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BTK inhibition in B cell malignancies

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Disclosures

- Roche: Honorarium, Advisory Board Honorarium,
- Gilead: Honorarium; Research support; Travel to scientific conferences
- KITE: Advisory Board Honorarium
- Takeda: Travel to scientific conferences
- Janssen: Honorarium
- Abbvie: Honorarium; Travel to scientific conferences
- AstraZeneca: Honorarium, Research funding
- Loxo Oncology: Advisory Board Honorarium, Trial steering committee
- Beigene: Advisory Board Honorarium, Research funding
- Incyte: Advisory Board Honorarium, Speaker Honorarium
- Autolus: Advisory Board Honorarium

Learning Objectives

- Understand the approval of covalent and non-covalent BTKi in 1L and R/R CLL
- Understand the approval of covalent and non-covalent BTKi in R/R MCL
- Understand resistance mechanisms to covalent BTK inhibitors
- Understand the difference in mechanism of action in different BTK classes
- Understand the future possible treatment pathways in CLL and MCL

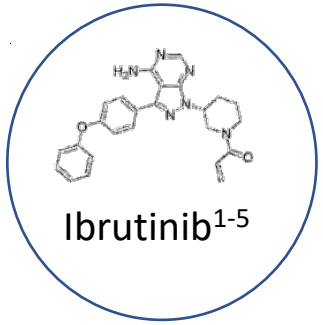
BTK Inhibitor Regulatory Status in CLL/SLL

	CLL/SLL (1L and R/R)	
	EU	US
Ibrutinib[1]	Approved	Approved
Acalabrutinib[2]	Approved	Approved
Zanubrutinib[3]	Approved	Approved
Pirtobrutinib	Phase 3 BRUIN CLL-313 (frontline vs BR; NCT05023980) Phase 3 BRUIN CLL-321 (NCT04666038) Phase BRUIN CLL-322 (NCT04965493)	
Nemtabrutinib		Phase 2 (NCT04728893)

Covalent/Noncovalent

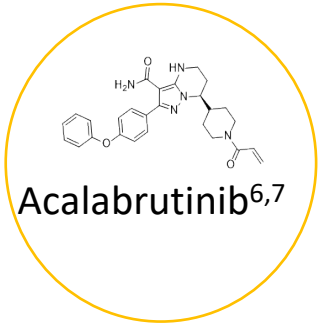
1. Imbruvica (ibrutinib) Prescribing Information. https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/210563s000lbl.pdf.
2. Calquence (acalabrutinib) Prescribing Information. https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/210259s006s007lbl.pdf.
3. Brukinsa (zanubrutinib) Prescribing Information. https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/213217s000lbl.pdf.

In CLL/SLL, Approvals of BTK Inhibitors Are Supported by Robust Phase 3 Evidence [1-9]



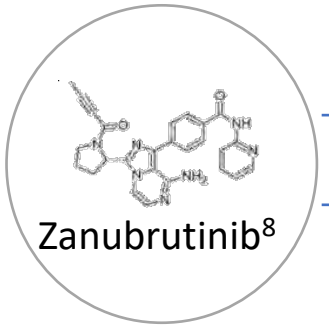
Ibrutinib[1-5]

- ✓ **RESONATE-2:** superior PFS and OS vs Clb
- ✓ **iLLUMINATE:** superior PFS vs GClb
- ✓ **ECOG 1912:** superior PFS and OS vs FCR in younger patients
- ✓ **ALLIANCE:** superior PFS vs BR in older patients
- ✓ **RESONATE:** superior PFS vs ofatumumab in R/R CLL



Acalabrutinib[6,7]

- ✓ **ELEVATE-TN:** superior PFS; trend for better OS vs GClb
- ✓ **ASCEND:** superior PFS in R/R CLL



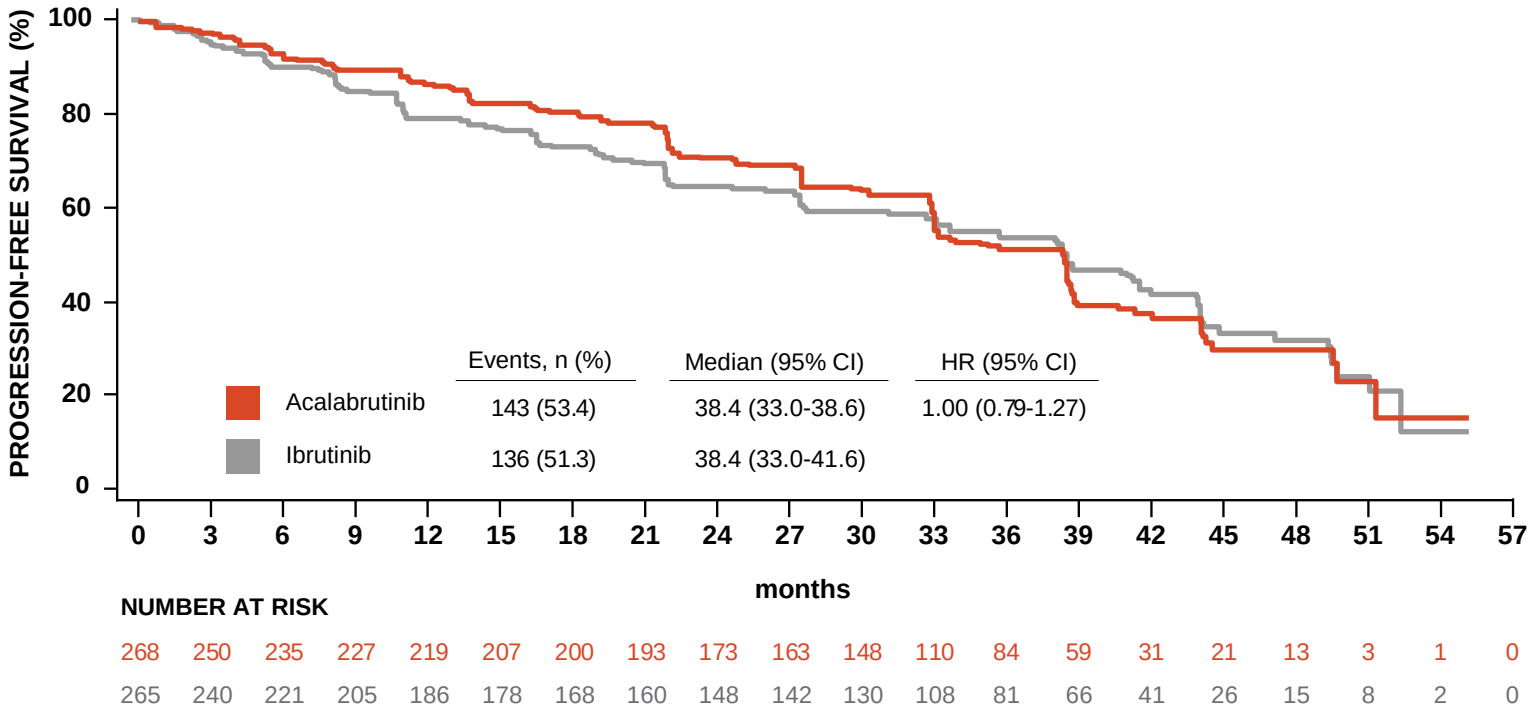
Zanubrutinib[8]

- ✓ **SEQUOIA:** superior PFS vs BR

1. Shanafelt TD et al. *N Engl J Med*. 2019;381:432-443. 2. Woyach JA et al. *N Engl J Med*. 2018;379:2517-2528. 3. Moreno C et al. *Lancet Oncol*. 2019;20:43-56.
4. Burger JA et al. *Leukemia*. 2020;34:787-798. 5. Munir T et al. *Am J Hematol*. 2019;94:1353-1363. 6. Sharman JP et al. *Lancet*. 2020;395:1278-1291.
7. Kater AP et al. 64th American Society of Hematology Annual Meeting & Exposition (ASH 2020). Abstract 125. 8. Tam C et al. ASH 2021. Abstract 396.

Primary Endpoint - IRC assessed PFS

Acalabrutinib was noninferior to ibrutinib based on IRC-assessed PFS*†[1]



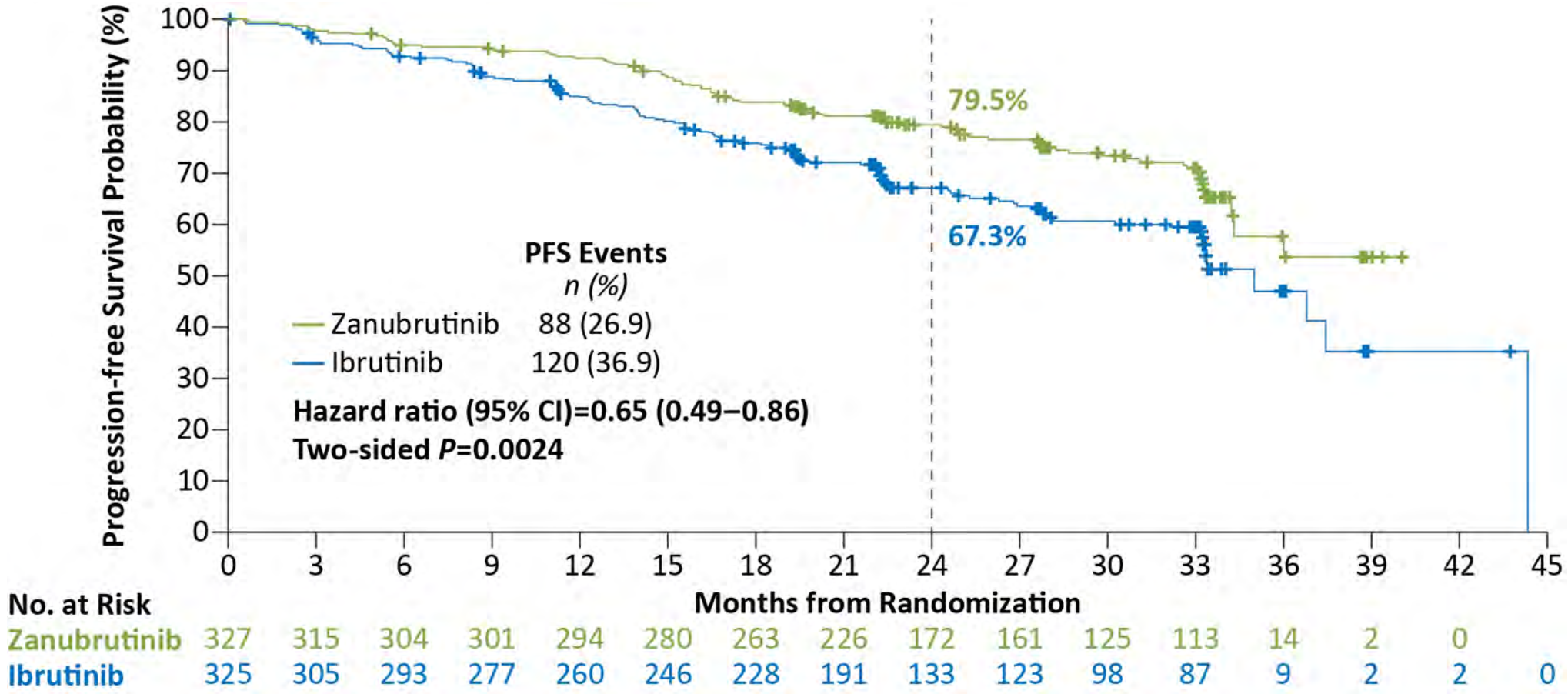
At a median follow-up of 40.9 months, acalabrutinib was noninferior to ibrutinib with a median IRC-assessed PFS of 38.4 months in both arms (95% CI acalabrutinib, 33.0 to 38.6 and ibrutinib, 33.0 to 41.6; hazard ratio: 1.00; 95% CI, 0.79 to 1.27).‡[1]

Adapted from Byrd JC, et al. J Clin Oncol. 2021.

1. Defined as time from random assignment until disease progression or death from any cause.1
2. †At the data cut-off for the final analysis, 124 (46.3%) acalabrutinib patients and 109 (41.1%) ibrutinib patients remained on treatment.1
3. ‡Three patients in the ibrutinib arm were censored because of PD or death immediately after missing ≥2 consecutive visits, and 7 patients in the acalabrutinib arm and 8 patients in the ibrutinib arm were censored at random assignment because of no baseline assessment and/or no adequate postbaseline assessment.1
4. CI = Confidence interval; HR = Hazard ratio; IRC = Independent review committee; PD = Progressive disease; PFS = Progression free survival.
5. 1. Byrd JC, et al. J Clin Oncol. 2021;39(31):3441-3452.

Zanubrutinib PFS by IRC Significantly Superior to Ibrutinib

Median study follow-up of 29.6 months



Data cutoff: 8 Aug 2022

1. Brown *et al*, Abstract LBA-6, presented at ASH 2022

Which 2nd generation BTK inhibitor to choose? * *Speaker's own opinion and experience

Acalabrutinib ELEVATE RR

PROS

- Long follow up (median 40.9 months)
- UK Physician experience
- Lower d/c due to toxicity/non-PD vs ibrutinib
- Broader improved safety profile (cardiac (AF and HTN) and non-cardiac) e.g. GI toxicity, musculoskeletal

CONS

- Headache
- No PFS advantage vs ibrutinib

Zanubrutinib ALPINE

PROS

- Improved PFS vs ibrutinib including TP53 mut/17p deleted CLL
- Lower d/c due to toxicity/non-PD vs ibrutinib
- Improved cardiac safety profile (AF and sudden cardiac death)

These studies contained different patient populations and study design; hence direct comparisons cannot be made.

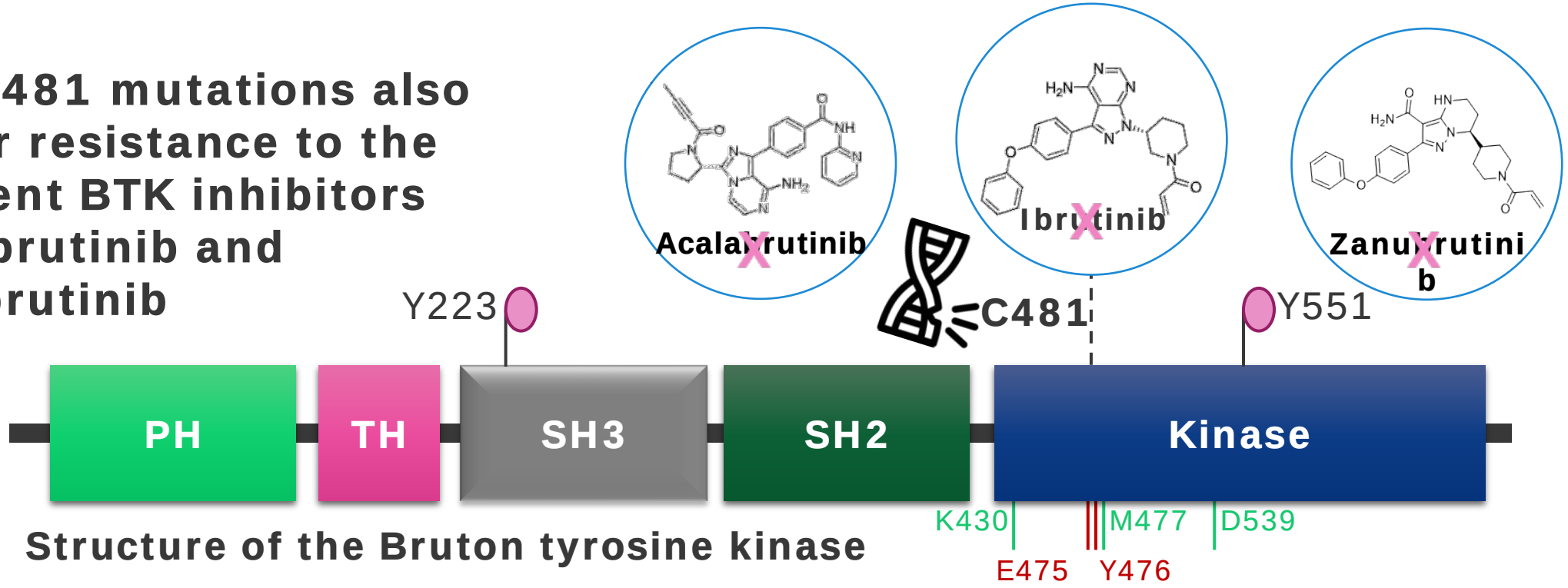
Further considerations*
*Speaker's own opinion

Acalabrutinib ELEVATE RR	Zanubrutinib ALPINE
▪ Higher risk cohort ▪ 11q and 17p deletion only ▪ Median 2 prior lines ▪ Earlier era of recruitment	• Lower risk cohort (23% TP53/17p del) • Median 1 prior lines • Era when acalabrutinib available subsequently

These studies contained different patient populations and study design; hence direct comparisons cannot be made.

Acquired Resistance to Covalent BTK Inhibitors Is Generally Driven by Mutations in BTK at the C481 Site

BTK C481 mutations also confer resistance to the covalent BTK inhibitors acalabrutinib and zanubrutinib



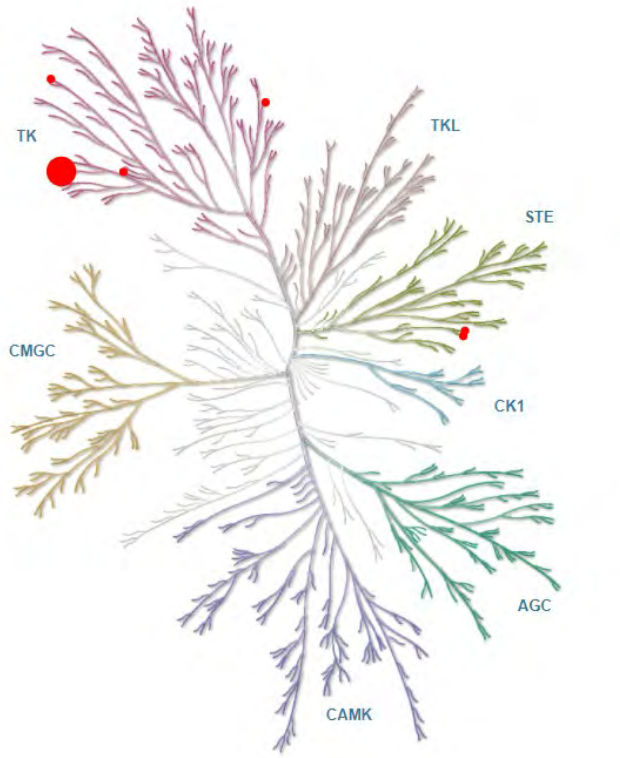
Structure of the Bruton tyrosine kinase

In summary, *BTK* resistance contributes to disease progression and diminishes the efficacy of <u>all covalent BTK inhibitors</u>

BRUIN Trial: Pirtobrutinib is a Highly Potent and Selective Non-Covalent (Reversible) BTK Inhibitor

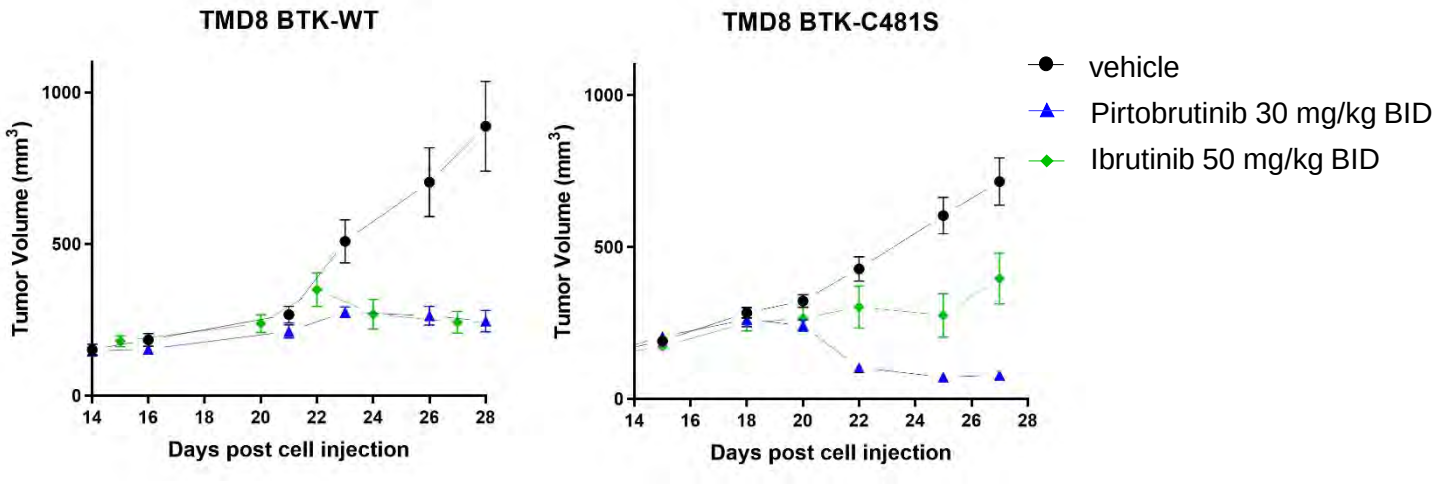
Kinome selectivity[1]

Highly selective for BTK



Xenograft models

In vivo activity similarly efficacious as ibrutinib in WT; superior in C481S



- Nanomolar potency against WT & C481-mutant BTK in cell and enzyme assays[2]
- >300-fold selectivity for BTK vs 370 other kinases[2]
- Due to reversible binding mode, BTK inhibition not impacted by intrinsic rate of BTK turnover[2]
- Favorable pharmacologic properties allow sustained BTK inhibition throughout dosing interval[2]

BID, twice-daily; BTK, Bruton tyrosine kinase. [1]Mato et al, *Lancet*, 2021:397:892-901. [2]Brandhuber BJ, et al. *Clin. Lymphoma Myeloma Leuk*. 2018.18:S216.
Illustration reproduced courtesy of Cell Signaling Technology, Inc. (www.cellsignal.com).

