CLL SOCIETY

Smart Patients Get Smart Care™

ASH 2021 Comes to You!

February 2, 2022

11:30 AM PT, 12:30 PM MT,
1:30 PM CT, 2:30 PM ET

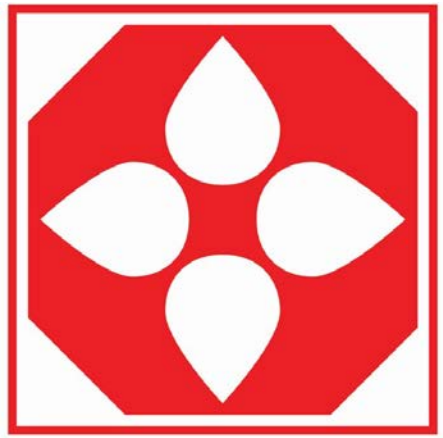
Speakers

Welcome
Robyn Brumble, MSN, RN
Director of Scientific Affairs and Research
CLL Society

Brian Koffman, MDCM (retired) MS Ed
Executive Vice President and Chief Medical Officer
CLL Society

Anthony Mato, MD, MSCE
Director, CLL Program
Memorial Sloan Kettering Cancer Center

CLL SOCIETY



CLL SOCIETY

Smart Patients Get Smart Care™

ASH 2021 Update: CLL

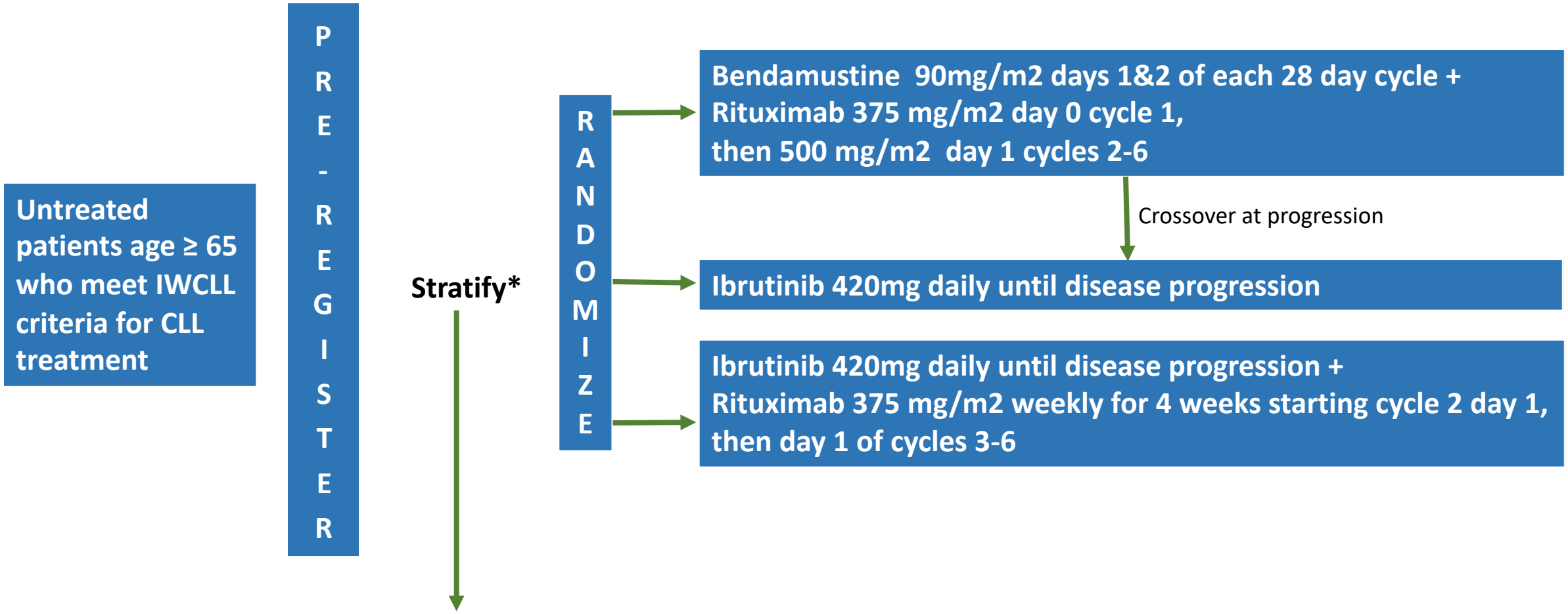
Anthony Mato, MD MSCE
MSKCC
CLL Program
Leukemia Service
New York, NY

Front Line CLL

Long term results of A041202 show continued advantage of ibrutinib-based regimens compared with bendamustine plus rituximab chemoimmunotherapy

Jennifer A. Woyach, MD, Amy S. Ruppert, PhD, Nyla A. Heerema, PhD, Weiqiang Zhao, MD, PhD, Allison M Booth, Wei Ding, MD, PhD, Nancy L. Bartlett, MD, Danielle M. Brander, MD, Paul M. Barr, MD, Kerry Rogers, MD, Sameer A. Parikh, MD, Steven Coutre, MD, Gerard Lozanski, MD, Sreenivasa Nattam, MD, Richard A. Larson, MD, Harry P. Erba, MD, PhD, Mark R. Litzow, MD, James S. Blachly, MD, Carolyn Owen, MD, Charles Kuzma, Jeremy S. Abramson, MD, Jennifer R Brown, MD, PhD, Richard F. Little, MD, MPH, Scott E. Smith, MD, PhD, Richard M. Stone, MD, Sumithra J Mandrekar, PhD and John C. Byrd, MD

Schema

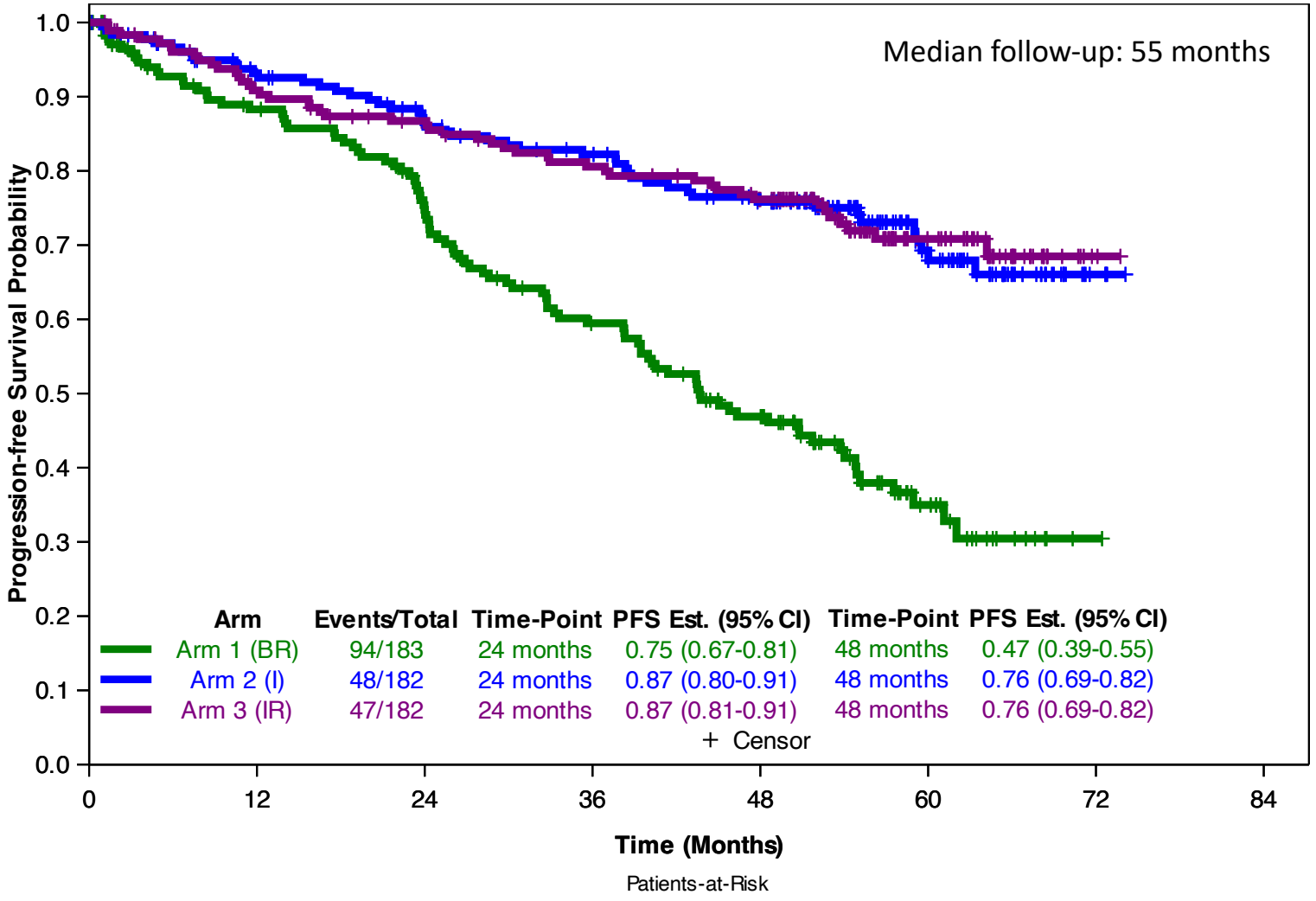


Stratification

- **High risk vs intermediate risk Rai Stage**
- **Presence vs absence of del(11q22.3) or del(17p13.1) on FISH performed locally**
- **< 20% vs ≥ 20% Zap-70 methylation of CpG 3 performed centrally**

ALLIANCE FOR CLINICAL TRIALS IN ONCOLOGY

Progression-free Survival



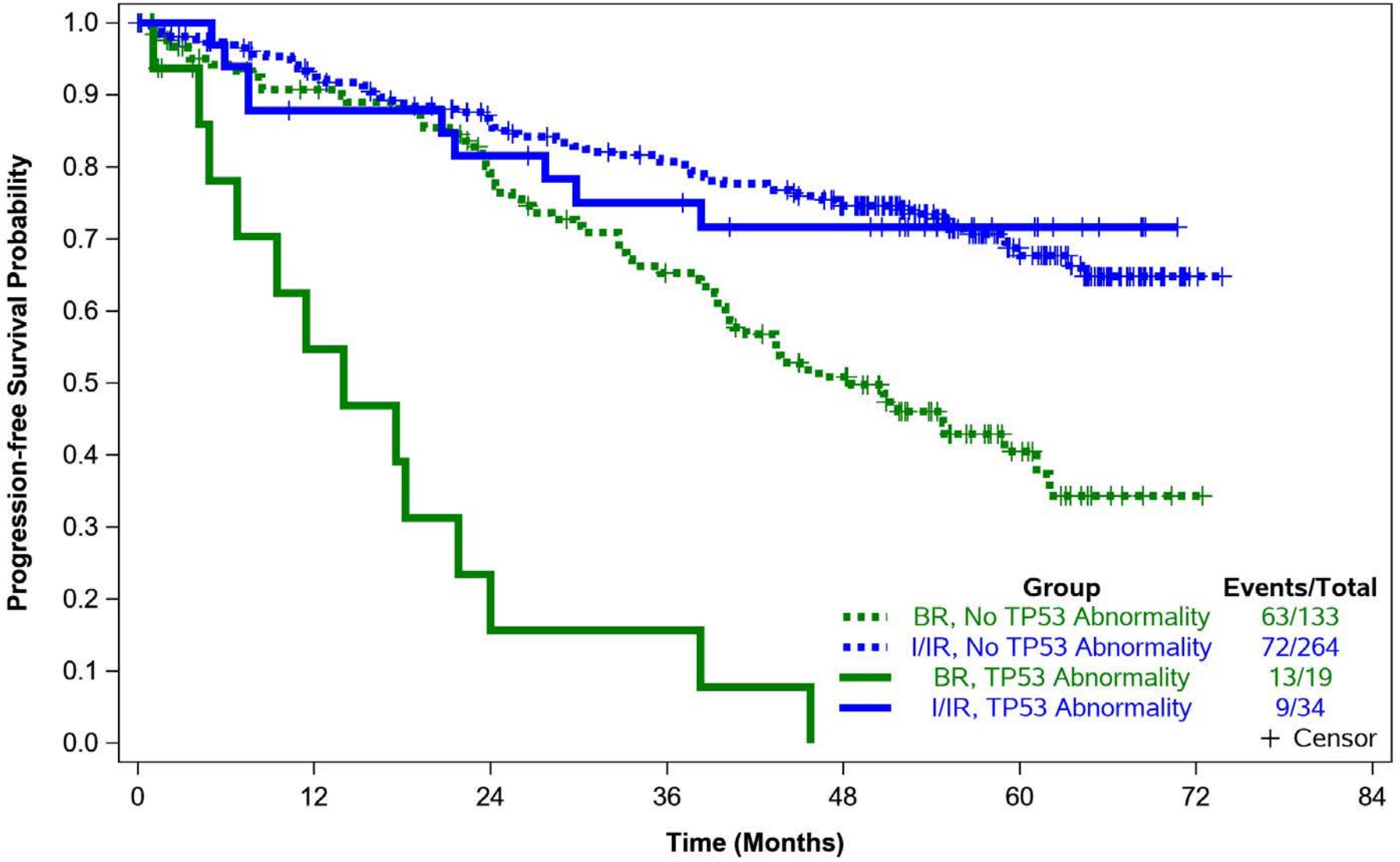
Pairwise Comparisons

I vs BR:
Hazard Ratio 0.36
95% CI: 0.26-0.52
P <0.0001

IR vs BR:
Hazard Ratio 0.36
95% CI: 0.25-0.51
P <0.0001

IR vs I:
Hazard Ratio 0.99
95% CI: 0.66-1.48
P = 0.96

Interaction: Treatment Group and TP53 Abnormalities



Treatment Effect
I/IR vs BR

No TP53 Abn
Hazard Ratio 0.39
95% CI: 0.27-0.55

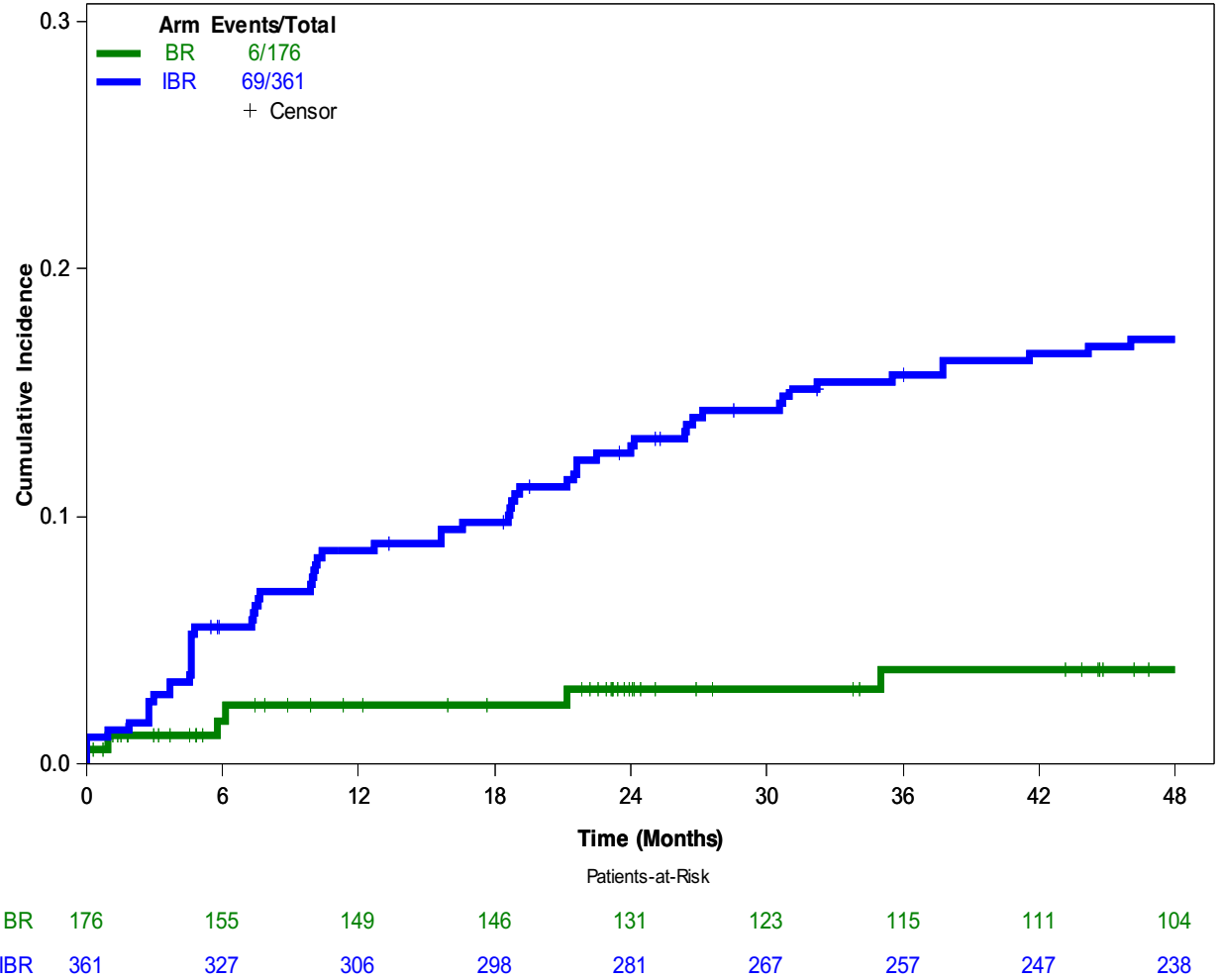
TP53 Abn
Hazard Ratio 0.07
95% CI: 0.03-0.18

