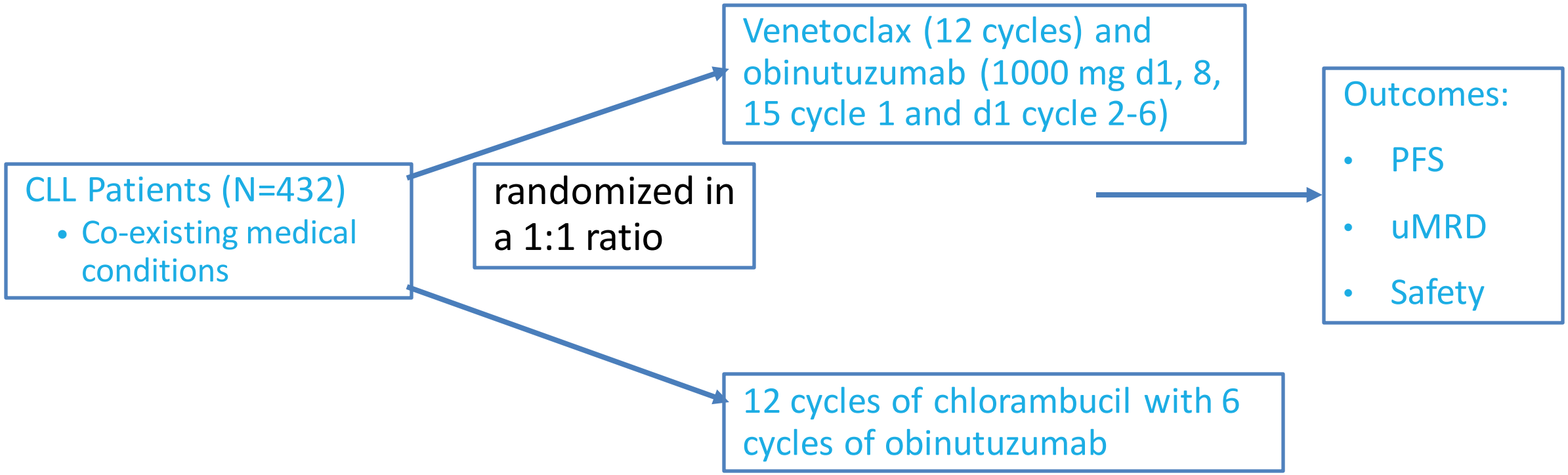
E1912 Trial FCR vs Ibrutinib + Rituximab



Blood (2022) 140 (2): 112–120.

Venetoclax Based Regimens

CLL 14: Time Limited Upfront Venetoclax + Obinutuzumab



EHA Library. Al-Sawaf O. 06/12/22; 357012; S148

5 Year Follow-Up CLL14

PFS

- Not Reached vs 36.4 months; [HR] 0.35 [95% CI 0.26-0.46], p<0.0001).
- Estimated PFS rate was 62.6% after Ven-Obi and 27.0% after Clb-Obi.