CLL / SLL Patient Characteristics

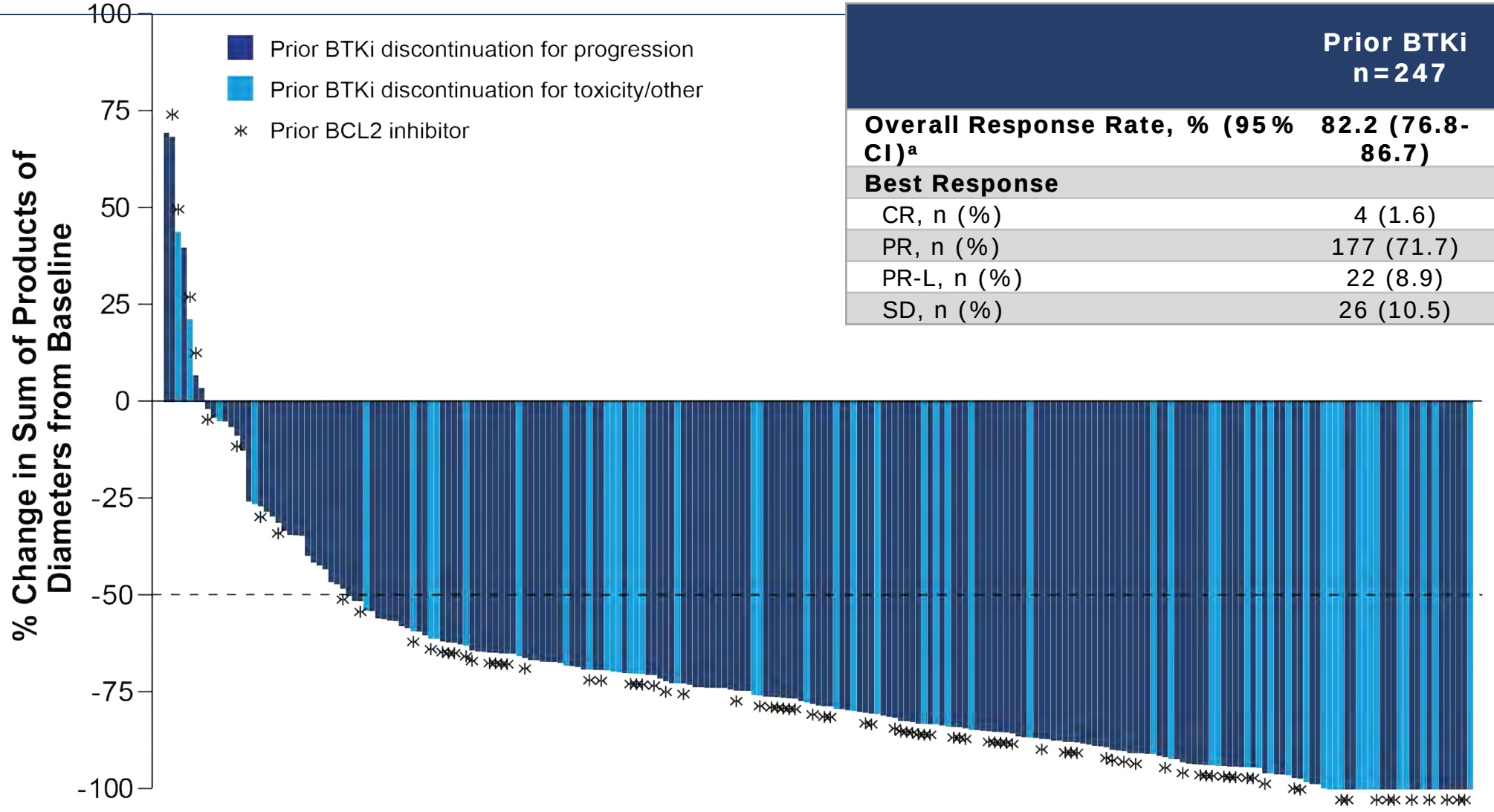
Characteristics	n=247
Median age, years (range)	69 (36-88)
Male, n (%)	168 (68)
Histology	
CLL	246 (>99)
SLL	1 (<1)
Rai staging[a]	
0-II	131 (53)
III-IV	102 (41)
Bulky Disease ≥5 cm, n (%)	78 (32)
ECOG PS, n (%)	
0	133 (54)
1	97 (39)
2	17 (7)
Median number of prior lines of systemic therapy, n (range)	3 (1-11)
Prior therapy, n (%)	
BTK inhibitor	247 (100)
Anti-CD20 antibody	217 (88)
Chemotherapy	195 (79)
BCL2 inhibitor	100 (41)
PI3K inhibitor	45 (18)
CAR-T	14 (6)
Allogeneic stem cell transplant	6 (2)
Median time from diagnosis to first dose, years (IQR)	11 (8-15)

Baseline Molecular Characteristics[b]	
Mutation status, n/n available (%)	
BTK C481-mutant	84/222 (38)
BTK C481-wildtype	138/222 (62)
PLCG2-mutant	18/222 (8)
PLCG2-wildtype	204/222 (92)
High Risk Molecular Features, n/n available (%)	
17p deletion	51/176 (29)
TP53 mutation	87/222 (39)
17p deletion and/or *TP53* mutation	90/193 (47)
Both 17p deletion and *TP53* mutation	48/170 (28)
IGHV unmutated	168/198 (85)
Complex Karyotype	24/57 (42)
11q deletion	44/176 (25)

Reason for prior BTKi discontinuation[c], n (%)	
Progressive disease	190 (77)
Toxicity/Other	57 (23)

ECOG PS, Eastern Cooperative Oncology Group Performance Score; Data cutoff date of 29 July 2022. [a]14 patients had missing data for Rai staging data. [b]Molecular characteristics were determined centrally and are presented based on data availability, in those patients with sufficient sample to pass assay quality control. [c]In the event more than one reason was noted for discontinuation, disease progression took priority.

Pirtobrutinib Efficacy in CLL/SLL Patients who Received Prior BTKi Treatment

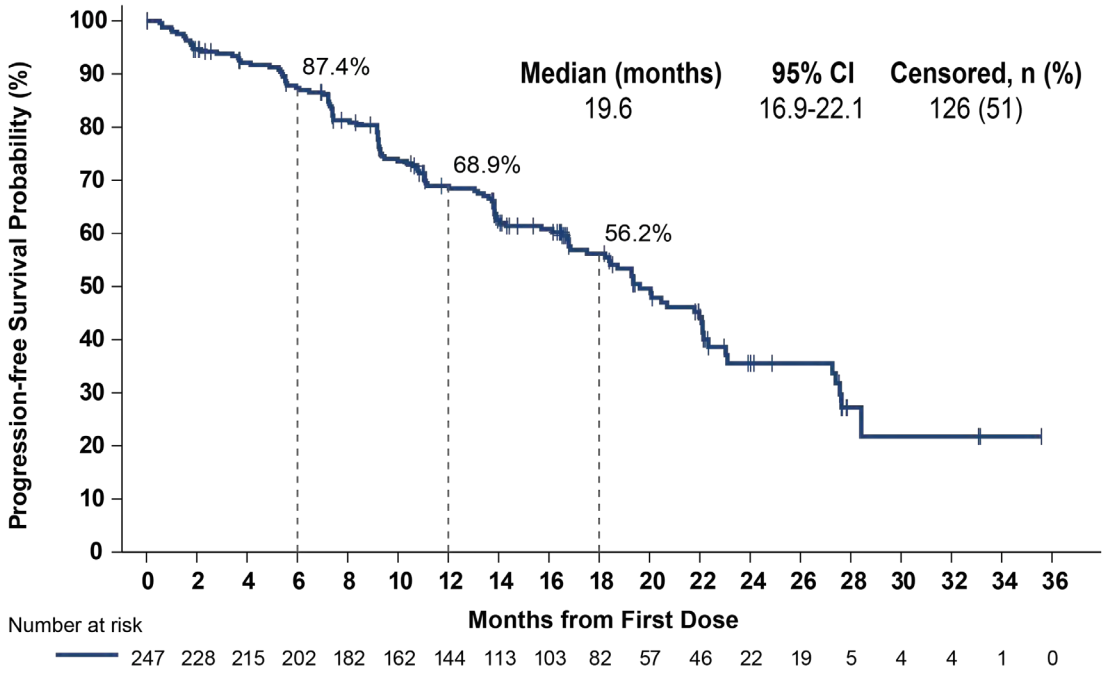


	Prior BTKi n=247	Prior BTKi+BCL2i n=100
Overall Response Rate, % (95% CI)[a]	**82.2 (76.8-86.7)**	**79.0 (69.7-86.5)**
Best Response		
CR, n (%)	4 (1.6)	0 (0.0)
PR, n (%)	177 (71.7)	70 (70.0)
PR-L, n (%)	22 (8.9)	9 (9.0)
SD, n (%)	26 (10.5)	11 (11.0)

Data cutoff date of 29 July 2022. Data for 24 patients are not shown in the waterfall plot due to no measurable target lesions identified by CT at baseline, discontinuation prior to first response assessment, or lack of adequate imaging in follow-up. [a]ORR includes patients with a best response of CR, PR, and PR-L. Response status per iwCLL 2018 according to independent review committee assessment.

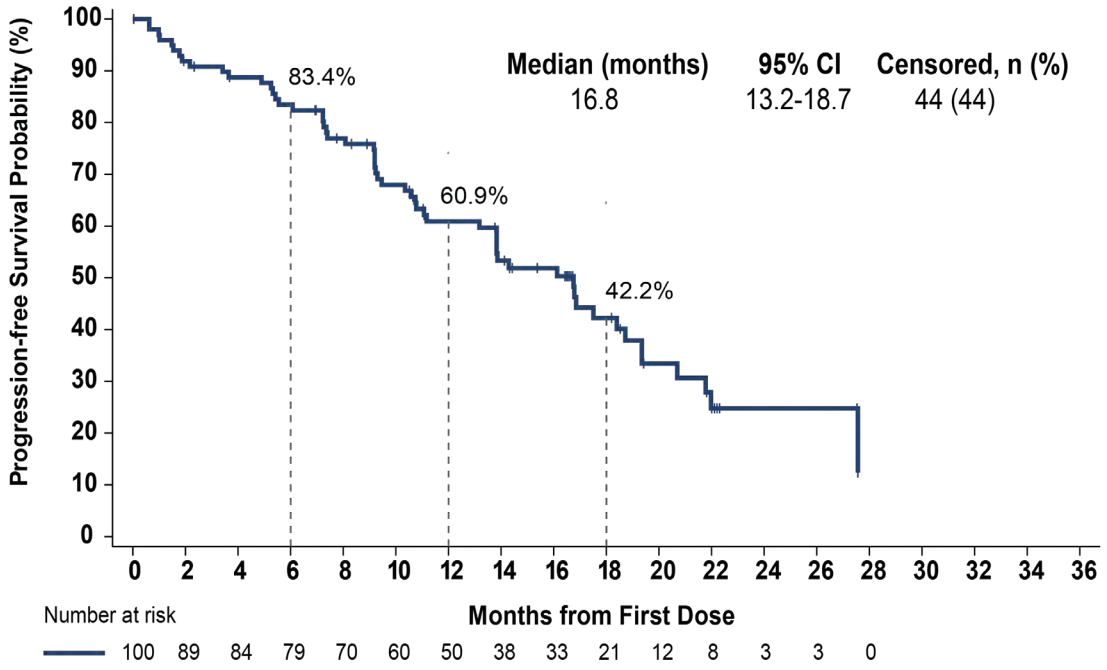
Progression-Free Survival in CLL/SLL Patients who Received Prior BTKi Treatment

All prior BTKi patients
Median prior lines = 3



- Median follow-up of 19.4 months for patients who received prior BTKi

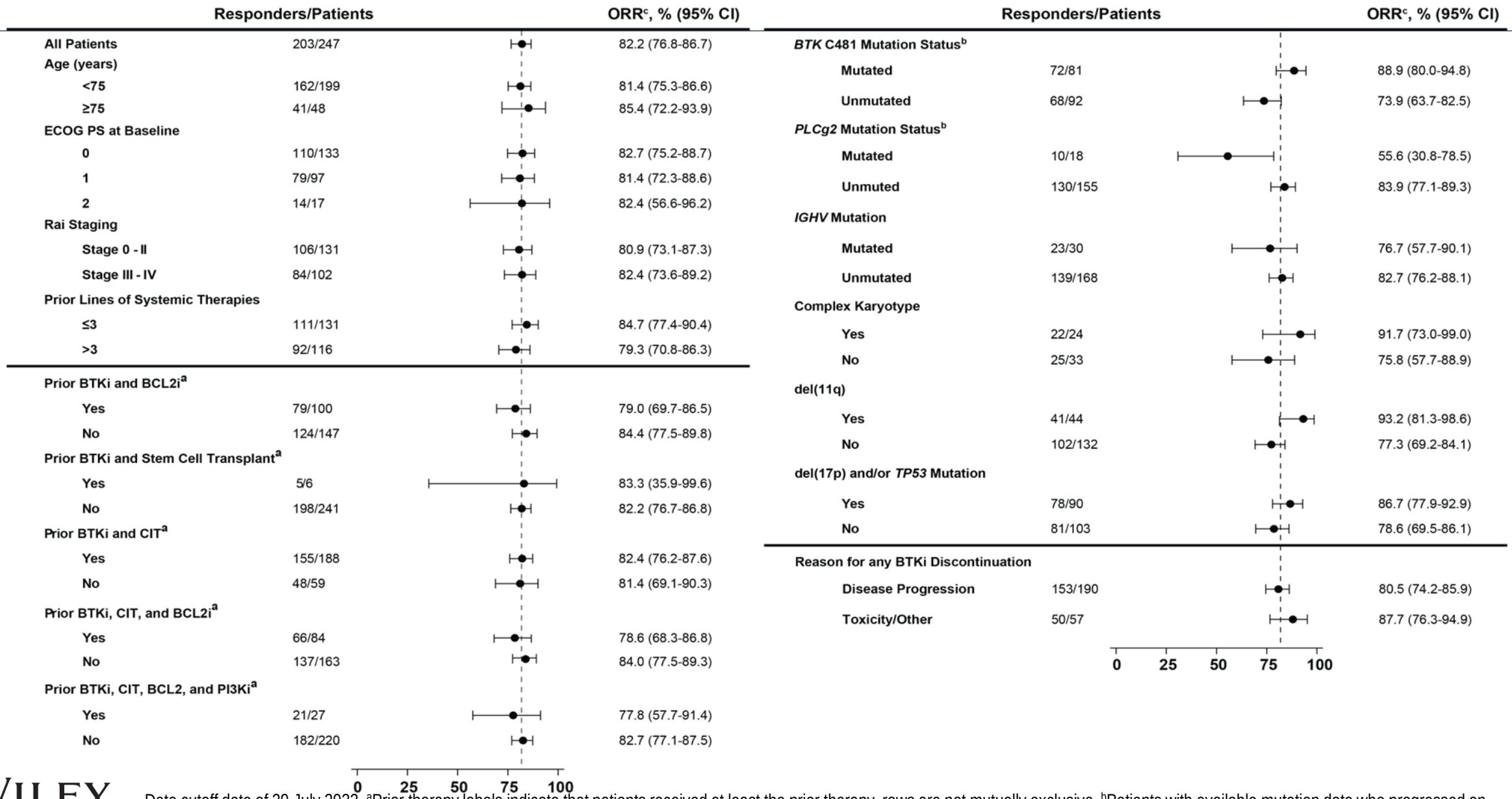
Prior BTKi and BCL2i patients
Median prior lines = 5



- Median follow-up of 18.2 months for patients who received prior BTKi and BCL2i

Data cutoff date of 29 July 2022. Response status per iwCLL 2018 according to independent review committee assessment.

Overall Response Rate in CLL/SLL Subgroups



Data cutoff date of 29 July 2022. [a]Prior therapy labels indicate that patients received at least the prior therapy, rows are not mutually exclusive. [b]Patients with available mutation data who progressed on any prior BTKi. [c]Response includes partial response with lymphocytosis. Response status per iwCLL 2018 according to independent review committee assessment.

Pirtobrutinib Safety Profile

	All Doses and Patients (N=773)			
	Treatment-Emergent AEs, (≥15%), %		Treatment-Related AEs, %	
Adverse Event (AEs)	Any Grade	Grade ≥ 3	Any Grade	Grade ≥ 3
Fatigue	28.7%	2.1%	9.3%	0.8%
Diarrhea	24.2%	0.9%	9.3%	0.4%
Neutropenia[a]	24.2%	20.4%	14.7%	11.5%
Contusion	19.4%	0.0%	12.8%	0.0%
Cough	17.5%	0.1%	2.3%	0.0%
Covid-19	16.7%	2.7%	1.3%	0.0%
Nausea	16.2%	0.1%	4.7%	0.1%
Dyspnea	15.5%	1.0%	3.0%	0.1%
Anemia	15.4%	8.8%	5.2%	2.1%
AEs of Special Interest[b]	Any Grade	Grade ≥ 3	Any Grade	Grade ≥ 3
Bruising[c]	23.7%	0.0%	15.1%	0.0%
Rash[d]	12.7%	0.5%	6.0%	0.4%
Arthralgia	14.4%	0.6%	3.5%	0.0%
Hemorrhage/Hematoma[e]	11.4%	1.8%	4.0%	0.6%
Hypertension	9.2%	2.3%	3.4%	0.6%
Atrial fibrillation/flutter[f,g]	2.8%	1.2%	0.8%	0.1%

Median time on treatment for the overall safety population was 9.6 months
Discontinuations due to treatment-related AEs occurred in 2.6% (n=20) of all patients
Dose reductions due to treatment-related AEs occurred in 4.5% (n=35) of all patients
Overall and CLL/SLL safety profiles are consistent[h]

Data cutoff date of 29 July 2022.. [a]Aggregate of neutropenia and neutrophil count decreased. [b]AEs of special interest are those that were previously associated with covalent BTK inhibitors. [c]Aggregate of contusion, petechiae, ecchymosis, and increased tendency to bruise. [d]Aggregate of all preferred terms including rash. [e]Aggregate of all preferred terms including hematoma or hemorrhage. [f]Aggregate of atrial fibrillation and atrial flutter. [g]Of the 22 total afib/aflutter TEAEs in the overall safety population, 7 occurred in patients with a prior medical history of atrial fibrillation. [h]CLL/SLL safety population data can be found via QR code.

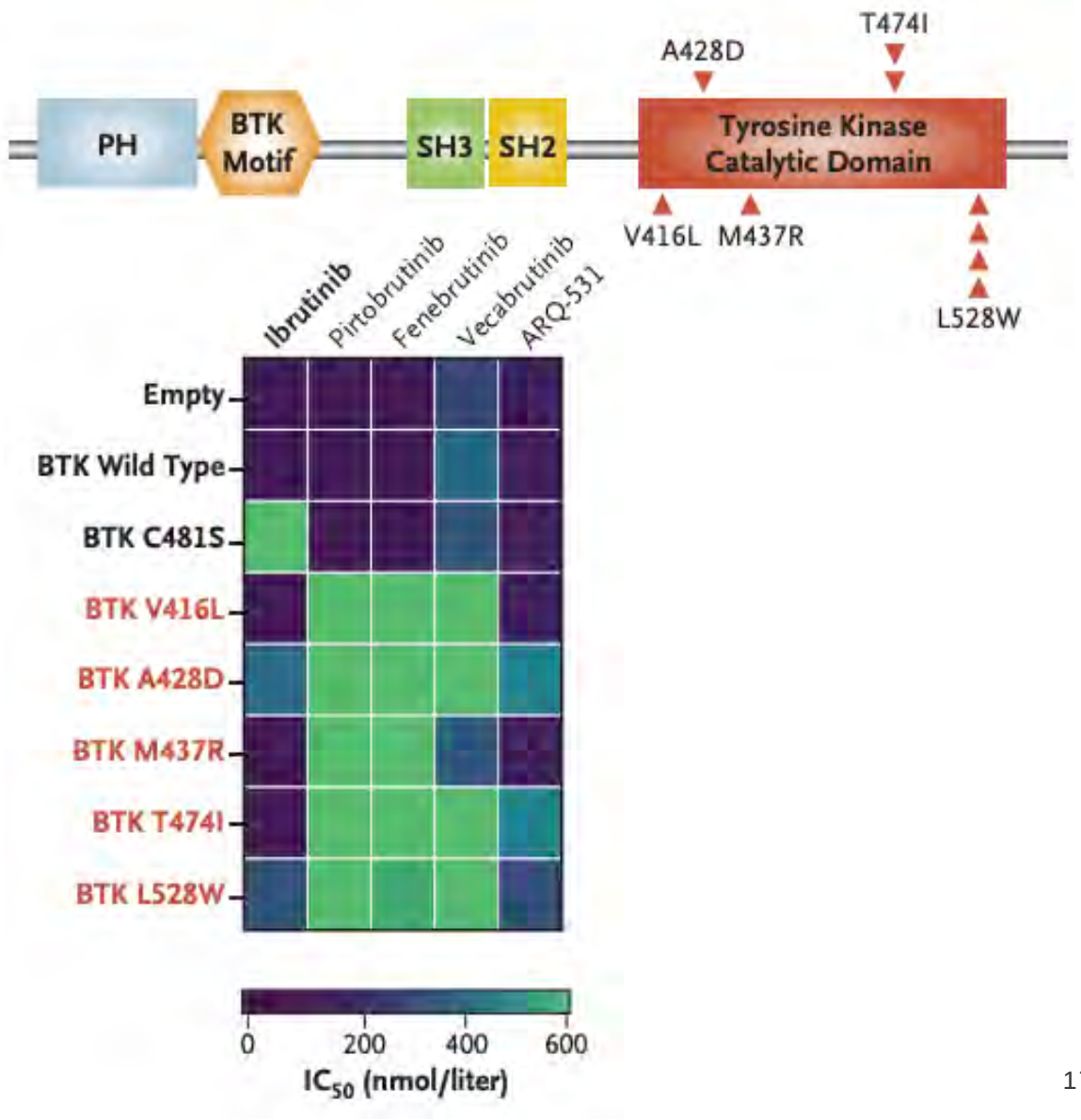
Certain Mutations Also Appear to Confer Resistance to Noncovalent BTK Inhibitors

Novel acquired mutations in BTK at the time of disease progression included:[1]

- BTK L528W
- BTK V416L
- BTK M437R
- BTK T474I
- BTK A428D

These mutations cluster around the tyrosine kinase catalytic domain of BTK.

Additionally, several patients with progressive disease had pre-existing PLCG2 mutations.



