Year in Review — Clinical Investigators Provide Perspectives on the Most Relevant New Publications, Data Sets and Advances in Oncology:

Chronic Lymphocytic Leukemia

Thursday, January 21, 2021
5:00 PM – 6:00 PM ET

Faculty

Matthew S Davids, MD, MMSc
Jennifer Woyach, MD

Moderator

Neil Love, MD

RTP Year in Review 2020

YiR Chronic Lymphocytic Leukemia Faculty

Matthew S Davids, MD, MMSc
Associate Professor of Medicine
Harvard Medical School
Director of Clinical Research, Division of Lymphoma
Dana-Farber Cancer Institute
Boston, Massachusetts

Jennifer Woyach, MD
Professor
Section Head, CLL and Hairy Cell Leukemia
Associate Division Director for Clinical Research
Division of Hematology
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The Ohio State University Comprehensive Cancer Center
Columbus, Ohio

Commercial Support

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Dr Love — Disclosures

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Dr Davids — Disclosures

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Dr Woyach — Disclosures

Advisory Committee	AbbVie Inc, ArQule Inc, Janssen Biotech Inc
Consulting Agreements	AbbVie Inc, ArQule Inc, AstraZeneca Pharmaceuticals LP, Janssen Biotech Inc, Pharmacyclics LLC, an AbbVie Company
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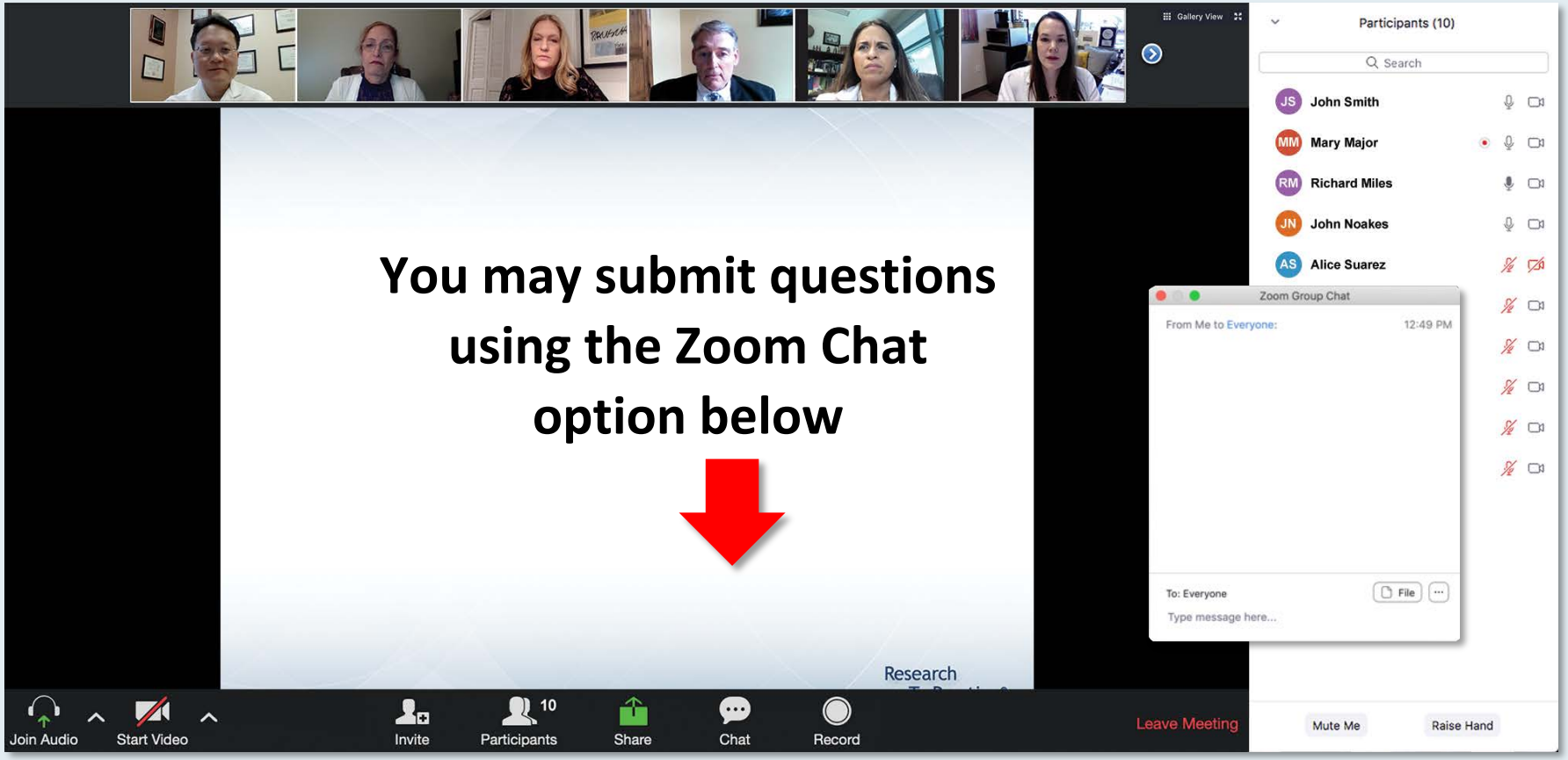
We Encourage Clinicians in Practice to Submit Questions



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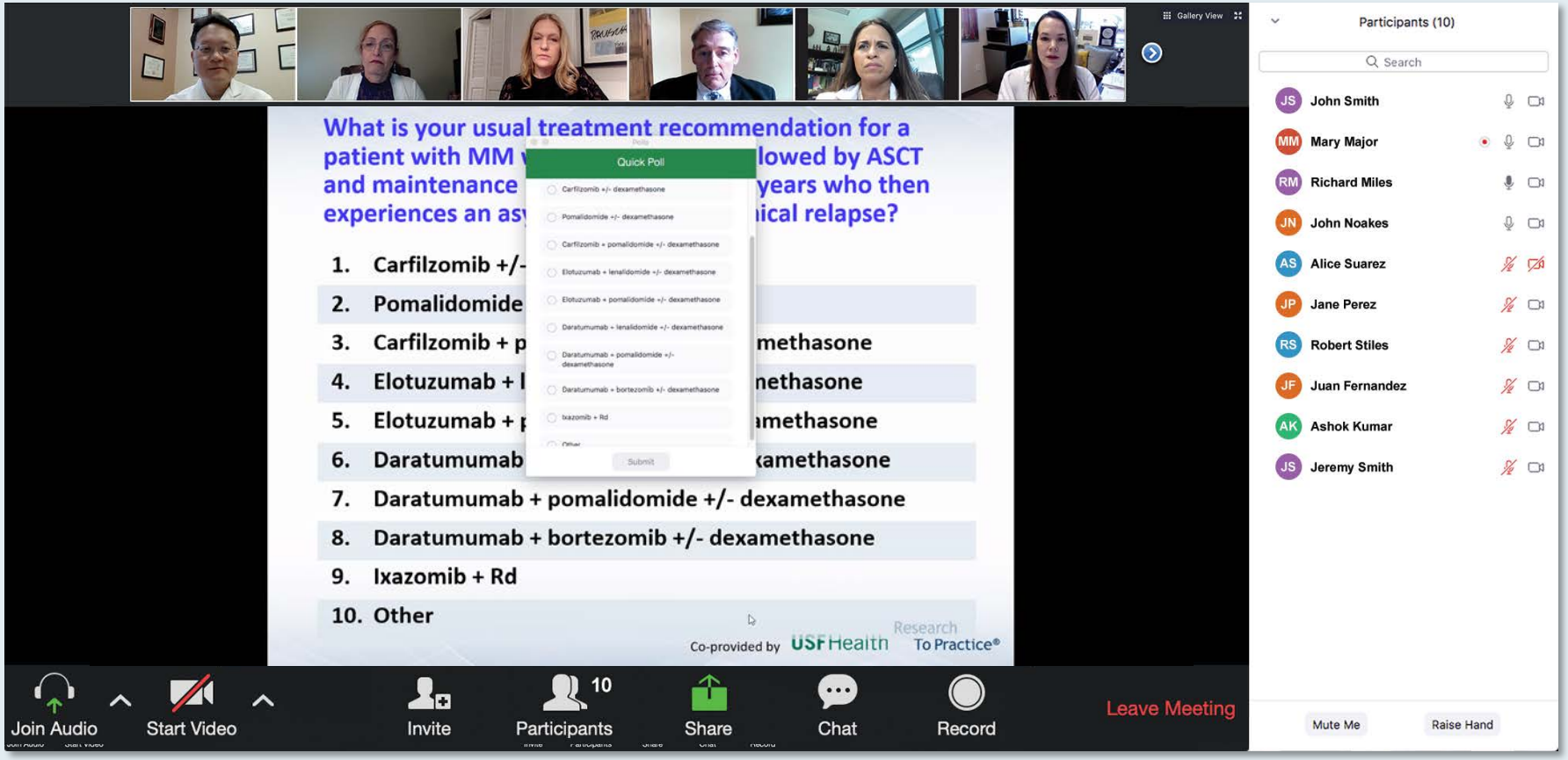
Familiarizing Yourself with the Zoom Interface

How to answer poll questions



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ONCOLOGY TODAY

WITH DR NEIL LOVE

FRONT-LINE TREATMENT OF CHRONIC LYMPHOCYTIC LEUKEMIA

DR JOHN PAGEL
SWEDISH CANCER INSTITUTE
SEATTLE, WASHINGTON

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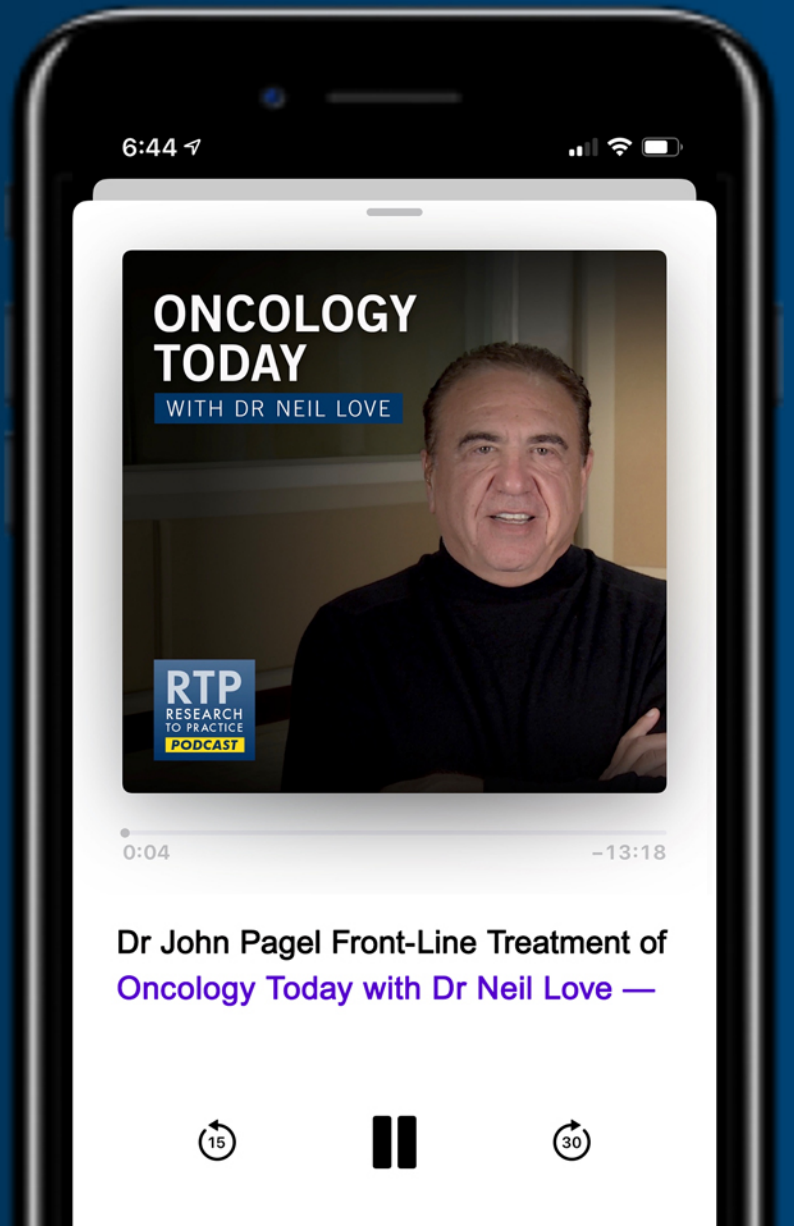

Meet The Professor
Management of Ovarian Cancer

Friday, January 22, 2021
1:15 PM – 2:15 PM ET

Faculty

Professor Jonathan A Ledermann, MD

Moderator

Neil Love, MD

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TO PRACTICE

Cancer Conference Update: What Happened at the 2020 San Antonio Breast Cancer Symposium®

Management of HER2-Positive Breast Cancer

Monday, January 25, 2021
5:00 PM – 6:00 PM ET

Faculty

Erika Hamilton, MD

Moderator

Neil Love, MD

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Year in Review — Clinical Investigators Provide Perspectives on the Most Relevant New Publications, Data Sets and Advances in Oncology:

Targeted Therapy for Lung Cancer

Tuesday, January 26, 2021
5:00 PM – 6:00 PM ET

Faculty

Joel W Neal, MD, PhD
Paul K Paik, MD

Moderator

Neil Love, MD

RTP Year in Review 2020

Cases from the Community: Investigators Discuss Emerging Research and Actual Patients with Hepatocellular Carcinoma (Part 1 of a 3-Part Series)

Wednesday, January 27, 2021
5:00 PM – 6:30 PM ET

Faculty

Richard S Finn, MD
Tim Greten, MD
James J Harding, MD
Ahmed Omar Kaseb, MD, CMQ

Moderator

Neil Love, MD

RTP RESEARCH TO PRACTICE

Year in Review — Clinical Investigators Provide Perspectives on the Most Relevant New Publications, Data Sets and Advances in Oncology:

Multiple Myeloma

Thursday, January 28, 2021
5:00 PM – 6:00 PM ET

Faculty

Rafael Fonseca, MD
Jonathan L Kaufman, MD

Moderator

Neil Love, MD

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Thank you for joining us!

CME and MOC credit information will be emailed to each participant within 5 business days.

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catch box


65 year old patient with IGHV unmutated, TP53 intact CLL


catch box


In your current clinical practice, what therapy would you recommend for this patient?
1. Venetoclax + obinutuzumab
2. Fludarabine + cyclophosphamide + rituximab
3. Bendamustine + rituximab
4. Ibrutinib
5. Ibrutinib ± obinutuzumab
6. Acalabrutinib ± obinutuzumab
7. Chlorambucil + obinutuzumab


Pre-Ven TL
Response =
MRD status
cytometry,
AEs = Grade
3 & 4, respo
Current stat
remission 1
completion


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

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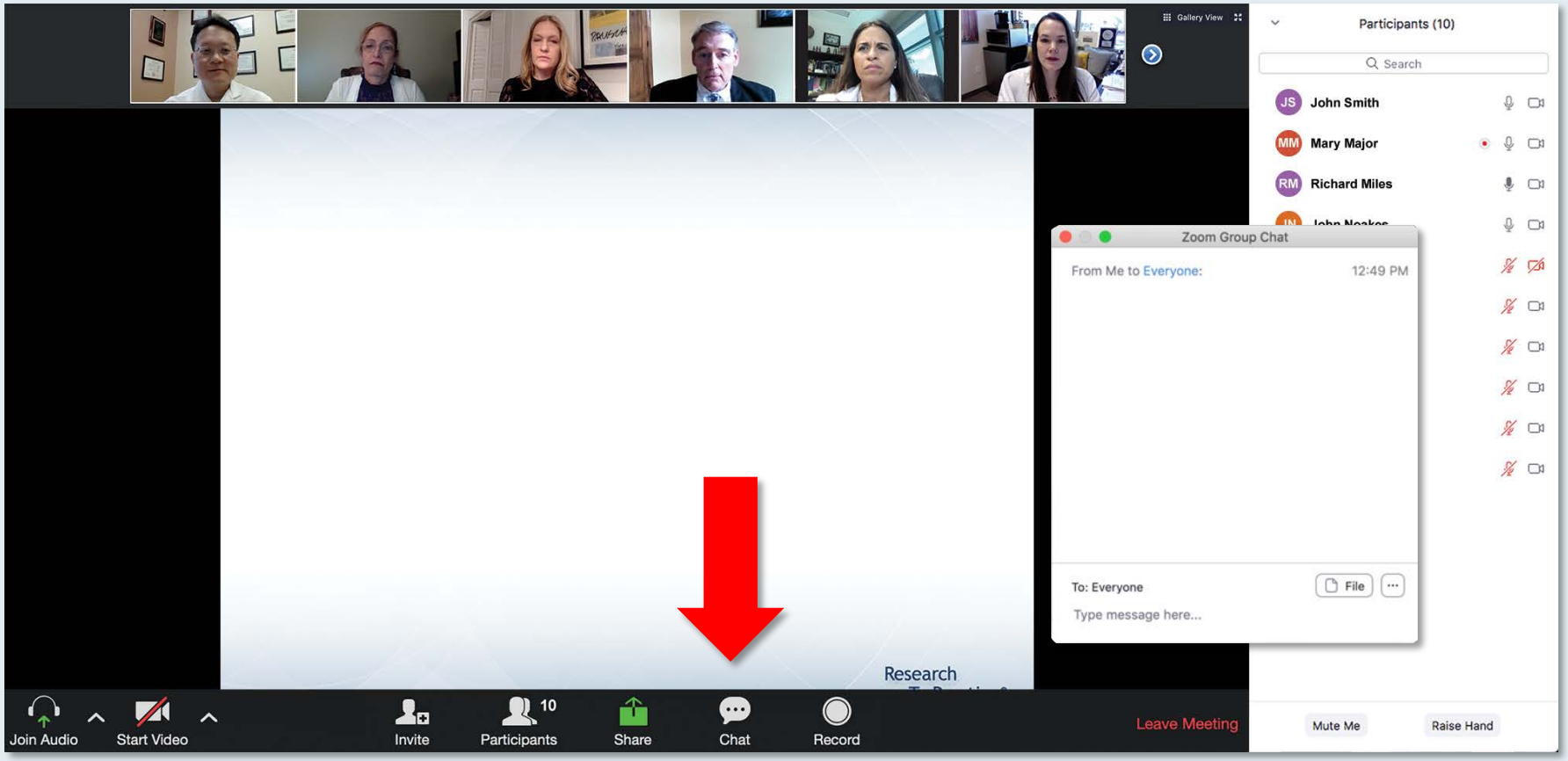

