Front-Line Treatment for Patients with Chronic Lymphocytic Leukemia (CLL)

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Key Factors in Managing Patients With CLL/SLL

Timing of Therapy

- Deciding when to start therapy
  - Many patients discovered incidentally; how to handle the "worried well"
  - Comorbidities and "fitness"; where the patient is in their "life cycle"
- Deciding when to stop therapy

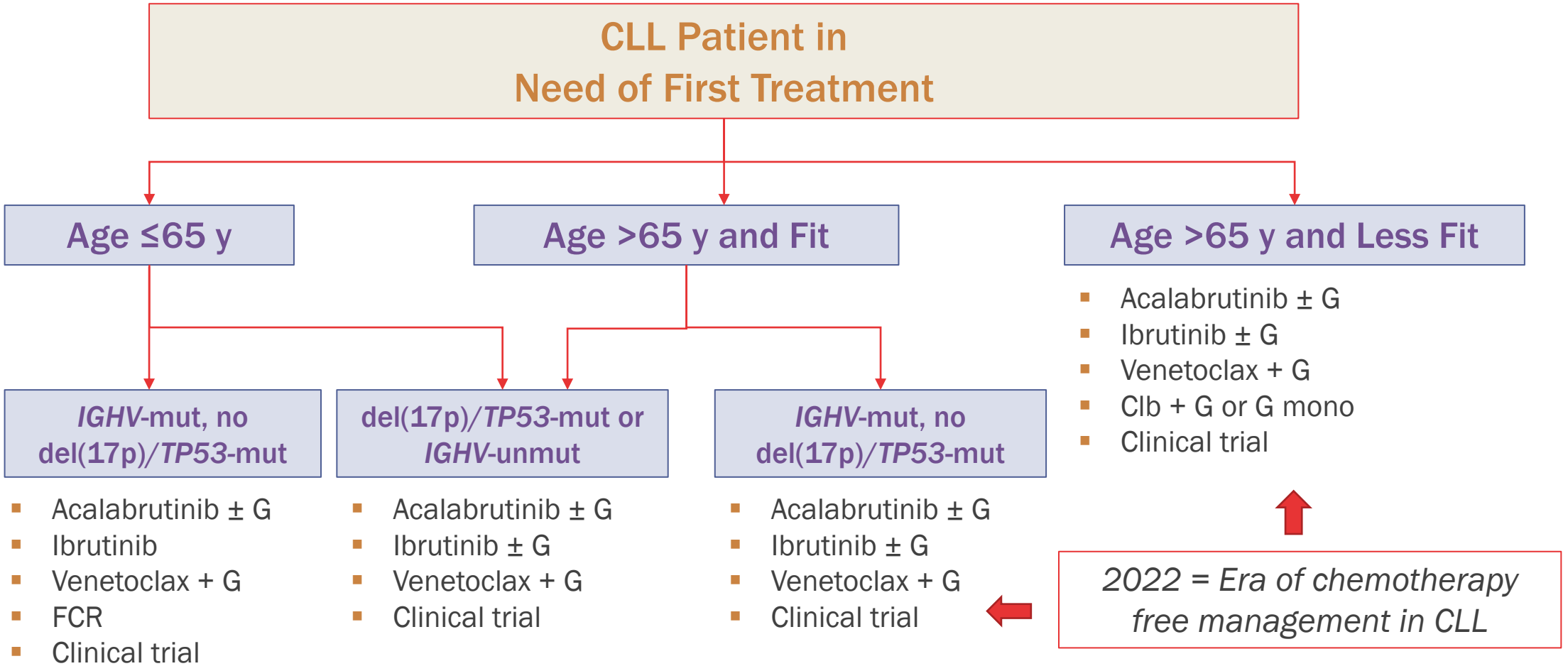
Key Prognostic Factors

- The importance of FISH; *TP53*; and mutational status of immunoglobulin genes
- How to test for MRD (ie, flow cytometry or molecular methods) and how to use it to guide clinical decision-making

Key Classes of Drugs

- BTK inhibitors (eg, ibrutinib, acalabrutinib, zanubrutinib)
- BCL-2 inhibitors (eg, venetoclax)
- Anti-CD20 antibodies (eg, rituximab, obinutuzumab)
- Chemotherapy/ chemoimmunotherapy (eg, chlorambucil, FCR, BR)

Common Approaches to Treatment of TN CLL in 2021



BR, bendamustine, rituximab; Clb, chlorambucil; CLL, chronic lymphocytic leukemia; G, obinutuzumab; FCR, fludarabine, cyclophosphamide, rituximab; IGHV, immunoglobulin heavy-chain variable region; mut, mutated; TN, treatment naive; unmut, unmutated.

Adapted from Woyach JA, et al. *Hematology Am Soc Hematol Educ Program*. 2019;2019(1):476-481.

High-Risk Cytogenetics and Mutational Status

Incidence of High-Risk Features in Previously Untreated Patients[1-4]

High-Risk Feature	Incidence in CLL
17p deletion	~10%
TP53 mutation	~10%
11q deletion	~20%
Unmutated *IGHV*	~60%
Complex karyotype (≥3 abnormalities)	~20%

Real-World Prognostic Testing Patterns in TN CLL[5]

	Frontline CLL Patients (n=889)
Genetic testing performed	65%
FISH testing	58%
Cytogenetic testing	39%
FISH and cytogenetic testing	32%
IGHV testing performed	8%

MAJOR EDUCATIONAL OPPORTUNITY TO GUIDE TREATMENT DECISION MAKING!

CLL, chronic lymphocytic leukemia; FISH, fluorescence in situ hybridization; IGHV, immunoglobulin heavy-chain variable region; TN, treatment naive.

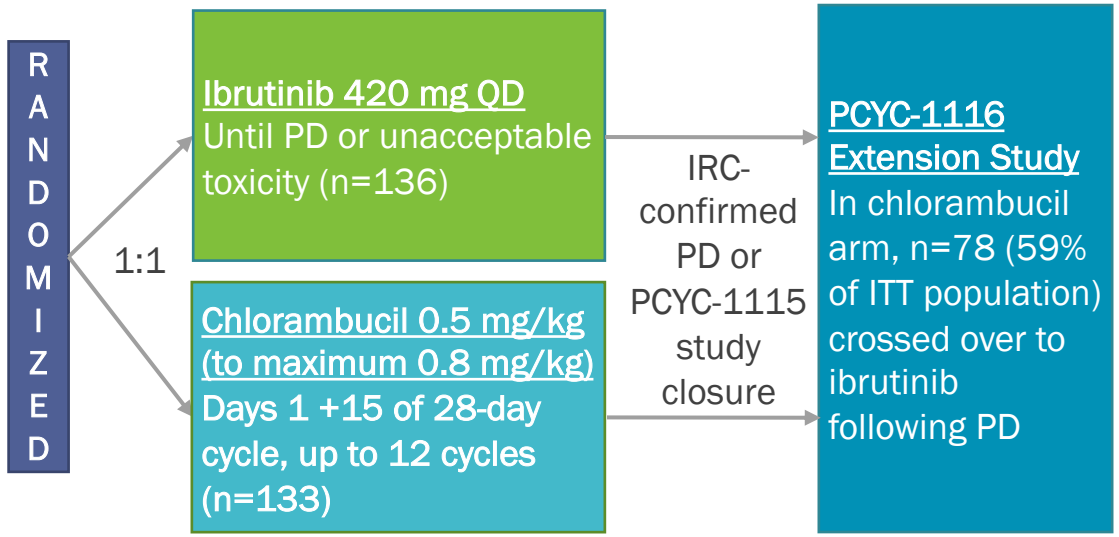
1. Campo E, et al. *Haematologica*. 2018;103(12):1956-1968. 2. Cavallari M, et al. *Oncotarget*. 2018;9(76):34398-34412. 3. International CLL-IPI working group. *Lancet Oncol*. 2016;17(6):779-790. 4. Rigolin GM, et al. *Oncotarget*. 2017;8(17):28008-28020. 5. Mato A, et al. *Clin Lymphoma Myeloma Leuk*. 2018;18(2):114-124.

Ibrutinib in treatment naïve CLL

How does long-term follow-up data from RESONATE 2 inform clinical decision making?

7 Years of Follow-Up in the RESONATE-2 Study of Ibrutinib for Patients With TN CLL: Study Design and Patients

Key eligibility criteria
- TN CLL/SLL requiring treatment
- Age ≥65 years
- No del(17p)



Objective: Describe the long-term efficacy and safety from RESONATE-2

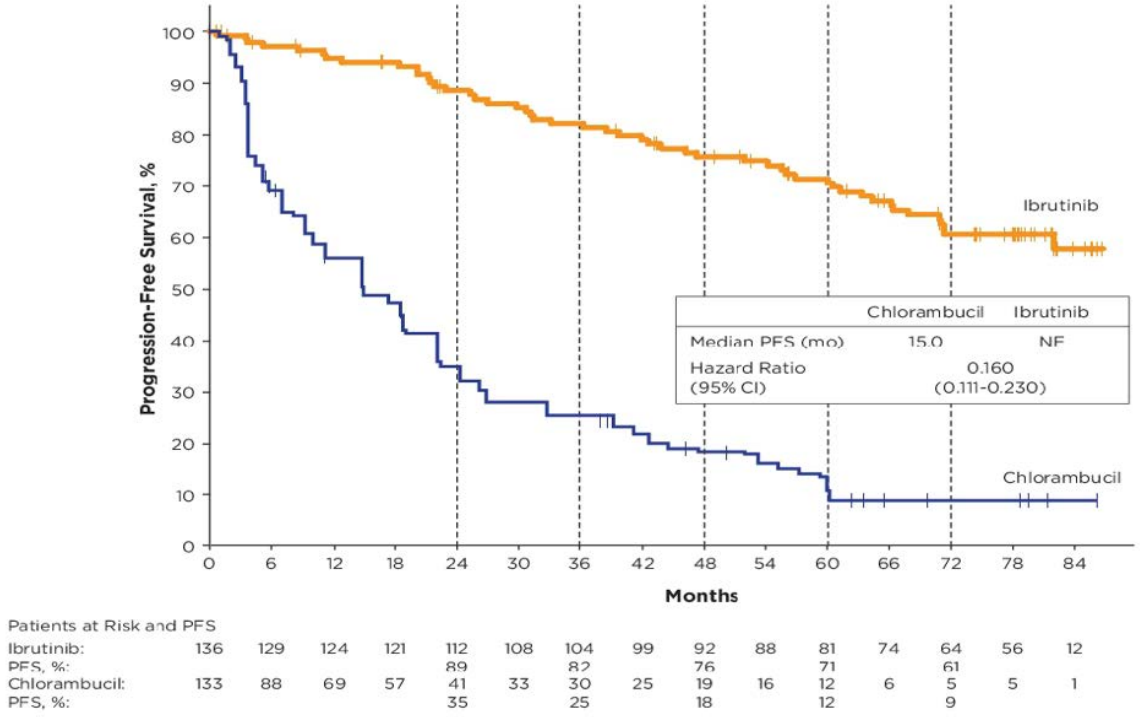
Patient Characteristics, %		(N=269)
Median age, years		73
Bulky disease		35
Anemia (Hb <11g/dL)		39
Elevated β2M (>3.5 mg/L)		65
ITT Population, % (n/N)	One or more high-risk features (*TP53* mutation, del[11q], and/or unmutated *IGHV*)	53 (142/269)
Evaluable Population, % (n/N)	Del(11q)	22 (54/251)
	Unmutated *IGHV*	58 (118/204)