1. Wang *et al. N Engl J Med* 2022

Genomic Evolution and Resistance to Pirtobrutinib in Covalent BTK-Inhibitor (cBTKi) Pre-treated Chronic Lymphocytic Leukemia (CLL) Patients: Results from the Phase I/II BRUIN Study

Jennifer R. Brown, MD, PhD[1], Sai Prasad Desikan MD[2], Bastien Nguyen, PhD[3], Helen Won, PhD[3], Shady I. Tantawy, MD[2], Samuel C. McNeely, PhD[3], Narasimha Marella, PhD[3], Kevin Ebata, PhD[3], Jennifer A. Woyach, MD[4], Krish Patel, MD[5], Constantine S. Tam, MD[6], Toby A. Eyre, MBChB, MD[7], Chan Y. Cheah, MD[8, 9], Nirav N. Shah, MD[10], Paolo Ghia, MD, PhD[11], Wojciech Jurczak, MD, PhD[12], Minna Balbas, PhD[3], Binoj Nair, PhD[3], Paolo Abada, MD, PhD[3], Chunxiao Wang, PhD[13], Denise Wang, PhD[3], Anthony R. Mato, MD, MSCE[14], Varsha Gandhi, PhD[2] , William G. Wierda, MD, PhD[2]

[1]Dana-Farber Cancer Institute and Harvard Medical School, Boston, MA, USA; [2]University of Texas MD Anderson Cancer Center. Houston, TX, USA; [3]Loxo@Lilly, Indianapolis, IN, USA; [4]The Ohio State University Comprehensive Cancer Center, Columbus, OH, USA; [5]Swedish Cancer Institute, Seattle, WA, USA; [6]Alfred Health and Monash University, Melbourne, Victoria, AUS; [7]Oxford University Hospitals NHS Foundation Trust, Oxford, UK; [8]Linear Clinical Research, Perth, AUS; [9]Sir Charles Gairdner Hospital, Perth, AUS; [10]Medical College of Wisconsin, Milwaukee, WI, USA; [11]Università Vita-Salute San Raffaele and IRCCS Ospedale San Raffaele, Milan, ITA; [12]Maria Sklodowska-Curie National Research Institute of Oncology, Krakow, POL; [13]Eli Lilly and Company, Indianapolis, IN, USA[14]Memorial Sloan Kettering Cancer Center, New York, NY, USA

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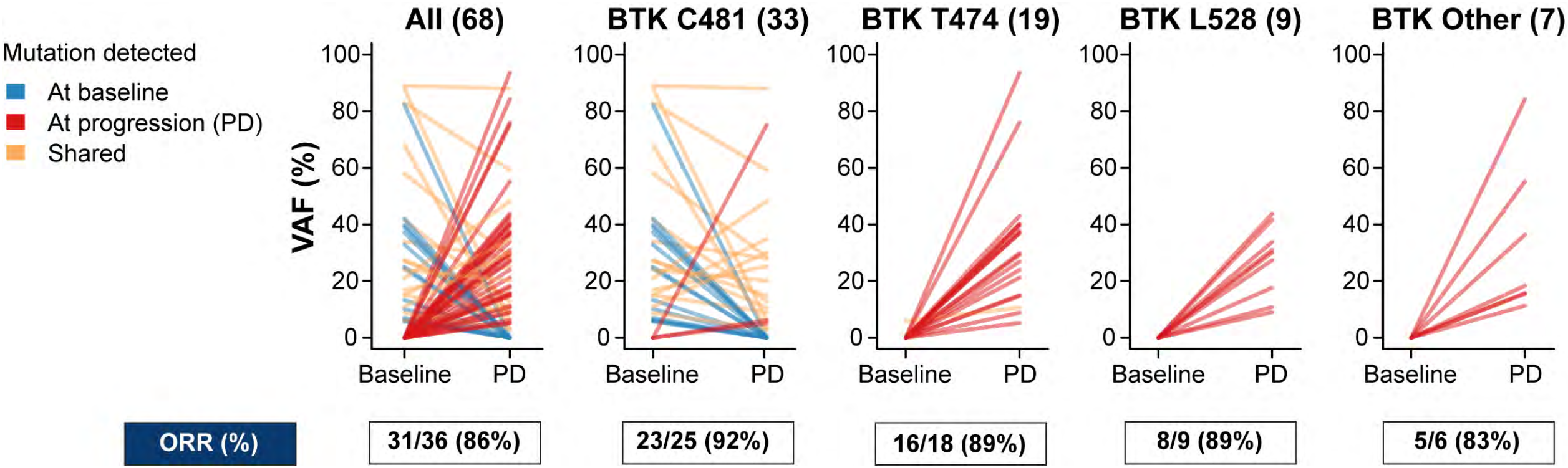
Majority of BTK Acquired Mutations were BTK T474, L528



- **Decrease/clearance of C481 clones observed at progression on pirtobrutinib in 92% (22/24) patients[a]**
- ***BTK* C481R/S/Y, T474, L528, other kinase mutations arose at/near progression (n=27 patients[b])**
- **ORR were similar across groups regardless of the acquired BTK mutation**

[a]Number of mutations is higher than number of patients because patients had multiple BTK mutations. [b]9 patients acquired multiple *BTK* mutations. VAF, variant allele frequency; VUS, variants of unknown significance; PD, at progressive disease.

Preliminary Efficacy and Safety of MK-1026, a Non-Covalent Inhibitor of Wild-type and C481S Mutated Bruton Tyrosine Kinase, in B-cell Malignancies: A Phase 2 Dose Expansion Study

- **Jennifer Woyach,[1] Ian W. Flinn,[2] Farrukh Awan,[3] Herbert Eradat,[4] Danielle M. Brander,[5] Michael Tees,[6] Sameer A. Parikh,[7] Tycel Phillips,[8] Wayne Wang,[9] Nishitha M. Reddy,[10] Mohammed Z.H Farooqui,[10] John C. Byrd,[11] Deborah M. Stephens[12]**

- [1]Division of Hematology, The Ohio State University, Columbus, OH, USA; [2]Sarah Cannon Center Research Institute, Nashville, TN, USA; [3]Department of Internal Medicine, University of Texas Southwestern Medical Center, Dallas, TX, USA; [4]Department of Hematology-Oncology, David Geffen School of Medicine at UCLA, Los Angeles, CA, USA; [5]Duke Cancer Institute, Duke University Medical Center, Durham, NC, USA; [6]Colorado Blood Cancer Institute, Denver, CO; [7]Division of Hematology, Mayo Clinic, Rochester, MN, USA; [8]Division of Hematology and Oncology, University of Michigan Rogel Cancer Center, Ann Arbor, MI, USA; [9]Veristat, LLC, Southborough, MA, USA; [10]Merck & Co., Inc., Kenilworth, NJ, USA; [11]Department of Internal Medicine, University of Cincinnati College of Medicine, Cincinnati, OH, USA; [12]Division of Hematology and Hematologic Malignancies, University of Utah Huntsman Cancer Institute, Salt Lake City, Utah, USA

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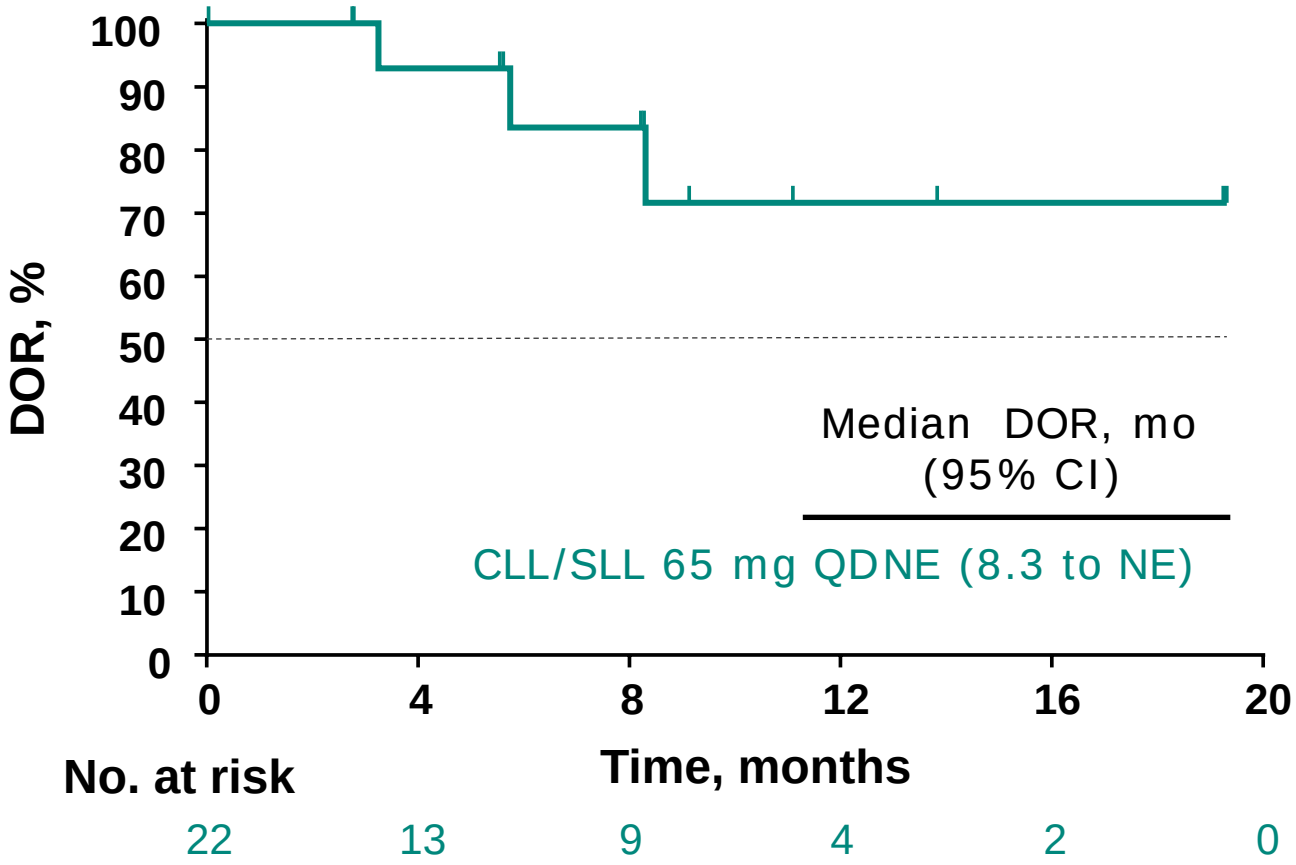
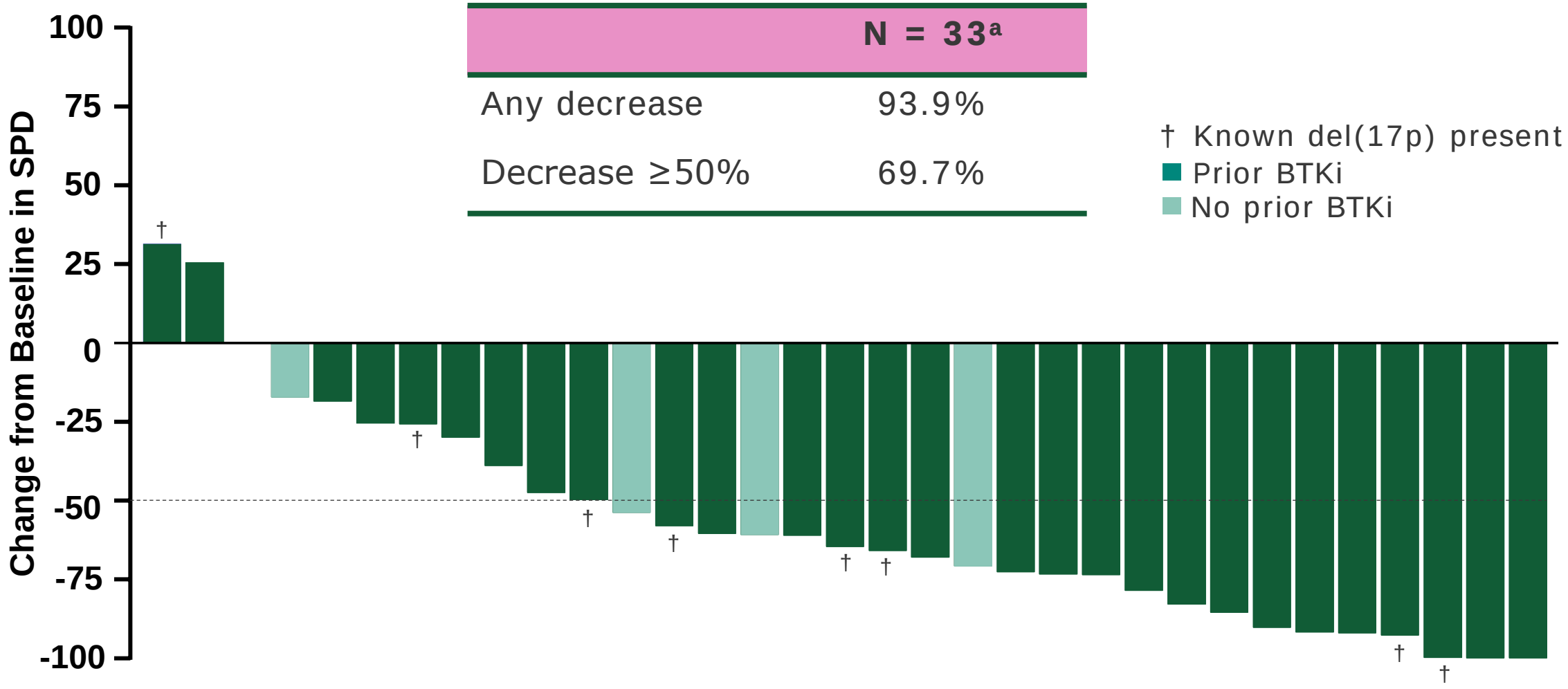
Summary of Response (CLL/SLL), Efficacy Evaluable Population

n (%) [95% CI]	CLL/SLL 65 mg QD N = 38[a]
ORR	**22 (57.9%) [40.8-73.6]**
CR	1 (2.6%) [0.0-13.8]
PR	12 (31.6%) [17.5-48.6]
PR-L	9 (23.7%) [11.4-40.2]
SD	15 (39.5%) [24.0-5.6]



- [a]Efficacy evaluable patients with CLL/SLL who received at least one cycle of MK-1026 at preliminary RP2D of 65 mg QD and had ≥1 post-baseline assessment; Response assessed per iwCLL criteria Data cut-off: April 7, 2021.

Percent Change From Baseline in SPD (CLL/SLL), Efficacy Evaluable Population



- [a]33 of 38 patients with ≥1 assessment post-baseline were evaluable for change from baseline in sum of product of diameters (SPD); Data cut-off: April 7, 2021.

Treatment-Emergent AEs

Events, n (%)		All Patients N = 118
All TEAEs		114 (96.6)
Grade ≥3 TEAEs[a]		80 (68.0)
MK-1026-related TEAE		78 (66.1)
Grade ≥3 related TEAEs[b]		31 (26.3)
Related TEAEs leading to discontinuation		9 (7.6)
TEAEs ≥20%	**All**	**Grade ≥3**
Fatigue	33.1%	3.4%
Constipation	31.4%	0.8%
Dysgeusia	28.0%	0
Cough	24.6%	0
Nausea	24.6%	0.8%
Pyrexia	24.6%	0
Dizziness	22.9%	0
Hypertension	22.9%	9.3%
Peripheral edema	22.0%	0
Diarrhea	21.2%	0.8%
Arthralgia	20.3%	0

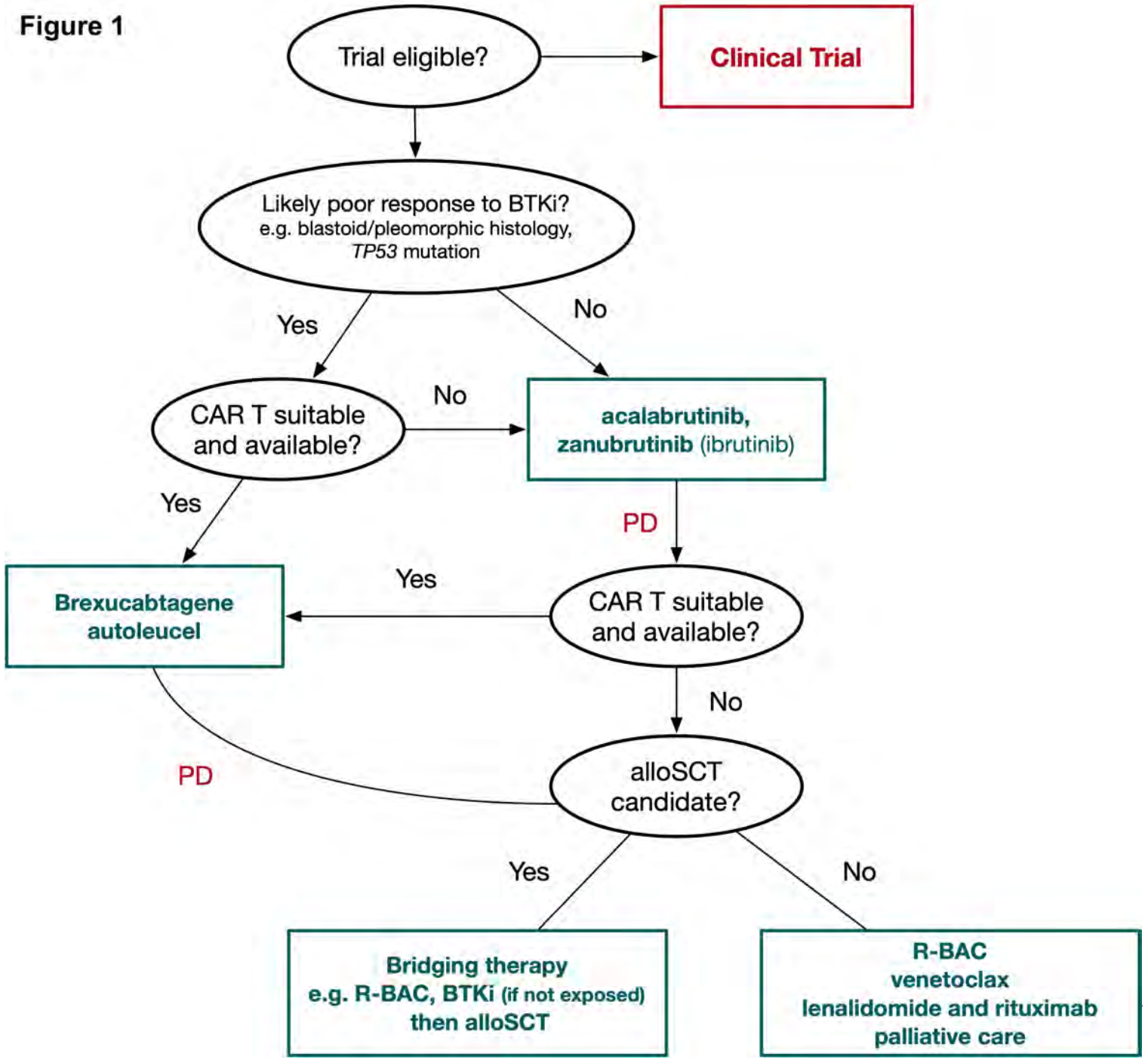
- Data cut-off: April 7, 2021; [a]8 patients had grade 5 TEAEs including death after PD (n=3), sepsis (n=1), dyspnea (n=1), and respiratory failure (n=2); [b]No grade 5 drug-related TEAEs were reported.

BTK Inhibitor Regulatory Status in MCL

		MCL	
		European Union	United States
Covalent	Ibrutinib[1]	Approved (2L)	Indication withdrawn
Covalent	Acalabrutinib[2]	Phase 3	Approved (2L)
Covalent	Zanubrutinib[3]	Phase 3	Approved (2L)
Noncovalent	Pirtobrutinib[4]	Under regulatory review (EMA has recommended conditional approval)	Approved (after ≥2 lines of systemic therapy, including a BTK inhibitor)
Noncovalent	Pirtobrutinib[4]	Phase 3	
Noncovalent	Nemtabrutinib[5]	Phase 2	

1. Imbruvica (ibrutinib) Prescribing Information. https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/210563s000lbl.pdf.
2. Calquence (acalabrutinib) Prescribing Information. https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/210259s006s007lbl.pdf.
3. Brukinsa (zanubrutinib) Prescribing Information. https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/213217s000lbl.pdf.
4. https://clinicaltrials.gov/ct2/show/NCT04662255. 5. https://clinicaltrials.gov/ct2/show/NCT04728893.

R/R MCL: treatment algorithm



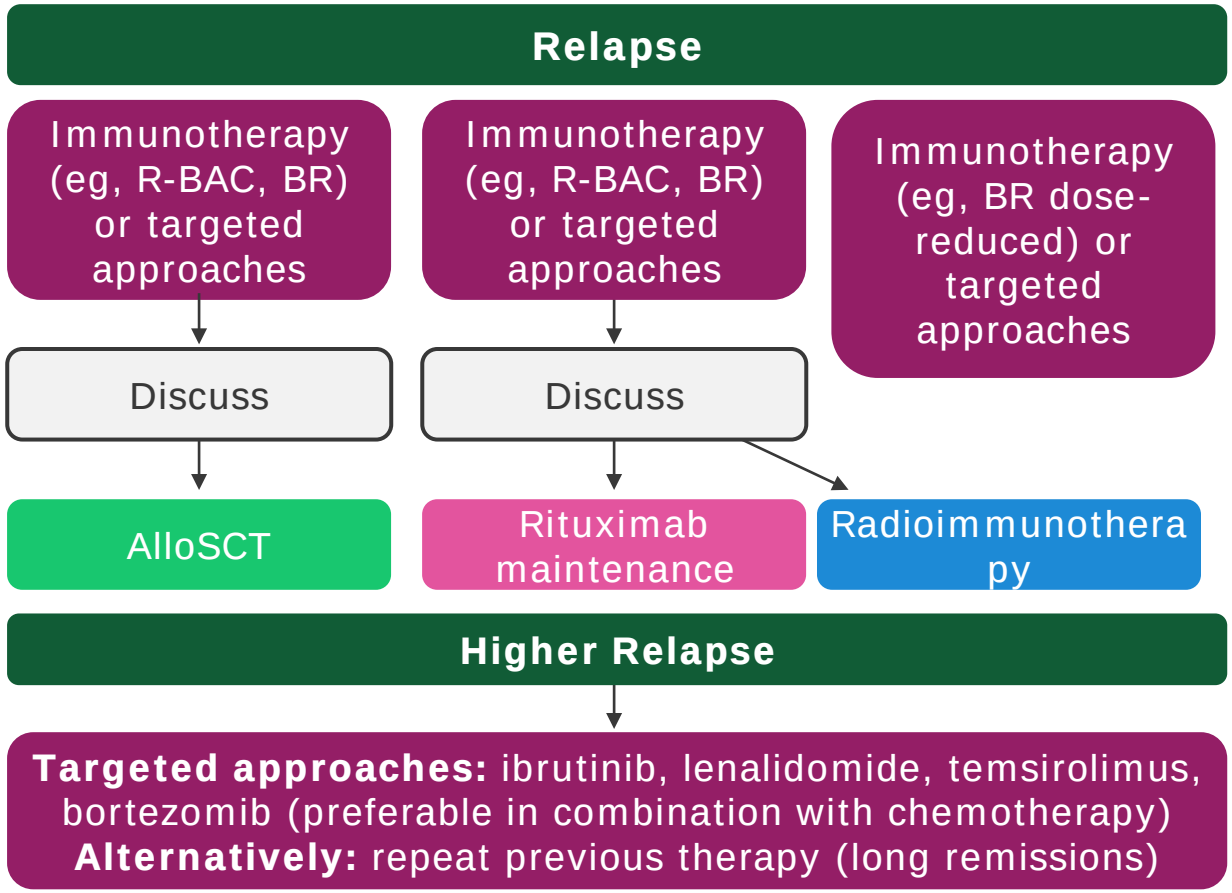
Eyre, *et al* Blood. 2021

… In the MCL Setting, BTKi Are Part of Standard 2L Treatment Options

NCCN Guidelines Include Covalent BTKi as Preferred 2L Options in R/R MCL (2022)[1]

2L and Subsequent Therapy	2L Consolidation	3L Therapy
• Preferred regimens *(alphabetical)* – BTKi ➢ Acalabrutinib ➢ Ibrutinib ± rituximab ➢ Zanubrutinib – Lenalidomide + rituximab	• Allogeneic hematopoietic cell transplant (nonmyeloablative or myeloablative)	• Brexucabtagene autoleucel (only given after CIT and BTKi)