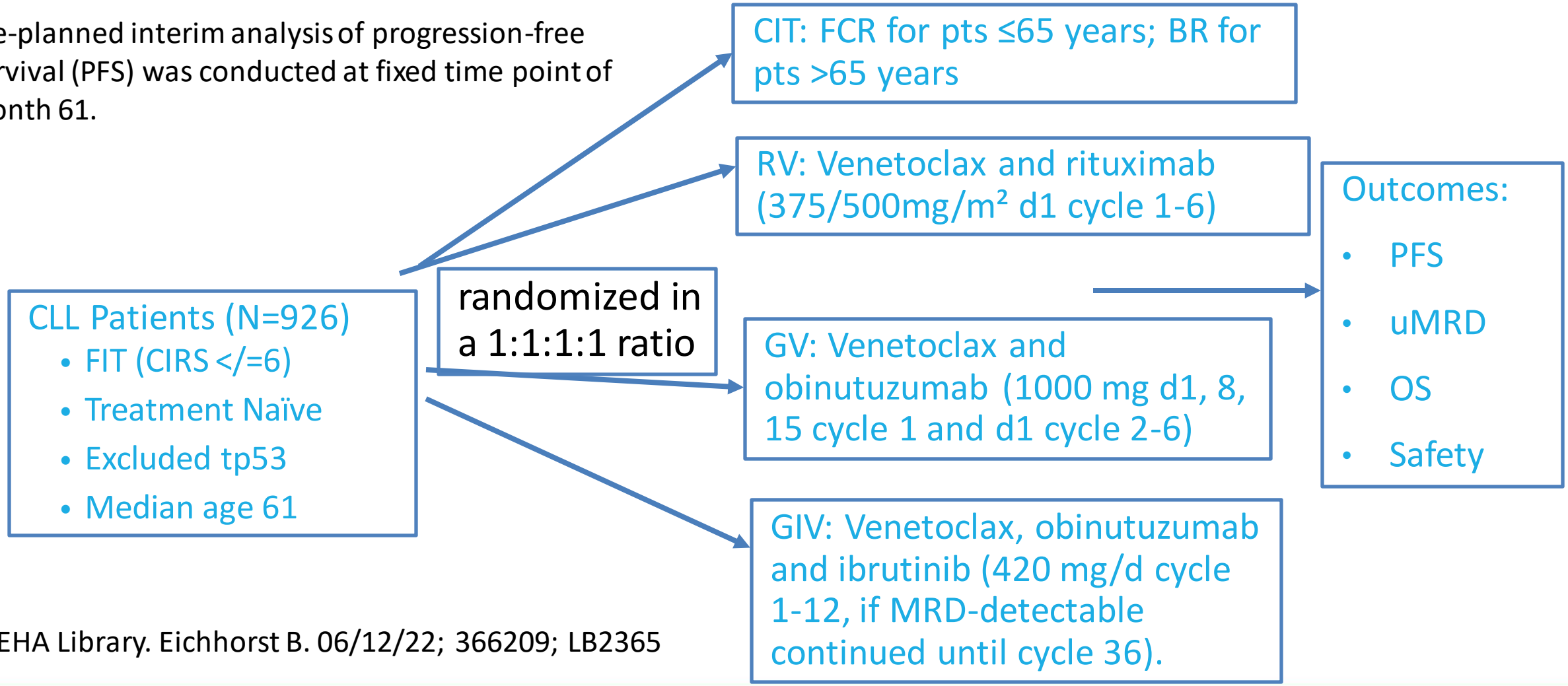
***TP53* mutation/deletion**

- 5-year PFS 40.6% vs 15.6%

EHA Library. Al-Sawaf O. 06/12/22; 357012; S148

phase III GAIA/CLL13

Pre-planned interim analysis of progression-free survival (PFS) was conducted at fixed time point of month 61.



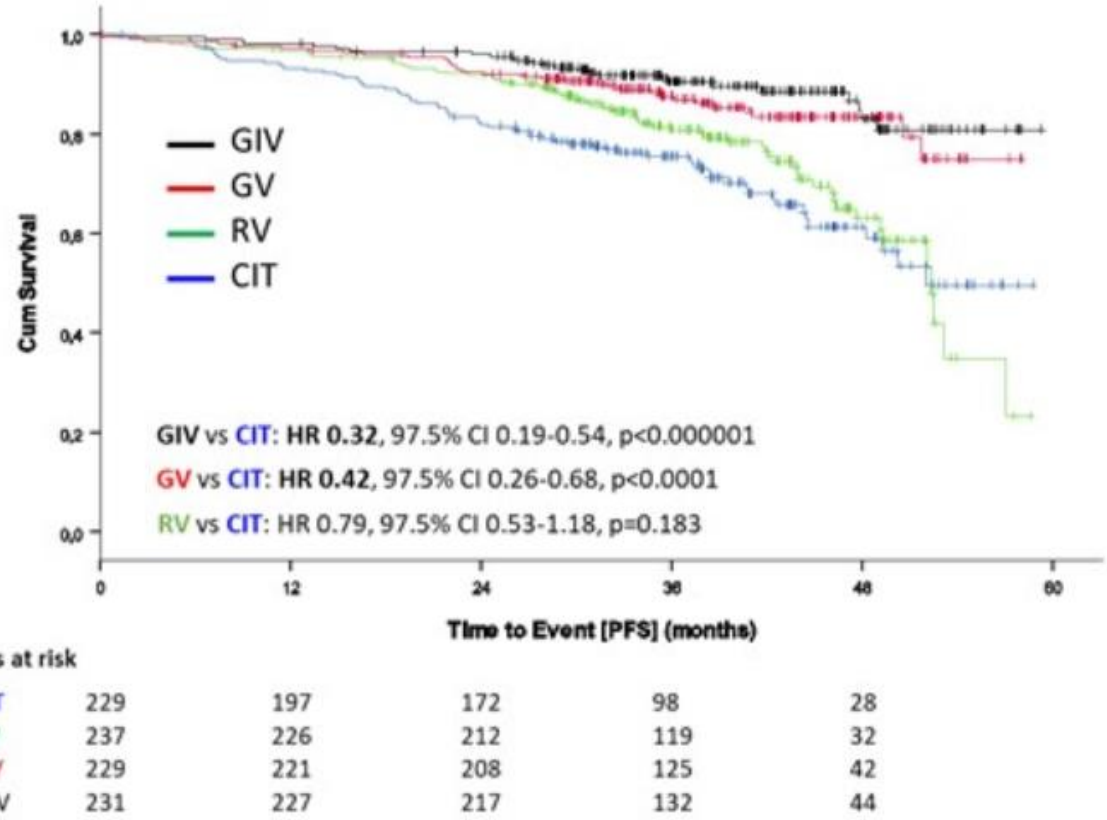
EHA Library. Eichhorst B. 06/12/22; 366209; LB2365