[a]Patients could enroll in separate extensions study PCYC-1116 after IRC-confirmed PD or at study PCYC-1115 closure for continuing treatment and follow-up

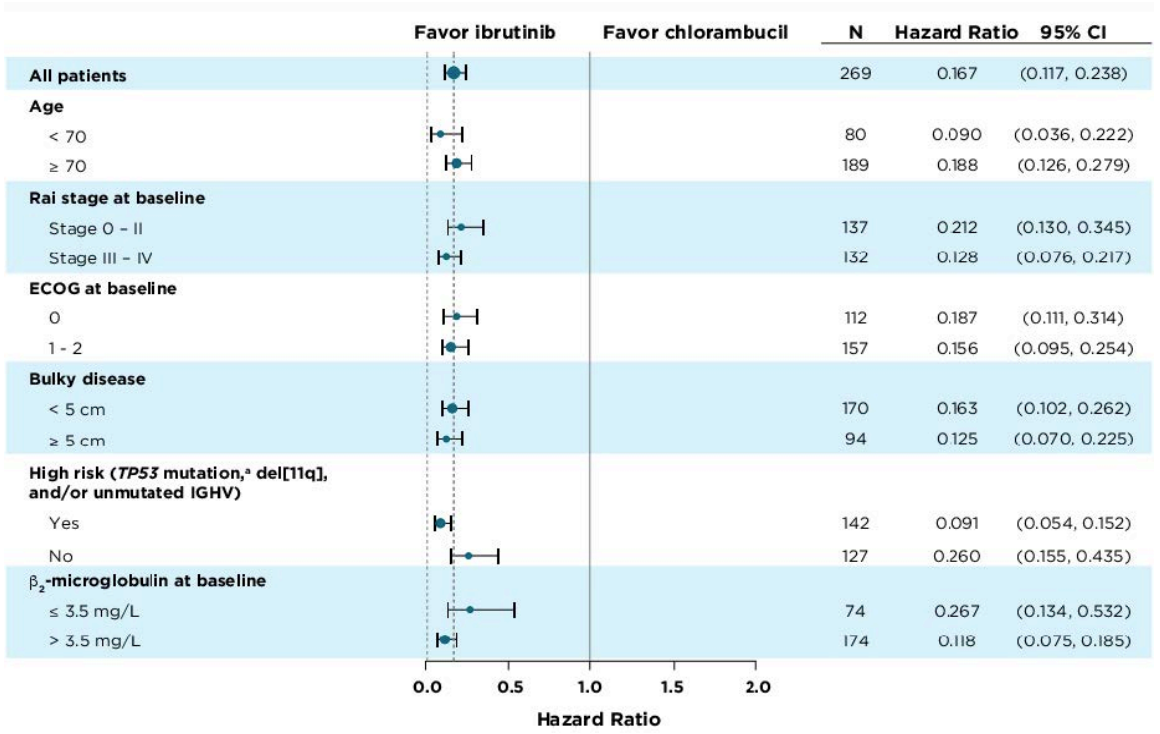
Barr PB, et al. ASCO 2020. Abstract 7523.

Up to 7 Years of Follow-Up in the RESONATE-2 Study of Ibrutinib for Patients With TN CLL: Efficacy

PFS: Ibrutinib vs Chlorambucil



PFS in Patient Subgroups of Interest



Efficacy

- Ibrutinib-treated patients had an 84% reduction in risk of progression or death
- Ibrutinib led to a 97% reduction in risk of PD or death in patients with del(11q) and 80% for those without del(11q) vs chlorambucil
- Ibrutinib led to an 89% and 80% reduction in risk of PD or death in patients with unmutated and mutated *IGHV*, respectively, vs chlorambucil

Barr PB, et al. ASCO 2020. Abstract 7523.

Up to 7 Years of Follow-Up in the RESONATE-2 Study of Ibrutinib for Patients With TN CLL: Treatment and Summary

Ibrutinib Treatment Disposition	First-Line Ibrutinib (N=136[c])
Median duration of ibrutinib treatment, years[a] (range)	6.2 (0.06-7.2)
Continuing ibrutinib on study, n (%)	64 (47)
Discontinued ibrutinib, n (%)	**53%**
AE	31 (23)
PD	16 (12)
Death	11 (8)
Withdrawal by patient	9 (7)
Investigator decision	4 (3)

Summary

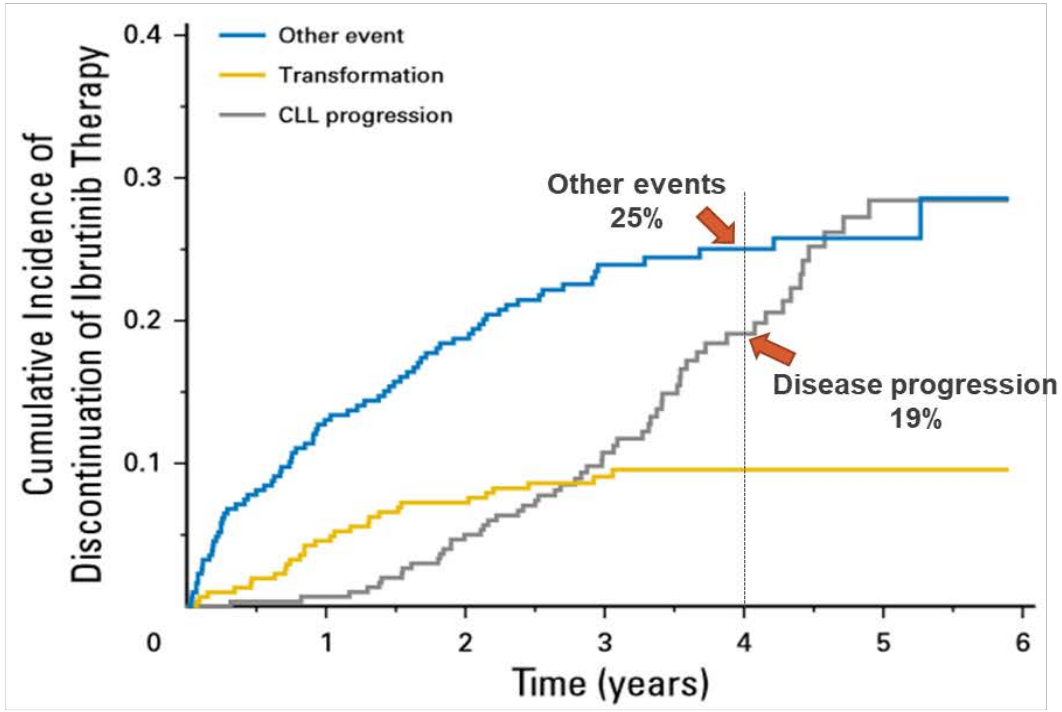
- Single-agent ibrutinib displayed sustained PFS and OS benefit vs chlorambucil over 7 years of follow up
- Ibrutinib treatment arm did not reach median PFS and OS, though 6.5-year estimates were 61% and 78%, respectively
- PFS benefit for ibrutinib vs chlorambucil was similar for patients with high-risk and lower-risk genomic features, and CR/CRi rates increased over time with ibrutinib
- No new safety signals developed with long-term follow-up
- Nearly half of patients maintained ibrutinib use at up to 7 years of follow-up

Room for improvement?
Overall 53% discontinuation rate
50% of all discontinuations are due to AE

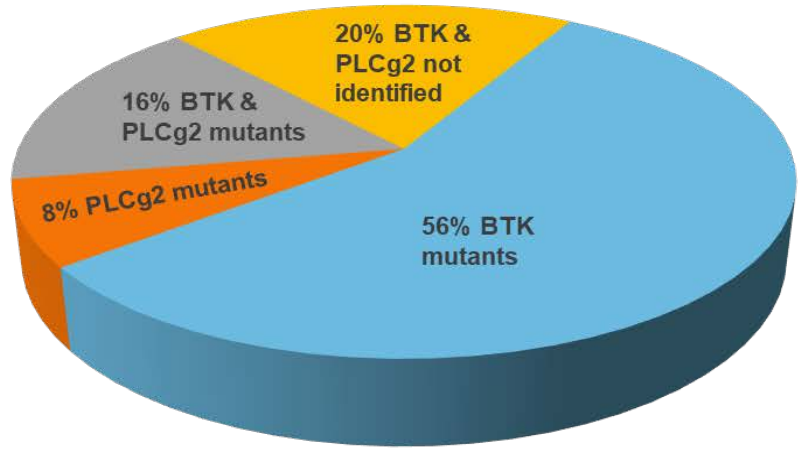
[a]74.0 months (0.7-86.8).
Barr PB, et al. ASCO 2020. Abstract 7523.