ESMO Guidelines Included BTKi (eg, Ibrutinib) as Options in R/R MCL

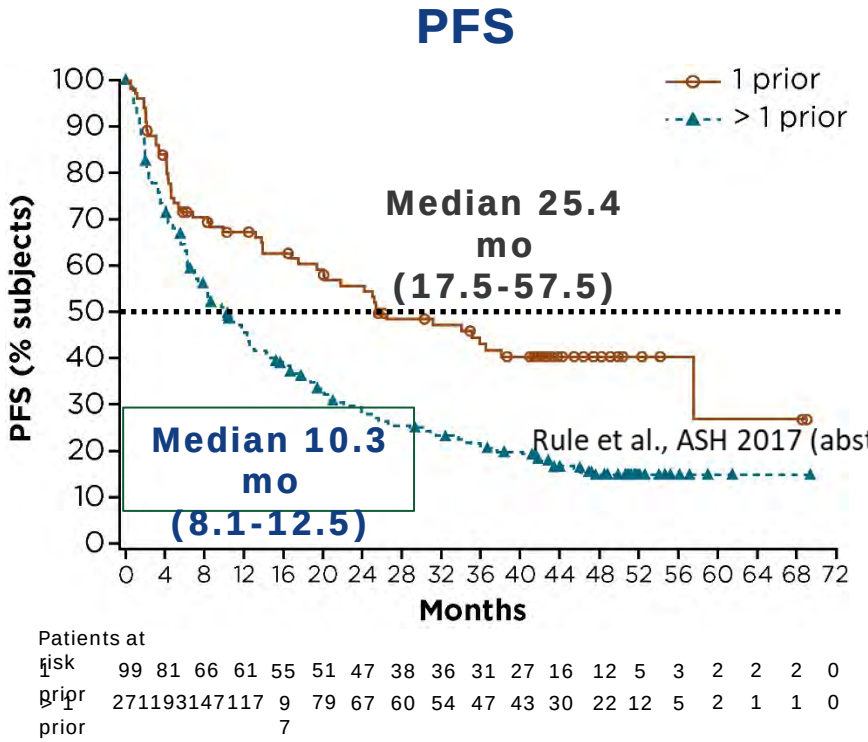


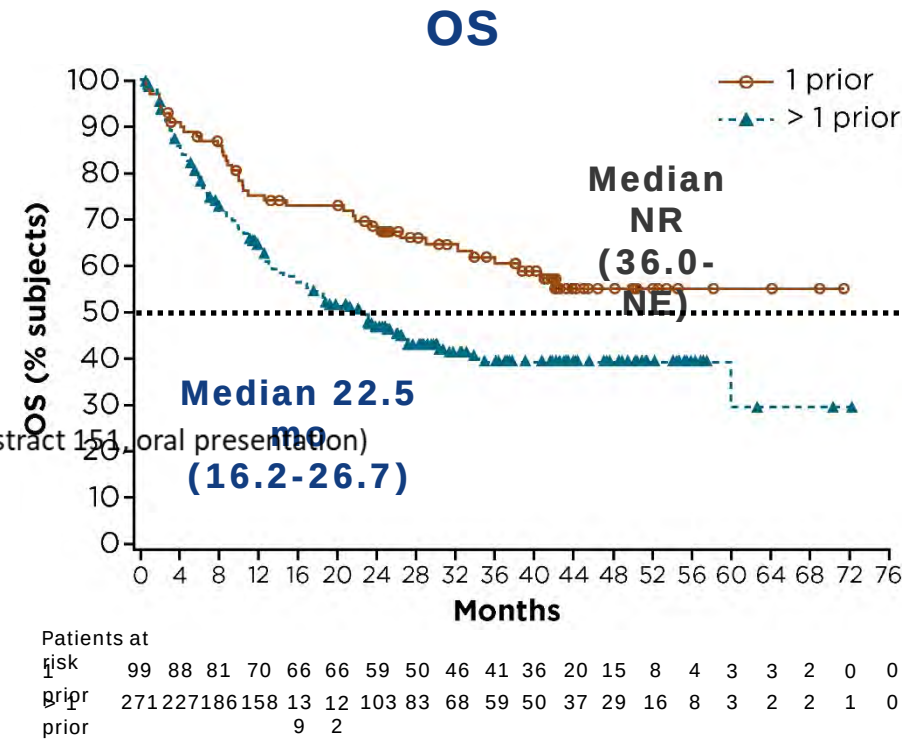
1. NCCN Clinical Practice Guidelines in Oncology. B-Cell Lymphomas. Version 3.2022. https://www.nccn.org/professionals/physician_gls/pdf/b-cell.pdf.
2. Dreyling M et al. *Ann Oncol*. 2017;28 (suppl 4):iv62–iv71.

Covalent BTKi monotherapy in R/R MCL

Ibrutinib	Wang et al, 2013	Phase II	111	-	68	3 (1-5)	49%	ORR 68% CR 21%	13.9 (7.0-NE)	Neutropenia 16% Thrombocytopenia 11%
Ibrutinib	Dreyling et al, 2015	Phase III	139	-	67	2 (1-9)	22%	ORR 72% CR 19%	14.6 (10.4-NE)	Neutropenia 13%
Ibrutinib	Rule et al, 2019	Pooled analysis	370	-	68	2 (1-9)	32%	ORR 70% CR 27%	12.5 (9.8-16.6)	Neutropenia 17% Thrombocytopenia 12.4% Pneumonia 12.7% Anemia 10.0%
Acalabrutinib	Wang et al, 2018, 2021	Phase II	124	-	68	2 (1-2)	17%	ORR 81% CR 40%	22 (16.6-33.3)	Neutropenia 12% Anaemia 12%
Zanubrutinib	Song et al 2020, 2021	Phase II	86	-	60.5	2 (1-4)	38.4%	ORR 83.7% CR 77.9%	33 (19.4-NE)	Neutropenia 18.6% Infection 18.6% Pneumonia 12.8%
Zanubrutinib	Tam et al, 2021	Phase I/II	32	-	70.5	1 (1-4)	31.3%	ORR 90.6% CR 31.3%	21.1 months (13.2 – NE)	Infections 18.8% Anemia 12.5%

Pooled analysis of MCL Ibrutinib Trials: PFS and OS by Prior Line of Therapy





Rule et al., ASH 2017 (abstract 151, oral presentation)

Median PFS overall (95% CI): 12.5 (9.8-16.6) months

Median OS overall (95% CI): 26.7 (22.5-38.4) months

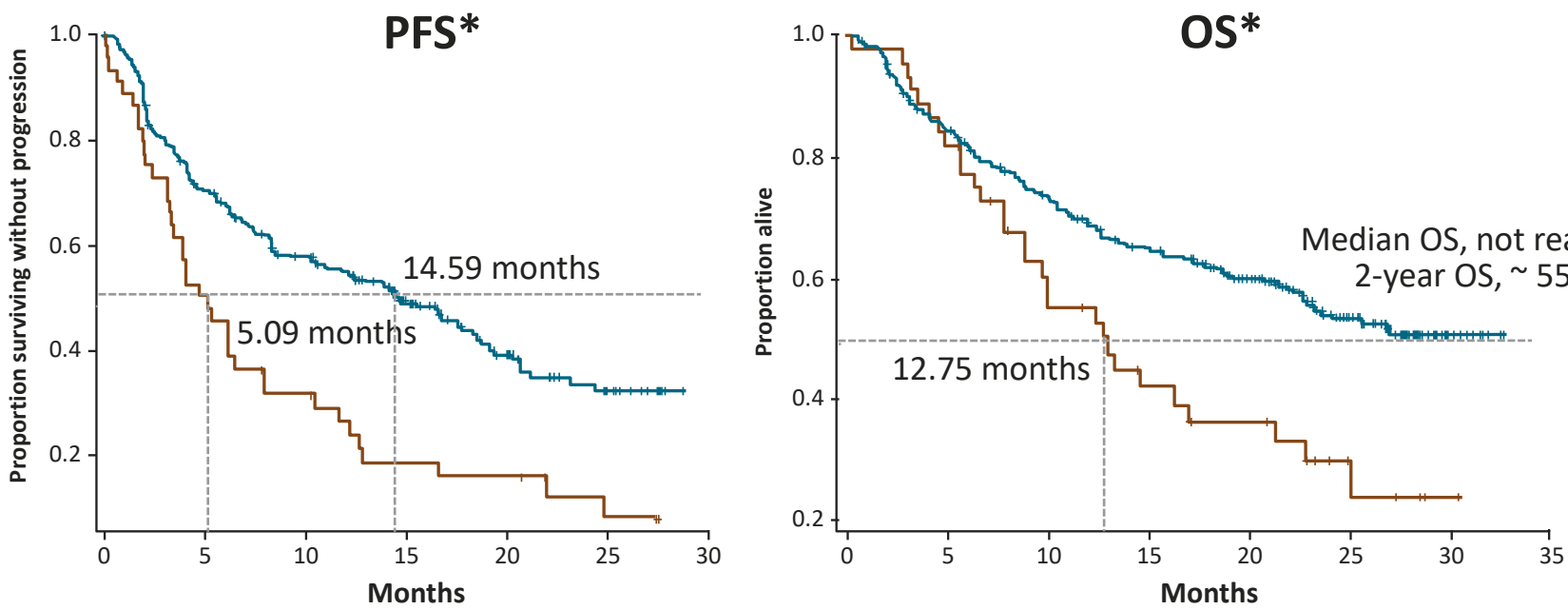
- **Median PFS was just over 2 years in patients with 1 prior line of therapy**

Patients censored from OS analysis upon study discontinuation.
CI, confidence interval; NE, not estimable.

Pooled analysis of MCL Ibrutinib Trials: Pooled MCL Analysis: PFS and OS by Blastoid Histology

20 (13.9%) mutated TP53

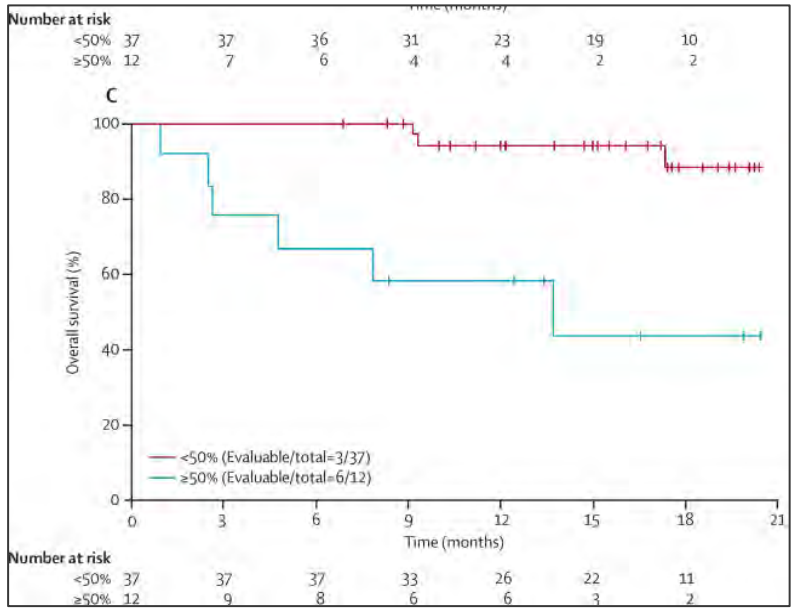
-ORR 55.0%
-median PFS was 4.0



+ Censored

Non-blastoid (n = 326) Blastoid (n = 44)

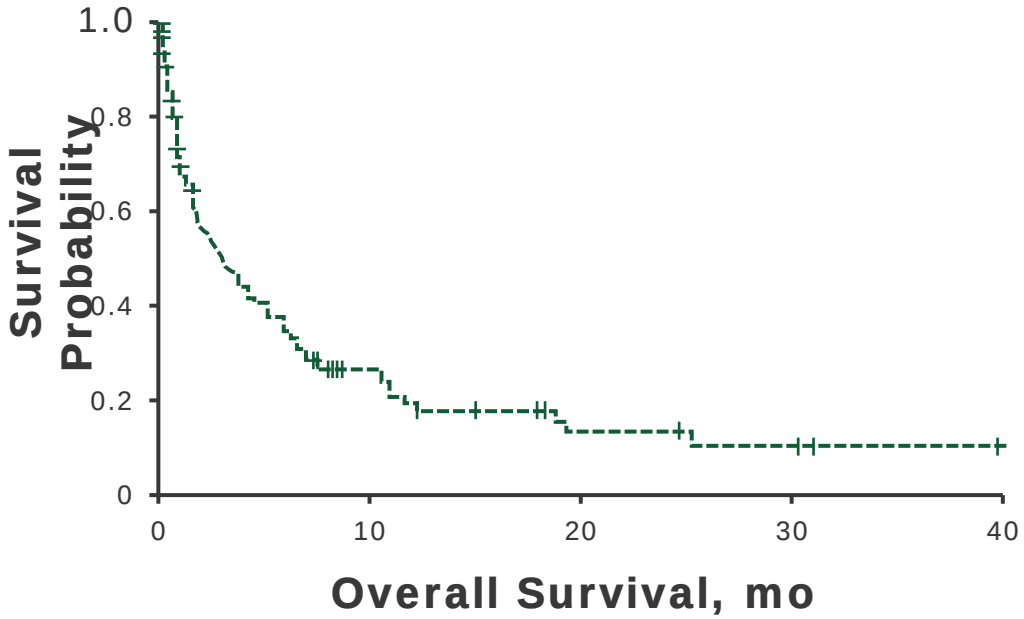
CI, confidence interval.
*Statistically significant



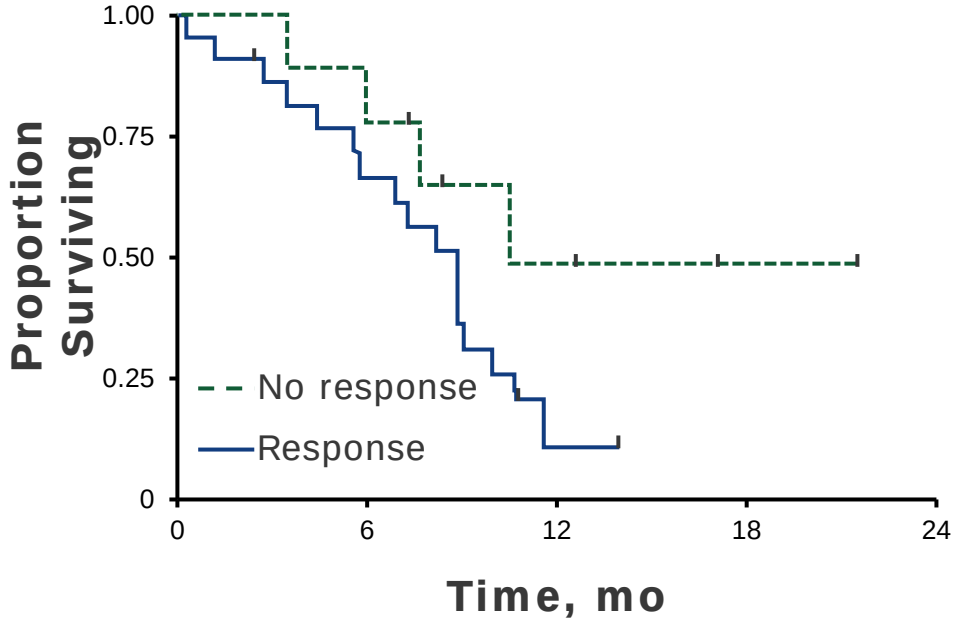
Rule *et al.*, ASH 2017 (abstract 151, oral presentation);
Wang *et al Lancet Oncol* 2016 17:48-56

Median OS Following Cessation of Covalent BTKi Therapy in MCL Is Poor, Supporting a Need for Better Options

- **Median OS of 2.9 months[1]**
- N = 141 global patients



- **Median OS of 8.4 months[2]**
- N = 31 US patients



Covalent BTK inhibitor resistance in MCL is incompletely understood, but poor clinical outcomes have been noted in the majority of patients with primary or secondary ibrutinib

1. Martin P et al. *Blood*. 2016;127:1559-1563. 2. Cheah CY et al. *Ann Oncol*. 2015;26:1175-1179.

Pirtobrutinib in R/R MCL: BRUIN Trial Patient Characteristics

Characteristics	Prior cBTKi (n=90)	cBTKi Naïve (n=14)
Median age, years (range)	70 (46-87)	67 (60-86)
Male, n (%)	72 (80)	10 (71)
Histology, n (%)		
Classic	70 (78)	11 (79)
Pleomorphic/Blastoid	20 (22)	3 (21)
ECOG PS, n (%)		
0	61 (68)	5 (36)
1	28 (31)	8 (57)
2	1 (1)	1 (7)
sMIPI Score, n (%)		
Low risk (0-3)	20 (22)	3 (21)
Intermediate risk (4-5)	50 (56)	5 (36)
High risk (6-11)	20 (22)	6 (43)
Tumor Bulk (cm), n (%)		
<5 / ≥5	66 (73) / 24 (27)	9 (64) / 5 (36)
<10 / ≥10	87 (97) / 3 (3)	12 (86) / 2 (14)
Bone Marrow Involvement, n (%)		
Yes	46 (51)	4 (29)
No	44 (49)	10 (71)

Characteristics	Prior cBTKi (n=90)	cBTKi Naïve (n=14)
Reason discontinued any prior cBTKi[a], n (%)		
Progressive disease	74 (82)	-
Toxicity/Other	16 (18)	-
Median number prior lines of systemic therapy (range)	3 (1-8)	2 (1-3)
Prior therapy, n (%)		
BTK inhibitor	90 (100)	0 (0)
Anti-CD20 antibody	86 (96)	14 (100)
Chemotherapy	79 (88)	14 (100)
Immunomodulator	19 (21)	1 (7)
Stem cell transplant	19 (21)	7 (50)
Autologous	17 (19)	7 (50)
Allogeneic	4 (4)	0 (0)
BCL2 inhibitor	14 (16)	0 (0)
CAR-T	4 (4)	0 (0)
PI3K inhibitor	3 (3)	1 (7)

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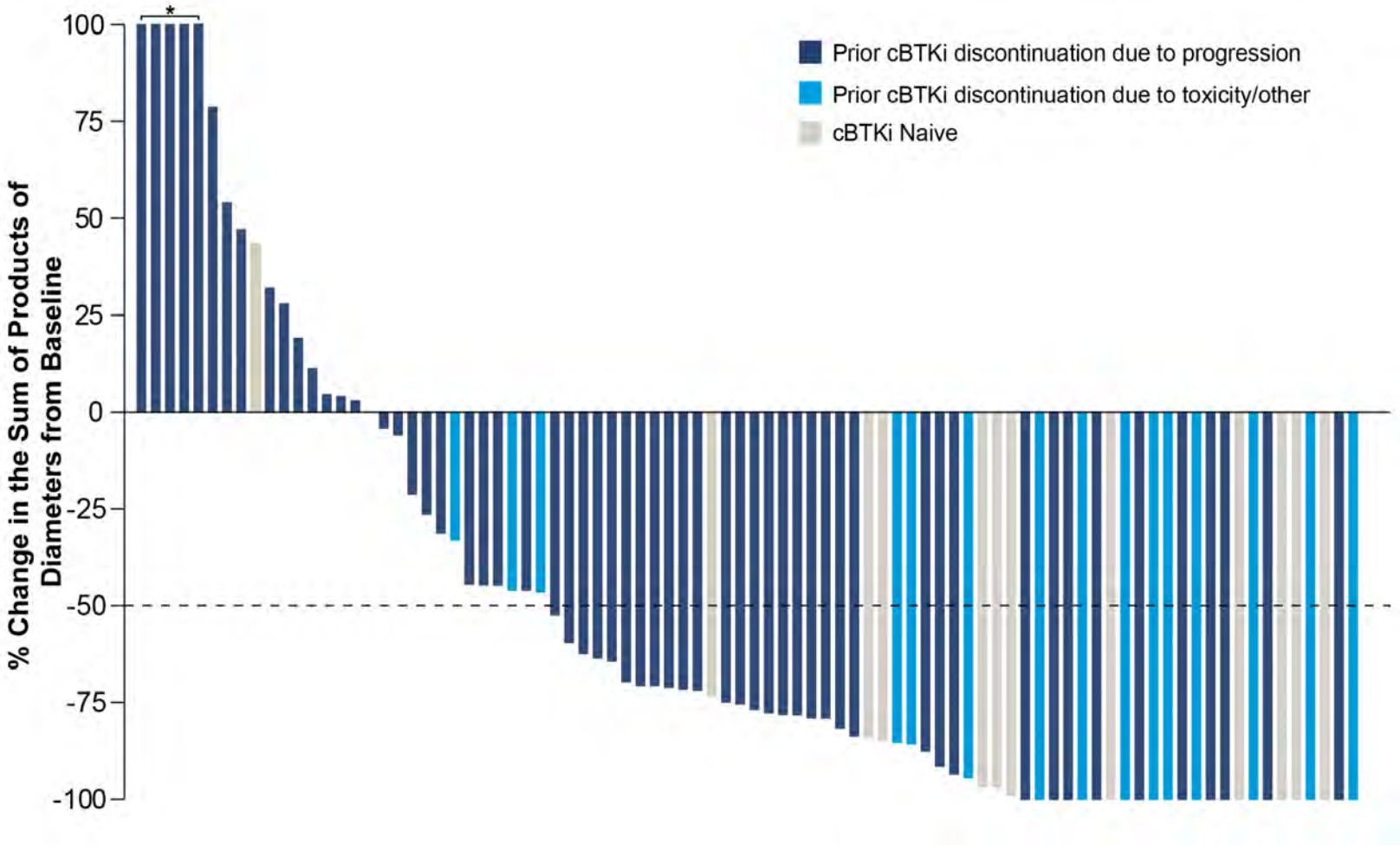
Data cutoff date of 31 January 2022. [a]Calculated as percent of patients who received prior cBTKi.

Pirtobrutinib Efficacy in Mantle Cell Lymphoma



Prior cBTKi MCL Patients	n=90
Overall Response Rate[a], % (95% CI)	**57.8% (46.9-68.1)**
Best Response[b]	
CR, n (%)	18 (20.0)
PR, n (%)	34 (37.8)
SD, n (%)	14 (15.6)
PD, n (%)	15 (16.7)

cBTKi Naïve MCL Patients	n=14
Overall Response Rate[a], % (95% CI)	**85.7% (57.2-98.2)**
Best Response[c]	
CR, n (%)	5 (35.7)
PR, n (%)	7 (50.0)
SD, n (%)	0 (0.0)
PD, n (%)	1 (7.1)

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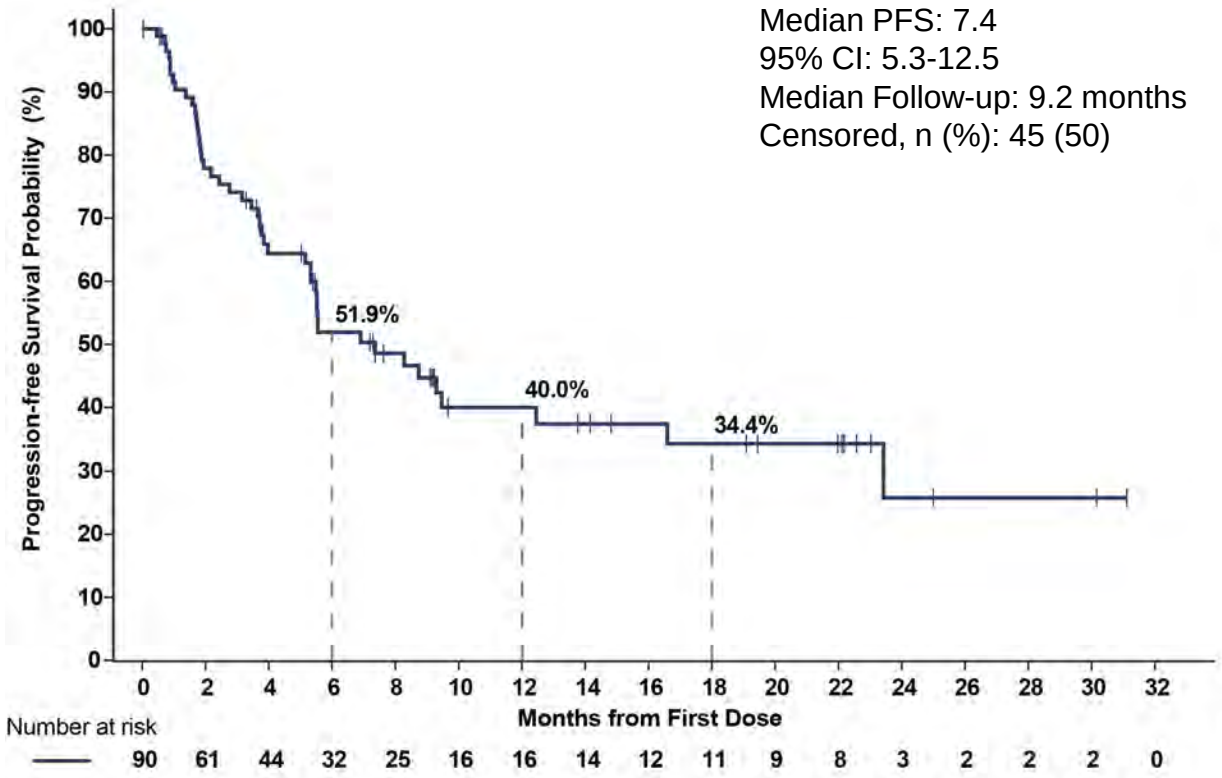
Data cutoff date of 31 January 2022. Data for 18 patients are not shown in the waterfall plot due to no measurable target lesions identified by CT at baseline, discontinuation prior to first response assessment, or lack of adequate imaging in follow-up. *Indicates patients with >100% increase in SPD. [a]ORR includes patients with a best response of CR and PR. [b]9 cBTKi pre-treated MCL patients were not evaluable. [c]1 cBTKi naïve patient was not evaluable. Response status per Lugano 2014 criteria based on IRC assessment.