Efficacy

	PFS	PFS IgH mutated	PFS IgH unmutated
CIT	75.5%	89.9%	65.5%
RV	80.8%	87%	76.4%
GV	87.7%	93.6%	82.9%
GIV	90.5%	96%	86.6%

- Superior PFS was also observed for GV vs CIT (HR 0.42, 97.5% CI 0.26-0.68, p<0.0001)
- PFS was not significantly different between RV and CIT (HR 0.79, 97.5% CI 0.53-1.18, p=0.183)

Figure 1A. Progression-free survival according to treatment arm



EHA Library. Eichhorst B. 06/12/22; 366209; LB2365

So How Do You Decide?

- Cytogenetics/Disease Characteristics
  - Del17p
  - Complex karyotype
- Co-morbidities
- Patient Preference

What’s on the horizon?

7501 – Phase 2 Captivate study: Fixed Duration Cohort

CLL patients </= 70 yo, previously Treated

3 cycles of Ibrutinib then 12 cycles of Ibrutinib+Venetoclax

<u>159 Patients Enrolled:</u>

- Median age 60 yo
- High-risk features included
  - del(17p)/*TP53* mutation, 17%
  - del(11q), 18%
  - Complex karyotype, 19%
  - Unmutated IGHV, 56%.
- 147 (92%) and 149 (94%) pts completed Ibrutinib and Venetoclax, respectively.
- Median time on study was 27.9 mo (range, 0.8–33.2).

Ghia, P. J Clin Oncol 39, 2021 (suppl 15; abstr 7501)

Captivate: Fixed Duration Results 3 Year Follow-Up

	FD Cohort – All treated population	del(17p)/*TP53*	uIGHV
Efficacy outcomes	**N=159**	**n=27**	**n=89**
ORR, n (%)	153 (96)	26 (96)	86 (97)
CR, n (%)[a]	91 (57)	15 (56)	57 (64)
36-mo PFS, % (95% CI)	88 (82–92)	80 (58–91)	86 (77–92)
36-mo OS, % (95% CI)	98 (94–99)	96 (76–99)	97 (90–99)

[a]Included 3 pts with CRi.

*Progression-free ≥12 cycles from first CR.

Ghia, P. J Clin Oncol 39, 2021 (suppl 15; abstr 7501)
Wierda, WG. J Clin Oncol 40, 2022 (suppl 16; abstr 7519)

Adverse Events

Overall Adverse Events

- Primarly Grade ½
- Most Common Grade ¾ AEs:
  - Neutropenia (33%)
  - Hypertension (6%)
  - Neutrophil Count Decreased (5%)
- Led to discontinuation of ibrutinib in 4% and venetoclax in 2%.