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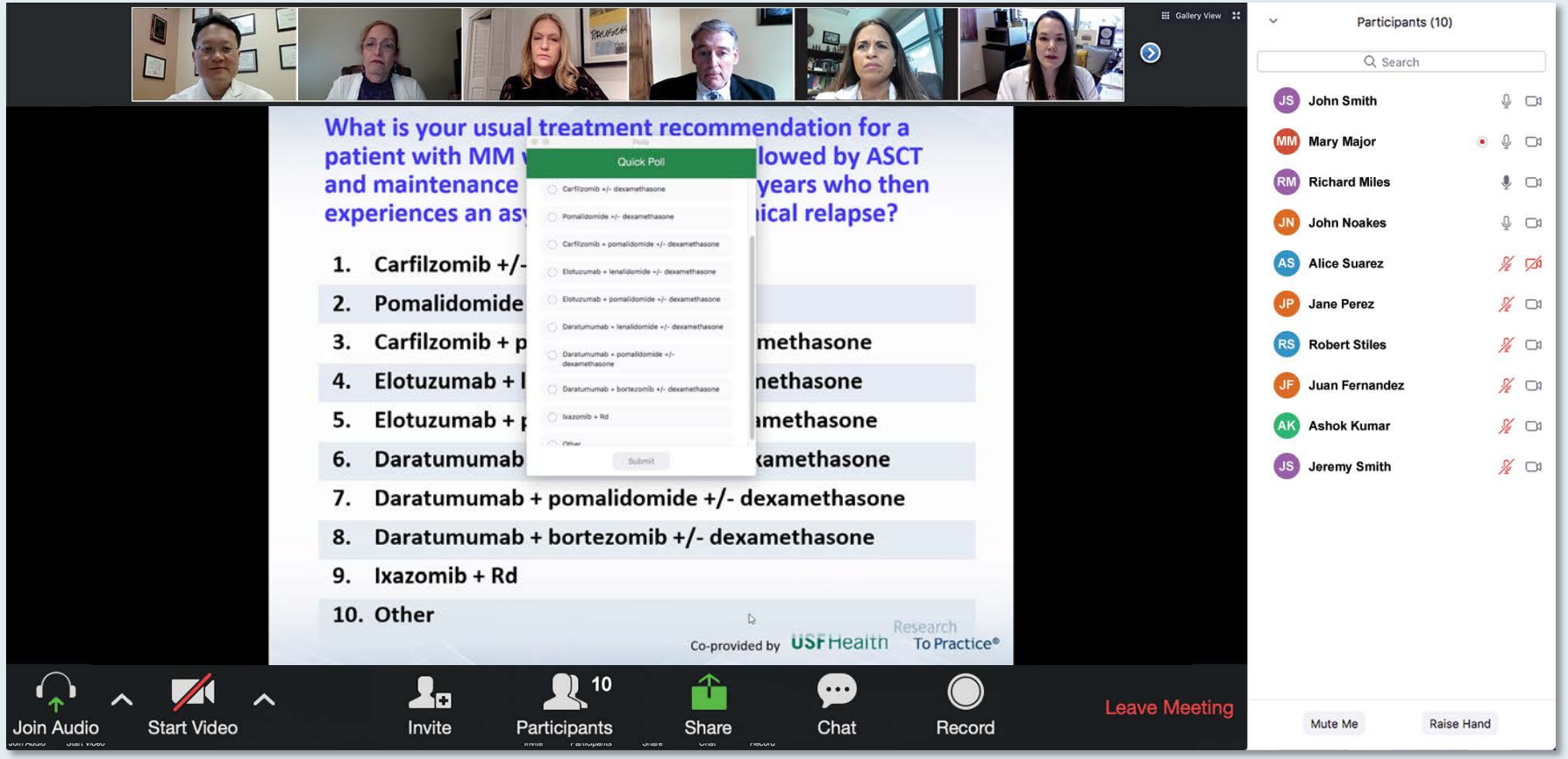

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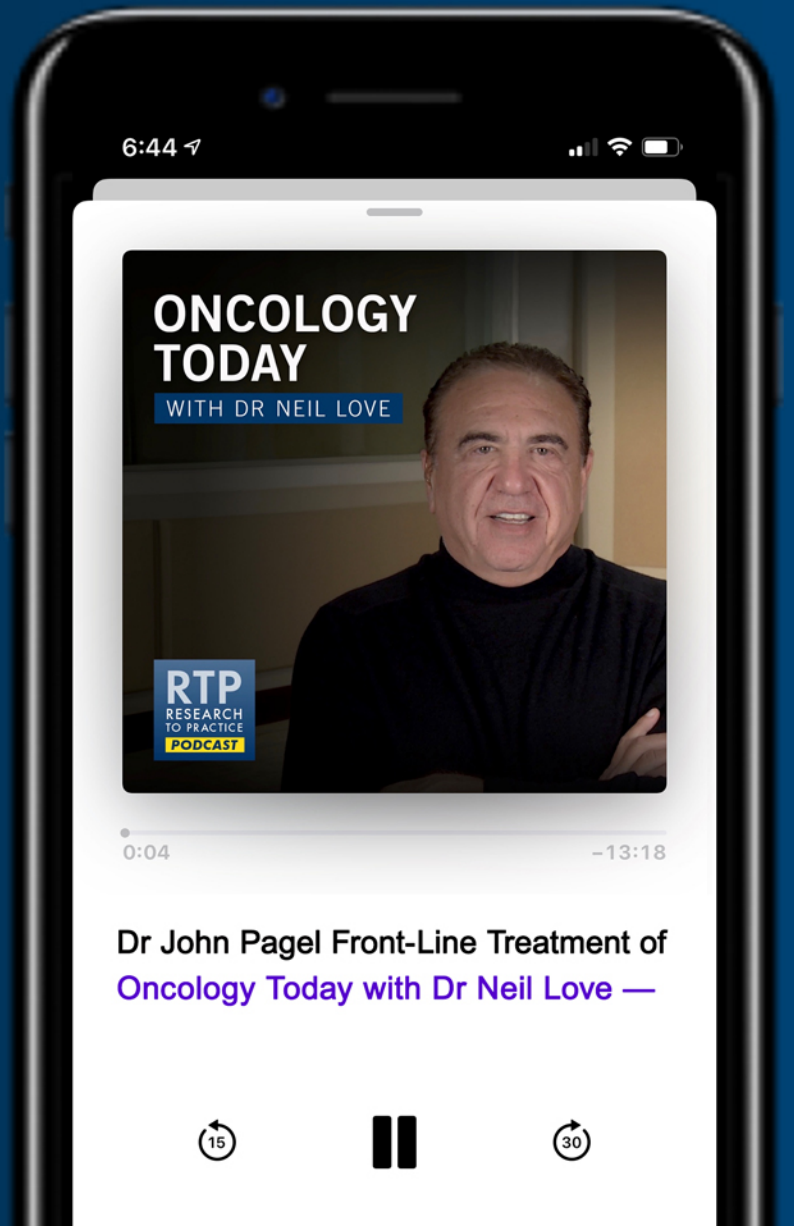

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RTP Year in Review 2020

Agenda

Module 1: Venetoclax combinations — Azacitidine, decitabine, LDAC, pracinostat

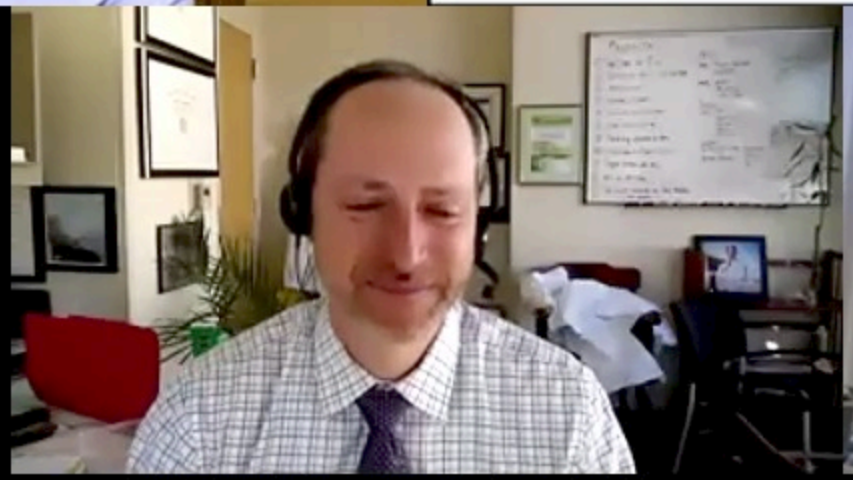
Module 2: FLT3 inhibitors — Midostaurin, gilteritinib, quizartinib

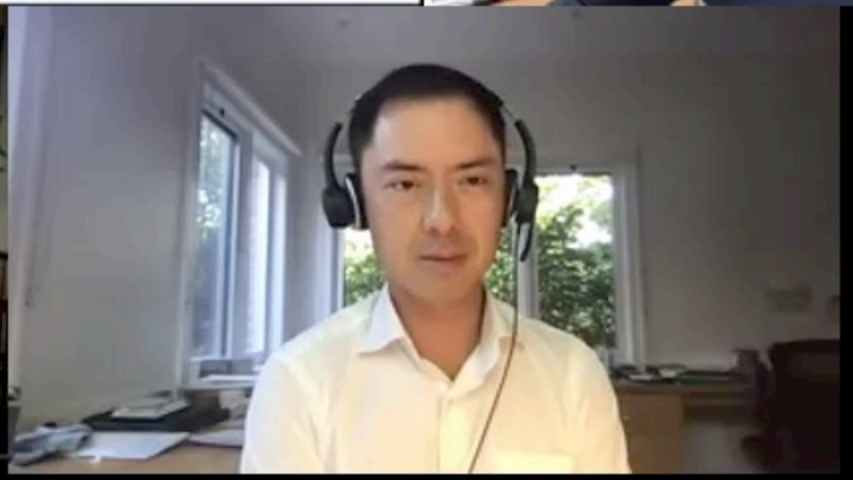
Module 3: IDH inhibitors — Ivosidenib, enasidenib

Module 4: Oral azacitidine (CC-486)

Module 5: Secondary AML — CPX-351

Module 6: Novel agents and strategies — Gemtuzumab ozogamicin, glasdegib, magrolimab





AML ASH Review
January 20, 2021
Question from Chat Room

Vladimir …… Therapy for younger patient with AML very fit and eligible for chemotherapy who has TP53 mutation and complex karyotype. Chemotherapy or AZA VEN? Other combo? If CR proceed to Tx or not at all. Tx only for molecular CR? TP53 VAF < 5%? Is there any future for Tx for TP53mut AML? Please, honest response outside a trial and simple answer: What do you do 21 January 2020 in such a patient?

Agenda

Module 1: BTK Inhibitors

Module 2: Bcl-2 Inhibitors

Module 3: Novel Strategies – U2 Regimen (Umbralisib, Ublituximab)
CAR T-Cell Therapy

Agenda

Module 1: BTK Inhibitors

Module 2: Bcl-2 Inhibitors

Module 3: Novel Strategies – U2 Regimen (Umbralisib, Ublituximab)
CAR T-Cell Therapy

To what extent do issues related to COVID-19 (social distancing, avoiding lymphopenia, etc) affect your first-line therapy recommendation for a patient with CLL in their mid-70s with minor comorbidities and moderate disease burden who requires treatment?

1. Minimal or no effect
2. Now more likely to use BTK inhibitors
3. Now more likely to use venetoclax/obinutuzumab

In general, what first-line therapy do you recommend for a patient with CLL in their mid-70s with minor comorbidities and moderate disease burden and no IGHV, del(17p) or TP53 mutation who requires treatment?

1. Ibrutinib
2. Ibrutinib/anti-CD20 antibody
3. Acalabrutinib
4. Acalabrutinib/anti-CD20 antibody
5. Venetoclax/obinutuzumab
6. BR
7. Other

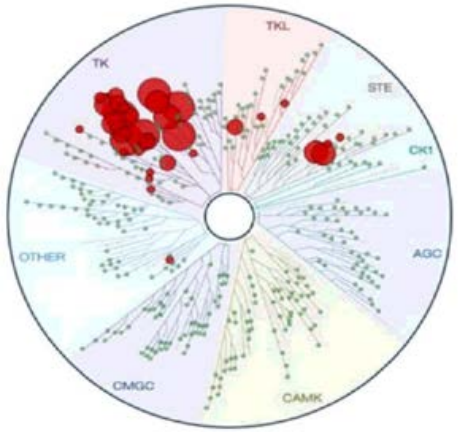
Module 1: BTK Inhibitors

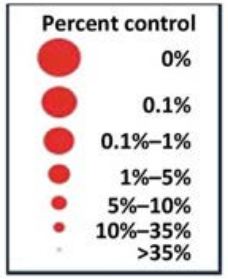
- **Key Relevant Data Sets**
  - ECOG-E1912: Extended follow-up
  - RESONATE-2: Five-year update of first-line ibrutinib
  - ACE-CL-001: Acalabrutinib for treatment-naïve CLL
  - ELEVATE-TN: Acalabrutinib +/- obinutuzumab
  - AVO: Acalabrutinib/venetoclax/obinutuzumab
  - MAIC: Acalabrutinib +/- obinutuzumab
  - SEQUOIA: Zanubrutinib for treatment-naïve del(17p) CLL
  - BTK inhibition for venetoclax-refractory CLL
  - BRUIN: Next-generation BTK inhibitor LOXO-305

The BTKi floodgates have opened…

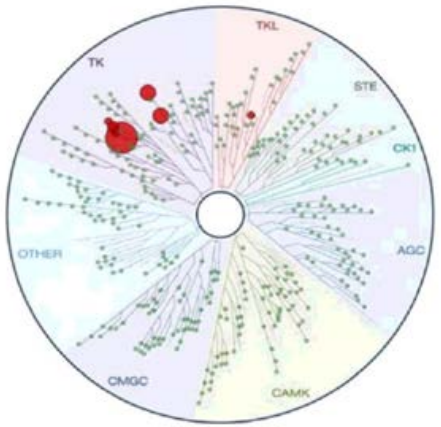
Irreversible

Ibrutinib

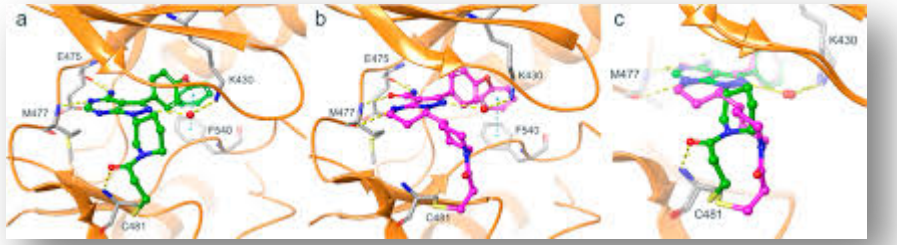




Acalabrutinib

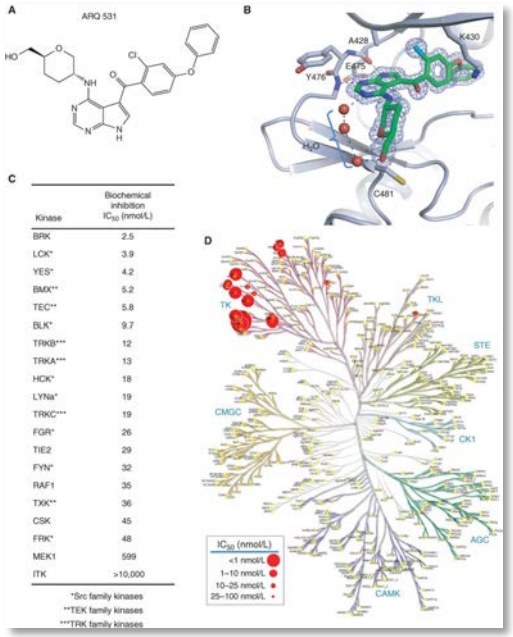


Zanubrutinib

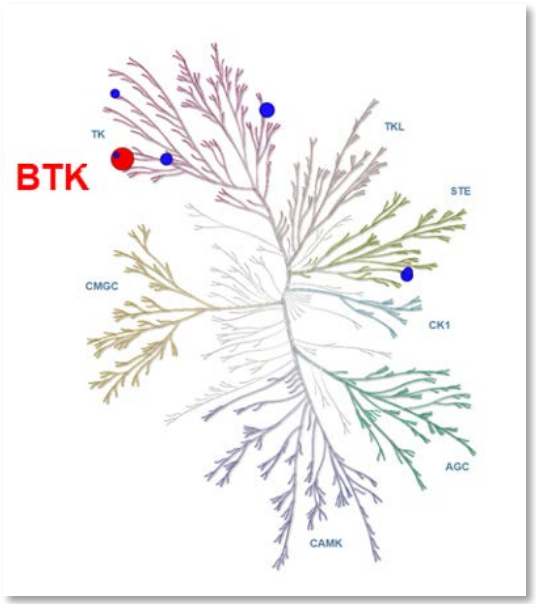


Reversible

ARQ-531 (MK-1026)



