What I Tell My Patients:
New Treatments and Clinical Trial Options

An NCPD Hybrid Symposium Series
Held During the 47th Annual ONS Congress

Chronic Lymphocytic Leukemia

Friday, April 29, 2022
12:15 PM – 1:45 PM PT

Faculty

Lesley Camille Ballance, MSN, FNP-BC
Amy Goodrich, CRNP
Lowell L Hart, MD
Anthony R Mato, MD, MSCE

Moderator

Neil Love, MD

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Faculty

Lesley Camille Ballance, MSN, FNP-BC
Sarah Cannon Center for Blood Cancer
Tennessee Oncology
Nashville, Tennessee

Amy Goodrich, CRNP
Nurse Practitioner
The Sidney Kimmel Comprehensive Cancer Center
Johns Hopkins Medicine
Baltimore, Maryland

Lowell L Hart, MD
Scientific Director of Clinical Research
Florida Cancer Specialists and Research Institute
Fort Myers, Florida
Associate Professor of Internal Medicine, Hematology and Oncology
Wake Forest University School of Medicine
Winston-Salem, North Carolina

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

Moderator

Neil Love, MD
Research To Practice
Miami, Florida

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Ms Ballance — Disclosures

Consulting Agreement	AbbVie Inc
Speakers Bureau	AbbVie Inc, AstraZeneca Pharmaceuticals LP, Seagen Inc

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Ms Goodrich — Disclosures

No relevant conflicts of interest to disclose

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Dr Hart — Disclosures

Advisory Committee	Boehringer Ingelheim Pharmaceuticals Inc, G1 Therapeutics Inc, Novartis
Speakers Bureau	Circulogene

Dr Mato — Disclosures

Consultant and/or Advisor	AbbVie Inc, Acerta Pharma — A member of the AstraZeneca Group, Adaptive Biotechnologies Corporation, Celgene Corporation, DTRM Biopharma Co Ltd, Genentech, a member of the Roche Group, Genmab, Johnson & Johnson Services Inc, Nurix Therapeutics Inc, Octapharma Plasma, Pharmacyclics LLC, an AbbVie Company, Sunesis Pharmaceuticals Inc, TG Therapeutics Inc, Verastem Inc
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Commercial Support

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Research To Practice CME Planning Committee Members, Staff and Reviewers

Planners, scientific staff and independent reviewers for Research To Practice have no relevant conflicts of interest to disclose.

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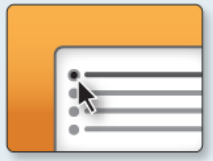
Clinicians in the Meeting Room

Networked iPads are available.

Review Program Slides: Tap the Program Slides button to review speaker presentations and other program content.



Answer Survey Questions: Complete the premeeting survey before the meeting. Survey results will be presented and discussed throughout the meeting.

Ask a Question: Tap Ask a Question to submit a challenging case or question for discussion. We will aim to address as many questions as possible during the program.

Complete Your Evaluation: Tap the CME Evaluation button to complete your evaluation electronically to receive credit for your participation.

For assistance, please raise your hand. Devices will be collected at the conclusion of the activity.

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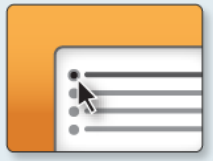
Clinicians Attending via Zoom

Review Program Slides: A link to the program slides will be posted in the chat room at the start of the program.



Answer Survey Questions: Complete the premeeting survey before the meeting. Survey results will be presented and discussed throughout the meeting.

Ask a Question: Submit a challenging case or question for discussion using the Zoom chat room.

Get CME Credit: A CME credit link will be provided in the chat room at the conclusion of the program.

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About the Enduring Program

- The live meeting is being video and audio recorded.
- The proceedings from today will be edited and developed into an enduring web-based video/PowerPoint program.
  An email will be sent to all attendees when the activity is available.
- To learn more about our education programs, visit our website, **www.ResearchToPractice.com**

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"What I Tell My Patients"
14th Annual RTP-ONS NCPD Symposium Series
ONS Congress, Anaheim, California — April 27 - May 1, 2022

Thursday April 28	**Prostate Cancer** 6:00 AM – 7:30 AM PT (9:00 AM – 10:30 AM ET)
	Ovarian Cancer 12:15 PM – 1:45 PM PT (3:15 PM – 4:45 PM ET)
	Non–Small Cell Lung Cancer 6:00 PM – 8:00 PM PT (9:00 PM – 11:00 PM ET)
	Hepatobiliary Cancers 8:20 PM – 9:20 PM PT (11:20 PM – 12:20 AM ET)
Friday April 29	**Small Cell Lung Cancer** 6:00 AM – 7:30 AM PT (9:00 AM – 10:30 AM ET)
	Chronic Lymphocytic Leukemia 12:15 PM – 1:45 PM PT (3:15 PM – 4:45 PM ET)
	Breast Cancer 6:00 PM – 8:00 PM PT (9:00 PM – 11:00 PM ET)
	Acute Myeloid Leukemia and Myelodysplastic Syndromes 8:20 PM – 9:20 PM PT (11:20 PM – 12:20 AM ET)
Saturday April 30	**Cervical and Endometrial Cancer** 6:00 AM – 7:30 AM PT (9:00 AM – 10:30 AM ET)
	Bladder Cancer 12:15 PM – 1:45 PM PT (3:15 PM – 4:45 PM ET)

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What I Tell My Patients: Expert Insights into Patient Education on New Treatments and Clinical Trial Participation

An NCPD Hybrid Symposium Series Held During the 47th Annual ONS Congress

Prostate Cancer

Thursday, April 28, 2022

6:00 AM – 7:30 AM PT (9:00 AM – 10:30 AM ET)

Faculty

Kathy D Burns, RN, MSN, AGACNP-BC, OCN
Robert Dreicer, MD, MS
Sandy Srinivas, MD
Ronald Stein, JD, MSN, NP-C, AOCNP

Non-Small Cell Lung Cancer

Thursday, April 28, 2022

6:00 PM – 8:00 PM PT (9:00 PM – 11:00 PM ET)

Faculty

Edward B Garon, MD, MS
Kelly EH Goodwin, MSN, RN, ANP-BC
Tara Plues, APRN, MSN
Anne S Tsao, MD, MBA

Ovarian Cancer

Thursday, April 28, 2022

12:15 PM – 1:45 PM PT (3:15 PM – 4:45 PM ET)

Faculty

Jennifer Filipi, MSN, NP
Kathleen N Moore, MD, MS
Krishnansu S Tewari, MD
Deborah Wright, MSN, APRN, AGCNS-BC

Hepatobiliary Cancers

Thursday, April 28, 2022

8:20 PM – 9:20 PM PT (11:20 PM – 12:20 AM ET)

Faculty

Richard S Finn, MD
Amanda K Wagner, APRN-CNP, AOCNP

What I Tell My Patients: Expert Insights into Patient Education on New Treatments and Clinical Trial Participation

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Small Cell Lung Cancer

Friday, April 29, 2022

6:00 AM – 7:30 AM PT (9:00 AM – 10:30 AM ET)

Faculty

Marianne J Davies, DNP, MSN, RN, APRN
Matthew Gubens, MD, MS
Lowell L Hart, MD
Chaely J Medley, MSN, AGNP

Breast Cancer

Friday, April 29, 2022

6:00 PM – 8:00 PM PT (9:00 PM – 11:00 PM ET)

Faculty

Jamie Carroll, APRN, MSN, CNP
Sara A Hurvitz, MD
Kelly Leonard, MSN, FNP-BC
Hope S Rugo, MD

Chronic Lymphocytic Leukemia

Friday, April 29, 2022

12:15 PM – 1:45 PM PT (3:15 PM – 4:45 PM ET)

Faculty

Lesley Camille Ballance, MSN, FNP-BC
Amy Goodrich, CRNP
Lowell L Hart, MD
Anthony R Mato, MD, MSCE

Acute Myeloid Leukemia and Myelodysplastic Syndromes

Friday, April 29, 2022

8:20 PM – 9:20 PM PT (11:20 PM – 12:20 AM ET)

Faculty

Ilene Galinsky, NP
Eunice S Wang, MD

What I Tell My Patients: Expert Insights into Patient Education on New Treatments and Clinical Trial Participation

An NCPD Hybrid Symposium Series Held During the 47th Annual ONS Congress

Cervical and Endometrial Cancer

Saturday, April 30, 2022
6:00 AM – 7:30 AM PT (9:00 AM – 10:30 AM ET)

Faculty
Paula J Anastasia, MN, RN, AOCN
Robert L Coleman, MD
David M O'Malley, MD
Jaclyn Shaver, MS, APRN, CNP, WHNP

Bladder Cancer

Saturday, April 30, 2022
12:15 PM – 1:45 PM PT (3:15 PM – 4:45 PM ET)

Faculty
Monica Averia, MSN, AOCNP, NP-C
Shilpa Gupta, MD
Brenda Martone, MSN, NP-BC, AOCNP
Sumanta Kumar Pal, MD

Join Us After ONS for Our Series Continuation

What I Tell My Patients —
A 2-Part NCPD Webinar Series

Hodgkin and Non-Hodgkin Lymphomas

Date and time to be announced

Gastroesophageal Cancers

Wednesday, May 18, 2022

5:00 PM – 6:00 PM ET

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How was it different to take care of this patient versus another patient in the same oncologic setting?

What unique biopsychosocial factors (eg, attitude, comorbidities, social support) were considered in the overall management of this case?

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I feel very satisfied with my work.

1. Never
2. A few times per year
3. Once a month
4. A few times per month
5. Once a week
6. A few times per week
7. Every day

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Faculty

Lesley Camille Ballance, MSN, FNP-BC
Sarah Cannon Center for Blood Cancer
Tennessee Oncology
Nashville, Tennessee

Amy Goodrich, CRNP
Nurse Practitioner
The Sidney Kimmel Comprehensive Cancer Center
Johns Hopkins Medicine
Baltimore, Maryland

Lowell L Hart, MD
Scientific Director of Clinical Research
Florida Cancer Specialists and Research Institute
Fort Myers, Florida
Associate Professor of Internal Medicine, Hematology and Oncology
Wake Forest University School of Medicine
Winston-Salem, North Carolina

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

Moderator

Neil Love, MD
Research To Practice
Miami, Florida

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RTP RESEARCH TO PRACTICE

Agenda

Module 1 – Overview of CLL

Module 2 – Bruton Tyrosine Kinase Inhibitors

Module 3 – Venetoclax and Anti-CD20 Antibody Therapy

Module 4 – Future Strategies

Agenda

Module 1 – Overview of CLL

Module 2 – Bruton Tyrosine Kinase Inhibitors

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Module 4 – Future Strategies

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SELF-ASSESSMENT QUIZ

Patients with newly diagnosed chronic lymphocytic leukemia (CLL) who feel well and are asymptomatic require treatment if…

1. Del(17p)/TP53 mutation is detected
2. White blood cell count exceeds 200,000 mm^3
3. Both 1 and 2
4. Neither 1 nor 2
5. I don’t know

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SELF-ASSESSMENT QUIZ

Patients with CLL and which of the following prognostic factors generally do not respond well to chemoimmunotherapy?