TLS Risk

- 34 Patients classified as high risk
- 32 Patients (94%) were moved to medium or low risk after ibrutinib
- No TLS occurred.

Ghia, P. J Clin Oncol 39, 2021 (suppl 15; abstr 7501)

What’s on the horizon

- Time limited combination therapy!
  - BTKi + venetoclax?
- Triple Therapy?
  - CD20 antibody + venetoclax + BTKi
- MRD

MRD

- Flow Cytometry or PCR
- MRD
  - Undetectable MRD = $<10^{-4}$ (<1 CLL cell per 10,000 leukocytes)
  - Low MRD = 10^{-2} – 10^{-4}.
  - High MRD $>10^{-2}$
- Prognostic
  - Rituximab + Venetoclax 2 year Treatment – 36 month follow up
    - 12% (16 of 130) of patients developed disease progression (11 high-level MRD, three low-level MRD).
    - 70% and 98% of patients with uMRD remained in uMRD and without disease progression
- Direct Time to Treatment?

Kater AP et al, J Clin Oncol. 2019;37(4):269. Epub 2018 Dec 3.

What’s on the horizon

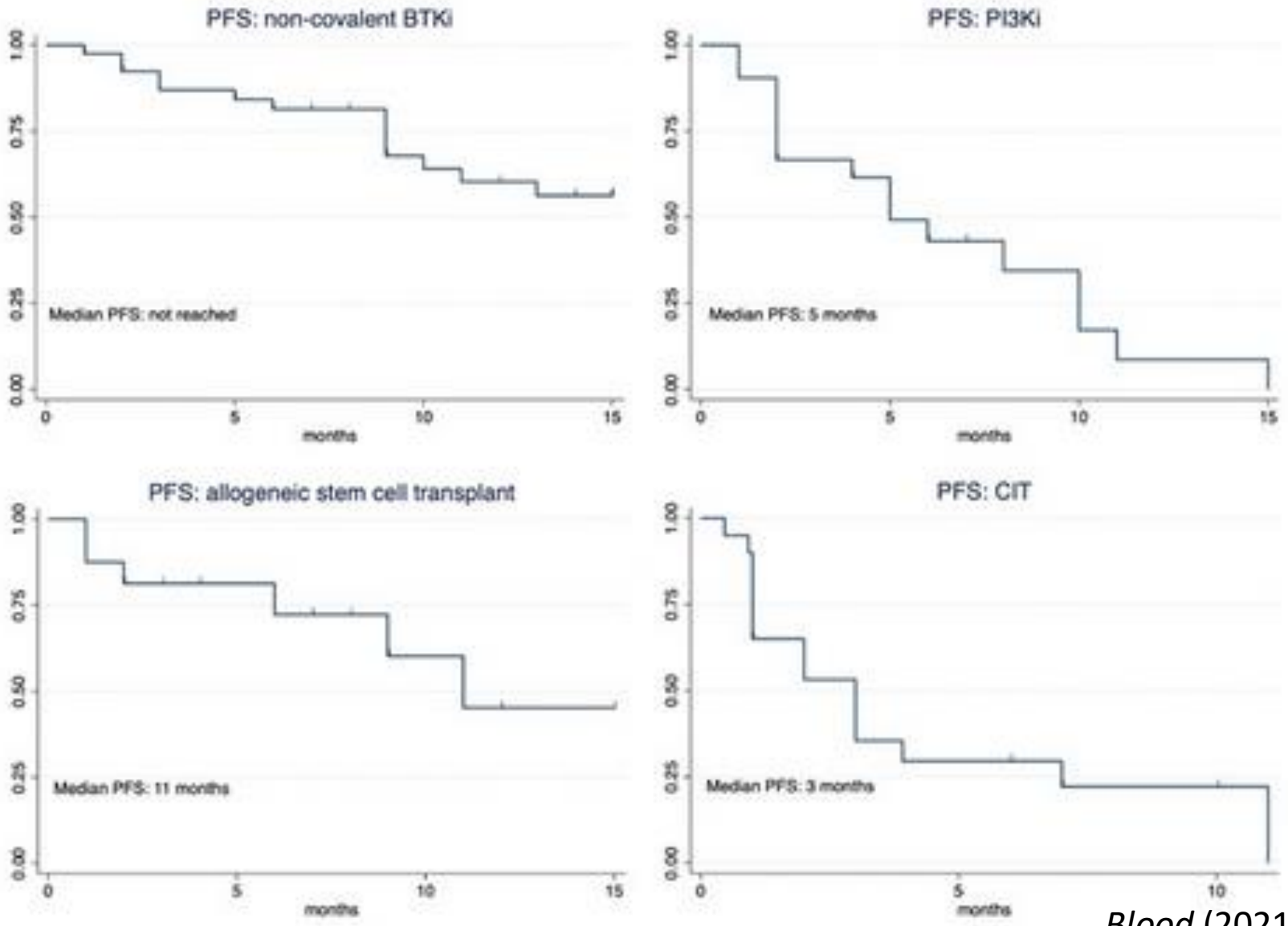
- Time limited combination therapy!
  - BTKi + venetoclax?
- Triple Therapy?
  - CD20 antibody + venetoclax + BTKi
- MRD
- New small molecule/targeted therapies
  - Non-covalent BTKi
- Should we treat earlier?
- CAR-T