Interaction P = 0.0006

ALLIANCE
FOR CLINICAL TRIALS IN ONCOLOGY

Notable Adverse Events: Atrial Fibrillation/Flutter

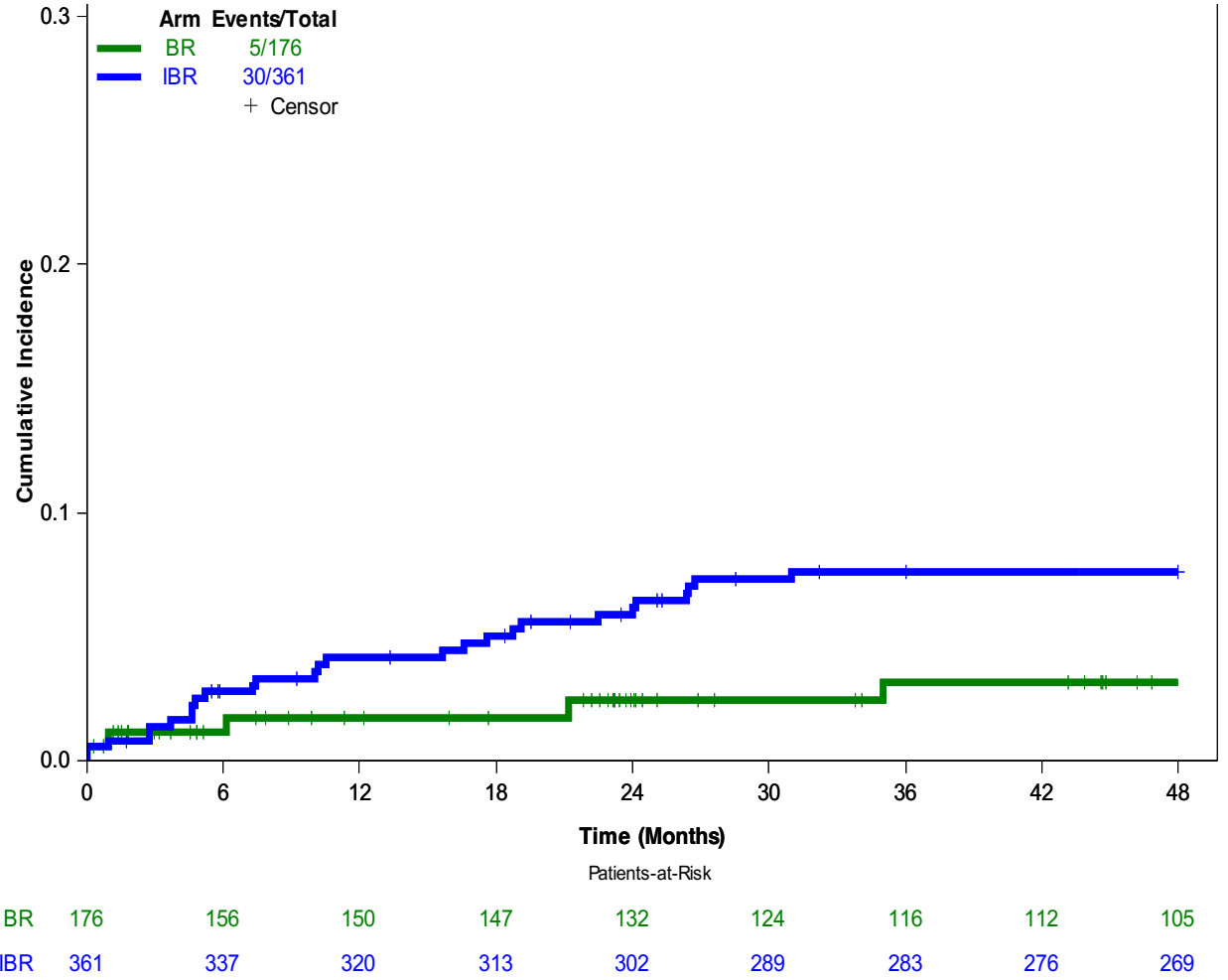
All Grades



Patients-at-Risk

BR	176	155	149	146	131	123	115	111	104
IBR	361	327	306	298	281	267	257	247	238

Grades 3+



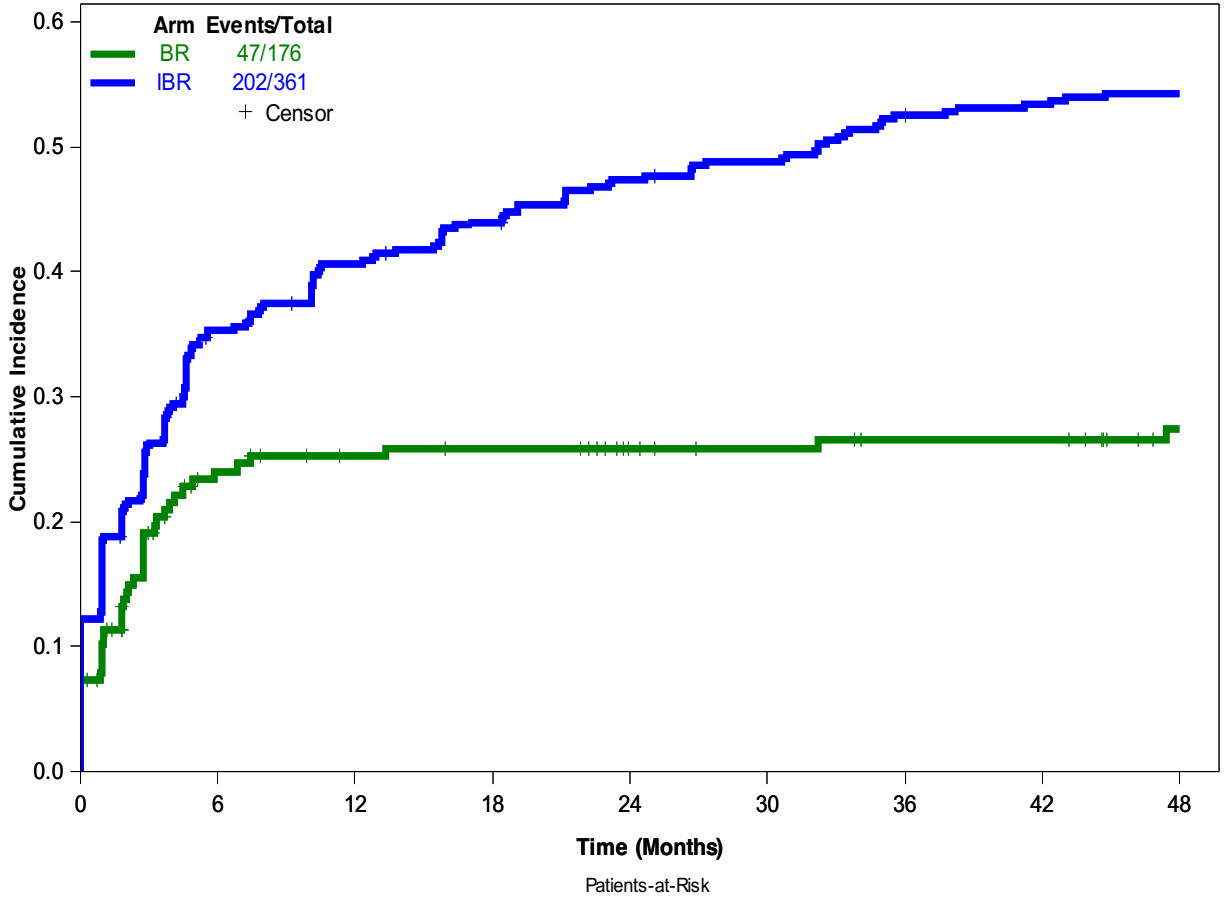
Patients-at-Risk

BR	176	156	150	147	132	124	116	112	105
IBR	361	337	320	313	302	289	283	276	269

Notable Adverse Events: Hypertension

New or Worsening

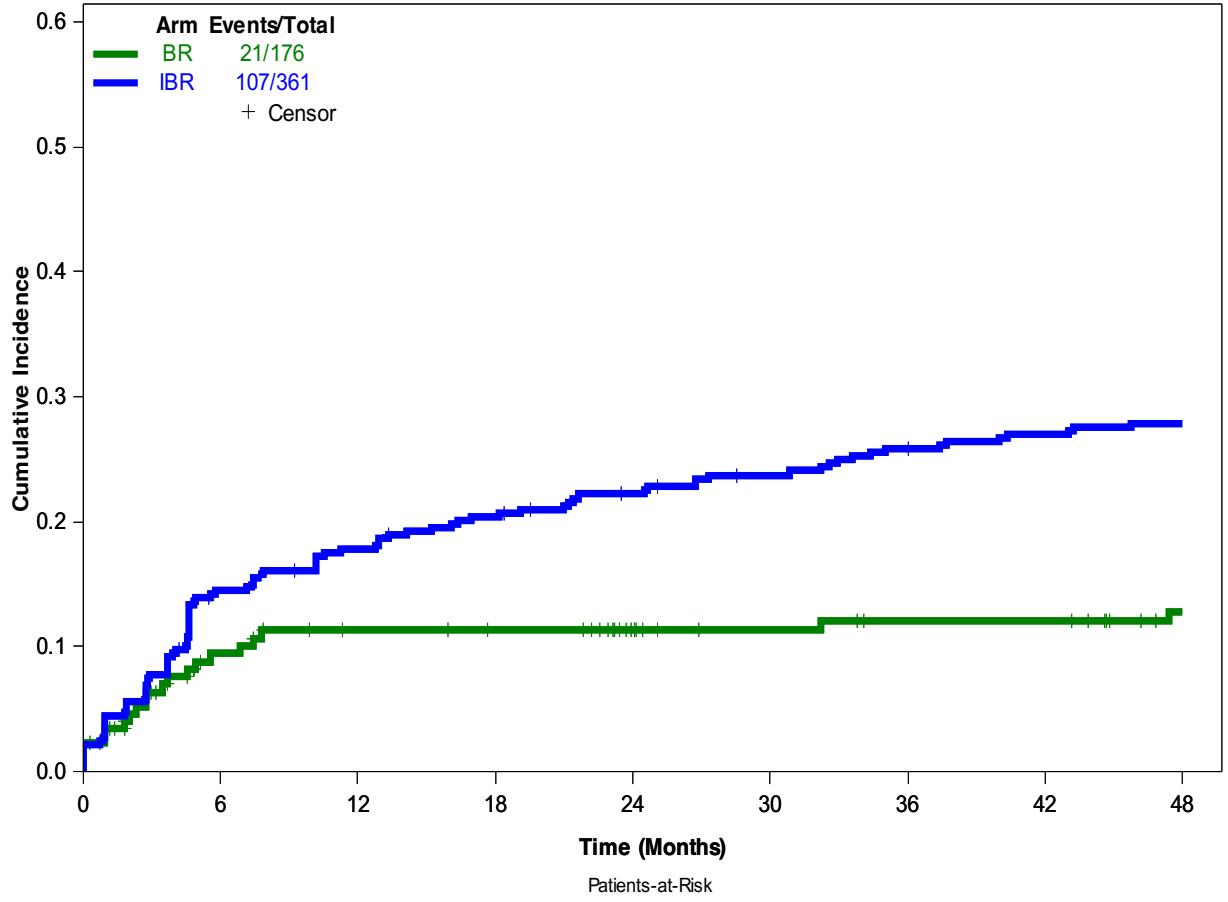
All Grades



Patients-at-Risk

BR	176	119	113	111	101	97	90	86	77
IBR	361	222	193	178	163	152	135	128	120

Grades 3+



Patients-at-Risk

BR	176	143	136	134	121	114	107	102	93
IBR	361	296	273	260	246	233	222	213	203

Ibrutinib Plus Rituximab Is Superior to FCR in Previously Untreated CLL: Results of the Phase III NCRI *Flair* Trial

Peter Hillmen, Alexandra Pitchford, Adrian Bloor, Angus Broom, Moya Young, Ben Kennedy, Renata Walewska, Michelle Furtado, Gavin Preston, Jeffrey R. Neilson, Nicholas Pemberton, Gamal Sidra, Nicholas Morley, Kate Cwynarski, Anna Schuh, Francesco Forconi, Nagah Elmusharaf, Shankara Paneesha, Christopher P. Fox, Dena Howard, Anna Hockaday, David Cairns, Sharon Jackson, Natasha Greatorex, Piers EM Patten, David Allsup and Talha Munir

Abstract No: 642, Oral Presentation, ASH Annual Meeting
Monday, December 13th 2021

National Cancer Research Institute

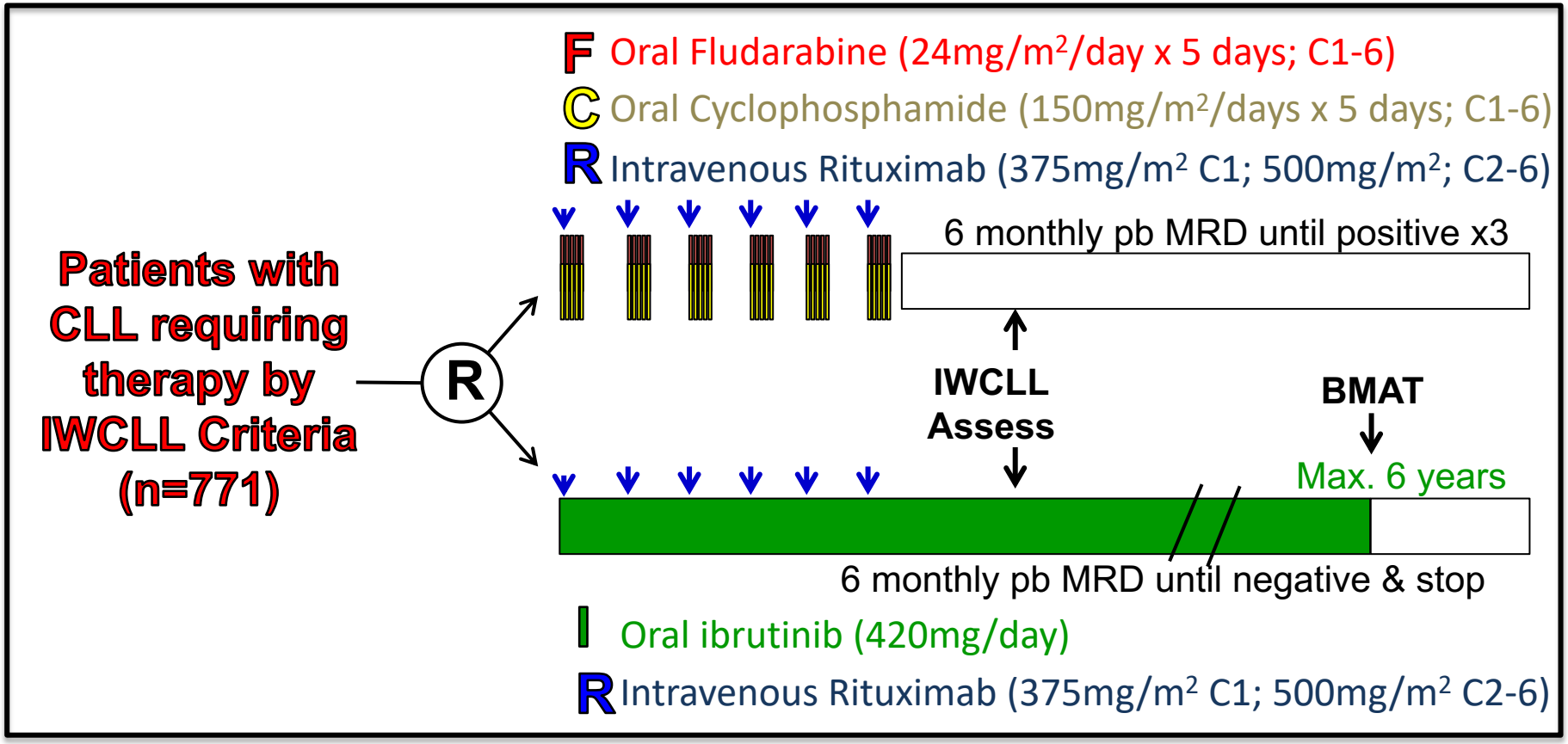
CANCER RESEARCH UK

ctru University of Leeds

LEEDS CLINICAL TRIALS UNIT

Front-line trial for patients fit for FCR: NCRI *Flair* Trial

Front Line therapy in CLL: Assessment of Ibrutinib plus Rituximab



Primary end-point:
To assess whether IR is superior to FCR in terms of PFS

Key secondary end-points:
Overall survival
Response including MRD
Safety and toxicity