LOXO-305



Courtesy of Matthew S Davids, MD, MMSc

Phase 3 E1912: IR vs FCR
IR Effective as Initial Treatment for CLL

Previously Untreated CLL (N = 529)
- Age ≤ 70
- ECOG 0-2
- CrCl>40
- Able to tolerate FCR
- **No deletion 17p by FISH**

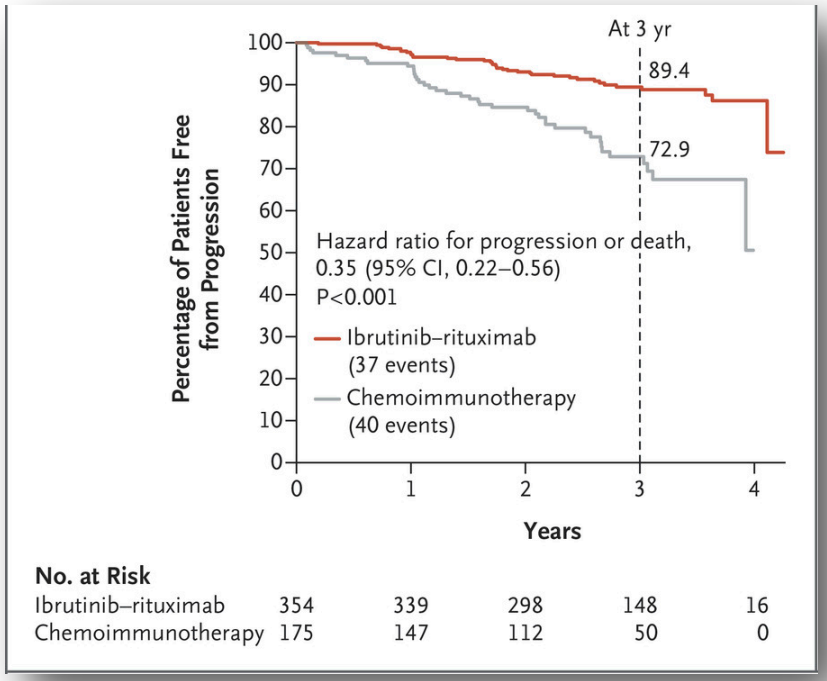
Randomized 2:1

- **Ibrutinib + Rituximab (IR)** → **Ibrutinib until PD**
- **FCR**

Primary Endpoint

PFS

PFS-All Patients



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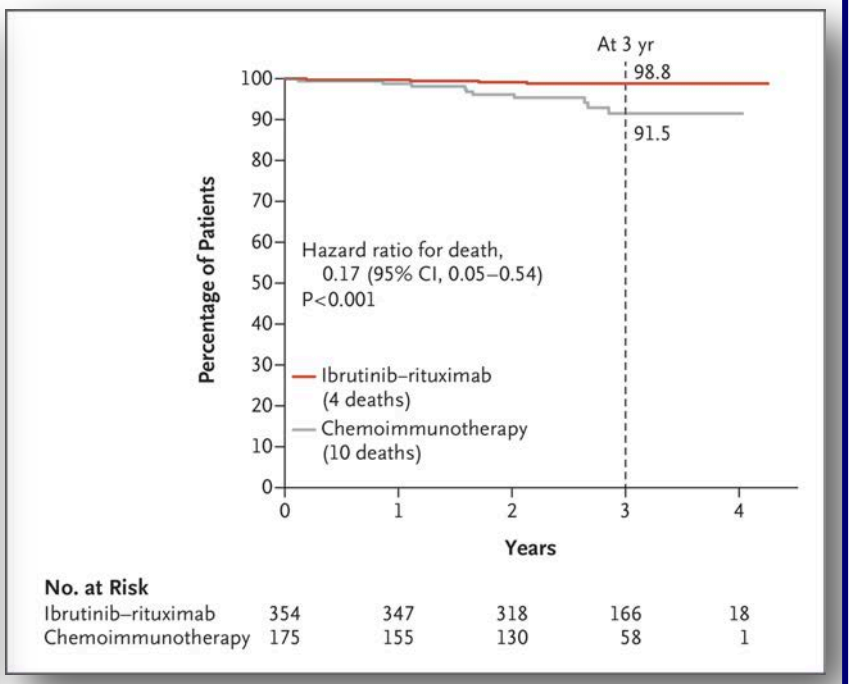


- IR was superior to FCR for *IGHV* unmutated patients
- AEs grade ≥ 3
  - IR, 80.1%
  - FCR, 79.7%
- Infectious complications of grade ≥ 3
  - IR, 10.5%
  - FCR, 20.3%
- **April 21, 2020: FDA expanded the indication of ibrutinib to include its combination with rituximab for the initial treatment of adult patients with CLL/SLL**

Shanafelt T, et al. *N Engl J Med*. 2019;381:432-443. doi: 10.1056/NEJMoa1817073

Courtesy of Matthew S Davids, MD, MMSc

Phase 3 RESONATE-2 Trial: 5-Year Update

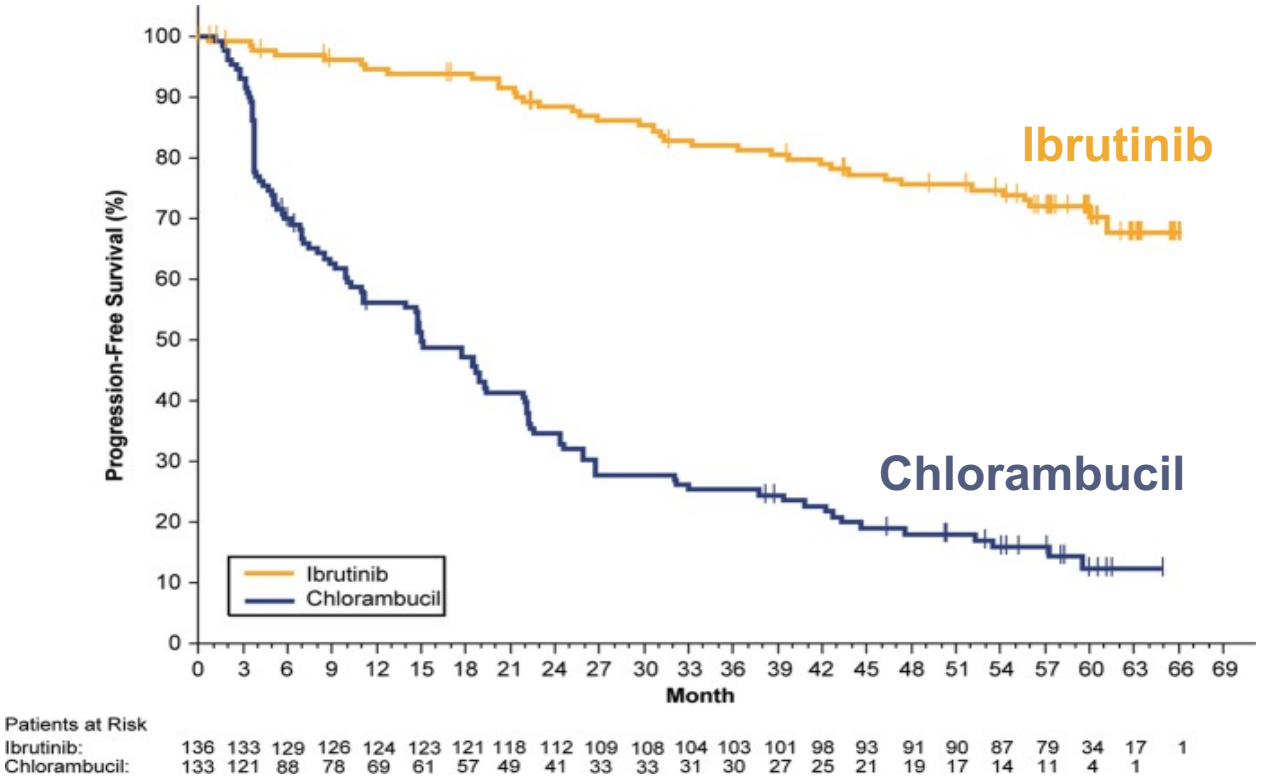
Ibrutinib Provides Durable Response as Initial Therapy in Frail Pts

Efficacy

- Ibrutinib benefit was also consistent in patients with high prognostic risk (*TP53* mutation, 11q deletion, and/or unmutated *IGHV*)

Safety

- Discontinuation due to AEs decreased over time, with 58% of ibrutinib pts continuing daily treatment



	Median PFS, mo	HR (95% CI)
Ibrutinib	NE	0.146 (0.098-0.218)
Chlorambucil	15.0	

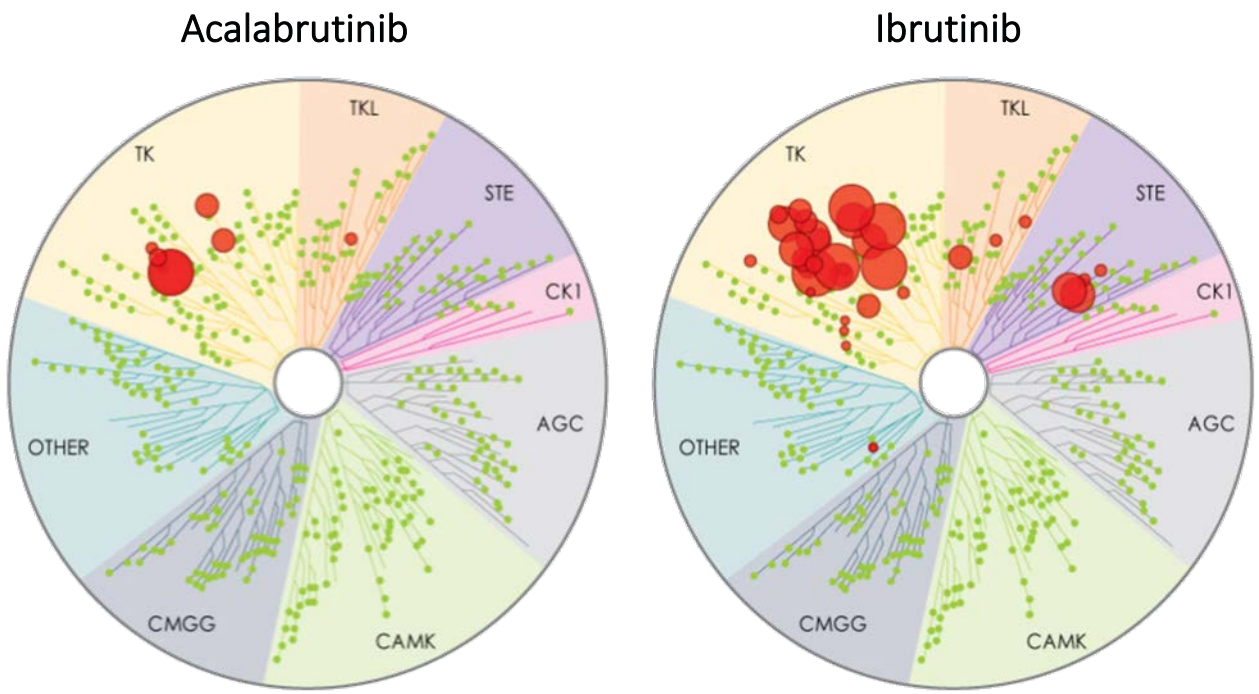
Burger JA, et al. *Leukemia.* 2020;34(3):787-798. doi: 10.1038/s41375-019-0602-x.

Courtesy of Matthew S Davids, MD, MMSc

Second Generation BTKi: Acalabrutinib: Agent Overview

- Highly-selective, potent kinase inhibitor
- Designed to minimize off-target activity with minimal effects on TEC, EGFR, or ITK signaling
- Dosing is 100 mg PO bid

Kinase selectivity profiling at 1 μM



The size of the red circle is proportional to the degree of inhibition.

Kinase Inhibition IC_{50} (nM)		
Kinase	**Acalabrutinib**	**Ibrutinib**
BTK	5.1	1.5
TEC	126	10
BMX	46	0.8
TXK	368	2.0
ERBB2	~1000	6.4
EGFR	>1000	5.3
ITK	>1000	4.9
JAK3	>1000	32
BLK	>1000	0.1

Barf T, et al. *J Pharmacol Exp Ther.* 2017.

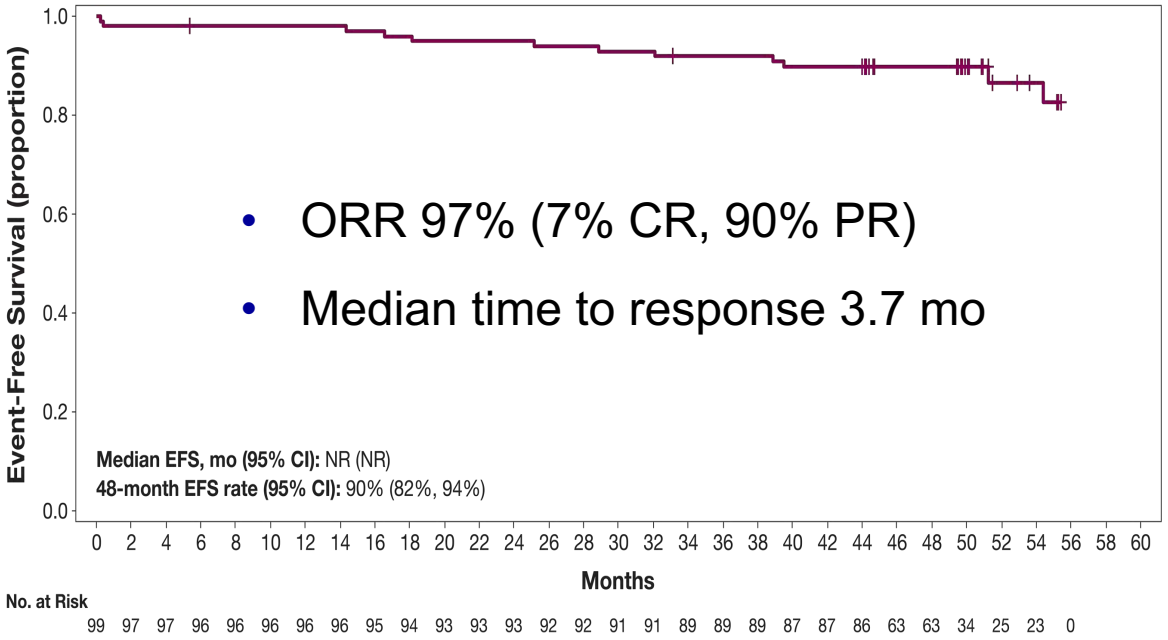
Courtesy of Matthew S Davids, MD, MMSc

Acalabrutinib is Highly Effective in Front-Line CLL

Phase 1/2 ACE-CL-001 Study in patients with previously untreated CLL requiring tx (N = 99)

→

Acalabrutinib
200 mg once daily
or
100 mg twice daily



- ORR 97% (7% CR, 90% PR)
- Median time to response 3.7 mo

ASCO/EHA 2020 Update: Acalabrutinib monotherapy demonstrated durable remissions and long-term tolerability (median follow-up of 53 months)

- 86% of patients remain on treatment
- Median DOR was not reached
  48-month DOR rate: 97% (95% CI, 90%–99%)
- Median EFS was not reached 48-month EFS rate: 90% (95% CI, 82%–94%)