Pirtobrutinib PFS and OS in Mantle Cell Lymphoma

Median DOR: 21.6 months 95% CI: 7.5-Not Estimable
Median Follow-up: 11.9 months Censored, n (%): 33 (64)

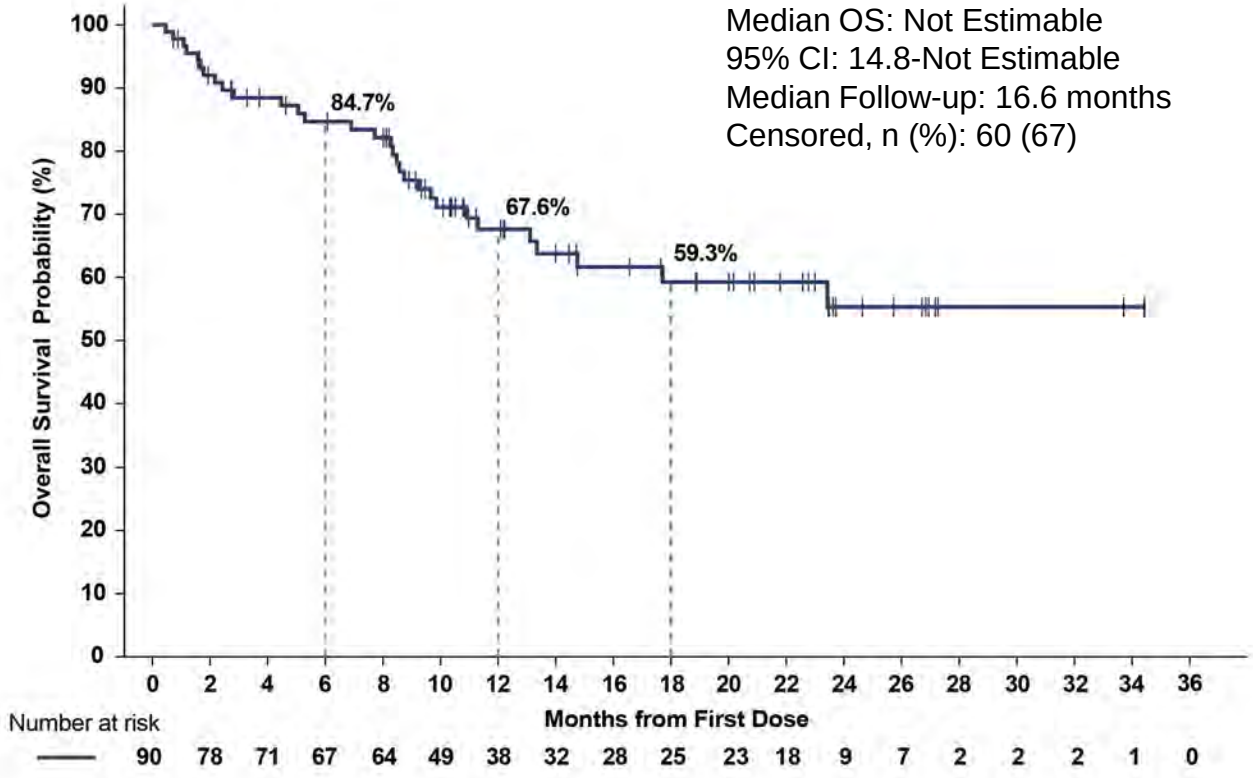
Progression-Free Survival

Median PFS: 7.4
95% CI: 5.3-12.5
Median Follow-up: 9.2 months
Censored, n (%): 45 (50)



Overall Survival

Median OS: Not Estimable
95% CI: 14.8-Not Estimable
Median Follow-up: 16.6 months
Censored, n (%): 60 (67)



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Data cutoff date of 31 January 2022. Response status per Lugano 2014 criteria based on IRC assessment.

Thank you!

WILEY

CLL Therapy in 2023

Dr Shankara Paneesha

Consultant Haematologist
Honorary Associate Clinical Professor, University of Birmingham
University Hospitals Birmingham NHS Foundation Trust

Speaker Disclosures

- Gilead
- AstraZeneca
- AbbVie
- Beigene
- Takeda

Learning Objectives

Identify treatment Decisions for Newly Diagnosed Patients With CLL

Describe First-line Management of CLL and Safety Considerations

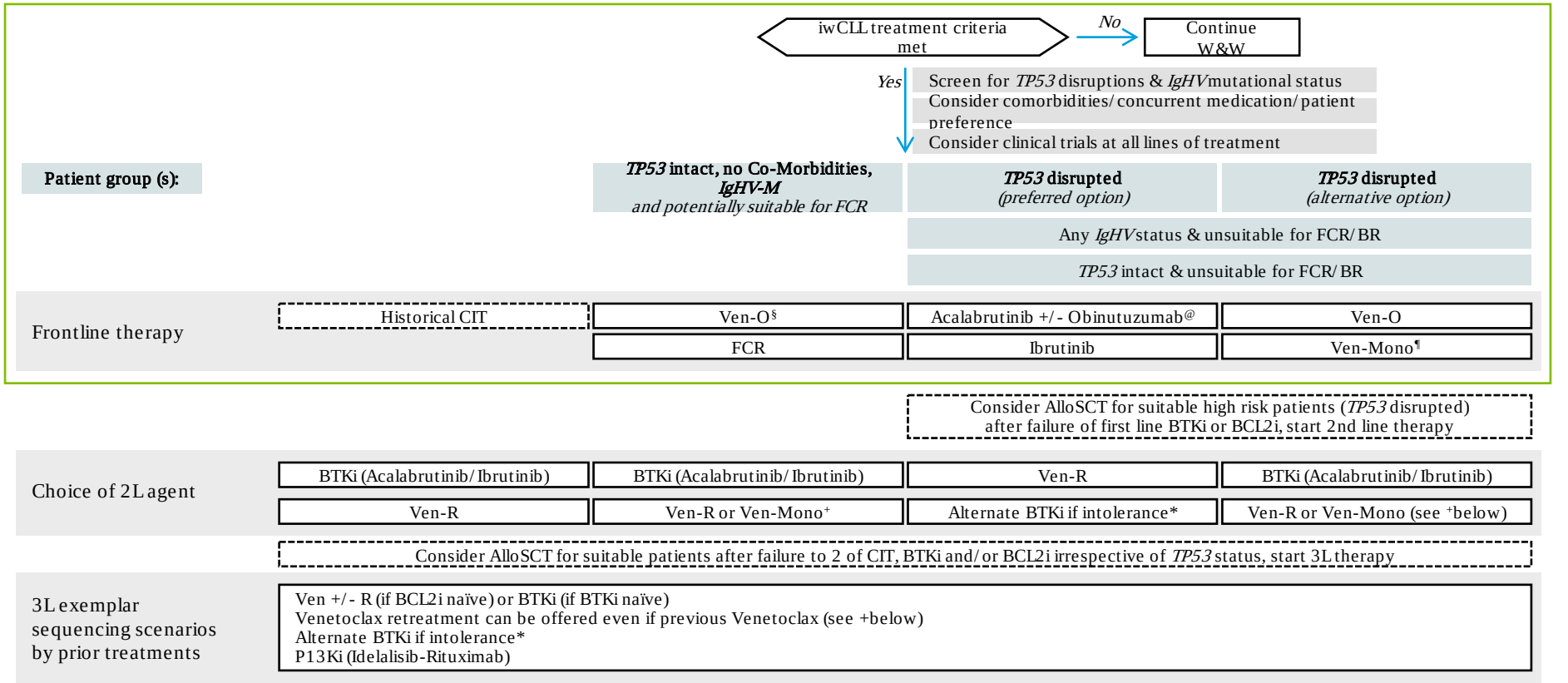
- Covalent BTK inhibitors

-Anti-CD20 antibodies

-BCL2 inhibition

Explain how patients can be involved in their care.

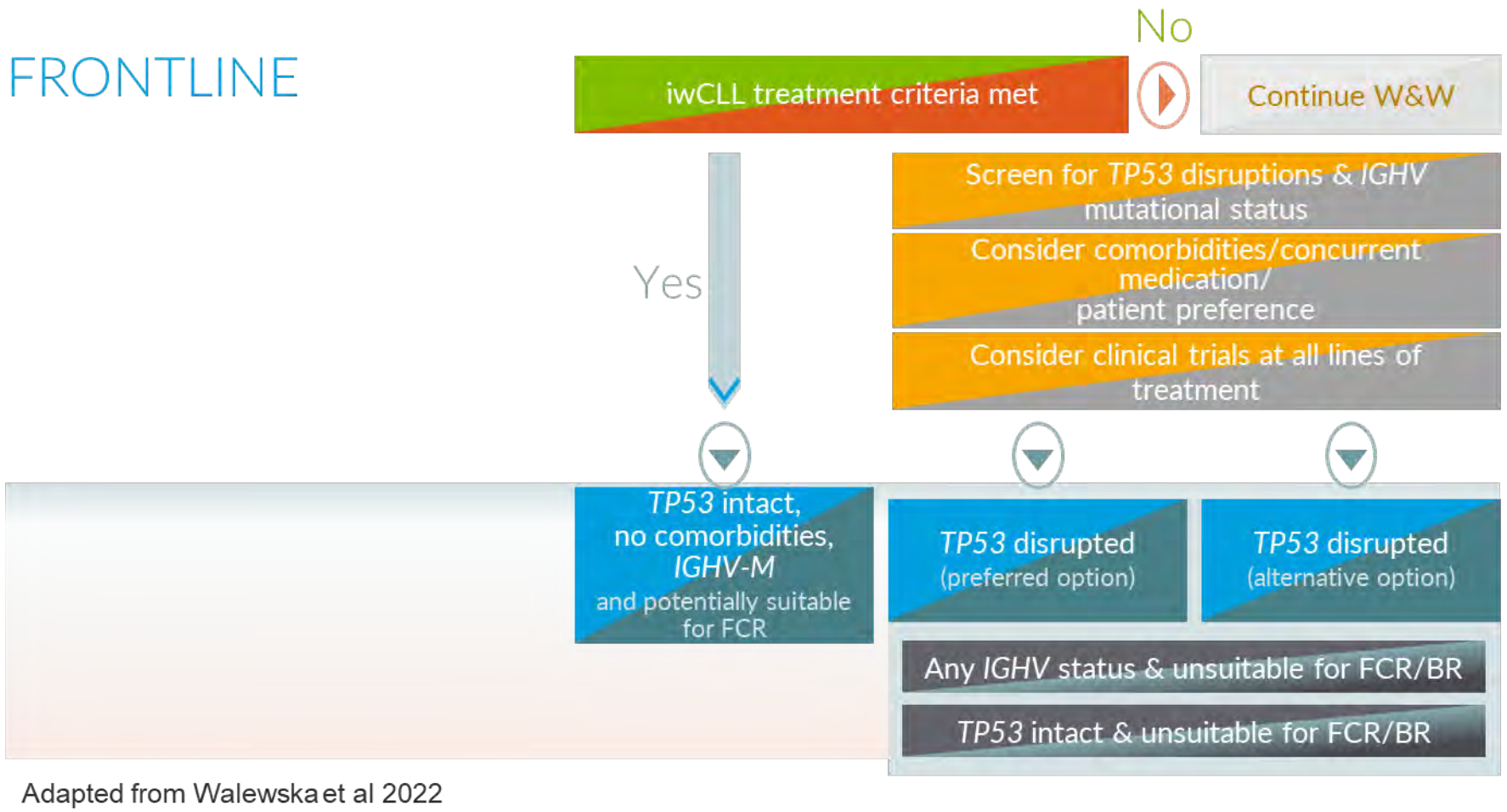
Guideline for the treatment of CLL[7]



- 2L, second line; 3L, third line; AlloSCT, allogenic stem cell transplantation; BR, bendamustine + rituximab; BCL2i, B-cell lymphoma 2 inhibitor; BTKi: Bruton tyrosine kinase inhibitors; CIT, chemoimmunotherapy; FCR, fludarabine + cyclophosphamide + rituximab; IgHV, immunoglobulin heavy chain variable region; iwCLL, International Workshop on Chronic Lymphocytic Leukaemia; P13Ki, phosphatidylinositol-3 kinase inhibitor; R/R, relapsed/refractory; TP53, tumour protein 53; Ven-Mono: single agent continuous venetoclax; Ven-O, venetoclax obinutuzumab 12 months; Ven-R, venetoclax-rituximab 24 months; W&W, watch & wait
- §Venetoclax + obinutuzumab is available for NHSE patients for this patient population and is preferred; *Alternate BTKi can be offered as an option if intolerant to initial BTKi choice and when feasible, it is preferred over P13Ki; ¶Only a first-line option for *TP53* disrupted patients who are ineligible for BTKi; +Venetoclax monotherapy can be offered to patients relapsing after fixed duration Venetoclax-based regimens

- 7. Walewska, et al. Br J Haematol 2022;197:544-57/bjh.18075 [Epub ahead of print]

BSH Guidance Treatment of CLL[7]

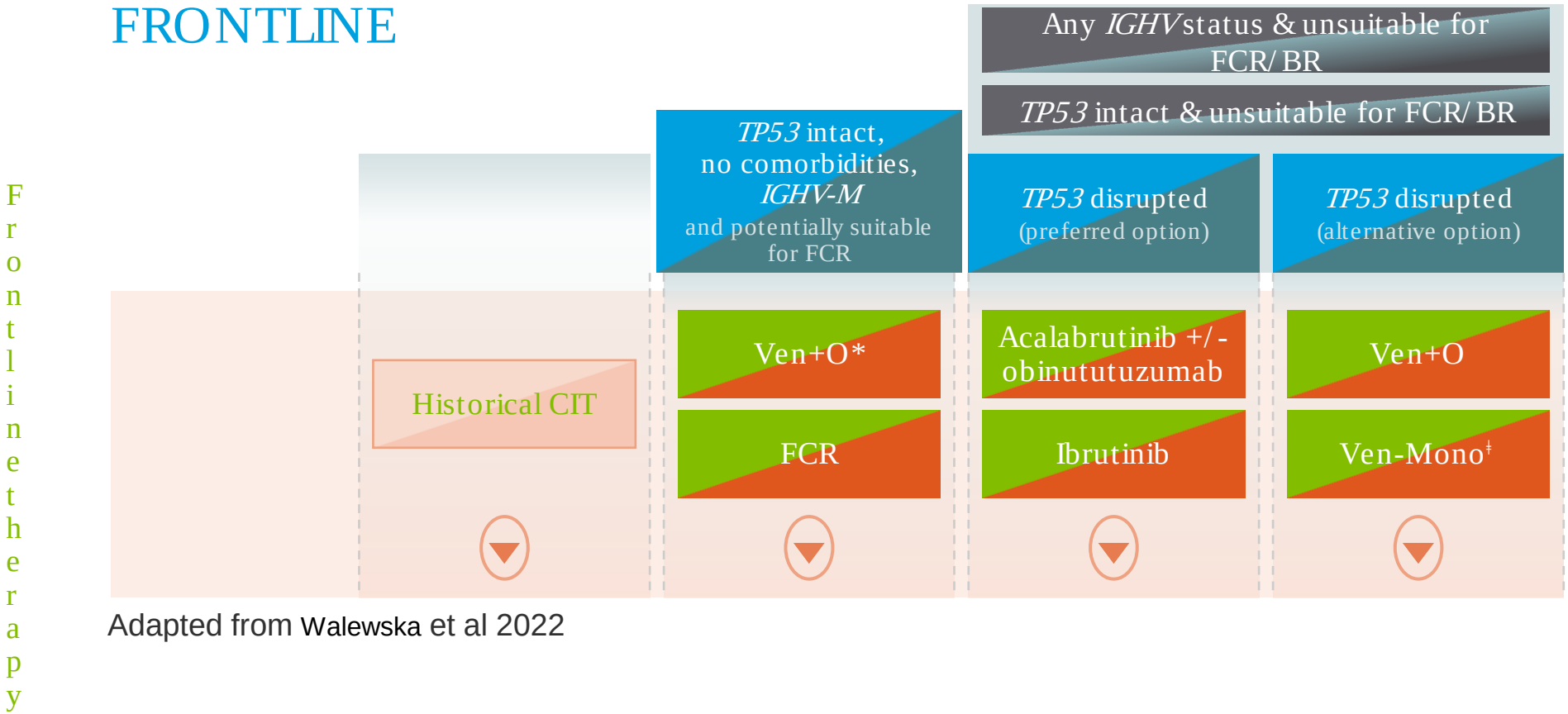


Adapted from Walewska et al 2022

BR, bendamustine + rituximab; FCR, fludarabine + cyclophosphamide + rituximab; *IGHV*, immunoglobulin heavy chain variable region; iwCLL, International Workshop on Chronic Lymphocytic Leukaemia; *TP53*, tumour protein 53; W&W, watch and wait

7. Walewska, et al. Br J Haematol 2022;197:544–57

BSH Guidance Treatment of CLL[7]

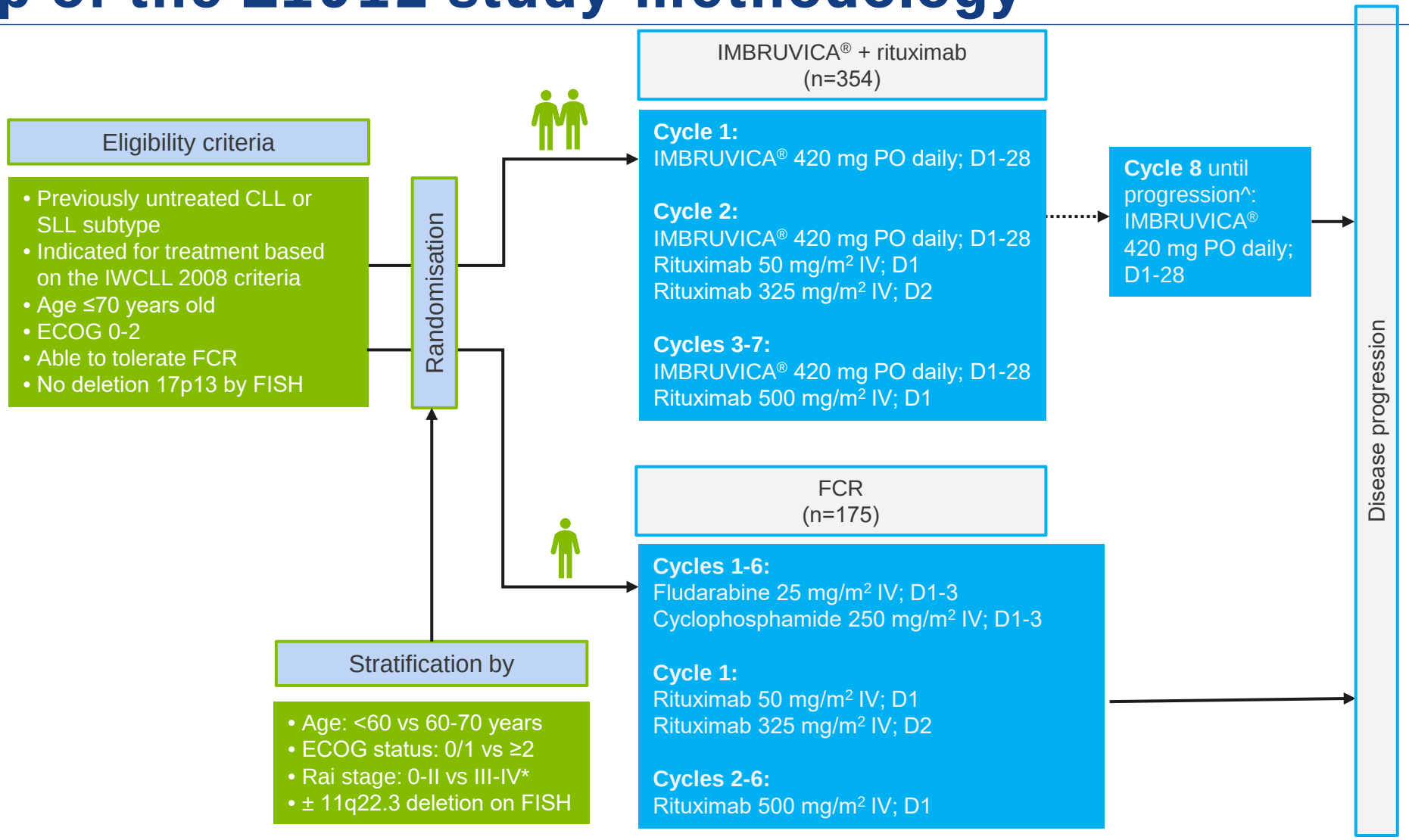


Adapted from Walewska et al 2022

- BR, bendamustine + rituximab; BTKi, Bruton tyrosine kinase inhibitor; CIT, chemoimmunotherapy; FCR, fludarabine + cyclophosphamide + rituximab; *IGHV*, immunoglobulin heavy chain variable region; iwCLL, International Workshop on Chronic Lymphocytic Leukaemia; NHSE, National Health Service England; *TP53*, tumour protein 53; Ven-Mono, single agent continuous venetoclax; Ven+O, venetoclax + obinutuzumab 12 months *Venetoclax-obinutuzumab is available for NHSE patients for this patient population and is preferred; ‡Only a first-line option for *TP53* disrupted patients who are ineligible for BTKi

7. Walewska, et al. Br J Haematol 2022;197:544–57

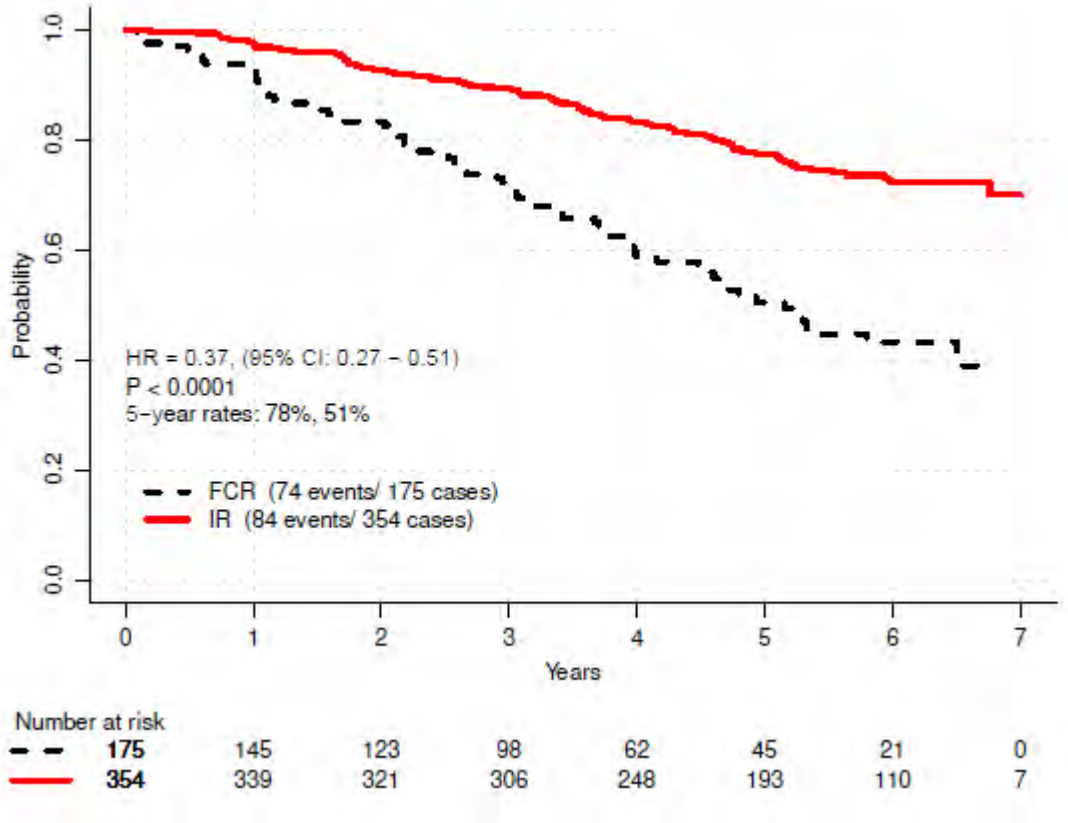
Recap of the E1912 study methodology[2,3]



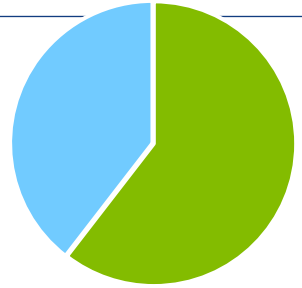
IMBRUVICA® was given until disease progression or an unacceptable level of side effects occurred. * Rai staging: 0-II = low or intermediate risk; III-IV = high risk; CLL, chronic lymphocytic leukaemia; D, day; ECOG, Eastern Cooperative Oncology Group Performance Status; FCR, fludarabine, cyclophosphamide and rituximab; FISH, fluorescence in situ hybridization; IV, intravenous; IWCLL, International Workshop on Chronic Lymphocytic Leukaemia; PO, orally; SLL, small lymphocytic lymphoma.

