Challenging Cases from Junior Investigators — The Application of Available and Emerging Clinical Research in the Care of Patients with Chronic Lymphocytic Leukemia

A CE/NCPD-Accredited Virtual Event in Partnership with the 2022 Pan Pacific Lymphoma Conference

Wednesday, October 12, 2022

5:00 PM – 6:30 PM ET

Faculty

Danielle Brander, MD
Matthew S Davids, MD, MMSc
Anthony R Mato, MD, MSCE
William G Wierda, MD, PhD

Moderator

Neil Love, MD

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Director, CLL and Lymphoma Clinical Research Program
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Durham, North Carolina

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Harvard Medical School
Director of Clinical Research
Division of Lymphoma
Dana-Farber Cancer Institute
Boston, Massachusetts

Anthony R Mato, MD, MSCE
Associate Attending
Director, Chronic Lymphocytic Leukemia Program
Memorial Sloan Kettering Cancer Center
New York, New York

William G Wierda, MD, PhD
Jane and John Justin Distinguished Chair in Leukemia Research in Honor of Dr Elihu Estey
Section Chief, Chronic Lymphocytic Leukemia
Center Medical Director
Department of Leukemia, Division of Cancer Medicine
Executive Medical Director, Inpatient Medical Services
The University of Texas MD Anderson Cancer Center
Houston, Texas

MODERATOR
Neil Love, MD
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The below planning committee members have nothing to disclose: Neil Love, MD — RTP President and Planner, Atif Hussein, MD — RTP Reviewer, Renee Paulin, MSN, RN, CWOCN — UNMC Planner and Reviewer, Brenda Ram, CMP, CHCP — UNMC Planner, Michele Williams, DNP, AGPCNP-BC — RTP Reviewer, and Kathryn Ault Ziel, PhD — RTP Staff and Planner.

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In support of improving patient care, this activity has been planned and implemented by University of Nebraska Medical Center and Research To Practice. University of Nebraska Medical Center is jointly accredited by the Accreditation Council for Continuing Medical Education (ACCME), the Accreditation Council for Pharmacy Education (ACPE), and the American Nurses Credentialing Center (ANCC), to provide continuing education for the healthcare team.

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Nonrelevant Financial Relationship	CLL Society (expert medical council), NCCN (panel member)

Dr Davids — Disclosures

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Honoraria	Aptitude Health, Curio Science
Nonrelevant Financial Relationship	Bio Ascend

Dr Mato — Disclosures

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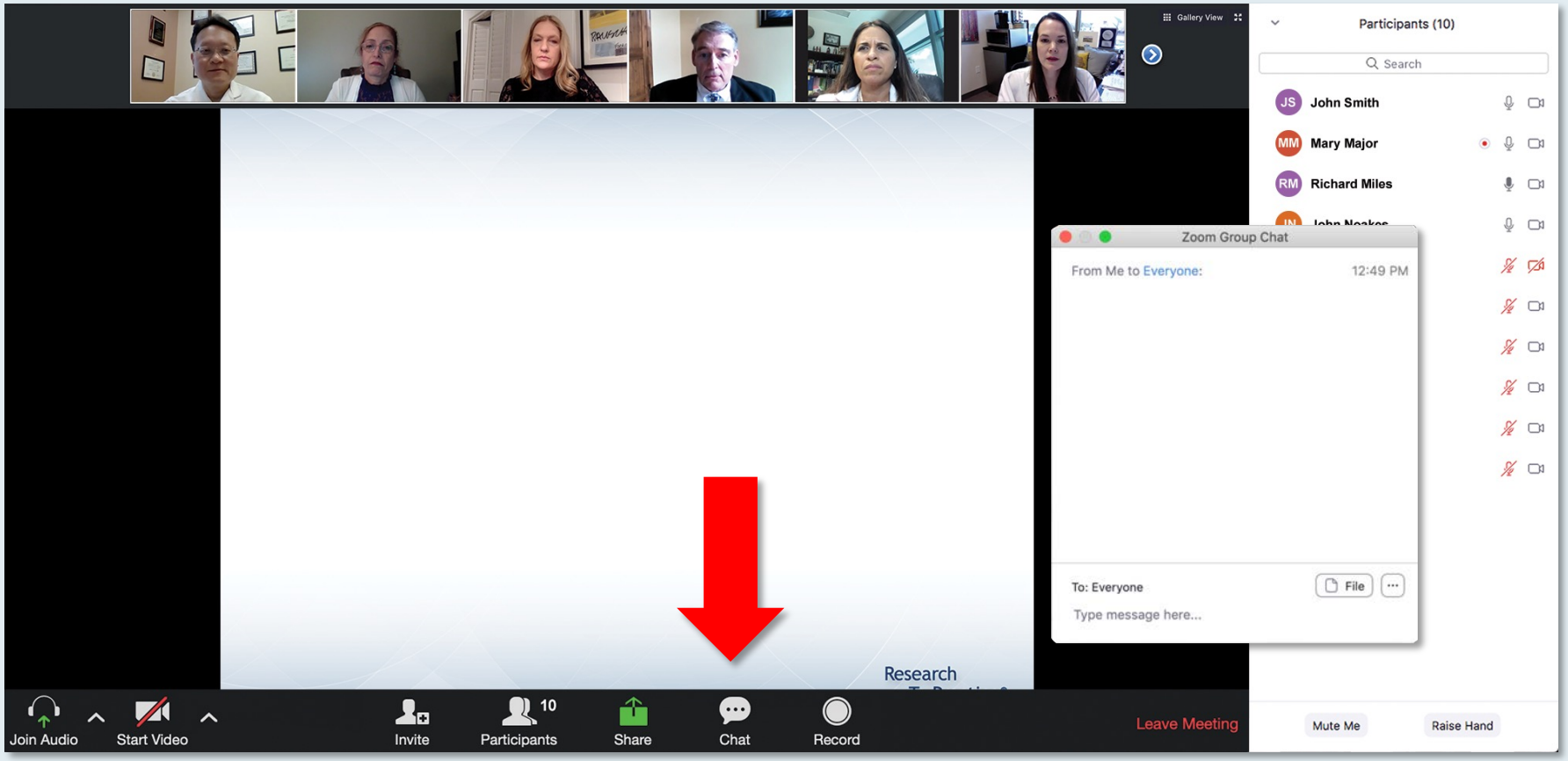
Dr Wierda — Disclosures

Contracted Research	AbbVie Inc, Acerta Pharma — A member of the AstraZeneca Group, Bristol-Myers Squibb Company, Cyclacel Pharmaceuticals Inc, Genentech, a member of the Roche Group, Gilead Sciences Inc, GlaxoSmithKline, Janssen Biotech Inc, Juno Therapeutics, a Celgene Company, Kite, A Gilead Company, Loxo Oncology Inc, a wholly owned subsidiary of Eli Lilly & Company, Miragen Therapeutics Inc, Novartis, Oncternal Therapeutics, Pharmacyclics LLC, an AbbVie Company, Sunesis Pharmaceuticals Inc, Xencor
Nonrelevant Financial Relationship	National Comprehensive Cancer Network (Chair, CLL)

We Encourage Clinicians in Practice to Submit Questions



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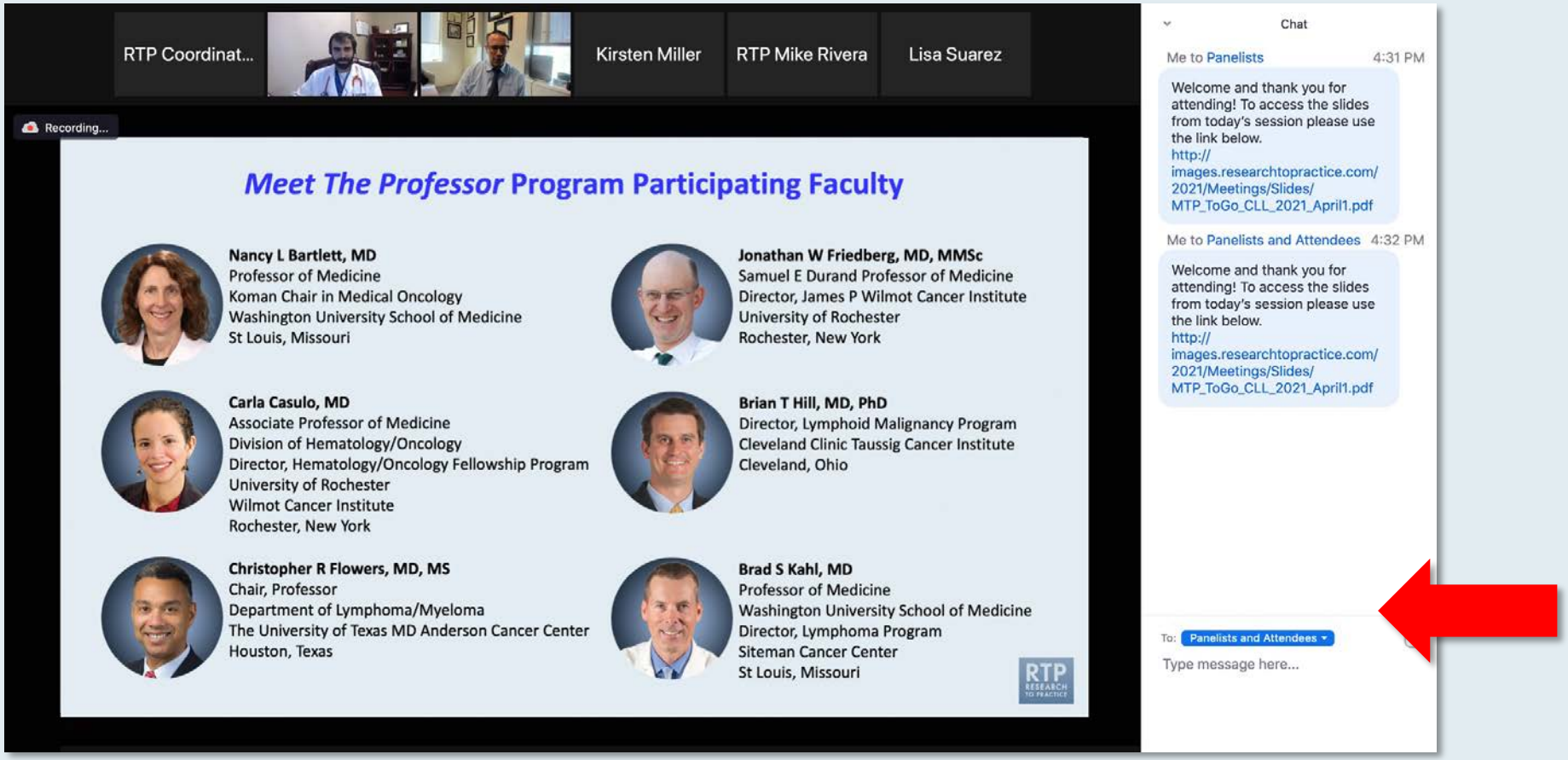

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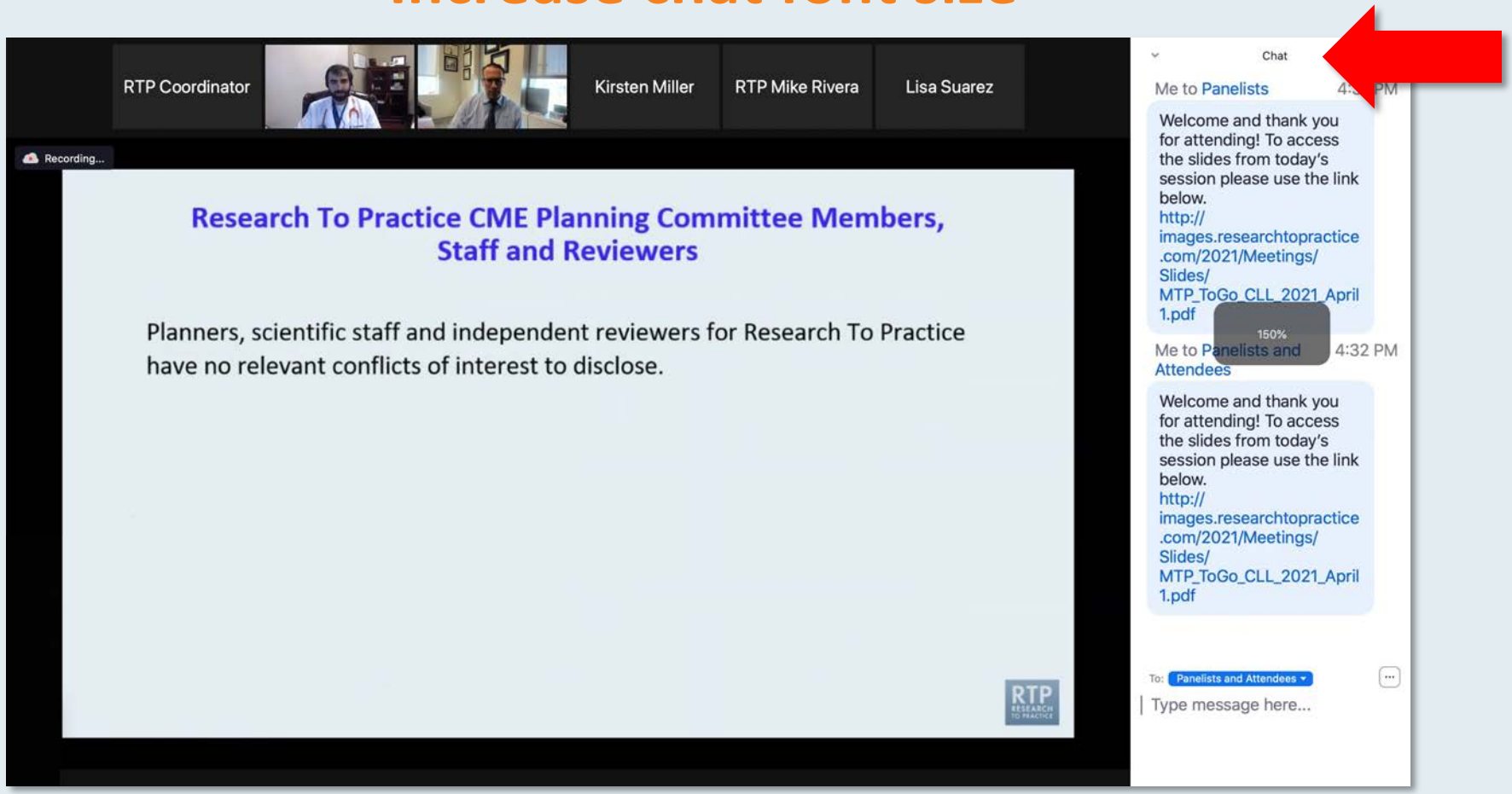

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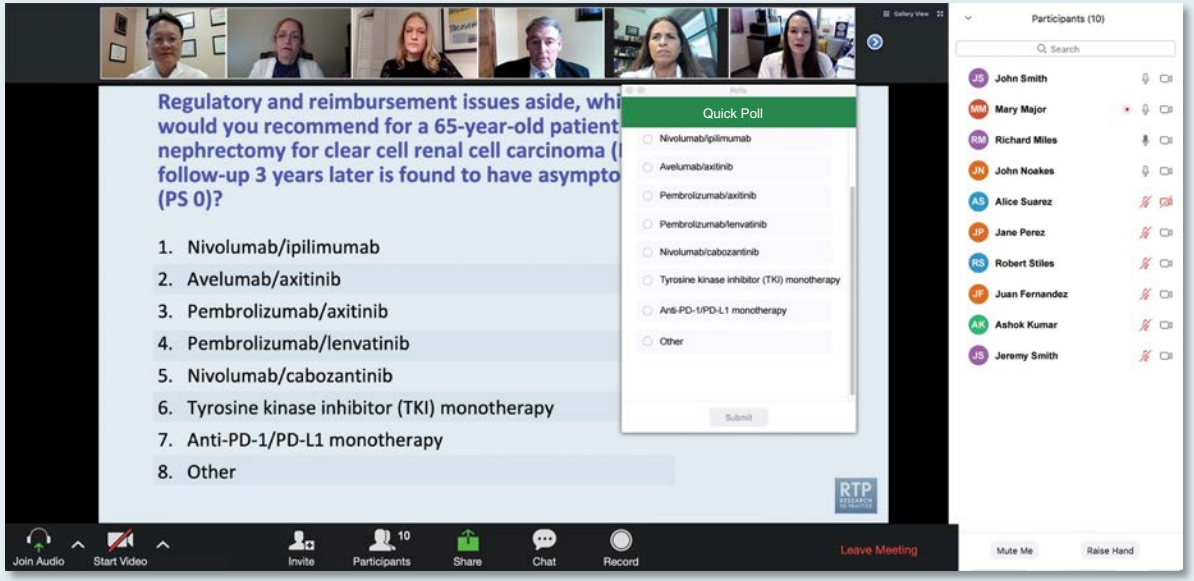

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7:30 AM – 5:30 PM ET

JW Marriott Orlando | Orlando, Florida

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Prof Georgina Long, AO, BSc, PhD, MBBS
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Thank you for joining us!

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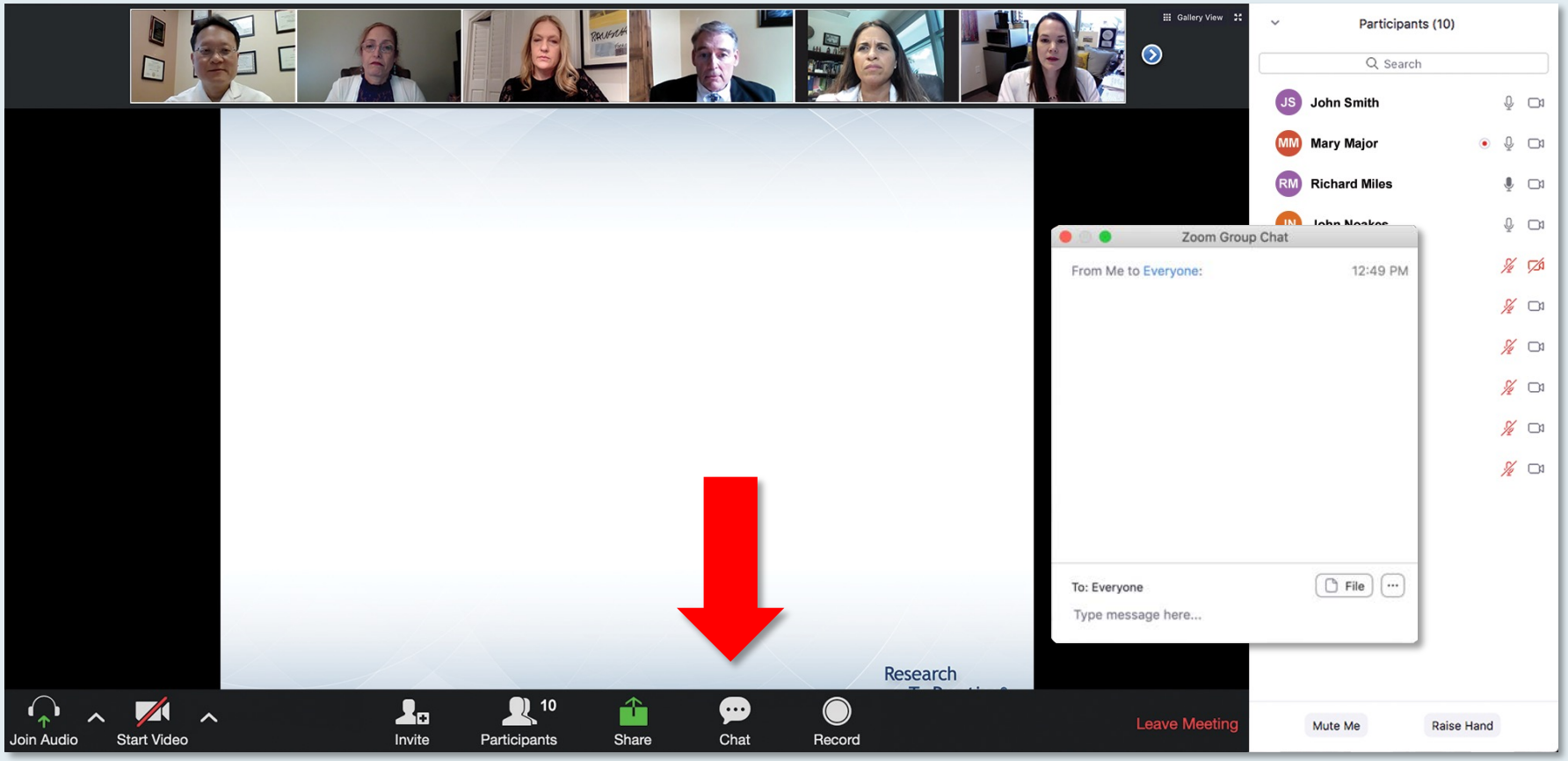

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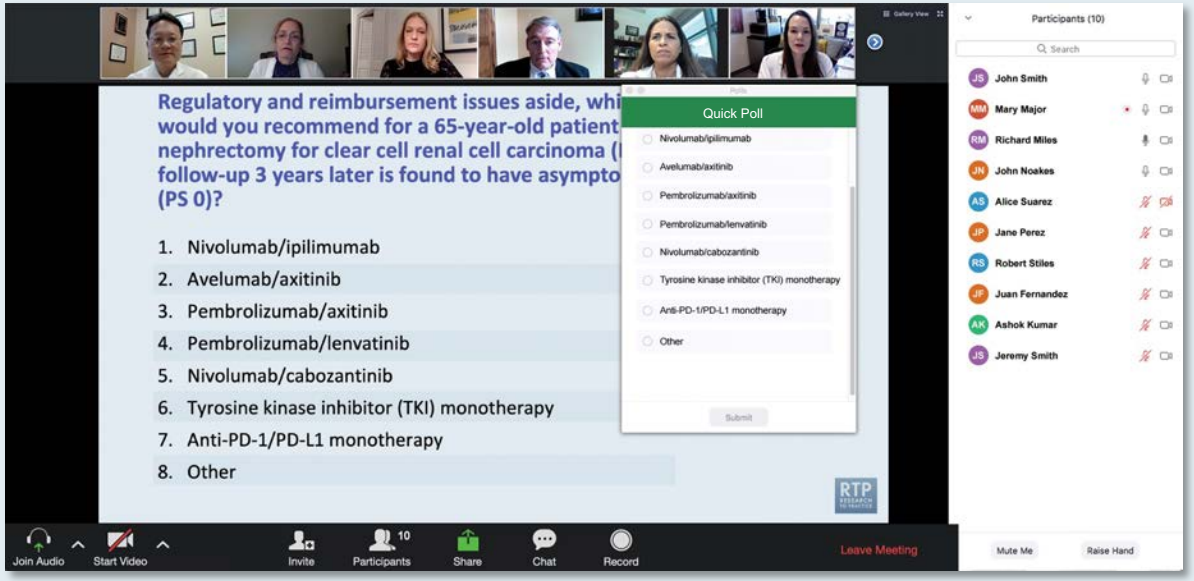

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Dr Davids — Disclosures

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Nonrelevant Financial Relationship	Bio Ascend

Dr Mato — Disclosures

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Dr Wierda — Disclosures

Contracted Research	AbbVie Inc, Acerta Pharma — A member of the AstraZeneca Group, Bristol-Myers Squibb Company, Cyclacel Pharmaceuticals Inc, Genentech, a member of the Roche Group, Gilead Sciences Inc, GlaxoSmithKline, Janssen Biotech Inc, Juno Therapeutics, a Celgene Company, Kite, A Gilead Company, Loxo Oncology Inc, a wholly owned subsidiary of Eli Lilly & Company, Miragen Therapeutics Inc, Novartis, Oncternal Therapeutics, Pharmacyclics LLC, an AbbVie Company, Sunesis Pharmaceuticals Inc, Xencor
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Adam S Kittai, MD
Assistant Professor
Division of Hematology
The Ohio State University
The OSUCCC – James
Columbus, Ohio

Christine E Ryan, MD
Clinical Fellow in Hematology/Oncology
Department of Medical Oncology
Dana-Farber Cancer Institute
Boston, Massachusetts

Agenda: CLL Update
A Meeting within a Meeting

MODULE 1: Front-Line CLL – Standard-Risk Patients — Dr Mato

MODULE 2: Chronic Lymphocytic Leukemia in 2022: Front-Line Therapy in Patients with High-Risk Disease — Dr Brander

MODULE 3: Fixed-Duration Targeted Therapy for CLL — Dr Wierda

MODULE 4: Novel Investigational Agents and Strategies in CLL — Dr Davids

MODULE 5: CLL 2030?