1. Del(17p)
2. TP53 mutation
3. IGHV mutation
4. All of the above
5. Del(17p) or TP53 mutation only
6. TP53 or IGHV mutations only
7. Del(17p) or IGHV mutation only
8. I don’t know

SELF-ASSESSMENT QUIZ

Which of the following patients with CLL should receive the Evusheld antibody?

1. All patients, including those on observation
2. All patients receiving active treatment for CLL
3. Both 1 and 2
4. Neither 1 nor 2
5. I don’t know

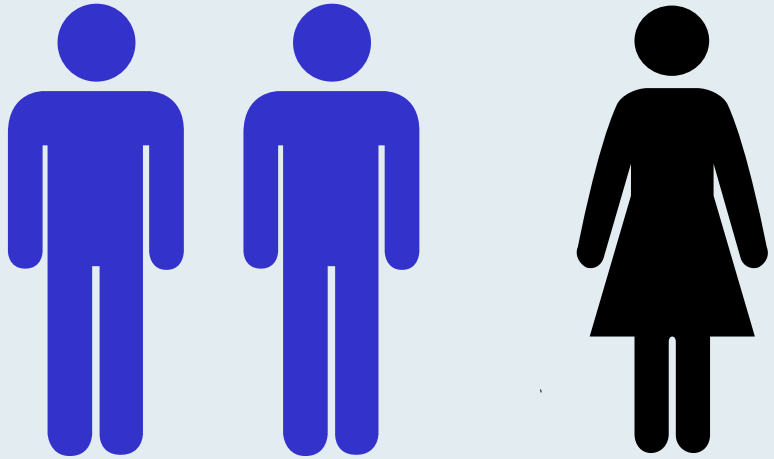
CLL Impacts a Significant Number of Patients Worldwide, Predominantly Affecting Older Patients

With an estimated 191,000 new cases globally, CLL represents 22% to 30% of all leukemia worldwide, being the most common leukemia in Western countries[1,2]

Median age at diagnosis[3]:

~90% of patients diagnosed with CLL are >55 years old[4]

Men are ~2X more likely to develop CLL[5]



1. Union for International Cancer Control. https://www.who.int/selection_medicines/committees/expert/20/applications/CLL.pdf. Accessed November 6, 2019. 2. Combest AJ, et al. *J Hematol Oncol Pharm*. 2016;6(2):54-56. 3. Eichhorst B, et al. *Ann Oncol*. 2015;26(suppl 5):v78-v84. 4. Lymphoma Coalition. https://lymphomacoalition.org/images/subtype-reports/CLL_Europe _2017_Report.pdf. Accessed November 6, 2019. 5. Scarfò L, et al. *Crit Rev Oncol Hematol*. 2016;104:169-182.

Courtesy of John M Pagel, MD, PhD

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Indications for treatment:

- Disease-related symptoms
  - Fatigue can by tricky
- Progressive bulky disease
  - spleen > 6 cm below costal margin; LN > 10 cm
- Progressive bone marrow failure, manifesting as anemia or thrombocytopenia
- Autoimmune complications poorly responsive to steroids
- Progressive lymphocytosis: Lymphocyte doubling time < 6 months, or increase in ≥ 50% in a two-month period

*Note: Absolute lymphocyte count alone not an indication for treatment

Courtesy of Brad S Kahl, MD

Potential clinical manifestions of CLL

1. None
2. Marrow failure syndrome
    1. Anemia, Thrombocytopenia
3. Autoimmune cytopenias
    1. Anemia, thrombocytopenia, neutropenia
4. Immunodeficiency (low Ig levels)
    1. Recurrent infections
5. Symptoms
    1. Fatigue, night sweats, weight loss, fevers, pain

Courtesy of Brad S Kahl, MD

CLL special consideration

- High frequency of AI complications
  - ITP, AIHA, neutropenia
- High frequency of infections
  - Check Ig levels
  - Consider IVIg replacement therapy if recurrent infections and IgG < 300
- High rate of skin cancer
  - Low threshold to send to Dermatology

Courtesy of Brad S Kahl, MD

Questions — Lowell L Hart, MD

Patients with abnormal routine CBC found to have CLL

- **How is it determined whether therapy should be initiated, and how do patients react to the idea of “watch and wait”?**

Questions — Lesley Camille Ballance, MSN, FNP-BC

CLL and COVID-19

- **How has COVID-19 impacted your clinical management of chronic lymphocytic leukemia?**
- **What are some of the psychosocial issues that arise in this situation?**

Commentary — Lesley Camille Ballance, MSN, FNP-BC

CLL and COVID-19

CLL Management

- Infection risk and mortality rate
- Vaccine timing
- Treatment decisions
- Comorbidities
- Example: 51-year-old male with CLL on 2nd line treatment w/ Venetoclax and Obinutuzumab in early February 2020

Psychosocial Issues

- Social distancing
- Isolation
- Increased anxiety and depression
- Personal beliefs about vaccines
- Family and friends' COVID beliefs and practices

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Agenda

Module 1 – Overview of CLL

Module 2 – Bruton Tyrosine Kinase Inhibitors

Module 3 – Venetoclax and Anti-CD20 Antibody Therapy

Module 4 – Future Strategies

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SELF-ASSESSMENT QUIZ

Ibrutinib…

1. Often initially increases white blood cell count in patients with CLL
2. Results in significant objective responses in most patients with CLL
3. Generally does not result in a complete clinical response in patients with CLL
4. All of the above
5. None of the above
6. I don’t know

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SELF-ASSESSMENT QUIZ

Ibrutinib should be temporarily discontinued for patients scheduled to undergo surgical procedures.

1. Agree
2. Disagree
3. I don’t know

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SELF-ASSESSMENT QUIZ

A new preparation of acalabrutinib has been reported, which will allow patients to receive acalabrutinib concurrently with….

1. Corticosteroids
2. Proton pump inhibitors
3. CYP3A inhibitors
4. I don’t know

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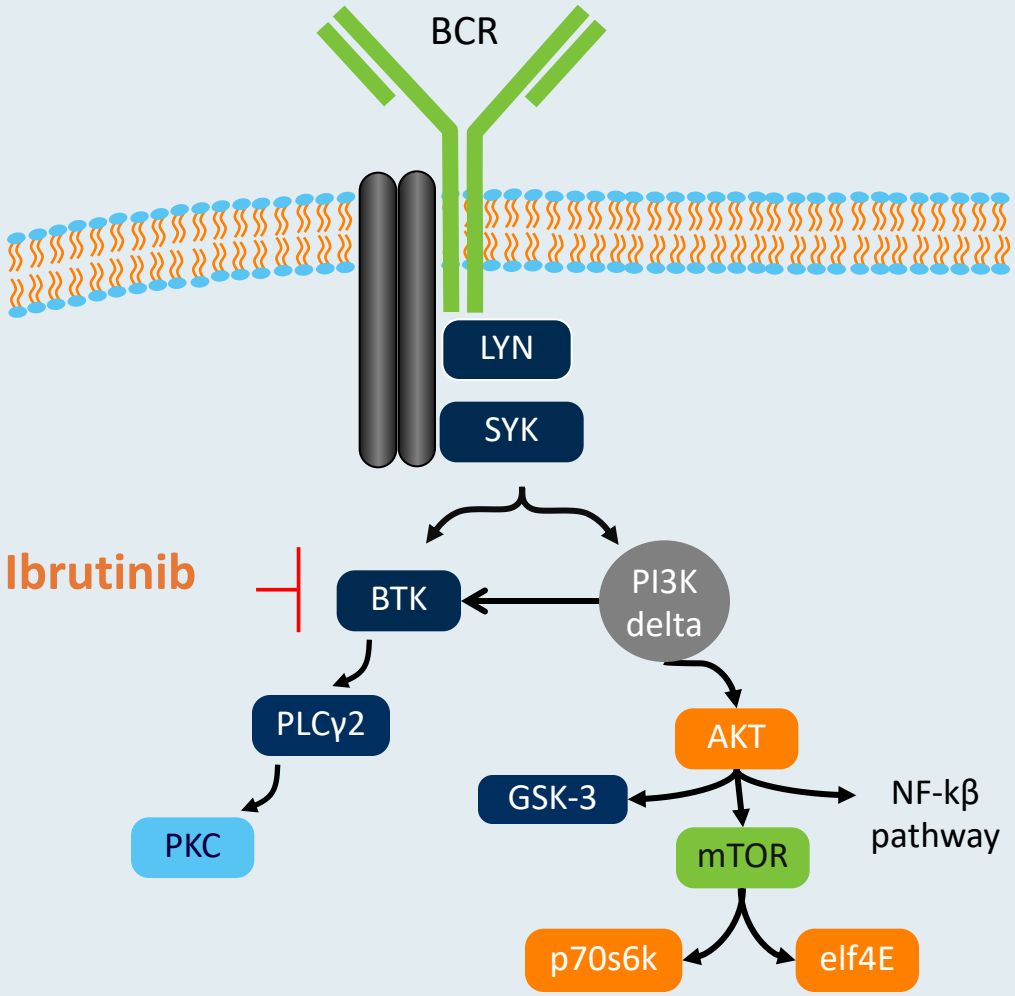
SELF-ASSESSMENT QUIZ

Which of the following cardiac issues has been reported in patients with CLL receiving BTK (Bruton tyrosine kinase) inhibitors?

1. Atrial fibrillation
2. Ventricular arrhythmias
3. Both 1 and 2
4. Neither 1 nor 2
5. I don’t know

Mechanism of Action of Ibrutinib



Woyach JA et al. *Blood* 2012;120(6):1175-84.