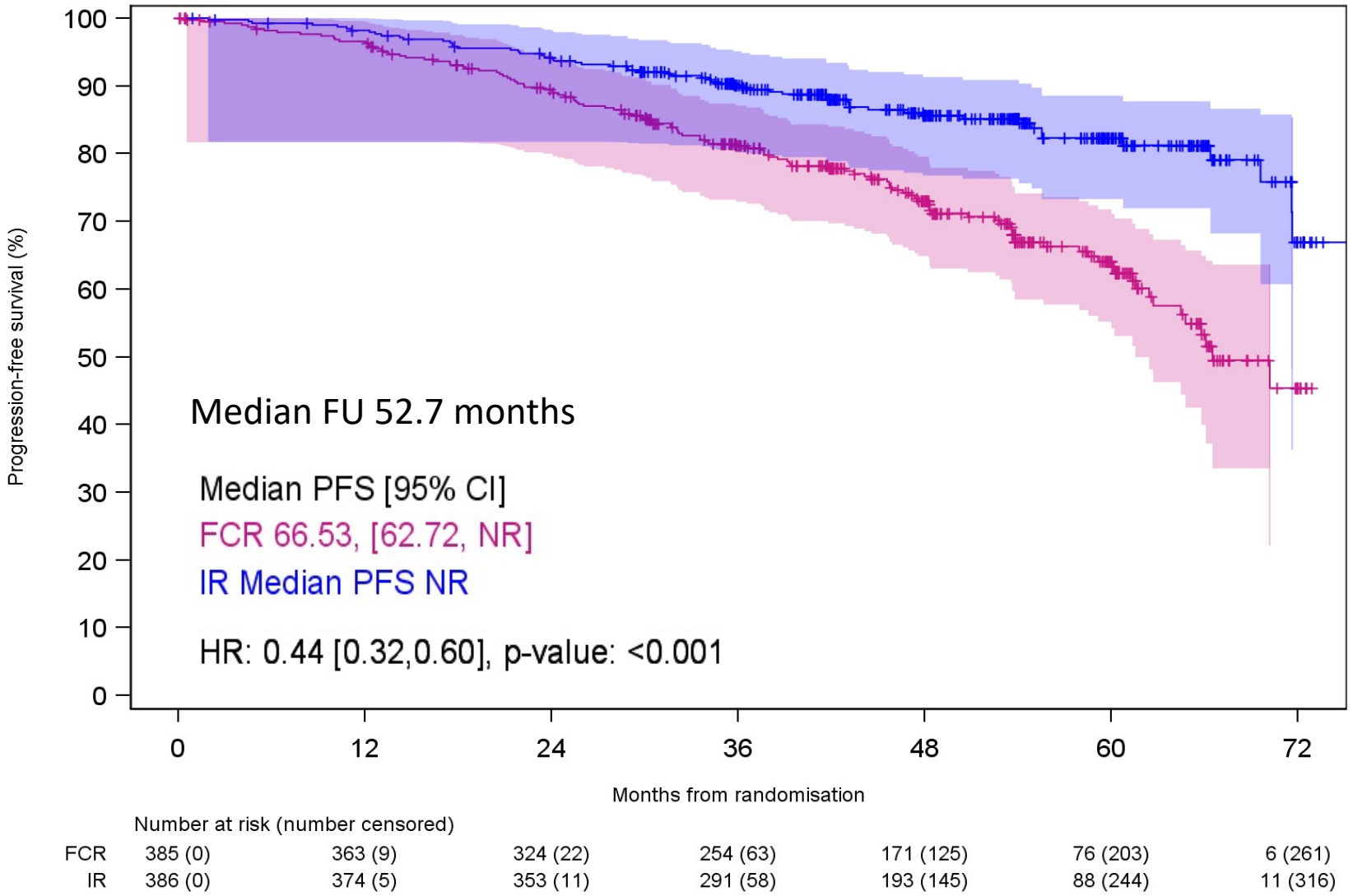
Key Inclusion Criteria:

- Previously untreated CLL requiring therapy by IWCLL criteria
- Considered fit for FCR
- ≤75 years old

Key Exclusion Criteria:
Prior therapy for CLL; History of Richter's transformation; >20% TP53 deletion by FISH; Concomitant warfarin (or equivalent) Symptomatic cardiac failure or angina

Hillmen *et al.*, Abstract 642, ASH 2021

Flair Primary end-point: Progression Free Survival



Number at risk (number censored)

FCR	385 (0)	363 (9)	324 (22)	254 (63)	171 (125)	76 (203)	6 (261)
IR	386 (0)	374 (5)	353 (11)	291 (58)	193 (145)	88 (244)	11 (316)

National Cancer Research Institute

Data-lock: 24th May 2021

Hillmen *et al.,* Abstract 642, ASH 2021

CANCER RESEARCH UK | ctru University of Leeds | LEEDS CLINICAL TRIALS UNIT

SEQUOIA: RESULTS OF A PHASE 3 RANDOMIZED STUDY OF ZANUBRUTINIB VERSUS BENDAMUSTINE + RITUXIMAB IN PATIENTS WITH TREATMENT-NAIVE CHRONIC LYMPHOCYTIC LEUKEMIA/SMALL LYMPHOCYTIC LYMPHOMA

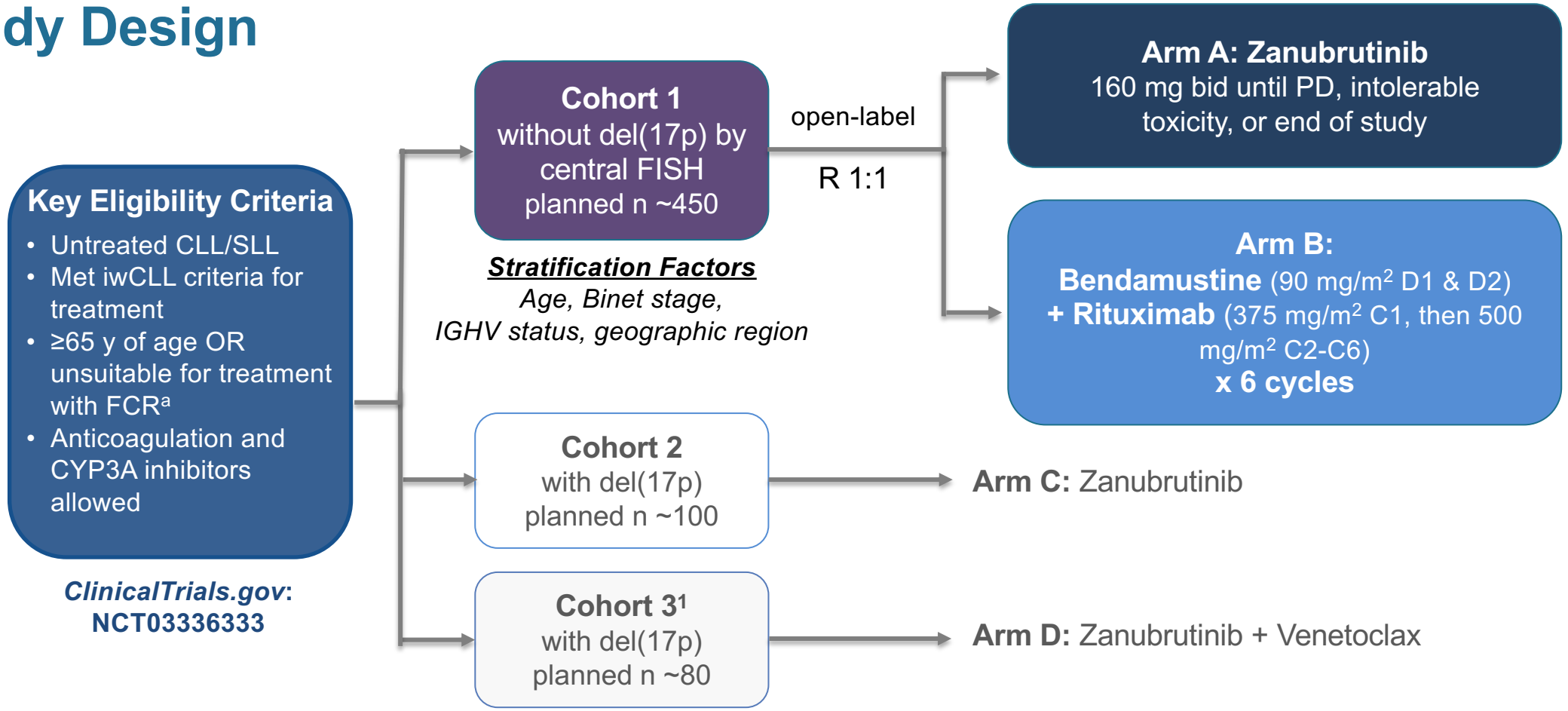
Constantine S. Tam, MBBS, MD[1,2,3,4]; Krzysztof Giannopoulos, MD, PhD[5,6]; Wojciech Jurczak, MD, PhD[7]; Martin Šimkovič, MD, PhD[8,9]; Mazyar Shadman, MD, MPH[10,11]; Anders Österborg, MD, PhD[12,13]; Luca Laurenti, MD[14]; Patricia Walker, MBBS, BMedSci, FRACP, FRCPA[15]; Stephen Opat, MBBS (Hons), FRACP, FRCPA[16,17]; Henry Chan, MBChB, FRACP, FRCPA[18]; Hanna Ciepluch, MD, PhD[19]; Richard Greil, MD[20,21,22]; Monica Tani, MD[23]; Marek Trněný, MD[24]; Danielle M. Brander, MD[25]; Ian W. Flinn, MD, PhD[26]; Sebastian Grosicki, MD, PhD[27]; Emma Verner, MBBS, BMedSci, FRCPA, FRACP[28,29]; Jennifer R. Brown MD, PhD[30]; Brad S. Kahl, MD[31]; Paolo Ghia, MD, PhD[32]; Jianyong Li, MD, PhD[33]; Tian Tian, PhD[34]; Lei Zhou, MD[34]; Carol Marimpietri[34]; Jason C. Paik, MD, PhD[34]; Aileen Cohen, MD, PhD[34]; Jane Huang, MD[34]; Tadeusz Robak, MD, PhD[35]; and Peter Hillmen, MBChB, PhD[36]

[1]Peter MacCallum Cancer Centre, Melbourne, Victoria, Australia; [2]University of Melbourne, Parkville, Victoria, Australia; [3]St Vincent's Hospital Melbourne, Fitzroy, Victoria, Australia; [4]Royal Melbourne Hospital, Parkville, Victoria, Australia; [5]Experimental Hematooncology Department, Medical University of Lublin, Lublin, Poland; [6]Hematology Department, St. John's Cancer Centre, Lublin, Poland; [7]Maria Sklodowska-Curie National Research Institute of Oncology, Krakow, Poland; [8]Fourth Department of Internal Medicine - Haematology, University Hospital, Hradec Kralove, Czech Republic; [9]Faculty of Medicine, Charles University, Prague, Czech Republic; [10]Fred Hutchinson Cancer Research Center, Seattle, WA, USA; [11]Department of Medicine, University of Washington, Seattle, WA, USA; [12]Department of Oncology-Pathology, Karolinska Institutet, Stockholm, Sweden; [13]Department of Hematology, Karolinska University Hospital, Stockholm, Sweden; [14]Fondazione Policlinico Universitario A Gemelli UCSC, Rome, Italy; [15]Peninsula Private Hospital, Frankston, Victoria, Australia; [16]Monash Health, Clayton, Victoria, Australia; [17]Monash University, Clayton, Victoria, Australia; [18]North Shore Hospital, Auckland, New Zealand; [19]Copernicus Regional Oncology Center, Gdansk, Poland; [20]Third Medical Department with Hematology, Medical Oncology, Rheumatology and Infectiology, Paracelsus Medical University, Salzburg, Austria; [21]Salzburg Cancer Research Institute (SCRI) Center for Clinical Cancer and Immunology Trials (CCCIT), Salzburg, Austria; [22]Cancer Cluster Salzburg (CCS), Salzburg, Austria; [23]Hematology Unit, Santa Maria delle Croci Hospital, Ravenna, Italy; [24]First Department of Medicine, First Faculty of Medicine, Charles University, General Hospital, Prague, Czech Republic; [25]Hematologic Malignancies and Cellular Therapy, Duke University School of Medicine, Durham, NC, USA; [26]Sarah Cannon Research Institute/Tennessee Oncology, Nashville, TN, USA; [27]Department of Hematology and Cancer Prevention, Health Sciences Faculty, Medical University of Silesia, Katowice, Poland; [28]Concord Repatriation General Hospital, Concord, New South Wales, Australia; [29]University of Sydney, Sydney, New South Wales, Australia; [30]Dana-Farber Cancer Institute, Boston, MA, USA; [31]Washington University School of Medicine, St Louis, MO, USA; [32]Università Vita-Salute San Raffaele and IRCCS Ospedale San Raffaele, Milano, Italy; [33]Department of Hematology, The First Affiliated Hospital of Nanjing Medical University, Jiansu Province Hospital, Nanjing, China; [34]BeiGene (Beijing) Co., Ltd., Beijing, China and BeiGene USA, Inc., San Mateo, CA, USA; [35]Medical University of Lodz, Lodz, Poland; and [36]St James's University Hospital, Leeds, United Kingdom

Sunday, December 12, 2021
642. Chronic Lymphocytic Leukemia: Clinical and Epidemiological I

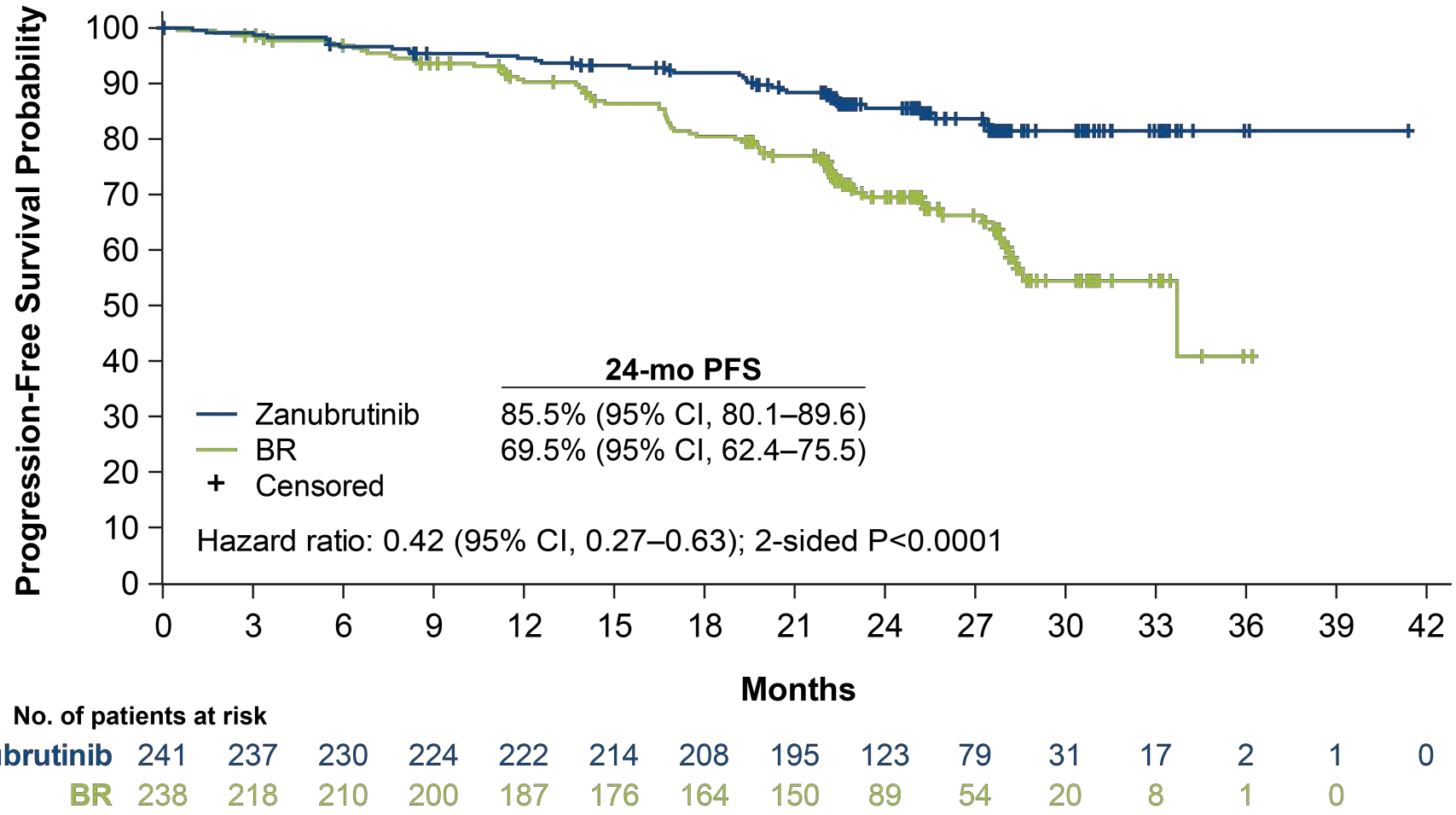
63rd ASH Annual Meeting and Exposition, December 11-14, 2021
Abstract 396

SEQUOIA (BGB-3111-304)
Study Design



[a]Defined as Cumulative Illness Rating Scale >6, creatinine clearance <70 mL/min, or a history of previous severe infection or multiple infections within the last 2 years.
C, cycle; CLL/SLL, chronic lymphocytic leukemia/small lymphocytic lymphoma; CYP3A, cytochrome P450, family 3, subfamily A; D, day; del(17p), chromosome 17p deletion; FCR, fludarabine, cyclophosphamide, and rituximab; FISH, fluorescence in-situ hybridization; IRC, independent review committee; IGHV, gene encoding the immunoglobulin heavy chain variable region; iwCLL, International Workshop on CLL; ORR, overall response rate; PD, progressive disease; R, randomized.
1. Tedeschi A, et al. ASH 2021. Abstract 67.