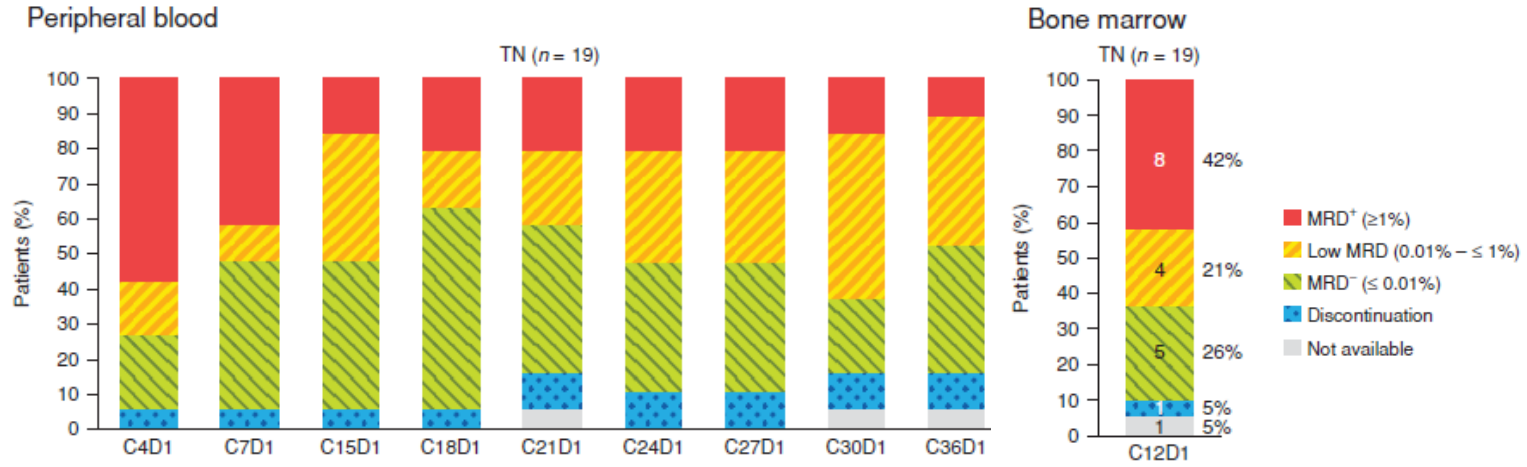
Courtesy of Matthew S Davids, MD, MMSc

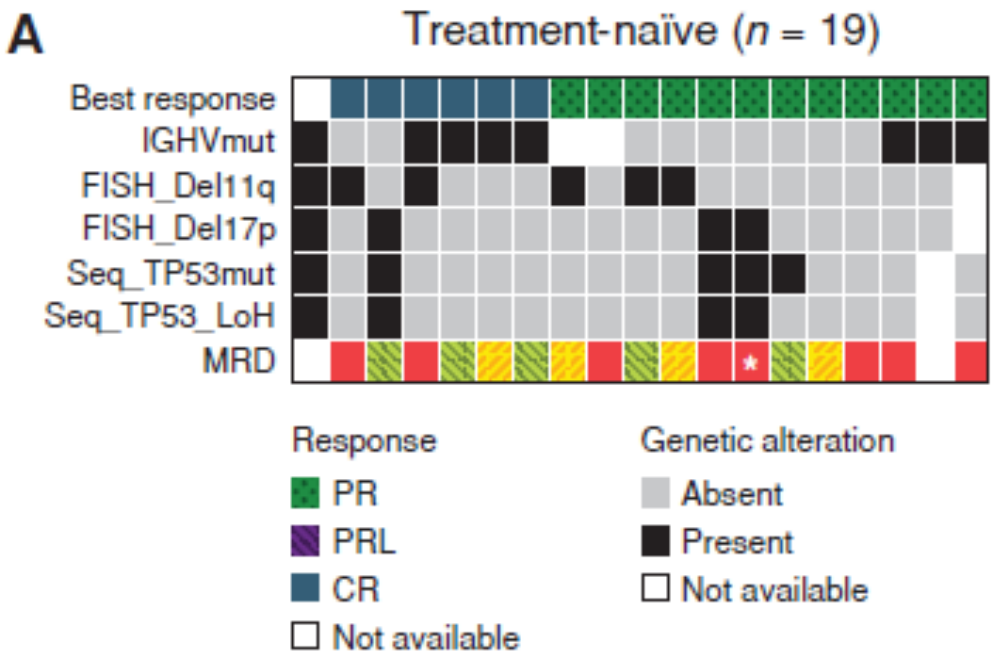
Byrd, et al. *Blood*. 2018; 132 (Supplement 1): 692. doi.org/10.1182/blood-2018-99-110451. Byrd, et al. *J Clin Oncol. 2020;*38, no. 15_suppl:8024-8024.. doi.org/10.1200/JCO.2020.38.15_suppl.8024.

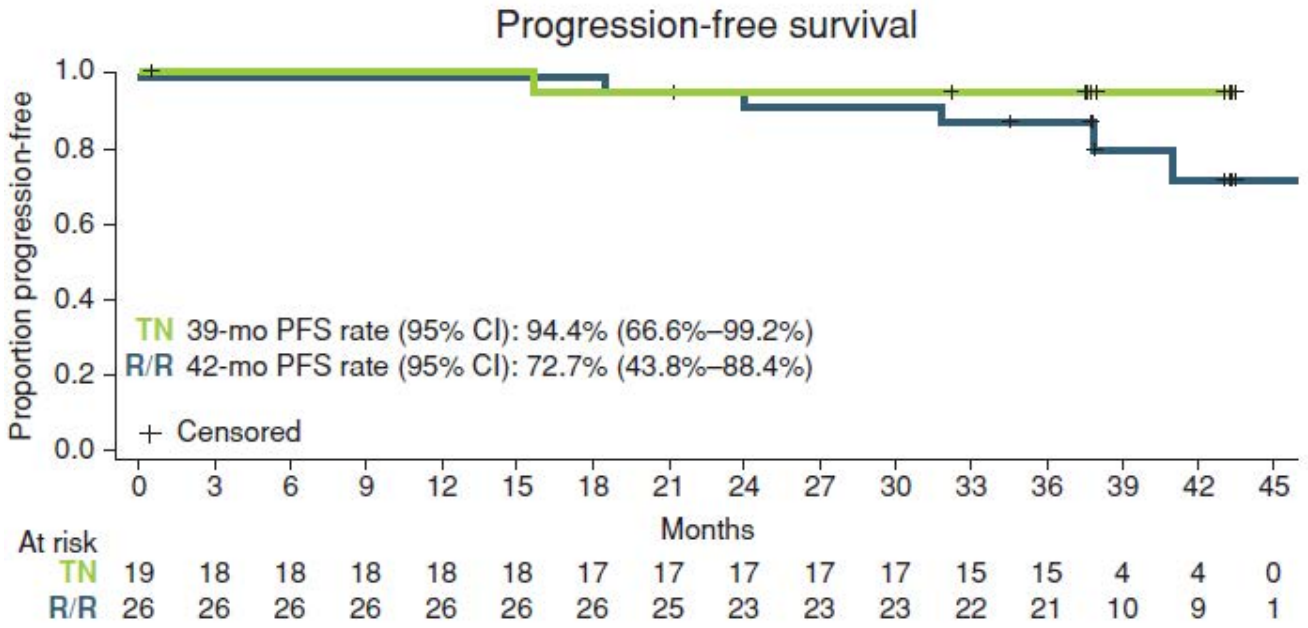
RESEARCH ARTICLE

Acalabrutinib plus Obinutuzumab in Treatment-Naïve and Relapsed/Refractory Chronic Lymphocytic Leukemia

Jennifer A. Woyach[1], James S. Blachly[1], Kerry A. Rogers[1], Seema A. Bhat[1], Mojgan Jianfar[1], Gerard Lozanski[1], David M. Weiss[1], Barbara L. Andersen[1], Michael Gulrajani[2], Melanie M. Frigault[2], Ahmed Hamdy[2], Raquel Izumi[2], Veerendra Munugalavadla[2], Cheng Quah[2], Min-Hui Wang[2], and John C. Byrd[1]







Woyach et al, Cancer Discovery, 2020

Courtesy of Matthew S Davids, MD, MMSc

Phase 3 ELEVATE-CLL TN: Acalabrutinib is Superior to Obinutuzumab + Chlorambucil for Treatment-Naïve CLL

Treatment-naive CLL (N=535)

Age ≥65 or <65 years with coexisting conditions:

- CIRS score >6, or
- creatinine clearance <70 mL/min

Stratification

- del(17p), y vs n
- ECOG PS 0-1 vs 2
- Geographic region (N America, W Europe, or other)

RANDOMIZE

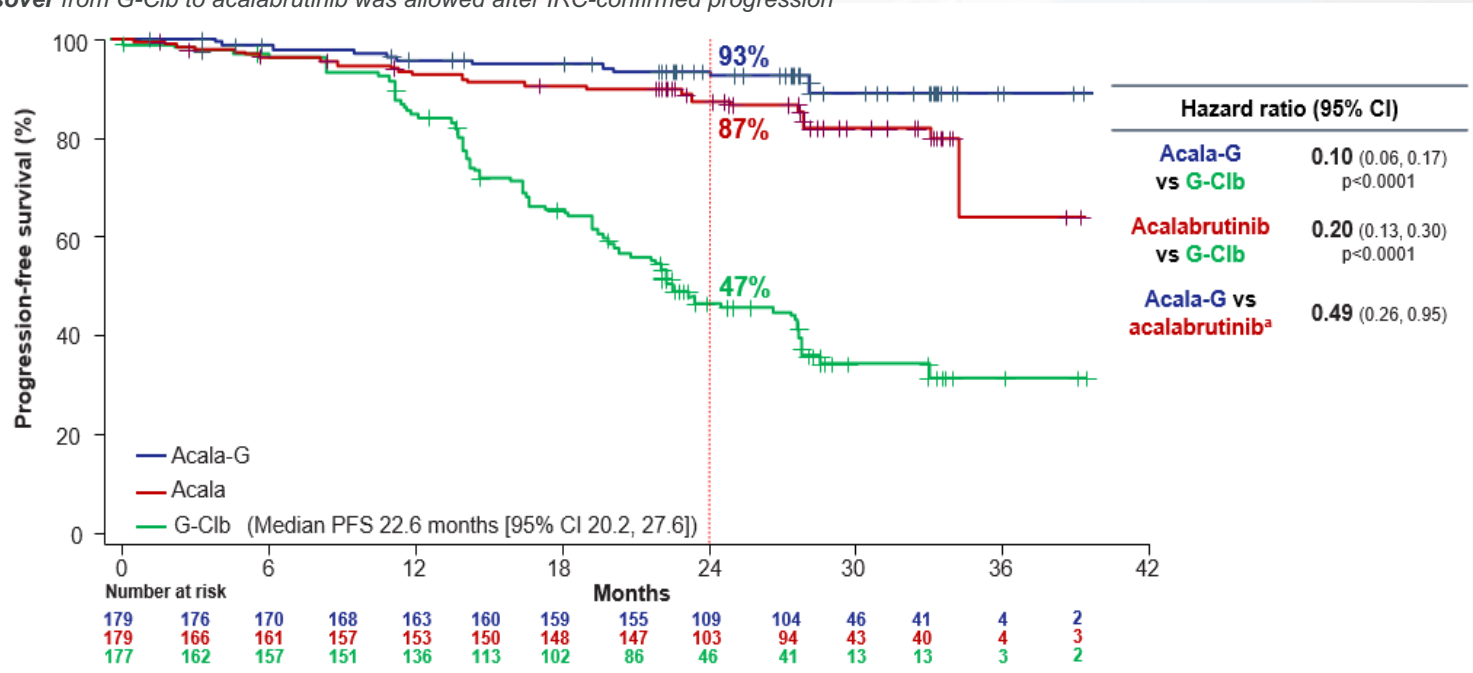
- **Acalabrutinib + Obinutuzumab (G)**
- **Acalabrutinib**
- **Obinutuzumab (G) + Chlorambucil (Clb)**

Primary endpoint

- PFS (assessed by IRC) Acala-G vs G-Clb

Crossover *from G-Clb to acalabrutinib was allowed after IRC-confirmed progression*

- Median follow-up: 28.3 months
- 90% reduction in disease progression or death with acalabrutinib + obinutuzumab
- On November 21, 2019, the FDA approved acalabrutinib monotherapy for the treatment of adult patients with chronic CLL based on analyses from the ELEVATE-TN and ASCEND phase III trials.



Sharman, et al. *Lancet.* 2020;395(10232):1278-1291. doi: 10.1016/S0140-6736(20)30262-2.

Courtesy of Matthew S Davids, MD, MMSc

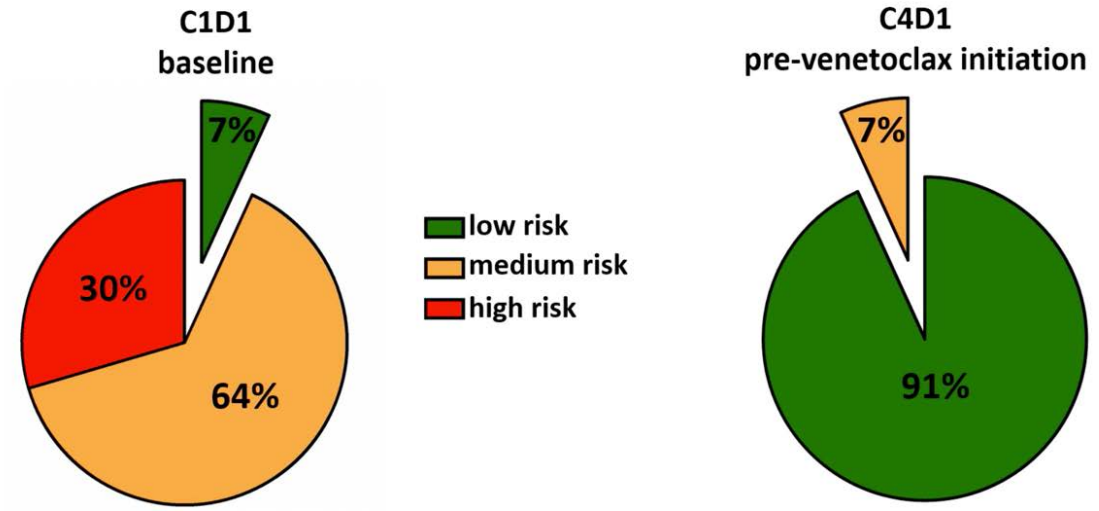
A Phase 2 Study of Acalabrutinib, Venetoclax and Obinutuzumab (AVO) for 1L CLL: Safety

AEs (N=44), %		All Grades	Grade ≥3
Most frequent hematologic	Neutropenia	77	34
	Thrombocytopenia	70	22
	Anemia	52	5
Non-hematologic (≥20%)	Headache	80	2
	Fatigue	77	2
	Bruising	57	0
	Nausea	45	0
	Hypocalcemia	34	2
	Rash	32	0
	Diarrhea	27	0
	GERD	25	0
	IRR	25	2
	Elevated creatinine	23	0

SAEs

- Grade 4 neutropenia (n=4), grade 4 hyperkalemia (n=1; in the setting of AKI just prior to C4D1 without TLS), grade 3 cardiac troponin I elevated (n=1; in the setting of O IRR), grade 3 lung infection (n=1)

3 cycle lead-in with acalabrutinib and obinutuzumab reduces TLS risk at the time of ven initiation (n=44)



AEs of special interest

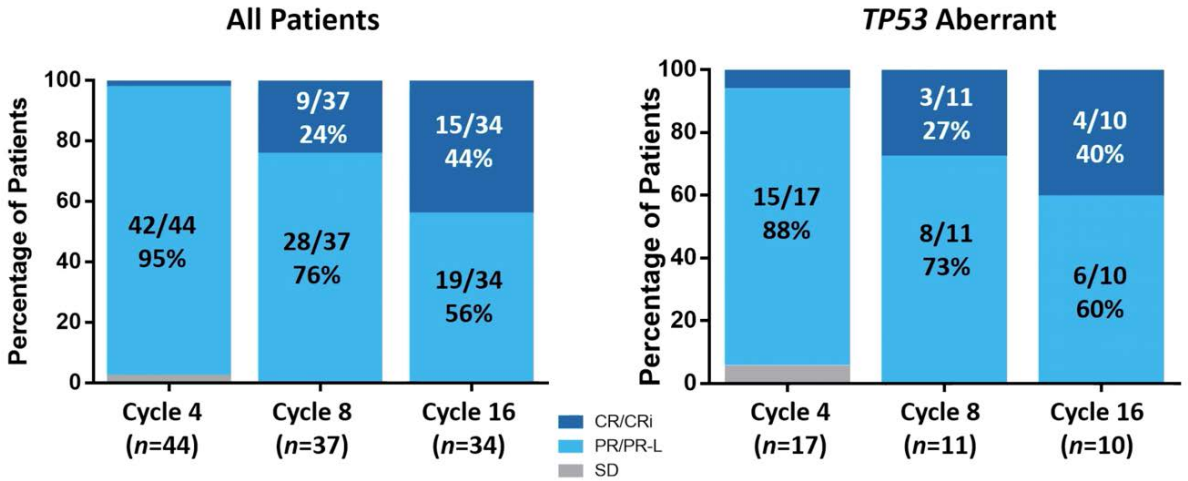
- Grade ≥3 infections: 1 (2.3%, grade 3 lung infection)
- IRRs: 11 (25%, including 23% grade 1/2, 2% grade 3)
- Hypertension: 5 (11%; no grade ≥3)
- Afib: 1 grade 3
- Lab TLS: 2 grade 3 (both after O and prior to V)

Davids MS, et al. ASH 2020. Abstract 2216.