2. Shanafelt TD, et al. Ibrutinib–Rituximab or Chemoimmunotherapy for Chronic Lymphocytic Leukemia. N Eng J Med. 2019;381:432–43 (including Appendix)
3. Shanafelt TD, et al. Presented at the 61st American Society of Hematology Annual Meeting and Exposition, Orlando, Florida, USA. 7-10 December 2019; #33.

IMBRUVICA® + rituximab shows superior 5-year PFS rates vs FCR in treatment-naïve patients with CLL[1]



Adapted from Shanafelt TD, et al. Blood. 2022.[1]



78% of patients on IMBRUVICA® + rituximab had PFS

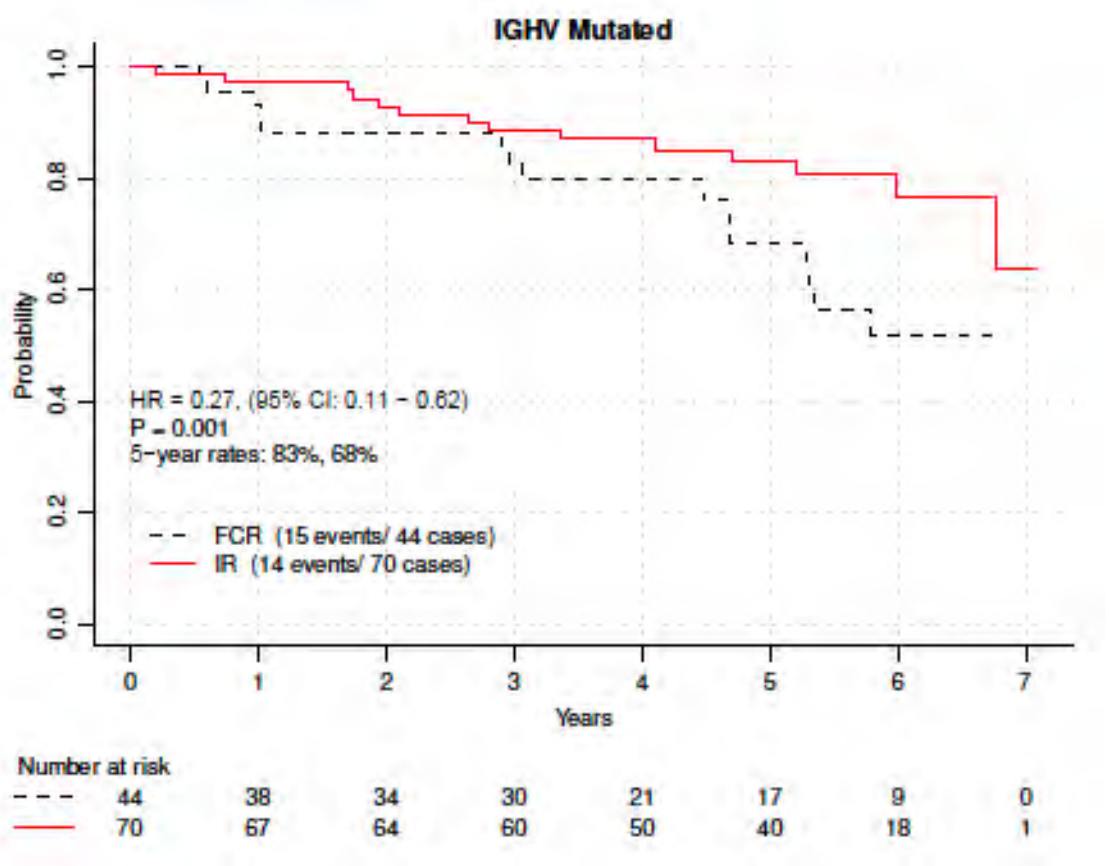
(vs 51% of patients treated with FCR)

- Among the 354 patients randomised to the IR arm, 60.5% continue IMBRUVICA® and 65.7% of those in the FCR arm remain on surveillance at the time of the present analysis
- The PFS at 6 years for IMBRUVICA®-treated patients with current follow-up is 72.6% (vs 43.3% of patients treated with FCR)

CI, confidence interval; CLL, chronic lymphocytic leukaemia; FCR, fludarabine, cyclophosphamide and rituximab; HR, hazard ratio; IR, IMBRUVICA® + rituximab; PFS, progression-free survival.

1. Shanafelt TD, et al. Long-term outcomes for ibrutinib–rituximab and chemoimmunotherapy in CLL: updated results of the E1912 trial. Blood. 2022;140:112–20.

5-year PFS rates stratified by IGHV status significantly favoured IMBRUVICA® + rituximab vs FCR in the mutated subgroup[1]



Adapted from Shanafelt TD, et al. Blood.2022.[1]

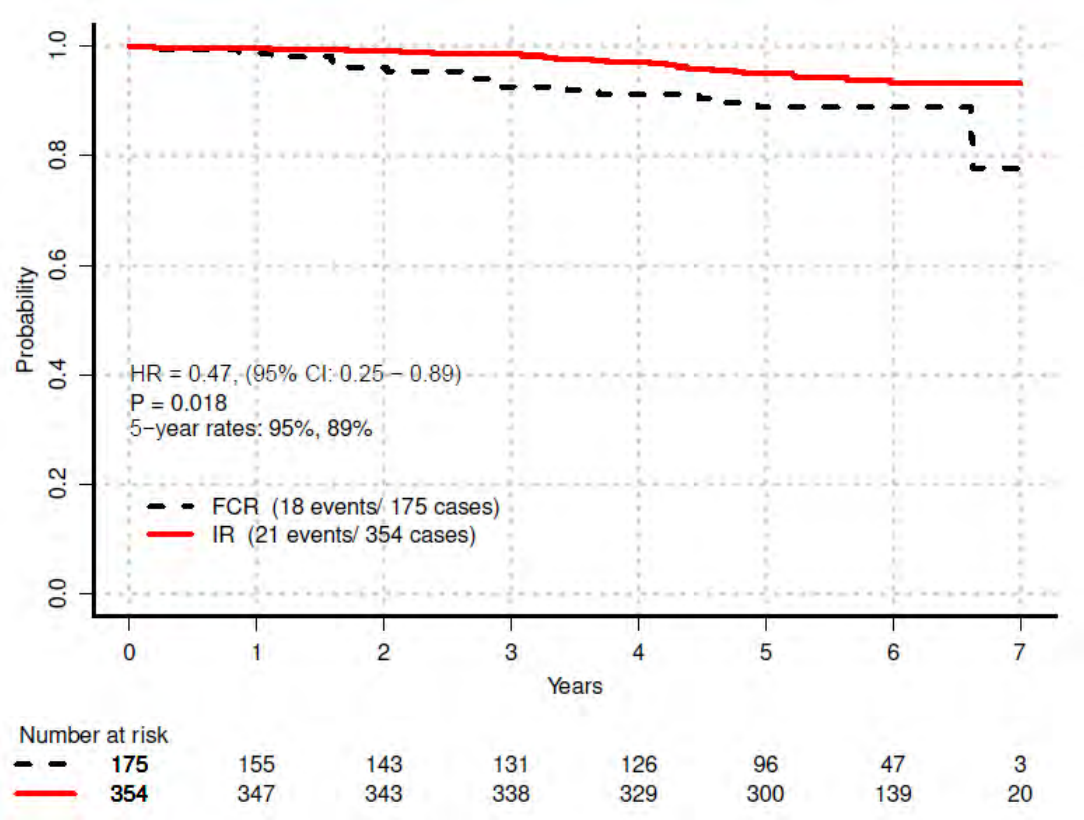
83% of patients with IGHV mutation on IMBRUVICA® + rituximab had PFS
(vs 68% of patients treated with FCR)

- In the 3-year follow-up study,[3] patients on treatment with IR demonstrated a trend in PFS benefit compared to FCR in patients with IGHV mutation (p=0.086)
- IR therapy offers statistically superior PFS to FCR in IGHV-mutated CLL patients on longer follow-up[1]

CI, confidence interval; CLL, chronic lymphocytic leukaemia; FCR, fludarabine, cyclophosphamide and rituximab; HR, hazard ratio; IGHV, immunoglobulin heavy-chain variable region genes; IR, IMBRUVICA® + rituximab; PFS, progression-free survival.

1. Shanafelt TD, et al. Long-term outcomes for ibrutinib–rituximab and chemoimmunotherapy in CLL: updated results of the E1912 trial. Blood. 2022;140:112–20
3. Shanafelt TD, et al. Presented at the 61st American Society of Hematology Annual Meeting and Exposition, Orlando, Florida, USA. 7-10 December 2019; #33.

5-year OS rates continued to significantly favour IMBRUVICA® + rituximab vs FCR[1]



Adapted from Shanafelt TD, et al. Blood.[1]

95% of patients on IMBRUVICA® + rituximab were alive
(vs 89% of patients treated with FCR)

- Although the power for the OS secondary analysis was limited, OS was statistically significant in IGHV-unmutated patients (HR 0.35; 95% CI 0.15,0.80, p=0.01) vs those with IGHV mutation (HR 0.72; 95% CI 0.15, 3.47, p=0.68)

CI, confidence interval; FCR, fludarabine, cyclophosphamide and rituximab; HR, hazard ratio; IGHV, immunoglobulin heavy-chain variable region genes IR, IMBRUVICA® + rituximab; OS, overall survival.

1. Shanafelt TD, et al. Long-term outcomes for ibrutinib–rituximab and chemoimmunotherapy in CLL: updated results of the E1912 trial. *Blood.* 2022;140:112–20.

Ibrutinib Is Superior to Chemoimmunotherapy

Select randomized phase III trials of frontline ibrutinib vs CIT for patients with CLL

Trial	Combination	Comparator	Population (n)	Median F/U, Mo	PFS	HR
RESONATE-2	--	Chlorambucil	≥65 yr, no del(17p) (269)	83	Median: NR vs 15 mo 7 yr: 59% vs 9%	0.154
iLLUMINATE	Obinutuzumab	Chlorambucil + obinutuzumab	≥65 yr or <65 yr + comorb (229)	45	Median: NR vs 22 mo 42 mo: 74% vs 33%	0.25
A041202	± Rituximab	BR	≥65 yr (547)	55	Median: NR (IR) vs NR (I) vs 44 mo 4 yr: 76% vs 76% vs 47%	0.36 (IR/I)
ECOG1912	Rituximab	FCR	≤70 yr, no del(17p) (529)	70	5 yr: 78% vs 51%	0.37
FLAIR	Rituximab	FCR	≤75 yr, ≤20% *TP53* deletion (771)	53	Median: NR vs 67 mo	0.44

Barr. Blood Adv. 2022;6:3440. Moreno. Haematologica. 2022. Woyach. ASH 2021. Abstr 639. Shanafelt. Blood. 2022;140:112. Hillmen. ASH 2021. Abstr 642.

ELEVATE-TN 5-Yr PFS Update: A ± O vs O + Chlorambucil in Treatment-Naive CLL[4]

Patients with untreated CLL aged ≥65 or 18-64 yr with comorbidities (N = 535)

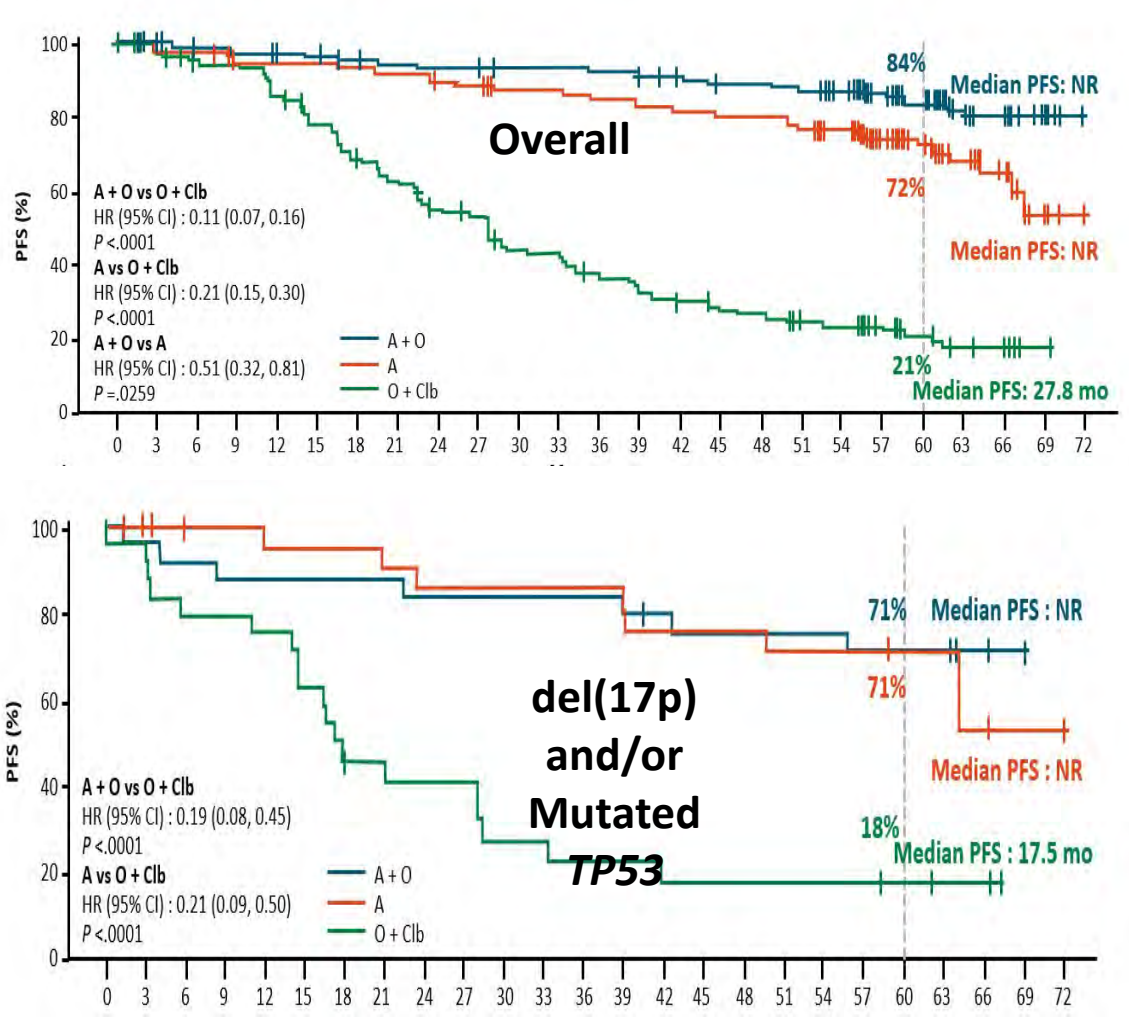
Acalabrutinib + Obinutuzumab (n = 179)

Acalabrutinib (n = 179)

Obinutuzumab + Chlorambucil (n = 177)

Primary endpoint:

IRC-assessed PFS for **A + O** vs **O + Clb**; after interim analysis, PFS assessed by investigator



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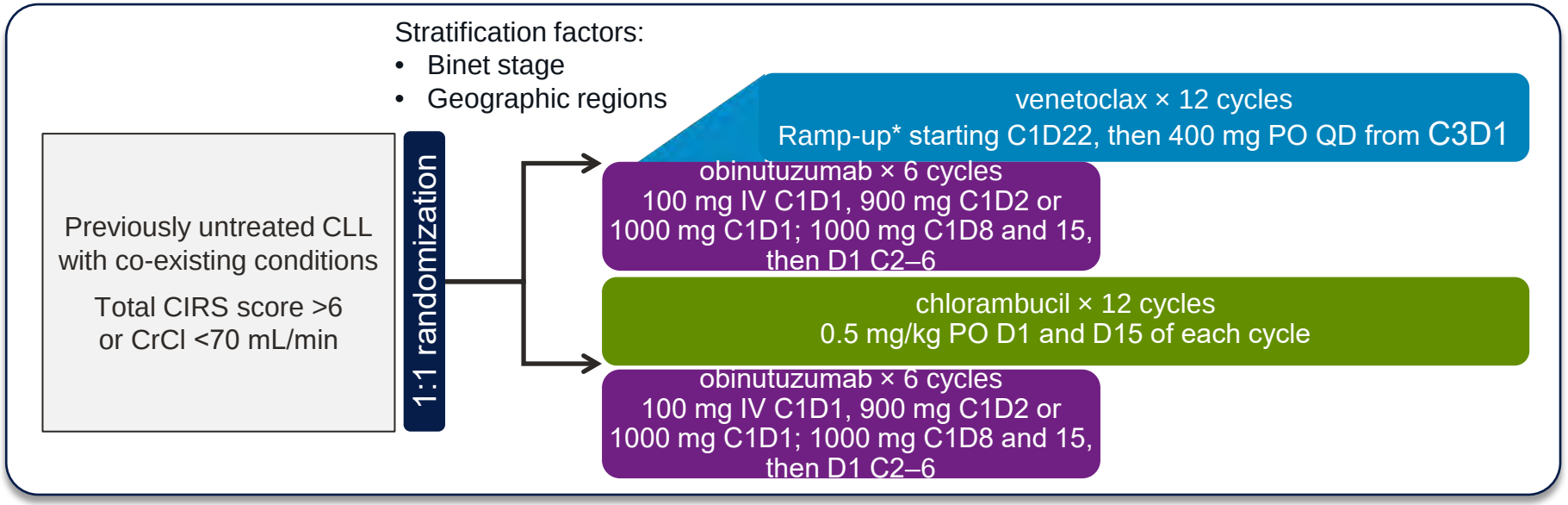
CLL14 Study Design
Multicentre, randomised, open-label, phase III[5]



Primary endpoint (ITT population):
- PFS – investigator assessed

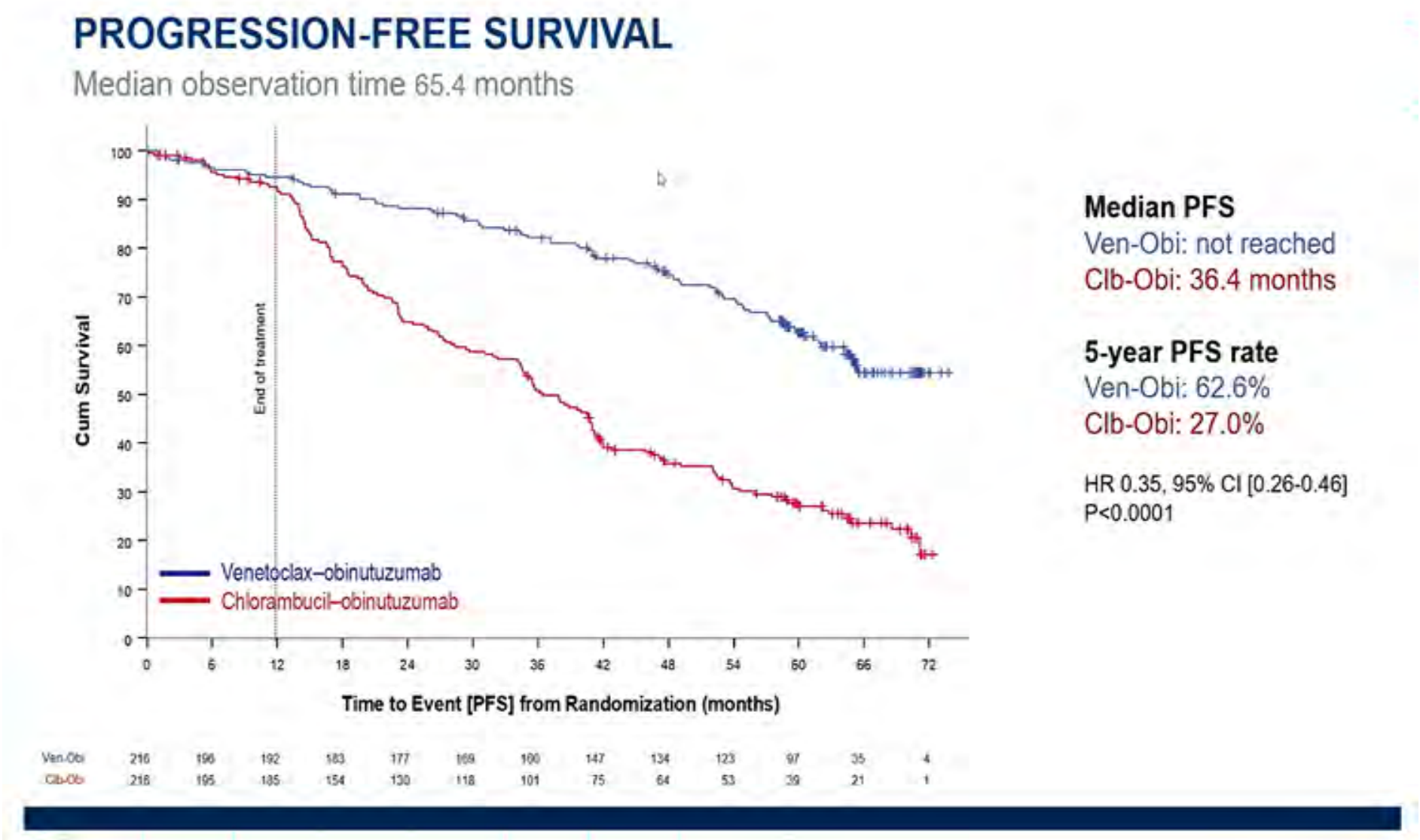
Key secondary endpoints (ITT population):
- PFS – IRC assessed
- ORR and CR 3 months after EoT
- MRD response rate (PB and BM) 3 months after EoT:
  - All patients
  - Patients with CR
- Overall survival

Analyses:
- Interim analysis: 110 PFS events
- Final PFS analysis: 170 PFS events
- Final OS analysis: End of study, 5 years after last patient enrolled

28-day cycles.* Venetoclax 5-week dose ramp-up starting C1D22: 1 week each of 20, 50, 100, and 200 mg, then 400 mg for 1 week, thereafter continuing at 400 mg until completion of cycle 12. BM, bone marrow; CR, complete remission; EoT, end of treatment; QD, daily.