Progression-Free Survival Per IRC Assessment



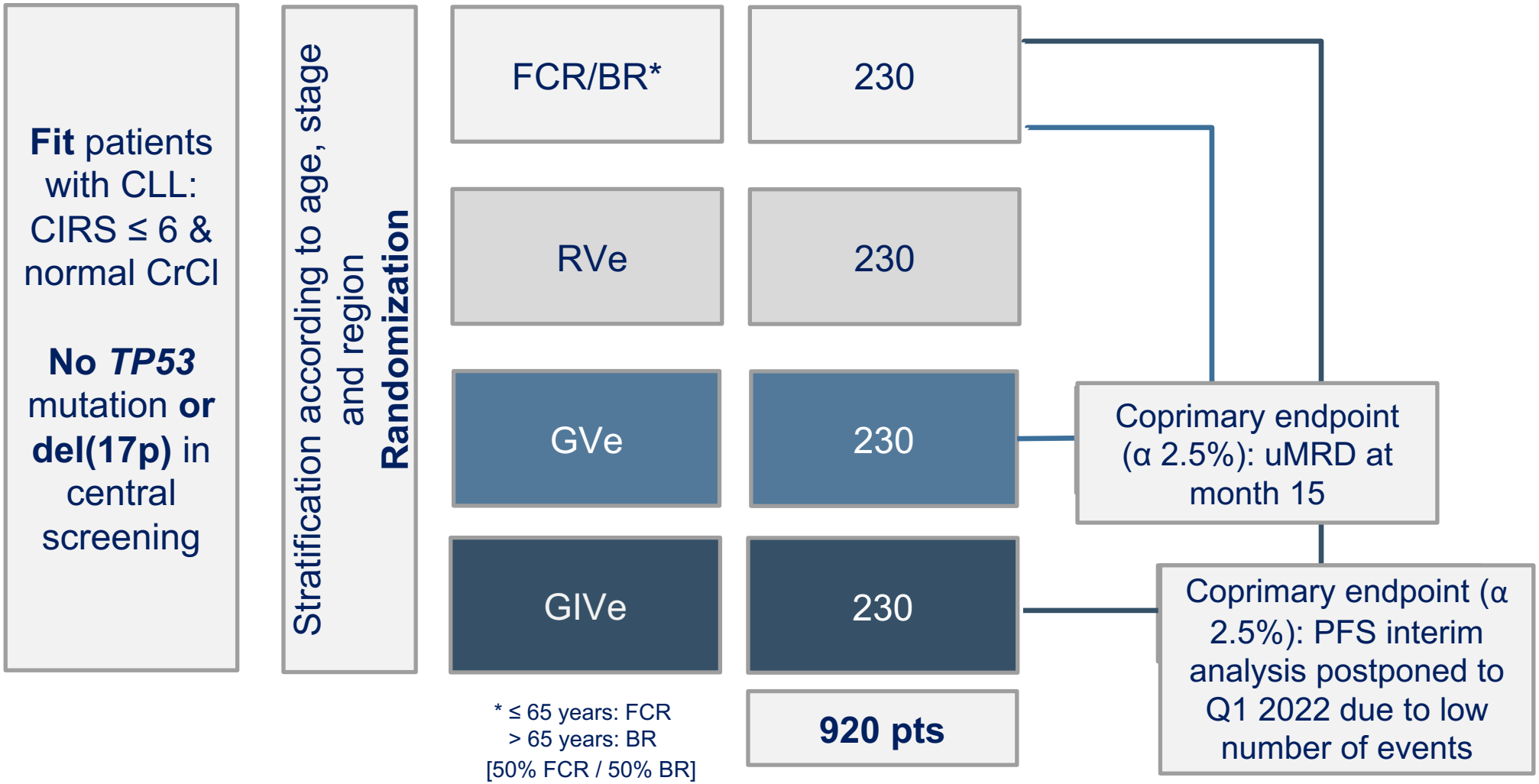
BR, bendamustine + rituximab; IRC, independent review committee; PFS, progression-free survival.

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 OF FIT PATIENTS: FIRST CO-PRIMARY ENDPOINT ANALYSIS OF THE INTERNATIONAL INTERGROUP GAIA (CLL13) TRIAL

Barbara Eichhorst, Carsten U Niemann, Arnon P Kater, Moritz Fürstenau, Julia von Tresckow, Can Zhang, Sandra Robrecht, Michael Gregor, Gunnar Juliusson, Patrick Thornton, Philipp B. Staber, Tamar Tadmor, Vesa Lindström, Caspar da Cunha-Bang, Christoph Schneider, Christian Poulsen, Thomas Illmer, Björn Schöttker, Ann Janssens, Ilse Christiansen, Thomas Nösslinger, Michael Baumann, Marjolein van der Klift, Ulrich Jäger, Henrik Frederiksen, Maria BL Leys, Mels Hoogendoorn, Kourosh Lotfi, Holger Hebart, Tobias Gaska, Harry Koene, Florian Simon, Nisha De Silva, Anna Fink, Kirsten Fischer, Clemens Wendtner, Karl A Kreuzer, Matthias Ritgen, Monika Brüggemann, Eugen Tausch, Mark-David Levin, Marinus van Oers, Christian Geisler, Stephan Stilgenbauer, Michael Hallek

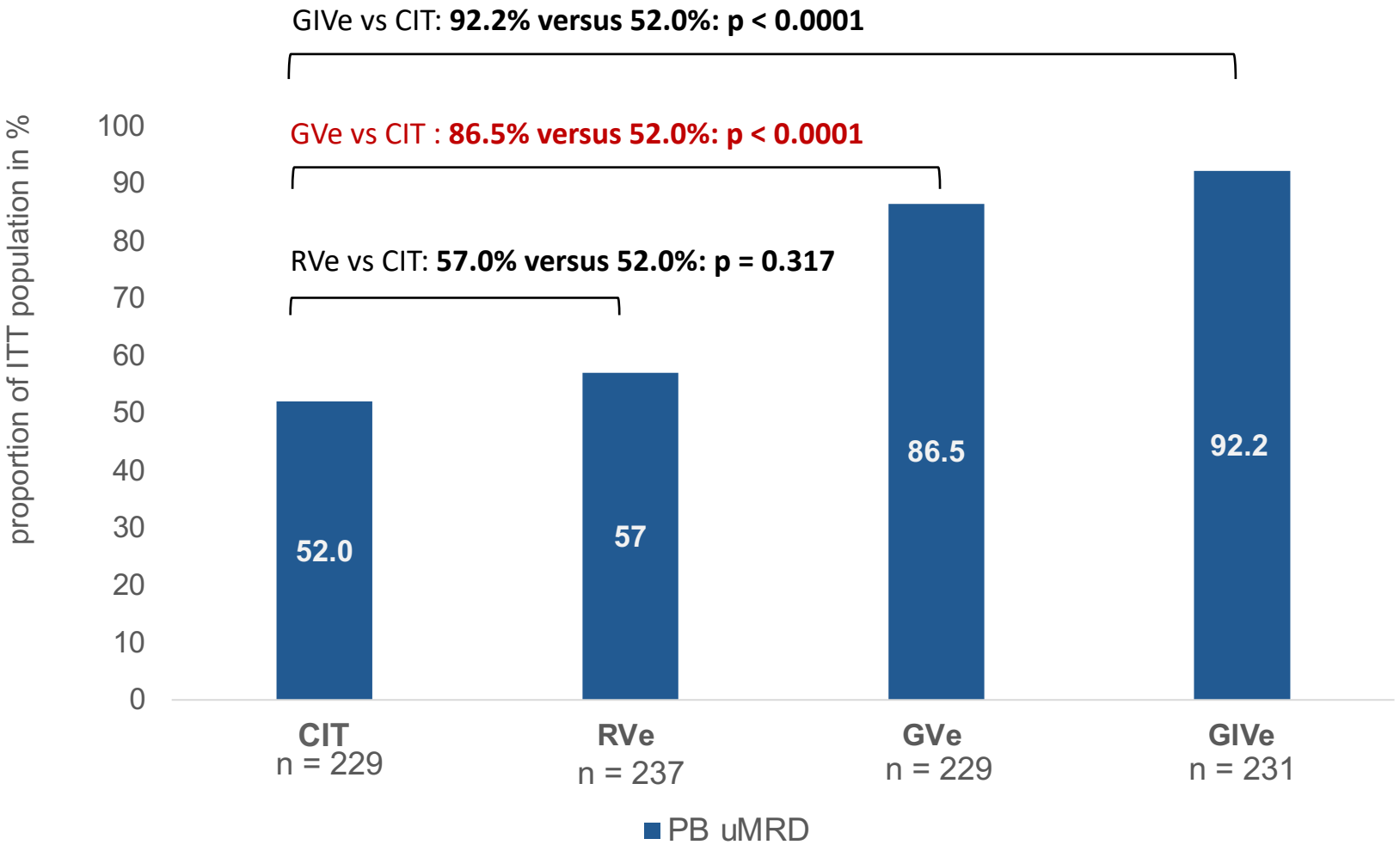
GAIA/CLL13 Study : Design

Chemoimmunotherapy (**FCR/BR**) versus **R**ituximab + **Ve**netoclax versus Obinutuzumab (**G**) + **Ve** versus **G** + **I**brutinib + **Ve**
Recruitment in 10 countries (DE, AU, CH, NL, BE, DK, SE, FL, IR, IL)



Coprimary endpoint: uMRD (< 10^{-4}) at Mo15 in PB by 4-colour-flow

ITT analysis: 63 pts (34 CIT, 15 RVe, 10 GVe, 4 GIVe) with missing samples (6.8%) were counted as MRD positive



	uMRD%	97.5% CI
GIVe	92.2	87.3 – 95.7
GVe	86.5	80.6 – 91.1
RVe	57.0	49.5 – 64.2
SCIT	52.0	44.4 – 59.5

Adverse Events ≥ CTC Grade 3 Overview

Severe AEs occurring in ≥5% of pts and AEs of interest independent from incidence

	CIT	RVe	GVe	GIVe
All patients [SP]	**216**	**237**	**228**	**231**
Anemia	16 (7.4)	9 (3.8)	11 (4.8)	9 (3.9)
Neutropenia	113 (52.3)	109 (46.0)	127 (55.7)	112 (48.5)
Thrombocytopenia	22 (10.2)	10 (4.2)	42 (18.4)	37 (16.0)
Febrile neutropenia	**24 (11.1)**	**10 (4.2)**	**7 (3.1)**	**18 (7.8)**
Infections	**43 (19.9)**	**27 (11.4)**	**32 (14.0)**	**51 (22.1)**
Tumor lysis syndrome*	**9 (4.2)**	**24 (10.1)**	**20 (8.8)**	**15 (6.5)**
Bleeding events	1 (0.5)	1 (0.4)	1 (0.4)	4 (1.7)
Atrial fibrillation	1 (0.5)	1 (0.4)	0 (0.0)	6 (2.6)

* Including clinical and laboratory TLS according to Cairo-Bishop

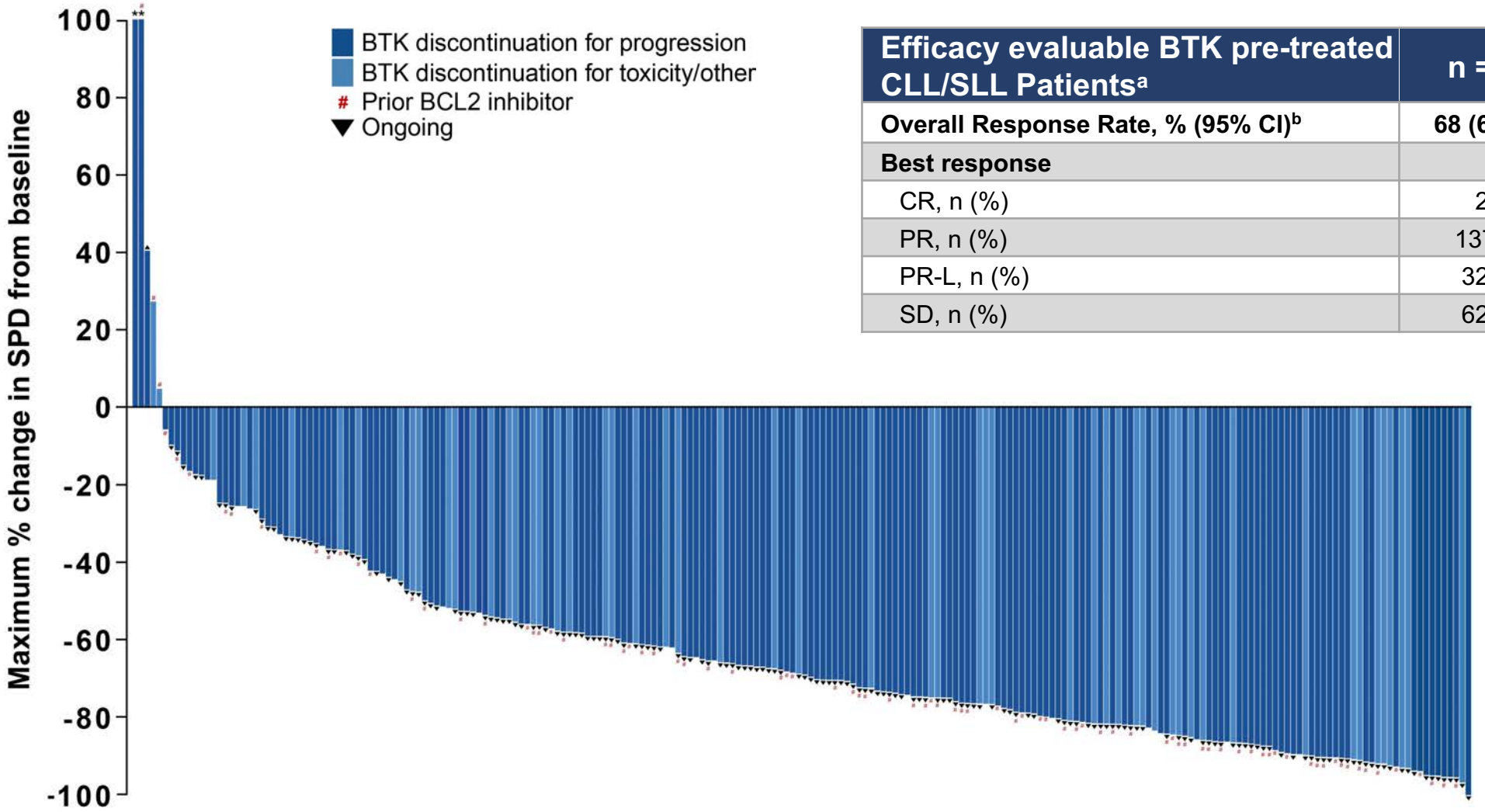
Relapsed/Refractory CLL

Pirtobrutinib, A Highly Selective, Non-covalent (Reversible) BTK Inhibitor In Previously Treated CLL/SLL: Updated Results From The Phase 1/2 BRUIN Study

Anthony R. Mato[1], John M. Pagel[2], Catherine C. Coombs[3], Nirav N. Shah[4], Nicole Lamanna[5], Talha Munir[6], Ewa Lech-Maranda[7], Toby A. Eyre[8], Jennifer A. Woyach[9], William G. Wierda[10], Chan Y. Cheah[11], Jonathan B. Cohen[12], Lindsey E. Roeker[1], Manish R. Patel[13], Bita Fakhri[14], Minal A. Barve[15], Constantine S. Tam[16], David J. Lewis[17], James N. Gerson[18], Alvaro J. Alencar[19], Chaitra S. Ujjani[20], Ian W. Flinn[21], Suchitra Sundaram[22], Shuo Ma[23], Deepa Jagadeesh[24], Joanna M. Rhodes[25], Justin Taylor[19], Omar Abdel-Wahab[1], Paolo Ghia[26], Stephen J. Schuster[18], Denise Wang[27], Binoj Nair[27], Edward Zhu[27], Donald E. Tsai[27], Matthew S. Davids[28], Jennifer R. Brown[28], Wojciech Jurczak[29]

[1]Memorial Sloan Kettering Cancer Center, New York, USA; [2]Swedish Cancer Institute, Seattle, USA; [3]University of North Carolina at Chapel Hill, Chapel Hill, USA; [4]Medical College of Wisconsin, Milwaukee, USA; [5]Herbert Irving Comprehensive Cancer Center, Columbia University, New York, USA; [6]Department of Haematology, St. James's University Hospital, Leeds, UK; [7]Institute of Hematology and Transfusion Medicine, Warsaw, Poland; [8]Oxford University Hospitals NHS Foundation Trust, Churchill Cancer Center, Oxford, UK; [9]The Ohio State University Comprehensive Cancer Center, Columbus, USA; [10]MD Anderson Cancer Center, Houston, USA; [11]Linear Clinical Research and Sir Charles Gairdner Hospital, Perth, Australia; [12]Winship Cancer Institute, Emory University, Atlanta, GA, USA; [13]Florida Cancer Specialists/Sarah Cannon Research Institute, Sarasota, USA; [14]University of California San Francisco, San Francisco, USA; [15]Mary Crowley Cancer Research, Dallas, USA; [16]Peter MacCallum Cancer Center, Royal Melbourne Hospital, and University of Melbourne, Melbourne, Australia; [17]Plymouth Hospitals NHS Trust - Derriford Hospital, Plymouth, UK; [18]Lymphoma Program, Abramson Cancer Center, University of Pennsylvania, Philadelphia, USA; [19]University of Miami Miller School of Medicine, Miami, USA; [20]Fred Hutchinson Cancer Research Center, [21]Sarah Cannon Research Institute, Nashville, USA; [22]Department of Hematology and Medical Oncology, Tisch Cancer Institute, Icahn School of Medicine at Mount Sinai, New York, NY, [23]Robert H. Lurie Comprehensive Cancer Center of Northwestern University, Chicago, IL, USA; [24]Cleveland Clinic, Cleveland, OH, USA; [25]Northwell Health Cancer Institute, Donald and Barbara Zucker School of Medicine at Hofstra/Northwell Health, New Hyde Park, NY; [26]Università Vita-Salute San Raffaele and IRCCS Ospedale San Raffaele, Milan, Italy; [27]Loxo Oncology at Lilly, Stamford, CT, USA; [28]Dana-Farber Cancer Institute and Harvard Medical School, Boston, USA; [29]Maria Sklodowska-Curie National Research Institute of Oncology, Krakow, Poland