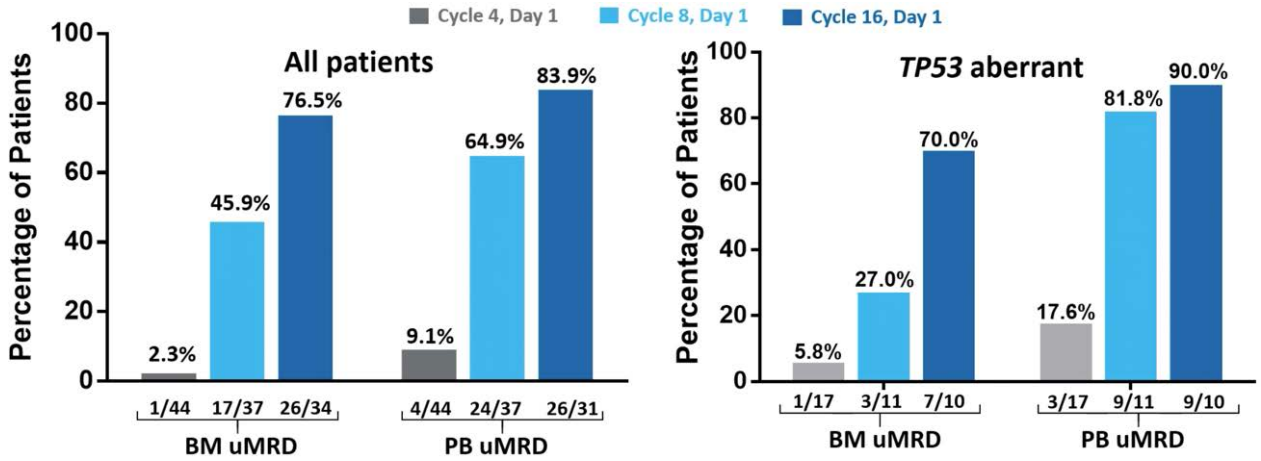
Courtesy of Matthew S Davids, MD, MMSc

A Phase 2 Study of Acalabrutinib, Venetoclax and Obinutuzumab (AVO) for 1L CLL: Efficacy and Summary

iwCLL Response



MRD by ITT



- 11 pts in BM-uMRD CR discontinued after 15 cycles, as per protocol
  - Median time off therapy: 4 months (range: 1-10)
- Median follow-up: 19 cycles (range, 6-26)
- No patients had progressed or had recurrent MRD to date

Summary

- AVO demonstrated efficacy and a favorable safety profile in patients with high-risk, TN CLL
- No TLS due to Ven was observed using a 4-week Ven ramp-up
- Accrual to a TP53-aberrant cohort is ongoing

Davids MS, et al. ASH 2020. Abstract 2216.

Courtesy of Matthew S Davids, MD, MMSc

MAIC: Acalabrutinib ± Obinutuzumab (G) Demonstrated Lower Rates of Several Clinically Important AEs vs Ibrutinib ± G in TN CLL

AEs With Statistically Significant Differences After Matching

Acalabrutinib vs Ibrutinib

AE rate, %	Acala ESS=79	Ibr n=136	Rate difference % (95% CI)	*P*-value
Grade 3/4 AEs				
Infections	12.4	24.0	−11.6 (−21.9,−1.0)	<0.05
Atrial fibrillation	0	4.0	−4.0 (−7.3 ,0.0)	<0.05
Grade 1-4 AEs				
Peripheral edema	7.5	21.0	−13.5 (−21.7,−5.0)	<0.001
Pyrexia	6.2	20.0	−13.8 (−21.6,−6.0)	<0.001
Hypertension	6.4	18.0	−11.6 (−19.9,−3.0)	<0.01
Major hemorrhage	1.8	7.0	−5.2 (−10.2,0.0)	<0.05

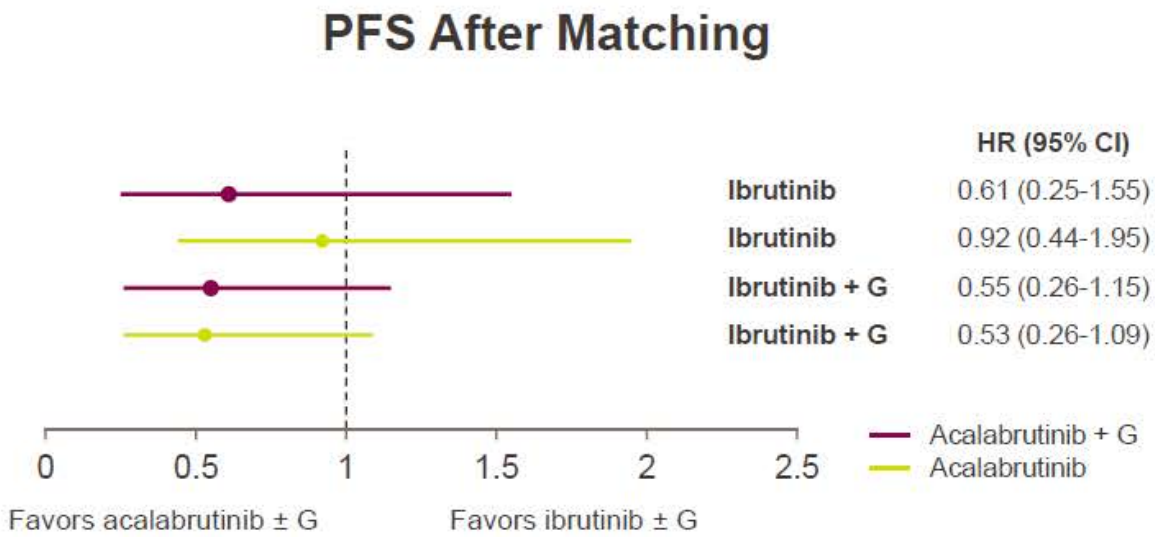
Acalabrutinib + G vs Ibrutinib + G

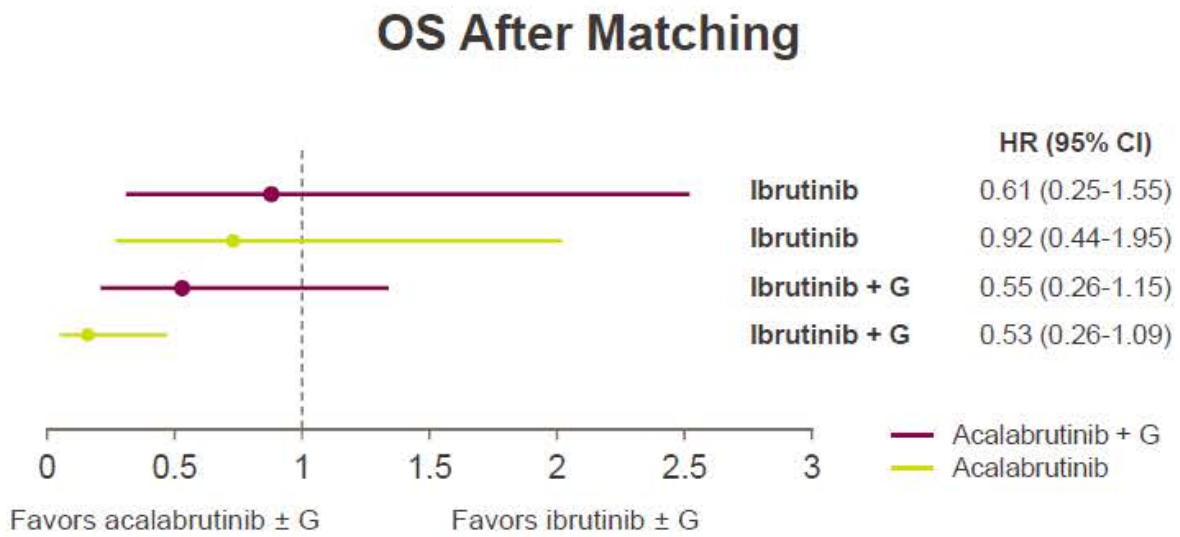
AE rate, %	Acala + G ESS=97	Ibr + G n=113	Rate difference % (95% CI)	*P*-value
Grade 3/4 AEs				
Peripheral edema	0.6	12.0	−11.4 (−17.5,−5.3)	<0.001
Febrile neutropenia	0.5	5.0	−4.5 (−8.6,−0.4)	<0.05
Grade 1-4 AEs				
Headache	32.1	8.0	+24.1 (+14.6,+33.6)	<0.001
Thrombocytopenia	20.7	36.0	−15.3 (−26.8,−3.9)	<0.01
Atrial fibrillation	3.4	12.0	−8.6 (−15.6,−1.7)	<0.05

Davids MS et al, EP724, Presented at 25th Annual congress of EHA. June 11-21, 2020

Courtesy of Matthew S Davids, MD, MMSc

MAIC: Acalabrutinib ± G Demonstrated a Trend Towards Improved PFS and OS vs Ibrutinib ± G in TN CLL





Acalabrutinib monotherapy significantly reduced risk of death compared with ibrutinib + G by 84% (*P*<0.001) after matching

Davids MS et al, EP724, Presented at 25th Annual congress of EHA. June 11-21, 2020

Courtesy of Matthew S Davids, MD, MMSc

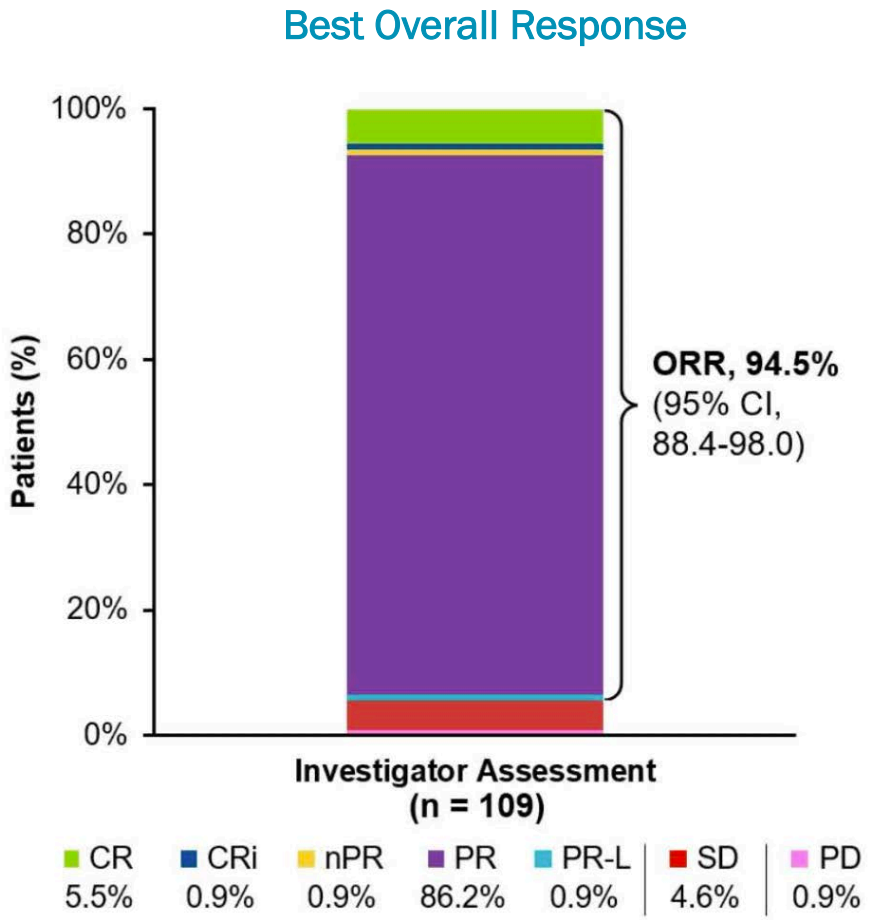
Zanubrutinib (BGB-3111): High BTK Selectivity

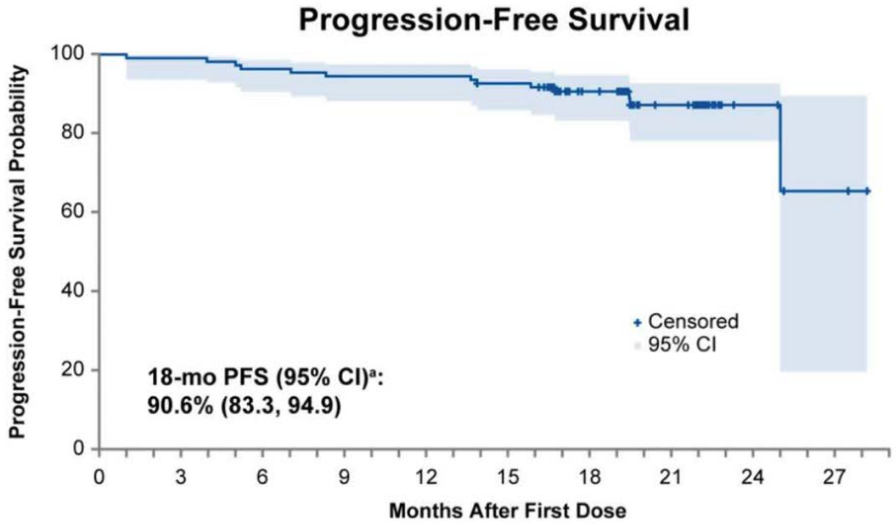
Targets	Assays	Ibrutinib IC_{50} (nM)	Zanubrutinib IC_{50} (nM)	Ratio (Zanubrutinib:Ibrutinib)
BTK	BTK-pY223 Cellular Assay	3.5	1.8	0.5
	Rec-1 Proliferation	0.34	0.36	1.1
	BTK Occupation Cellular Assay	2.3	2.2	1.0
	BTK Biochemical Assay	0.20	0.22	1.1
EGFR	p-EGFR HTRF Cellular Assay	101	606	6.0
	A431 Proliferation	323	3210	9.9
ITK	ITK Occupancy Cellular Assay	189	3265	17
	p-$PLC_{\gamma 1}$ Cellular Assay	77	3433	45
	IL-2 Production Cellular Assay	260	2536	9.8
	ITK Biochemical Assay	0.9	30	33
JAK3	JAK3 Biochemical Assay	3.9	200	51
HER2	HER2 Biochemical Assay	9.4	661	70
TEC	TEC Biochemical Assay	0.8	1.9	2.4

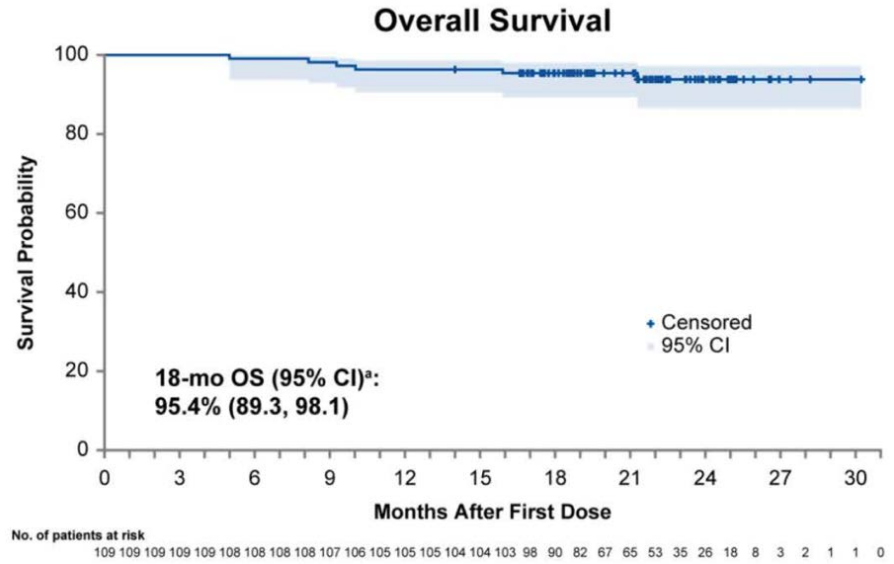
Brown JR, et al. ASH 2020. Abstract 1306.

Courtesy of Matthew S Davids, MD, MMSc

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







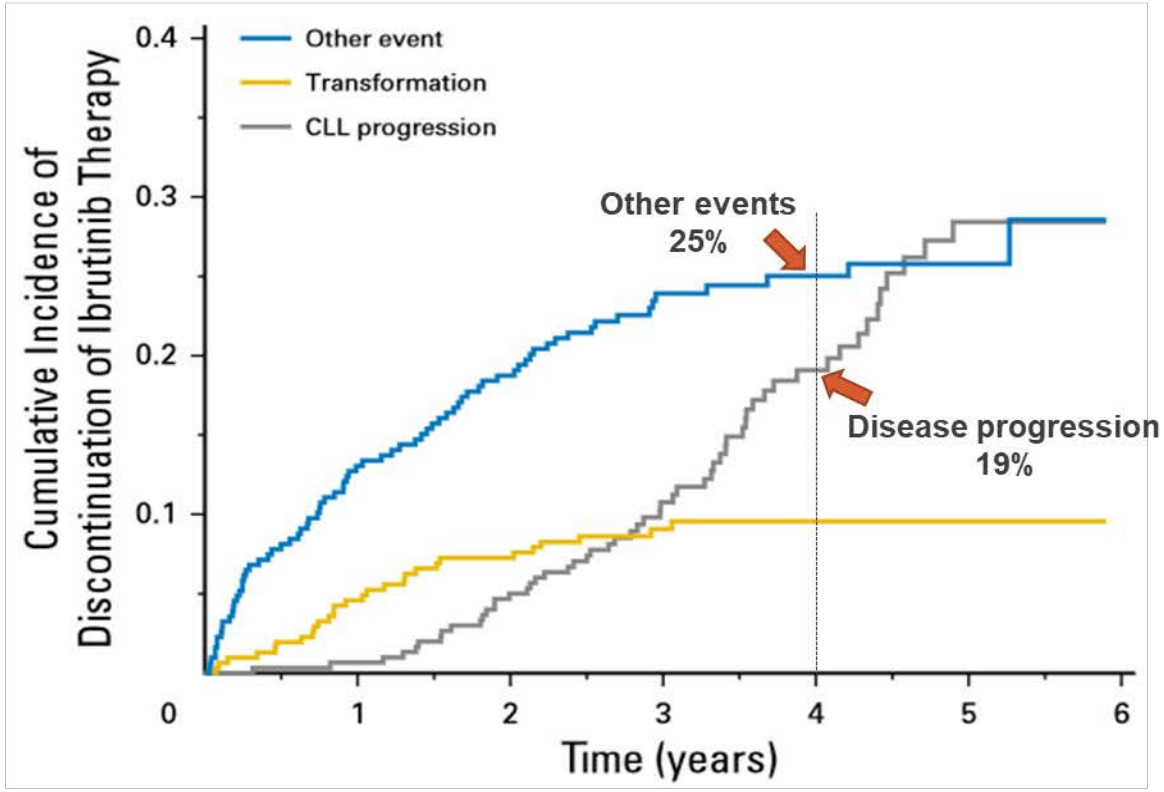
[a]Data cutoff for 2019 ASH presentation: August 7, 2019.
Brown JR, et al. ASH 2020. Abstract 1306.