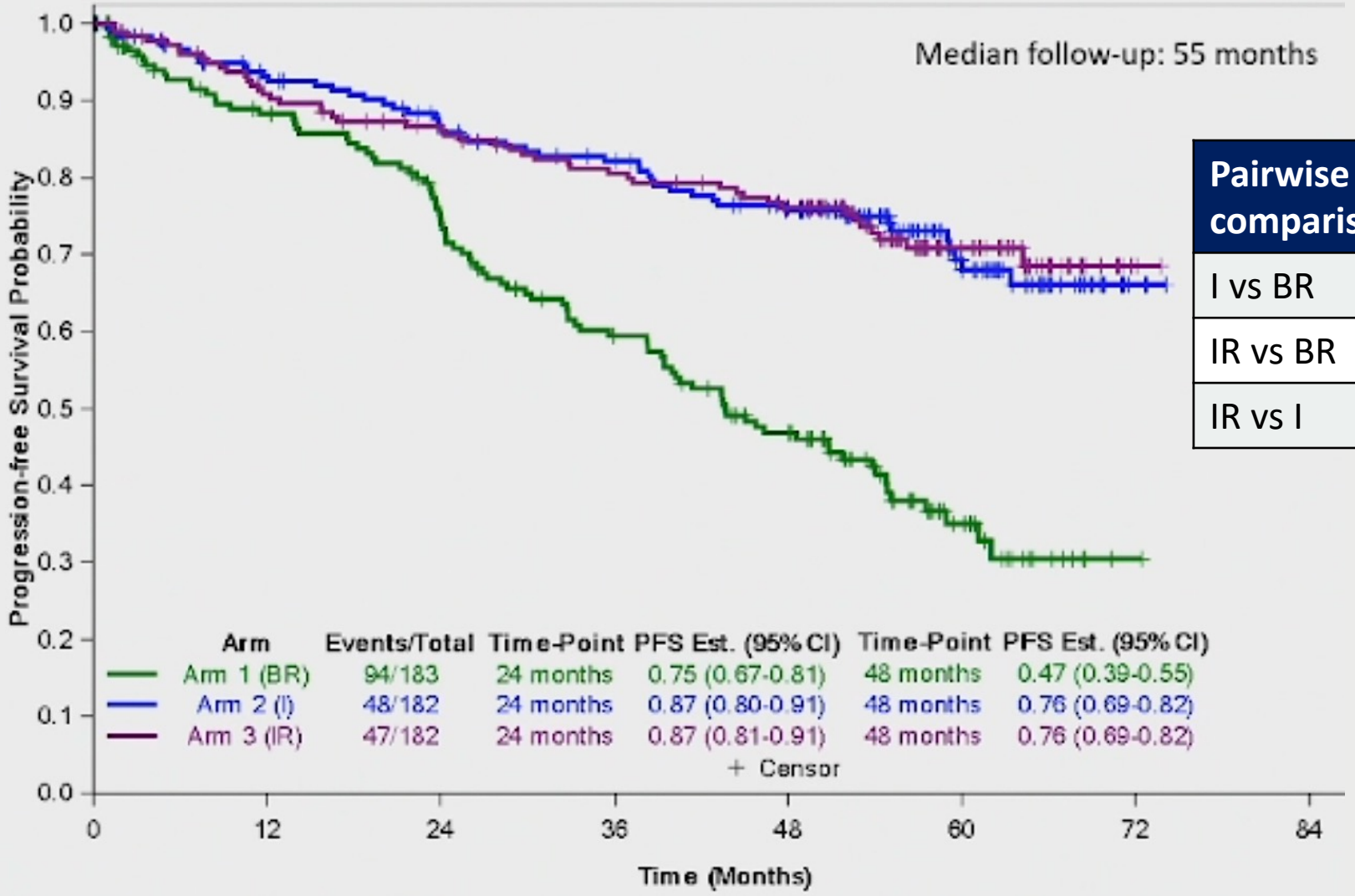
Long-Term Results of Alliance A041202 Show Continued Advantage of Ibrutinib-Based Regimens Compared with Bendamustine Plus Rituximab (BR) Chemoimmunotherapy

Woyach JA et al.

ASH 2021;Abstract 639.

Alliance A041202: First-Line Ibrutinib-Based Regimens versus Bendamustine and Rituximab (BR)

Progression-Free Survival



Pairwise comparisons	Hazard ratio	*p*-value
I vs BR	0.36	<0.0001
IR vs BR	0.36	<0.001
IR vs I	0.99	0.96

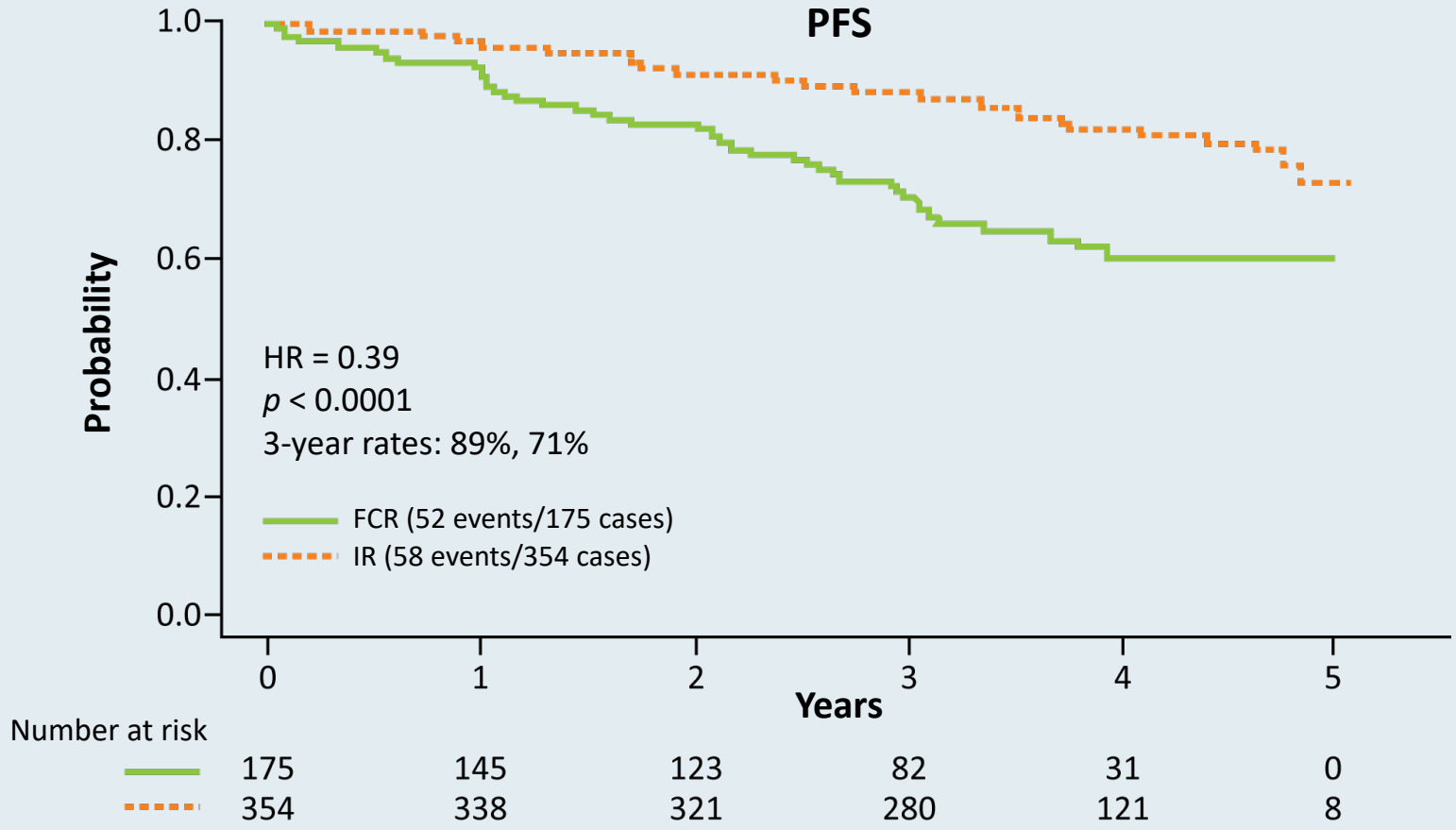
Woyach JA et al. ASH 2021;Abstract 639.

Ibrutinib and Rituximab Provides Superior Clinical Outcome Compared to FCR in Younger Patients with Chronic Lymphocytic Leukemia (CLL): Extended Follow-Up from the E1912 Trial

Shanafelt TD et al.

ASH 2019;Abstract 33.

ECOG-ACRIN E1912 Extended Follow-Up: Up-Front Ibrutinib/Rituximab (IR) Compared to Fludarabine/ Cyclophosphamide/Rituximab (FCR) for Younger Patients with CLL



- Grade ≥3 treatment-related adverse events were reported in 70% of patients receiving IR and 80% of patients receiving FCR (odds ratio = 0.56; $p = 0.013$).
- Among the 95 patients who discontinued ibrutinib, the most common cause was adverse event or complication.

Shanafelt TD et al. ASH 2019;Abstract 33.

CHRONIC LYMPHOCYTIC LEUKEMIA

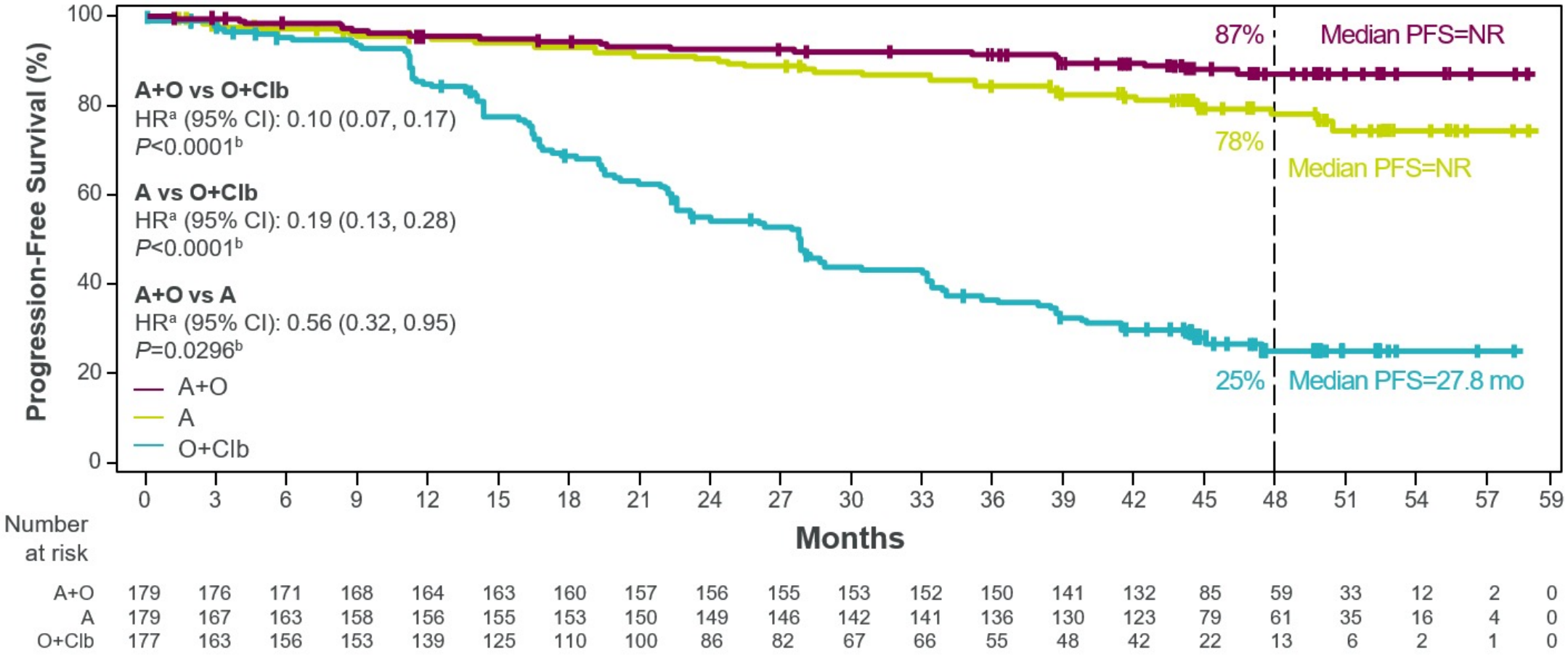
Leukemia 2022;[Online ahead of print].