Pirtobrutinib Efficacy in BTK Pre-treated CLL/SLL Patients

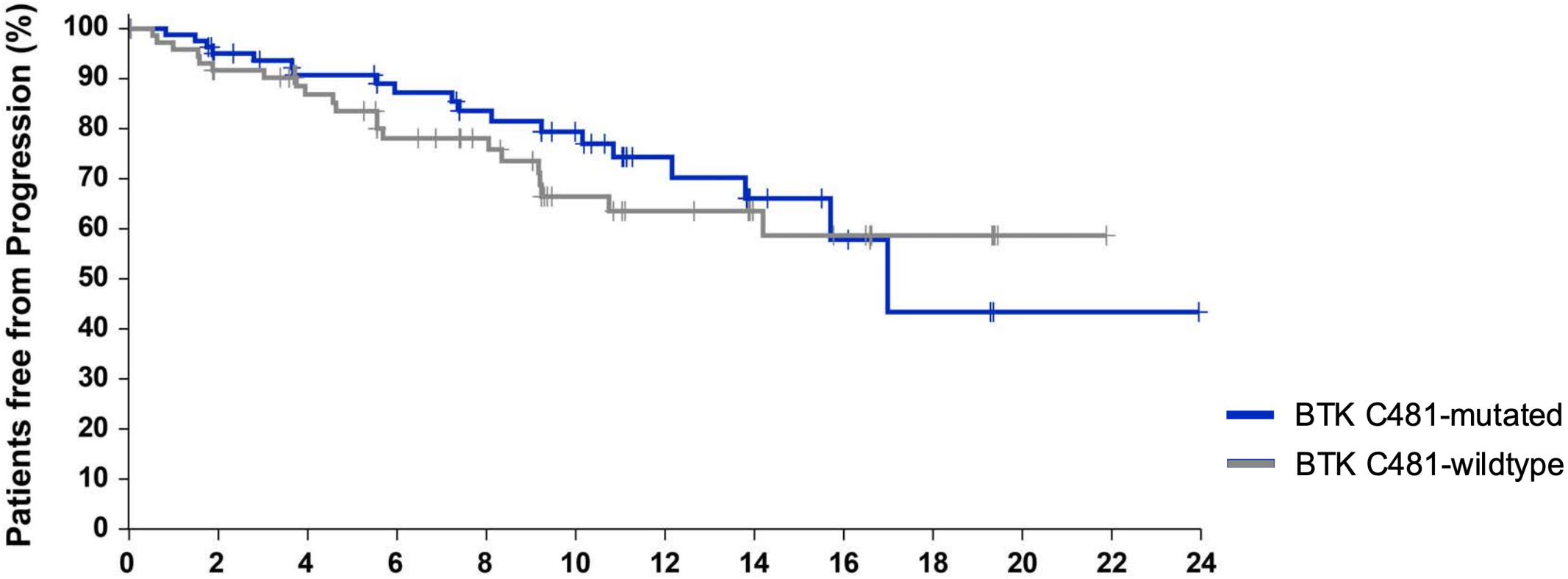


Efficacy evaluable BTK pre-treated CLL/SLL Patients[a]	n = 252
Overall Response Rate, % (95% CI)[b]	**68 (62 – 74)**
Best response	
CR, n (%)	2 (1)
PR, n (%)	137 (54)
PR-L, n (%)	32 (13)
SD, n (%)	62 (25)

Data cutoff date of 16 July 2021. *Patients with >100% increase in SPD. Data for 30 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]Efficacy evaluable patients are those who had at least one post-baseline response assessment or had discontinued treatment prior to first post-baseline response assessment. [b]ORR includes patients with a best response of CR, PR, and PR-L. Response status per iwCLL 2018 according to investigator assessment. Total % may be different than the sum of the individual components due to rounding.

BTK C481 Mutation Status is not Predictive of Pirtobrutinib Benefit

Progression-free survival by BTK C481 mutation status[a] in CLL/SLL patients with progression on a prior BTK inhibitor



Number at risk													
BTK C481-mutated	84	68	54	49	40	33	18	10	7	3	1	1	0
BTK C481-wildtype	74	62	52	40	35	23	19	13	11	5	1	0	

Data cutoff date of 16 July 2021. Response status per iwCLL 2018 according to investigator assessment. [a]BTK C481 mutation status was centrally determined and based on pre-treatment samples.

Pirtobrutinib Safety Profile

	All doses and patients (n=618)						
	Treatment-emergent AEs, (≥15%), %					Treatment-related AEs, %	
Adverse Event	Grade 1	Grade 2	Grade 3	Grade 4	Any Grade	Grades 3/4	Any Grade
Fatigue	13%	8%	1%	-	23%	1%	9%
Diarrhea	15%	4%	<1%	<1%	19%	<1%	8%
Neutropenia[a]	1%	2%	8%	6%	18%	8%	10%
Contusion	15%	2%	-	-	17%	-	12%
AEs of special interest[b]							
Bruising[c]	20%	2%	-	-	22%	-	15%
Rash[d]	9%	2%	<1%	-	11%	<1%	5%
Arthralgia	8%	3%	<1%	-	11%	-	3%
Hemorrhage[e]	5%	2%	1%[g]	-	8%	<1%	2%
Hypertension	1%	4%	2%	-	7%	<1%	2%
Atrial fibrillation/flutter[f]	-	1%	<1%	<1%	2%[h]	-	<1%

No DLTs reported and MTD not reached
96% of patients received ≥1 pirtobrutinib dose at or above RP2D of 200 mg daily
1% (n=6) of patients permanently discontinued due to treatment-related AEs

Data cutoff date of 16 July 2021. Total % may be different than the sum of the individual components due to rounding. [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]Represents 6 events (all grade 3), including 2 cases of post-operative bleeding, 1 case each of GI hemorrhage in the setting of sepsis, NSAID use, chronic peptic ulcer disease, and one case of subarachnoid hemorrhage in setting of traumatic bike accident. [h]Of 10 total afib/aflutter TEAEs, 3 occurred in patients with a prior medical history of atrial fibrillation, 2 in patients presenting with concurrent systemic infection, and 2 in patients with both.

CLL and COVID-19

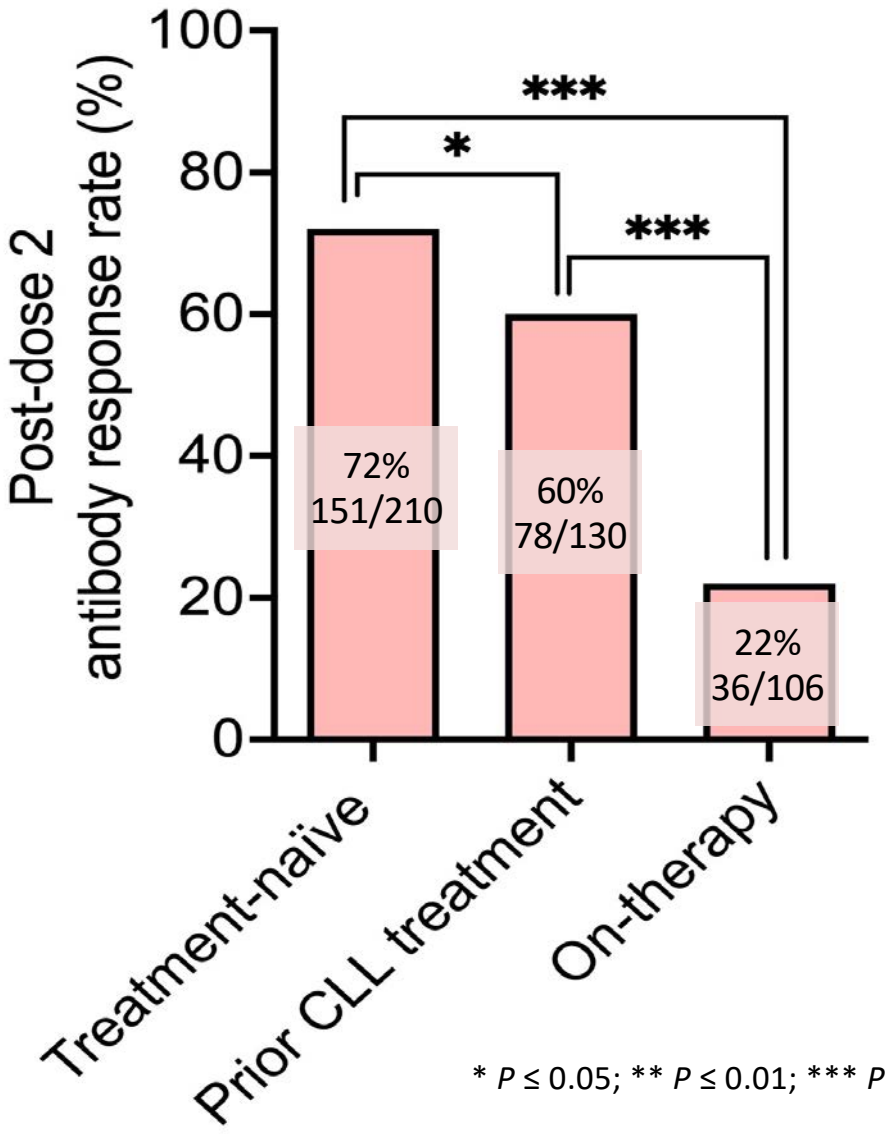
Humoral Response to mRNA Vaccines BNT162b2 and mRNA-1273 COVID-19 in Chronic Lymphocytic Leukemia Patients

Cristina Bagacean, Rémi Letestu, Chadi Al Nawakil, Ségolène Brichler, Vincent Lévy, Nanthara Sritharan, Alain Delmer, Caroline Dartigeas, Véronique Leblond, Damien Roos-Weil, Marie C Béné, Aline Clavert, Driss Chaoui, Philippe Genet, Romain Guieze, Kamel Laribi, Yamina Touileb, Bernard Drénou, Lise Willems, Cécile Tomowiak, Fatiha Merabet, Christian Puppink, Hugo Legendre, Xavier Troussard, Stéphanie Malartre, Florence Cymbalista and Anne-Sophie Michallet

Study of the French Innovative Leukemia Organization

FRENCH INNOVATIVE LEUKEMIA ORGANIZATION

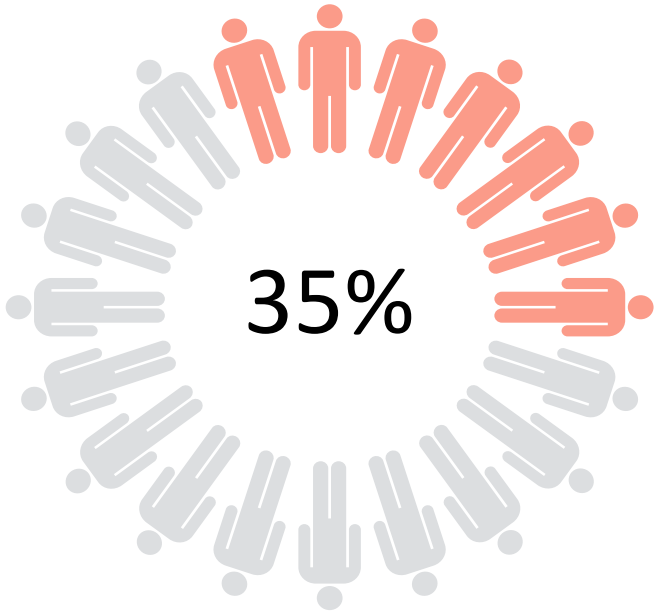
Post-dose 2 response rate and treatment



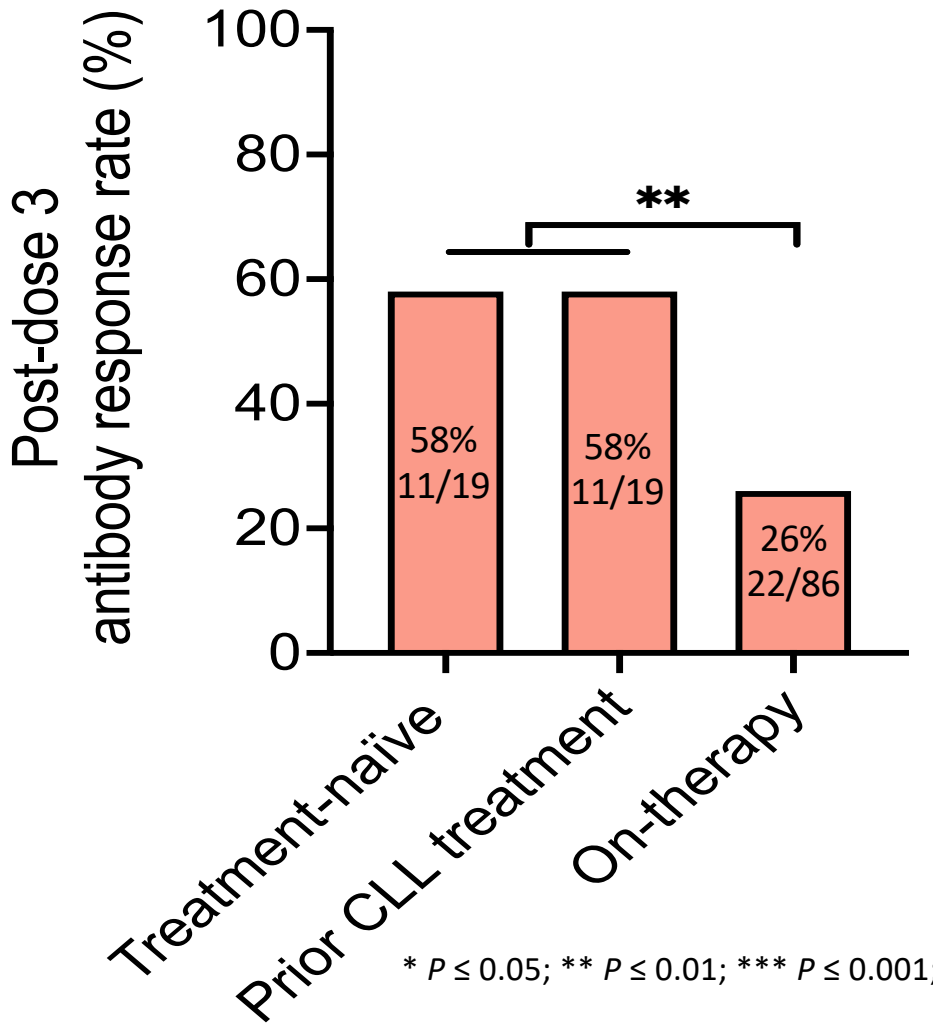
- Treatment-naïve patients had the highest response rate as compared with previously treated patients (*P*=0.02) and with patients on therapy (*P*<0.001)

* $P \leq 0.05$; ** $P \leq 0.01$; *** $P \leq 0.001$; **** $P \leq 0.0001$

Post-dose 3 response rate of patients seronegative after 2 doses



Response rate post-dose 3
(44/124)

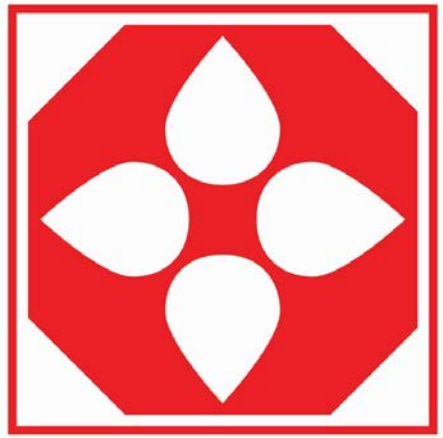


- Treatment-naïve patients and previously treated patients had a significantly higher response rate as compared with patients on therapy (*P*=0.01)
- The majority of patients on therapy were receiving BTKi (71%, 61/86) and had a response rate of 31% (19/61)

* $P \leq 0.05$; ** $P \leq 0.01$; *** $P \leq 0.001$; **** $P \leq 0.0001$

Key Points: CLL

- Frontline BTK and BCL2 inhibitors are more effective than chemo-immunotherapy for high risk CLL patients
- Use of BTK inhibitors yields potential cardio-vascular risk, and novel and safer BTK inhibitors are being developed
- Novel and safer PI3K inhibitors could be used in the future to consolidate patients previously treated with a BTK inhibitor
- Novel and more potent BTK inhibitors are being developed for patients who develop BTK resistance
- COVID19 booster is recommended for CLL patients treated with biological therapy
- Clinica trials should continue to be the preferred option for RS patients