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Cases and Questions: Autoimmune Cytopenias

Adam Kittai, MD

Christine Ryan, MD

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Cases and Questions: Discussing “Watch and Wait”

Adam Kittai, MD

Christine Ryan, MD

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Cases and Questions:
First-Line Treatment for Younger Patients; MAJIC Study

Christine Ryan, MD

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Cases and Questions:
First-Line Treatment for High-Risk Disease; EVOLVE CLL/SLL Study

Adam Kittai, MD

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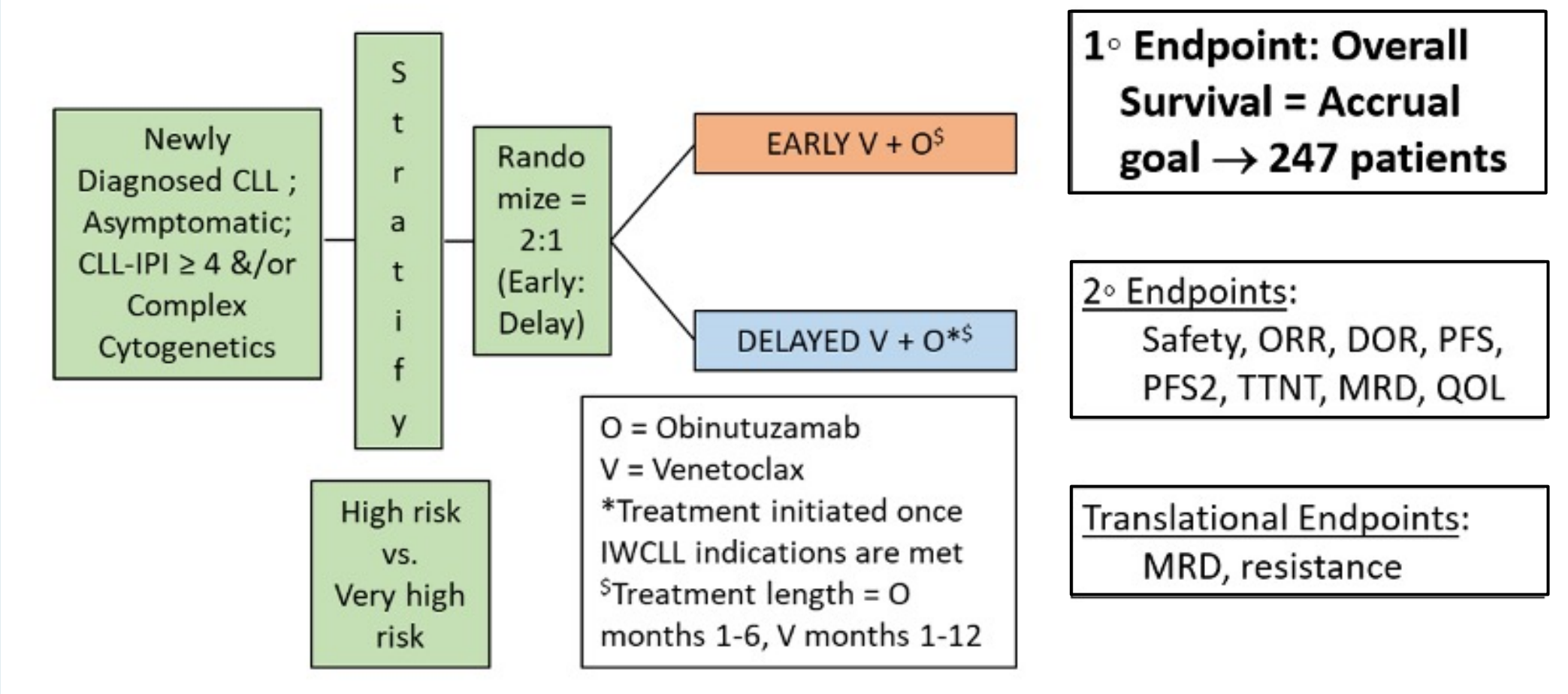
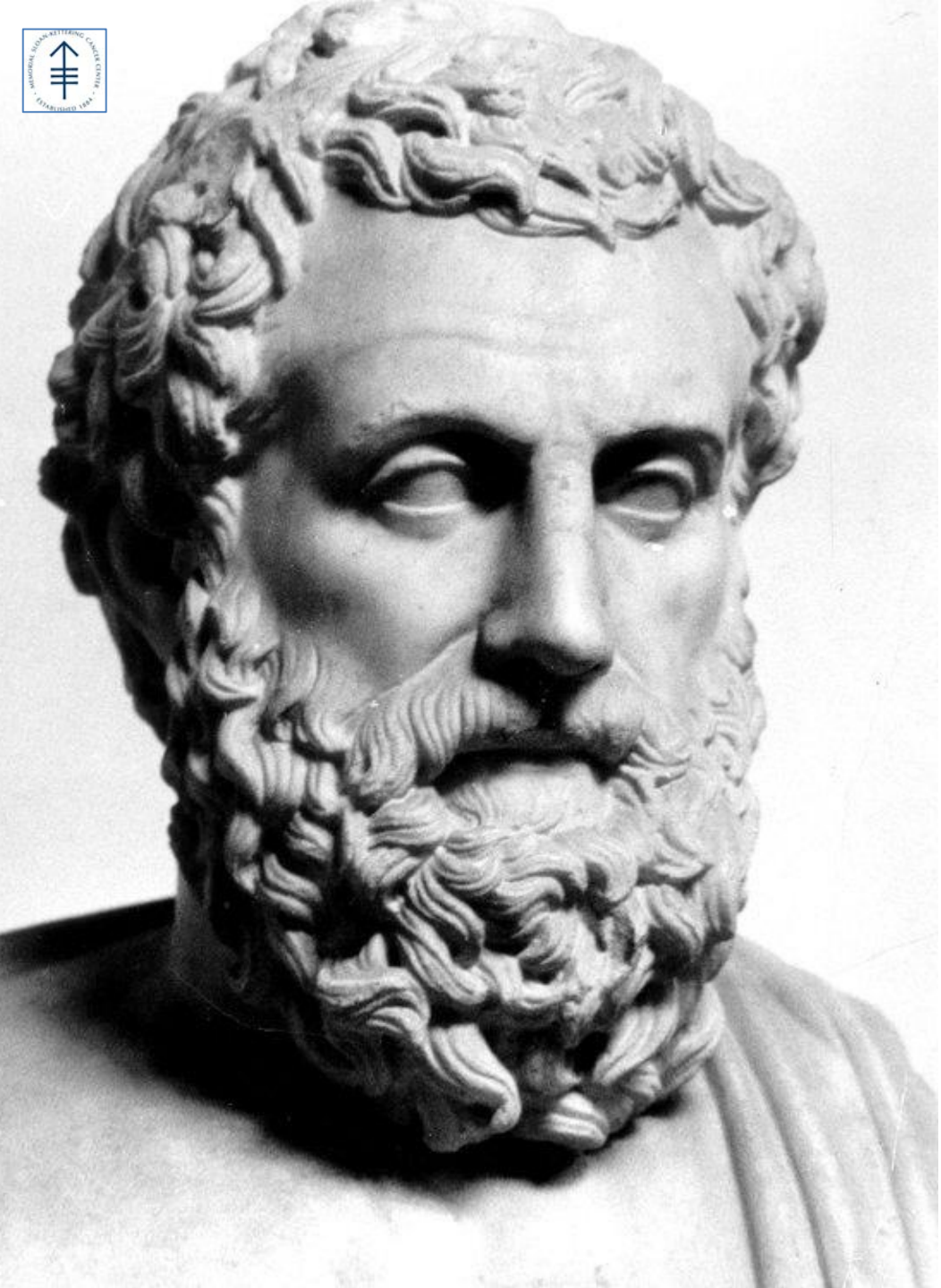
SWOG-S1925 (EVOLVE CLL/SLL): Ongoing Phase III Study Design



Stephens DM et al. ASCO 2021;Abstract TPS7567.



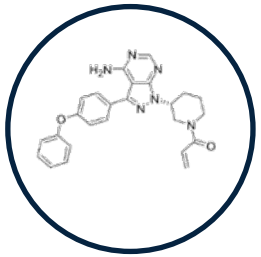
Front Line CLL – Standard Risk Patients

“Is the whole greater than the sum of its parts?”
(Aristotle, 360 BC)

Anthony Mato, MD MSCE
Director, CLL Program
Memorial Sloan Kettering Cancer Center
RTP 2022 Pan Pacific Summary

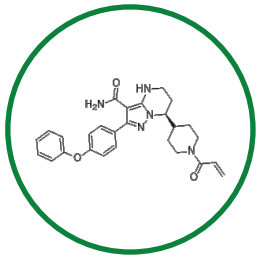
The gold standards for future comparison of new agents and current standard of care should be either be BTK-based or Ven-G based therapy.

Major Phase 3 Trials Support the Use of Continuous BTKi Therapy in TN CLL: *BTKi are standard of care*



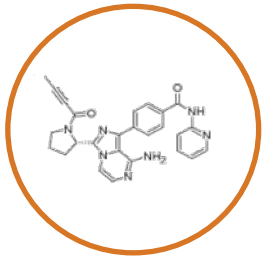
Ibrutinib[1-5]

- ✓ **RESONATE-2:** superior PFS and OS vs Clb
- ✓ **iLLUMINATE:** superior PFS vs GClb
- ✓ **ALLIANCE:** superior PFS vs BR in older patients
- ✓ **FLAIR:** superior PFS for IR vs FCR
- ✓ **ECOG 1912:** superior PFS and OS with IR vs FCR in younger patients



Acalabrutinib[6]

- ✓ **ELEVATE-TN:** superior PFS and showed a trend for better OS with acalabrutinib regimens vs GClb



Zanubrutinib[7]

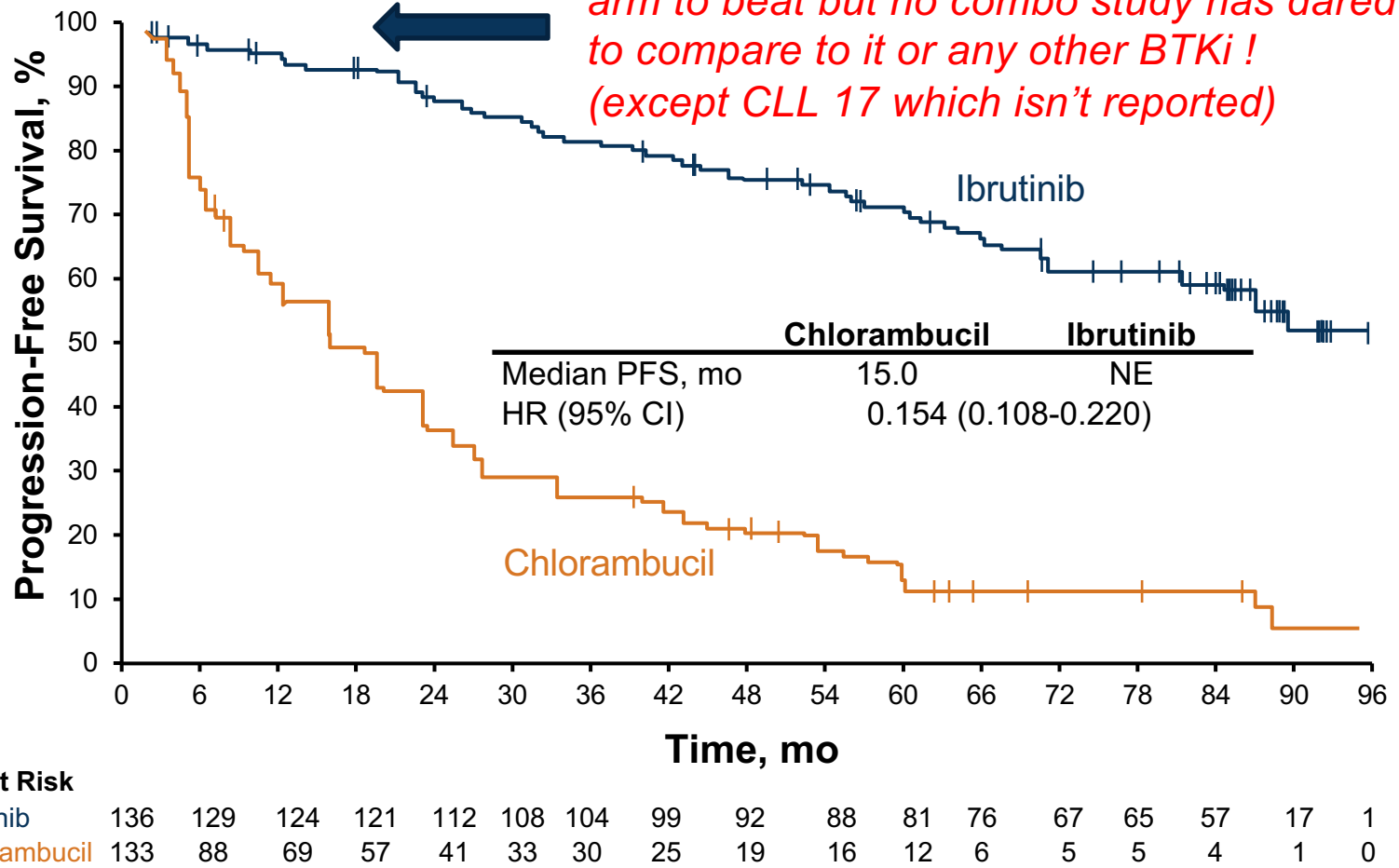
- ✓ **SEQUOIA:** superior PFS vs BR

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. Hillmen P et al. ASH 2021. Abstract 642. 6. Sharman JP et al. *Lancet.* 2020;395:1278-1291. 7. Tam C et al. ASH 2021. Abstract 396.

8-Year Follow-Up From RESONATE-2 Continues to Show Clinical Benefit of Ibrutinib Monotherapy in CLL

- Longest follow-up to date with a single-agent BTK inhibitor from a phase 3 study[1]
- Sustained PFS benefit with ibrutinib versus chlorambucil
- Benefit was similar for mutated and unmutated IGHV

Excellent long-term data. This is a control arm to beat but no combo study has dared to compare to it or any other BTKi ! (except CLL 17 which isn't reported)



1. Barr PM et al. *Blood Adv.* 2022 Apr 4 [Epub ahead of print].

Summary of Significant Studies With AEs Occurring in Patients Treated With BTKi

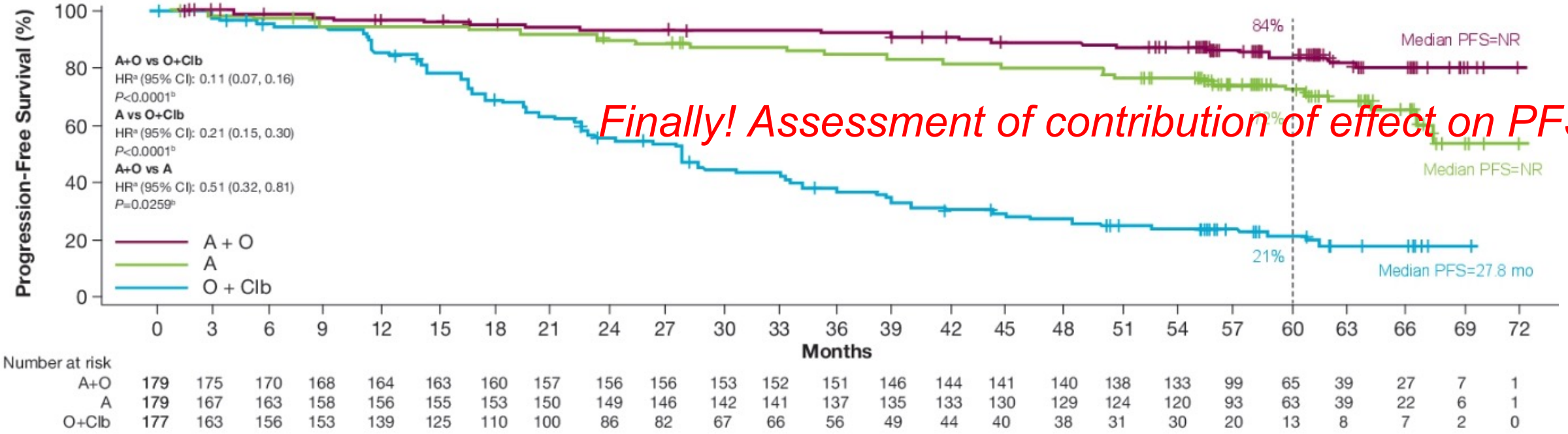
BTK Clinical Trial, AE %	Arthralgia	A-fib	Hematologic[a]	Bleeding/ Hemorrhage	Hypertension	Infection
RESONATE-2[1] Ibrutinib (n = 136)	–	6	–	4	14	–
iLLUMINATE[2] Ibrutinib + G vs GClb (n = 113)	22	12	17-44	NR	17	14[c]
ALLIANCE A041202[3] Ibrutinib (n = 180) Ibrutinib + rituximab (n = 181); vs BR	1[d] 2[d]	17[b] 14[b]	41[d] 39[d]	2[d] 4[d]	29[d] 34[d]	20[d] 20[d]
ECOG-1912[4] Ibrutinib + rituximab (n = 352); vs FCR	4.8[d]	6.5[d]	34.7[d]	1.1[d]	18.8[d]	10.5[d]
FLAIR[5]	**SAEs by organ class for FCR vs IR:** infections in 33.6% of patients vs 27.1%; blood and lymphatic in 19.8% vs 10.7%; and cardiac in 1.1% vs 8.3%					

[a] Includes anemia, neutropenia, and thrombocytopenia. [b] Any grade, most commonly petechiae, including ecchymosis. [c] Upper respiratory tract. [d] Grade 3 or higher.

1. Burger JA et al. *Leukemia*. 2020;34:787-798. 2. Moreno C et al. iwCLL 2019. Abstract 2069. 3. Woyach J et al. *N Engl J Med*. 2018;379:2517-2528.
4. Shanafelt TD et al. *N Engl J Med*. 2019;381:432-443. 5. Hillmen P et al. ASH 2021. Abstract 642.

Longer Follow-Up From ELEVATE-TN Shows Sustained PFS Benefit With Acalabrutinib ± Obinutuzumab[1]

5-year update, median follow-up of 58.2 months



Finally! Assessment of contribution of effect on PFS!

	HR (95% CI)	*P*
A + G vs GClb	0.11 (0.07-0.16)	< .0001
A vs GClb	0.21 (0.15-0.30)	< .000
A + G vs A	0.51 (0.32-0.81)	.0295

Data from 4-year follow-up showed PFS in unmutated IGHV CLL was 86%/77% for A + G/A vs 4% for GClb[2]

1. Sharman JP et al. ASCO 2022. Abstract 7539. 2. Sharman JP et al. ASCO 2021. Abstract 7509.

Summary of Significant Studies With AEs Occurring in Patients Treated With Next Gen BTKi

BTK Clinical Trial, AE %	Arthralgia	A-fib	Hematologic[a]	Bleeding/ Hemorrhage	Hypertension	Infection
ELEVATE-TN[1]						
Acalabrutinib (n = 179)	15.6[b] (0.6)	4.0[b]	9.5[d]	15.1[b] (2)	2[d]	14[d]
Acalabrutinib + G (n = 179); vs GClb	21.9[b] (1.1)	3.4[b]	29.8[d]	23.6[b] (2)	3[d]	21[d]
BGB-3111-206/ BGB-311-AU-003[2]						
Zanubrutinib (n = 118)	14	2	25[d]	11	14	11[d]

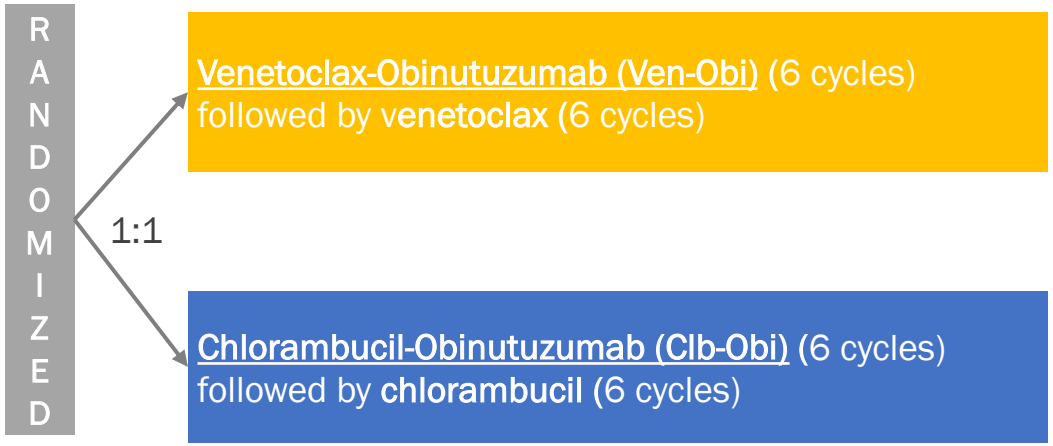
[a] Includes anemia, neutropenia, and thrombocytopenia. [b] Any grade, most commonly petechiae, including ecchymoses.
[c] Anemia and neutropenia, grade 3 or higher. [d] Grade 3 or higher.

1. Sharman JP et al. *Lancet*. 2020;395:1278-1291. 2. Tam CS et al. ASH 2019. Abstract 500.

5-Year Results From the CLL14 Phase 3 Study of Obinutuzumab + Venetoclax in Patients With TN CLL: Study Design and Patients

Key Eligibility Criteria

- Patients with TN CLL and coexisting medical conditions
- CIRS >6 and/or CrCl <70 mL/min



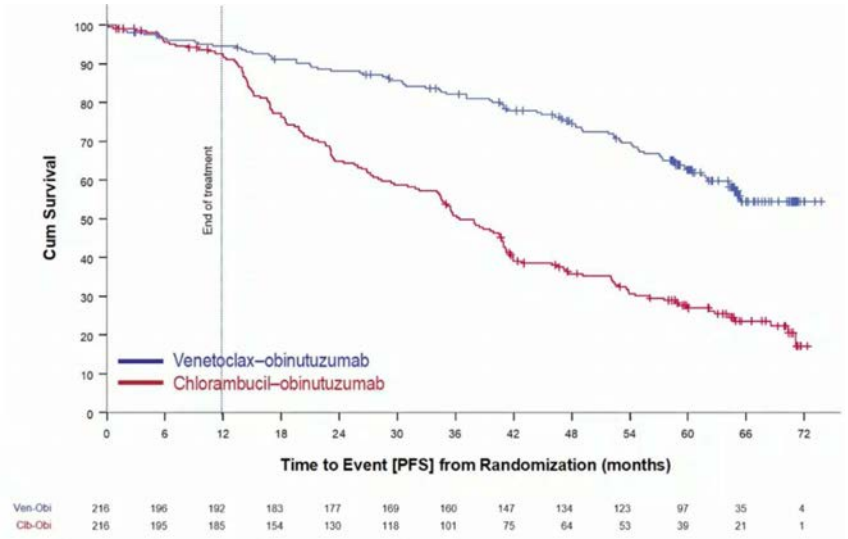
Primary endpoint: PFS
Secondary endpoints: response, MRD, OS

Patient Characteristics		Ven-Obi (n=216)	Clb-Obi (n=216)
Median age, years		72	71
Binet stage, %	A	21	20
	B	35	37
	C	44	43
Median total CIRS score (range)		9 (0-23)	8 (1-28)
Median estimated CrCl, mL/min		65.2	67.4
TLS risk category, %	Low	14	12
	Intermediate	64	68
	High	22	20
IGHV mutated, %		38	40
TP53 deleted and/or mutated, %		12	12
Cytogenic subgroups, %	del(17p)	8	7
	del(11q)	17	18
	Trisomy 12	17	19
	No abnormalities	24	20
	del(13q) alone	34	36

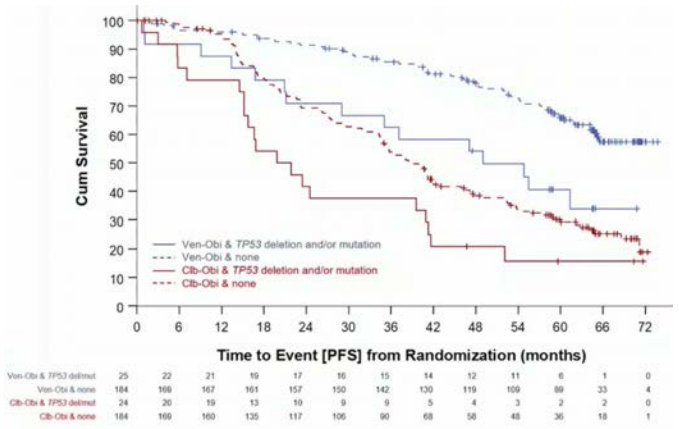
Al-Sawaf O, et al. EHA 2022. Abstract S148.

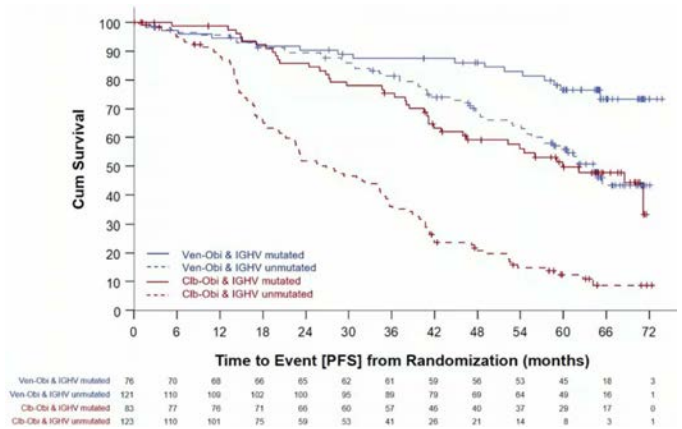
5-Year Results From the CLL14 Phase 3 Study of Obinutuzumab + Venetoclax in Patients With TN CLL: Efficacy

PFS: All Patients



PFS by *TP53* & *IGHV* Status





PFS by Subgroup		Ven-Obi (n=216)	Clb-Obi (n=216)
All patients	Median, months	NR	36.4
	5-year rate, %	62.6	27.0
	HR (95% CI); *P* value	0.35 (0.26-0.46); <0.0001	
Median, months			
TP53 del/mut	No	NR (n=184)	38.9 (n=184)
	Yes	49.0 (n=25)	19.8 (n=24)
IGHV status	Mut	NR (n=76)	59.9 (n=83)
	Unmut	64.2 (n=121)	26.9 (n=123)

- For Ven-Obi, pretreatment disease burden (max. LN size >5 cm and ANC >25 G/l) and del(17p) were independent prognostic factors for PFS

Median observation time: 65.4 months.

Al-Sawaf O, et al. EHA 2022. Abstract S148.

The conundrum remains: to use all our best agents at once or save ammunition for the future.

FIRST LINE: IBRUTINIB MONO = MEDIAN PFS ESTIMATED TO CONSERVATIVELY TO BE … 100 months (likely longer)

SECOND LINE:

- VENETOCLAX MONOTHERAY ESTIMATED TO BE … 24+ months (Jones et al, Lancet Oncology 2017).
- VR even longer ~ hard to estimate ~ 40 months (after BTKi)

Third line: Pirtobrutinib ~ 18-20 months

I+V MEDIAN PFS MUST BE BETTER THAN …. 130-140 months

- Almost no data on retreatment or mechanisms of resistance

And without LONG TERM data we should not dangle the word **CURE** with any novel agent combination based on **high rate of undetecable MRD** data alone

Agenda: CLL Update
A Meeting within a Meeting

MODULE 1: Front-Line CLL – Standard-Risk Patients — Dr Mato

MODULE 2: Chronic Lymphocytic Leukemia in 2022: Front-Line Therapy in Patients with High-Risk Disease — Dr Brander

MODULE 3: Fixed-Duration Targeted Therapy for CLL — Dr Wierda

MODULE 4: Novel Investigational Agents and Strategies in CLL — Dr Davids

MODULE 5: CLL 2030?