Limitation to Ibrutinib: Resistance and Intolerance

Ibrutinib discontinuation from 4 sequential studies[1]



Ibrutinib acquired resistance in patients with progressive CLL[2]



Do next generation cBTKi address the issues of resistance and intolerance?

- Front line: Ibrutinib discontinuation rate at 5 years = 41%[1]
- Relapsed/refractory: Predicted ibrutinib discontinuation rate at 5 years = 53.7% (4 sequential studies)[7]
- The appearance of BTK C481 mutations is the dominant reason for progressive CLL after covalent BTK inhibitors[1-8]
- BTK C481 mutations prevent covalent BTK inhibitors from effective target inhibition[1-6]

Slide Courtesy of Mato A.

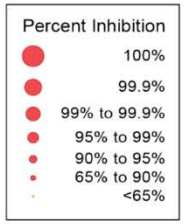
BTK, Bruton tyrosine kinase; CLL, chronic lymphocytic leukemia; PLCg2, phospholipase C gamma 2.

1. Woyach JA, et al. *J Clin Oncol*. 2017;35(13):1437-1443. 2. Lampson BL, Brown JR. *Expert Rev Hematol*. 2018;11(3):185-194. 3. Woyach JA, et al. *N Engl J Med*. 2014;370(24):2286-2294. 4. Byrd JC, et al. *N Engl J Med*. 2016;374(4):323-332. 5. Xu L, et al. *Blood*. 2017;129(18):2519-2525. 6. Hershkovitz-Rokah O, et al. *Br J Haematol*. 2018;181(3):306-319. 7. Burger JA, et al. *Leukemia*. 2020;34(3):787-798. 8. Woyach JA, et al. Presented at: American Society of Hematology (ASH) 2019.

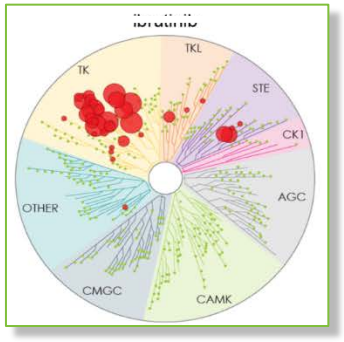
Alternative BTKis in treatment naïve CLL

Several BTKi options to consider with differences in BTKi specificity, MOA and potential for off target effects

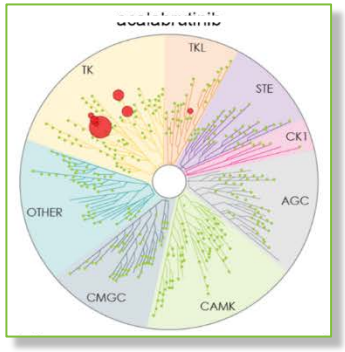
Irreversible



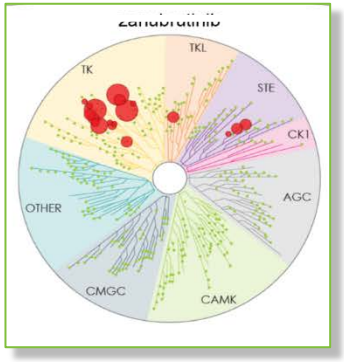
Ibrutinib



Acalabrutinib



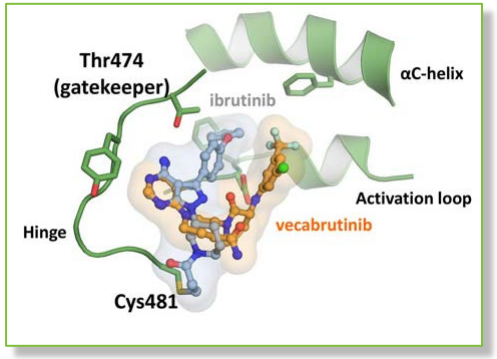
Zanubrutinib



TG-1701

Reversible

Vecabrutinib



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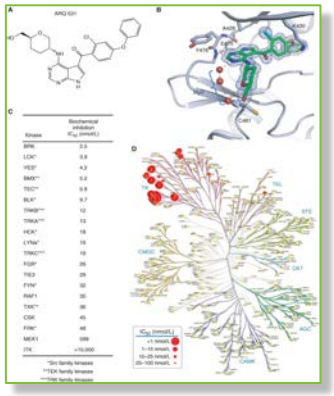
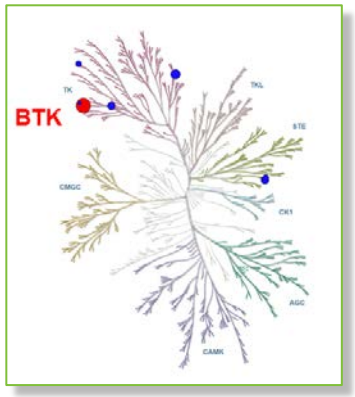


LOXO-305



BTKi, Burton tyrosine kinase inhibitor; MOA, mechanism of action.

Kaptein A, de Bruin G, Emmelot-van Hoek M, et al. *Blood.* 2018;132(Supplement 1):1871.
Ribeiro ML, et al. AACR 2020. Abstract 2205.

4-Year Follow Up of ELEVATE-TN, Acalabrutinib ± Obinutuzumab vs Obinutuzumab + Chlorambucil in TN CLL: Study Design

Key Eligibility Criteria

- Age ≥65 years or >18 to <65 years with comorbidities (defined as CrCl 30-69 mL/min and CIRS-G >6)
- Untreated CLL requiring treatment per iwCLL 2008 criteria
- ECOG PS ≤2
- No significant cardiovascular disease

RANDOMIZED 1:1:1

Acalabrutinib + Obinutuzumab (A+O)
Acala 100 mg PO BID until PD or unacceptable toxicity
6 cycles

Acalabrutinib Monotherapy (A)
Acala 100 mg PO BID until PD or unacceptable toxicity
Crossover from O+Clb to A allowed after IRC-confirmed PD

Obinutuzumab + Chlorambucil (O+Clb)
6 cycles

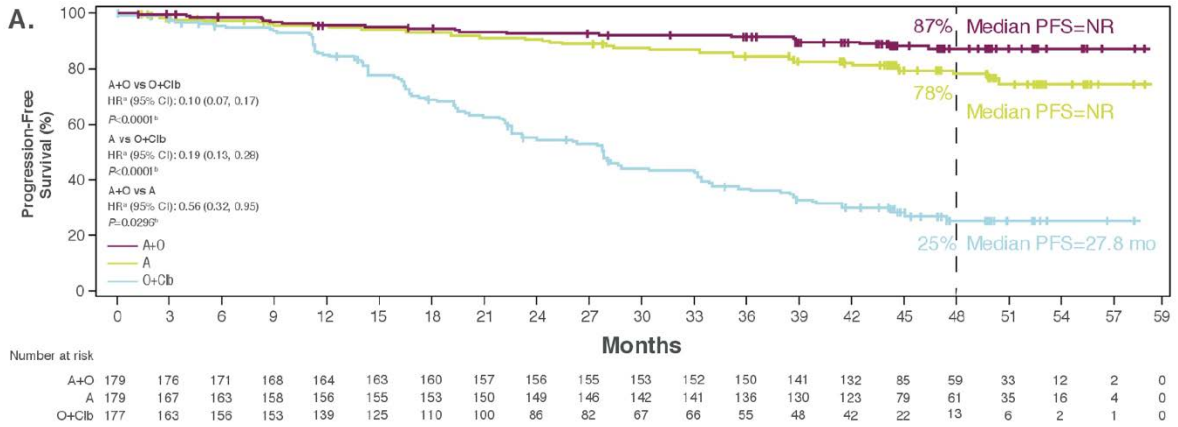
Primary endpoint: IRC-assessed PFS (A+O vs O+Clb)
Secondary endpoints: IRC-assessed PFS (A vs O+Clb), INV-assessed PFS, ORR, TTNT, OS, uMRD, safety

Patient Characteristics		A+O (n=179)	A (n=179)	O+Clb (n=177)
Median age (range), years		70 (41-88)	70 (44-87)	71 (46-91)
ECOG PS, n (%)	0-1	169 (94.4)	165 (92.2)	167 (94.4)
	2	10 (5.6)	14 (7.8)	10 (5.6)
Bulky disease ≥5 cm, n (%)		46 (25.7)	68 (38.0)	54 (30.5)
Rai stage, n (%)	III	47 (26.3)	51 (28.5)	40 (22.6)
	IV	38 (21.2)	37 (20.7)	38 (21.5)
Cytogenetics, n (%)	del(17p)	17 (9.5)	16 (8.9)	16 (9.0)
	del(17p) and/or mut *TP53*	25 (14.0)	23 (12.8)	25 (14.1)
	del(11q)	31 (17.3)	31 (17.3)	33 (18.6)
	Complex karyotype	15 (8.4)	13 (7.3)	25 (14.1)
Mutated *TP53*, n (%)		21 (11.7)	19 (10.6)	21 (11.9)
Unmutated IGHV, n (%)		103 (57.5)	119 (66.5)	116 (65.5)
Treatment ongoing, n (%)		134 (74.9)	124 (69.3)	0

Data cutoff: September 11, 2020.
Sharman JP, et al. EHA 2021. Abstract S148.