CLL SOCIETY

Smart Patients Get Smart Care™

ASH 2021

Brian Koffman, MDCM
(retired) MS Ed
EVP and CMO
CLL Society

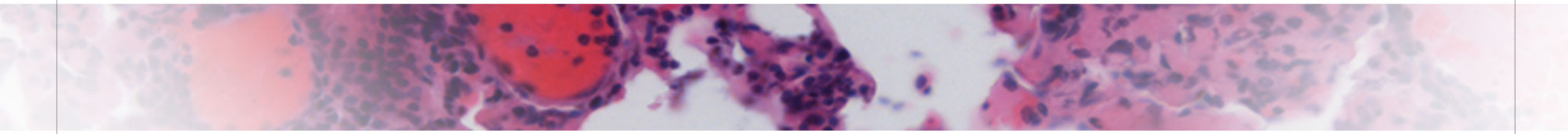
CLL SOCIETY

ASH 2021 Abstracts

The Patient and Real-World Perspective

American Society *of* Hematology

Helping hematologists conquer blood diseases worldwide



Awareness, Knowledge, and Preferences of United States (US) Patients with Chronic Lymphocytic Leukemia (CLL) and Their Caregivers Related to Finite Duration (FD)Therapy and Minimal (Measurable) Residual Disease (MRD)

B. Koffman[1], C. Stewart[2], L. Avruch[1], N. Bailey[3], R. Brumble[1], J. Byrd[4], A. Danilov[5], M. Davids[6], R. Furman[7], N. Jain[8], N. Kay[9], N. Lamanna[10], A. Mato[11], A. Skarbnik[12], C. Ujjani [13,] J. Pagel[3]

1 CLL Society, Chula Vista CA; 2 Gallup Inc; 3 Swedish Cancer Institute, Seattle, WA; 4 University of Cincinnati College of Medicine, Cincinnati, OH; 5 City of Hope National Medical Center, Duarte , CA; 6Dana Farber Cancer Institute, Boston, MA; 7 Weill Cornell Medicine, New York, NY; 8 University of Texas MD Anderson Cancer Center, Houston, TX; 9 Mayo Clinic, Rochester, MN; 10Columbia University Medical Center, New York, NY; 11 Memorial Sloan Kettering Cancer Center, New York, NY; 12 Novant Health, Charlotte, NC; 13 University of Washington/Fred Hutchinson Cancer Research Center, Seattle, WA

Awareness, Knowledge, and Preferences of United States (US) Patients with Chronic Lymphocytic Leukemia (CLL) and Their Caregivers Related to Finite Duration (FD)Therapy and Minimal (Measurable) Residual Disease (MRD)

B. Koffman[1], C. Stewart[2], L. Avruch[1], N. Bailey[3], R. Brumble[1], J. Byrd[4], A. Danilov[5], M. Davids[6], R. Furman[7], N. Jain[8], N. Kay[9], N. Lamanna[10], A. Mato[11], A. Skarbnik[12], C. Ujjani[13], J. Pagel[3],

[1] CLL Society, Chula Vista CA; [2] Gallup Inc; [3]Swedish Cancer Institute, Seattle, WA; [4] University of Cincinnati College of Medicine, Cincinnati, OH; [5] City of Hope National Medical Center, Duarte , CA; [6]Dana Farber Cancer Institute, Boston, MA; [7] Weill Cornell Medicine, New York, NY; [8] University of Texas MD Anderson Cancer Center, Houston, TX; [9] Mayo Clinic, Rochester, MN; [10]Columbia University Medical Center, New York, NY; [11] Memorial Sloan Kettering Cancer Center, New York, NY; [12] Novant Health, Charlotte, NC; [13] University of Washington/Fred Hutchinson Cancer Research Center, Seattle, WA

BACKGROUND & INTRODUCTION

- Until the introduction of novel agents, such as Bruton tyrosine kinase inhibitors (BTKi), the management of CLL patients primarily utilized limited duration chemoimmunotherapy (CIT). The use of BTKi significantly changed the CLL treatment paradigm to include continuous single-agent oral therapy delivered until disease progression or intolerance.
- More recently, similar to past CIT protocols, new combinations of non-CIT agents are being used that can be given over a finite duration (AKA fixed or limited duration). In addition, measurable (minimal) residual disease (MRD) assessment is emerging as an important clinical tool. Understanding the patients' perspective on these trends is critical to providing best care.
- CLL Society, a patient-facing, physician-curated nonprofit organization focused on the unmet needs of the CLL community, sought to understand patients' self-assessed awareness, understanding and preferences related to this changing therapeutic landscape with the addition of finite duration non-CIT options and MRD testing, and to research how they influence patients' decisions around treatment.

OBJECTIVES

- Understand patients' self-assessed awareness, understanding and preferences related to finite therapies and MRD testing in the present treatment era.
- Assess how these influence their decisions related to therapy.
- Identify gaps and misconceptions in awareness and understanding that can be addressed through improved patient education and shared decision making.

METHODS

Study Design
CLL Society developed a survey instrument to assess patient and caregiver awareness, understanding, and preferences associated with the concepts of MRD and finite duration therapies. The opt-in survey was conducted via a web-based data collection mode.

Inclusion criteria
- Respondents must be age 18 or older,
- Have a diagnosis of CLL/SLL or be caring for someone with CLL/SLL,
- Be an American resident with a working knowledge of English.

Survey Recruitment
Patients and caregivers were invited by CLL Society via message boards, CLL Society website, emails, and multiple online communities. The survey was administered anonymously.

Statistical Analysis
Data were analyzed using descriptive methods. Answers in individual surveys were cross checked for validity.

RESULTS

630 Responses
608 CLL patients
22 CLL Caregivers

5 Months
The survey was administered from SEP-2020 to FEB-2021

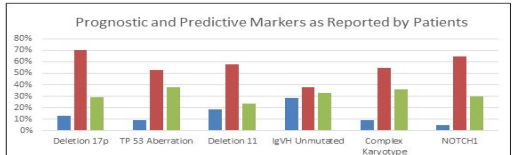
2 Formats
Options to respond via PC or mobile device

Patient Demographics

Age, Median (range)	63 (30-90)
Age, >70	35%
Sex, Female	55%
Does not have caregiver	48%
Treatment Status	
Watch and Wait	27%
Received of completed 1st treatment	38%
Received of completed 2nd or later treatment	34%

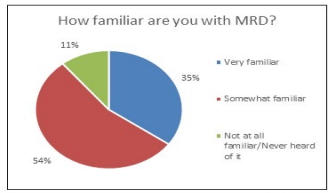
630 Respondents throughout every state in the USA

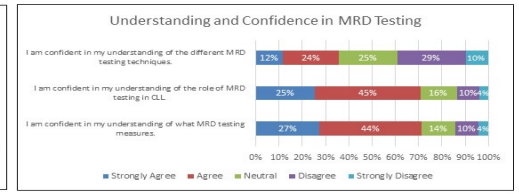
CLL Disease and Treatment Status and Awareness

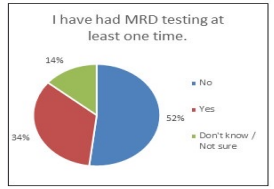


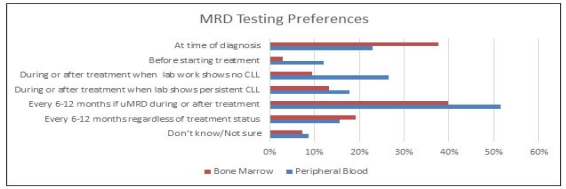
RESULTS (CONTINUED)

Measurable Residual Disease

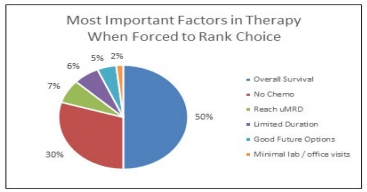


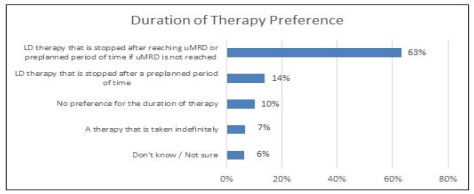


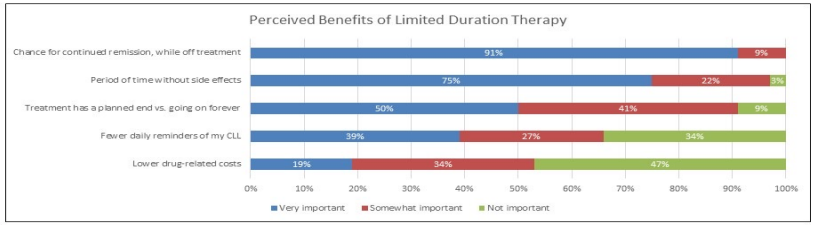


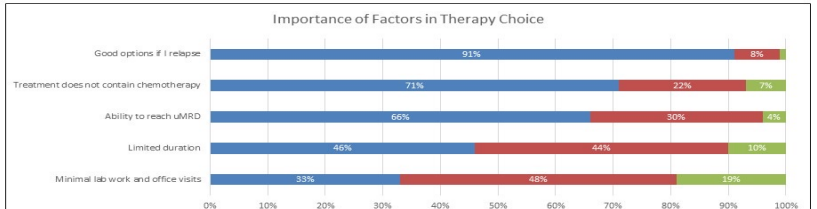


Limited Duration Therapy and Treatment Choice









RESULTS (CONTINUED)

Highlights: Awareness, Understanding, and Preferences

Areas of higher awareness, understanding and positive preferences	CLL Disease and Treatment Awareness	I am aware that some novel therapies may be **prescribed continuously.** Examples include **ibrutinib, acalabrutinib, idelalisib and duvelisib).**	Yes - 93%
		I am aware that some novel drug therapies may be prescribed for a **limited duration.** Examples include **venetoclax, obinutuzumab, and others.**	Yes - 90%
	Measurable Residual Disease (MRD)	Familiar about **MRD's role** in CLL.	Highly Confident / Confident 70%
		Confident in their understanding of **what MRD measures.**	Highly Confident / Confident 71%
		If I became MRD detectable after being undetectable on a previous test, **I would ask my doctor to consider:**	Frequent monitoring, but no treatment change - 58%
		If I tested MRD detectable at the end of treatment, **I would ask my doctor to consider:**	Frequent monitoring, but no treatment change - 63%
	Factors Effecting Duration of Therapy	**Factors when considering benefits of a limited duration treatment:** Chance for continued remission, while off treatment	Very Important - 92%
		Factors when considering benefits of a limited duration treatment: Period of time without side effects	Very Important - 76%
Areas of lower awareness, understanding and preferences	CLL Disease and Treatment Awareness	Regarding awareness of their own prognostic and predictive factors (del 17p, TP53 mutation, del 11q, IgVH status, Notch1 mutation)	TP53 (38%) Complex Karyotype (36%) Mean (29%) Didn't know / not sure
	Minimal Residual Disease (MRD)	I am confident in my understanding of the different MRD testing techniques.	Neutral / Disagree / Strongly Disagree - 29%
		I would be satisfied with testing for MRD that looked for a specific of sensitivity (E.g. uMRD-6, uMRD-5, uMRD-4):	Don't know / not sure - 44%
		Regarding understanding which treatments can achieve uMRD (BCL2, BTKi, Chemoimmunotherapy)	Don't know / not sure – 33%

CONCLUSIONS

- Preserving future treatment options and overall survival (OS) were the 1st and 2nd very or somewhat important factors respectively in choosing a treatment. Ability to reach uMRD was rated more important than the duration of therapy. When forced to rank treatment preference on a fixed scale, OS was ranked 1st by 50%. Continued remission post- treatment was the major perceived benefit of finite therapy, followed by time without side effects off medication.
- Despite high levels of self reported confidence in understanding MRD, some patients had preferences for MRD testing when it was not indicated such as 18% of respondents wanting testing of peripheral blood when routine labs demonstrated persistent CLL. Regarding understanding of which treatments (BCL2, BTKi, Chemoimmunotherapy) can achieve uMRD about one third of patients were unsure.
- Given its opt-in nature the results may not be reflective of all patients and caregivers.
- The patients' rating of future treatment options over OS is an opportunity for doctor/patient discussion. As the importance of MRD and finite therapy grows in CLL management, it will be incumbent upon providers to better understand and consider their patients' awareness, understanding, and preferences and to help patients become more informed about evolving practices so patients can make more informed therapeutic decisions.

ABOUT CLL SOCIETY

CLL Society is a USA-based 501(c)3 nonprofit with a global reach. It is focused on patient education, support, advocacy and research to address the unmet needs of the CLL community through:

- CLL Society website https://cllsociety.org which contains up-to-date, accurate and patient-friendly information with >1,000,000 pageviews a year.
- The CLL Tribune, a quarterly online newsletter with patient, physician and related experts as authors.
- 39 CLL-specific local patient support and education groups with members in 3 continents.
- Live (now all virtual) educational forums and webinars presented in 3 different continents.
- Free virtual Expert Access™ to CLL experts providing consults to patients who would otherwise have no such access.
- Research on the patient journey and sharing results in major congresses and peer reviewed journals.

CHECK OUT

Awareness, Knowledge, and Preferences of United States (US) Patients with Chronic Lymphocytic Leukemia (CLL) and Their Caregivers Related to Finite Duration (FD)Therapy and Minimal (Measurable) Residual Disease (MRD)

CLL SOCIETY

BACKGROUND & INTRODUCTION

- Until the introduction of novel agents, such as Bruton tyrosine kinase inhibitors (BTKi), the management of CLL patients primarily utilized limited duration chemoimmunotherapy (CIT). The use of BTKi significantly changed the CLL treatment paradigm to include continuous single-agent oral therapy delivered until disease progression or intolerance.

- More recently, similar to past CIT protocols, new combinations of non-CIT agents are being used that can be given over a finite duration (AKA fixed or limited duration). In addition, measurable (minimal) residual disease (MRD) assessment is emerging as an important clinical tool. Understanding the patients' perspective on these trends is critical to providing best care.

- CLL Society, a patient-facing, physician-curated nonprofit organization focused on the unmet needs of the CLL community, sought to understand patients' self-assessed awareness, understanding and preferences related to this changing therapeutic landscape with the addition of finite duration non-CIT options and MRD testing, and to research how they influence patients' decisions around treatment.

Presented at the 62nd American Society of Hematology Annual Meeting, December 5–8, 2020 (Virtual Event)

Awareness, Knowledge, and Preferences of United States (US) Patients with Chronic Lymphocytic Leukemia (CLL) and Their Caregivers Related to Finite Duration (FD)Therapy and Minimal (Measurable) Residual Disease (MRD)

CLL SOCIETY

OBJECTIVES

- Understand patients' self-assessed awareness, understanding and preferences related to finite therapies and MRD testing in the present treatment era.
- Assess how these influence their decisions related to therapy.
- Identify gaps and misconceptions in awareness and understanding that can be addressed through improved patient education and shared decision making.

630 Responses

608 CLL patients
22 CLL Caregivers

5 Months

The survey was administered from SEP-2020 to FEB-2021

2 Formats

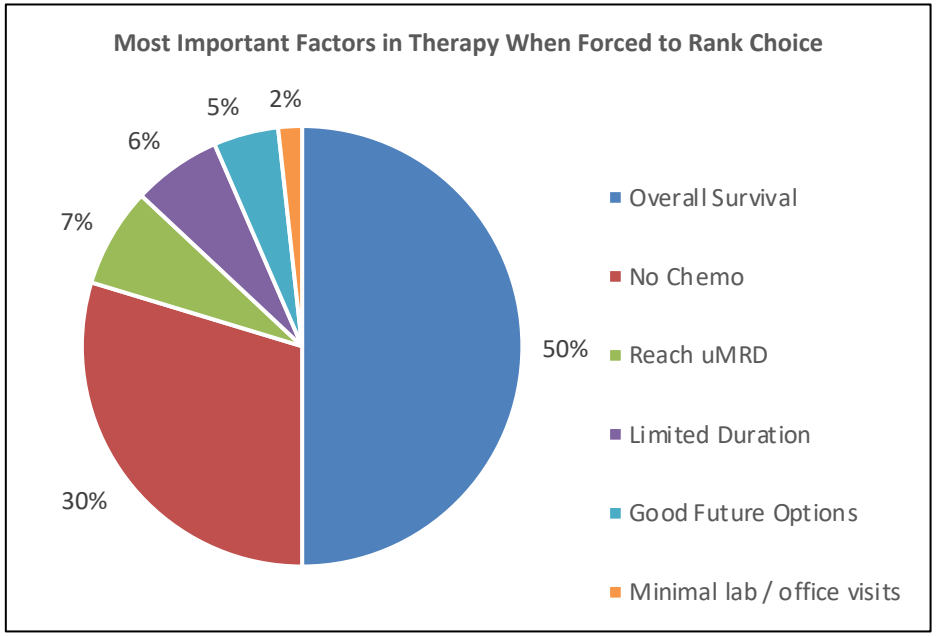
Options to respond via PC or mobile device