Courtesy of Matthew S Davids, MD, MMSc

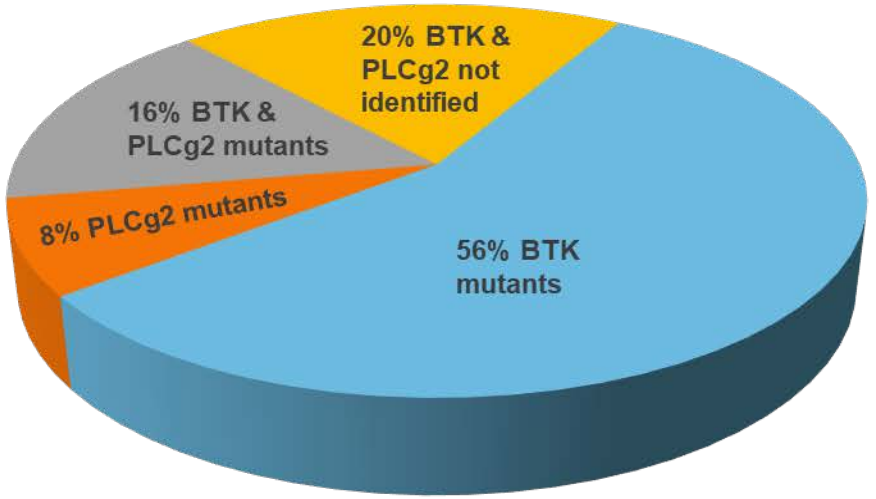
Median follow-up: 21.9 months (range, 5.0-30.2)

Resistance and Intolerance Limit Covalent BTK Inhibitor Outcomes

Ibrutinib discontinuation from 4 sequential studies[1]



Ibrutinib acquired resistance in patients with progressive CLL[2]



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

References: 1. Woyach et al. *J Clin Oncol*. 2017; 35:1437–43. 2. Lampson et al. *Expert Rev Hematol*. 2018 Mar;11(3):185-94. 3. Woyach et al. *N Engl J Med*. 2014; 370:2286–94. 4. Byrd et al. *N Engl J Med*. 2016; 374:323–32. 5. Xu et al. *Blood*. 2017; 129:2519–25. 6. Hershkovitz-Rokah et al. *Br J Haematol*. 2018; 181:306–19. 7. Burger. *Leukemia*. 2019;[Epub]. 8. Woyach et al. ASH2019.

Courtesy of Matthew S Davids, MD, MMSc

(Courtesy of A. Mato)

Phase 1/2 BRUIN Study of LOXO-305 in Patients With R/R CLL/SLL: Safety

Adverse Events, at All Doses and Patients (N=323), n (%)		Treatment-Emergent AEs, (≥10%)[a]				Treatment-Related AEs	
		Any Grade	Grade 1	Grade 2	Grade 3	Any Grade	Grade 3/4
Fatigue		65 (20)	40 (12)	22 (7)	3 (1)	27 (8)	2 (<1)
Diarrhea		55 (17)	45 (14)	10 (3)	-	28 (9)	-
Contusion		42 (13)	37 (12)	5 (2)	-	29 (9)	-
AEs of special interest, [b,c]	Bruising	53 (16)	48 (15)	5 (2)	-	37 (12)	-
	Rash	35 (11)	30 (9)	5 (2)	-	18 (6)	-
	Arthralgia	16 (5)	13 (4)	3 (1)	-	5 (2)	-
	Hemorrhage	15 (5)	10 (3)	4 (1)	1 (<1)[d]	5 (2)	-
	Hypertension	15 (5)	2 (<1)	9 (3)	4 (1)	4 (1)	-
	AFib/Flutter	2 (<1)	-	2 (<1)[e]	-	-	-

- No DLTs reported and MTD not reached
- 5 (1.5%) discontinued due to treatment-related AEs
- 200 mg QD selected as recommended phase 2 dose

Data cutoff date of 27 September 2020.[a]TheAEs listed are the most common that occurred at any grade in at least 10% of the patients, regardless of attribution. [b]AEs of special interest are those that were previously associated with covalent BTKi. [c]Bruising includes contusion, petechia, ecchymosis and increased tendency to bruise. Hemorrhage includes hematoma, epistaxis, rectal hemorrhage, subarachnoid hemorrhage, upper gastrointestinal hemorrhage, vitreous hemorrhage and wound hemorrhage. Rash includes rash maculo-papular, rash, rash macular, rash erythematous, rash popular, rash pruritic and rash pustular. [d]Subarachnoid bleed sustained during a bicycle accident, considered by investigator as unrelated to LOXO-305. [e]Both events considered by investigators as unrelated to LOXO-305 due to a history of prior atrial fibrillation in each.

Mato AR, et al. ASH 2020. Abstract 542

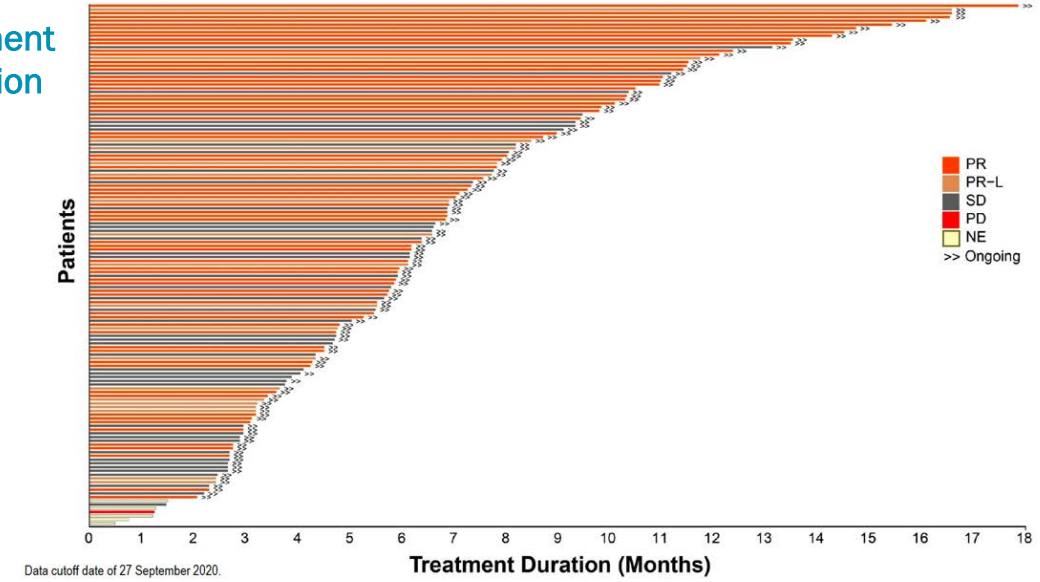
Courtesy of Matthew S Davids, MD, MMSc

Phase 1/2 BRUIN Study of LOXO-305 in Patients With R/R CLL/SLL: Efficacy

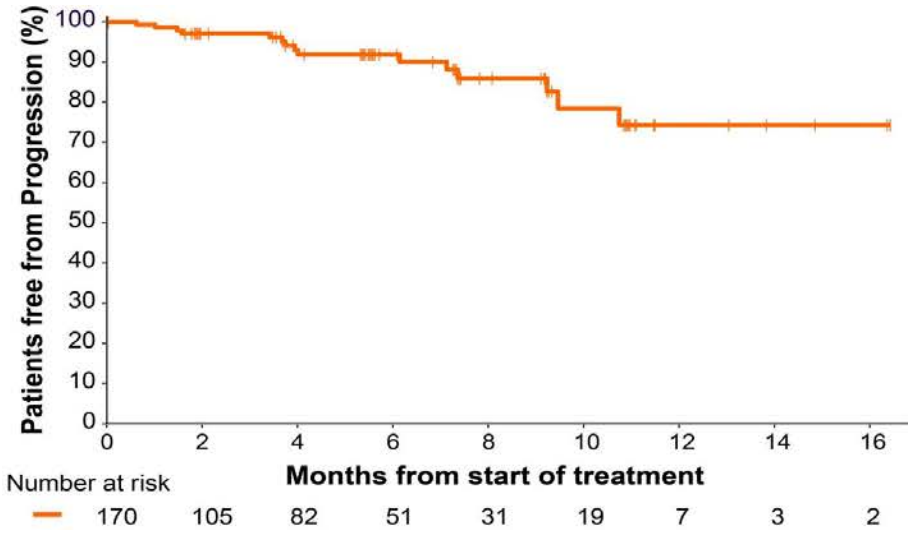
Response Rates		All Patients[a] (N=139)	BTK Pre-Treated Patients[a] (n=121)
ORR, % (95% CI)		63 (55-71)	62 (53-71)
Best response, n (%)	CR	0	0
	PR	69 (50)	57 (47)
	PR-L	19 (14)	18 (15)
	SD	45 (32)	41 (34)

- ORR increased over time: PR/PR-L 63% to 86% from start of treatment to ≥10 months follow-up
- Median follow-up: 6 months (0.6-17.8+) for efficacy-evaluable[a] pts
- 83 (94%) of responding patients with CLL/SLL are ongoing/in response
  - 5 responders discontinued: 4 for PD, 1 in PR electively underwent transplantation

Treatment Duration



PFS



[a]Efficacy evaluable patients are those who had at least one evaluable post-baseline assessment or had discontinued treatment prior to first post-baseline assessment.

Mato AR, et al. ASH 2020. Abstract 542.

Courtesy of Matthew S Davids, MD, MMSc

What is your usual preferred initial regimen for a 60-year-old patient with CLL with IGHV mutation but without del(17p) or TP53 mutation who requires treatment?

1. FCR (fludarabine/cyclophosphamide/rituximab)
2. BR (bendamustine/rituximab)
3. Ibrutinib
4. Ibrutinib + rituximab
5. Acalabrutinib
6. Acalabrutinib + obinutuzumab
7. Venetoclax + obinutuzumab
8. Other

What is your usual preferred initial regimen for a 60-year-old patient with del(17p) CLL who requires treatment?

1. FCR
2. BR
3. Ibrutinib
4. Ibrutinib + rituximab
5. Acalabrutinib
6. Acalabrutinib + obinutuzumab
7. Venetoclax + obinutuzumab
8. Other

RTP
RESEARCH
TO PRACTICE

Which second-line systemic therapy would you recommend for a 60-year-old patient with CLL with IGHV mutation but without del(17p) or TP53 mutation who responds to FCR and then experiences disease progression 3 years later?

1. Ibrutinib
2. Ibrutinib + rituximab
3. Acalabrutinib
4. Acalabrutinib + obinutuzumab
5. Venetoclax + rituximab
6. Venetoclax + obinutuzumab
7. Idelalisib
8. Duvelisib
9. Other

RTP
RESEARCH
TO PRACTICE

Agenda

Module 1: BTK Inhibitors

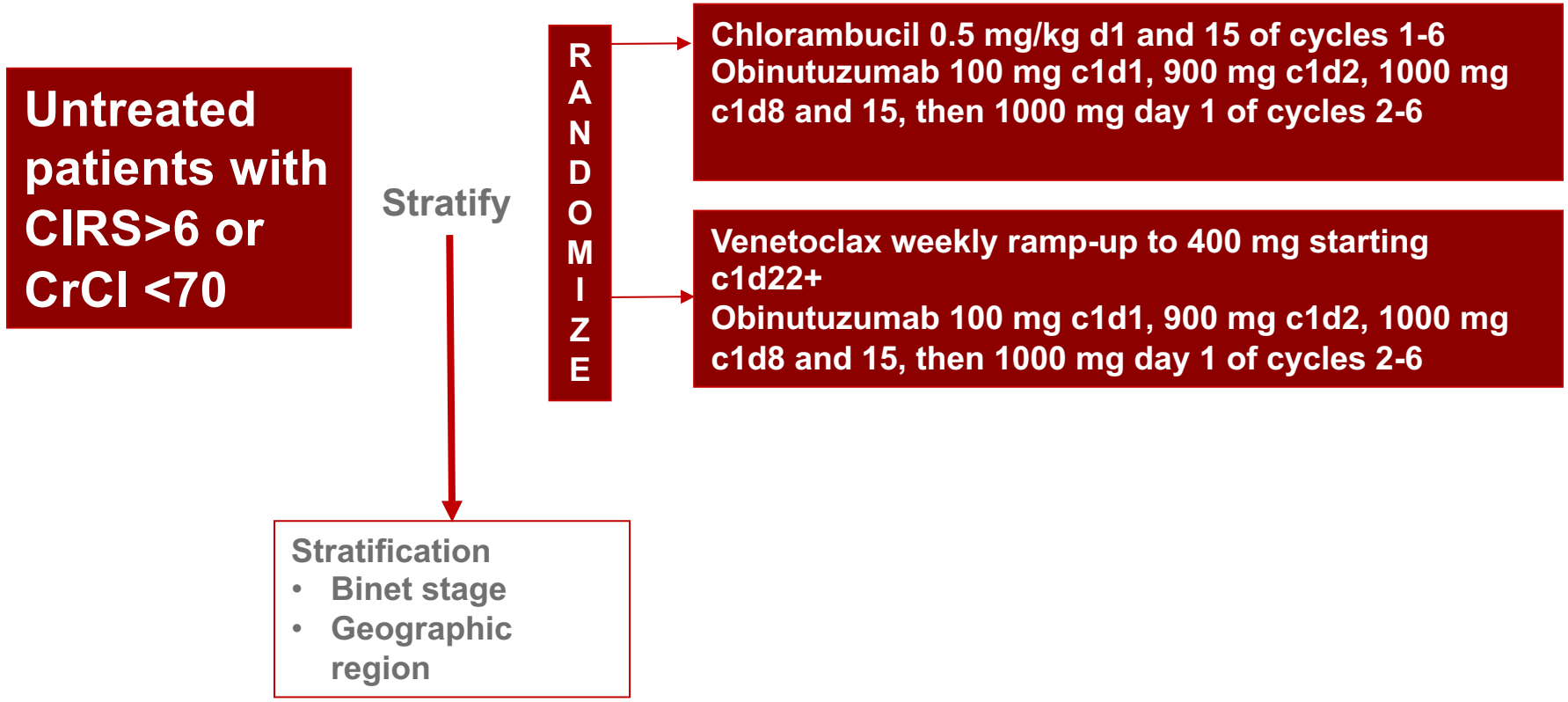
Module 2: Bcl-2 Inhibitors

Module 3: Novel Strategies – U2 Regimen (Umbralisib, Ublituximab)
CAR T-Cell Therapy

Module 2: Bcl-2 Inhibitors

- **Key Relevant Data Sets**
  - CLL14: Follow-up results with front-line venetoclax/obinutuzumab
  - MURANO: Five-year analysis of fixed-duration venetoclax/rituximab
  - CAPTIVATE: First-line ibrutinib + venetoclax
  - Phase II trial of ibrutinib/venetoclax/obinutuzumab: Three-year follow-up
  - CLARITY: Long-term responses to ibrutinib/venetoclax
  - MRD-driven, time-limited therapy with zanubrutinib, obinutuzumab, venetoclax