4-Year Follow Up of ELEVATE-TN, Acalabrutinib ± Obinutuzumab vs Obinutuzumab + Chlorambucil in TN CLL: PFS and OS

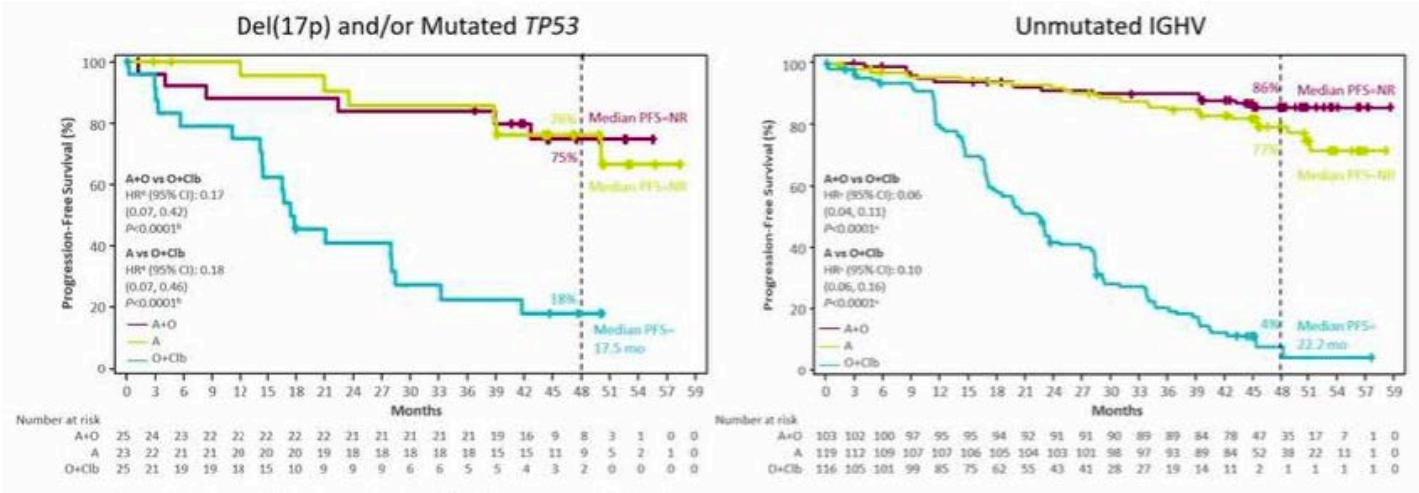
INV-Assessed PFS Overall



A beautiful study design!

Assessment of the relative contribution of obinutuzumab to acalabrutinib.

INV-Assessed PFS in Patients With del(17p) and/or Mutated *TP53* or Unmutated IGHV

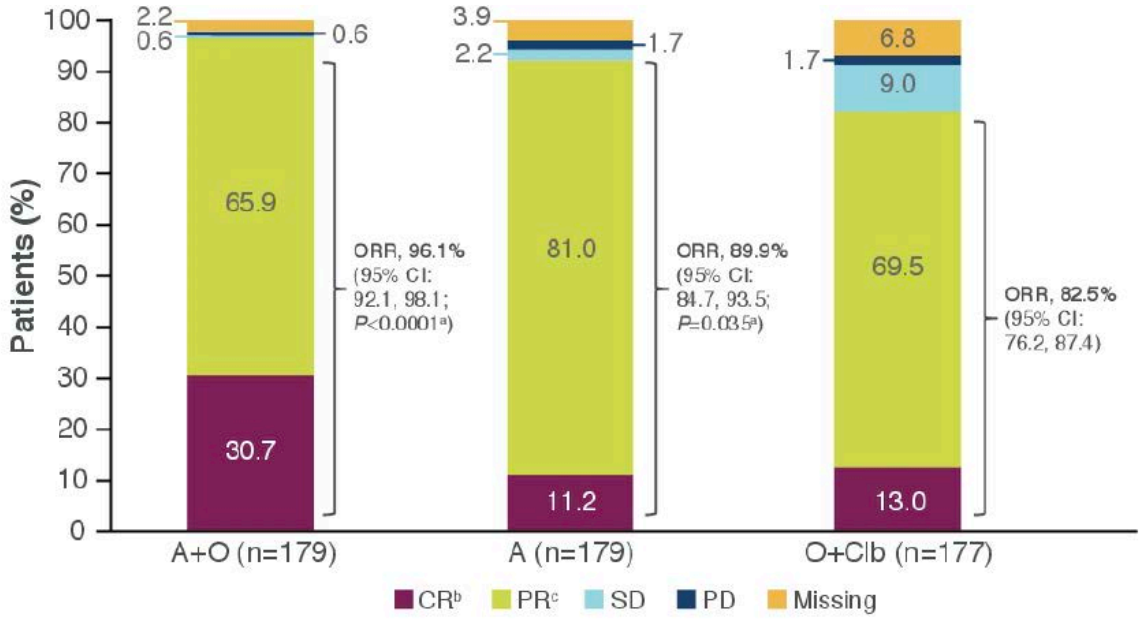


AO combination: IGHV mutated and TP53 intact benefit most

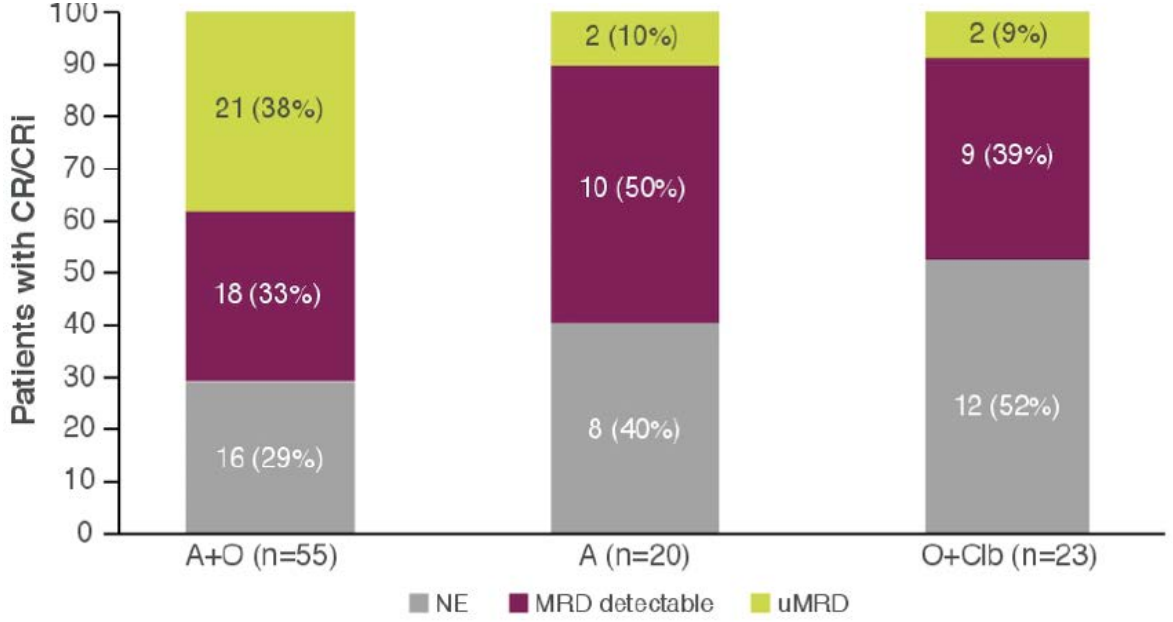
Sharman JP, et al. EHA 2021. Abstract S148.

4-Year Follow Up of ELEVATE-TN, Acalabrutinib ± Obinutuzumab vs Obinutuzumab + Chlorambucil in TN CLL: Response

INV-Assessed ORR



MRD Status in Patients With CR/CRi



AO results in deeper remissions (CR / uMRD): Does this open the window for BTK+CD20 as a time limited therapy?

Sharman JP, et al. EHA 2021. Abstract S148.

4-Year Follow Up of ELEVATE-TN, Acalabrutinib ± Obinutuzumab vs Obinutuzumab + Chlorambucil in TN CLL: Safety and Summary

AEs of Clinical Interest, n (%)	A+O (n=178)		A (n=179)		O+Clb (n=169)	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3	Any Grade	Grade ≥3
Cardiac events	37 (20.8)	14 (7.9)	34 (19.0)	15 (8.4)	13 (7.7)	3 (1.8)
Atrial fibrillation	7 (3.9)	1 (0.6)	11 (6.1)	2 (1.1)	1 (0.6)	0
Bleeding	84 (47.2)	5 (2.8)	75 (41.9)	5 (2.8)	20 (11.8)	0
Major bleeding	7 (3.9)	5 (2.8)	7 (3.9)	5 (2.8)	2 (1.2)	0
Hypertension	14 (7.9)	6 (3.4)	13 (7.3)	5 (2.8)	7 (4.1)	6 (3.6)
Infections	134 (75.3)	42 (23.6)	132 (73.7)	29 (16.2)	75 (44.4)	14 (8.3)
SPMs	28 (15.7)	13 (7.3)	24 (13.4)	5 (2.8)	7 (4.1)	3 (1.8)
Excluding non-melanoma skin	15 (8.4)	10 (5.6)	11 (6.1)	4 (2.2)	3 (1.8)	2 (1.2)

Safety

- Most AEs in the A-containing arms occurred primarily during the 1st year of treatment
- AEs that occurred more frequently in A+O and A vs O+Clb included headache, diarrhea, fatigue, arthralgia, cough, and URTI
- AEs that occurred more frequently with O+Clb included neutropenia, nausea, and IRR

Authors' Conclusions

- Acalabrutinib ± obinutuzumab demonstrated durable disease control, tolerability, and flexibility to tailor treatment as a monotherapy or in combination

Sharman JP, et al. EHA 2021. Abstract S148.