RTP RESEARCH TO PRACTICE

Cases and Questions: Management of High-Risk CLL

Adam S Kittai, MD

Christine E Ryan, MD

RTP
RESEARCH
TO PRACTICE

Cases and Questions: Richter's Syndrome

Adam Kittai, MD

RTP RESEARCH TO PRACTICE

Chronic Lymphocytic Leukemia (CLL) in 2022:
frontline therapy in patients with high risk disease

Danielle M. Brander, MD

Duke Cancer Institute

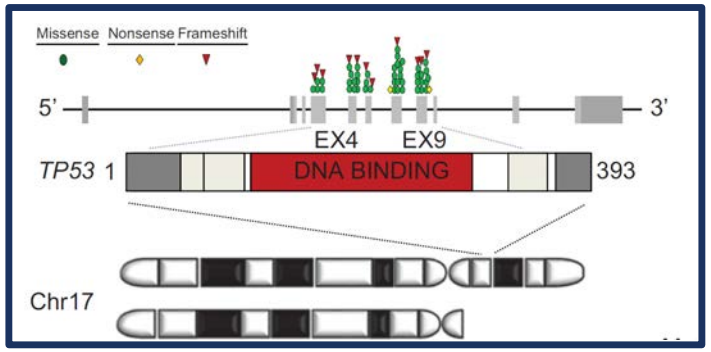
danielle.brander@duke.edu

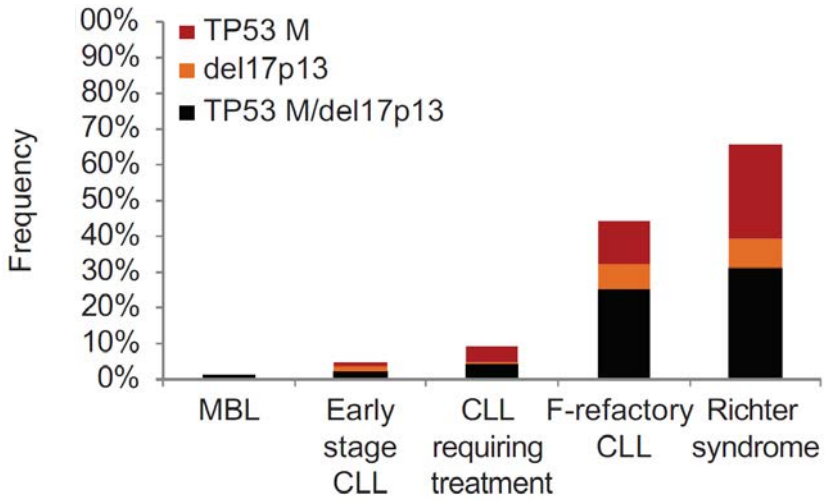
Research To Practice – Application in the Care of Complex Patients with CLL

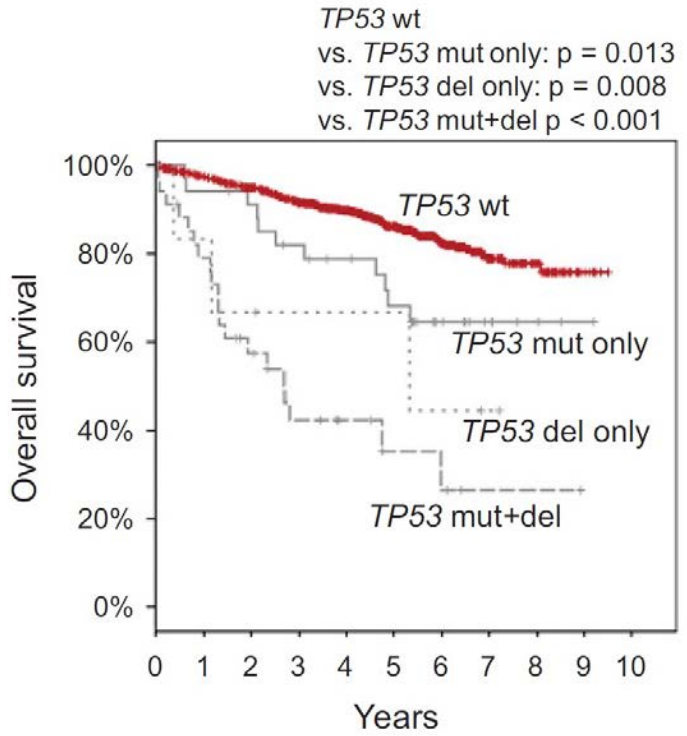
2022 Pan Pacific Lymphoma Conference

12 October 2022

HISTORICAL IN ERA OF CHEMOIMMUNOTHERAPY (CIT): del(17p) / TP53 mutation







TP53 aberrations & CIT:

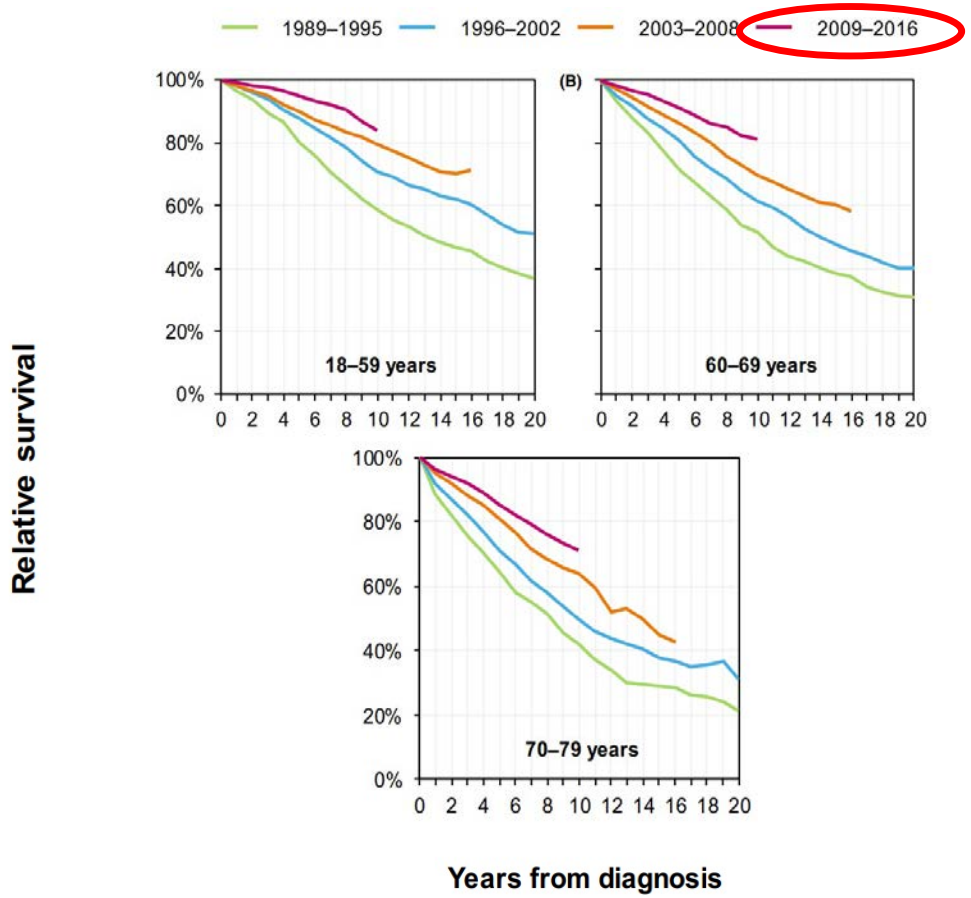
responses for treatment naïve
BR: mPFS of 7.9mo
FCR: 3 yr PFS of 18%

survival
~ 32 months mOS

Dohner et al. N Engl J Med 2000;343:1910; Stengel et al. Leukemia (2017) 31, 705; Rossi et al. Leukemia & Lymphoma. 2017; 58: 1548

bjh correspondence

Survival continues to increase in chronic lymphocytic leukaemia: a population-based analysis among 20 468 patients diagnosed in the Netherlands between 1989 and 2016

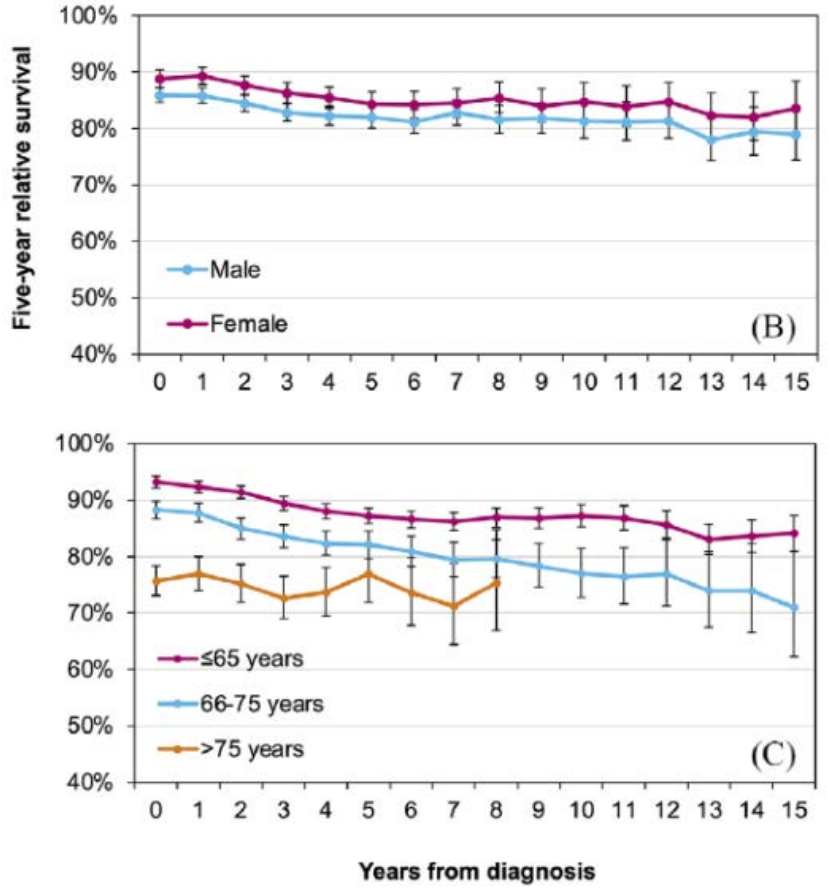


SHORT REPORT

eJHaem

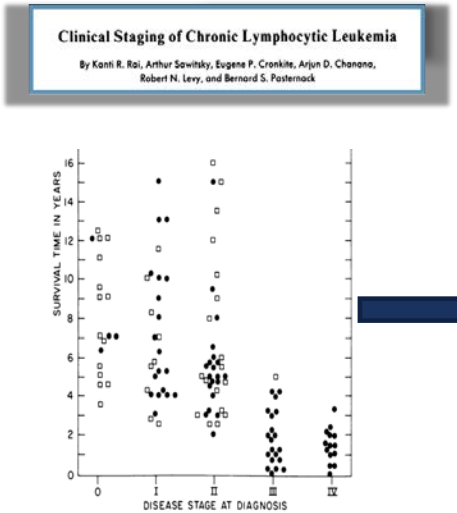
Conditional relative survival among patients with chronic lymphocytic leukaemia: A population-based study in the Netherlands

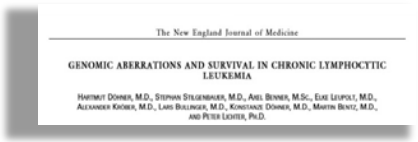
Lina van der Straten[1,2,3] | Mark-David Levin[2] | Otto Visser[4] | Eduardus F.M. Posthuma[5,6] | Jeanette K. Doorduijn[7] | Arnon P. Kater[8] | Avinash G. Dinmohamed[1,8,9,10]

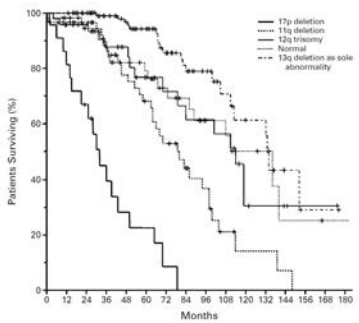


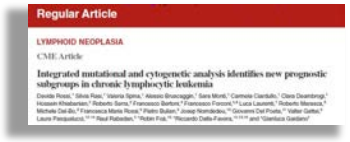
Van der Straten et al. BJH. 2020;189: 574
Van der Straten et al. eJHaem. 2022;3:180

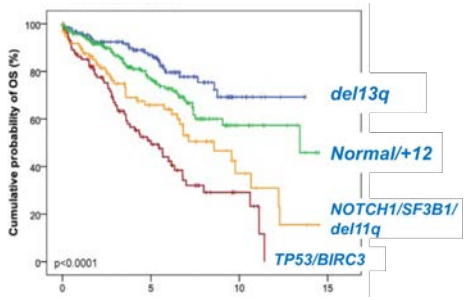
STAGING, MARKERS, PROGNOSTICS – HOW BEST TO ASSESS AND INCORPORATE ?

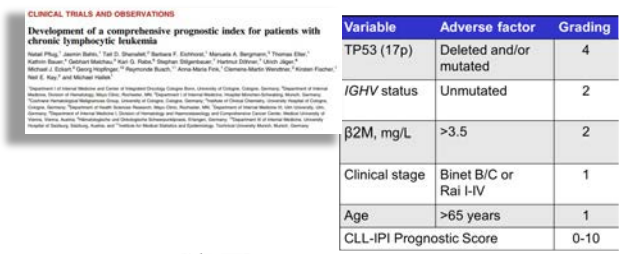




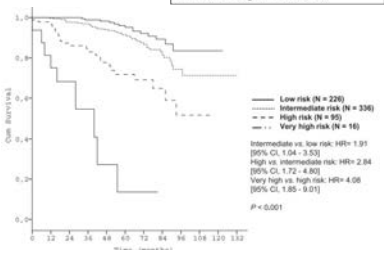


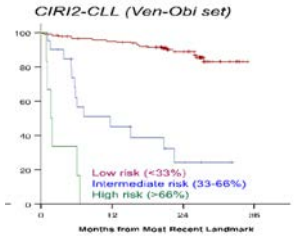


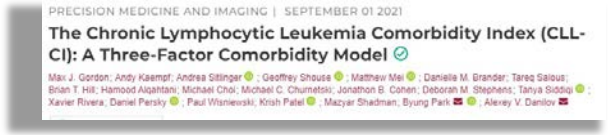


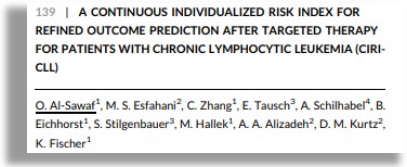


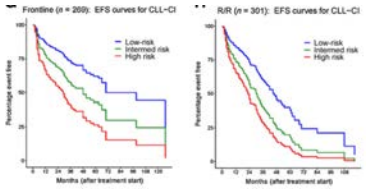
Variable	Adverse factor	Grading
TP53 (17p)	Deleted and/or mutated	4
IGHV status	Unmutated	2
β2M, mg/L	>3.5	2
Clinical stage	Binet B/C or Rai I-IV	1
Age	>65 years	1
CLL-IPI Prognostic Score		0-10

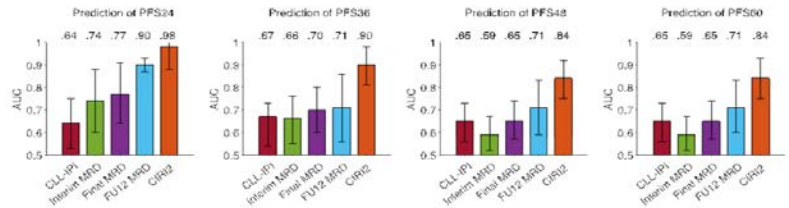












What is the role of co-morbidities?
Of MRD?
Of time to response?

Rai et al. Blood. 1975; 46:219. Rossi et al. Blood. 2013;121:1403. Dohner et al. N Engl J Med 2000;343:1910. Pflug et al. Blood. 2014; 124:49-64. Gordon et al. Clin Cancer Res 2021;27:4814. Al-Sawak et al. iwCLL oral presentation and Hematological Oncology Supplement Abstracts 139. 2021.

CLL/SLL TARGETED/NOVEL THERAPY

APPROVED & IN DEVELOPMENT (PARTIAL) IN VARIOUS TREATMENT SETTINGS

	BTKi	BCL2i *BH3 mimetics*	PI3Ki	anti-CD20 Ab	Others
Drugs	**ibrutinib +/- anti-CD20** **acalabrutinib +/- anti-CD20** **zanubrutinib (BGB-3111)** [a] **tirabrutinib (ONO-4059/GS-4059)** **DTRMWXHS-12** **vecabrutinib (SNS-062)** [b] **pirtobrutinib (LOXO-305)**[b] **nemtabrutinib (MK-1026/ARQ-531)**[b] **LP-168**[c]	**venetoclax** **S55746** **lisaftoclax (APG-2575)** **BGB-11417** **LOXO-338** **LP-118** ***Dual*** **navitoclax (ABT-263)** **AZD0466** ***MCL1*****	**idelalisib*** **duvelisib** **umbralisib (TGR-1202)**[d] **zandelisib (MEI-401)**[e]	**rituximab** **obinutuzumab** **ofatumumab** **ublituximab**	**CAR-T (liso-cel +/- novel)** **CVAY736 (anti-BAFF Ab)** **CAP-100 (anti-CC7 Ab)** **cirmtuzumab (ROR1 Ab)**
Notes	a. cat 1 NCCN for CLL b. Noncovalent BTK inhibitor c. Dual WT covalent/C481S noncovalent	** phase I studies across heme malignancies	d. Approved in FL, MZL e. Trial in FL		

CLL/SLL TARGETED/NOVEL THERAPY

National Comprehensive Cancer Network®

NCCN Guidelines Version 1.2023
Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma

SUGGESTED TREATMENT REGIMENS[a,b,c,d]
CLL/SLL with del(17p)/*TP53* mutation
(alphabetical by category)
CIT is not recommended since del(17p)/*TP53* mutation is associated with low response rates.

FIRST-LINE THERAPY[e]	
Preferred regimens	**Other recommended regimens**
• Acalabrutinib[f] ± obinutuzumab • Venetoclax[f,g] + obinutuzumab • Zanubrutinib[f]	• Alemtuzumab[r] ± rituximab • HDMP + rituximab • Ibrutinib[f,h] • Obinutuzumab • Ibrutinib + venetoclax[f,g] (category 2B)

SECOND-LINE AND SUBSEQUENT THERAPY[e]	
Preferred regimens	**Other recommended regimens**
• Acalabrutinib[f,q] (category 1) • Venetoclax[f,g] + rituximab (category 1) • Venetoclax[f,g] • Zanubrutinib[f,q]	• Ibrutinib[f,h] (category 1) Alemtuzumab[r] ± rituximab • Duvelisib[f] • HDMP + rituximab • Idelalisib[f] ± rituximab[s] • Lenalidomide[t] ± rituximab

LOW FREQUENCY OF FISH/*IGHV* TESTING

bjh research paper

Real-world clinical experience in the Connect® chronic lymphocytic leukaemia registry: a prospective cohort study of 1494 patients across 199 US centres

Original Study

Check for updates

Prognostic Testing and Treatment Patterns in Chronic Lymphocytic Leukemia in the Era of Novel Targeted Therapies: Results From the informCLL Registry

Anthony R. Mato,[1] Jacqueline C. Barrientos,[2] Nilanjan Ghosh,[3] John M. Pagel,[4] Danielle M. Brander,[5] Meghan Gutierrez,[6] Karen Kadish,[7] Brian Tomlinson,[8] Reethi Iyengar,[9] David Ipe,[9] Sandhya Upasani,[9] Carlos I. Amaya-Chanaga,[9] Murali Sundaram,[10] Jennifer Han,[10] Nick Giafis,[9] Jeff P. Sharman[11]

Connect CLL US Database (2010 – 2014)

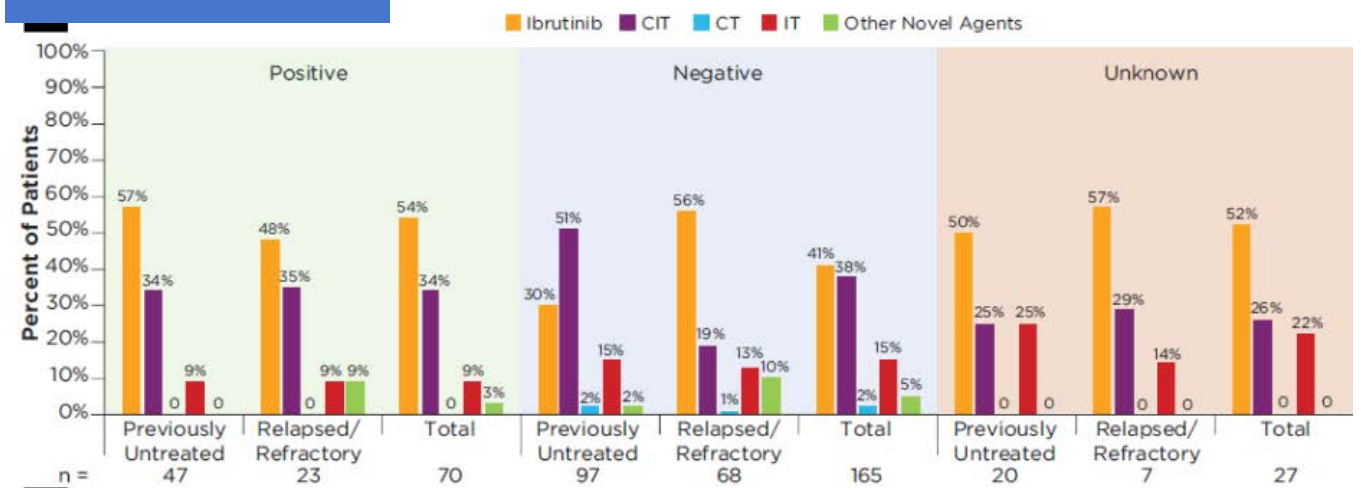
First line (n=889)
Second line (n=260)

informCLL Registry (2015-)

interim analysis (n=840)
Untreated (n=459, 55%)
Previously tx (n=381, 45%)

Test	% tested (first line)	% tested (2nd line)
Metaphase cytogenetics	39%	31.2%
FISH	58%	40.4%
IGHV	7.9%	5% (not required if prior)

del17p



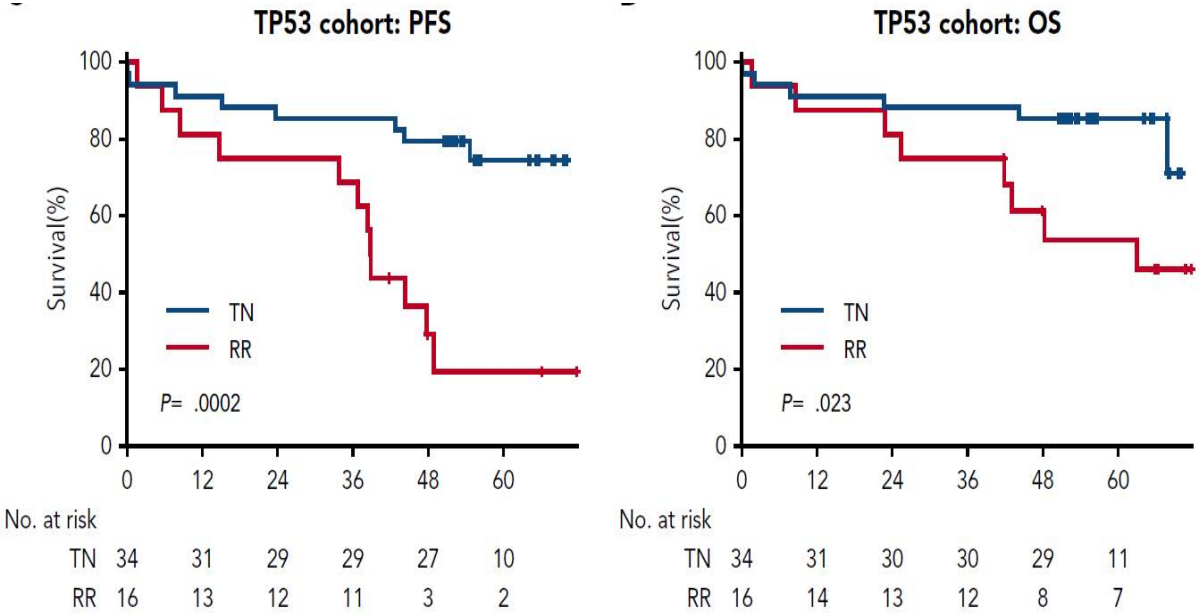
Mato et al. *BJH*. 2016;175z;892
Mato et al. Clinical Leukemia Lymphoma Myeloma. 2020; 20:174

IBRUTINIB FRONTLINE

TP53 aberrations

Ahn et al 2018
TP53 aberration cohort (n=51; 34 TN)

In TN TP53:
5 year PFS was 74%
5 year OS was 85%
In R/R TP53: 19% 5 year PFS

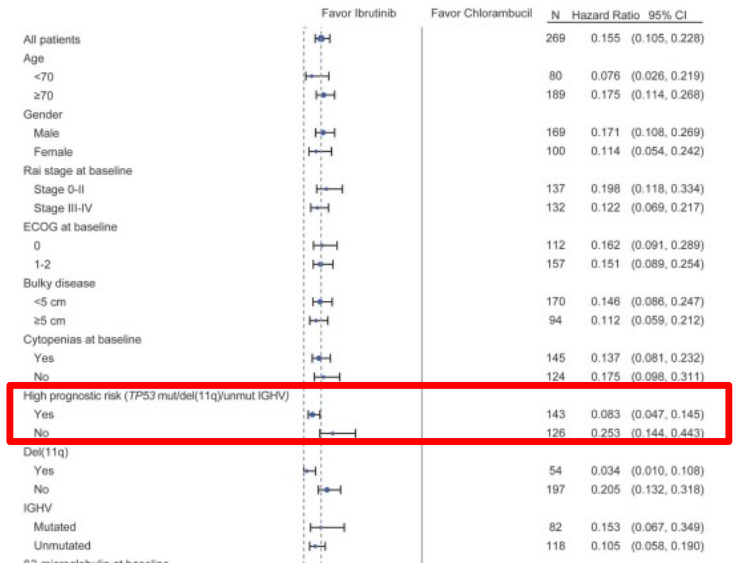


RESONATE-2 (no del17p):
12 pts with TP53 mutations in ibrutinib arm

Ibrutinib mPFS in TP53 mutation vs TP53 WT:
mPFS not reached

5 yrs PFS est:
56% TP53mut vs 73% in WT

Only 3 pts with TP53 in chlorambucil arm



Ahn et al. Blood. 2018;131:2357. O'Brien et al. Blood. 2018;131:1910. Barr et al. Haematologica. 2018;103:1502. Burger et al. Leukemia. 2020; 34:787.

FRONTLINE: IBRUTINIB VS. CHEMOIMMUNOTHERAPY

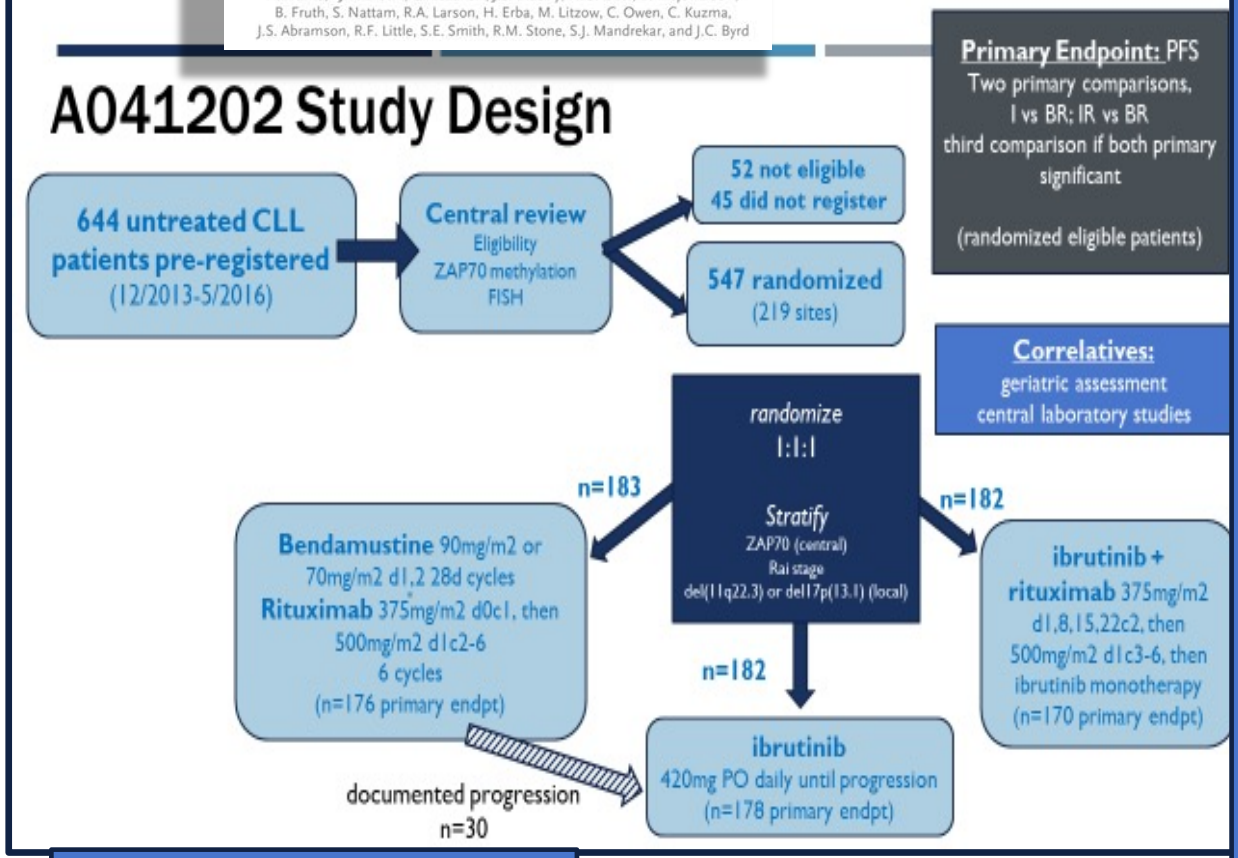
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Ibrutinib Regimens versus Chemoimmunotherapy in Older Patients with Untreated CLL

J.A. Woyach, A.S. Ruppert, N.A. Heerema, W. Zhao, A.M. Booth, W. Ding, N.L. Bartlett, D.M. Brander, P.M. Barr, K.A. Rogers, S.A. Parikh, S. Coutre, A. Hurria, J.R. Brown, G. Lozanski, J.S. Blachly, H.G. Ozer, B. Major-Elechi, B. Fruth, S. Nattam, R.A. Larson, H. Erba, M. Litzow, C. Owen, C. Kuzma, J.S. Abramson, R.F. Little, S.E. Smith, R.M. Stone, S.J. Mandrekar, and J.C. Byrd

A041202 Study Design



Primary Endpoint: PFS
BR: mPFS 43 mos
Ibr: mPFS NR
Ibr+R: mPFS: NR

No difference in PFS ibrutinib vs ibrutinib + R

NOTE: Other randomized studies did not include del17p/TP53 mutations especially after SOC changed → keep in mind when reviewing study long term follow up

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Woyach et al. N Engl J Med. A041202 2018;379:2517. Shanafelt et al. N Engl J Med 2019;381:432