Efficacy and safety in a 4-year follow-up of the ELEVATE-TN study comparing acalabrutinib with or without obinutuzumab versus obinutuzumab plus chlorambucil in treatment-naïve chronic lymphocytic leukemia

Jeff P. Sharman[1]✉, Miklos Egyed[2], Wojciech Jurczak[3], Alan Skarbnik[4], John M. Pagel[5], Ian W. Flinn[6], Manali Kamdar[7], Talha Munir[8], Renata Walewska[9], Gillian Corbett[10], Laura Maria Fogliatto[11], Yair Herishanu[12], Versha Banerji[13], Steven Coutre[14], George Follows[15], Patricia Walker[16], Karin Karlsson[17], Paolo Ghia[18], Ann Janssens[19], Florence Cymbalista[20], Jennifer A. Woyach[21], Emmanuelle Ferrant[22], William G. Wierda[23], Veerendra Munugalavadla[24], Ting Yu[24], Min Hui Wang[24] and John C. Byrd[21]

ELEVATE-TN: Investigator-Assessed PFS (Overall)

4-Year Follow-Up



Sharman JP et al. *Leukemia* 2022;[Online ahead of print].

RTP RESEARCH TO PRACTICE

original reports

Acalabrutinib Versus Ibrutinib in Previously Treated Chronic Lymphocytic Leukemia: Results of the First Randomized Phase III Trial

John C. Byrd, MD[1]; Peter Hillmen, MD, MBChB, PhD[2]; Paolo Ghia, MD, PhD[3,4]; Arnon P. Kater, MD, PhD[5]; Asher Chanan-Khan, MD[6]; Richard R. Furman, MD[7]; Susan O'Brien, MD[8]; Mustafa Nuri Yenerel, MD[9]; Arpad Illés, MD[10]; Neil Kay, MD[11]; Jose A. Garcia-Marco, MD, PhD[12]; Anthony Mato, MD[13]; Javier Pinilla-Ibarz, MD, PhD[14]; John F. Seymour, PhD[15]; Stephane Lepretre, MD[16,17]; Stephan Stilgenbauer, MD[18]; Tadeusz Robak, PhD[19]; Wayne Rothbaum, MS[20]; Raquel Izumi, PhD[20]; Ahmed Hamdy, MD[20]; Priti Patel, MD[21]; Kara Higgins, MS[21]; Sophia Sohoni, MD[21]; and Wojciech Jurczak, MD, PhD[22]

J Clin Oncol 2021;39(31):3441-52.

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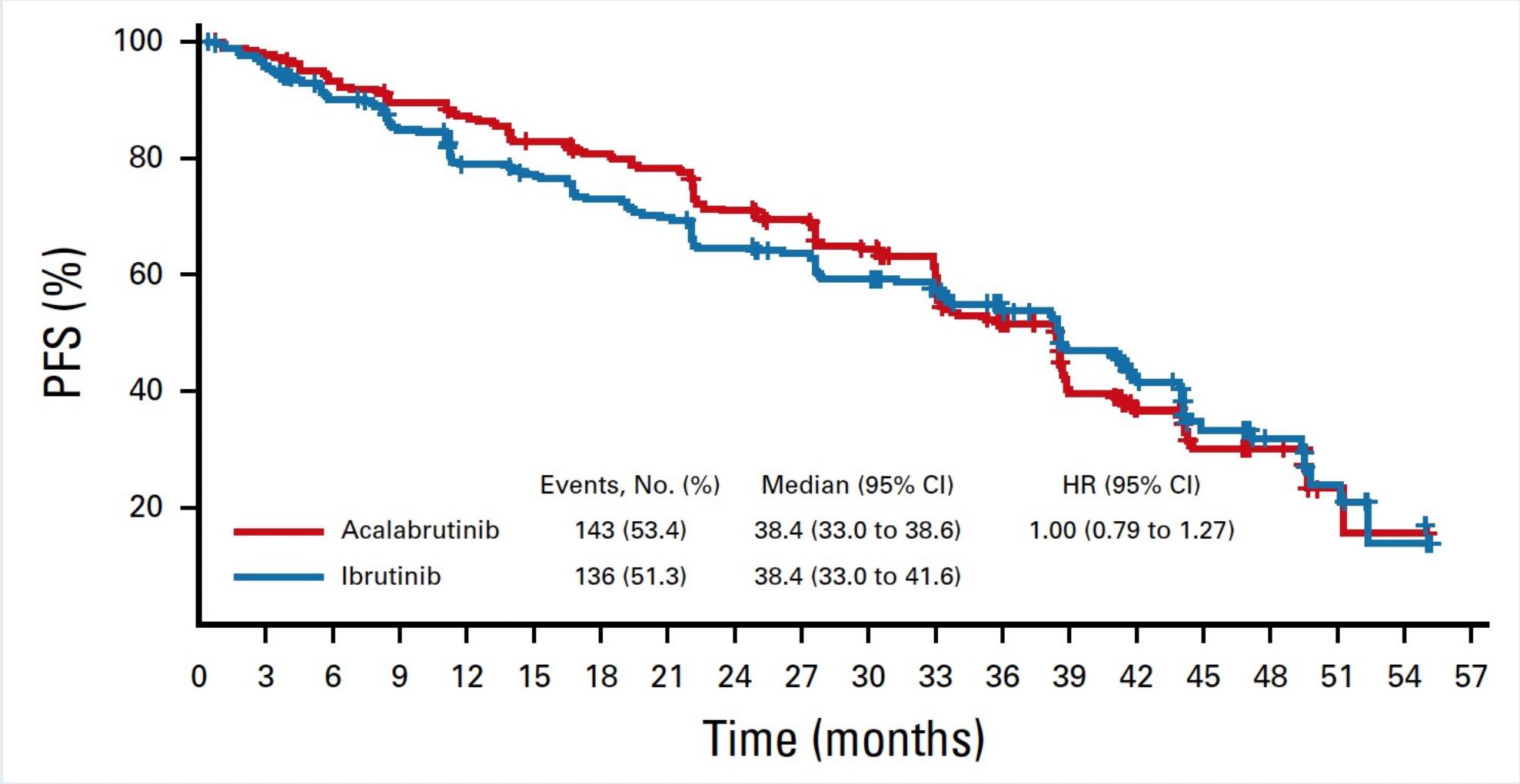
ELEVATE-RR: Acalabrutinib versus Ibrutinib for Relapsed CLL

Independent Review Committee-Assessed Progression-Free Survival (PFS)



Byrd JC et al. *J Clin Oncol* 2021;39(31):3441-52.

New Acalabrutinib Formulation Enables Co-Administration with Proton Pump Inhibitors and Dosing in Patients Unable to Swallow Capsules (ELEVATE-PLUS)

Sharma S et al. ASH 2021;Abstract 4365.

Author Conclusions: Acalabrutinib maleate, administered as a tablet or suspension, is safe and well tolerated. Based on the PK (and associated variability), BTK-TO, and established exposure-efficacy/safety relationship, AMT clinical effect is expected to be comparable to acalabrutinib capsules at the approved 100-mg BID dosing, regardless of use of PPIs and ingestion of food. Additionally, AMT improves swallowing ability given the film coating and a 50% reduced volume compared with the capsule, and can be easily suspended in a small amount of water to allow dosing in patients unable to swallow tablets.