Results From Arm C of the Phase 3 SEQUOIA Trial of Zanubrutinib for Patients With TN del(17p) CLL/SLL: Study Design and Patients

Key eligibility criteria

- Age ≥65 years or unsuitable for treatment with FCR
- Verification of del(17p) by FISH with >7% aberrant nuclei[a]
- TN with treatment required per iwCLL criteria
- Anticoagulants and CYP3A inhibitors allowed

Cohort 2 with del(17p) (n~100)

↓

Arm C (n=109)

- Nonrandomized; zanubrutinib 160 mg BID until PD, intolerable toxicity, or end of study

Primary endpoint: PFS (IRC)
Secondary endpoints: ORR (IRC and INV), DOR, safety

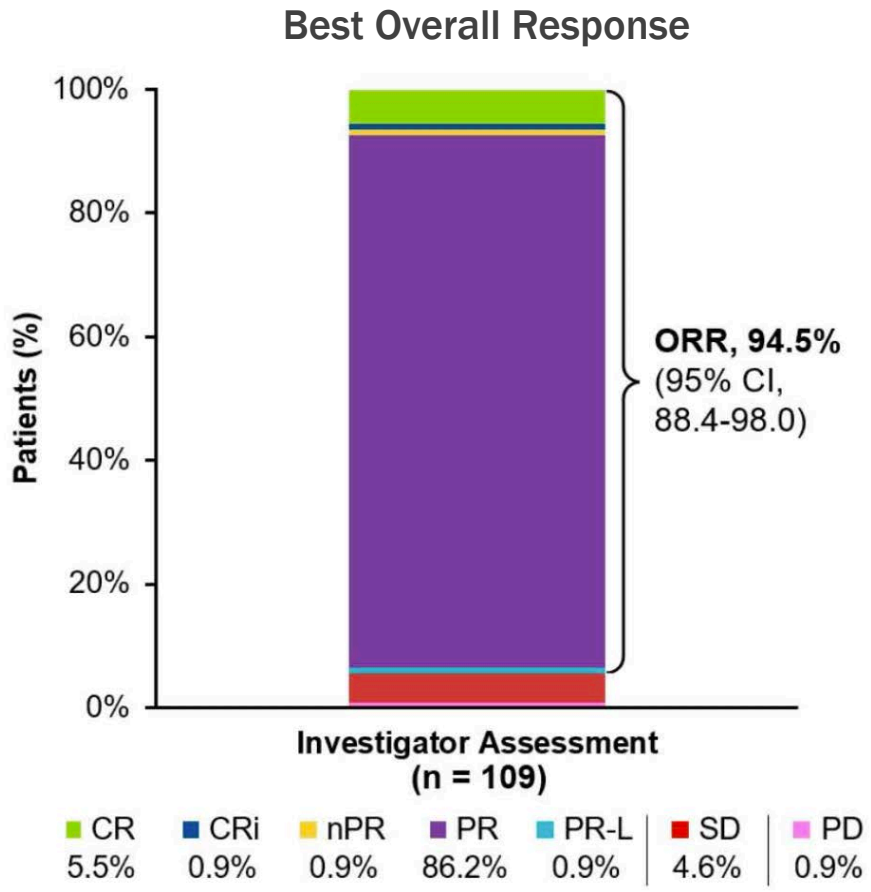
Patient Characteristics			(N=109)
Median age (range), years			70.0 (42-86)
ECOG PS 2, n (%)			14 (12.8)
Median time since diagnosis (Q1-Q3), months			21.62 (7.69-54.77)
SLL, n (%)			10 (9.2)
Binet stage C for CLL, n/N (%)			40/99 (40.4)
del(13q), n (%)			72 (66.1)
del(11q), n (%)			37 (33.9)
IGHV unmutated, n/N (%)			69/104 (66.3)
Bulky disease, n (%)	Any target lesion LDi ≥5 cm		42 (38.5)
	Any target lesion LDi ≥10 cm		11 (10.1)
Karyotype,[b] n (%)	Non-complex (0-2 abnormalities)		54/86 (62.8)
	Complex (abnormalities)	3 or more	32/86 (37.2)
		5 or more	23/86 (26.7)

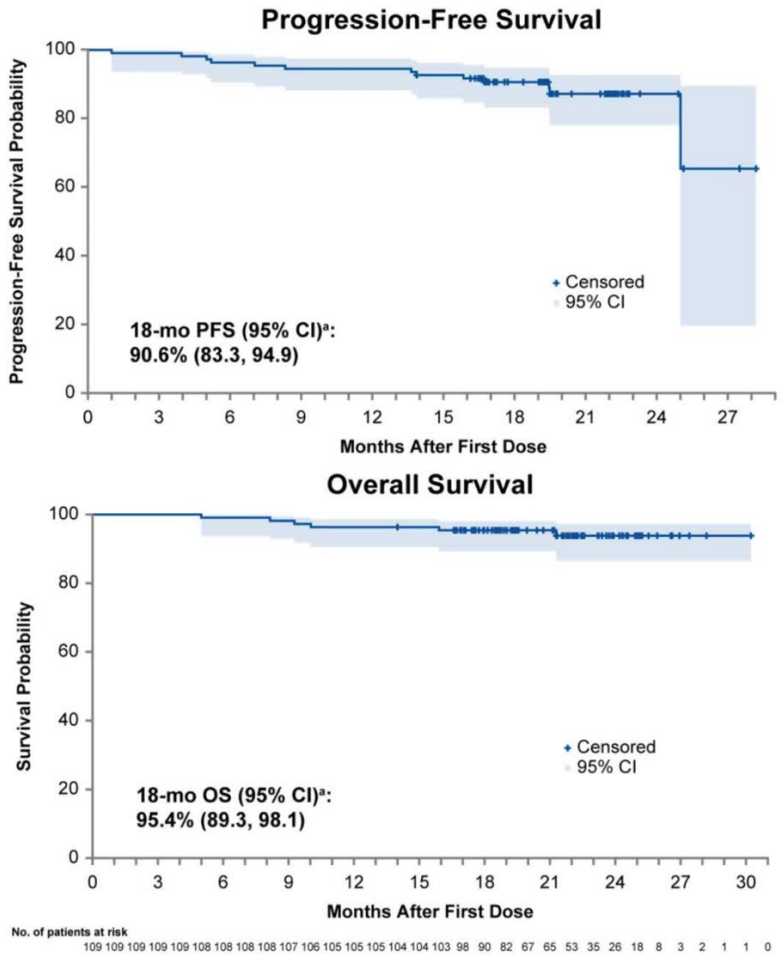
BID, twice daily; CLL, chronic lymphocytic leukemia; DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; FCR, fludarabine, cyclophosphamide, rituximab; FISH, fluorescence in situ hybridization; IGHV, immunoglobulin heavy-chain variable region; INV, investigator; IRC, independent review committee; LDi, longest travers diameter of a lesion; ORR, overall response rate; PD, progressive disease; PFS, progression-free survival; SLL, small lymphocytic leukemia; TN, treatment naive.

[a]*TP53* mutational status was not centrally assessed prior to enrollment. [b]23 patients had insufficient metaphases available for analysis.

Brown JR, et al. ASH 2020. Abstract 1306

Results From Arm C of the Phase 3 SEQUOIA Trial of Zanubrutinib for Patients With TN del(17p) CLL/SLL: Efficacy





Largest front line dataset for BTKi in del17p CLL

Will this be BTKi of choice for high-risk patients?

How do these data compare to Ven-G in high-risk disease?

CR, complete response; CRi, complete response with incomplete blood count recovery; nPR, nodular partial response; ORR, overall response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PR, partial response; PR-L, partial response with lymphocytosis; SD, stable disease.
[a]Data cutoff for 2019 ASH presentation: August 7, 2019.
Brown JR, et al. ASH 2020. Abstract 1306.

Positive Topline Results Announced from the Phase III SEQUOIA Trial: Zanubrutinib versus BR for Treatment-Naïve CLL

Press Release: July 29, 2021

"The SEQUOIA trial met the primary endpoint at interim analysis, with zanubrutinib significantly prolonging progression-free survival compared to chemoimmunotherapy, and safety and tolerability consistent with its known profile. SEQUOIA is the second positive global Phase 3 trial of zanubrutinib in chronic lymphocytic leukemia, following ALPINE in the relapsed or refractory setting.

With a median follow-up of 25.8 months, the SEQUOIA trial met the primary endpoint of progression-free survival (PFS) as assessed by independent review committee (IRC), as zanubrutinib achieved a highly statistically significant improvement in PFS compared to B + R.

In addition, the trial demonstrated a statistically significant improvement in PFS per investigator assessment, a secondary endpoint. Zanubrutinib was also generally well-tolerated, consistent with its known safety profile."

https://www.businesswire.com/news/home/20210729006225/en/BeiGene-Announces-Positive-Topline-Results-from-Phase-3-SEQUOIA-Trial-Comparing-BRUKINSA%C2%AE-Zanubrutinib-to-Bendamustine-Plus-Rituximab-in-Patients-with-Treatment-Na%C3%AFve-Chronic-Lymphocytic-Leukemia

Summary: Alternate covalent BTK inhibitors

- **Intolerance:** Front line setting: Cross trial comparisons suggest next generation cBTKi MAY lead to lower discontinuation rates due to AEs BUT no data to suggest < AEs lead to better PFS. No head to head data available for front line setting.

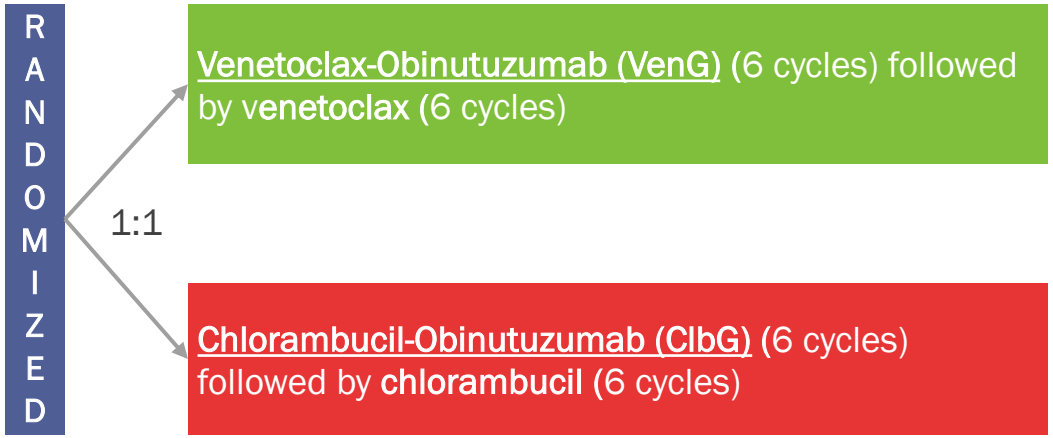
- **Resistance:** Limited data from more selective cBTKi suggest similar mechanisms of resistance

Venetoclax in treatment naïve CLL

Who should and should not be receiving venetoclax based time limited therapy?