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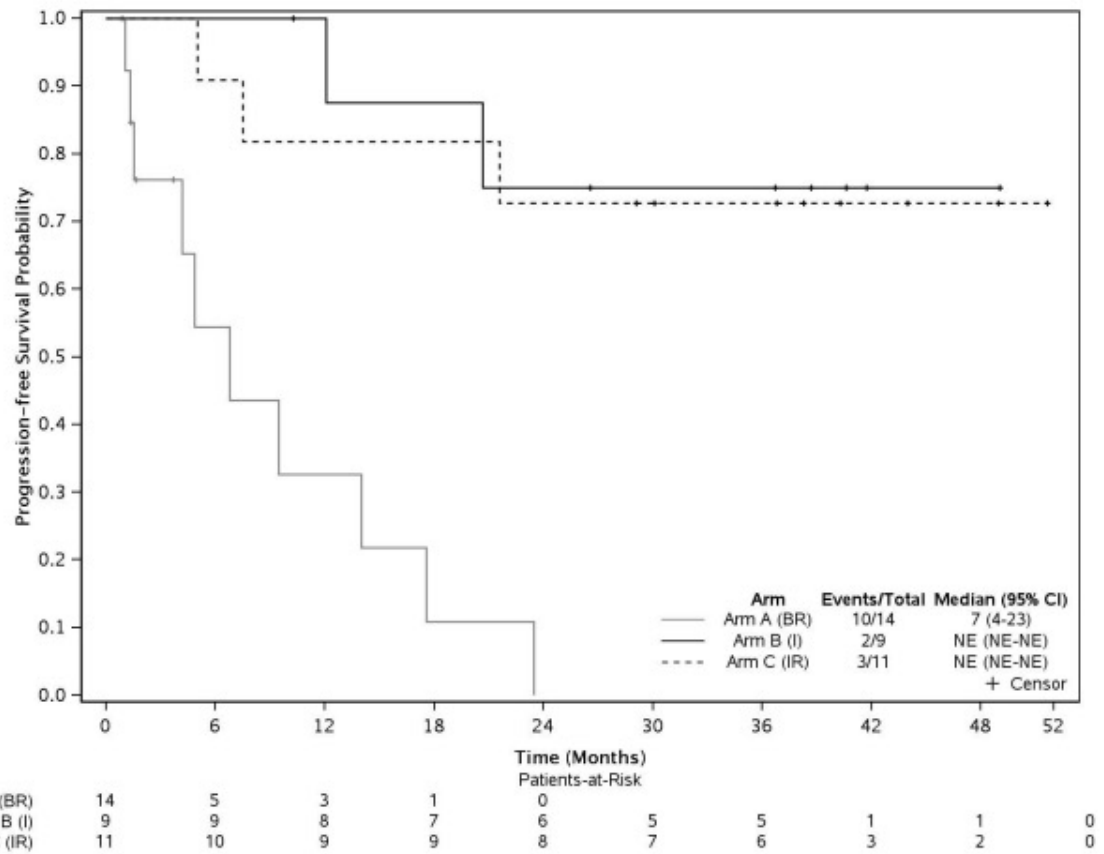
Figure S2: Progression-Free Survival by arm and Dohner's Hierarchy. Progression-Free Survival for A) del(17p); B) del(11q); C) Patients with neither del(17p) nor del(11q)

A



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Woyach et al. N Engl J Med. A041202 2018;379:2517. Shanafelt et al. N Engl J Med 2019;381:432

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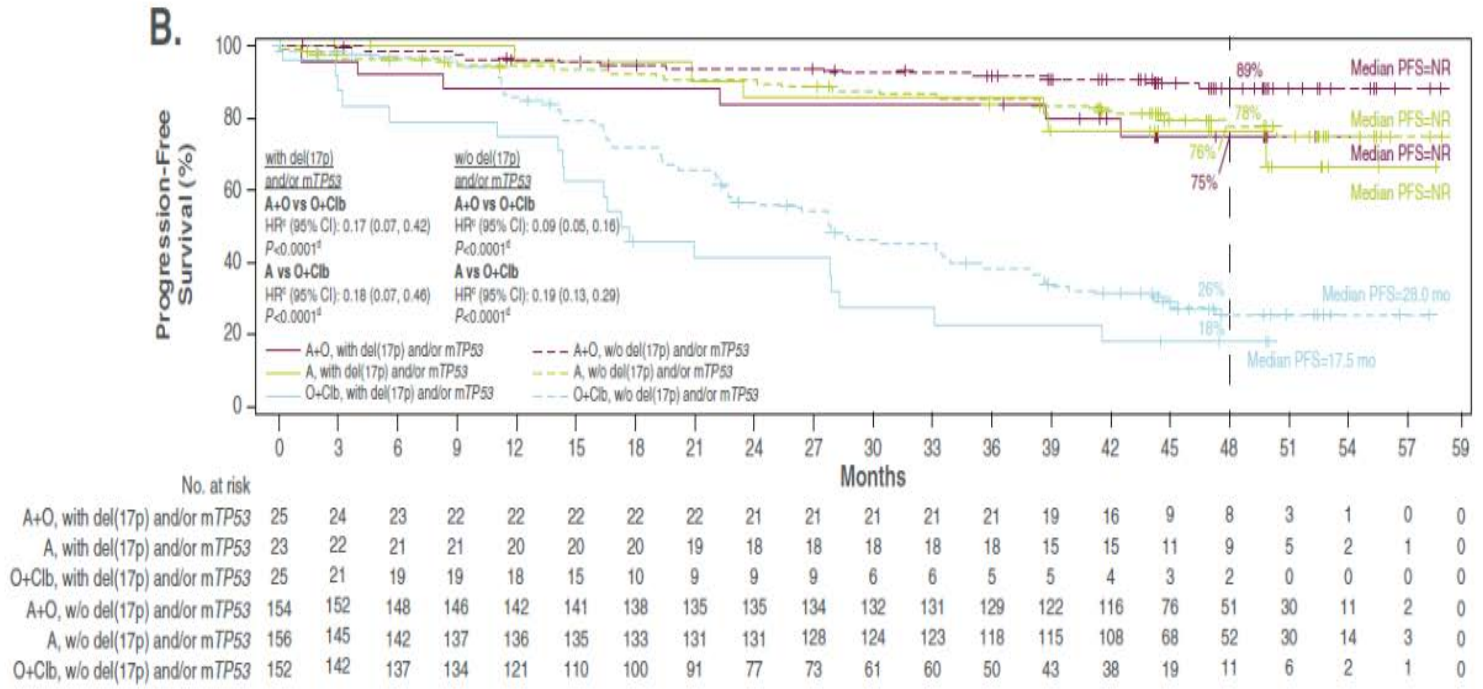
ACALABRUTINIB FOR FRONTLINE CLL: *ELEVATE-TN*
PFS – Investigator assessed PFS by del17p and TP53

mPFS in del17p and/or TP53 mut:
G-acala and acala: NR
G-chlor: 17.5 mos

48 month PFS estimates in del17p and/or TP53 mut:
G-acala: 74.8%
Acala: 76.2%



No. at risk																				
A+O, with del(17p) and/or mTP53	25	24	23	22	22	22	22	22	21	21	21	21	21	19	16	9	8	3	1	0	0
A, with del(17p) and/or mTP53	23	22	21	21	20	20	20	19	18	18	18	18	18	15	15	11	9	5	2	1	0
O+Clb, with del(17p) and/or mTP53	25	21	19	19	18	15	10	9	9	9	6	6	5	5	4	3	2	0	0	0	0
A+O, w/o del(17p) and/or mTP53	154	152	148	146	142	141	138	135	135	134	132	131	129	122	116	76	51	30	11	2	0
A, w/o del(17p) and/or mTP53	156	145	142	137	136	135	133	131	131	128	124	123	118	115	108	68	52	30	14	3	0
O+Clb, w/o del(17p) and/or mTP53	152	142	137	134	121	110	100	91	77	73	61	60	50	43	38	19	11	6	2	1	0

Sharman et al. Leukemia. 2021; https://doi.org/10.1038/s41375-021-01485

CLL14
EXTENDED FOLLOW UP

Minimal Residual Disease Dynamics after Venetoclax-Obinutuzumab Treatment: Extended Off-Treatment Follow-up From the Randomized CLL14 Study

Othman Al-Sawaf, MD[1,2,3]; Can Zhang, PhD[1]; Tong Lu, PhD[4]; Michael Z. Liao, PhD[4]; Anesh Panchal, MSc[5]; Sandra Robrecht, PhD[1]; Travers Ching, PhD[6]; Maneesh Tandon, MBChB[5]; Anna-Maria Fink, MD[1]; Eugen Tausch, MD[7]; Christof Schneider, MD[7]; Matthias Ritgen, MD[8]; Sebastian Böttcher, MD[9]; Karl-Anton Kreuzer, MD[1]; Brenda Chyla, PhD[10]; Dale Miles, PhD[4]; Clemens-Martin Wendtner, MD[11]; Barbara Eichhorst, MD[1]; Stephan Stilgenbauer, MD[7,12]; Yanwen Jiang, PhD[4]; Michael Hallek, MD[1]; and Kirsten Fischer, MD[1]

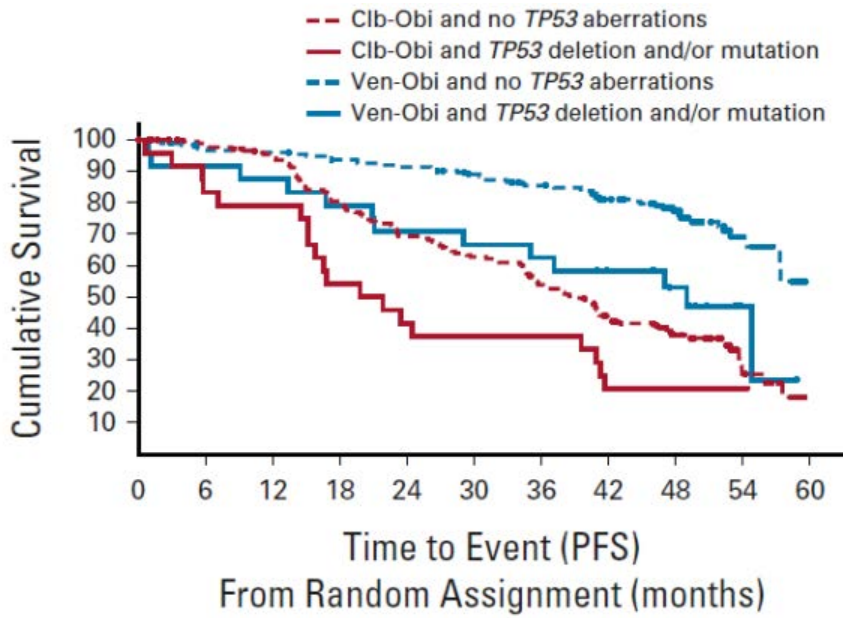
4 year follow up
(3 yrs off drug):

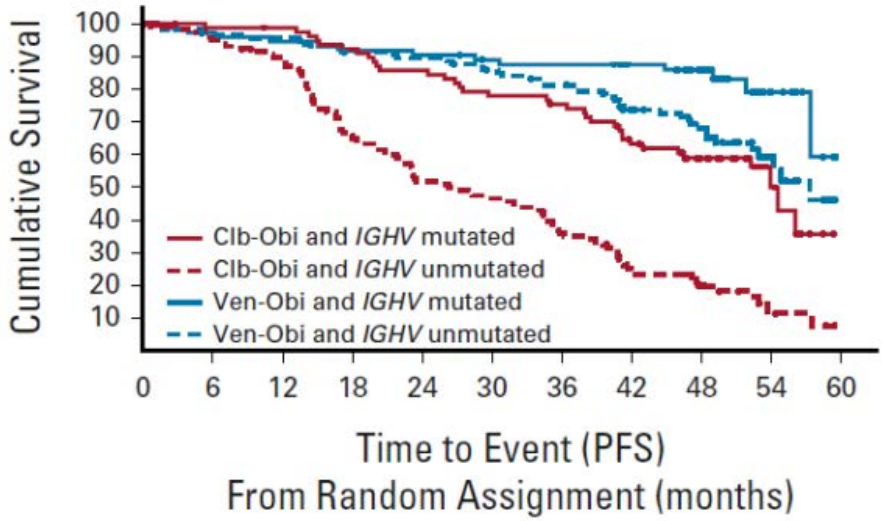
4 yr PFS
all
Ven-G: 74%
G-chlor: 35%

TP53
Ven-G: 53%
G-chlor: 21%

Unmutated IGHV
Ven-G: 68%
G-chlor: 20%

4 yr OS
Ven-G: 85%
G-chlor: 83%





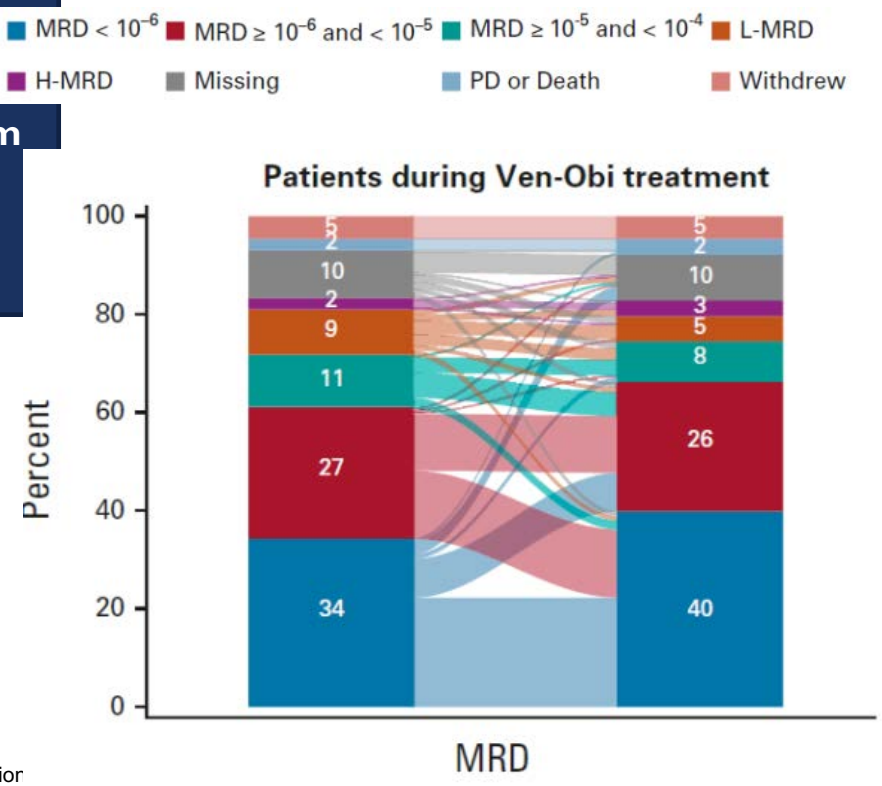
Al-Sawaf O, et al. ASH 2020. Abs 127.
Al-Sawaf O, Et al. EHA 2021. Absr S146
Al-Sawaf O et al. JCO. 2021; 39:4049

CLL14
EXTENDED FOLLOW UP

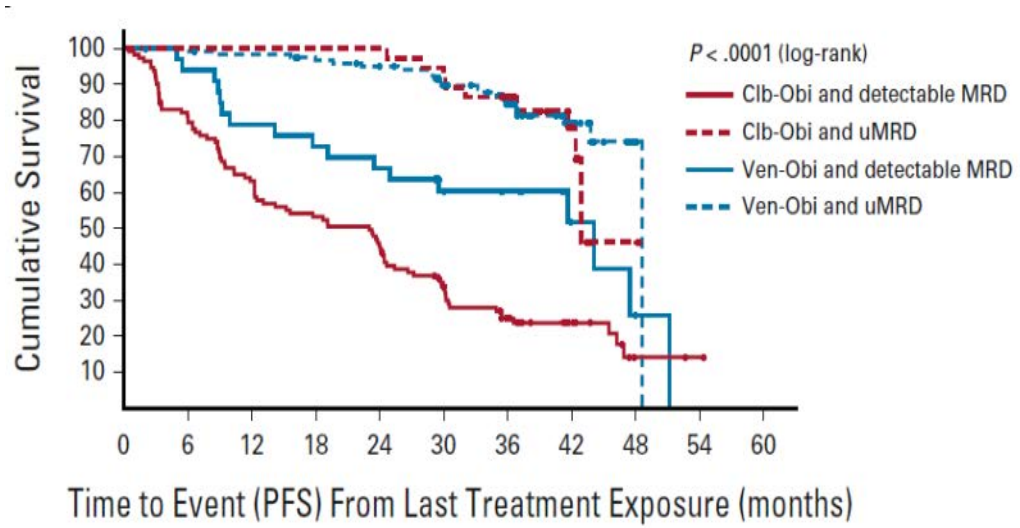
MRD by adaptive clonoSEQ®

MRD at EOT
74% venG,
32% Gchl

Many patients in venG arm had uMRD at C7, 25% deepened response



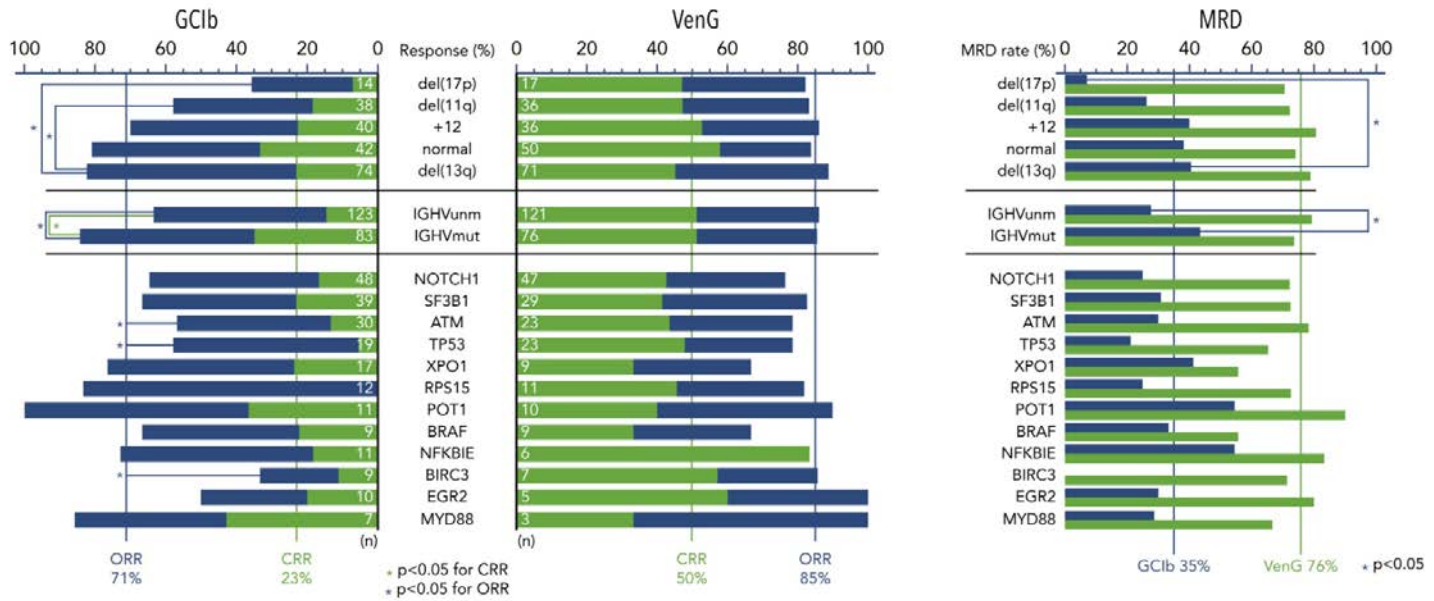
PFS by MRD



Al-Sawaf O, et al. ASH 2020. Abs 127.
Al-Sawaf O, Et al. EHA 2021. Absr S146
Al-Sawaf O et al. JCO. 2021; 39:4049

CLL14
ROLE OF MARKERS IN ORR AND MRD

Assessment of NGS including minor mutations (VAF 2-10%)
No BCL2 G101V mutations found



ORR and MRD by markers – how to improve ORR and PFS in highest risk patients?

52 months follow up (markers):

PFS (p<0.05):
Ven-G: del17p/TP53+, UM-IGHV

G-chlor: del17p/TP53+, ATM+, BIRC3+, NOTCH1+, SF3B1+, UM-IGHV

OS (p<0.05):
Ven-G: del17p/TP53+

G-chlor: del17p/TP53+, SF3B1+, UM-IGHV

Al-Sawaf O, et al. ASH 2020. Abs 127.
Al-Sawaf O, Et al. EHA 2021. Absr S146
Tausch et al. Blood. 2020;135: 2402.

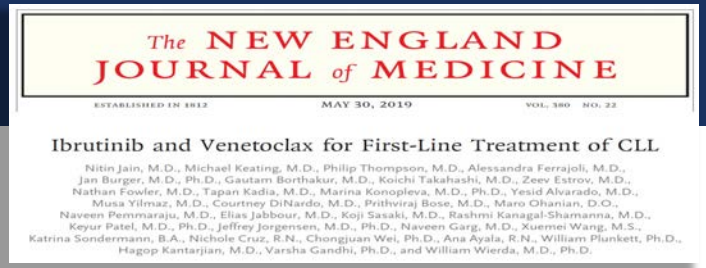
IBRUTINIB + VENETOCLAX FRONTLINE - *MDACC PH2*

Treatment Naïve CLL + High Risk (1 of following):

TP53 aberration (del17p and/or TP53 mut)
Del11q
Unmutated *IGHV*
Age >65 yo

Treatment plan:

Ibr x 3cycles → 24 cycles combination V+Ibr
If BM MRD+ @ 24mo → continue Ibr
AMD: 24mo BM MRD+: can cont.V+ibr



The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 MAY 30, 2019 VOL. 380 NO. 22

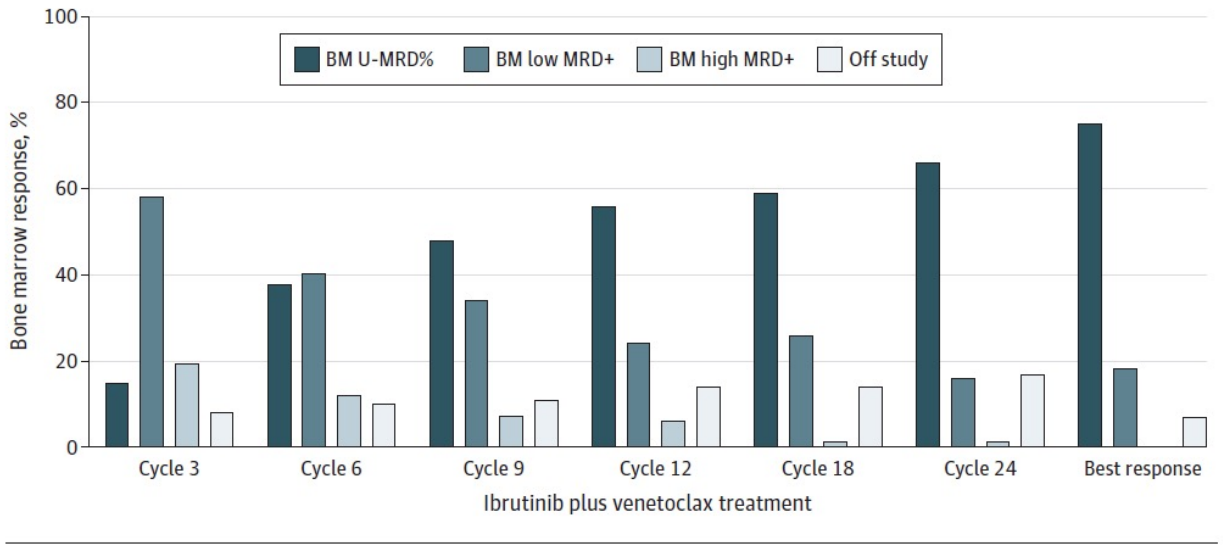
Ibrutinib and Venetoclax for First-Line Treatment of CLL

Nitin Jain, M.D., Michael Keating, M.D., Philip Thompson, M.D., Alessandra Ferrajoli, M.D., Jan Burger, M.D., Ph.D., Gautam Borthakur, M.D., Koichi Takahashi, M.D., Zeev Estrov, M.D., Nathan Fowler, M.D., Tapan Kadia, M.D., Marina Konopleva, M.D., Ph.D., Yesid Alvarado, M.D., Musa Yilmaz, M.D., Courtney DiNardo, M.D., Prithviraj Bose, M.D., Maro Ohanian, D.O., Naveen Pemmaraju, M.D., Elias Jabbour, M.D., Koji Sasaki, M.D., Rashmi Kanagal-Shamanna, M.D., Keyur Patel, M.D., Ph.D., Jeffrey Jorgensen, M.D., Ph.D., Naveen Garg, M.D., Xuemei Wang, M.S., Katrina Sondermann, B.A., Nichole Cruz, R.N., Chongjuan Wei, Ph.D., Ana Ayala, R.N., William Plunkett, Ph.D., Hagop Kantarjian, M.D., Varsha Gandhi, Ph.D., and William Wierda, M.D., Ph.D.

BM uMRD:

12C: 56%
24C: 66%
Best: 75%

Figure 1. Bone Marrow (BM) Measurable Residual Disease (MRD) Response at Serial Points on an Intent-to-Treat Basis in 80 Patients



3 year PFS (m38 mos follow up): 93%

(authors report ~80% 3yrs PFS in pooled ibrutinib monotherapy and 82% in CLL14)

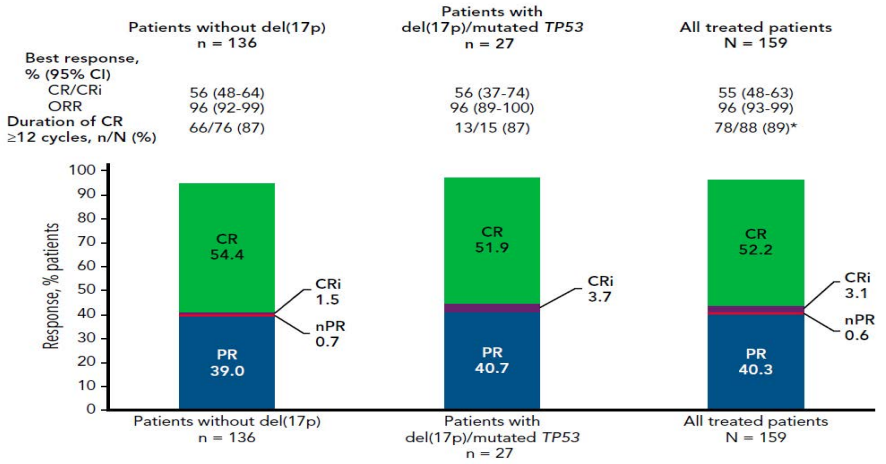
Jain et al. N Engl J Med 2019;380:2095-103. Jain et al. JAMA Oncol. doi:10.1001/jamaoncol.2021.1649

IBRUTINIB + VENETOCLAX FRONTLINE, *CAPTIVATE (PCYC-1142)*

Fixed Duration Cohort

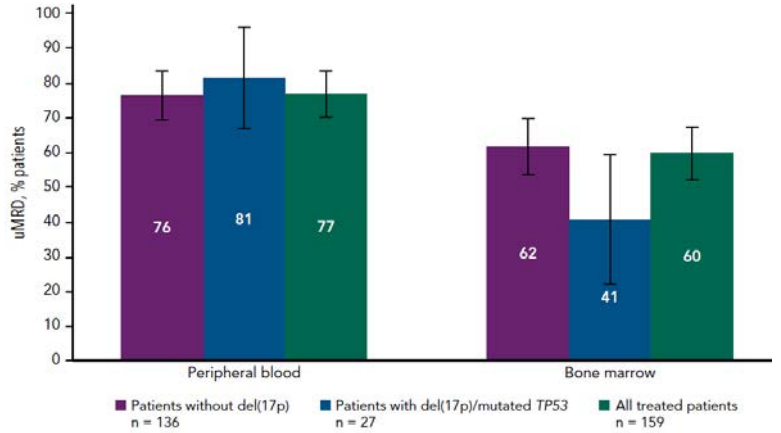
Median time on study: ~28 months
Median time off treatment: ~14 months

Characteristic	All treated patients (n = 159), n (%)
Hierarchical cytogenetics (FISH) classification*	
Del(17p)	20 (13)
Del(11q)	28 (18)
Trisomy 12	23 (14)
Normal	33 (21)
Del(13q)	54 (34)
Unknown	1 (1)
Mutated *TP53*	
Yes	16 (10)
No	142 (89)
Unknown	1 (1)
Del(17p) or mutated *TP53*	
Yes	27 (17)
No	129 (81)
Unknown	3 (2)



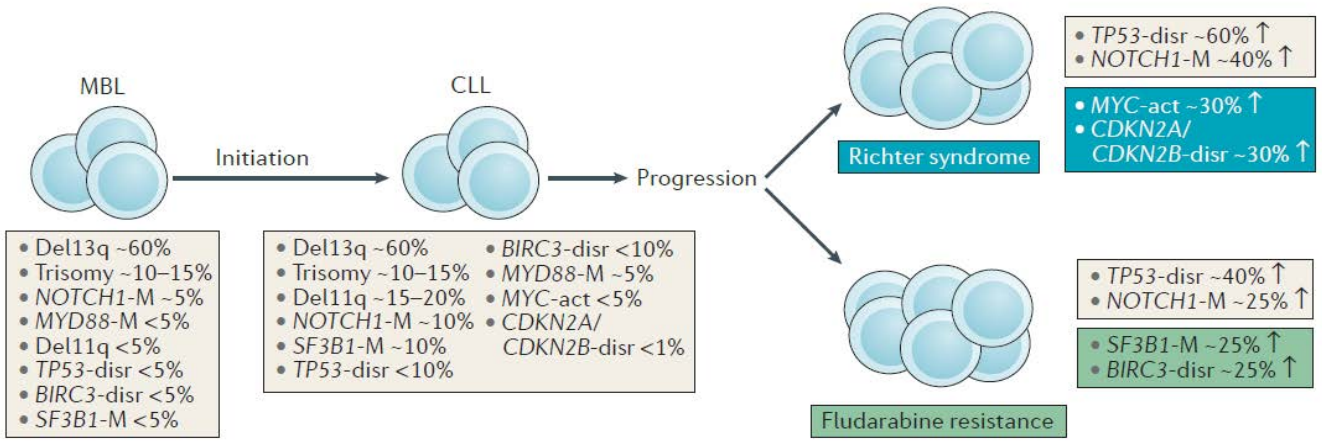
Primary endpoint:
Investigator CR/CRi rate
In patients without del17p: 56%
(min rate of 37%)

MRD



Ghia et al. ASCO 2021. Abr
Tam et al. Blood. 2022; 139:3278.