Pirtobrutinib in relapsed or refractory B-cell malignancies (BRUIN): a phase 1/2 study

- 323 patients treated across seven dose levels (25 mg-300 mg once per day)
- 17p deletion 25%, TP53 mutation 30%, and unmutated IGHV 88%
- Median number of prior lines of therapies was 3 (1-11).
  - prior BTKi (86%), an anti-CD20 antibody (90%), or a chemotherapy (82%).
- The ORR was 63% (95% CI 55-71)
  - Among the 121 BTKi pretreated pts, the ORR was 62% (95% CI 53-71).

EHA Library. R. Mato A. 06/12/22; 357011; S147

Figure 1. Progression Free Survival for Selected Therapies for "Double Exposed" Patients



Blood (2021) 138 (Supplement 1): 2628.

"Double Exposed Patients"

Table 2. Response to selected therapies in "double exposed" CLL patients

Subsequent therapy	Non-covalent BTKi	PI3Ki	Allogeneic stem cell transplant	CAR T-cell therapy	CIT
Total number of pts treated*	45	24	17	9	23
ORR	75.0%	40.9%	76.5%	85.7%	31.8%
(n=available responses)	n=43	n=22	n=17	n=7	n=22
Median PFS (mos)	not reached	5	11	4	3
(n=number with follow-up)	n=40	n=21	n=16	n=9	n=20
Median follow-up (mos)	9	4	6.5	3	2

Abbreviations: CLL: chronic lymphocytic leukemia; BTKi: Bruton's Tyrosine Kinase inhibitor; PI3Ki: phosphatidylinositol 3-kinase

Blood (2021) 138 (Supplement 1): 2628.

What’s on the horizon

- Time limited combination therapy!
  - BTKi + venetoclax?
- Triple Therapy?
  - CD20 antibody + venetoclax + BTKi
- MRD
- New small molecule/targeted therapies
  - Non-covalent BTKi
- CAR-T
- Should we treat earlier?

Survival trends in chronic lymphocytic leukemia in the era of oral targeted therapies in the United States: SEER database analyses (1985 to 2017).

	Diagnosed 1985-1989	Diagnosed 2010-2014
Males 5 Year Adjusted Relative Survival Rate	72.%	88.2%
Female 5 Year Adjusted Relative Survival Rate	76.8%	90.8%
Male 10 Year Adjusted Relative Survival Rate	47.3%	72.5%
Female 10 Year Adjusted Relative Survival Rate	58.2%	78.7%

J Clin Oncol 39, 2021 (suppl 15; abstr 7524)