4-Year Follow-Up From the CLL14 Study: Study Design and Patients

Key Eligibility Criteria
- Patients with TN CLL and coexisting medical conditions
- CIRS >6 and/or CrCl <70 ml/min



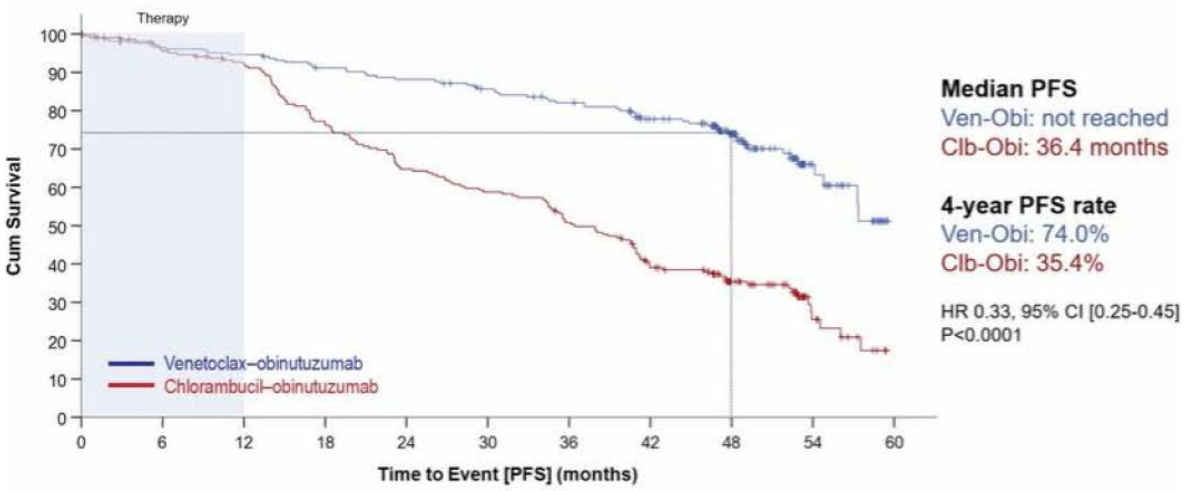
Primary endpoint: PFS
Secondary endpoints: Response, MRD, OS

Patient Characteristics		VenG (n=216)	ClbG (n=216)
Median age, years		72	71
Binet stage, %	A	21	20
	B	35	37
	C	44	43
Median total CIRS score		9	8
Median estimated CrCl, ml/min		65.2	67.4
TLS risk category, %	Low	14	12
	Intermediate	64	68
	High	22	20

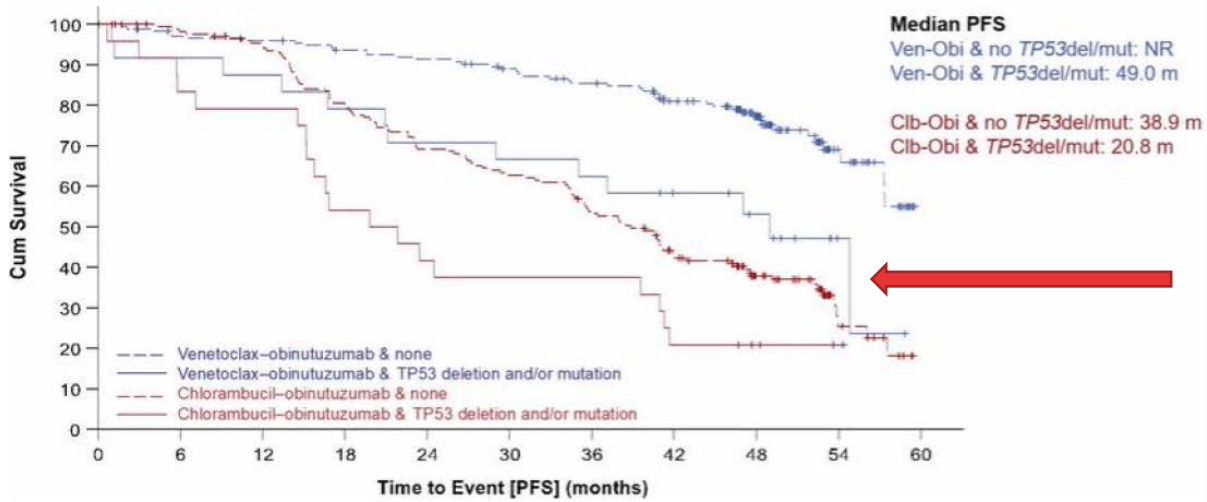
Al-Sawaf O, et al. EHA 2021. Abstract S146.

4-Year Follow-Up From the CLL14 Study: PFS

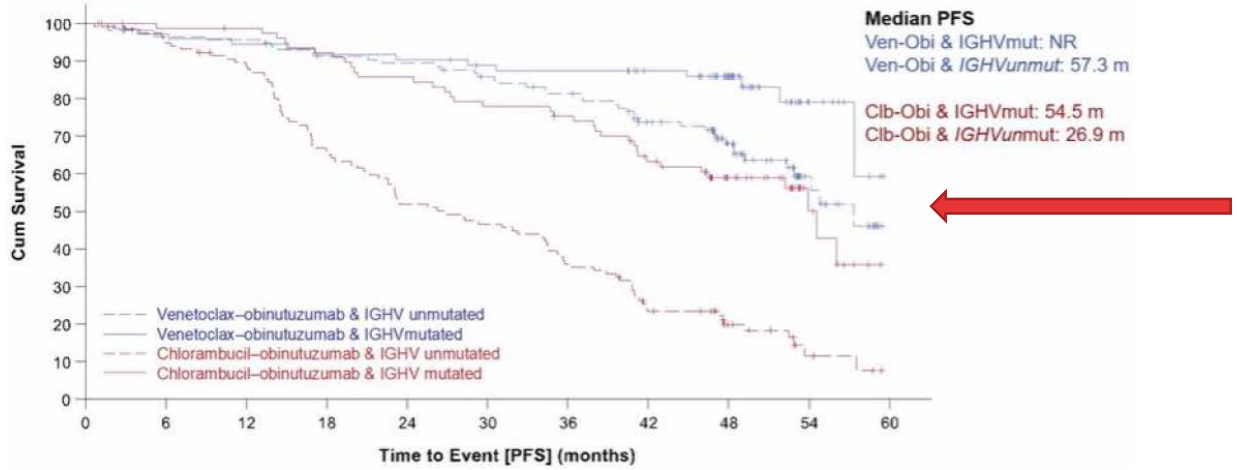
PFS (All Patients)



PFS by *TP53* Status



PFS by IGHV Status

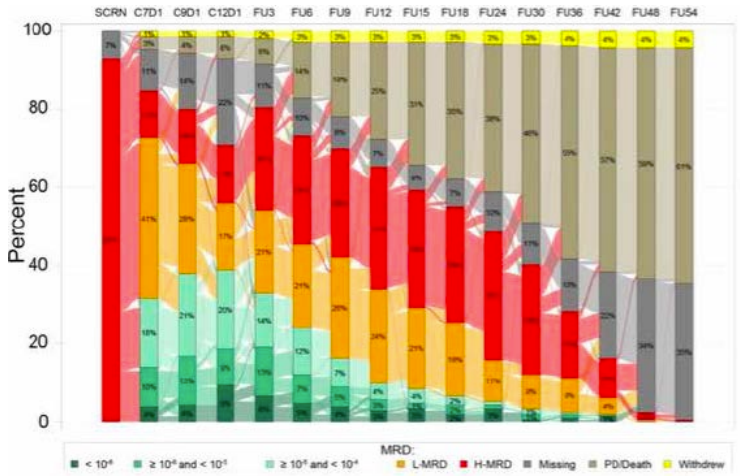


We need re-treatment data for del17p and IGHV unmutated CLL in front line in order to fully assess these curves.

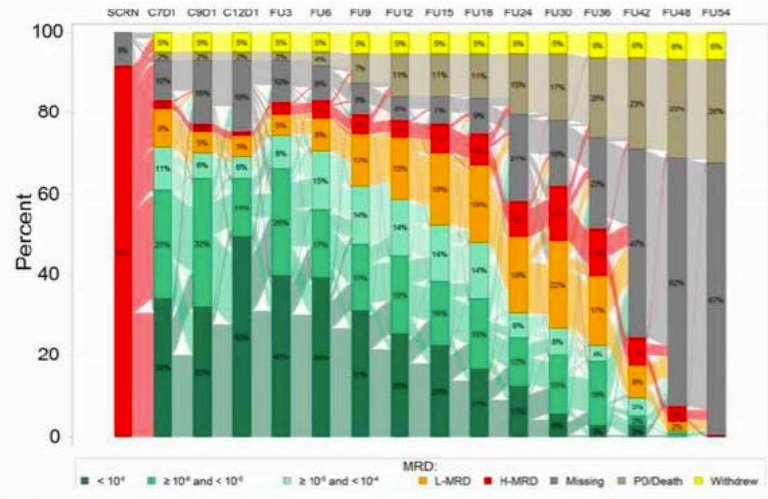
Median observation time: 52.4 months.
Al-Sawaf O, et al. EHA 2021. Abstract S146.