RICHTER'S TRANSFORMATION



SWOG CLL Study S1925

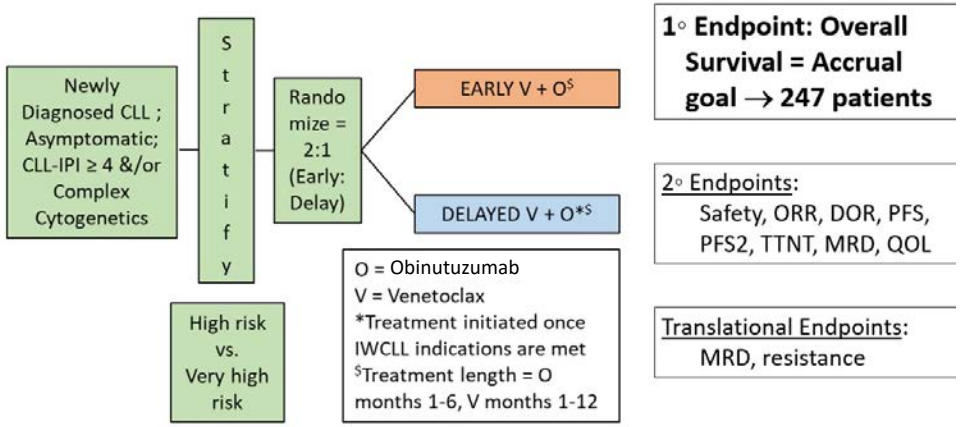
Randomized, Phase III Study of Early Intervention with Venetoclax and Obinutuzumab versus DeLayed Therapy with VEnetoclax and Obinutuzumab in Newly Diagnosed Asymptomatic High-Risk Patients with CLL:
EVOLVE CLL Study

SWOG CLL Study Group

Debbie Stephens, Brian Hill, John Pagel, Alexey Danilov, Mazyar Shadman, Susan O'Brien, Steve Coutre
ECOG Champion: Anthony Mato
Alliance Champion: Danielle M Brander

SWOG

S1925: EVOLVE Study



SWOG

Fabbri. Nature Reviews Cancer. 2016; 16:147.

Agenda: CLL Update
A Meeting within a Meeting

MODULE 1: Front-Line CLL – Standard-Risk Patients — Dr Mato

MODULE 2: Chronic Lymphocytic Leukemia in 2022: Front-Line Therapy in Patients with High-Risk Disease — Dr Brander

MODULE 3: Fixed-Duration Targeted Therapy for CLL — Dr Wierda

MODULE 4: Novel Investigational Agents and Strategies in CLL — Dr Davids

MODULE 5: CLL 2030?

RTP
RESEARCH
TO PRACTICE

Cases and Questions: TLS and Venetoclax/Obinutuzumab

Adam Kittai, MD

RTP
RESEARCH
TO PRACTICE

A 60-year-old patient with CLL, an absolute lymphocyte count of 80,000 and several involved lymph nodes that are larger than 5 centimeters is about to receive venetoclax. If a local tertiary center offered to start this patient on treatment and then transfer the patient back to you, would you likely use this service?

- Yes
- No
- No, but I would if they helped me manage the case virtually
- I’m not sure

Cases and Questions: Management of BTK- and Venetoclax-Refractory CLL

Christine Ryan, MD

RTP RESEARCH TO PRACTICE

Have you administered or would you administer a BTK inhibitor in combination with venetoclax as first-line treatment for CLL?

- I have
- I have not but would for the right patient
- I have not and would not
- I'm not sure

What would be your most likely approach for a patient with newly diagnosed CLL to whom you decided to administer up-front venetoclax/obinutuzumab and who has detectable MRD after completing 1 year of treatment?

- Continue treatment
- Discontinue treatment
- I'm not sure

RTP RESEARCH TO PRACTICE

Fixed-duration Targeted Therapy for CLL

12 October 2022

WILLIAM G. WIERDA MD,PHD

PROFESSOR OF MEDICINE

SECTION HEAD, CLL

DEPARTMENT OF LEUKEMIA

U.T. M.D. ANDERSON CANCER CENTER

HOUSTON, TX USA

BTKi- *vs.* BCL-2i-based Treatment

BTK Inhibitor[1-4]

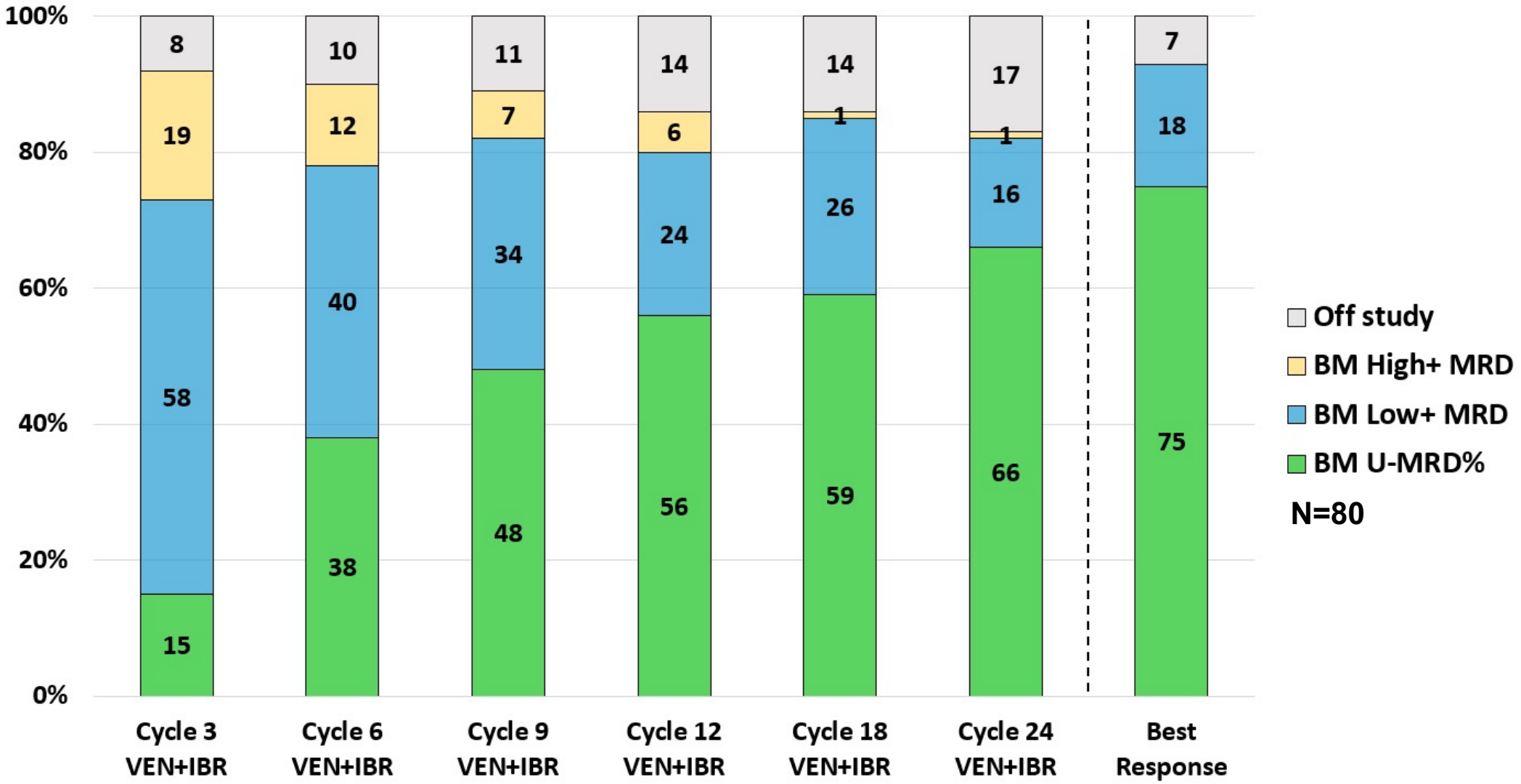
- Easy initiation
- Continuous and indefinite therapy
- Very low TLS risk
- More cardiac risk
- Some favor in del(17p)/ mutated-*TP53*
- Activity in nodal disease

BCL-2 Inhibitor[4,5]

- Risk for TLS requires monitoring for initiation
- Includes CD20 mAb – immunosuppression
- Fixed duration
- GFR sensitivity
- Concern for del(17p)/mutated-*TP53*
- Activity in BM and blood

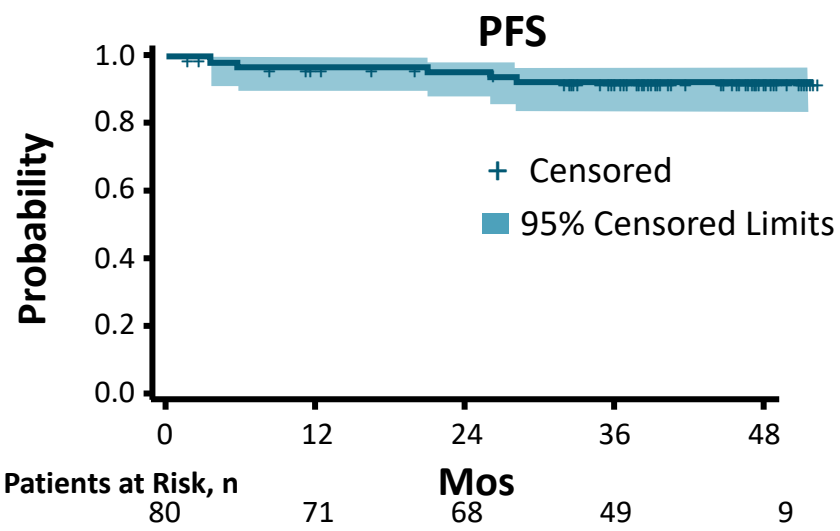
1. Acalabrutinib PI. 2. Ibrutinib PI. 3. Zanubrutinib PI. 4. Awan. Am Soc Clin Oncol Educ Book. 2020;40:1. 5. Venetoclax PI.

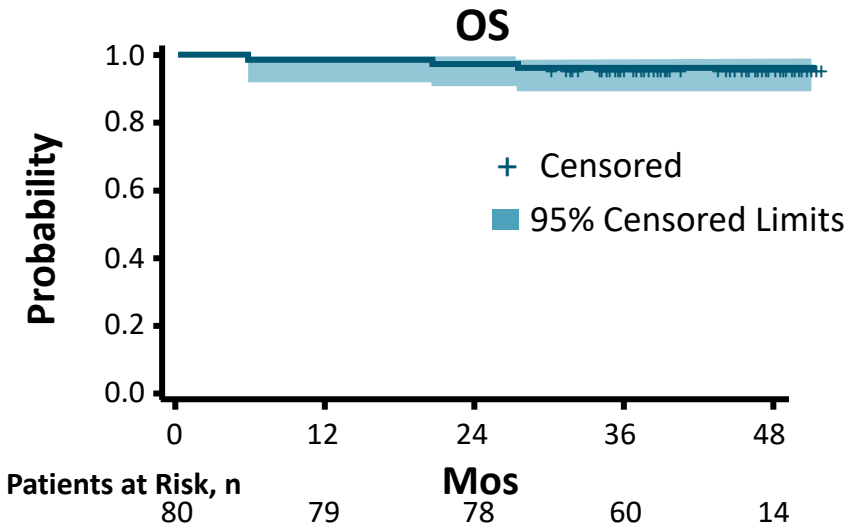
Firstline IBR+VEN BM MRD Responses Over Time

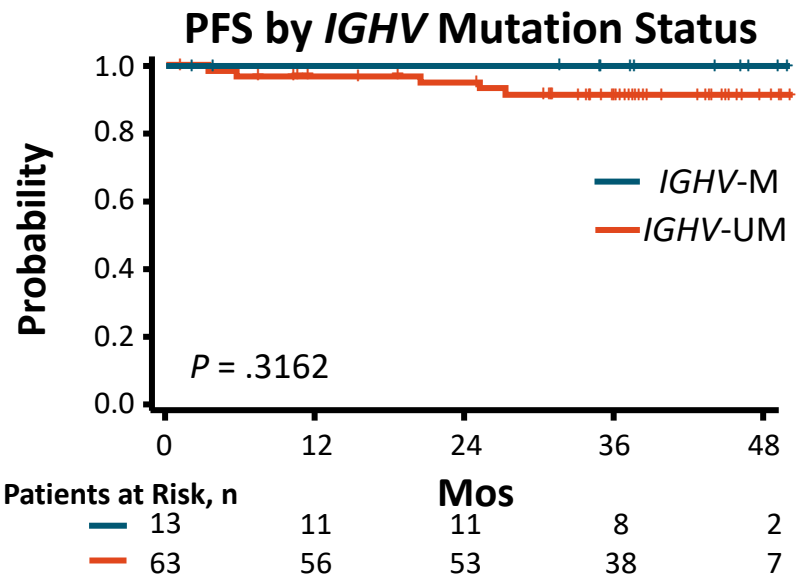


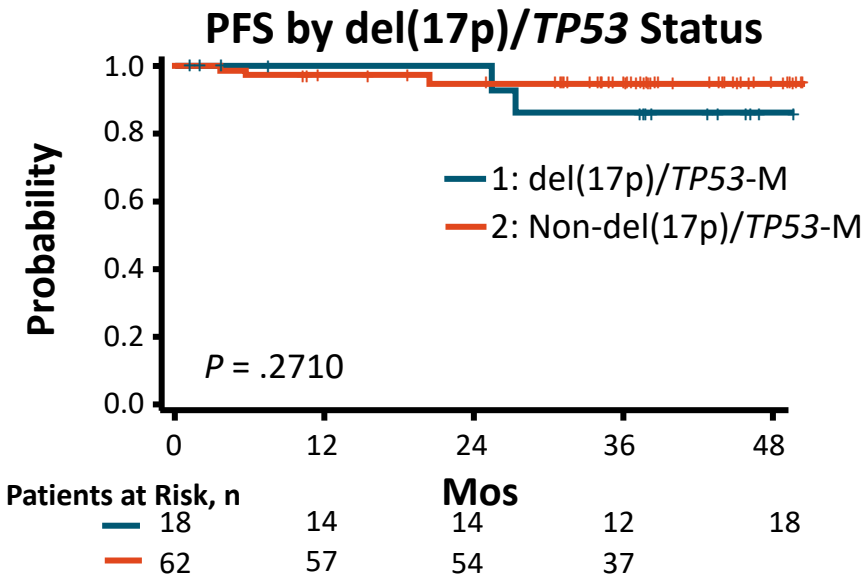
Jain et al., JAMA Oncology, 2021

Frontline Ibrutinib + Venetoclax: Survival Outcomes





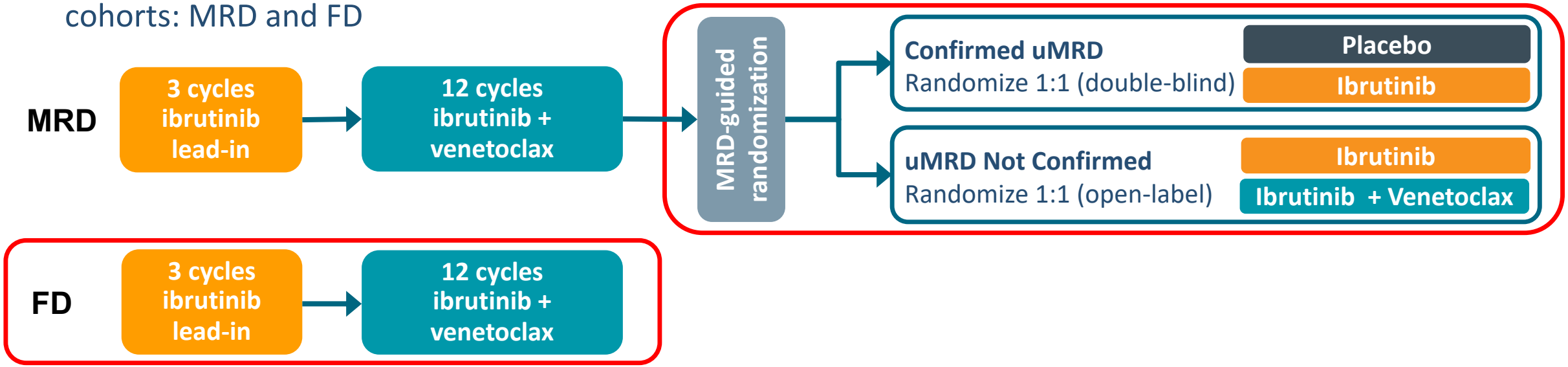




Jain et al., JAMA Oncology, 2021

Phase 2 CAPTIVATE Study

- CAPTIVATE (PCYC-1142) is an international, multicenter phase 2 study evaluating first-line treatment with 3 cycles of ibrutinib followed by 12 cycles of combined ibrutinib + venetoclax that comprises 2 cohorts: MRD and FD



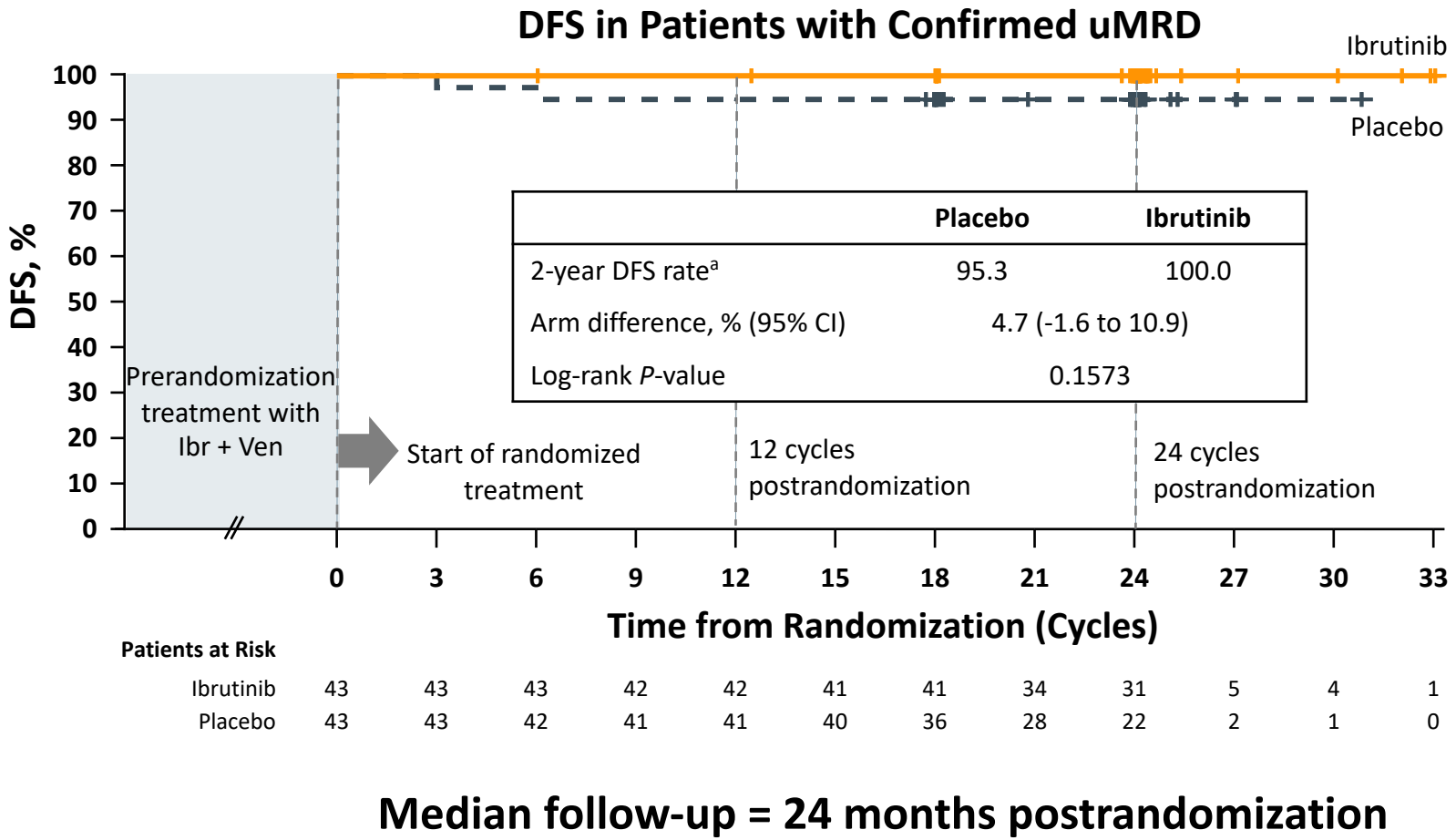
- Results from the MRD cohort demonstrated uMRD in more than two-thirds of patients treated with 12 cycles of ibrutinib + venetoclax (PB, 75%; BM, 68%), and 30-month PFS rates of ≥95% irrespective of subsequent MRD-guided randomized treatment[1]

- Primary analysis results from the FD cohort of CAPTIVATE are presented

BM, bone marrow; MRD, minimal residual disease; FD, fixed-duration; PB, peripheral blood; PFS, progression-free survival.

1. Wierda WG et al. ASH 2020, Abstract #123.

MRD Cohort: No New DFS Events Occurred Since Primary Analysis



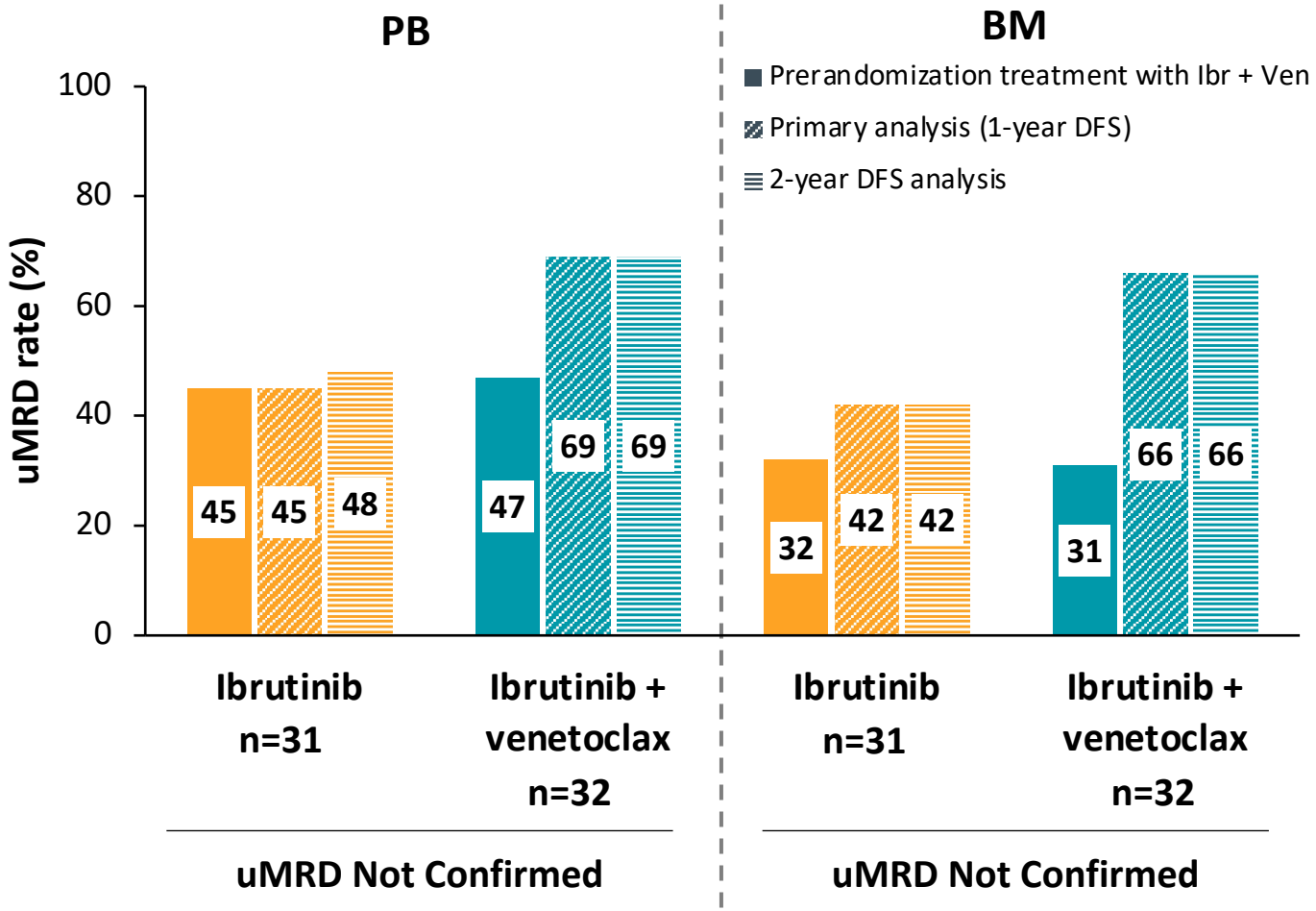
Median follow-up = 24 months postrandomization

- DFS was defined as freedom from MRD relapse (≥10^{-2} confirmed on 2 separate occasions) and without PD or death starting from randomization after 15 cycles of treatment
- In the additional year of follow-up since the 1-year DFS primary analysis, no new MRD relapses, PD, or deaths occurred in patients with Confirmed uMRD randomized to ibrutinib or placebo

DFS, disease-free survival; PD, progressive disease.
[a]24 cycles postrandomization.
Tick marks indicate patients with censored data.

Ghia, et al. CAPTIVATE-MRD; ASH 2021, Abstract #68

MRD Cohort: Best uMRD Rates Improved With Further Treatment in uMRD Not Confirmed Population



- As with CR rates, greatest uMRD rate improvements occurred during the first year of randomized treatment
  - Greater improvements with ibrutinib + venetoclax than with ibrutinib
- Improvements in uMRD rates were similar between patients achieving CR or PR

PR, partial response.