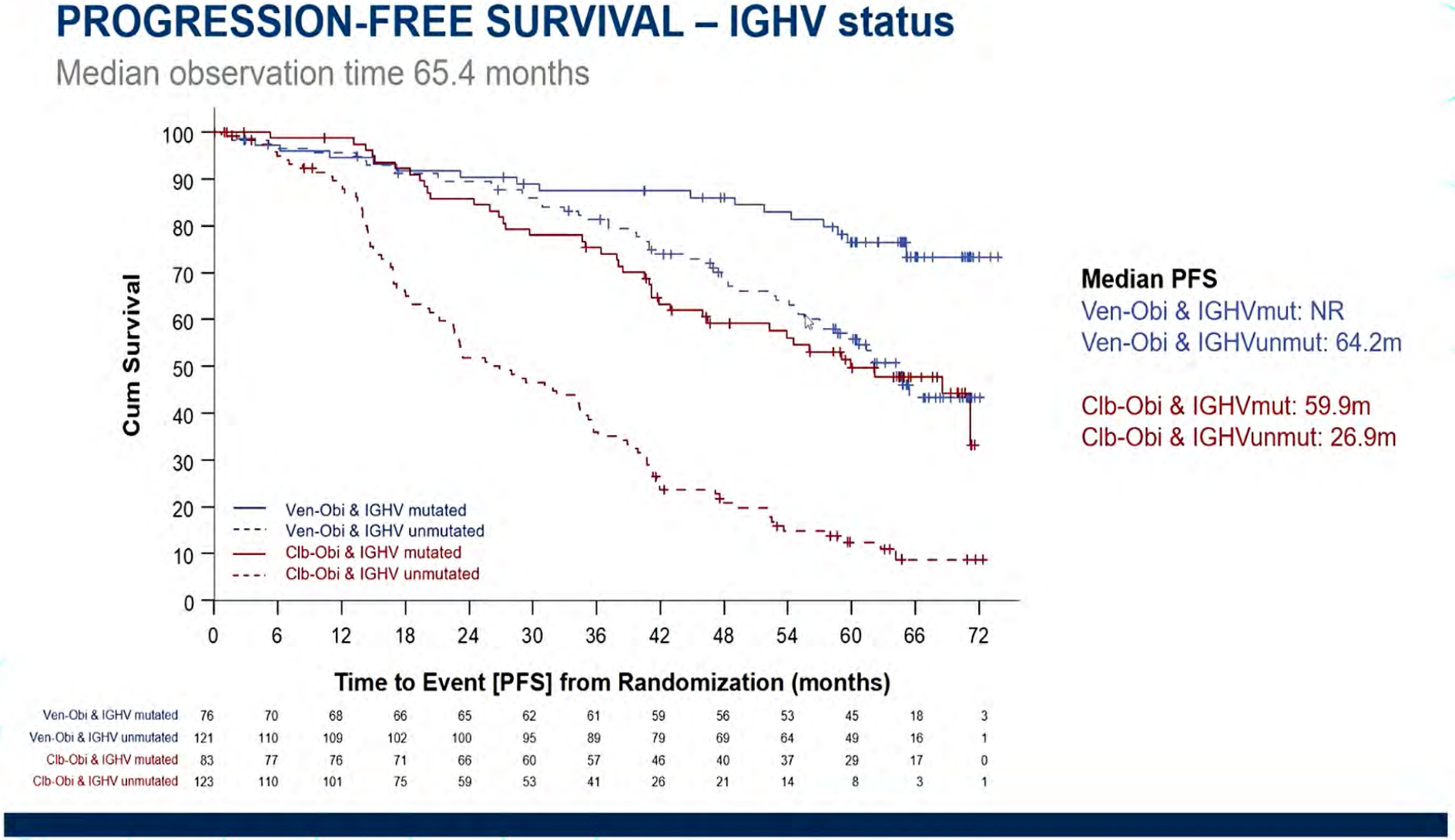
5. Fischer K, et al. *N Engl J Med*. 2019;380:2225-2236.

Investigator-Assessed PFS (ITT Population): 5 Years Post-Randomisation[6]



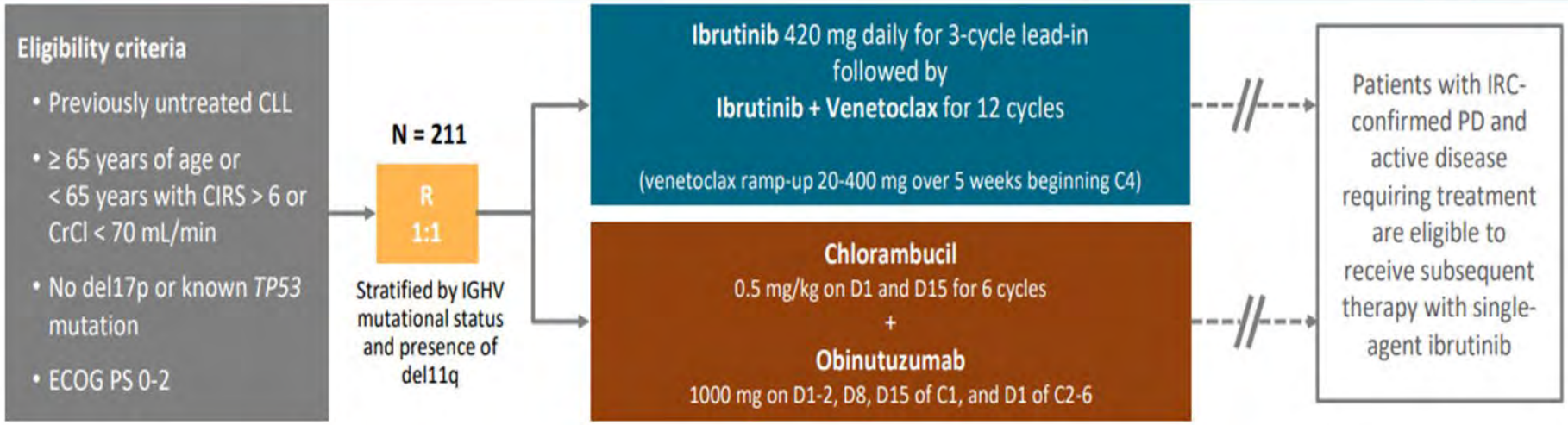
6. Al-Sawaf O, et al oral presentation at EHA 2022. S148

Investigator-Assessed PFS (IGHV status): 5 Years Post-Randomisation[6]



6. Al-Sawaf O, et al oral presentation at EHA 2022. S148

Phase 3 GLOW Study Design (NCT03462719)

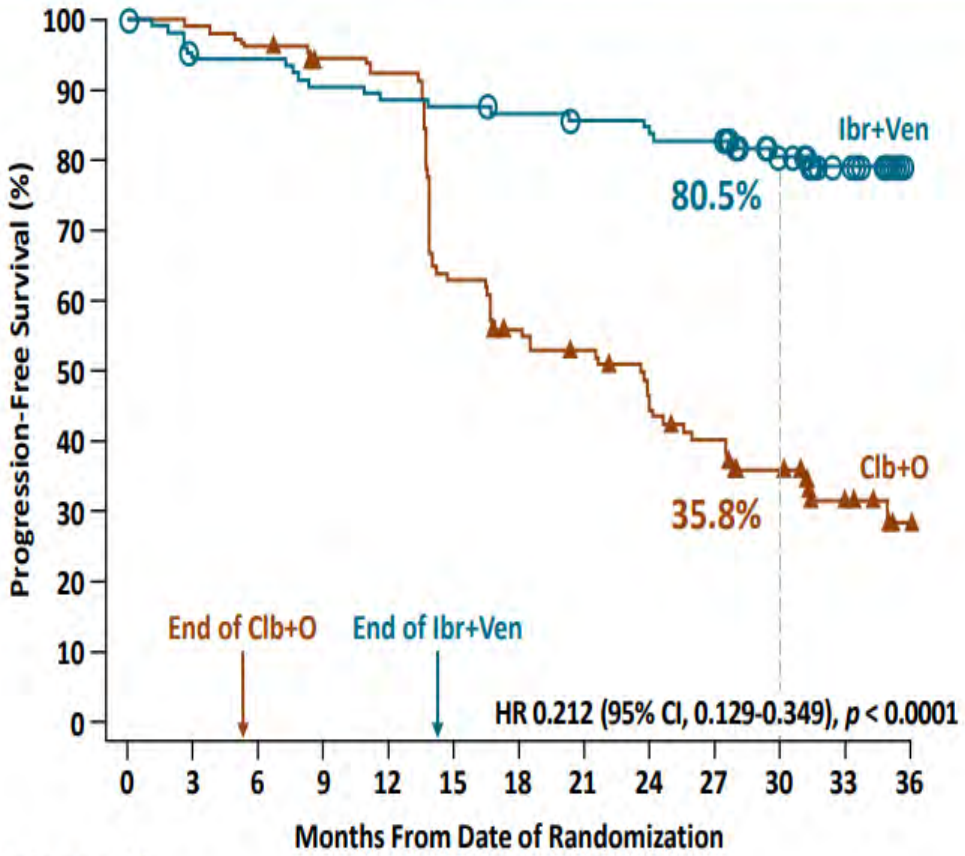


- **Study primary endpoint:** PFS as assessed by IRC
- **Current MRD analysis:**
  - MRD evaluated via NGS and reported with cutoffs of $< 10^{-4}$ and $< 10^{-5}$ (not all samples had sufficient cell yield to be analyzed at $< 10^{-6}$). NGS analysis not yet available beyond EOT+12 time point
  - PB/BM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

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

ASH 2021, Munir T, et al.

Superior Progression-Free Survival with Ibr+Ven vs Clb+O was Maintained with Median 34.1 months of Follow-up



Patients at risk

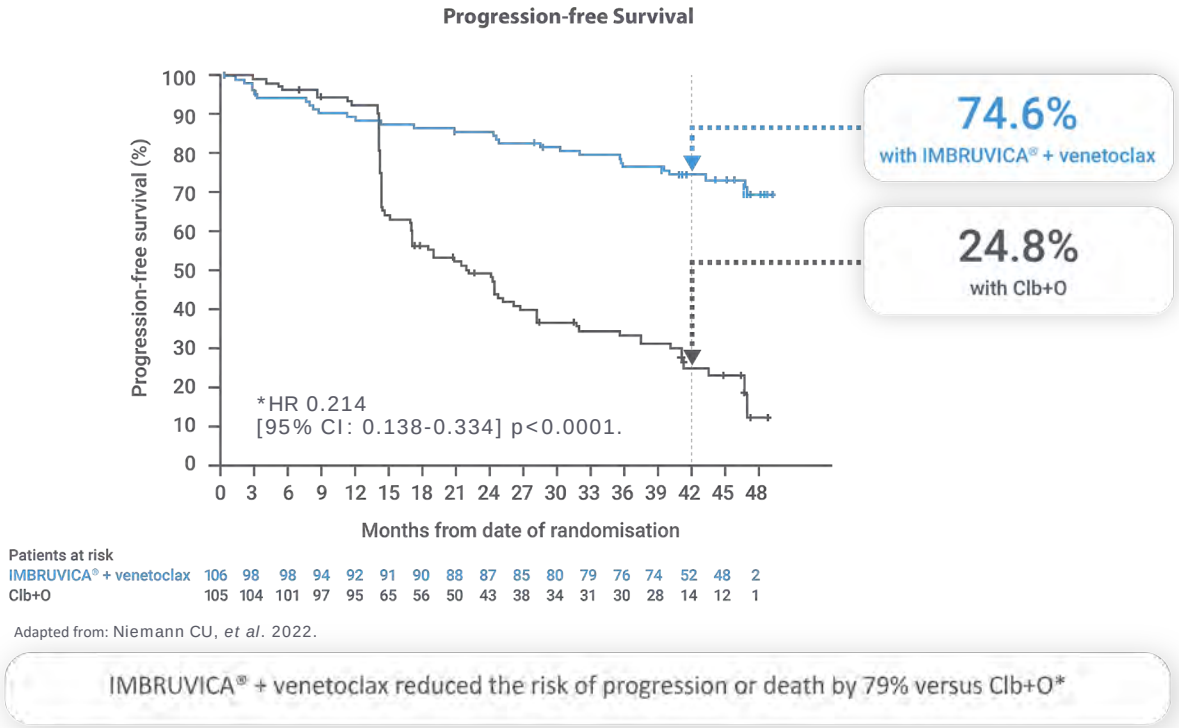
Ibr+Ven	106	98	98	94	92	91	89	87	86	84	71	42	1
Clb+O	105	104	101	96	94	64	55	51	43	37	30	13	3

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

ASH 2021, Munir T, et al.

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

PFS by IRC remained superior for IMBRUVICA® + venetoclax vs Clb+O with 4 years of study follow-up



Adapted from: Niemann CU, *et al*. 2022.

IMBRUVICA® + venetoclax reduced the risk of progression or death by 79% versus Clb+O*

Median study follow-up: 46 months.
CI = confidence interval; Clb+O = chlorambucil + obinutuzumab; HR = hazard ratio; IRC = independent review committee; PFS = progression-free survival.
Niemann CU, *et al*. Oral presentation at ASH 2022

GLOW 4-Year Follow-up: Conclusions

IMBRUVICA® + venetoclax is the only fixed-duration novel combination to demonstrate an OS advantage vs Clb+O in previously untreated CLL (HR: 0.487 vs Clb+O; nominal p=0.0205*)

- 75% of previously untreated older or comorbid patients were alive and progression free at 3.5 years with all-oral, once-daily, fixed-duration IMBRUVICA® + venetoclax (PFS HR 0.214 vs Clb+O)
- 2 years after end of treatment with IMBRUVICA® + venetoclax:
  - Nearly 40% of patients had uMRD $<10^{-4}$
  - Estimated PFS was ≥90% for patients with mIGHV CLL (independent of MRD[a] status) and for the 60% of patients with uIGHV CLL who achieved uMRD†
- Data from GLOW (elderly/comorbid) and CAPTIVATE (young/fit) continue to demonstrate sustained clinical and molecular responses with fixed-duration IMBRUVICA® + venetoclax in previously untreated CLL

*vs HR 1.048 at primary.
†At EOT +3.
Clb+O=chlorambucil + obinutuzumab; CLL=chronic lymphocytic leukaemia; HR=hazard ratio; (m)IGHV=(mutated) immunoglobulin heavy chain variable; OS=overall survival; PFS=progression-free survival; (u)MRD= (undetectable) minimal residual disease.
Niemann CU, et al. Oral presentation at ASH 2022

Results of CLL trials in patients not suitable for FCR

Study	Patients	Median follow-up in months	Results	Estimated PFS
Resonate-2	269 I:136 C:133	60	median not reached vs 15.0 months with 85% reduction in the risk of PD or death	5 years 70%: I 12%: C
CLL 14 trial	432 VO: 216; CO:216	52.4	median not reached vs 36.4 months	4 year PFS 74%: VO 35.4%: CO
Elevate-TN	535 A O: 179 A: 179 CO: 177	58.2	median not reached vs 22.6 months with 90% reduction in risk of PD or death with AO	5 year PFS 84% : AO 72%: A 21% : CO
Illuminate	229 I O: 113 C O:116	31·3	median not reached vs 19 months	30-month 79%: I O 31%: C O

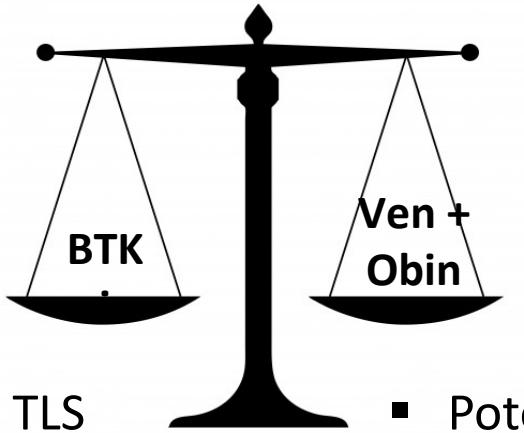
No head-to-head trials. No direct comparisons between studies can be made.

BTK Inhibitors for CLL/SLL: Regulatory Status

Agent	MoA	CLL/SLL	
		EU	US
Ibrutinib	Covalent	Approved	Approved
Acalabrutinib	Covalent	Approved	Approved
Zanubrutinib	Covalent	Approved	Not yet approved
Pirtobrutinib	Noncovalent	Not approved; phase III BRUIN CLL-313 (NCT05023980), BRUIN CLL-314 (NCT05254743), BRUIN CLL-321 (NCT04666038), BRUIN CLL-322 (NCT04965493) trials ongoing	
Nemtabrutinib	Noncovalent	Not approved; phase II (NCT04728893) ongoing	

Acalabrutinib SmPC. Ibrutinib SmPC. Zanubrutinib SmPC. Acalabrutinib PI. Ibrutinib PI. Zanubrutinib PI.

Frontline BTKi vs Venetoclax + Obinutuzumab: Factors to Consider



- Convenience (no infusions, TLS monitoring)
- Long-term efficacy data
- Phase III data compared with FCR and BR
- More data for efficacy of Ven at time of ibrutinib progression

- Potential for 1 yr time-limited therapy
- No known cardiac or bleeding risks
- Less concern for long-term adherence
- Potential for cost saving if 1 yr of therapy is durable

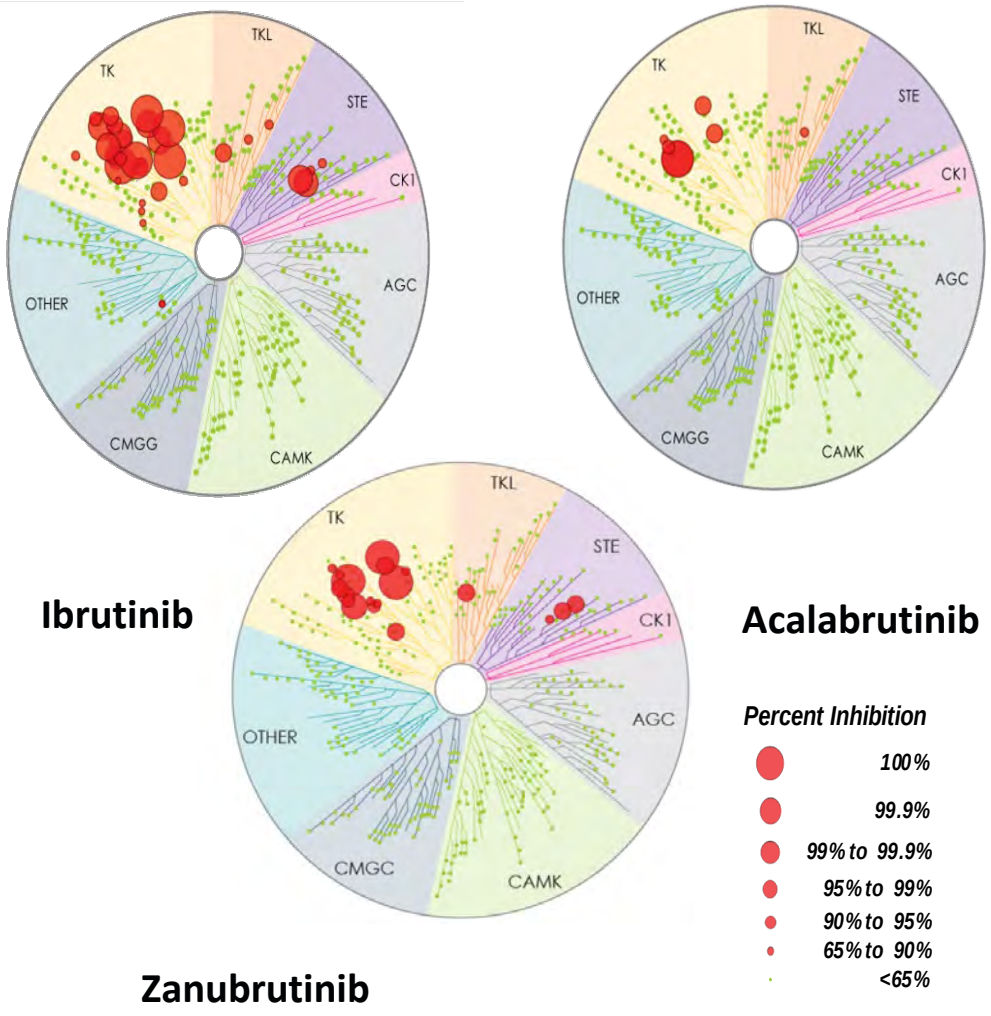
Brem. *Blood Adv*. 2022;6:1361. Molica. *Int J Hematol Oncol*. 2020;9:IJH31.

Kinase Selectivity of Covalent BTK Inhibitors in Vitro

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.

Which Therapy Is the Best Initial Therapy?