Phase 3 CLL14 Follow-Up



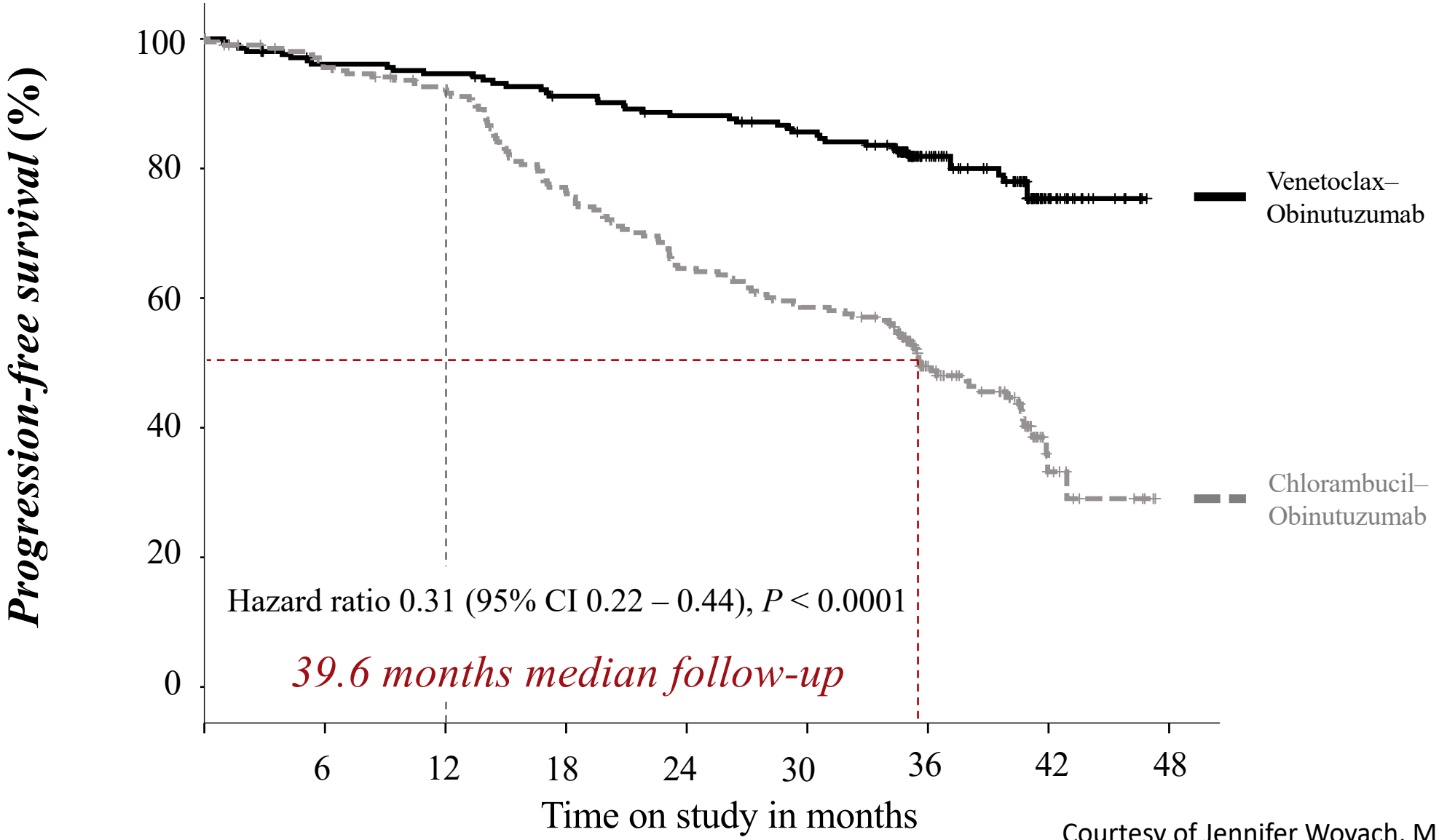
Key Points

- Median age 72
- 7-9% del(17p), 8-11% TP53 mutated
- 60% IGHV unmutated

Al-Sawaf O et al, Lancet Oncol 2020

Courtesy of Jennifer Woyach, MD

Phase 3 CLL14 Follow-Up



36 month PFS: 82% vs 50%

OS: no difference

uMRD peripheral blood 76% 3 months post-tx; 47% 18 months post-tx

Al-Sawaf O et al, Lancet Oncol 2020

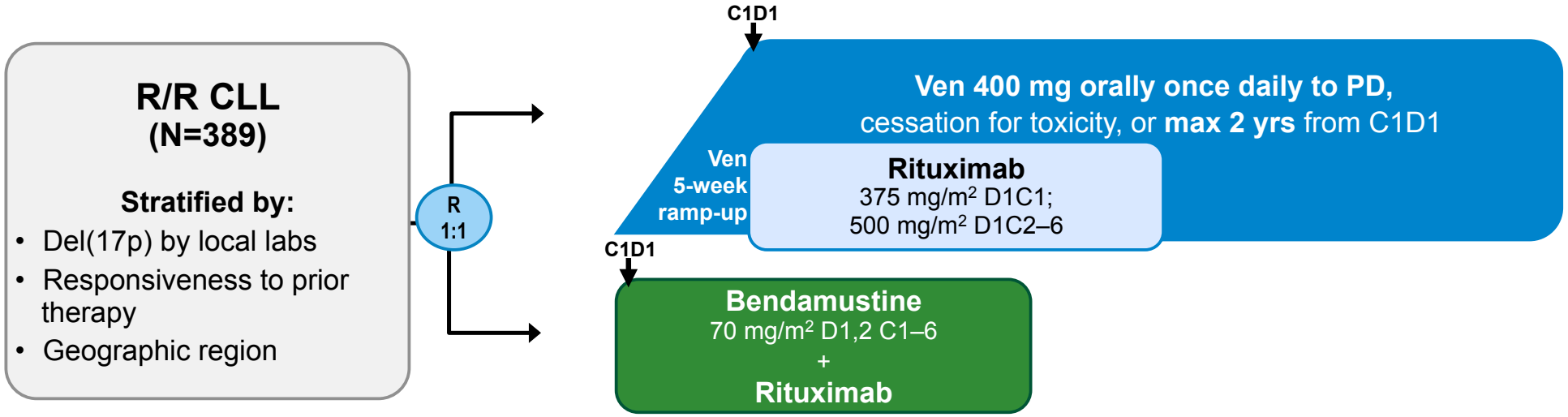
Courtesy of Jennifer Woyach, MD

The James

The Ohio State University Comprehensive Cancer Center

Phase 3 MURANO Study 5 Year Follow-Up

MURANO study design



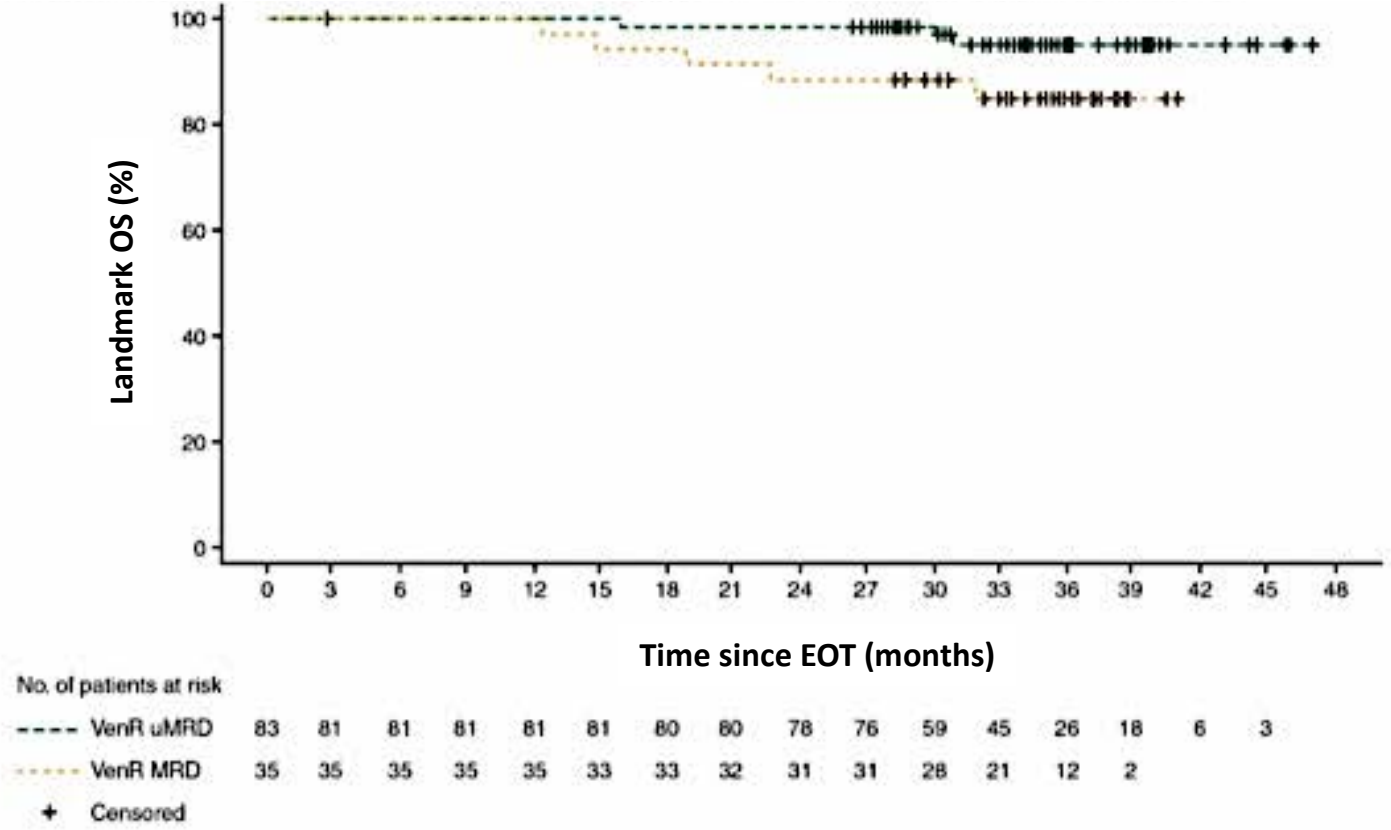
- Primary endpoint: investigator-assessed PFS; secondary endpoints include rate of undetectable MRD (uMRD)

Kater et al, ASH 2020

Courtesy of Jennifer Woyach, MD

Phase 3 MURANO Study 5 Year Follow-Up

Figure 1: Landmark OS by PB MRD status in pts that completed Ven Tx without PD.



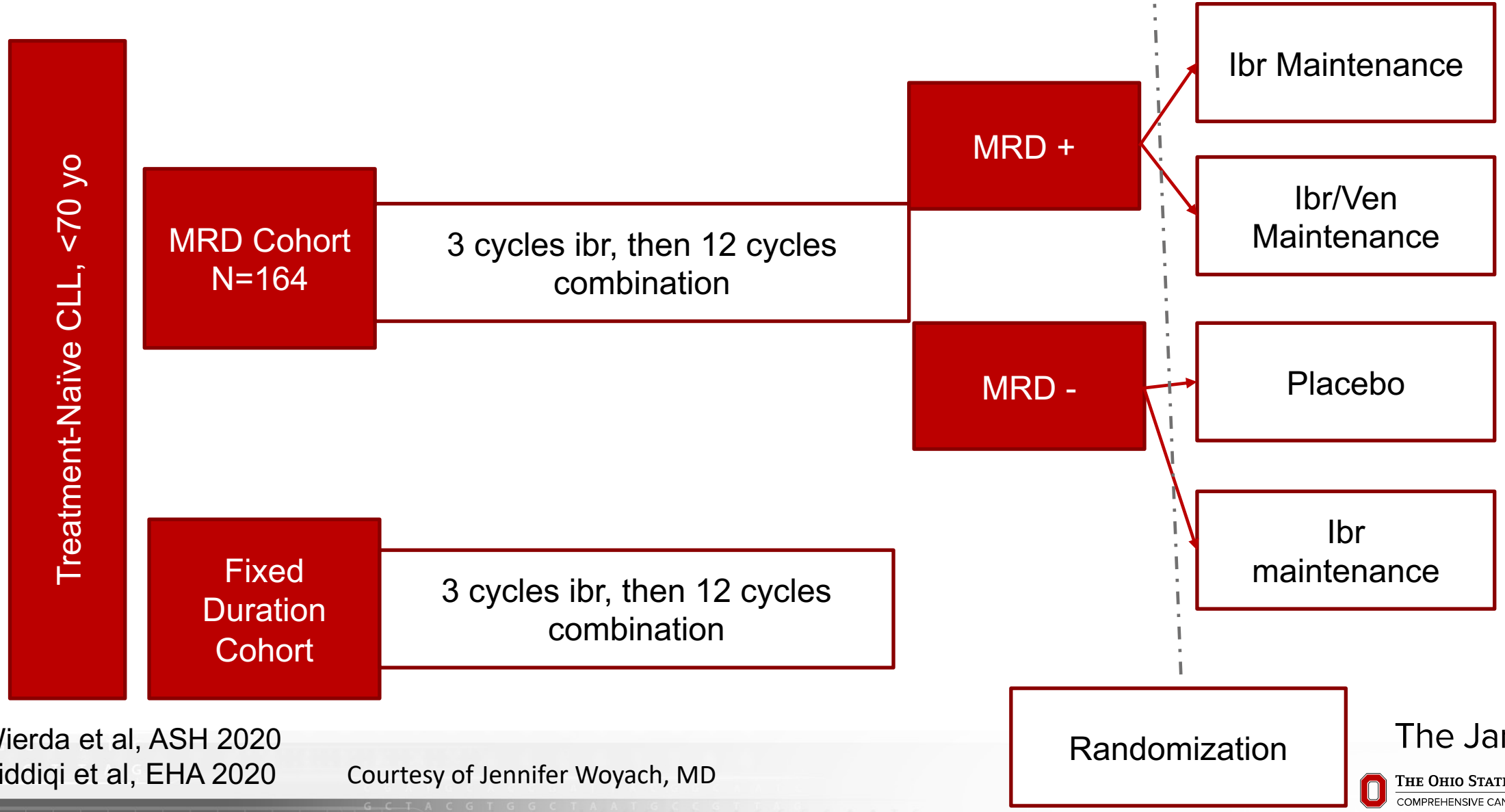
EOT, end of treatment; MRD, minimal residual disease; OS, overall survival; PB, peripheral blood; PD, progressive disease; pts, patients; Tx, therapy; uMRD, undetectable minimal residual disease; Ven, venetoclax.

- Median PFS for VenR 53.6 months
- 5 year OS 82%
- Of 83 pts with uMRD at EOT, 38.5% remained uMRD. Unmutated IGHV and del17p were risk factors
- 25 months was average time from MRD conversion to requirement for therapy

Kater et al, ASH 2020

Courtesy of Jennifer Woyach, MD

Phase 2 CAPTIVATE MRD Cohort

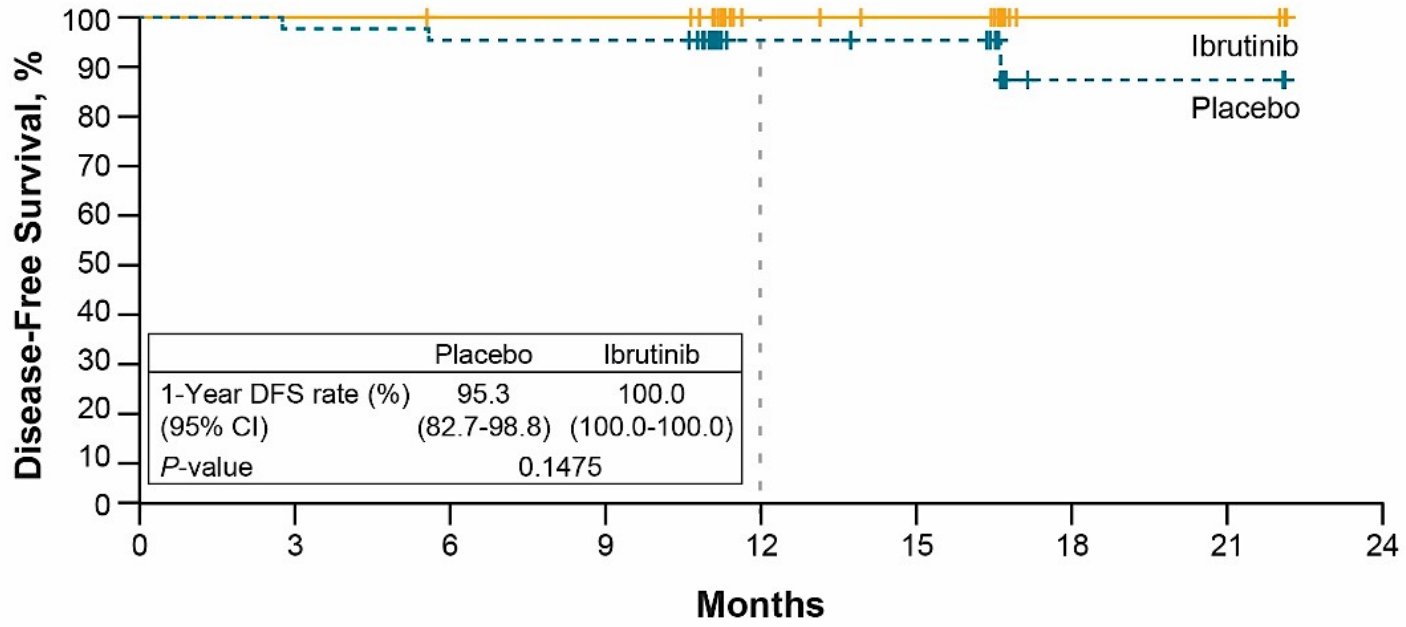


Wierda et al, ASH 2020
Siddiqi et al, EHA 2020

Courtesy of Jennifer Woyach, MD

Phase 2 CAPTIVATE MRD Cohort

Figure. DFS by Randomized Treatment Arm in Confirmed uMRD Group[a]



Patients at Risk

Placebo	43	42	41	41	22	21	3	3	0
Ibrutinib	43	43	42	42	25	23	5	5	0

[a]The 3 DFS events in placebo arm were disease progression in 2 patients and MRD relapse in 1 patient.