Conclusions

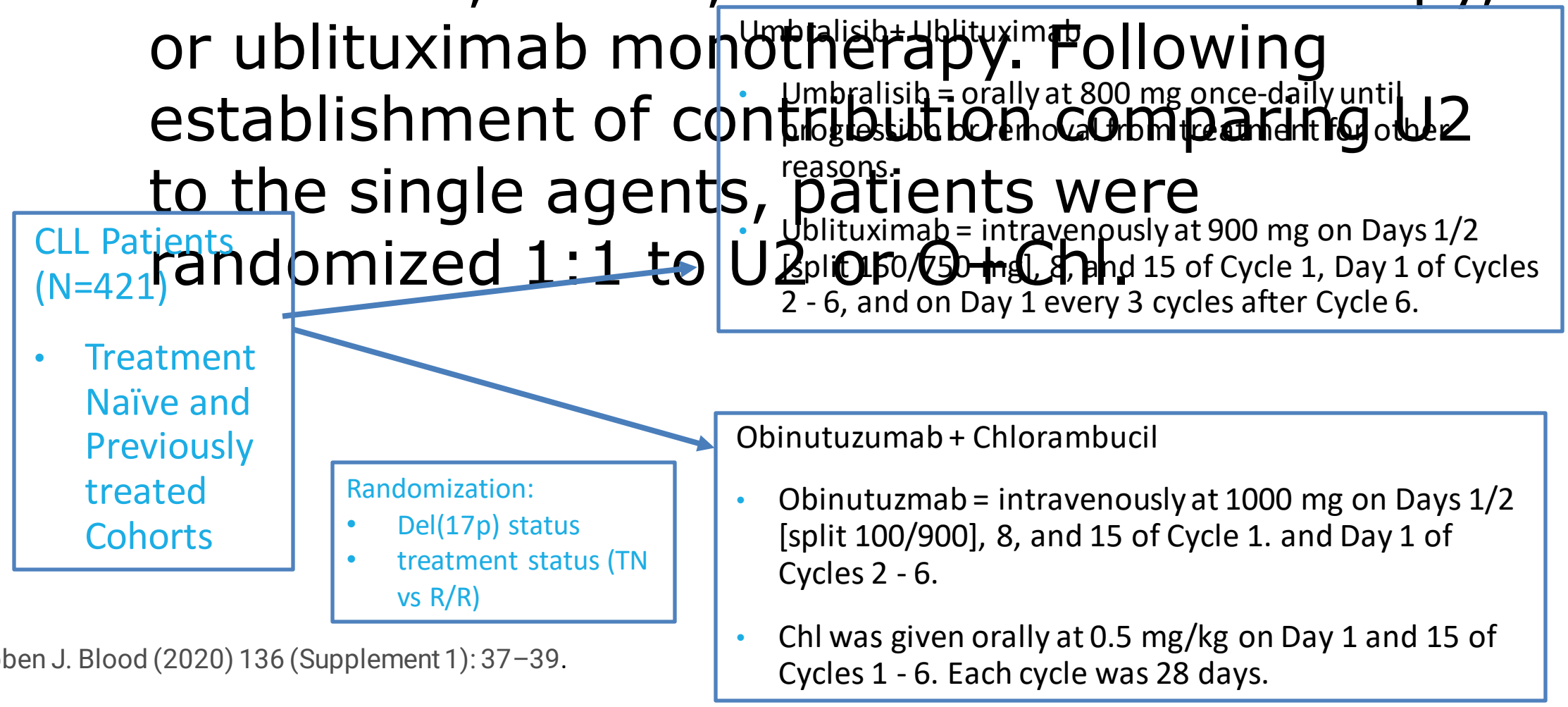
- The Treatment Landscape continues to dramatically change with increasing options
- Therapy is becoming more personalized as efficacy continues to improve.
- Addressing Side effects, co-morbidities, and multiple relapsed disease following targeted therapies are necessary paths forward