4-Year Follow-Up From the CLL14 Study: MRD

Longitudinal MRD Assessment by NGS in PB: ClbG

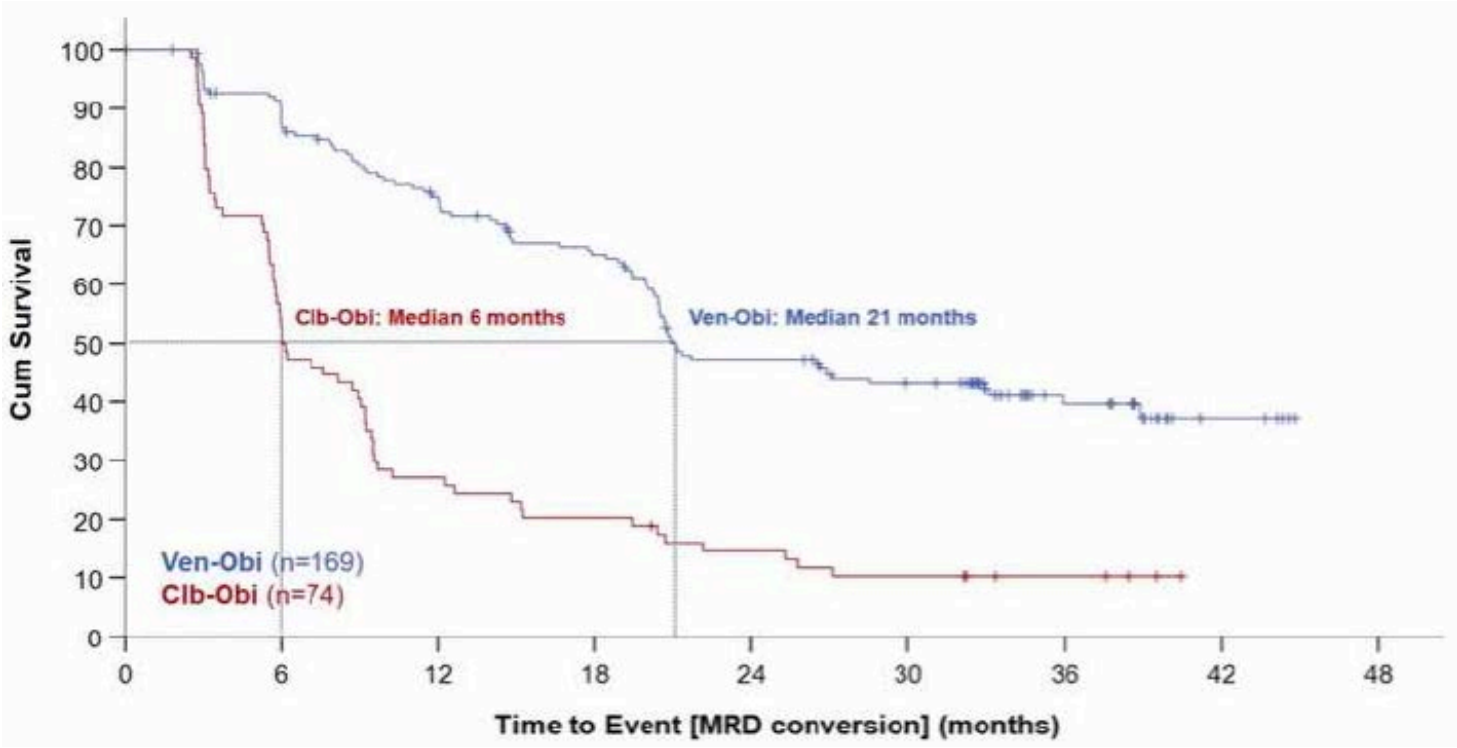


Longitudinal MRD Assessment by NGS in PB: VenG



Median observation time: 52.4 months.
Al-Sawaf O, et al. EHA 2021. Abstract S146.

Time to MRD Conversion from 10^{-4} by NGS at EoT



For Ven-based approaches: Fixed duration or MRD driven approach? Based on CLL14 and Captivate: Which approach does the data support?

BTKi Combinations for Patients With Treatment-Naïve CLL

Various Combinations With BTKi Are Being Explored for TN CLL

Doublet Regimens	Triplet Regimens
Ibrutinib + venetoclax (I+VEN)[1] ▪ Phase 3 study of ibrutinib + venetoclax vs G-Clb in TN CLL without del(17p) or TP53 mutation – Primary endpoint: PFS – Key secondary endpoints: MRD rates, ORR, CR rate, DOR, OS	**Ibrutinib + venetoclax + obinutuzumab (IVO)[2]** ▪ Phase 3 study of ibrutinib and venetoclax ± obinutuzumab in TN CLL <70 years of age, without del(17p) – Primary endpoint: PFS – Secondary endpoints: OS, safety – Exploratory endpoints: QOL, MRD, and adherence
Acalabrutinib + venetoclax (AV) and acalabrutinib + venetoclax + obinutuzumab (AVO)[3] ▪ Phase 3 study of AV or AVO vs FCR/BR in TN CLL without del(17p) or TP53 mutation – Primary endpoint: PFS (IRC-assessed) of AV vs FCR/BR – Secondary endpoints: PFS (IRC-assessed) of AVO vs FCR/BR, PFS (INV-assessed) of AV vs FCR/BR	
Zanubrutinib + venetoclax[4] ▪ Phase 3 study of zanubrutinib + venetoclax (Arm D) vs zanubrutinib (Arm C) in TN CLL with del(17p) or TP53 mutation – Key secondary endpoints for Arm D: ORR, PFS, DOR, MRD rates	**Zanubrutinib + venetoclax + obinutuzumab (BOVen)[5]** ▪ Phase 2 study of zanubrutinib, venetoclax, and obinutuzumab in TN CLL – Primary endpoint: MRD rates

BR, bendamustine, rituximab; BTKi, Bruton tyrosine kinase inhibitor; CLL, chronic lymphocytic leukemia; CR, complete response; DOR, duration of response; FCR, fludarabine, cyclophosphamide, rituximab; INV, investigator; IRC, independent review committee; MRD, minimal residual disease; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; QOL, quality of life; TN, treatment naive.

1. https://clinicaltrials.gov/ct2/show/NCT03462719. 2. https://clinicaltrials.gov/ct2/show/NCT03701282. 3. https://clinicaltrials.gov/ct2/show/NCT03836261. 4. https://clinicaltrials.gov/ct2/show/NCT03336333. 5. https://clinicaltrials.gov/ct2/show/NCT03824483.

How to judge success of novel agent combination therapy in CLL

- Does combination tx allow for a time limited approach? By inducing deep uMRD?
- Has the combination demonstrated superiority over a clinically relevant control?
- Has the combination been tested against sequential monotherapies that comprise the combination?
- Is the combination well tolerated?
- Do we have data on mechanisms of resistance to the combination?
- Do we have data on sequencing next therapies following the combination? Including retreatment?
- Does the combination prolong overall survival?

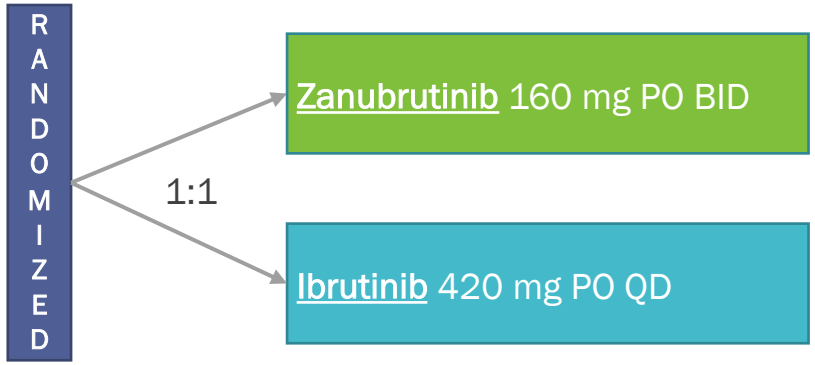
BTKi: Head-to-head comparisons

Can lessons learned be applied to the front-line setting?

ALPINE and ELEVATE R/R: Head to Head comparisons

Key Eligibility Criteria

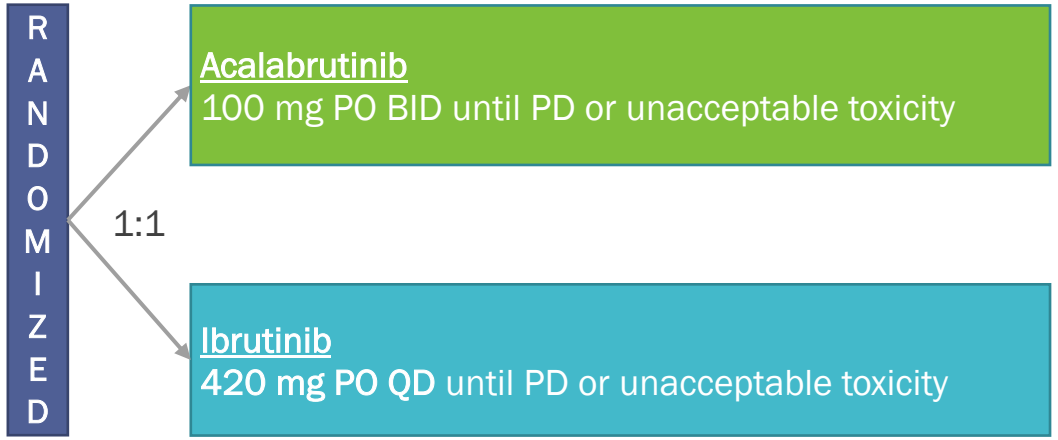
- R/R to ≥1 prior systemic therapy for CLL/SLL
- Measurable lymphadenopathy by CT or MRI
- No current or past RT, prior BTKi therapy, or warfarin/other VKA



Primary endpoint: ORR (CR+PR) noninferiority and INV-assessed superiority
Secondary endpoints: Any-grade atrial fibrillation, DoR, PFS, OS, time to treatment failure, PR-L or higher, PROs, safety

Key Eligibility Criteria

- Previously treated CLL requiring treatment per iwCLL 2008 criteria
- Presence of del(17p) or del(11q)
- ECOG PS ≤2
- No significant CV disease, no concomitant treatment with warfarin or equivalent vitamin K antagonist, and no prior treatment with ibrutinib, a BCRi, or a BCL-2i