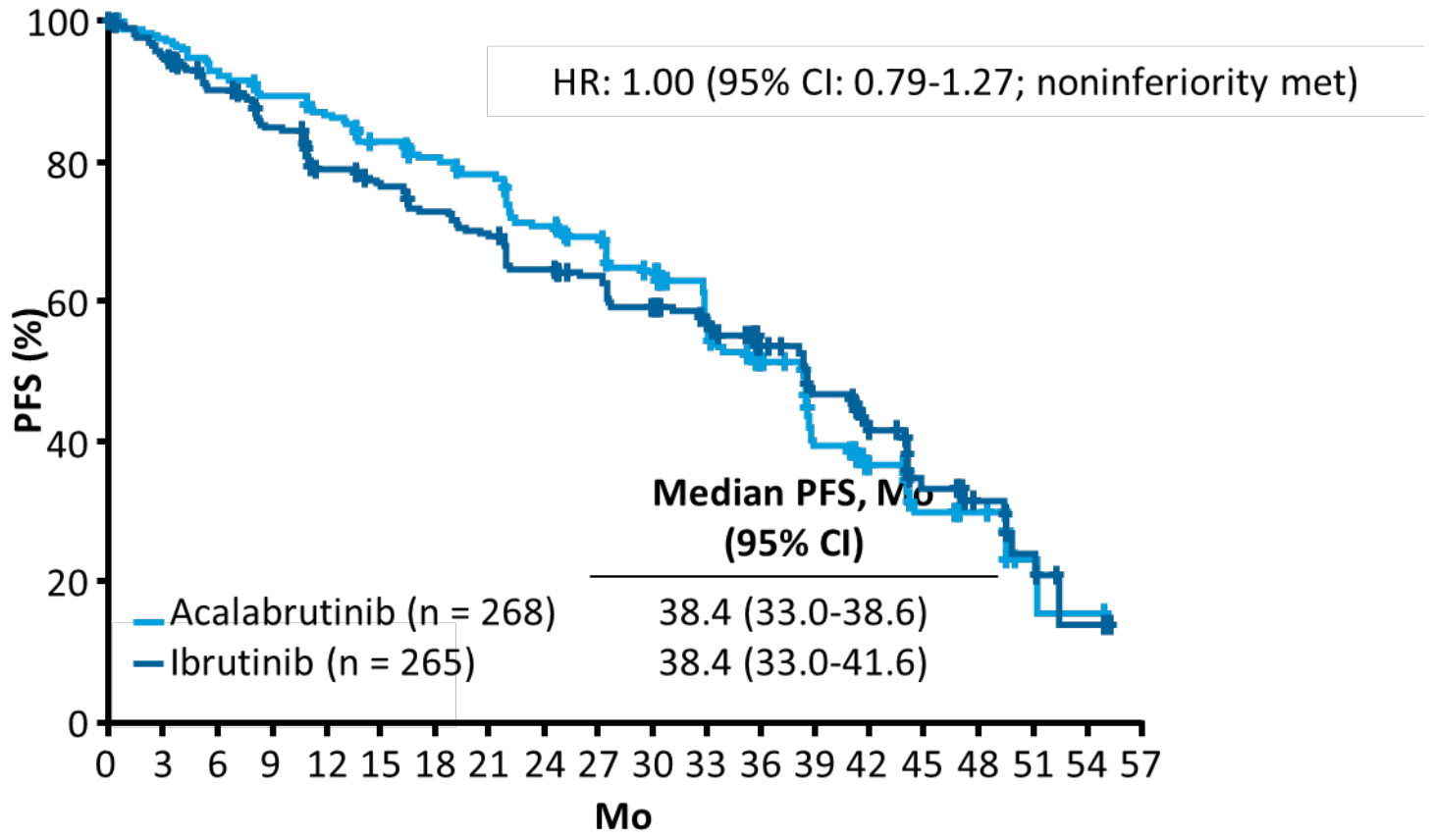
- There is no single best initial therapy
- Multiple factors are important in this evaluation: patient preference, comorbid conditions, toxicity considerations, available resources
- Efficacy and long-term disease control
- Options for salvage

Targeted Therapies	PFS Outcomes
E1912: ibrutinib + rituximab[1]	78% at 5 yr
ELEVATE-TN: acalabrutinib[2]	72% at 5 yr
ELEVATE-TN: acalabrutinib + obinutuzumab[2]	84% at 5 yr
CLL14: venetoclax + obinutuzumab[3]	74% at 5 yr
SEQUOIA: zanubrutinib[4]	~ >80% at 4 yr

1. Shanafelt. Blood. 2022;140:112. 2. Sharman. ASCO 2022. Abstr 7539.
3. Al-Sawaf. EHA 2021. Abstr S146. 4. Tam. Lancet Oncol. 2022;23:1031

BTK Inhibitor Head-to Head Comparisons: Acalabrutinib vs Ibrutinib (ELEVATE-RR)

Randomized phase III noninferiority trial of acalabrutinib vs ibrutinib for patients with previously treated CLL; presence of del(17p) or del(11q); no significant CV disease; no prior BTK, PI3K, Syk, or BCL-2 inhibitors (N = 533)

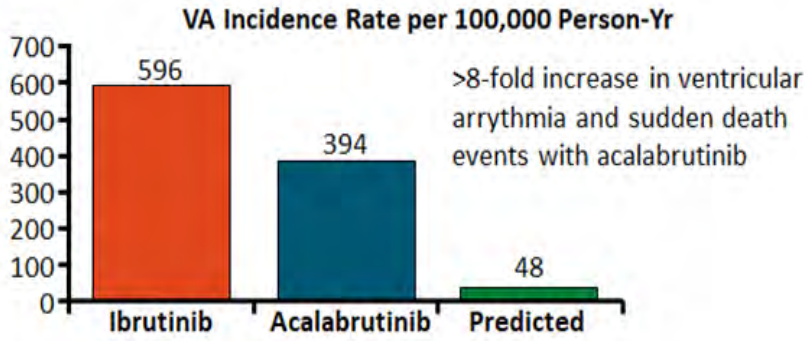


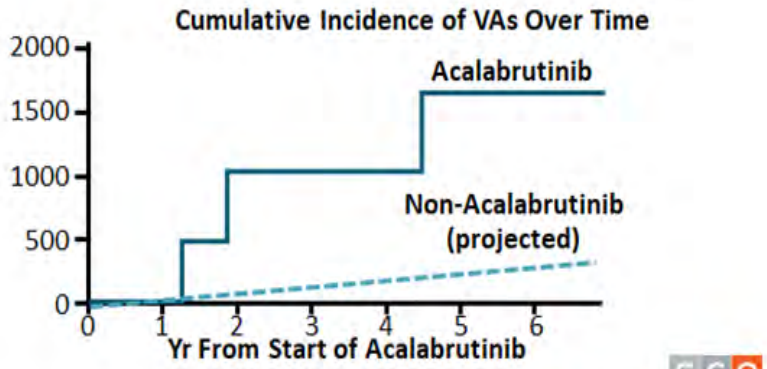
Byrd. ASCO 2021. Abstr 7500. Byrd. JCO. 2021;39:3441.

BTK Inhibitor Head-to-Head Comparisons: ELEVATE-RR

Events, n (%)	Any Grade		Grade ≥3	
	Acalabrutinib (n = 266)	Ibrutinib (n = 263)	Acalabrutinib (n = 266)	Ibrutinib (n = 263)
Cardiac events	64 (24.1)	79 (30.0)	23 (8.6)	25 (9.5)
▪ **Atrial fibrillation**	25 (9.4)	**42 (16.0)**	13 (4.9)	10 (3.8)
▪ Ventricular arrythmias	0	3 (1.1)	0	1 (0.4)
Bleeding events	101 (38.0)	**135 (51.3)**	10 (3.8)	12 (4.6)
▪ Major bleeding events	12 (4.5)	14 (5.3)	10 (3.8)	12 (4.6)
Hypertension	25 (9.4)	**61 (23.2)**	11 (4.1)	**24 (9.1)**
Infections	208 (78.2)	214 (81.4)	82 (30.8)	79 (30.0)
ILD/pneumonitis	7 (2.6)	**17 (6.5)**	1 (0.4)	2 (0.8)
SPMs excluding NMSC	24 (9.0)	20 (7.6)	16 (6.0)	14 (5.3)

- Cohort study of patients with B-cell malignancies treated with acalabrutinib (N = 290)



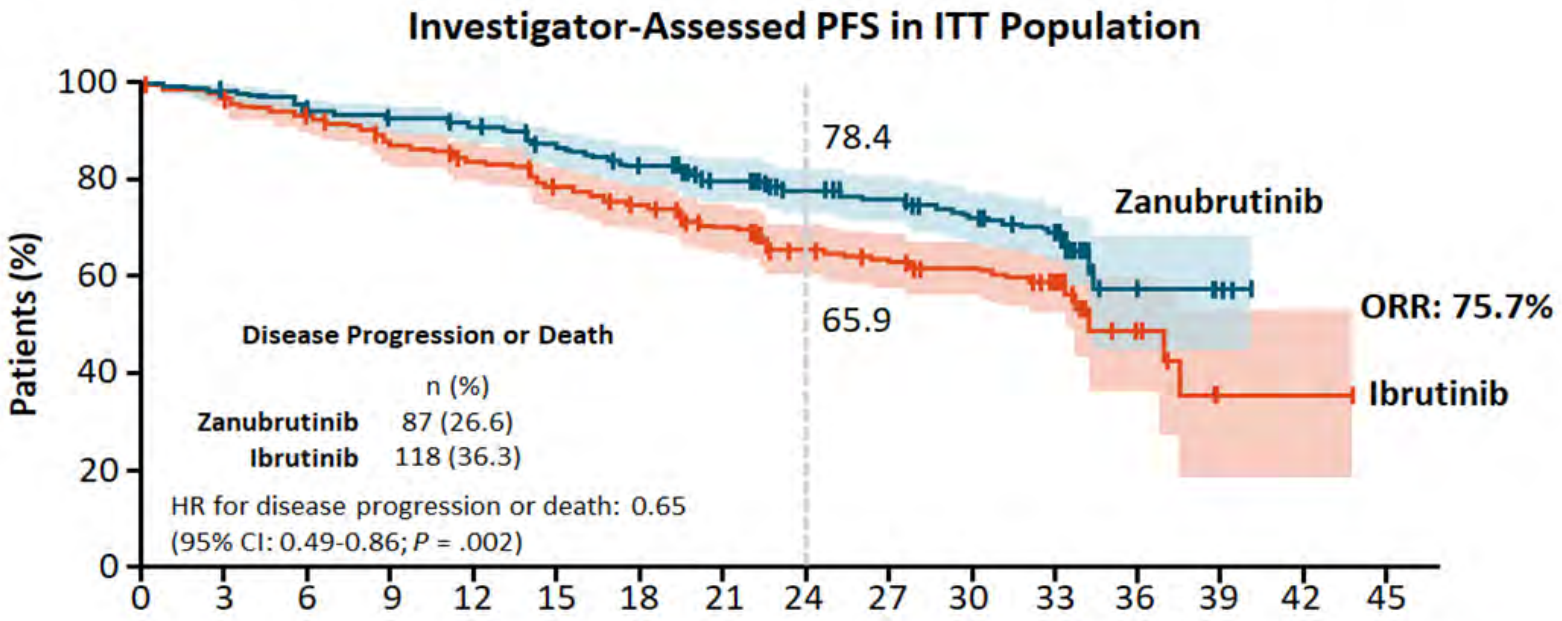


Byrd. ASCO 2021. Abstr 7500. Byrd. JCO. 2021;39:3441. Bhat. Blood. 2022;doi: 10.1182/blood.2022016953.

Slide credit: clinicaloptions.com

BTK Inhibitor Head-to-Head Comparisons: Zanubrutinib vs Ibrutinib (ALPINE)

- Randomized phase III trial of zanubrutinib vs ibrutinib for patients with R/R CLL/SLL; ≥1 prior systemic treatment for CLL/SLL; no prior BTK inhibitor (N = 652)



Brown. ASH 2022. Abstr LBA-6. Brown. NEJM. 2022;[Epub].

Slide credit: clinicaloptions.com

BTK Inhibitors: Toxicities

Please refer to individual SmPCs for full safety information

	Bleeding Risk	Cardiotoxicity	Infections
Mechanism	Mechanism of bleeding-related events is not well understood	Increased risk of atrial fibrillation, new or worsened hypertension, CV AEs*	Potential T-cell mediated immune effects. Impairment of macrophage response. Viral, bacterial, and fungal infections reported
Risk	• Patients on anticoagulation ± antiplatelet therapy • Concomitant CYP3A4 inhibitors	• Prior cardiac history • Concomitant CYP3A4 inhibitors	• History of opportunistic infections • High-dose steroids
BTKi			
Ibrutinib (any grade)	Haemorrhage/ bruising- very common	Caridac failure, AF, ventricular tacharrhythmia- common	Pneumonia, URTI, skin infection- very common. Sepsis, UTI, sinusitis- common
Acalabrutinib (any grade)	Haemorrhage/ haematoma- very common	AF/ atrial flutter- common	URTI, sinusitus- very common. Pneumonia, UTI, Nasopharyngitis, bronchitis, herpes viral infection- common

*Other major CV AEs include myocardial infarction, stroke, congestive heart failure, and cardiovascular death.

Ibrutinib SmPC. Acalabrutinib SmPC.

Very common (≥1/10) and common (≥1/100 to <1/10).

IMBRUVICA® dosing can be adjusted for patients who experience Grade >3 non-haematological toxicity, grade >3 neutropenia with infection or fever or grade 4 haematological toxicities[1]

- IMBRUVICA® therapy should be withheld for any new onset or worsening grade ≥3 non-haematological toxicity, grade 3 or greater neutropenia with infection or fever, or grade 4 haematological toxicities.
- Once the symptoms of the toxicity have resolved to grade 1 or baseline (recovery), IMBRUVICA therapy may be reinitiated at the starting dose. If the toxicity reoccurs, the once daily dose should be reduced by 140 mg.
- A second reduction of dose by 140 mg may be considered as needed.
- If these toxicities persist or recur following two dose reductions, discontinue the medicinal product.

Recommended dose modifications are described below:

Toxicity occurrence	Dose modification after recovery
First	Restart at 420 mg daily
Second	Restart at 280 mg daily
Third	Restart at 140 mg daily
Fourth	Discontinue IMBRUVICA®

When resuming treatment, restart at the same or lower dose based on benefit-risk evaluation. If the toxicity reoccurs, reduce daily dose by 140 mg.[2]

1. IMBRUVICA® Summary of Product Characteristics. https://www.medicines.org.uk/emc/search?q=imbruvica.
2. IMBRUVICA® (ibrutinib): DHPC. New risk minimisation measures, including dose modification recommendations, due to the increased risk for serious cardiac events https://www.medicines.org.uk/emc/product/10040/dhpcs

IMBRUVICA® dosing can be tailored for patients who experience Grade >2 cardiac failure or grade >3 cardiac arrhythmias[1]

IMBRUVICA® therapy should be withheld for any new onset or worsening grade 2 cardiac failure or grade 3 cardiac arrhythmias. Once the symptoms of the toxicity have resolved to grade 1 or baseline (recovery), resume IMBRUVICA® therapy at the recommended dose as per the table below:

Events	Toxicity occurrence	Dose modification after recovery
Grade 2 cardiac failure	First	Restart at 280 mg daily
	Second	Restart at 140 mg daily
	Third	Discontinue IMBRUVICA®
Grade 3 cardiac arrhythmias	First	Restart at 280 mg daily†
	Second	Discontinue IMBRUVICA®
Grade 3 or 4 cardiac failure Grade 4 cardiac arrhythmias	First	Discontinue IMBRUVICA®

† Evaluate the benefit-risk before resuming treatment.[1]

1. IMBRUVICA® (ibrutinib): DHPC. New risk minimisation measures, including dose modification recommendations, due to the increased risk for serious cardiac events https://www.medicines.org.uk/emc/product/10040/dhpcs

IMBRUVICA® dose adjustments for certain patients[1]

Renal impairment

IMBRUVICA® has minimal renal clearance. No specific studies have been conducted in patients with renal impairment.

Mild or moderate renal impairment (>30 mL/min creatinine clearance)	**Severe** renal impairment (<30 mL/min creatinine clearance)
• NO dose adjustment needed\ • Hydration should be maintained • Monitor serum creatinine levels periodically	• There are no data in patients with severe renal impairment or on dialysis • ONLY administer IMBRUVICA® if the benefit outweighs the risk • Monitor patients closely for signs of toxicity

Hepatic impairment

IMBRUVICA® is metabolised in the liver. Data from a hepatic impairment trial in non-cancer patients showed an increase in IMBRUVICA® exposure in those with hepatic impairment.

Mild hepatic impairment (Child-Pugh class A)	**Moderate** hepatic impairment (Child-Pugh class B)	**Severe** hepatic impairment (Child-Pugh class C)
• Recommended dose is 280 mg daily	• Recommended dose is 140 mg daily	• IMBRUVICA® is NOT recommended
• Monitor patients for signs of IMBRUVICA® toxicity and follow dose modification guidance as needed		

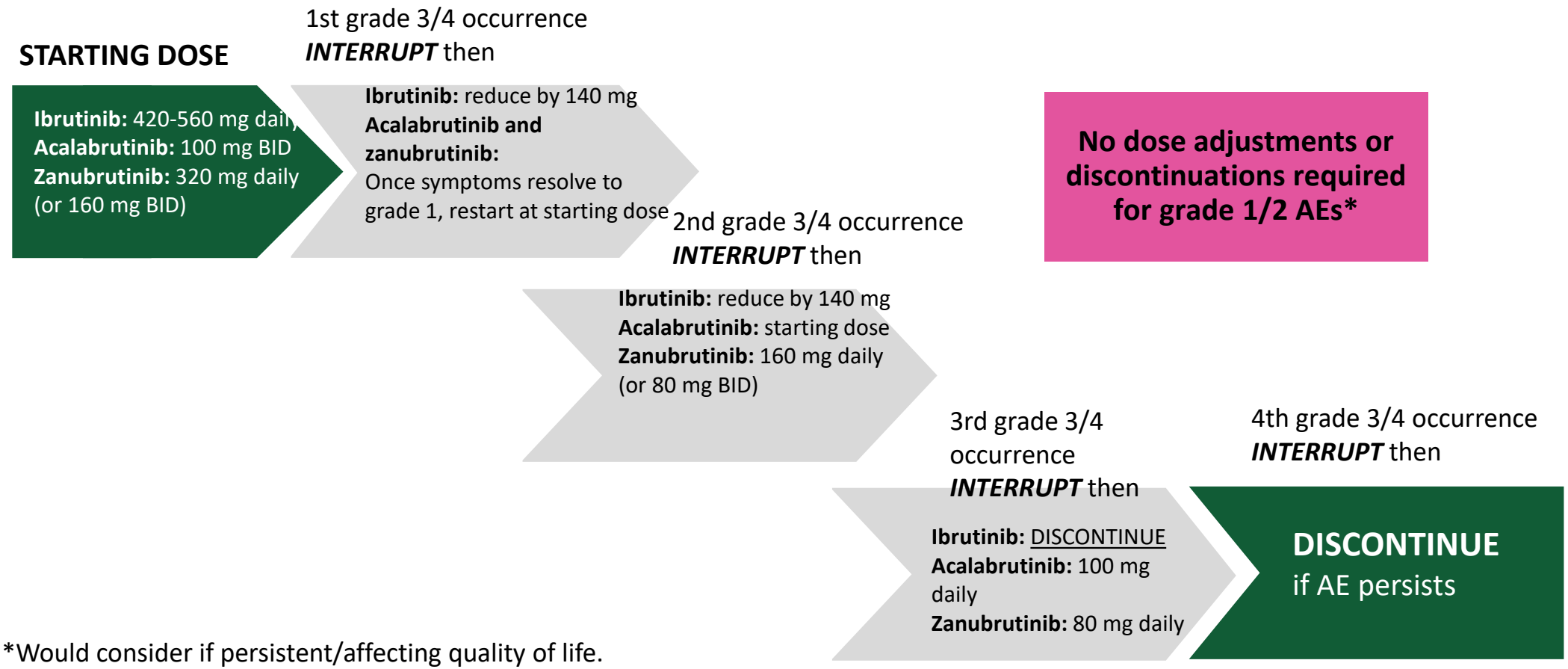
Other dose modifications / temporary interruptions:

- Reduce to 280 mg in patients:
  - Taking concomitant moderate CYP3A4 inhibitors
  - With mild hepatic impairment
- Reduce to 140 mg or withhold for up to 7 days in patients:
  - Taking concomitant strong CYP3A4 inhibitors
- Reduce to 140 mg in patients:
  - With moderate hepatic impairment
- Stop for 3–7 days pre- and post-surgery

WILEY

IMBRUVICA® Summary of Product Characteristics. https://www.medicines.org.uk/emc/search?q=imbruvica.

Dose Modifications for Nonhematologic AEs



*Would consider if persistent/affecting quality of life.

Acalabrutinib PI. Ibrutinib PI. Zanubrutinib PI.

Optimising CLL Therapy

Patient selection	▪ Past medical history, comorbid conditions ▪ Adherence assessment ▪ Goals of care (ie, desire to stop therapy) ▪ Financial implications of indefinite therapy
Drug interactions	▪ Thorough medicine reconciliation ▪ Evaluation of herbal medications ▪ Instruction to alert pharmacist of new medications
Adverse event management	▪ Optimize blood pressure (ibrutinib), TLS management (venetoclax) ▪ Manage headaches (acalabrutinib), IRRs (CD20 MAb) ▪ Counsel patients on common and serious adverse events ▪ Empower patients to self-manage when appropriate ▪ Provide patient-friendly information (oralchemoedsheets.com)

Drug Interactions

Avoid grapefruit juice!

	Ibrutinib	Acalabrutinib	Venetoclax
CYP3A4 inhibitors (mod)	Decrease to 280mg once daily	No dose adjustment required. Monitor patients more closely for AEs	Decrease by at least 50%
CYP3A4 inhibitors (strong)	Decrease to 140mg once daily or hold ibrutinib (≤7 days)	Avoid - If used short-term, interrupt acalabrutinib treatment	Contraindicated during initiation and ramp-up After dose titration reduce dose to ≤100mg (or by at least 75% if already modified for other reasons)
CYP3A4 inducers	If the benefit outweighs the risk and a strong or mod CYP3A4 inducer must be used, monitor patient closely for lack of efficacy St. John's Wort is contraindicated	Avoid strong CYP3A inducer	Avoid (strong and moderate) St. John's Wort is contraindicated
PgP inhibitors	Should be taken at least 6 hours before or after	Avoid. If used short-term, interrupt acalabrutinib treatment.	Avoid at initiation and dose titration. If must be used, monitor closely for signs of toxicities
Anticoagulants	Monitor for increased risk of bleeding		May increase warfarin concentration. Monitor INR closely
Antiplatelets	Monitor for increased risk of bleeding		N/A
Gastric Acid suppressants	N/A	*Antacids*: separate by at least 2 hr *H2RA*: administer acalabrutinib 2 hr prior or 10 hr after *PPIs*: Avoid	Does not affect bioavailability

1. Ibrutinib SmPC
2. Acalabrutinib SmPC
3. Venetoclax SmPC

Conclusions

- BTK inhibitors target a major vulnerability of CLL, thereby providing a highly effective treatment option in first line and relapse
- Continuous BTK inhibitor monotherapy has shown superiority vs CIT in several randomized studies
- Cardiovascular toxicity remains an important caveat of covalent BTK inhibitors
- Second-generation BTK inhibitors are safer to deliver and at least as effective as ibrutinib and can be valuable with ibrutinib intolerance
- A thorough clinical history encompassing comorbidities is of the utmost importance when considering therapy for patients with CLL
- Patients with problematic arrhythmias or poorly controlled hypertension may do better with other treatment modalities (eg, BCL-2 inhibition)
- Given the impressive efficacy of BTK inhibitors in the treatment of CLL, appropriate management of BTK inhibitor–emergent toxicities is of critical importance, as this class will remain a mainstay of therapy

Acknowledgments

- Some of the slides were adopted from clinical care options slide set

Thank you!