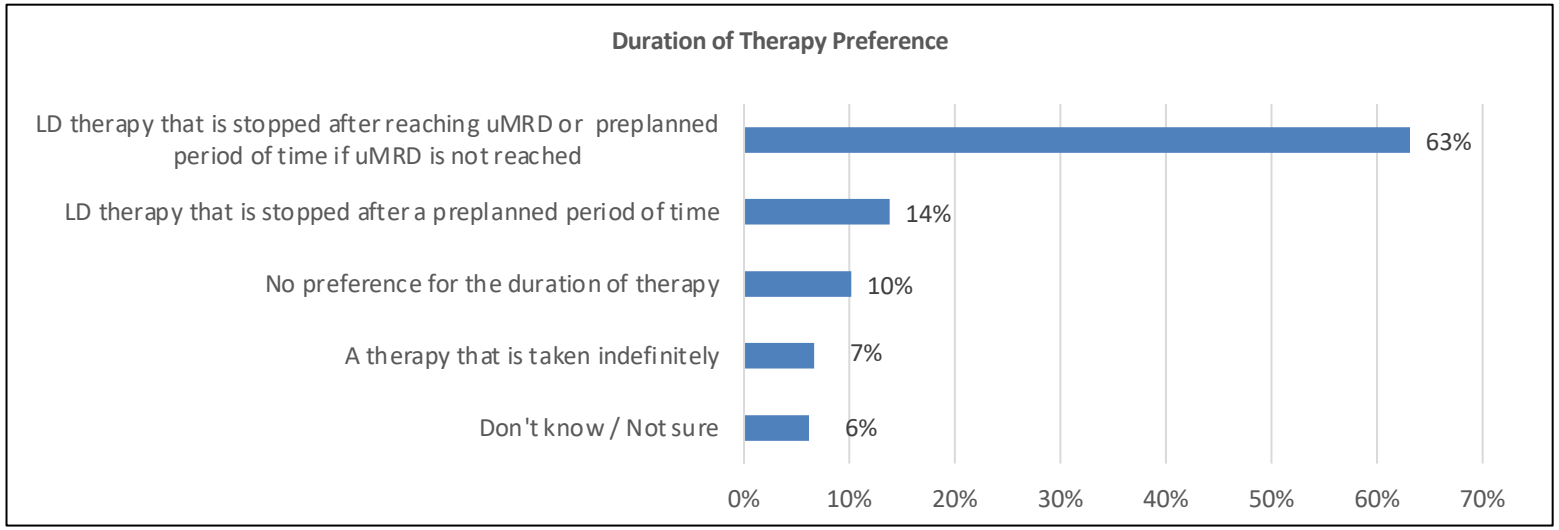
Patient Demographics

Age, Median (range)	63 (30-90)
Age, >70	35%
Sex, Female	55%
Does not have caregiver	48%
Treatment Status	
Watch and Wait	27%
Received or completed 1st treatment	38%
Received or completed 2nd or later treatment	34%

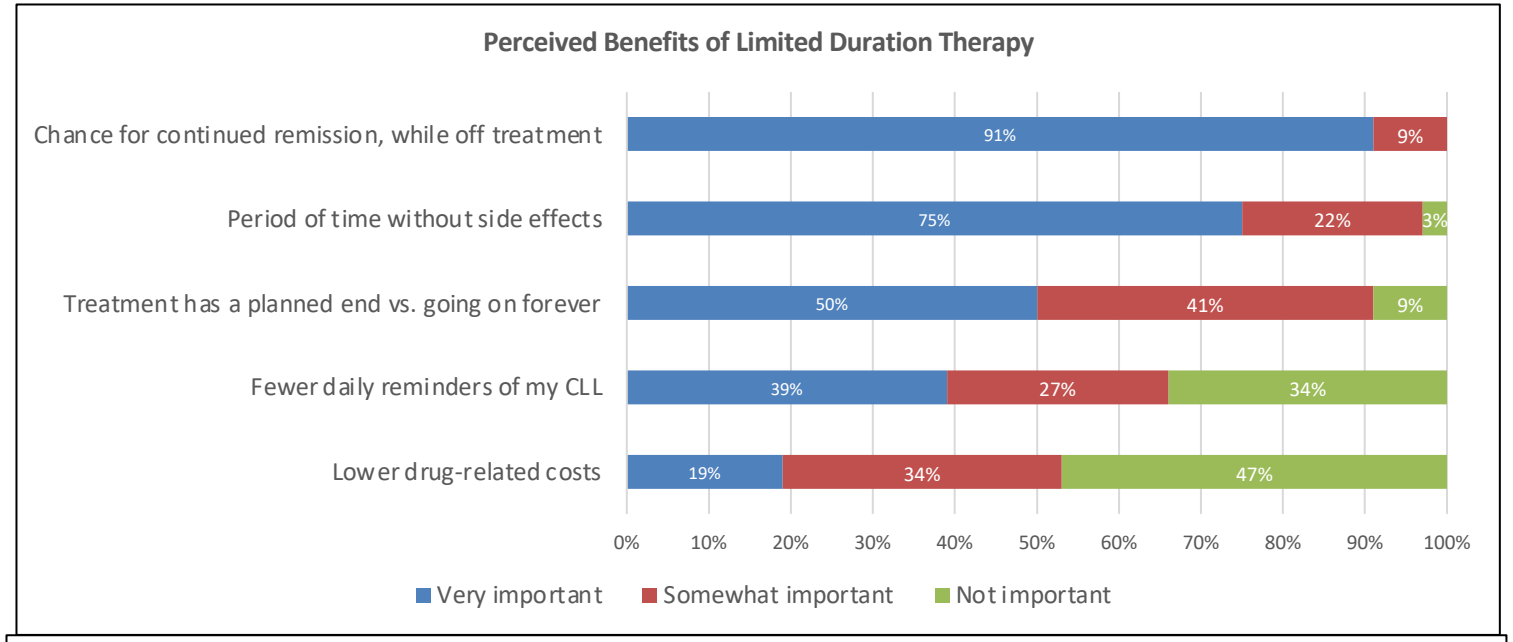
630 Respondents throughout every state in the USA

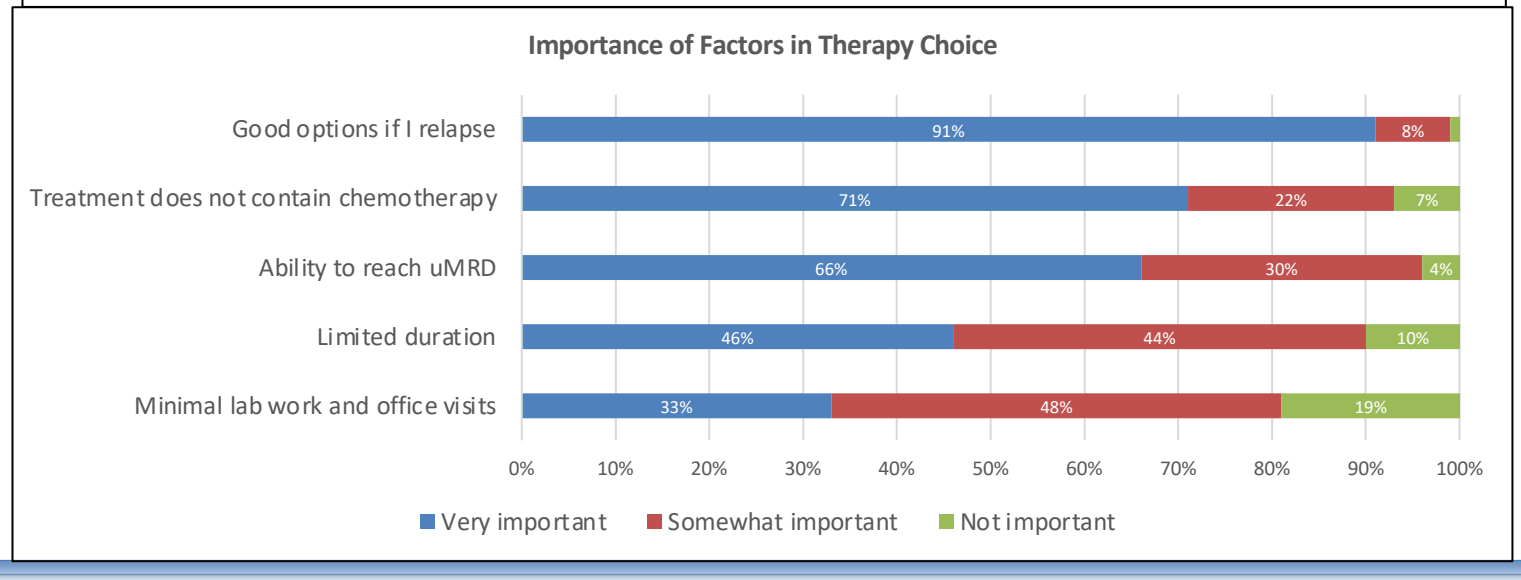
RESULTS: Limited Duration Therapy and Treatment Choice



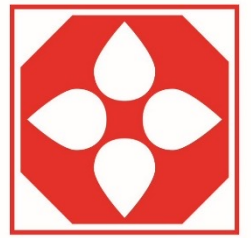


RESULTS: Limited Duration Therapy and Treatment Choice





Association between the Leukemia Mortality-to-Incidence Ratio and State Geographic Healthcare Disparities in the United States



- **INTRODUCTION:** Leukemia ((AML, CML, ALL, **CLL** and others) is the seventh leading cause of cancer death in the United States (US) in 2021.
- The Mortality Incidence Rate Ratio, also known as Mortality-to-Incidence Ratio (MIR), is calculated by dividing the mortality rate by the incidence rate for selected cancers and population.
- The MIR provides a population-based indicator of cancer survival which has previously been used to assess healthcare disparities.
- **RESULTS:** The highest MIR (worst survival) was found in Mississippi (0.579), Wyoming (0.570), and Ohio (0.569) The lowest MIR (best survival) was found in Florida (0.374), New York (0.391), and New Jersey (0.412)

Association between the Leukemia Mortality-to-Incidence Ratio and State Geographic Healthcare Disparities in the United States

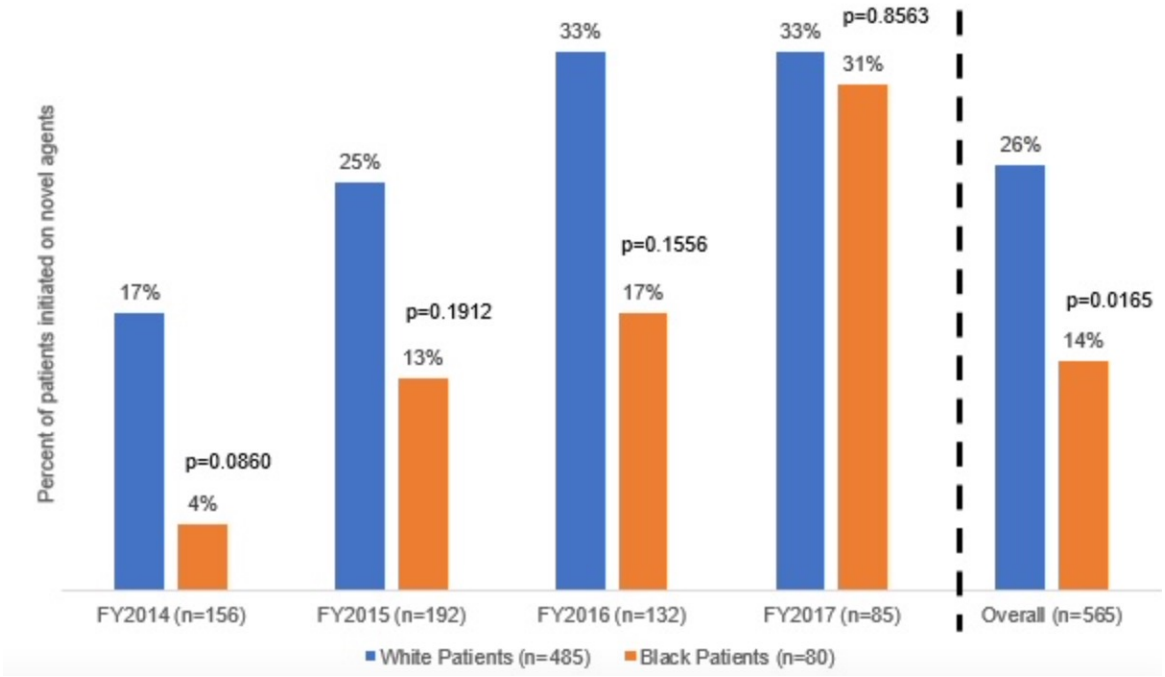
- **CONCLUSIONS:** There is a remarkable geographic difference in leukemia MIRs in the US between 2008-2017.
- Leukemia MIR was significantly associated with state health rankings.
- Quality of clinical care for leukemia patients remains to be an important predictor of mortality.
- Other determinants of health, including social, economic, and community and physical environment may also play a vital role in influencing leukemia survival. More in-depth analysis of these data focusing on specific leukemia subtypes as well as other factors (race, gender, age) may be helpful in identifying and addressing other non-medical issues negatively impacting on leukemia outcomes in different geographical regions in the US.

Uptake of Novel Agents (NAs) As First-Line Treatments for Black and White Patients with Chronic Lymphocytic Leukemia (CLL) in the Veterans Health Administration (VHA): A Retrospective Cohort Study

CLL SOCIETY

- **INTRODUCTION:** Since the introduction of NAs in 2013, the treatment paradigm for CLL has changed significantly with the increased uptake of NAs for first line (1L) and refractory CLL.
- Despite improvement in survival outcomes with CLL, black patients with CLL have demonstrated inferior overall survival.

Figure 2. Comparison of novel agent uptake by race by fiscal year, n=565



There was a statistically significant difference in the use of NAs between Black and White patients with CLL in the VHA. However, when NA use was examined by year, the disparity was largest in the early study years.

Addressing a New Challenge in Chronic Lymphocytic Leukemia: Outcomes of Therapies after Exposure to Both a Covalent Bruton's Tyrosine Kinase Inhibitor and Venetoclax

CLL SOCIETY

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

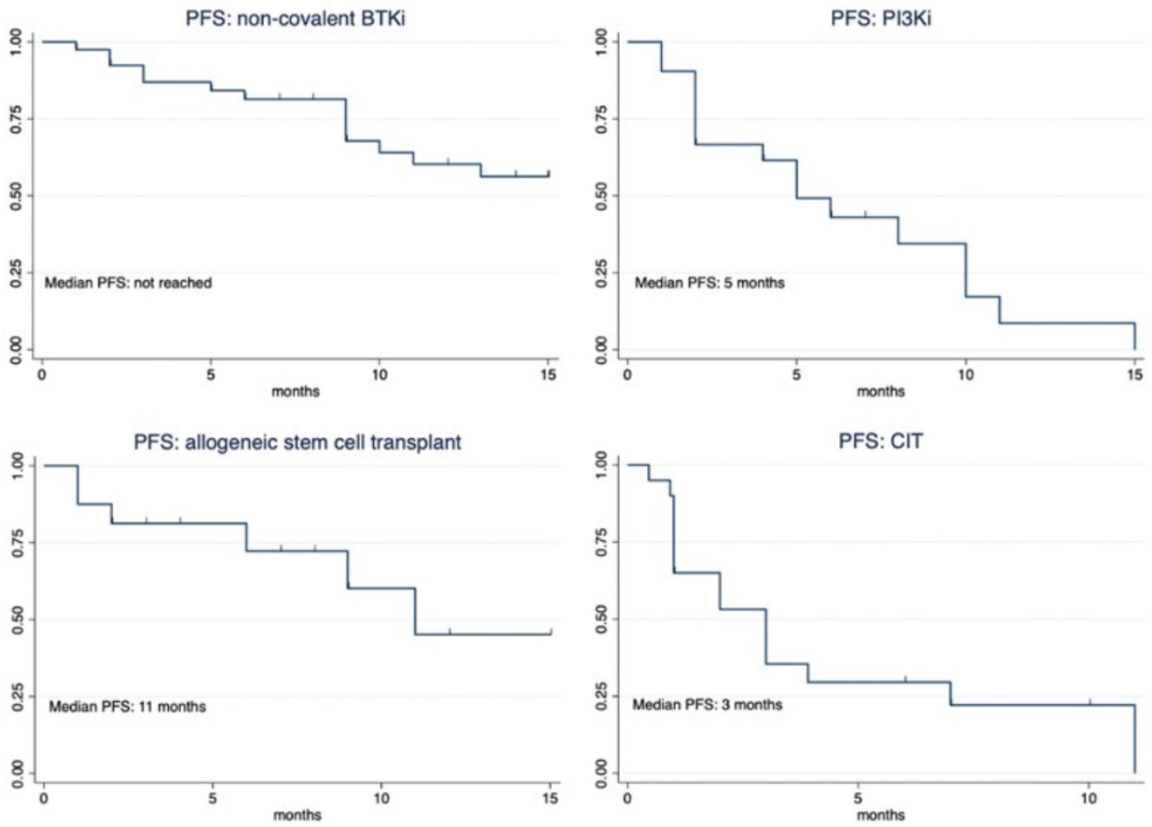
Abbreviations: CLL: chronic lymphocytic leukemia, BTKi: Bruton's Tyrosine Kinase inhibitor, PI3Ki: phosphatidylinositol 3-kinase inhibitor; CAR: chimeric antigen receptor; CIT: chemo+/-immunotherapy; mos: months; ORR: overall response rate; PFS: progression free survival.

*The 125 patients were treated with 211 cumulative lines of therapy following covalent BTKi and venetoclax. Of the 211 lines of therapy administered, 44 did not fit into one of the specified categories. Other therapies not listed in the table included: venetoclax re-treatment (n=6) and cBTKi (n=43).