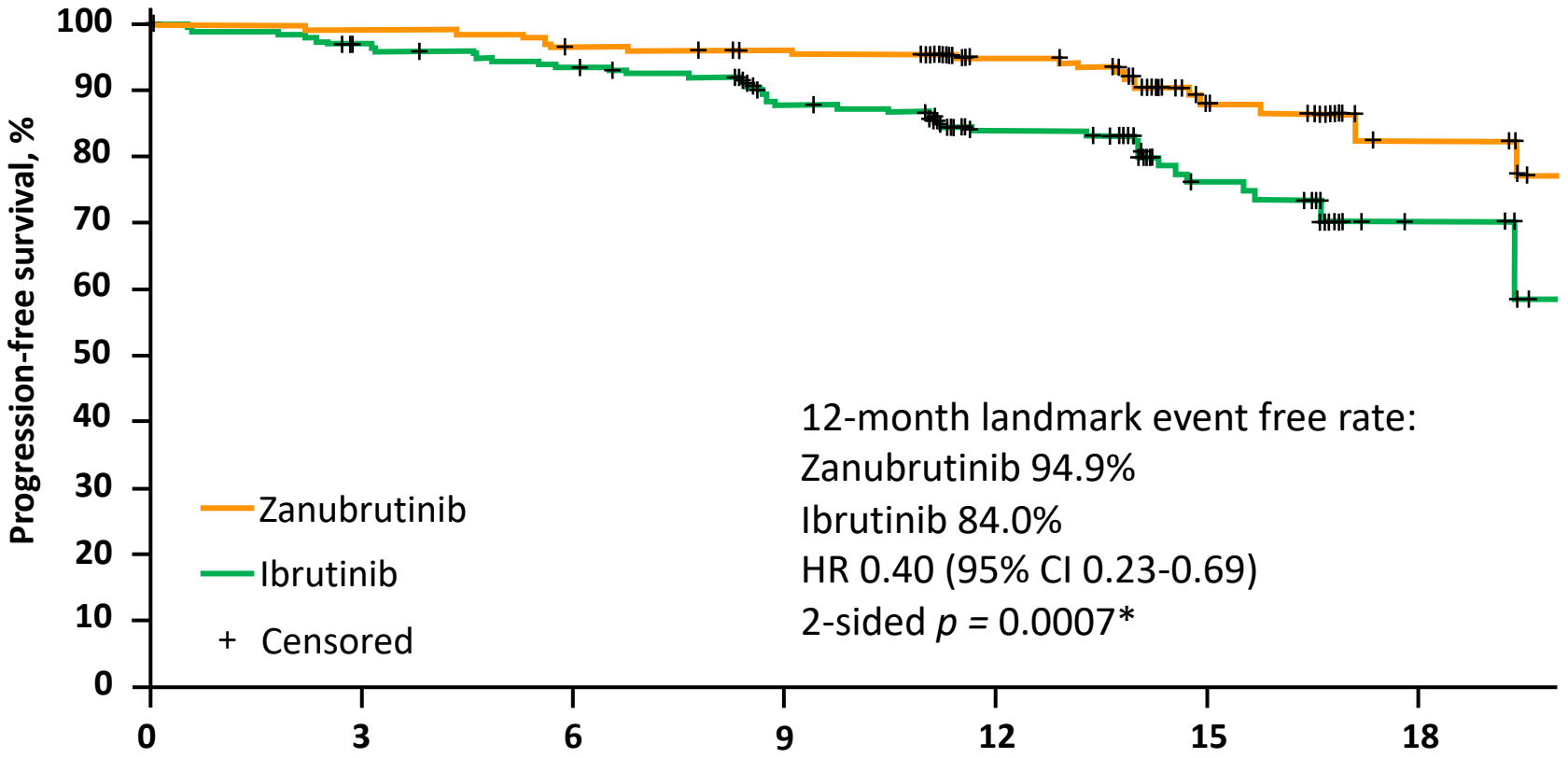
Primary endpoint: Noninferiority on IRC-assessed PFS
Secondary endpoints: Incidence of any atrial fibrillation/flutter, incidence of grade ≥3 infection, incidence of RT, OS

ALPINE: Primary Endpoint — ORR by Investigator Assessment

	Zanubrutinib (n = 207), n (%)	Ibrutinib (n = 208), n (%)
Primary endpoint: ORR (PR + CR)	162 **(78.3)** 95% CI: 72.0, 83.7	130 **(62.5)** 95% CI: 55.5, 69.1
	Superiority 2-sided *p* = 0.0006 compared with prespecified 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 first assessment	6 (2.9)	9 (4.3)
	Del(17p) (n = 24), n (%)	**Del(17p) (n = 26), n (%)**
ORR (PC + CR)	20 (83.3)	14 (53.8)

Hillmen P et al. EHA 2021;Abstract LB1900.

ALPINE: PFS by Investigator Assessment



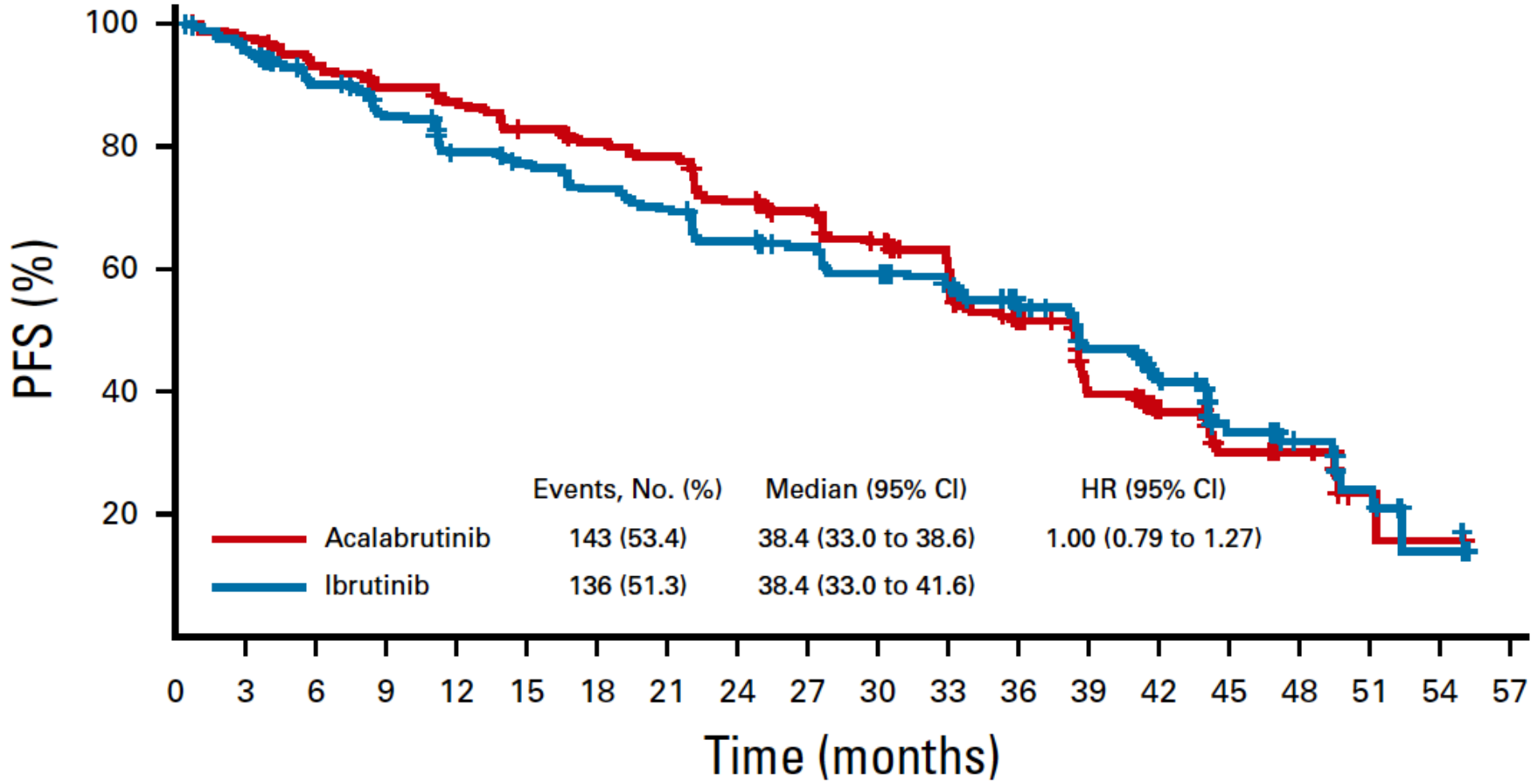
Patients at Risk							
Zanubrutinib	207	200	194	190	152	70	19
Ibrutinib	208	196	188	170	125	57	8

Although not a pre-specified analysis, the overall 12-month PFS was higher with zanubrutinib vs ibrutinib (94.9% vs 84.0%)

*Not a prespecified analysis; formal analysis of PFS will be based on all patients when the target number of events is reached.

Hillmen P et al. EHA 2021;Abstract LB1900.

ELEVATE-RR: Primary Endpoint — Noninferiority Met on IRC-Assessed PFS



Byrd JC et al. *J Clin Oncol* 2021;[Online ahead of print]; ASCO 2021;Abstract 7500.

Welcome to ASH 2021…

How will this meeting inform decision making in the frontline setting?

- Ibrutinib Plus Rituximab Is Superior to FCR in Previously Untreated CLL: Results of the Phase III NCRI FLAIR Trial Presenter: Peter Hillmen
- First-Line Treatment with Ibrutinib (Ibr) Plus Venetoclax (Ven) for Chronic Lymphocytic Leukemia (CLL): 2-Year Post-Randomization Disease-Free Survival (DFS) Results from the Minimal Residual Disease (MRD) Cohort of the Phase 2 Captivate Study Presenter: Paolo Ghia
- A Randomized Phase III Study of Venetoclax-Based Time-Limited Combination Treatments (RVe, GVe, GIVe) Vs Standard Chemoimmunotherapy (CIT: FCR/BR) in Frontline Chronic Lymphocytic Leukemia (CLL) of Fit Patients: First Co-Primary Endpoint Analysis of the International Intergroup GAIA (CLL13) Trial Presenter: Barbara Eichhorst
- Zanubrutinib in Combination with Venetoclax for Patients with Treatment-Naïve (TN) Chronic Lymphocytic Leukemia (CLL) or Small Lymphocytic Lymphoma (SLL) with del(17p): Early Results from Arm D of the SEQUOIA (BGB-3111-304) Trial Presenter: Alessandra Tedeschi
- First Prospective Data on Minimal Residual Disease (MRD) Outcomes after Fixed-Duration Ibrutinib Plus Venetoclax (Ibr+Ven) Versus Chlorambucil Plus Obinutuzumab (Clb+O) for First-Line Treatment of CLL in Elderly or Unfit Patients: The Glow Study Presenter: Tahla Muni