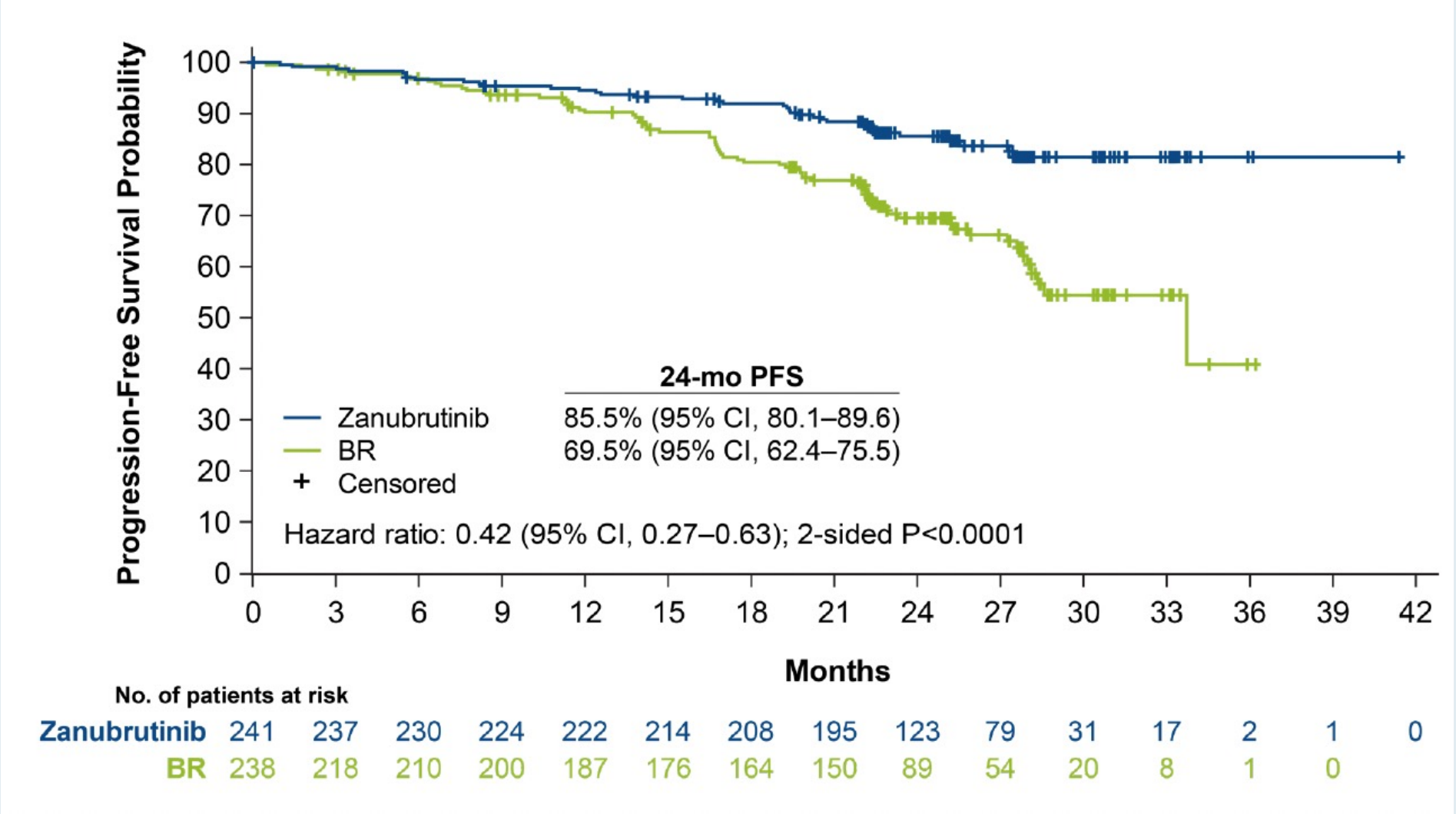
SEQUOIA: Results of a Phase 3 Randomized Study of Zanubrutinib versus Bendamustine + Rituximab (BR) in Patients with Treatment-Naïve (TN) Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma (CLL/SLL)

Tam CS et al.

ASH 2021;Abstract 396.

SEQUOIA: First-Line Zanubrutinib versus Bendamustine and Rituximab (BR)

Progression-Free Survival by IRC



Tam CS et al. ASH 2021;Abstract 396.

Questions — Anthony R Mato, MD, MSCE

Patients with CLL starting on a BTK inhibitor

- **How do you explain to patients what a Bruton tyrosine kinase (BTK) inhibitor is and the potential benefits and risks of these agents?**
- **How do you select which BTK inhibitor to use?**

Commentary — Anthony R Mato, MD, MSCE

Patients with CLL starting on a BTK inhibitor

- **How do you explain to patients what a BTK inhibitor is and the potential benefits and risks of these agents?**
  - Review mechanism of action
  - Review long term follow up data for ibrutinib in the front line and R/R settings
  - Review BTK specific adverse profile common to all BTK inhibitors
- **How do you select which BTK inhibitor to use?**
  - Review long term follow up data for ibrutinib
  - Review RCTs front line and R/R for ibrutinib
  - Review long term follow up for acalabrutinib and RCTs (ASCEND and ELEVATE-TN)
  - Review head to head comparisons for BTKis (ELEVATE-RR and ALPINE)
  - Review treatment schedules for BTKis with and without CD20 abs
  - Review DDIs for difference BTKis
  - Review emerging data for ncBTKis

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Commentary — Anthony R Mato, MD, MSCE

Actual clinical experiences with patients starting on a BTK inhibitor

- 35-year-old patient with del17p and complex karyotype starting ibrutinib in the front line setting
- 67-year-old patient with IGHV mutated CLL on acalabrutinib presents with palpitations and symptomatic HTN
- 73-year-old patient with standard risk CLL treated with FCR → Ibrutinib presents with progression of disease. Molecular panel shows new C481 mutation
- 49-year-old patient with IGHV unmutated del13q CLL considering Acalabrutinib vs Acalabrutinib + Obinutuzumab

Questions — Amy Goodrich, CRNP

Patients with CLL starting on a BTK inhibitor

- **What are some of the issues you discuss with patients who are about to begin a BTK inhibitor?**
- **How do you assess and monitor adherence to BTK inhibitors?**
- **What are some of the psychosocial issues that arise in this situation?**

Commentary — Amy Goodrich, CRNP

Patients with CLL starting on a BTK inhibitor

What I discuss when starting BTKi

- **Chronic therapy**
- **Common and severe side effects (lymphocytosis, GI, heme, bleeding, A-fib; headache with acalabrutinib)**
- **Strategies to reduce and manage side effects (antiemetics, antimotility agents, acetaminophen, bleeding precautions, holding for procedures, s/sx a-fib)**
- **Drug-drug interactions**
- **Adherence**
- **Spacing antacids with acalabrutinb**

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Commentary — Amy Goodrich, CRNP

How I assess and monitor adherence

- **Shared decision-making**
- **Health literacy**
- **Open communication**
- **No judgment**
- **How many doses have you missed?**

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Commentary — Amy Goodrich, CRNP

Patient #1

- **66 yo, diagnosed in 2010, Mutated IgVH, normal FISH, no TP53 abnormality**
- **Starts ibrutinib 1st line in 2016**
- **Experienced fatigue and low level nausea despite multiple antiemetics**
- **No weight loss**
- **3 months into treatment, responding well, admits skipping doses to reduce side effects**
- **Dose reduced to 280 mg daily**
- **Nausea improved on reduced dose**
- **Continues on ibrutinib, declines switching to acalabrutinib**

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Commentary — Amy Goodrich, CRNP

Patient #1 Psychosocial issues

- **Initially had difficulty working due to nausea, caused the skipped doses**
- **Some antiemetics worked well but caused drowsiness and impeded work**
- **Supportive wife, teenage daughter**
- **Long term relationship with health care team beneficial**
- **Fatigue improved, nausea well controlled**
- **Currently satisfied with side effect management**

Agenda

Module 1 – Overview of CLL

Module 2 – Bruton Tyrosine Kinase Inhibitors

Module 3 – Venetoclax and Anti-CD20 Antibody Therapy

Module 4 – Future Strategies

SELF-ASSESSMENT QUIZ

Which of the following side effects may be experienced by patients receiving the CLL14 regimen (venetoclax combined with obinutuzumab)?

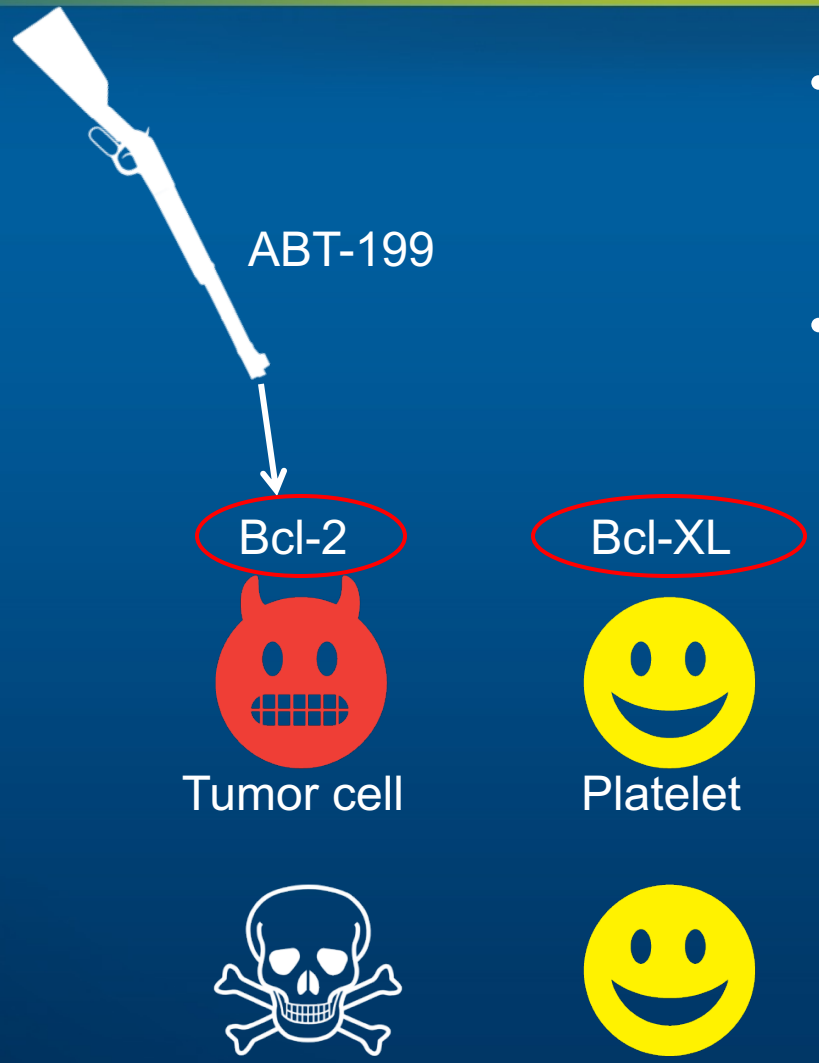
1. Tumor lysis syndrome (TLS)
2. Rapid reduction in white blood cell (WBC) count
3. Both TLS and rapid reduction in WBC count
4. Neither TLS nor rapid reduction in WBC count
5. I don’t know

SELF-ASSESSMENT QUIZ

The anti-CD20 monoclonal antibody obinutuzumab…

1. Has a similar mechanism of action to rituximab
2. Is indicated as first-line treatment for CLL in combination with chlorambucil, ibrutinib or venetoclax
3. Both 1 and 2
4. Neither 1 nor 2
5. I don’t know

Mechanism of Action of Venetoclax (ABT-199)



- Bcl-2 functions to prevent cell death by apoptosis
- Venetoclax is specific for Bcl-2 and inhibits its function, thereby removing the block on apoptosis

Adapted from Davids MS, Letai A. *Cancer Cell* 2013;23(2):139-41.