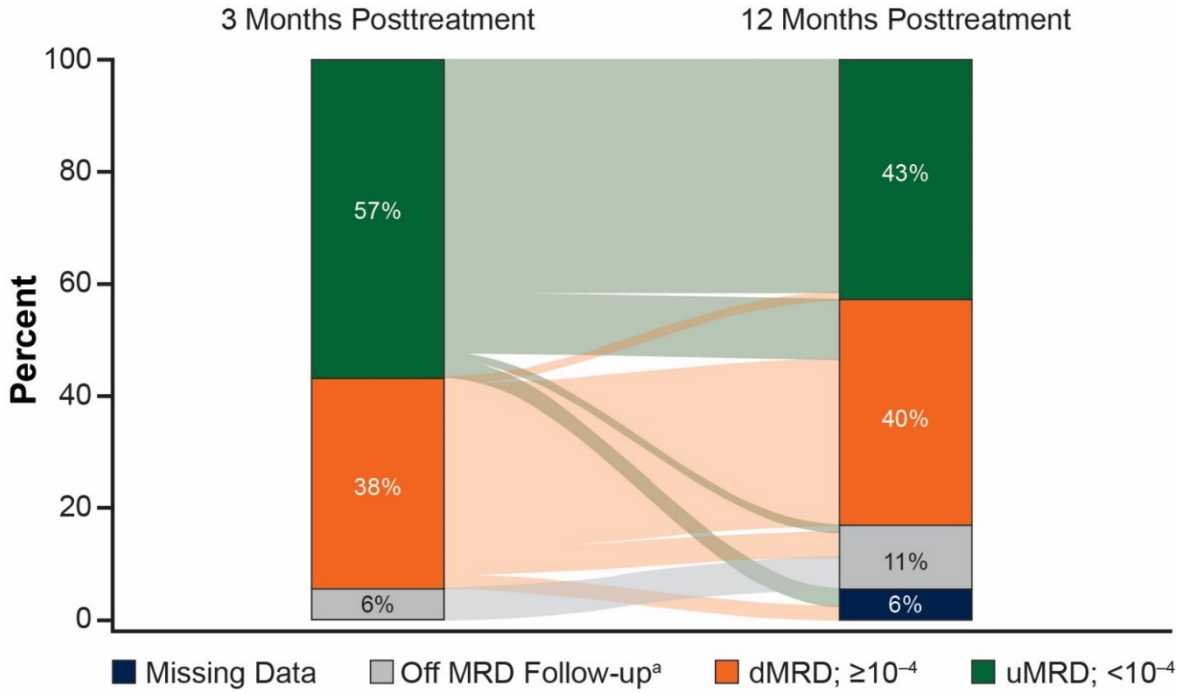
[a]Confirmed uMRD defined as having uMRD ($<10^{-4}$ by 8-color flow cytometry) serially over ≥2 assessments ≥3 months apart and in both PB and BM; the best uMRD rates in the Confirmed uMRD population were 100% in both PB and BM.

- Ghia, et al. CAPTIVATE-MRD; ASH 2021, Abstract #68

CAPTIVATE FD: With An Additional Year of Off-treatment Follow-up Since the Primary Analysis, Rates of CR and Undetectable MRD Remained High

- The CR rate in all treated patients increased from 55% (95% CI, 48–63) at primary analysis to 57% (95% CI, 50–65) with an additional year of follow-up off treatment
- 79% of patients (125/159) had a best response of uMRD in PB and/or BM

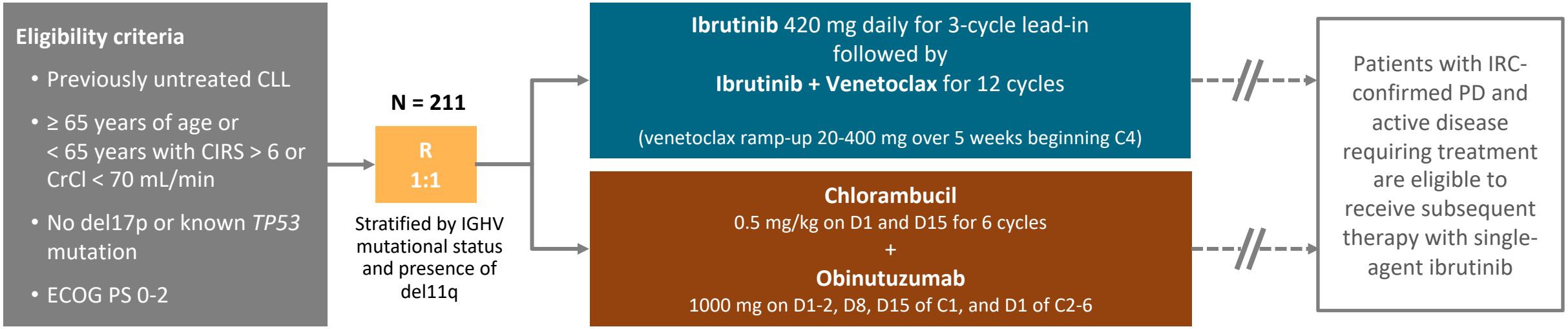
- Of patients with uMRD in PB at 3 months posttreatment, 78% (66/85) of evaluable patients maintained uMRD through 12 months posttreatment



[a]Off MRD Follow-up included patients who met any one of the criteria: progressive disease, initiation of subsequent therapy, death, or withdrawal from study.
BM, bone marrow; dMRD, detectable minimal residual disease; MRD, minimal residual disease; PB, peripheral blood; uMRD, undetectable minimal residual disease.

ASCO 2022, PCYC-1142 FD CAPTIVATE; Wierda et al.

Phase 3 GLOW Study Design (NCT03462719)

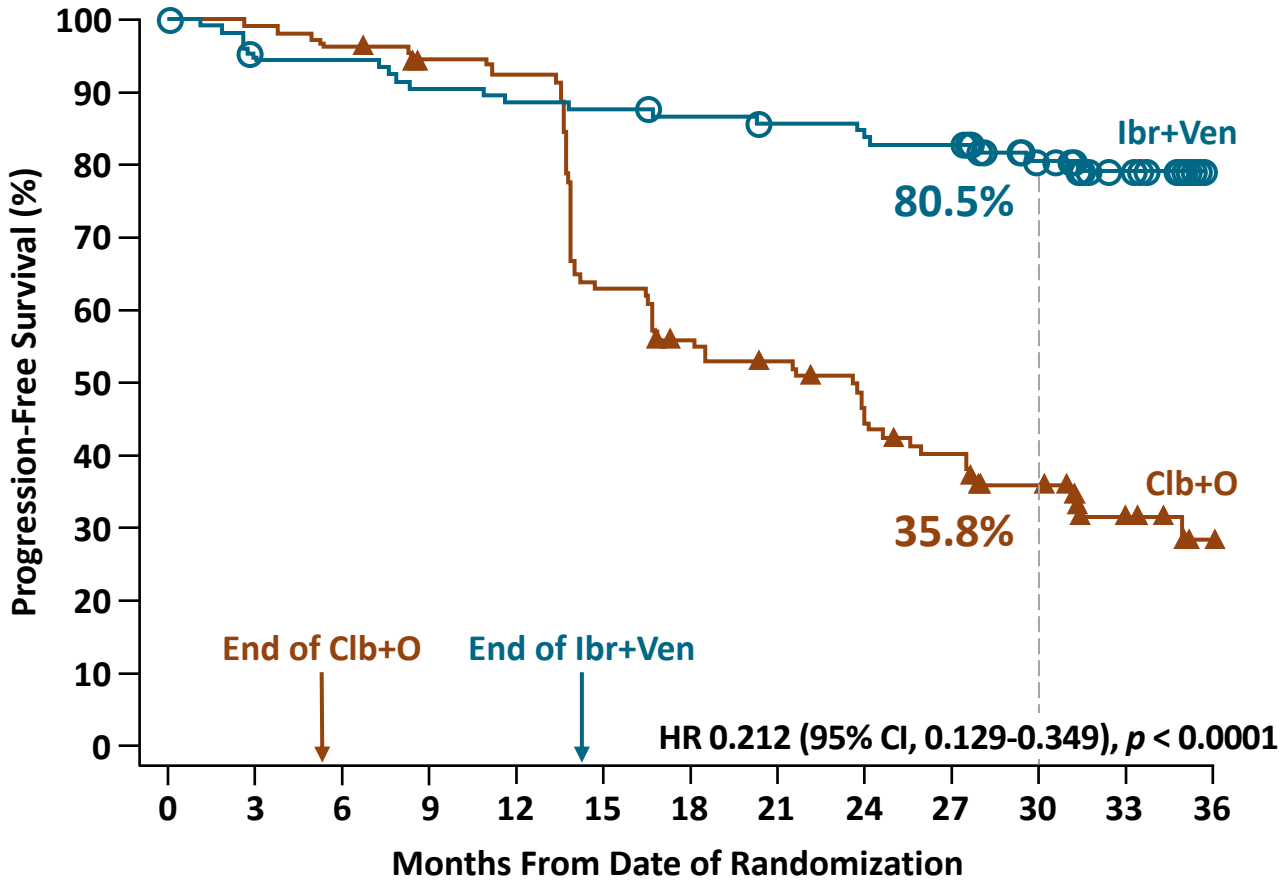


- **Study primary endpoint:** PFS as assessed by IRC
- **Current MRD analysis:**
  - MRD evaluated via NGS and reported with cutoffs of < 10^{-4} and < 10^{-5} (not all samples had sufficient cell yield to be analyzed at < 10^{-6}). NGS analysis not yet available beyond EOT+12 time point
  - PB/BM concordance 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.

Munir T, et al. ASH 2021, Abstract #70

GLOW: Superior Progression-Free Survival With Ibr+Ven vs Clb+O Was Maintained With Median 34.1 Months of Follow-up



Patients at risk

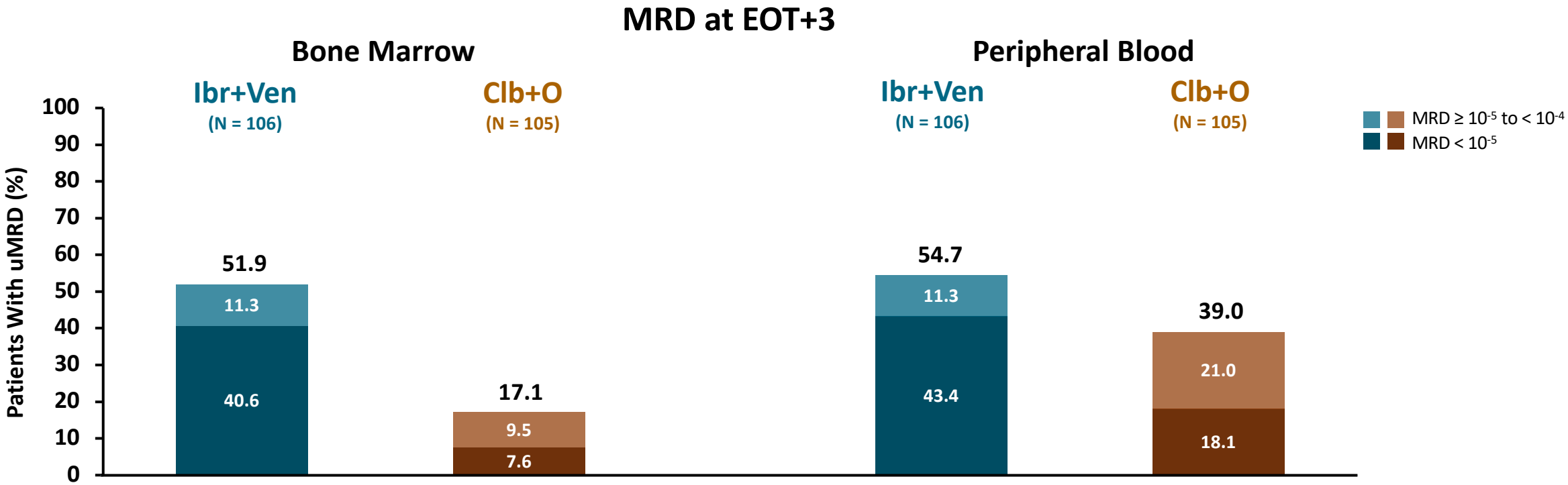
Ibr+Ven	106	98	98	94	92	91	89	87	86	84	71	42	1
Clb+O	105	104	101	96	94	64	55	51	43	37	30	13	3

- 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

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

Munir T, et al. ASH 2021, Abstract #70

GLOW: uMRD Rate < 10^{-5} Was Higher With Ibr+Ven vs Clb+O in Both Compartments



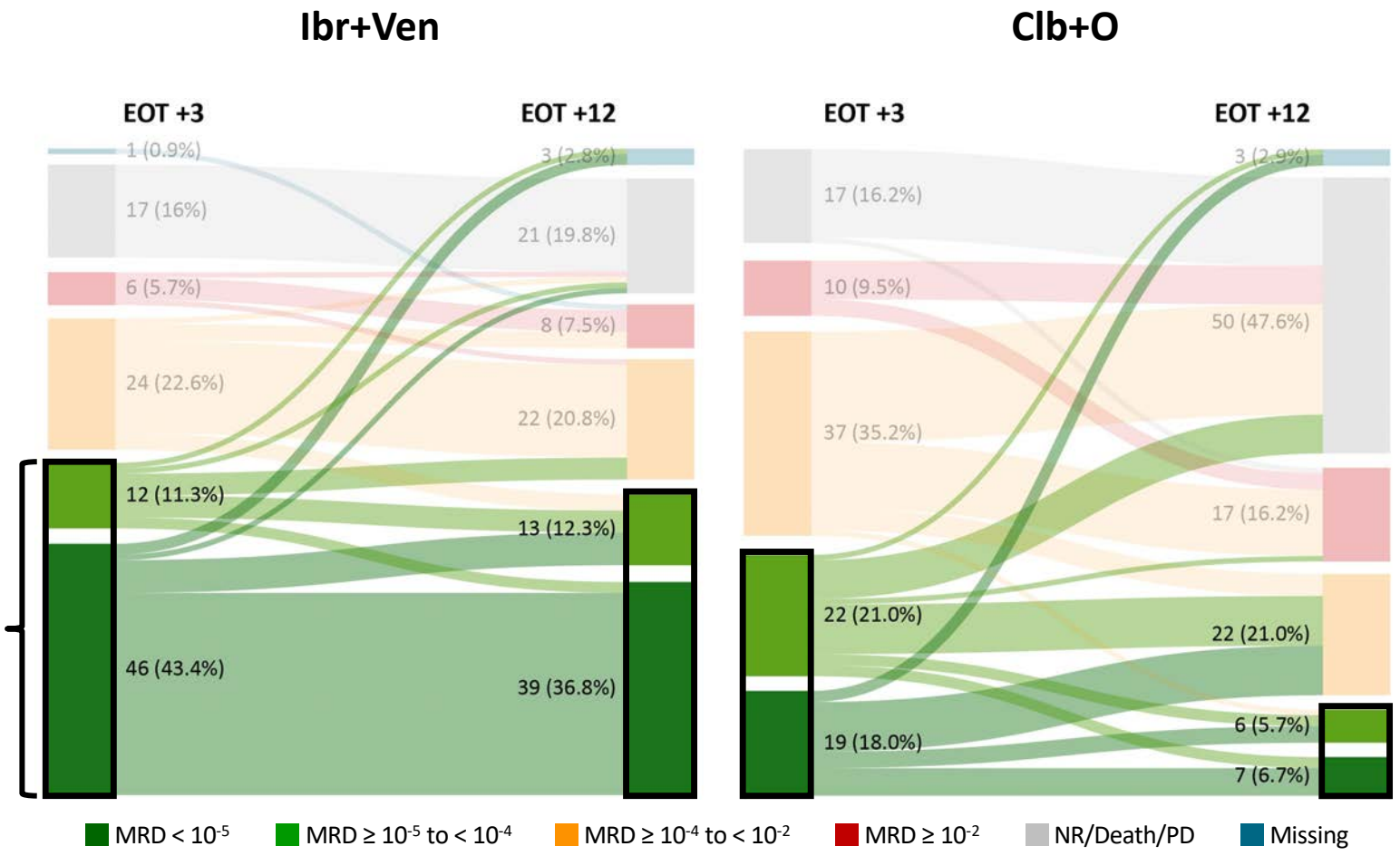
- In the Ibr+Ven arm, but not the Clb+O arm, most patients with uMRD < 10^{-4} had deep responses of uMRD < 10^{-5}
- uMRD concordance at < 10^{-5} in PB/BM: **90.9%** for Ibr+Ven vs **36.8%** for Clb+O

MRD results by next-generation sequencing at EOT+3. Note: Numbers may not add up due to rounding.
BM, bone marrow; EOT, end of treatment; PB, peripheral blood.

Munir T, et al. ASH 2021, Abstract #70

GLOW: uMRD in PB Was Better Sustained With Ibr+Ven From EOT+3 to EOT+12

- **84.5%** (49/58) of patients had sustained uMRD < 10^{-4} and **80.4%** (37/46) had sustained uMRD < 10^{-5} with Ibr+Ven[a]
  - 29.3% (12/41) and 26.3% (5/19) with Clb+O
- uMRD < 10^{-4} rate decreased 6% with Ibr+Ven vs 27% with Clb+O



[a]Sustained uMRD rate is calculated on a per-patient basis, not using intent-to-treat MRD rates at EOT+3 and EOT+12.
EOT, end of treatment; NR, nonresponder; PB, peripheral blood; PD, progressive disease.

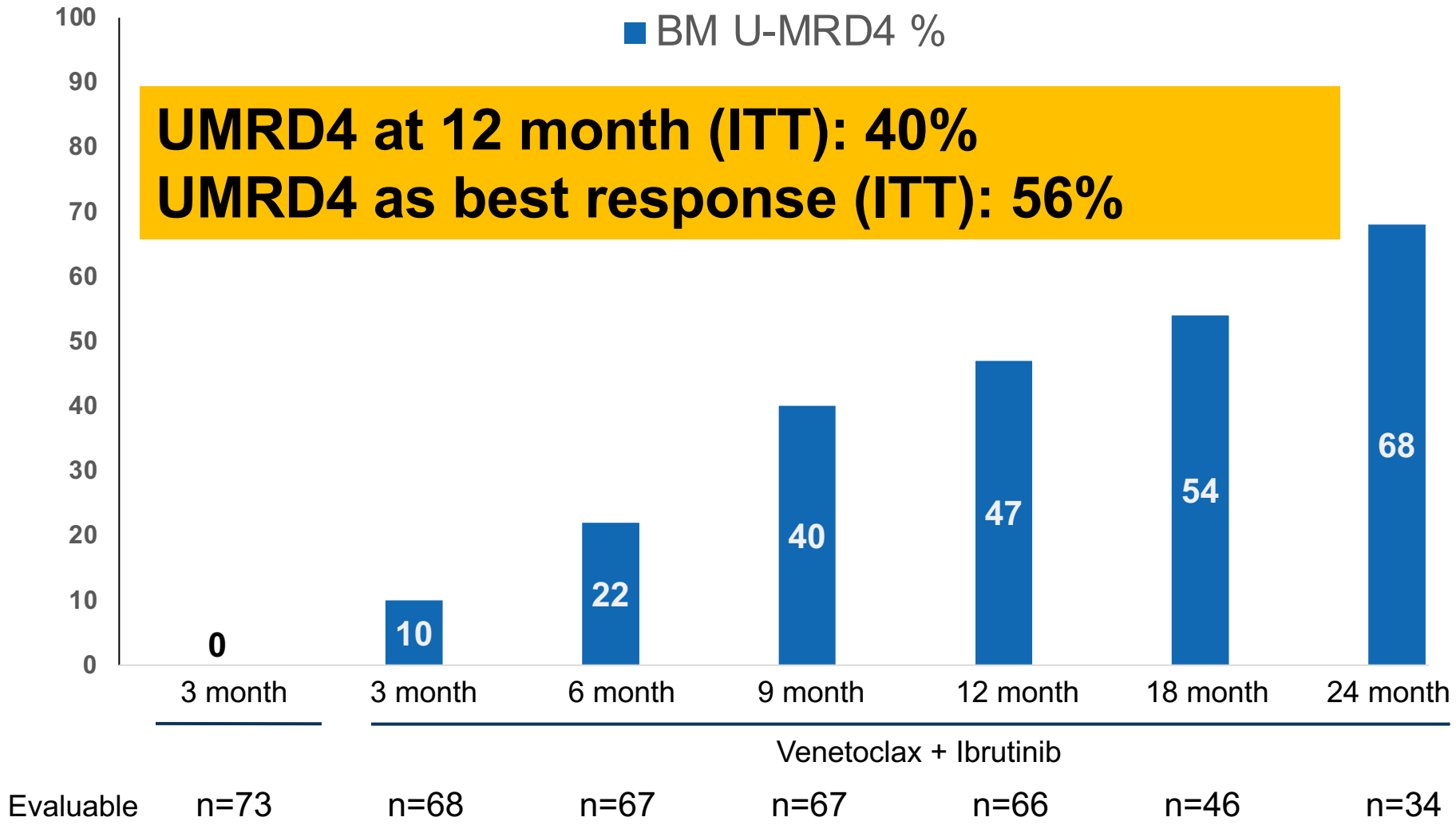
Munir T, et al. ASH 2021, Abstract #70

Select Ongoing First-line Phase III Clinical Trials

Trial	Subgroup	N	Status*	MRD	Treatment Arms			
GAIA/CLL13 (NCT02950051)	Fit pts	926	Enrolled	Co-Primary	IbrVenOb	VenOb	VenR	FCR/BR
EA9161 (NCT03701282)	Fit, 18-69 yo	720	Enrolled	Secondary	IbrVenOb	IbrOb		
A041702 (NCT03737981)	≥70 yo	454	Enrolled	Secondary	IbrVenOb	IbrOb		
ACE-CL-311 (NCT03836261)	All pts	780	Enrolling	Secondary	AcaVenOb	AcaVen		FCR/BR
CRISTALLO (NCT04285567)	Fit pts [no del(17p)]	165	Enrolling	Primary	VenOb			FCR/BR
CLL17 (NCT04608318)	All pts	897	Enrolling	Secondary	IbrVen	VenOb	Ibr	
GCLLSG (NCT05197192)	High-risk	650	Enrolling	Secondary	AcaVenOb	VenOb		
MAJIC (NCT05057494)	All	600	Enrolling	Secondary	AcaVen	VenOb		

*Status as of September 2022

MDACC: IBR + VEN in R/R CLL
BM MRD4 Responses at Serial Time-Points



1 pt was U-MRD at baseline and is excluded

Jain, N. et al., ASH 2019, Abstract #359

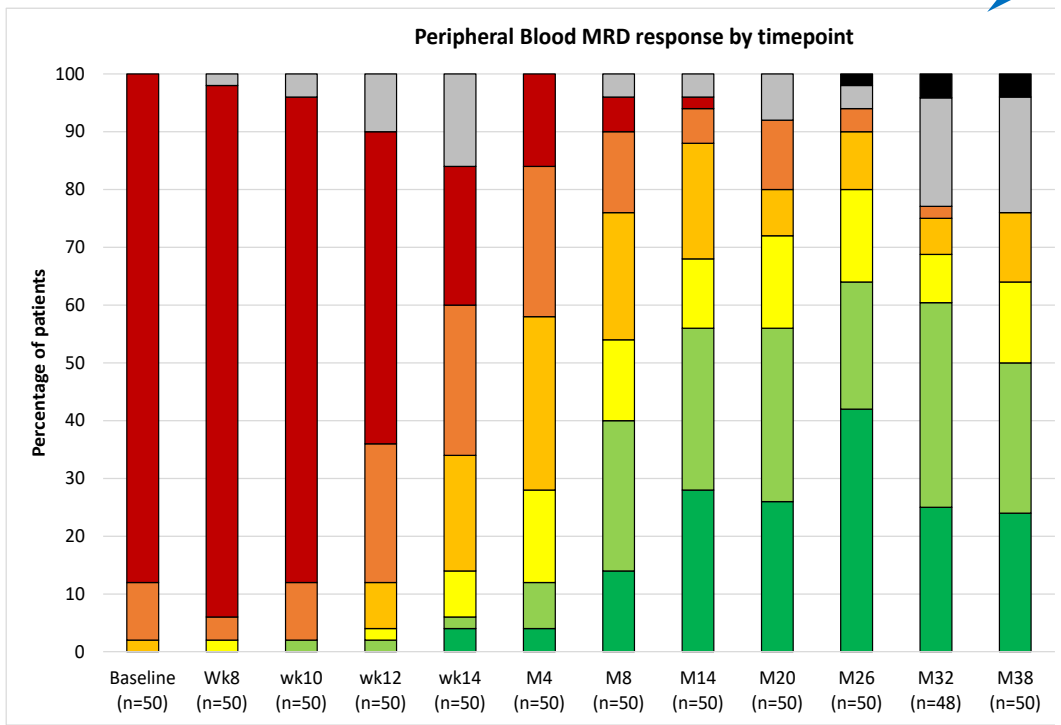
CLARITY: MRD level by time-point (up to Month 38)

At month 38, MRD4 (<0.01%) negative rates were 50% and 40% in peripheral blood and bone marrow respectively in all evaluable patients*