- Confirmed uMRD 30 month PFS
  - 95.3% placebo
  - 100% ibrutinib
- Without confirmed uMRD 30 month PFS
  - 95.2% ibrutinib
  - 96.7% ibr/ven

Courtesy of Jennifer Woyach, MD

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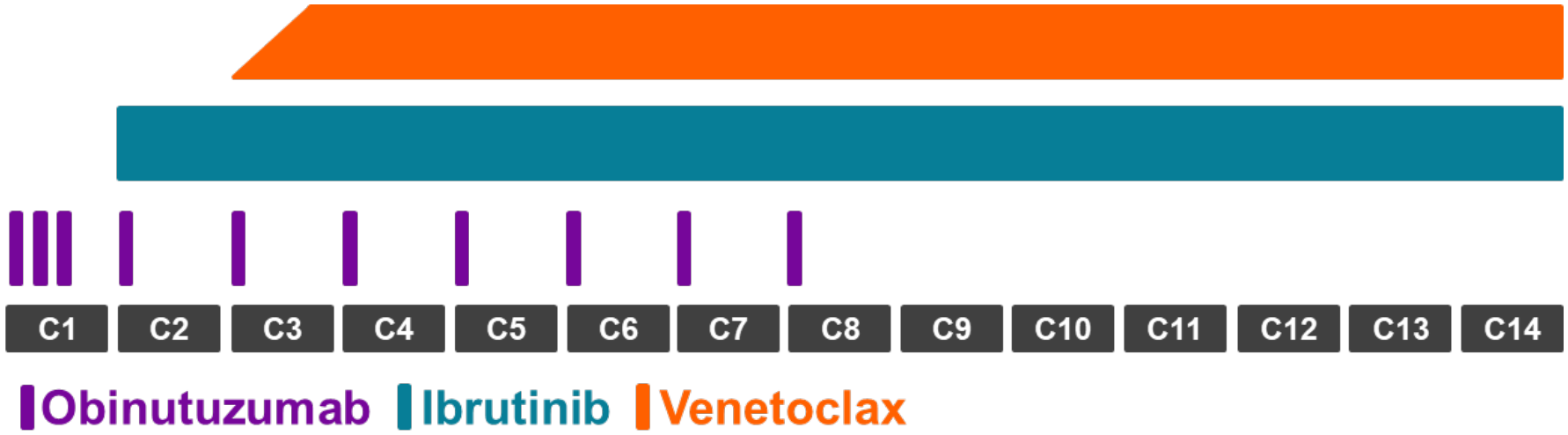
Comprehensive Cancer Center

Phase 2 Ibrutinib/Venetoclax/Obinutuzumab 3 year follow-up

- Phase 2 study of 1 year fixed duration ibr/ven/obin
- 25 treatment-naïve and 25 relapsed/refractory patients



Rogers et al, J Clin Oncol 2020

Courtesy of Jennifer Woyach, MD

Phase 2 Ibrutinib/Venetoclax/Obinutuzumab 3 year follow-up

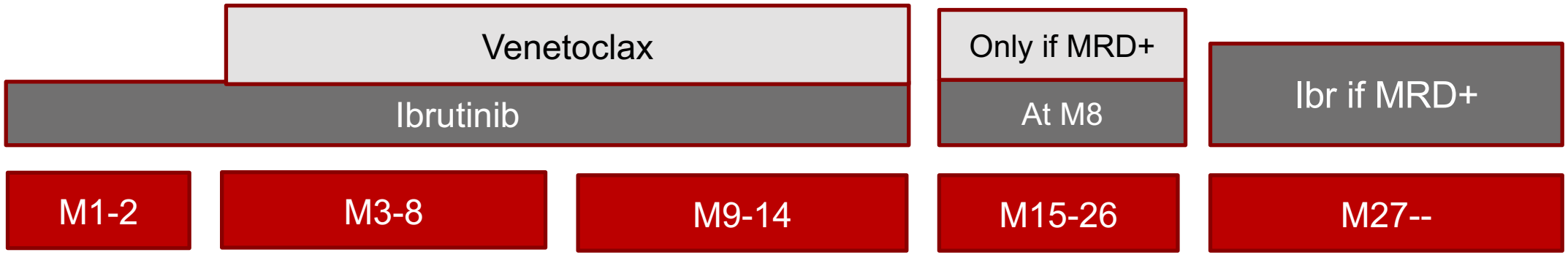
- 67% of TN and 50% RR patients developed uMRD in blood and marrow
- At approximately 2 years post-completion of therapy, one patient in TN cohort died of infection, and one in RR cohort relapsed
- T and NK cells remain suppressed 1 year after completion of therapy

Rogers et al, J Clin Oncol 2020

Courtesy of Jennifer Woyach, MD

Phase 2 CLARITY Trial

- 50 patients with relapsed/refractory CLL
- MRD in blood/marrow determined duration of therapy



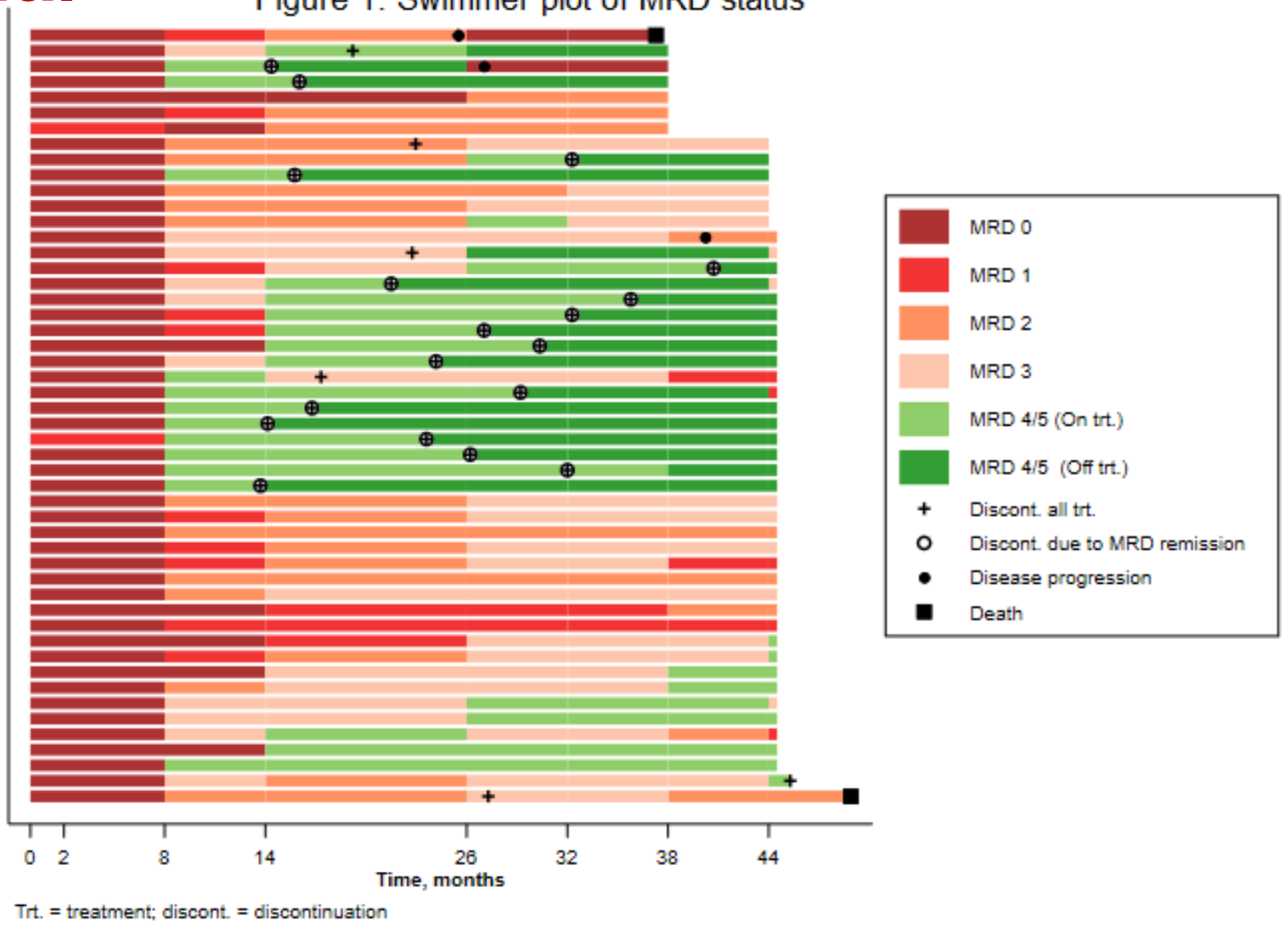
Hillmen et al, J Clin Oncol 2019
Hillmen et al, ASH 2020

Courtesy of Jennifer Woyach, MD

Phase 2 CLARITY Trial

- 4 patients discontinued ibr in first 8 weeks and were replaced
- 23 pts stopped both treatments at or before M38, 17/23 were in uMRD4
- 40% achieved uMRD at month 14 and 48% at M26

Figure 1: Swimmer plot of MRD status



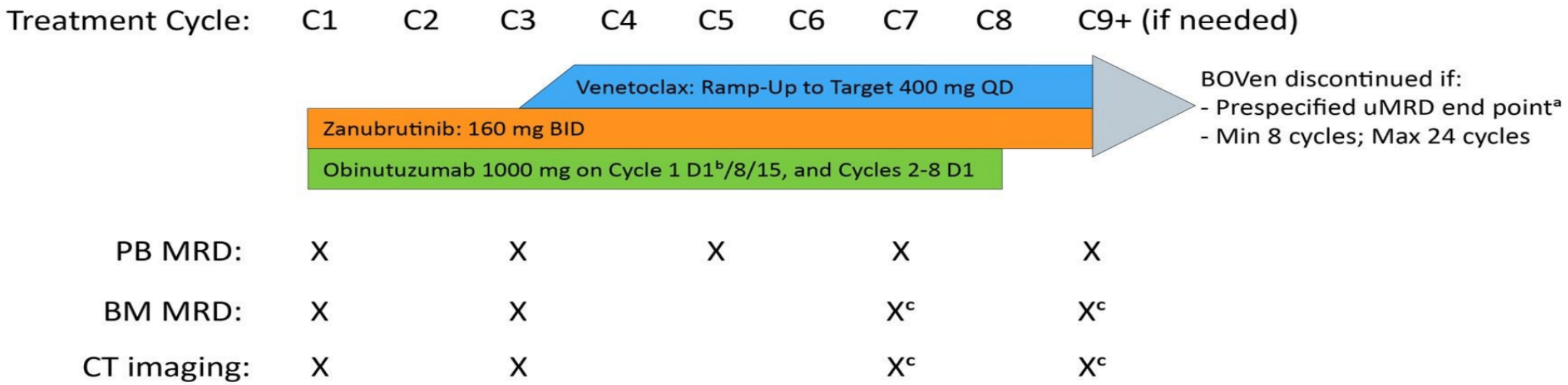
Trt. = treatment; discont. = discontinuation

Hillmen et al, J Clin Oncol 2019
Hillmen et al, ASH 2020

Courtesy of Jennifer Woyach, MD

Phase 2 BOVen in TN CLL

- 39 patients
- 72% high or very-high CLL-IPI



a- Once peripheral blood (PB) uMRD is determined and confirmed in bone marrow (BM), patients complete 2 additional cycles followed by confirmatory MRD peripheral blood testing; if PB uMRD x 2 and BM uMRD x 1, therapy is discontinued.
b- Obinutuzumab split over days 1-2 of cycle 1 if ALC >25,000.
c- BM biopsy obtained at Screening and C3D1; thereafter BM is only obtained if PB-uMRD.
CT imaging obtained at Screening, C3D1, C7D1, EOT, then every 6 months during post-treatment surveillance.

Soumerai et al, ASH 2020

Courtesy of Jennifer Woyach, MD

Phase 2 BOVen in TN CLL

- Median follow-up 14 months
  - 92% have achieved uMRD in peripheral blood and 84% in marrow
  - Median time to BM uMRD is 6 months
  - 77% of patients discontinued therapy at median 10 months
  - No recurrent MRD or progression has been observed

Soumerai et al, ASH 2020

Courtesy of Jennifer Woyach, MD

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

1. Continue treatment
2. Discontinue treatment

Agenda

Module 1: BTK Inhibitors

Module 2: Bcl-2 Inhibitors

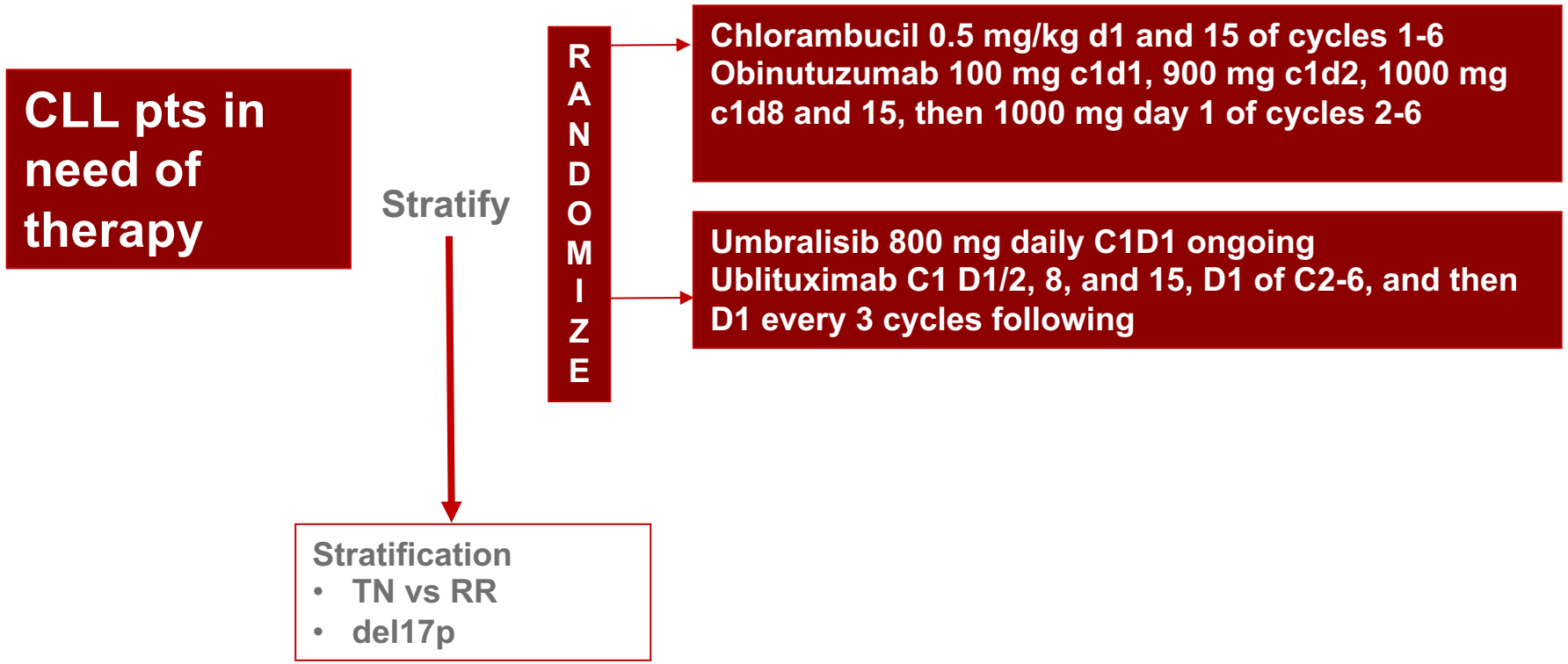
Module 3: Novel Strategies – U2 Regimen (Umbralisib, Ublituximab), CAR T-Cell Therapy

Module 3: Novel Strategies – U2 Regimen (Umbralisib, Ublituximab), CAR T-Cell Therapy

- **Key Relevant Data Sets**
  - UNITY-CLL: Umbralisib + ublituximab (U2)
  - TRANSCEND CLL 004: Lisocabtagene maraleucel (liso-cel) + ibrutinib

Phase 3 UNITY-CLL Study

- 421 total patients
- 57% TN
- 56% IGHV unmutated
- 10% del17p



Gribben et al, ASH 2020 Abstract 543

Courtesy of Jennifer Woyach, MD

Phase 3 UNITY-CLL Study

- Median follow-up 36 months
- Median PFS U2 31.9 mo vs 17.9 mo overall
- In TN, U2 PFS 38.5 mo vs 26.1 mo
- In RR, U2 PFS 19.5 mo vs 12.9 mo
- G3+ Colitis in 3.4%, Transaminitis G3+ in 8.3%, G3+ pneumonitis in 2.9%

Courtesy of Jennifer Woyach, MD

Phase 1 TRANSCEND CLL 004 Study: Liso-Cel Plus Ibrutinib

- Liso-Cel is 4-1BB CAR-T product with equal CD4/CD8
- In this cohort patients had to have previously received ibrutinib, reinitiated or continued at study start and continued at least 90 days post CAR-T
- Lymphodepletion with Flu/Cy

Wierda et al, ASH 2020 Abstract 544

Courtesy of Jennifer Woyach, MD

Phase 1 TRANSCEND CLL 004 Study: Liso-Cel Plus Ibrutinib

- 19 patients included
- Median 4 prior therapies
- 74% had BTKi as last therapy and 53% had also received venetoclax
- 74% CRS, 1 grade 3; 16% G3+ neurologic events
- ORR 95%, 47% CR/CRi
- 83% maintained response at 3 months
- 79% had uMRD in marrow

Wierda et al, ASH 2020 Abstract 544

Courtesy of Jennifer Woyach, MD

Phase 1 TRANSCEND CLL 004 Study: Liso-cel monotherapy

- Study schema same as previous, but without ibrutinib
- 23 pts evaluable for safety, 22 for efficacy
- Median 6 prior therapies, all with prior ibr and 48% with ven too
- ORR 82%, CR/CRi 45%
- Median PFS 18 months, 5/8 progressions were RT
- G3+ CRS 9%, G3+ neuro events 22%

Siddiqi et al, ASH 2020 Abstract 546

Courtesy of Jennifer Woyach, MD

Meet The Professor
Management of Ovarian Cancer

Friday, January 22, 2021
1:15 PM – 2:15 PM ET

Faculty

Professor Jonathan A Ledermann, MD

Moderator

Neil Love, MD

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Thank you for joining us!

CME and MOC credit information will be emailed to each participant within 5 business days.

RTP Year in Review 2020