Questions

Extra Slides

Unity-CLL

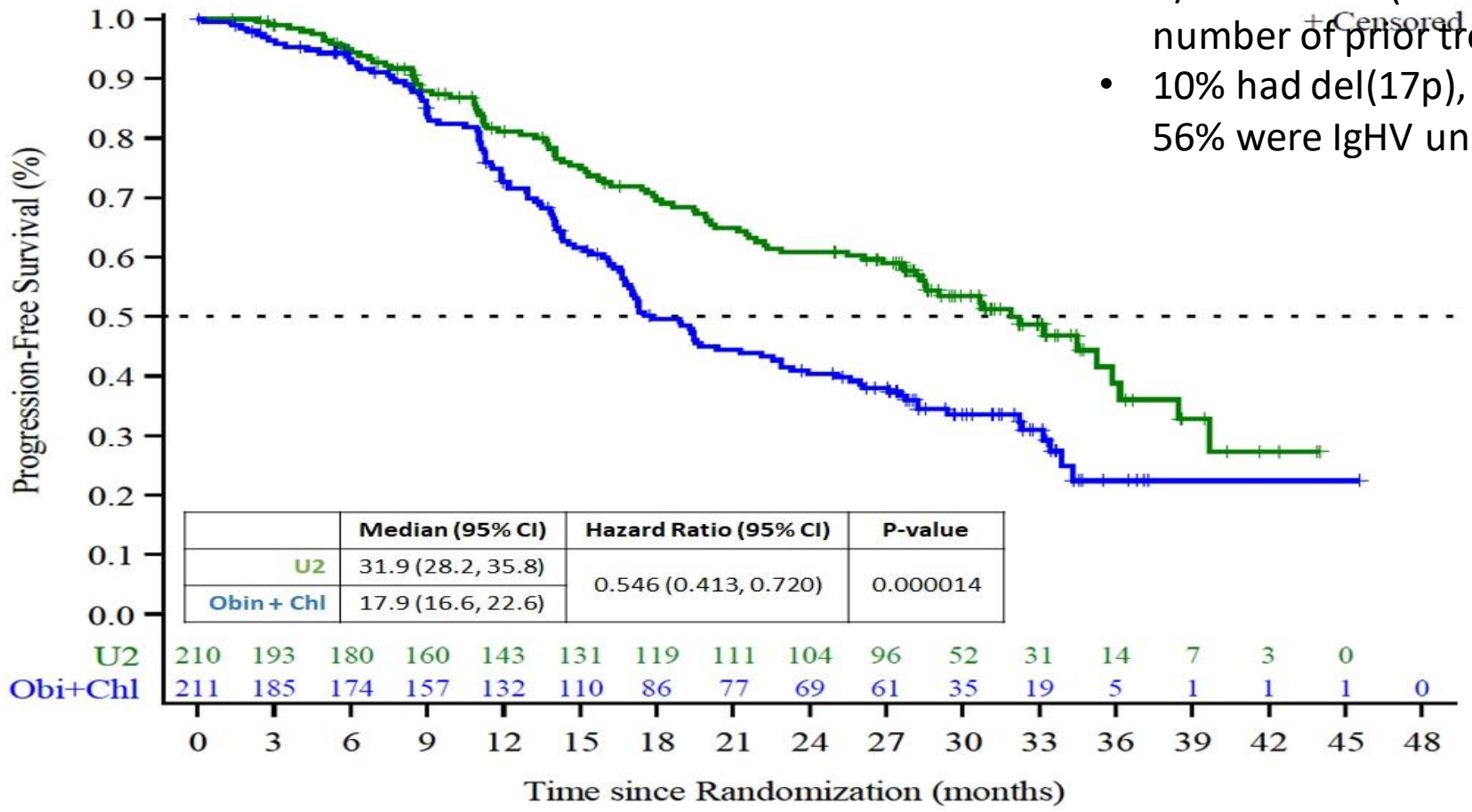
- Phase 3 - Initially randomized 1:1:1:1 to receive U2, O+Chl, umbralisib monotherapy, or ublituximab monotherapy. Following establishment of contribution comparing U2 to the single agents, patients were randomized 1:1 to U2 or O+Chl.



Gribben J. Blood (2020) 136 (Supplement 1): 37–39.

Unity-CLL

- Median age was 67 y (range, 36-91);
- Treatment Naïve: 57% of patients (n=240)
- R/R CLL: 43% (n=181) with median number of prior treatments = 1
- 10% had del(17p), 20% del(11q), and 56% were IgHV unmutated.



Gribben J. Blood (2020) 136 (Supplement 1): 37–39.

Unity-CLL – Grade ¾ Adverse Events

Adverse Event	U2	O+Chl
Neutropenia	30.6%	34.7%
Thrombocytopenia	3.4%	13.1%
Diarrhea	12.1%	2.5%
Infusion Reaction	1.9%	3.5%
Elevated AST/ALTs	8.3%	2%
Colitis	3.4%	0%
Pneumonitis	2.9%	0%

Gribben J. Blood (2020) 136 (Supplement 1): 37–39.