Blood

Venetoclax

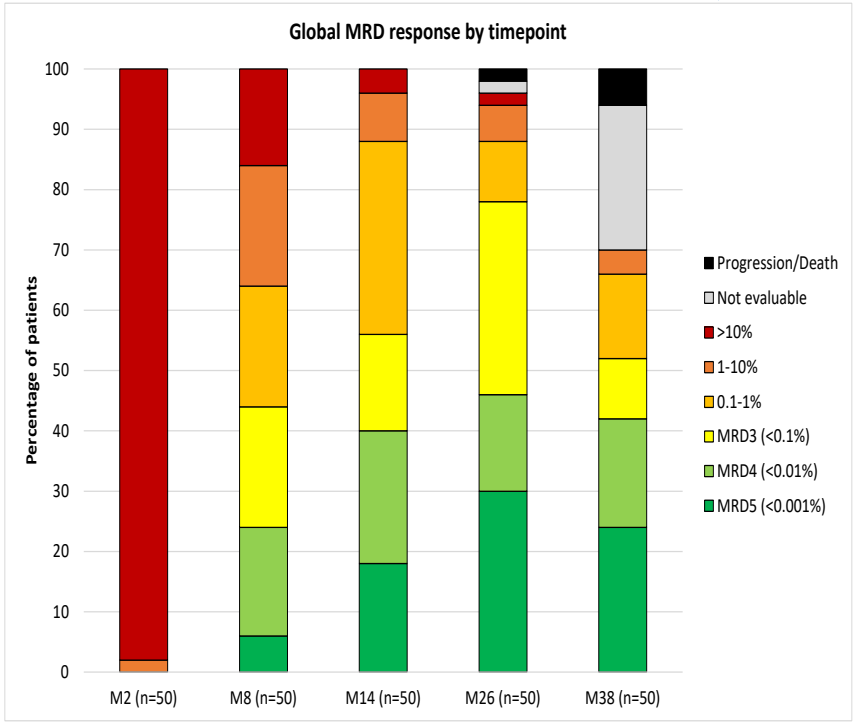
Ibrutinib



Marrow

Venetoclax

Ibrutinib



*Data missing at month 38 due to Covid Pandemic

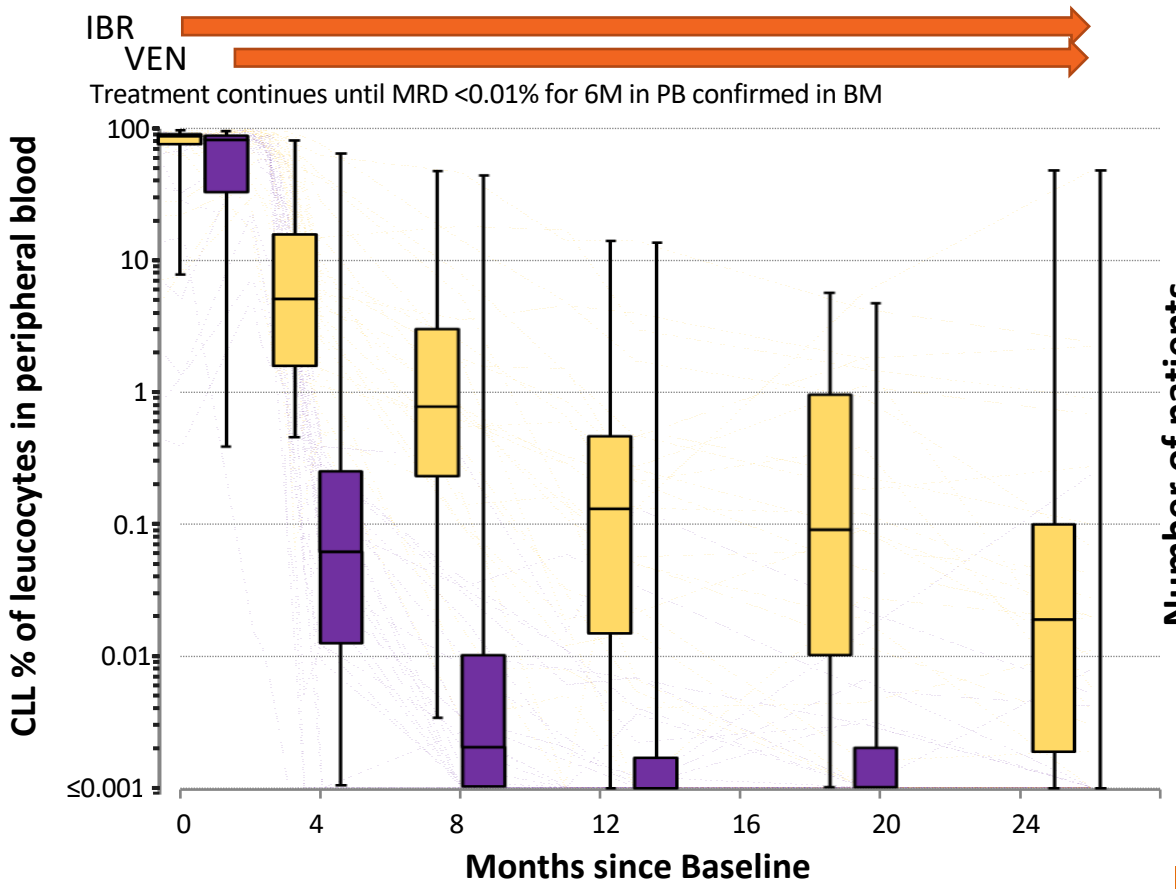
Date of data lock: 6th Nov, 2020

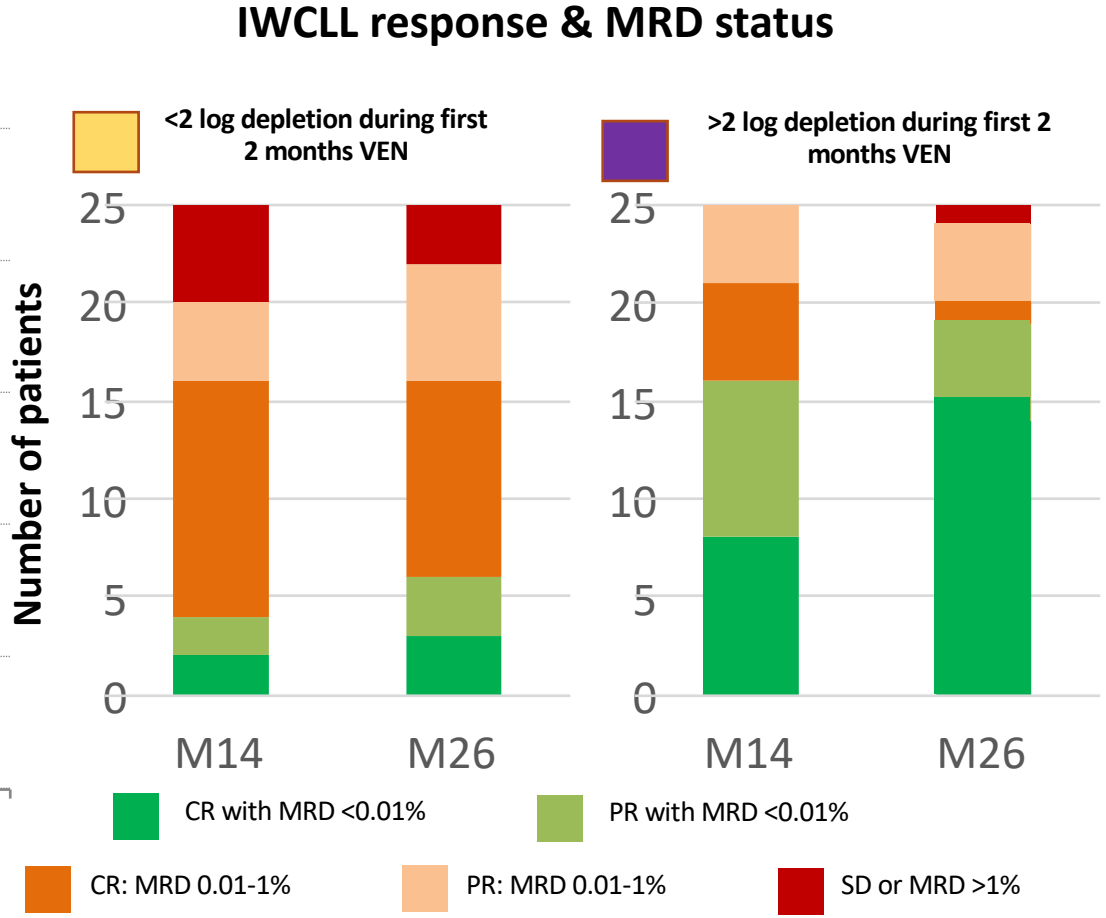
M14 M26 M38

M14 M26 M38

Munir et al. ASH 2020 Abstract #124

CLARITY: Response Correlated with Initial Depletion Rate





Date of data lock:06-Nov-2020

Munir et al. ASH 2020 Abstract #124

Conclusions

- Combined targeted therapy (ibrutinib + venetoclax) results in deep remissions (uMRD) with finite-duration treatment and is well-tolerated and safe
- Ongoing phase III clinical trials will help to clarify optimal first-line combined targeted therapy and potentially ideal patient for regimen
- MRD is critical to optimizing finite-duration targeted therapy
  - Important early endpoint given deep and durable remissions
- For clarification:
  - Ideal patient for combined targeted treatment
  - Optimal combination
  - Remission duration, long-term outcomes (exposure ≠ resistance = progression on treatment)

Agenda: CLL Update
A Meeting within a Meeting

MODULE 1: Front-Line CLL – Standard-Risk Patients — Dr Mato

MODULE 2: Chronic Lymphocytic Leukemia in 2022: Front-Line Therapy in Patients with High-Risk Disease — Dr Brander

MODULE 3: Fixed-Duration Targeted Therapy for CLL — Dr Wierda

MODULE 4: Novel Investigational Agents and Strategies in CLL — Dr Davids

MODULE 5: CLL 2030?

RTP RESEARCH TO PRACTICE

Cases and Questions:
Management of CLL with BTK Resistance Mutations; Role of Transplant

Adam Kittai, MD

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RESEARCH
TO PRACTICE

Cases and Questions: New Agents and Strategies

Adam Kittai, MD

RTP
RESEARCH
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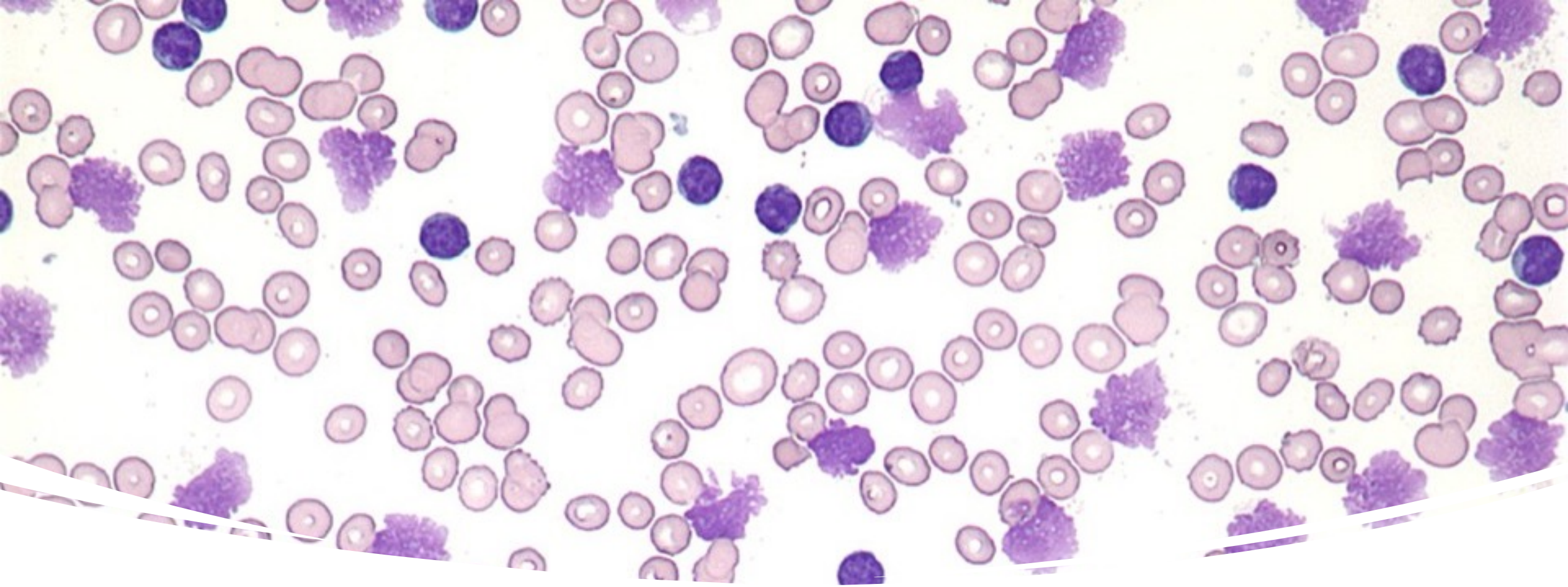


Novel investigational agents and strategies in CLL

Matthew S. Davids, MD, MMSc

Dana-Farber Cancer Institute | Harvard Medical School

2022 UNMC Pan Pacific CLL | Research To Practice

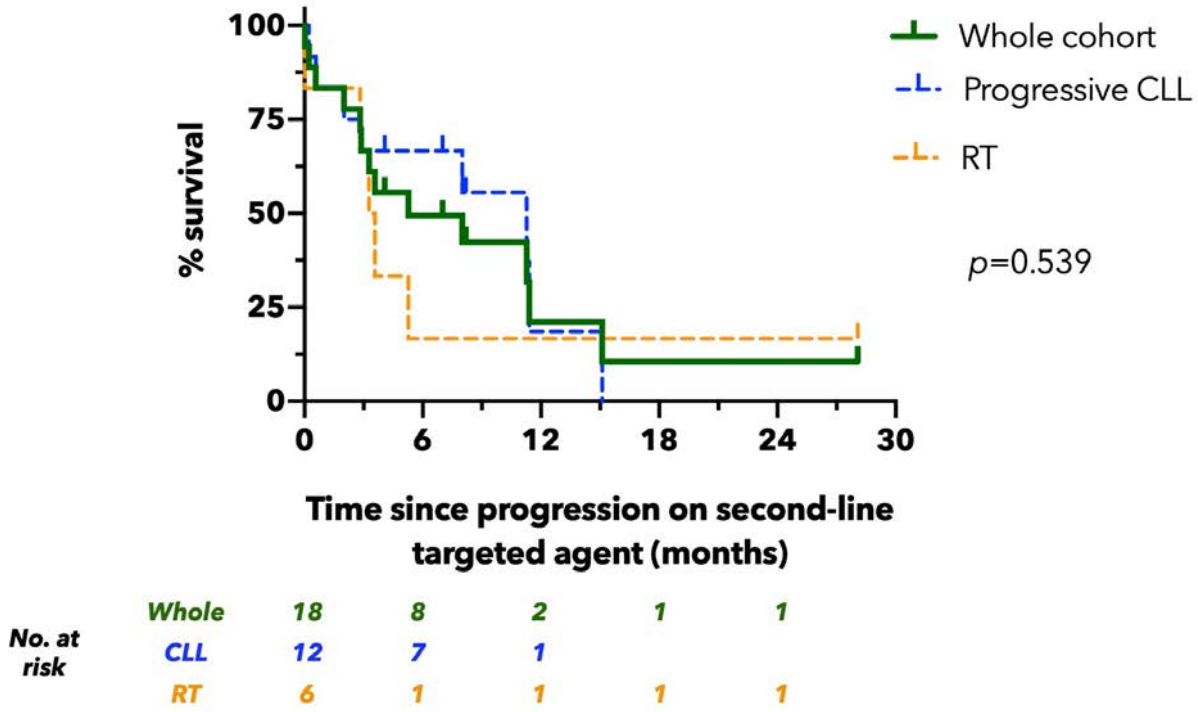
October 12, 2022

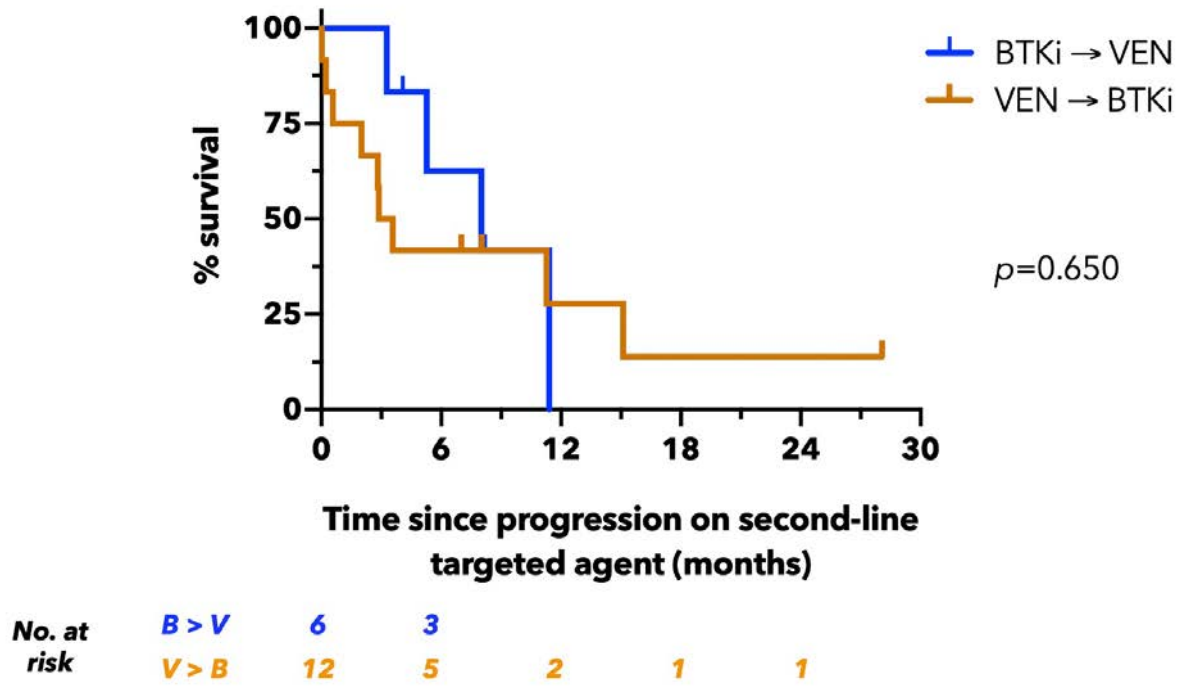
Dana-Farber Cancer Institute

Harvard Medical School

Outcomes for "double class resistant" CLL are poor

2011 to 2020: 165 pts treated with Ven or BTKi → 42 double exposed → 18 double refractory





- Whole cohort median OS: 5.3 months
- No difference in OS between progressive CLL (11.3 months) and RT (3.4 months)

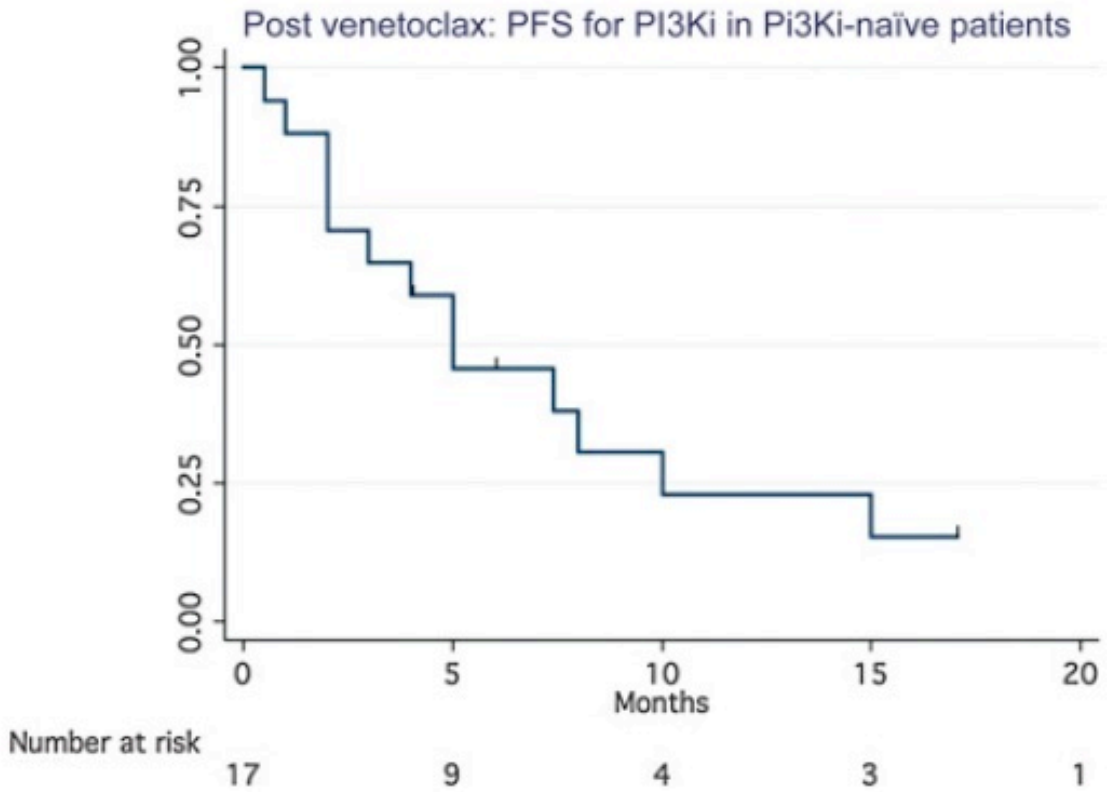
- No difference in OS between BTKi → VEN (8 months) and VEN → BTKi (3.2 months)

Lin VS iwCLL 2021; updated from Blood Advances 5:4054-8, 2021

Real-world data suggest PI3Ki following Ven & BTKi have activity but limited durability

17 pts, median 4 prior tx, included BTKi intolerant & resistant

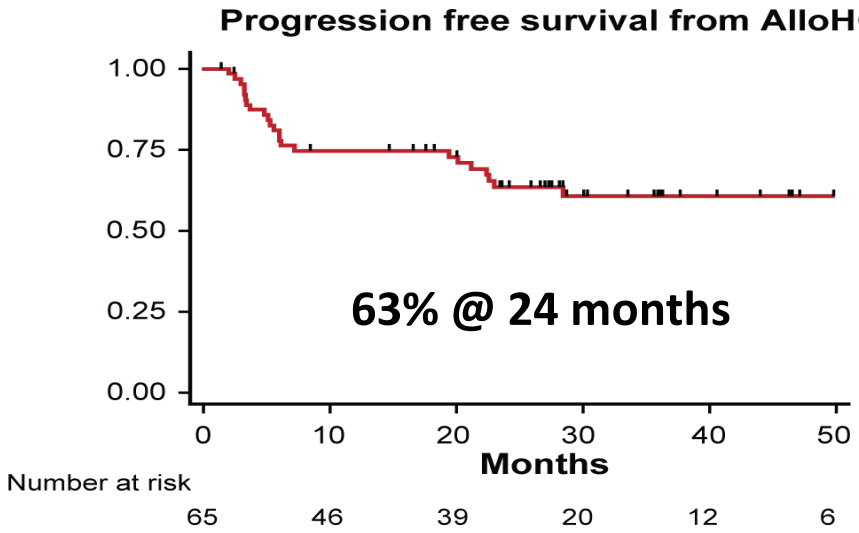
- **ORR 47%**
- **Median PFS 5 months**

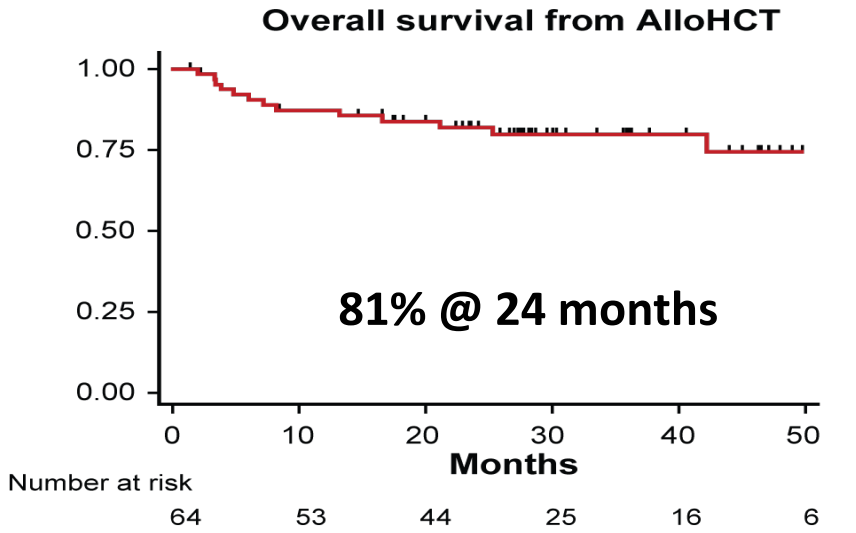


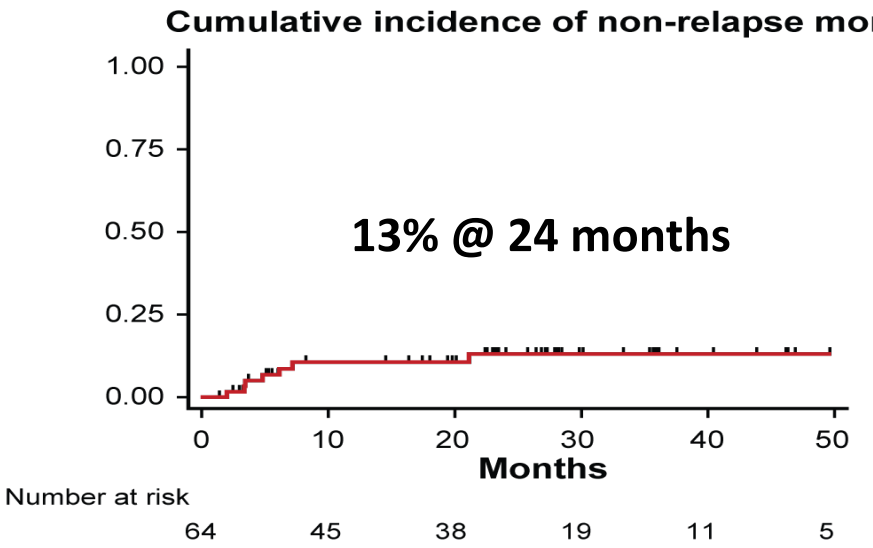
Mato AR, *et al*. *Clin Cancer Res* 26:3589-96, 2020

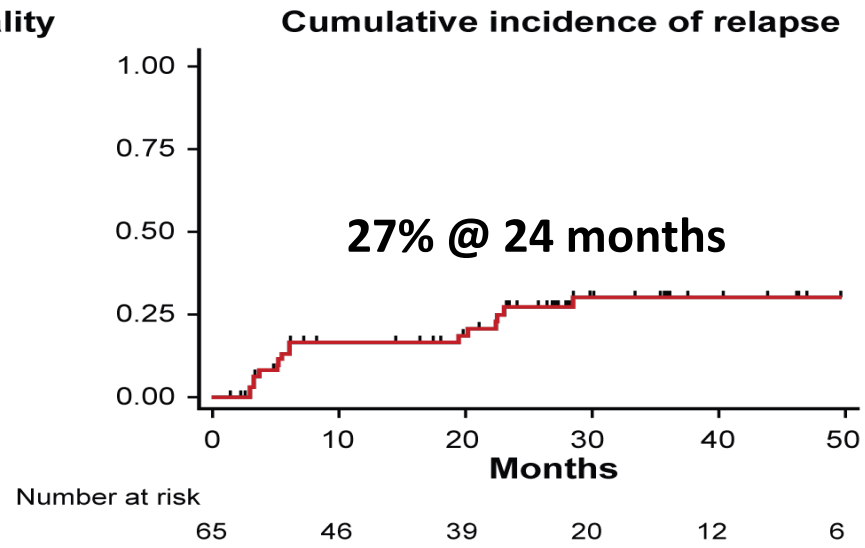
Allogeneic transplant remains effective in double class exposed CLL

Multicenter study (n=65); 82% BTKi, 40% Ven, both 17%. Likely few pts truly double-refractory





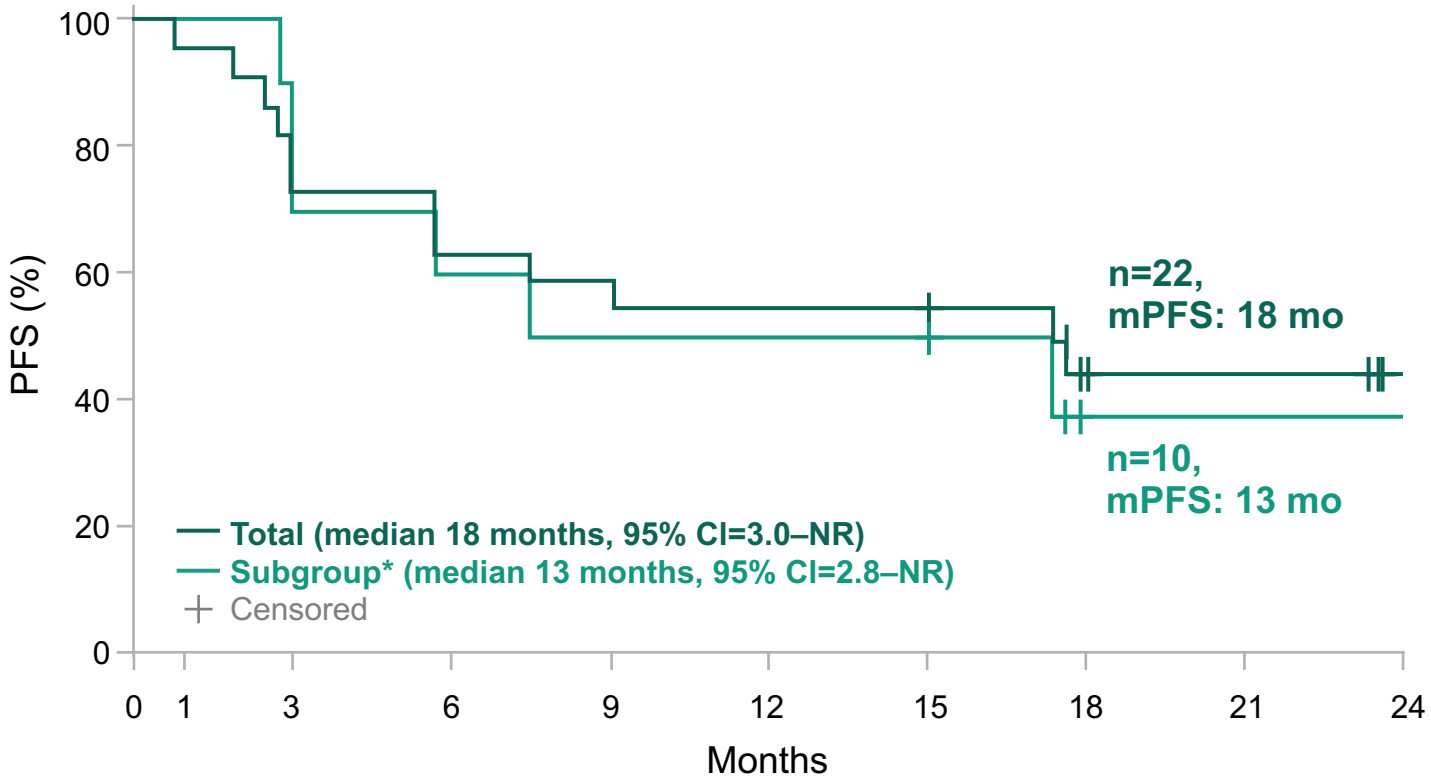




Roeker LE, *et al.* Blood Advances 4:3977-89, 2020.

Is anti-CD19 CAR T-cell therapy effective for patients with double-refractory CLL?