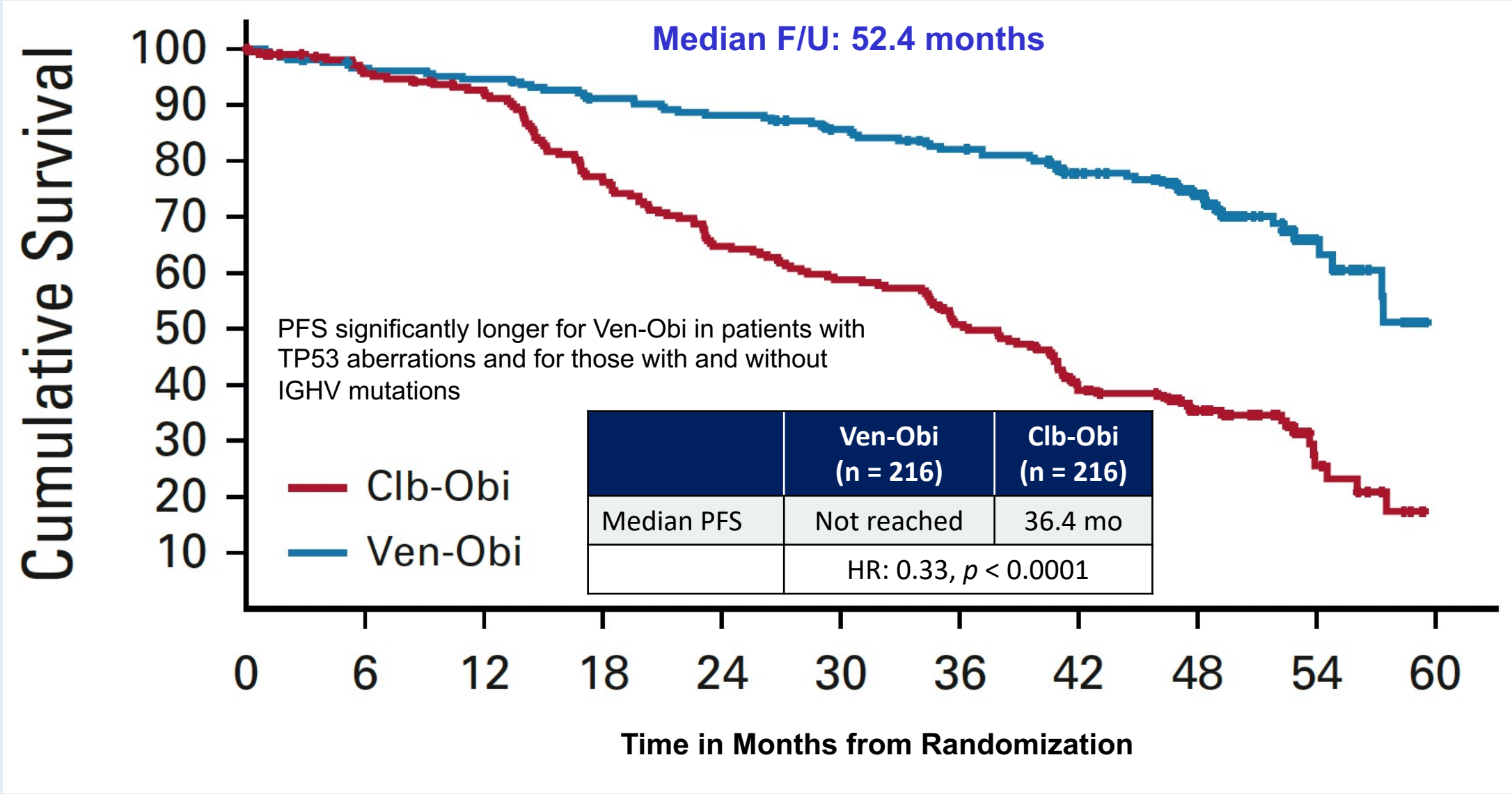
original reports

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]

J Clin Oncol 2021;39(36):4049-60.

CLL14 Update: Progression-Free Survival



	Ven-Obi (n = 216)	Clb-Obi (n = 216)
Median PFS	Not reached	36.4 mo
	HR: 0.33, $p < 0.0001$	

Al-Sawaf O et al. *J Clin Oncol* 2021;39(36):4049-60.

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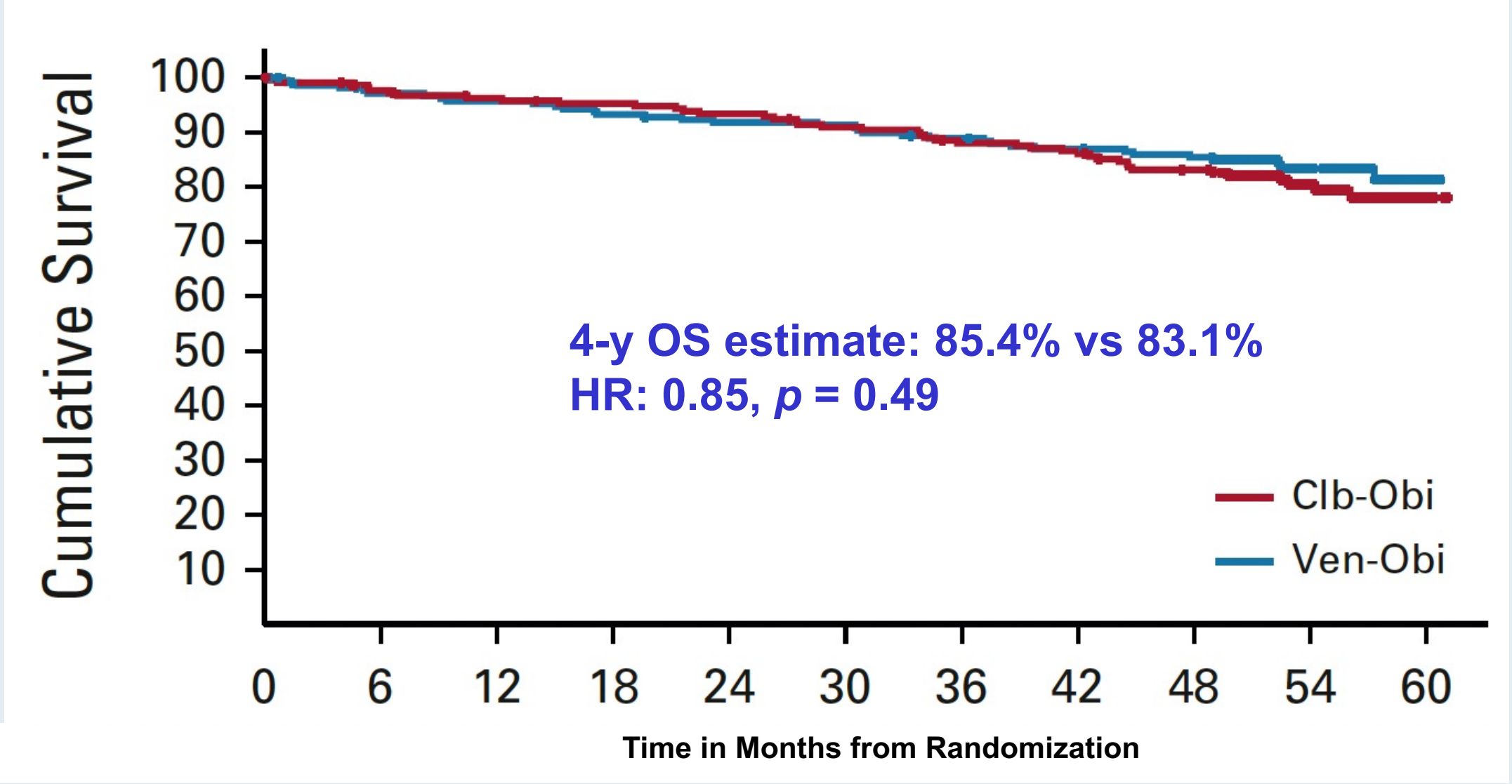
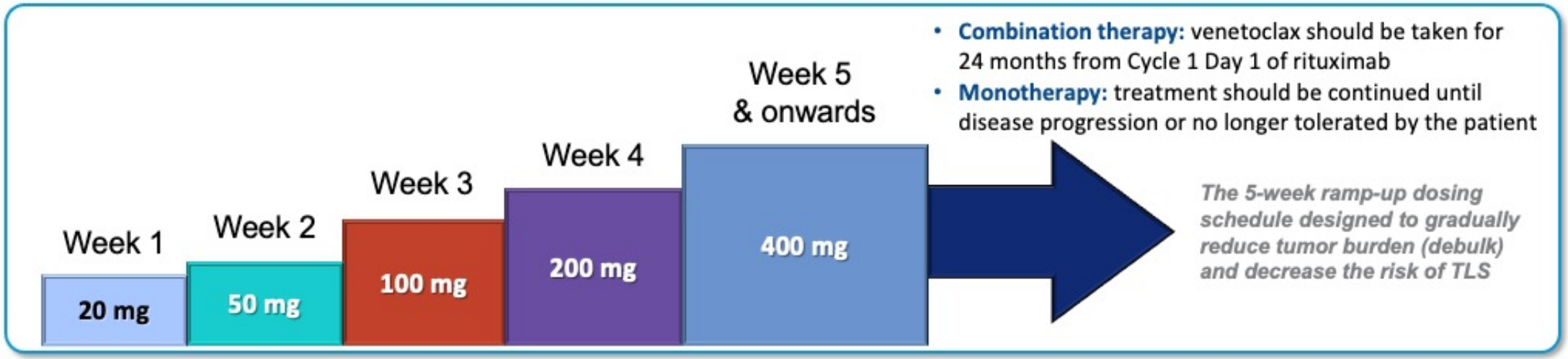
CLL14 Update: Overall Survival



Al-Sawaf O et al. *J Clin Oncol* 2021;39(36):4049-60.

Venetoclax Dose Initiation



The 5-week dose-titration schedule is designed to gradually reduce tumour burden and decrease the risk of TLS

Combination therapy: recommended dose of venetoclax in combination with rituximab is 400 mg once daily; rituximab should be administered after the patient has completed the dose-titration schedule and has received the recommended daily dose of 400 mg venetoclax for 7 days.

Monotherapy: the recommended dose of venetoclax is 400 mg once daily.

Venetoclax SmPC: https://www.medicines.org.uk/emc/product/2267/smpc (accessed October 2019).