Addressing a New Challenge in Chronic Lymphocytic Leukemia: Outcomes of Therapies after Exposure to Both a Covalent Bruton's Tyrosine Kinase Inhibitor and Venetoclax

CLL SOCIETY

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



Abbreviations: PFS: progression free survival; BTKi: Bruton's Tyrosine Kinase inhibitor; PI3Ki: phosphatidylinositol 3-kinase inhibitor; CIT: chemo+/-immunotherapy

CLL SOCIETY

ASH 2021 Abstracts

News We Can Use Now

Characterization of Bruton Tyrosine Kinase Inhibitor (BTKi)-Related Adverse Events in a Head-to-Head Trial of Acalabrutinib Versus Ibrutinib in Previously Treated Chronic Lymphocytic Leukemia (CLL)

CLL SOCIETY

- **BACKGROUND***:* The prior phase 3 head-to-head trial of acalabrutinib (acala) vs. ibrutinib (ibr) (NCT02477696) demonstrated non-inferior efficacy and improved tolerability with acala in previously treated CLL.
- **CONCLUSIONS***:* In this head-to-head trial of BTKis in CLL, event-based analyses demonstrated a higher BTKi-related toxicity burden with ibr, with a lower impact of CV-related toxicity with acala across subgroups.

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

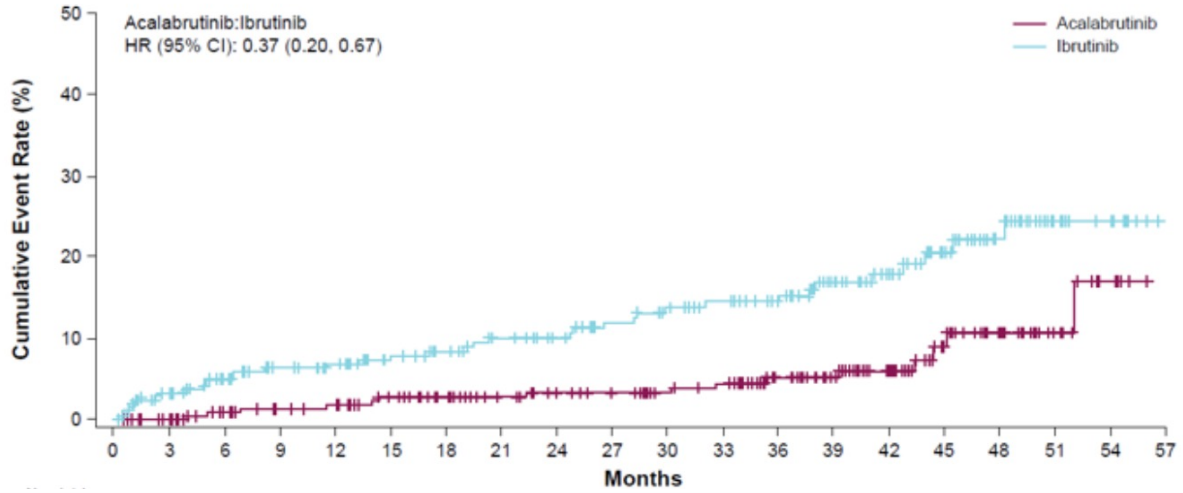
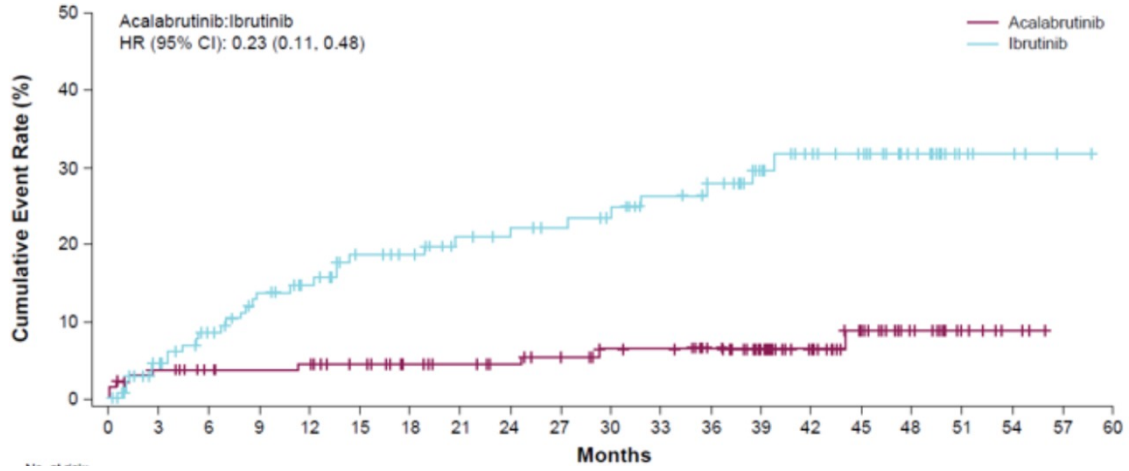


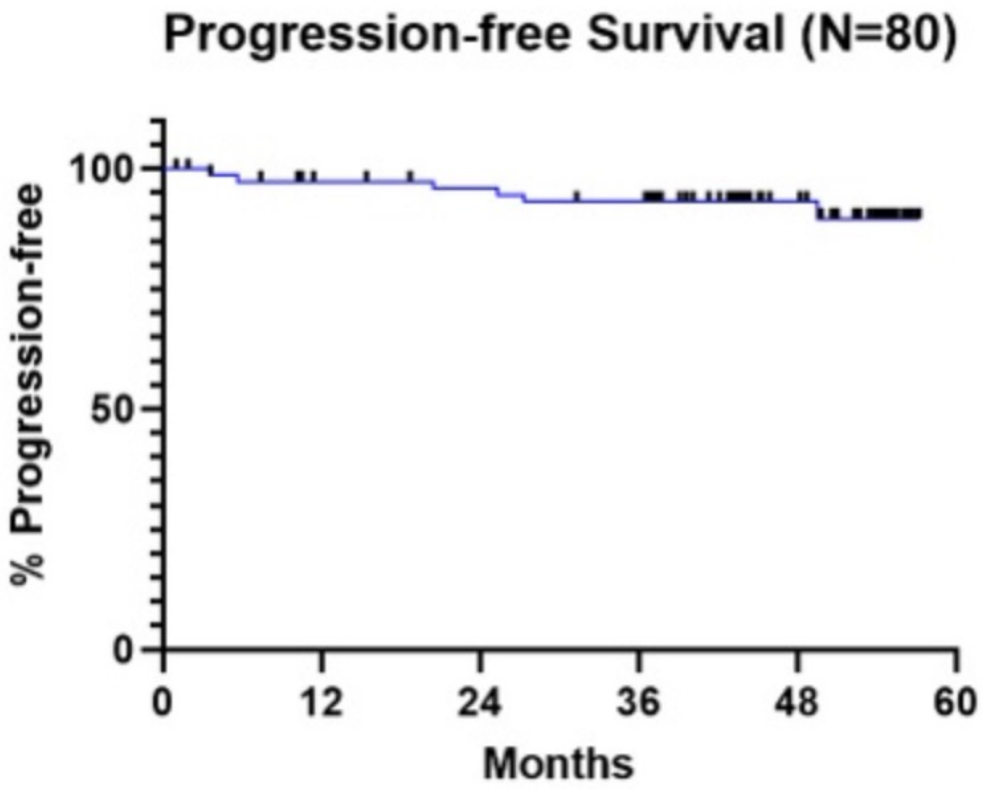
Figure 2. Cumulative Incidence of Hypertension in Patients Without a Prior History



Combined Ibrutinib and Venetoclax for First-Line Treatment of Patients with Chronic Lymphocytic Leukemia (CLL)- Focus on Long-Term MRD Results

CLL SOCIETY

- **BACKGROUND:** Ibrutinib (IBR) and venetoclax (VEN) combination is a highly effective therapy in first-line CLL.
- **CONCLUSIONS:** Remissions were durable with some pts having recurrence of blood MRD in follow-up, which may be an early indicator of relapse.
- In a small subset of the pts with bone marrow (BM) MRD+ disease at 24 cycles of combined therapy, additional VEN appears to lead to U-MRD remission in majority of pts.
- Whether this will lead to improved long-term progression free survival (PFS) remains to be determined.

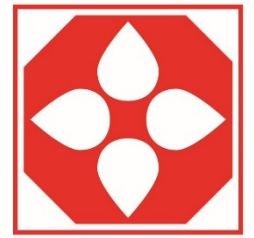


CLL SOCIETY

ASH 2021 Abstracts

Promising Future Directions

Venetoclax, Obinutuzumab and Atezolizumab (PD-L1 Checkpoint Inhibitor) for Treatment for Patients with Richter Transformation

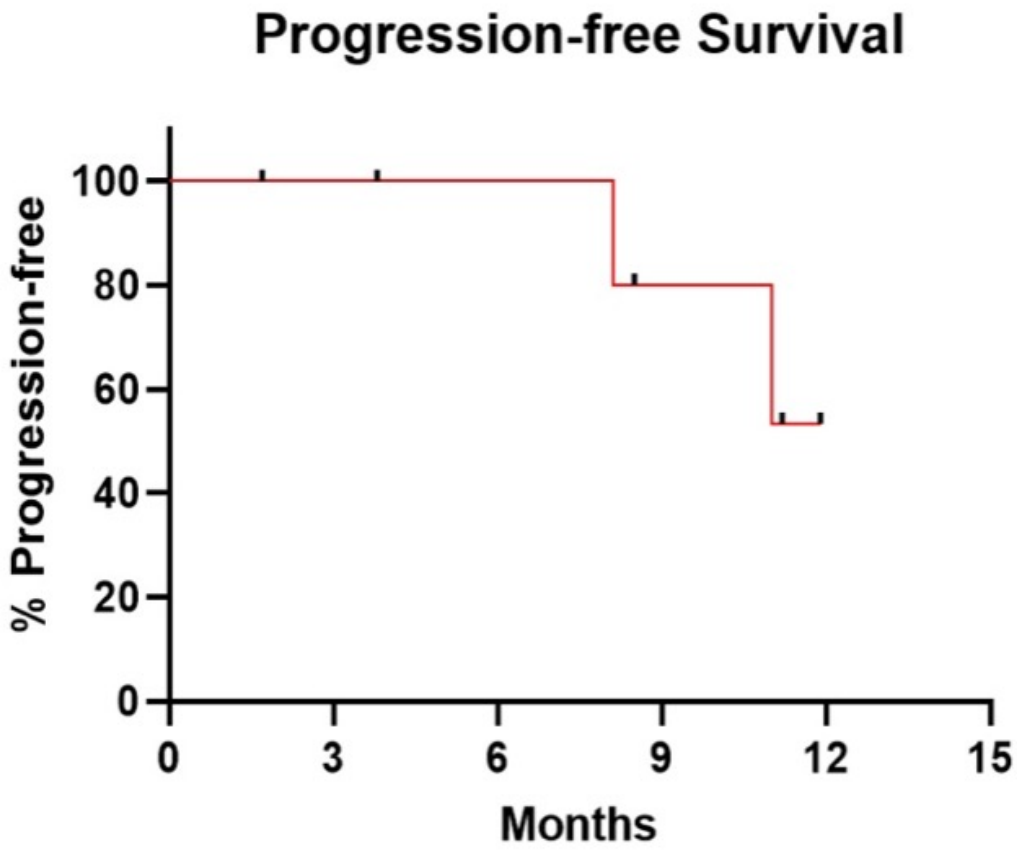


- **BACKGROUND:** Richter's Transformation (RT) is a great unmet needs in CLL.
- Dysfunction of T cells, natural killer (N cells and other immune subsets is common in patients (pts) with CLL and RT.
- Venetoclax (VEN), a BCL-2 inhibitor and obinutuzumab (OBIN), a CD20 monoclonal antibody (mAb) have clinical activity in pts with DLBCL and RT.
- Atezolizumab, a PD-L1 checkpoint inhibitor (CPI), is approved for melanoma, lung cancer and other solid tumors.
- It takes the brakes of the T, NK and other immune cells to attack the RT.
- **RESULTS:** All 7/7 (100%) pts achieved a response (complete metabolic response, n=5; partial metabolic response, n=2).

Venetoclax, Obinutuzumab and Atezolizumab (PD-L1 Checkpoint Inhibitor) for Treatment for Patients with Richter Transformation

CLL SOCIETY

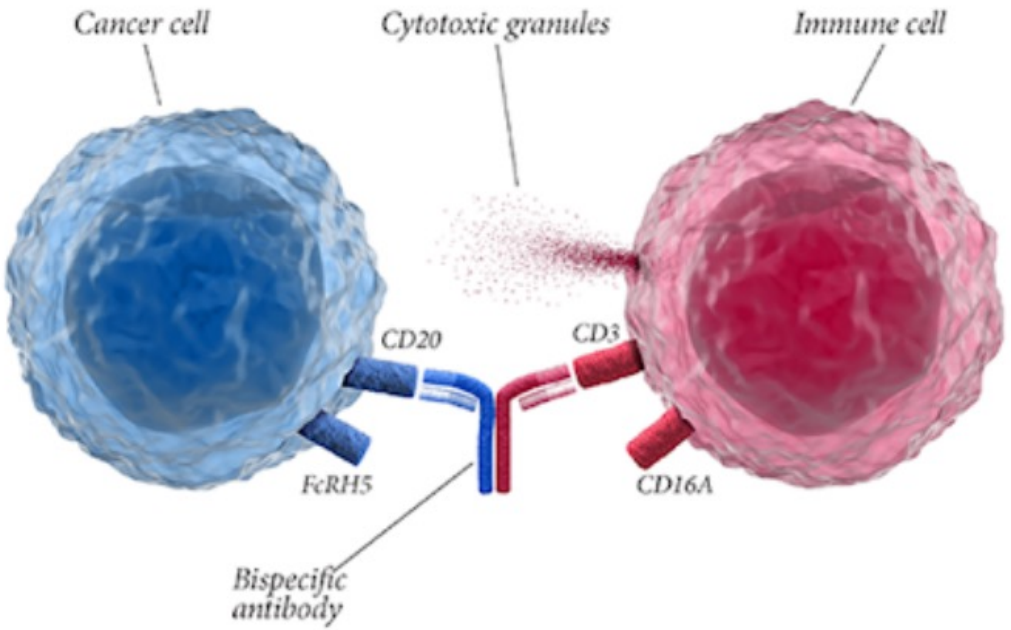
- Three pts proceeded to an allogeneic stem cell transplant (allo-SCT) in complete metabolic remission after 4.1, 4.2 and 6.6 months; these 3 pts also achieved bone marrow undetectable (U)-MRD remission.



Subcutaneous Epcoritamab in Patients with Relapsed/Refractory (R/R) Chronic Lymphocytic Leukemia: Preliminary Results

CLL SOCIETY

- **BACKGROUND:** Epcoritamab (CD3×CD20) is a bispecific antibody that can induce potent activation and cytotoxic activity of CD4+ and CD8+ T cells to specifically eliminate CD20-expressing cells.



Subcutaneous Epcoritamab in Patients with Relapsed/Refractory (R/R) Chronic Lymphocytic Leukemia: Preliminary Results

CLL SOCIETY

- **RESULTS:** 7 pts with R/R CLL received epcoritamab. 5 pts were fully assessed.
- Pts had received a median of 4 lines of prior therapy. 6 of 7 pts had poor-risk features of del(17p), *TP53* mutations, or both. 3 of 7 pts had bulky disease.
- All pts experienced cytokine release syndrome (CRS) in the first cycle, but it was mild. No neurotoxicity or tumor lysis syndrome (TLS) was observed.
- Antileukemic activity has been observed at both dose levels, with partial responses in 3 of 5 pts.

1: Nx-5948, a Selective Degrader of BTK with Activity in Preclinical Models of Hematologic and Brain Malignancies

CLL SOCIETY

2: Targeting Venetoclax-Resistant CLL By Bcl-XL Degradation

- Resistance often develops to drugs that inhibit BTK such as ibrutinib or acalabrutinib or BCL-2 such as venetoclax when the targets mutate and the drugs can no longer bind to block them.
- Selective degraders uses the cells system to clear out unneeded proteins but are targeted at the overactive proteins such as BTK and BLC-2 to actually destroy them.
- Watch for trials with proteolysis targeting chimeras (PROTACs).

Investigating the Addition of Ianalumab (VAY736) to Ibrutinib in Patients with Chronic Lymphocytic Leukemia (CLL) on Ibrutinib Therapy- Results from a Phase Ib Study: Anti-BAFF-R antibody

Characterization of LP-118, a Novel Small Molecule Inhibitor of Bcl-2 and Bcl-XI in Chronic Lymphocytic Leukemia Resistant to Venetoclax: Upregulation of Bcl-xL has been shown to drive resistance to venetoclax

A Phase 1 Study to Evaluate the Safety, Pharmacokinetics (PK) and Pharmacodynamics (PD) of Lisaftoclax (APG-2575), a Novel BCL-2 Inhibitor (BCL-2i), in Patients (pts) with Certain Relapsed or Refractory (R/R) Hematologic Malignancies (HMs): First-in-human study suggested the feasibility of an abbreviated ramp-up

Efficacy and Safety of the BTK Inhibitor MK-1026 in Patients with Hematologic Malignancies: MK-1026 (formerly ARQ 531) is an orally available, reversible, noncovalent competitive inhibitor of wild-type and C481S-mutant BTK

Conclusions

- Patients' voices are increasingly being heard, but there is more to do.
- Inequities remain that must be addressed.
- Unmet needs are being researched:
  - Double refractory disease
  - Richter's Transformation
  - Medication intolerance
- The future includes improved versions of existing classes of drugs and entirely new drugs.

CLL SOCIETY

Audience Questions & Answers

Thank You for Attending!

Please take a moment to complete our **post-event survey**, your feedback is important to us

If you're question was not answered, please feel free to email asktheexpert@cllsociety.org

Save the Date! Friday, March 18th for our next **Webinar on COVID-19**

CLL Society is invested in your long life. Please invest in the long life of the CLL Society by supporting our work

cllsociety.org/donate-to-cll-society/