TRANSCEND-CLL-004: PFS with liso-cel ± ibrutinib (N=23)
(median follow-up: 24 months)



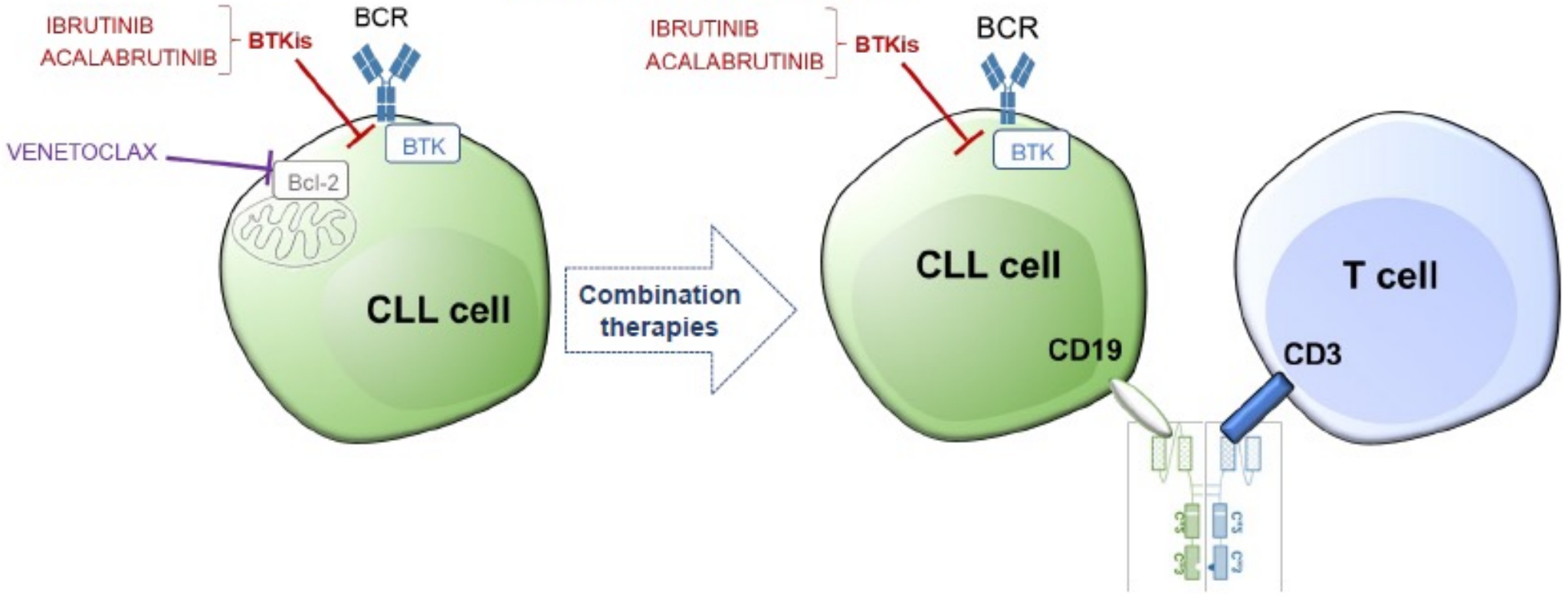
Subgroup included patients with:

- **BTKi progression and**
- **venetoclax failure because of**
  - progression
  - intolerance
  - failure to respond after ≥3 months of therapy

Siddiqi T, *et al.* Blood 2022; 139:1794–1806.

Bi-specific antibodies may eventually play a role in CLL treatment

Successful treatment modalities for CLL but variable patient responses and drug resistance
-> Call for adjunct therapies



Anti-CD19/CD3

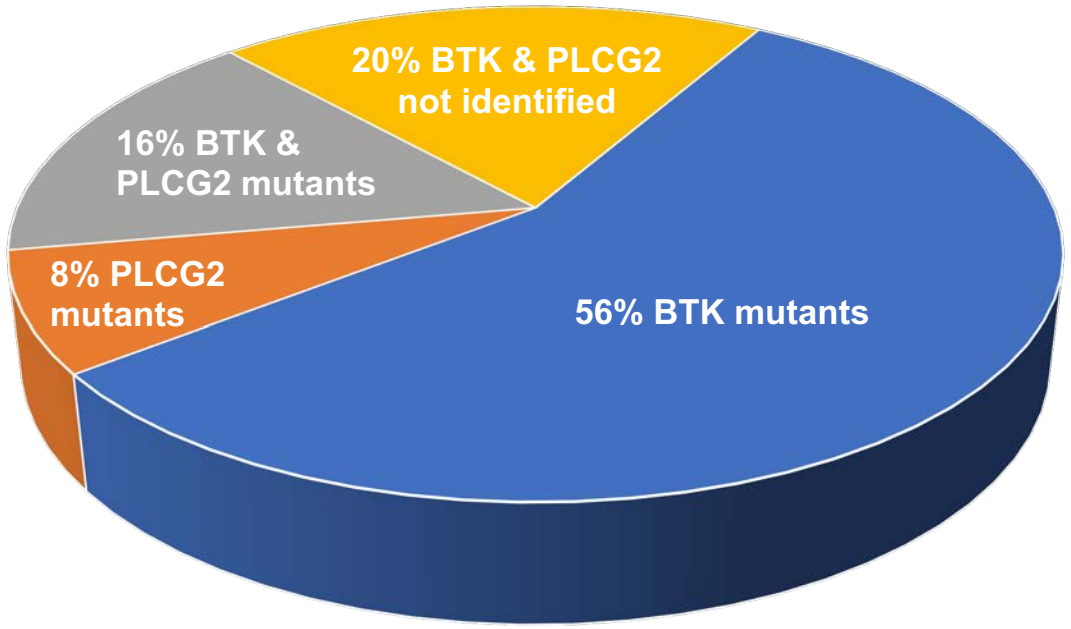
Combining BTKis with a CD19/CD3 bispecific antibody

- Enhanced T-cytotoxicity activity against CLL cells

Mhibik et al., Blood 2021

BTK mutations are a common cause of resistance

Acquired Resistance to Ibrutinib in Patients With Progressive CLL[1]



- BTK C481 mutations are the principal reason for progressive CLL after treatment with covalent BTK inhibitors[2]
- BTK C481 mutations impair target inhibition by covalent BTK inhibitors[2]

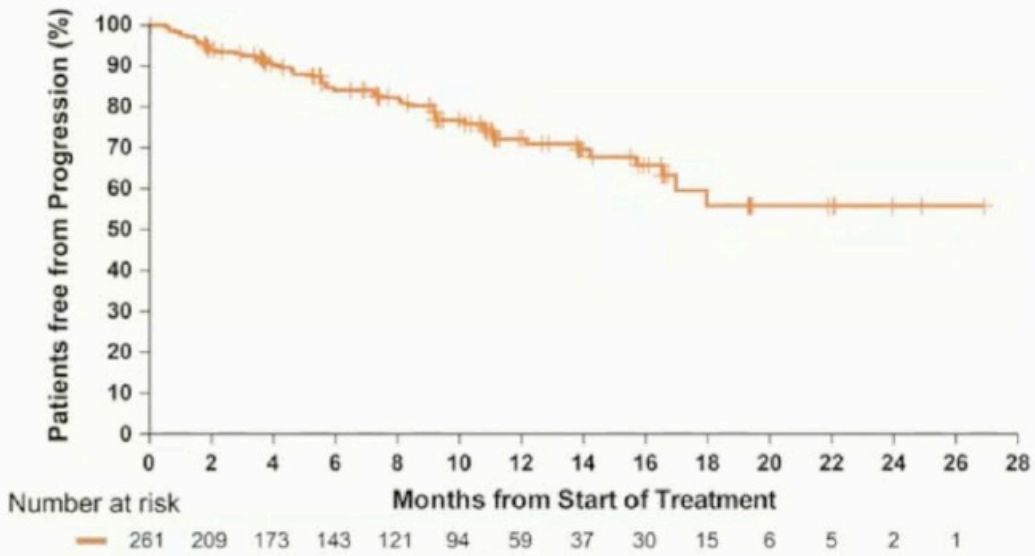
BTK, Bruton tyrosine kinase; CLL, chronic lymphocytic leukemia; PLCG2, phospholipase C gamma 2.

1. Lampson BL. *Expert Rev Hematol*. 2018;11(3):185-194. 2. Mato AR. *Lancet*. 2021;397(10277):892-901.

Pirtobrutinib is highly active in double class exposed CLL

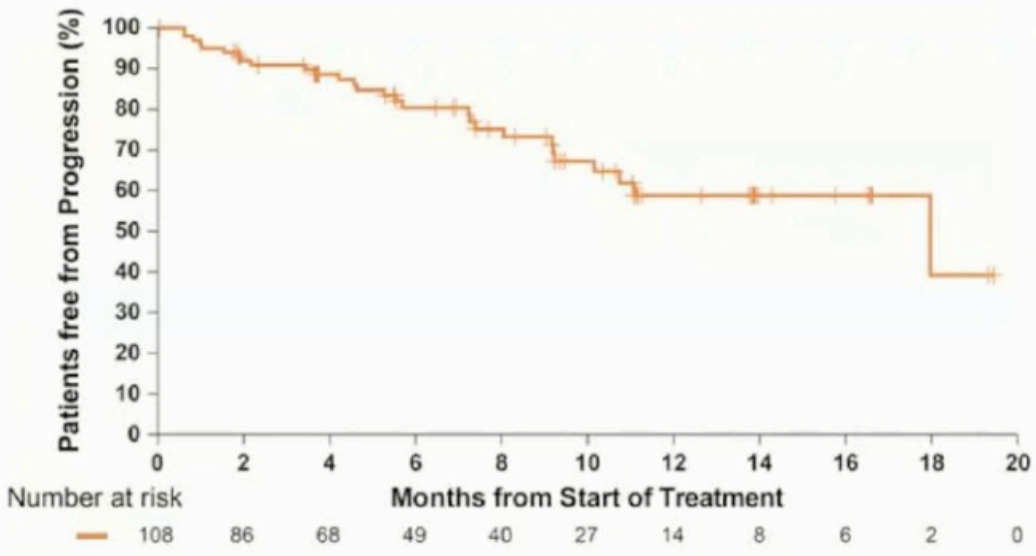
Progression-Free Survival in BTK Pre-Treated CLL/SLL Patients

PFS in at least BTK pre-treated patients
Median prior lines = 3



Median PFS: Not Estimable (95% CI: 17.0 months – Not Estimable)

PFS in at least BTK and BCL2 pre-treated patients
Median prior lines = 5



Median PFS: 18 months (95% CI: 10.7 months – Not Estimable)

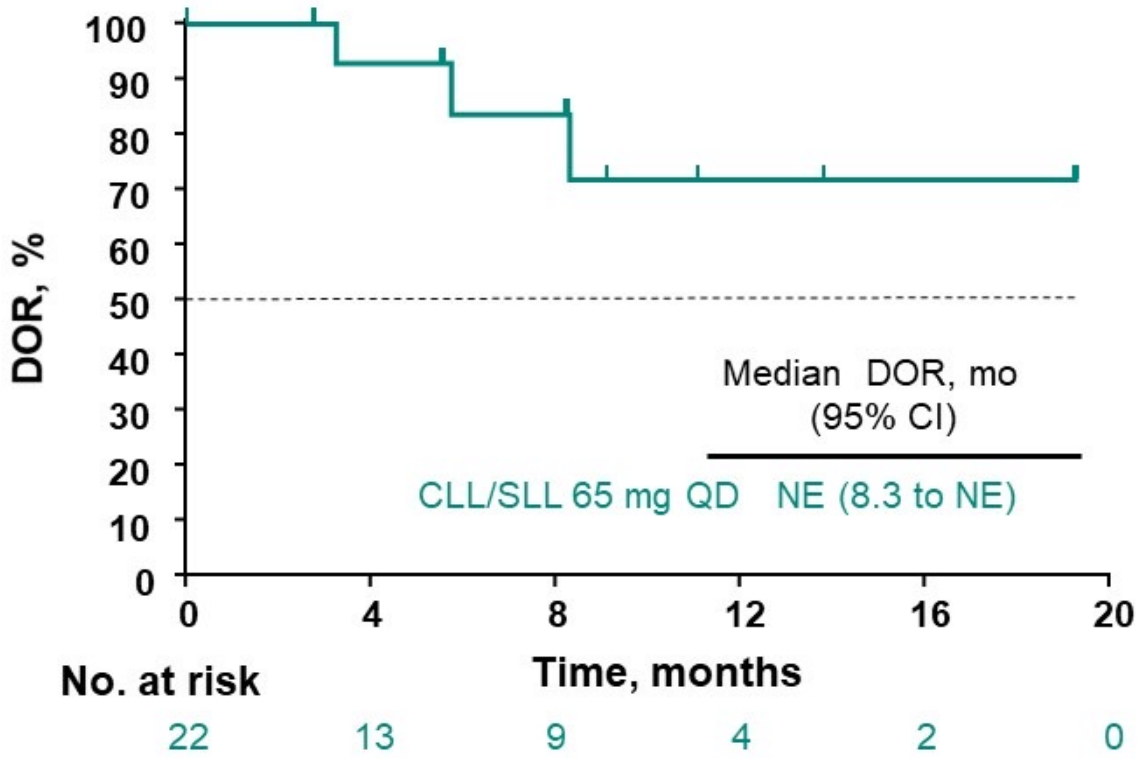
Mato AR, *et al*. EHA 2022 (Abstr S147)

Nemtabrutinib is also active in R/R CLL, though f/u is short

Woyach MK-1026 ASH 2021

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

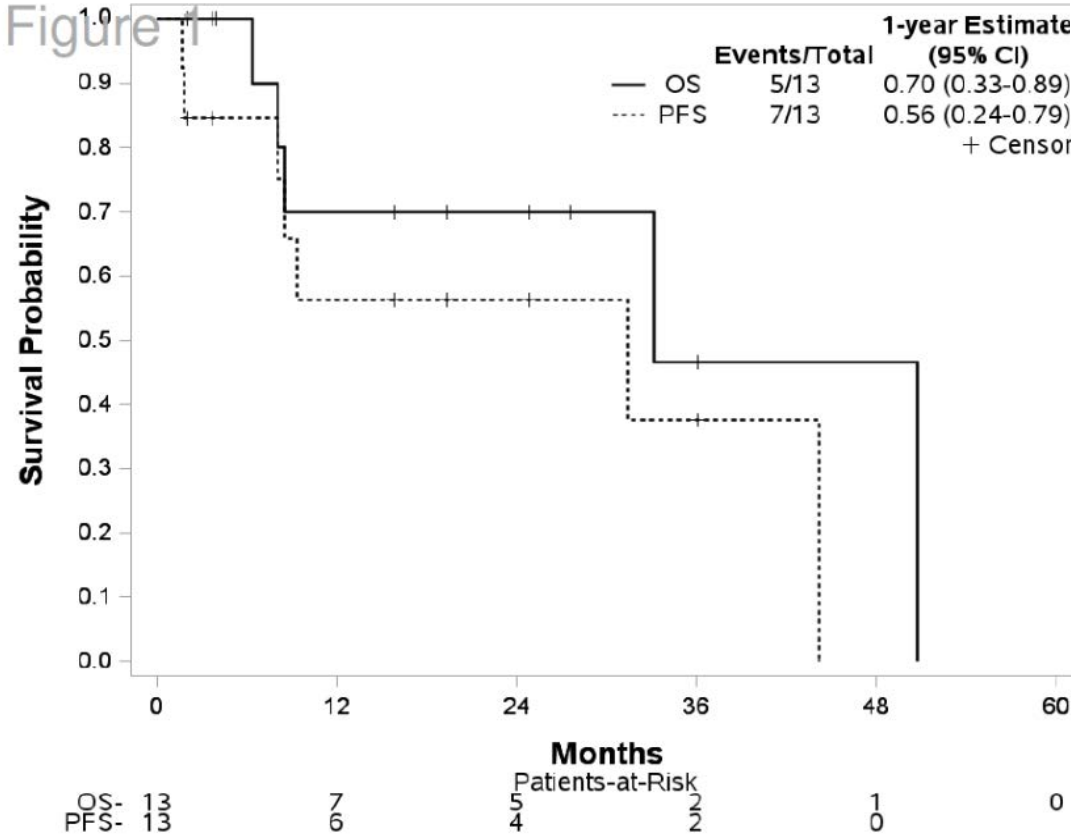
n (%) [95% CI]	CLL/SLL 65 mg QD N = 38[a]
ORR	**22 (57.9%)**
	[40.8-73.6]
CR	1 (2.6%) [0.0-13.8]
PR	12 (31.6%) [17.5-48.6]
PR-L	9 (23.7%) [11.4-40.2]
SD	15 (39.5%) [24.0-5.6]



[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.

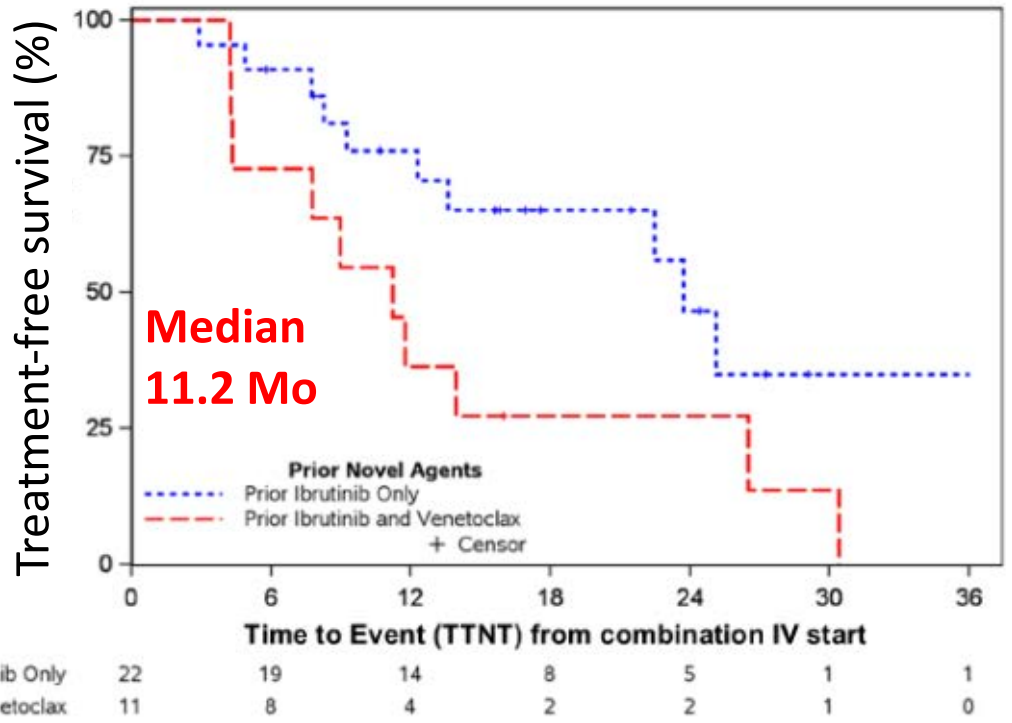
Combination Ven/BTKi has activity after sequential single agent exposure / resistance

Ohio State; n = 13, 69% ORR. 4/6 double refr



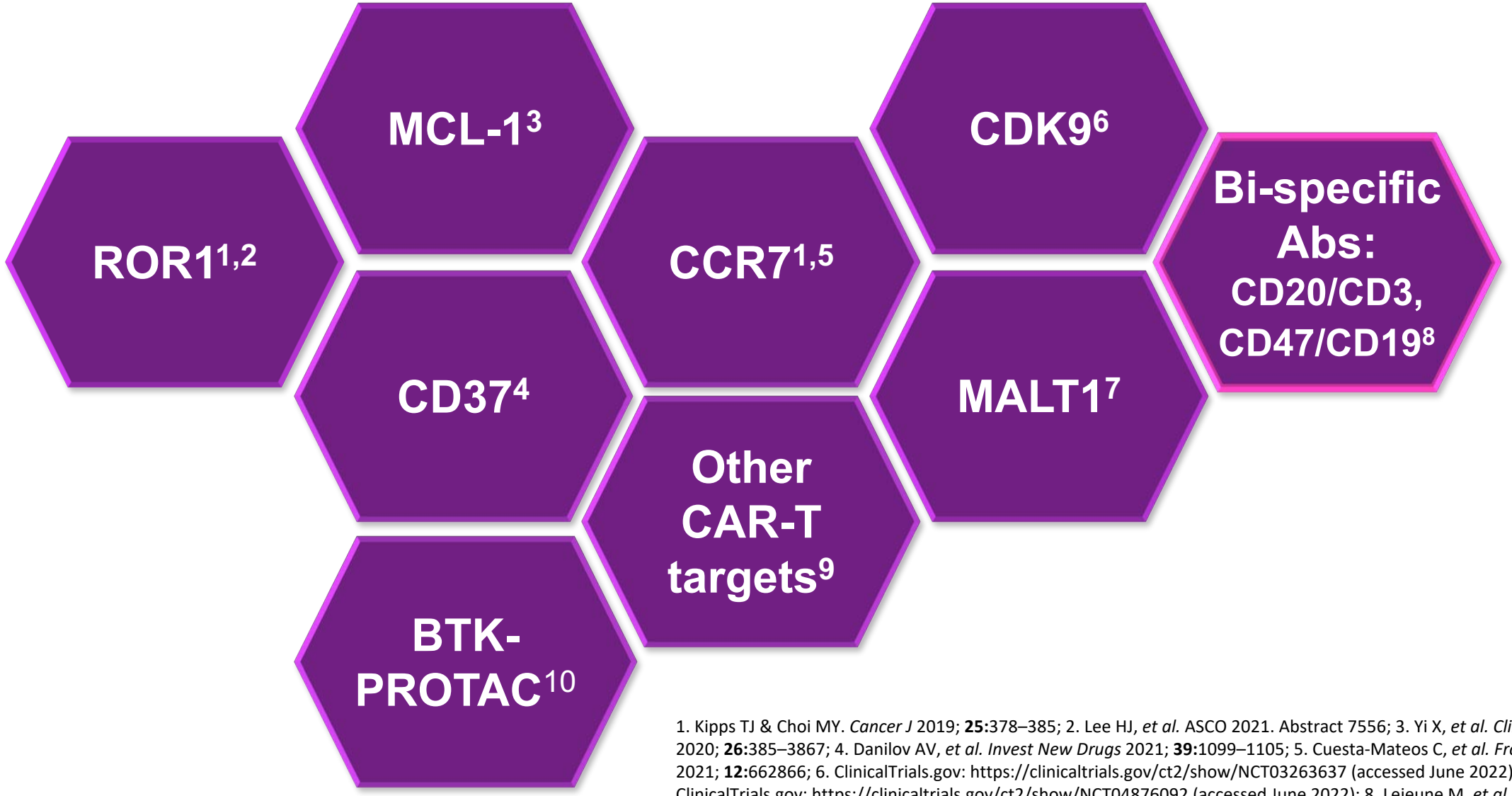
Hyak JM, *et al*. *Blood Adv* online Jul 2022

Mayo Clinic; n = 11, 100% ORR



Hampel PJ *et al*. *Br J Haematol* online Jul 2022

Future directions: Novel pathways/targets under investigation



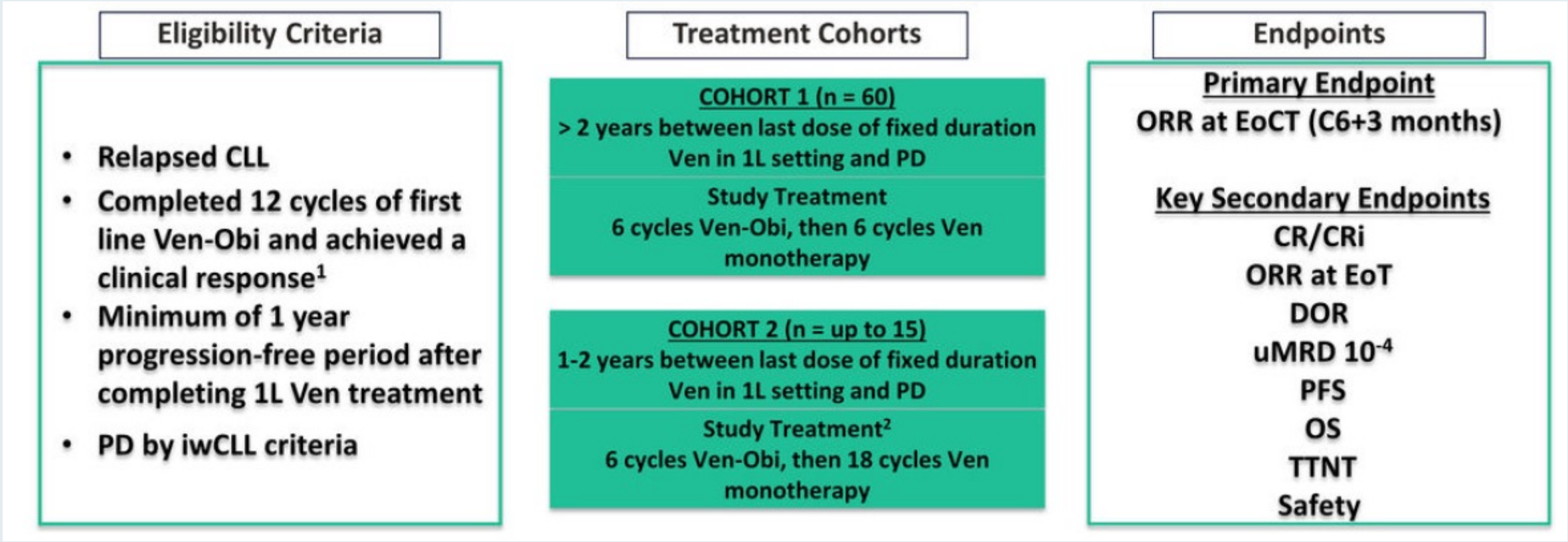
1. Kipps TJ & Choi MY. *Cancer J* 2019; **25:**378–385; 2. Lee HJ, *et al.* ASCO 2021. Abstract 7556; 3. Yi X, *et al. Clin Cancer Res* 2020; **26:**385–3867; 4. Danilov AV, *et al. Invest New Drugs* 2021; **39:**1099–1105; 5. Cuesta-Mateos C, *et al. Front Immunol* 2021; **12:**662866; 6. ClinicalTrials.gov: https://clinicaltrials.gov/ct2/show/NCT03263637 (accessed June 2022); 7. ClinicalTrials.gov: https://clinicaltrials.gov/ct2/show/NCT04876092 (accessed June 2022); 8. Lejeune M, *et al. Front Immunol* 2020; **11:**762; 9. Kharfan-Dabaja MA, *et al. Transplant Cell Ther* 2022; **22:**5–17. **10.** Beigene BGB-16673 & Nurix NX-2127

Cases and Questions: Venetoclax Retreatment; ReVenG Study

Christine Ryan, MD

RTP
RESEARCH
TO PRACTICE

ReVenG: An Ongoing Phase II Study of Venetoclax in Combination with Obinutuzumab Retreatment for Relapsed CLL



Davids MS et al. ASH 2021;Abstract 2634.

RTP RESEARCH TO PRACTICE

Cases and Questions: CLL and COVID-19

Adam Kittai, MD

Christine Ryan, MD

RTP
RESEARCH
TO PRACTICE

Agenda: CLL Update
A Meeting within a Meeting

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MODULE 4: Novel Investigational Agents and Strategies in CLL — Dr Davids

MODULE 5: CLL 2030?

RTP RESEARCH TO PRACTICE

The Clinical Implications of Key Recent Data Sets in Oncology: A Daylong Multitumor Educational Symposium in Partnership with Florida Cancer Specialists

Saturday, October 22, 2022

7:30 AM – 5:30 PM ET

JW Marriott Orlando | Orlando, Florida

Faculty

Ghassan Abou-Alfa, MD, MBA
Matthew P Goetz, MD
Ian E Krop, MD, PhD
Ann S LaCasce, MD, MMSc
Corey J Langer, MD
Prof Georgina Long, AO, BSc, PhD, MBBS
Christine M Lovly, MD, PhD
Wells A Messersmith, MD
Alicia K Morgans, MD, MPH
David M O'Malley, MD
Thomas Powles, MBBS, MRCP, MD
Mitchell R Smith, MD, PhD
John Strickler, MD
Saad Zafar Usmani, MD, MBA
Shannon N Westin, MD, MPH
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Moderator

Neil Love, MD

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Thank you for joining us!

CME and NCPD credit information will be emailed to each participant within 3 business days.

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