Courtesy of Matthew S Davids, MD, MMSc

Venetoclax: TLS Prophylaxis and Monitoring

[a] **HYDRATION**	**Oral** (1.5 – 2 L); start 2 days prior to treatment start.	**IV** if needed due to higher TLS risk
ANTI-HYPER-URICAEMIC AGENTS	Patients with high uric acid or TLS risk should be administered with anti-hyperuricaemic agents **2 to 3 days prior** to treatment start	
[b,c] **LABORATORY MONITORING**	• **Pre-dose, 6–8, 24 hours** (at 1st dose of 20 mg and 50 mg, and for patients who continue to be at risk • Pre-dose at subsequent ramp-up doses	Evaluate blood chemistries and review in real time
HOSPITALIZATION	Based on physician assessment, some patients consider hospitalisation on first dose of venetoclax for more intensive prophylaxis and monitoring during the first 24 hours.	

[a]Administer intravenous hydration for any patient who cannot tolerate oral hydration; [b]Evaluate blood chemistries (potassium, uric acid, phosphorus, calcium, and creatinine); review in real time; [c]For patients at risk of TLS, monitor blood chemistries at 6–8 hours and at 24 hours at each subsequent ramp-up dose. Changes in blood chemistries consistent with TLS that require prompt management can occur as early as 6-8 hours following the first dose of venetoclax, and at each dose increase. **LN,** lymph node; **ALC**, absolute lymphocyte count; **TLS**, tumour lysis syndrome; **VEN**, venetoclax

1. Venetoclax SPC https://www.medicines.org.uk/emc/product/2267/smpc (accessed October 2019); 2. Stilgenbauer S, et al. *Lancet Oncol*. 2016; 17:768–778

Courtesy of Matthew S Davids, MD, MMSc

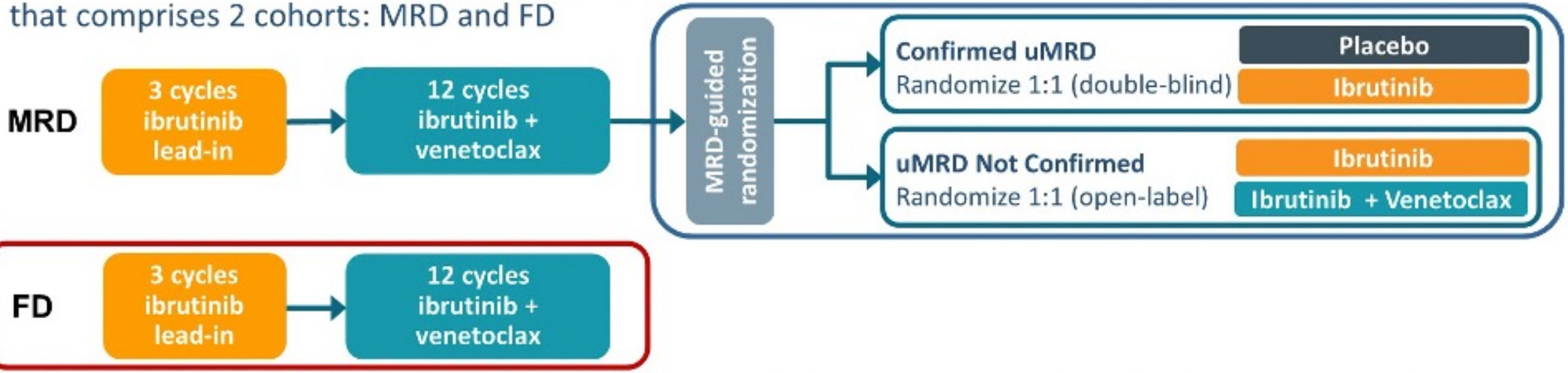
Fixed-Duration (FD) Ibrutinib (Ibr) + Venetoclax (Ven) for First-Line Treatment of Chronic Lymphocytic Leukemia (CLL) in Patients (pts) with High-Risk Features: Phase 2 CAPTIVATE Study

Allan JN et al.

AACR 2022;Abstract CTMS02.

CAPTIVATE Study Design

- 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]

Ghia P et al. ASCO 2021;Abstract 7051.

CAPTIVATE: Efficacy and Safety Summary of Fixed-Duration First-Line Ibrutinib and Venetoclax

Efficacy outcomes	Pts with high-risk features (N = 129)
Overall response rate	98%
Complete response	59%
18-mo DoR rate	95%
uMRD $<10^{-4}$ by flow – peripheral blood	88%
uMRD $<10^{-4}$ by flow – bone marrow	72%
24-mo PFS rate	94%
24-mo OS rate	98%
Grade 3/4 adverse events	
Neutropenia	29%
Hypertension	9%
Neutrophil count decreased	7%

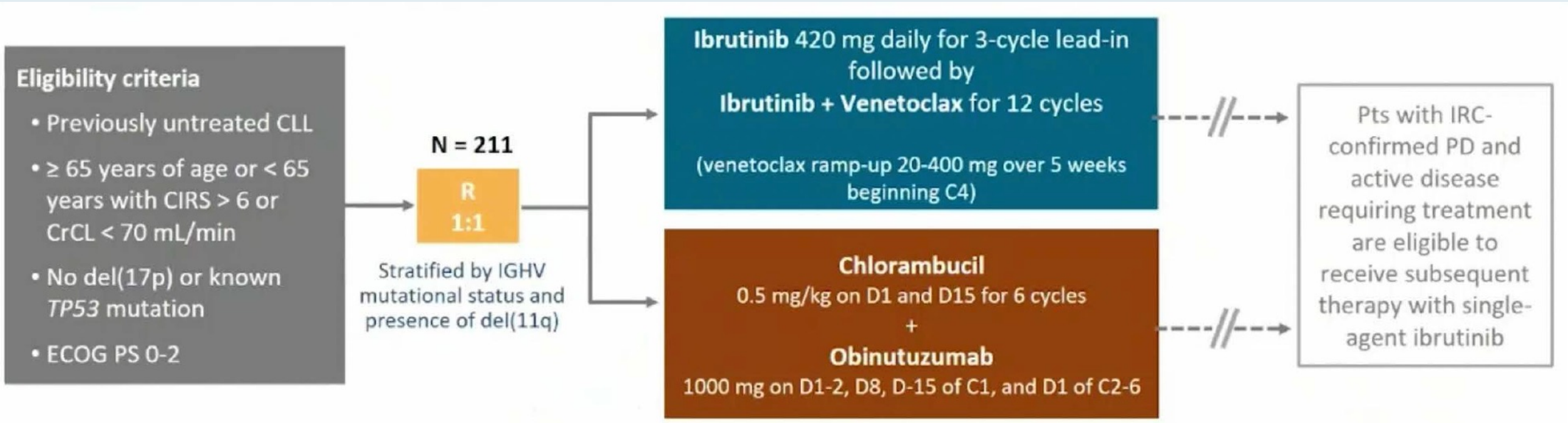
Allan JN et al. AACR 2022;Abstract CT028.

Fixed-Duration Ibrutinib and Venetoclax (I + V) versus Chlorambucil plus Obinutuzumab (Clb + O) for First-Line (1L) Chronic Lymphocytic Leukemia (CLL): Primary Analysis of the Phase 3 GLOW Study

Kater A et al.

EHA 2021;Abstract LB1902.

GLOW: Study Design and Endpoints



Primary end point: Progression-free survival by independent review committee (IRC)

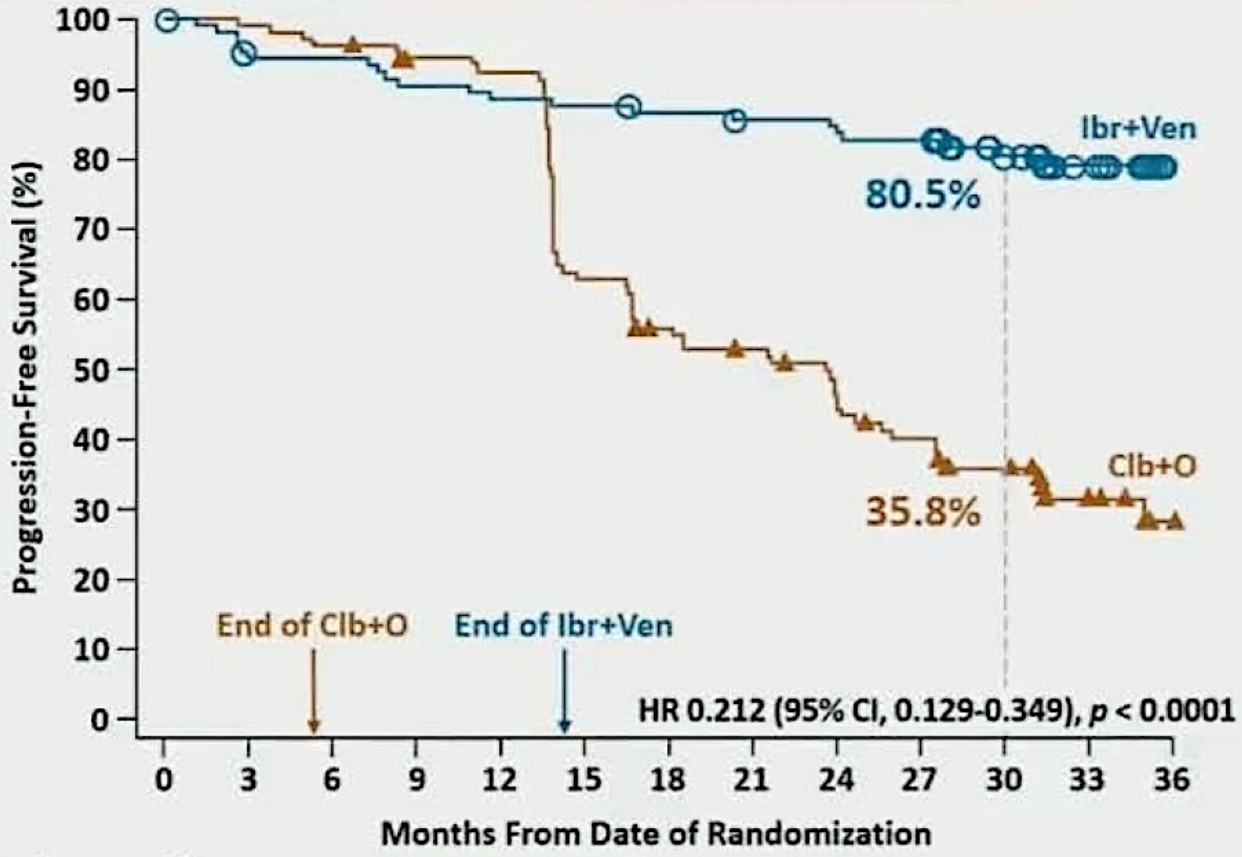
- 71 PFS events to detect an effect size with an HR = 0.5 (80% power at a 2-sided significance level of 0.05)

Key secondary end points: Undetectable MRD in BM, CR rate (IRC), ORR (IRC), OS; safety was also evaluated.

Kater A et al. EHA 2021;Abstract LB1902.

GLOW: First-Line Ibrutinib/Venetoclax versus Obinutuzumab/Chlorambucil

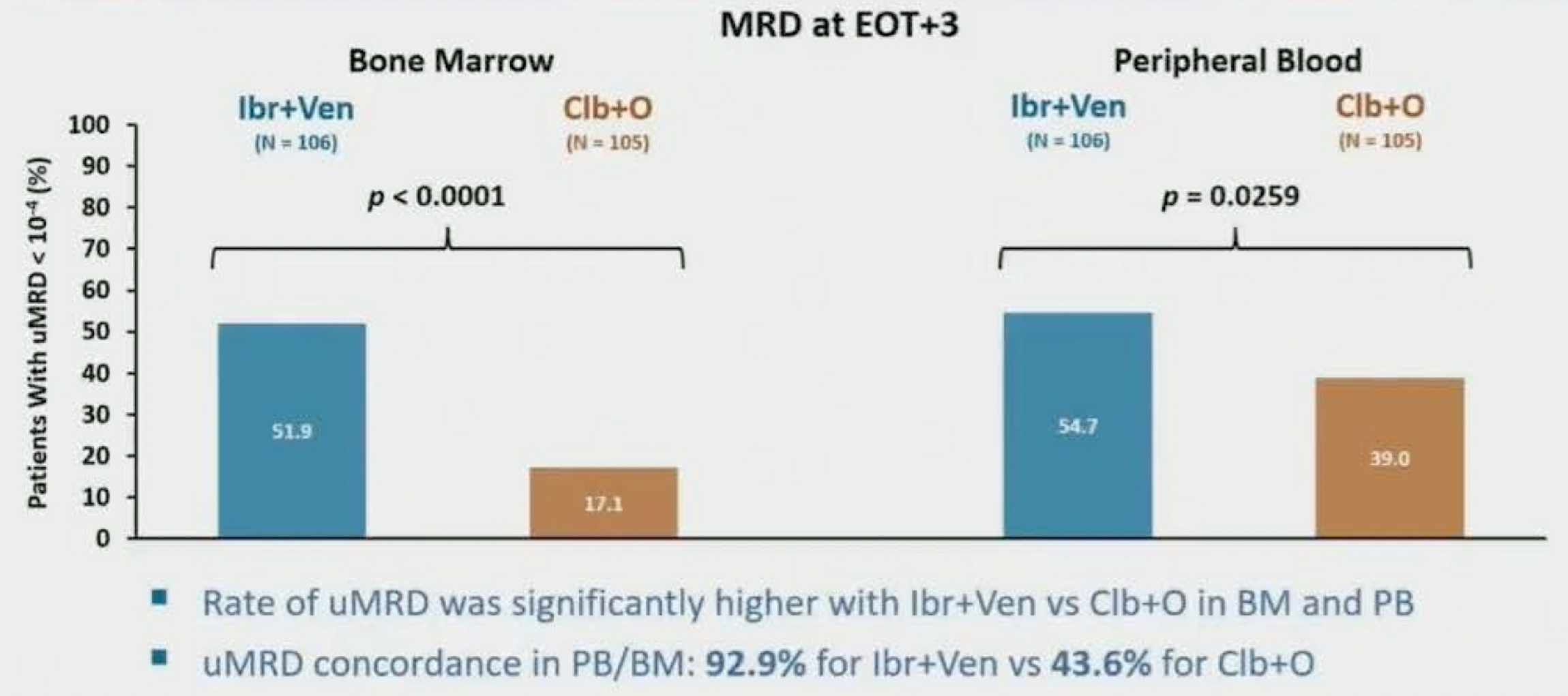
IRC-Assessed Progression-Free Survival (PFS)



- 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

Munir T et al. ASH 2021;Abstract 70.

GLOW: uMRD Rate $<10^{-4}$



Munir T et al. ASH 2021;Abstract 70.

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Questions — Lowell L Hart, MD

Patients with CLL starting on venetoclax/anti-CD20 antibody

- **How do you explain to patients what venetoclax is and the potential benefits of this agent and how it is combined with an anti-CD20 antibody?**

Questions — Lesley Camille Ballance, MSN, FNP-BC

Patients with CLL starting on venetoclax/anti-CD20 antibody

- **What are some of the issues you discuss with patients about to begin a venetoclax/anti-CD20 antibody combination?**
- **How do you explain the process to prevent tumor lysis syndrome?**
- **What are some of the psychosocial issues that arise in this situation?**

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Commentary — Lesley Camille Ballance, MSN, FNP-BC

Patients with CLL starting on venetoclax/anti-CD20 antibody

Potential Problems

- TLS
- Neutropenia
- B-cell aplasia
- Treatment intensity
- Pt Example: 71-year-old female with SLL started on front-line therapy with Venetoclax and Obinutuzumab

Psychosocial Issues

- Anxiety over new therapy
- Financial worries
- Travel
- Family support

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Agenda

Module 1 – Overview of CLL

Module 2 – Bruton Tyrosine Kinase Inhibitors

Module 3 – Venetoclax and Anti-CD20 Antibody Therapy

Module 4 – Future Strategies

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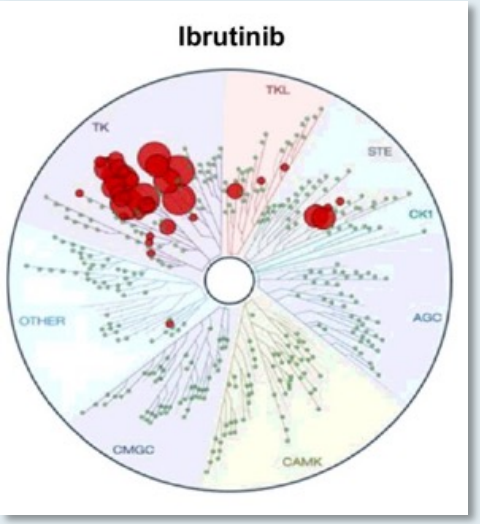
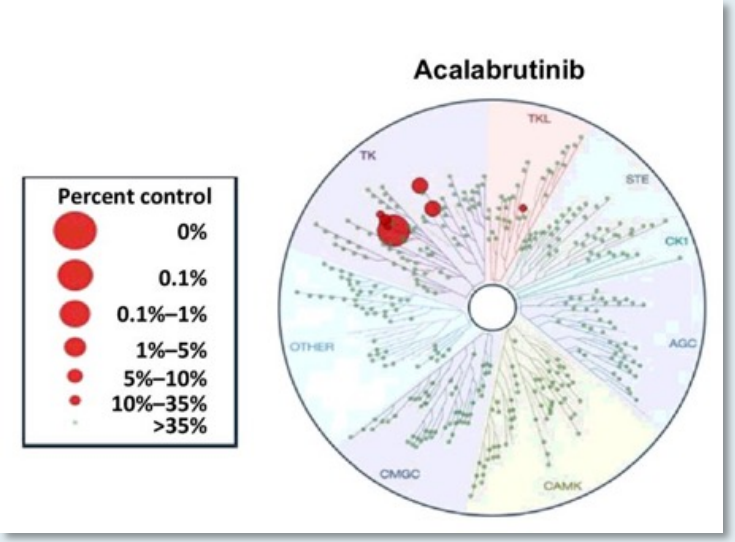
Overview of BTK Inhibitors in CLL

Irreversible

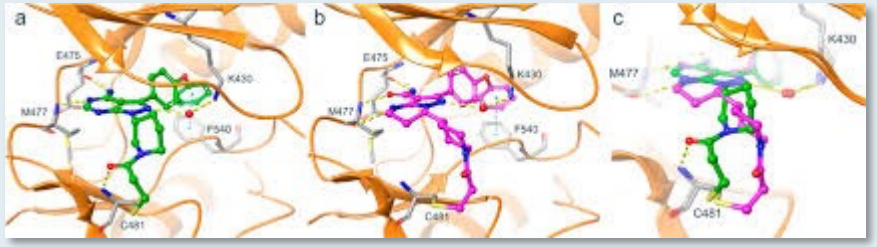
Ibrutinib



Acalabrutinib

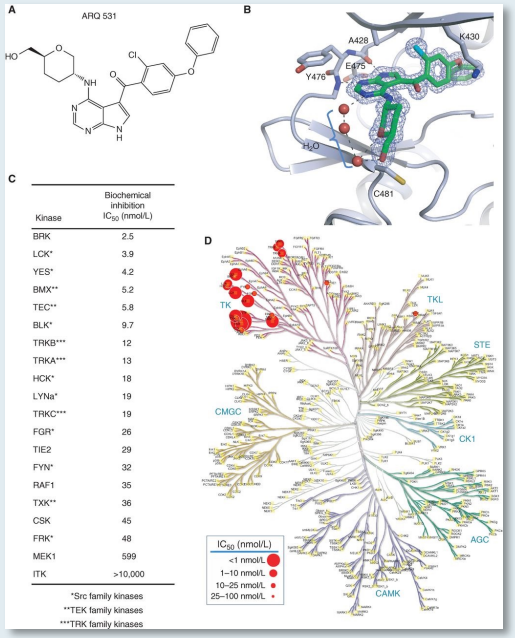


Zanubrutinib

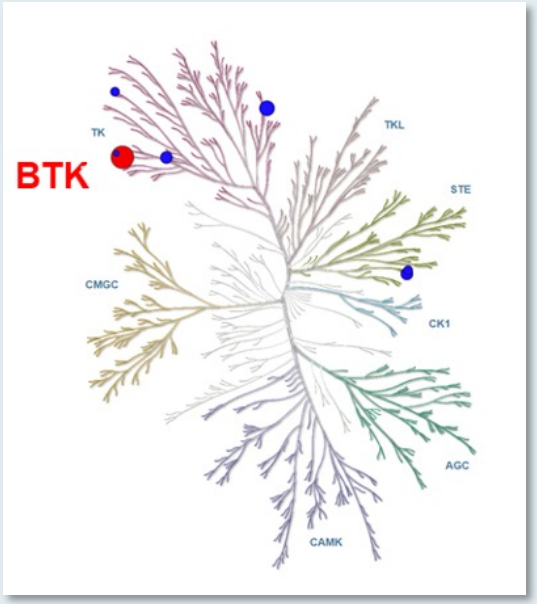


Reversible

ARQ-531 (MK-1026)



Pirtobrutinib (LOXO-305)



Courtesy of Matthew S Davids, MD, MMSc

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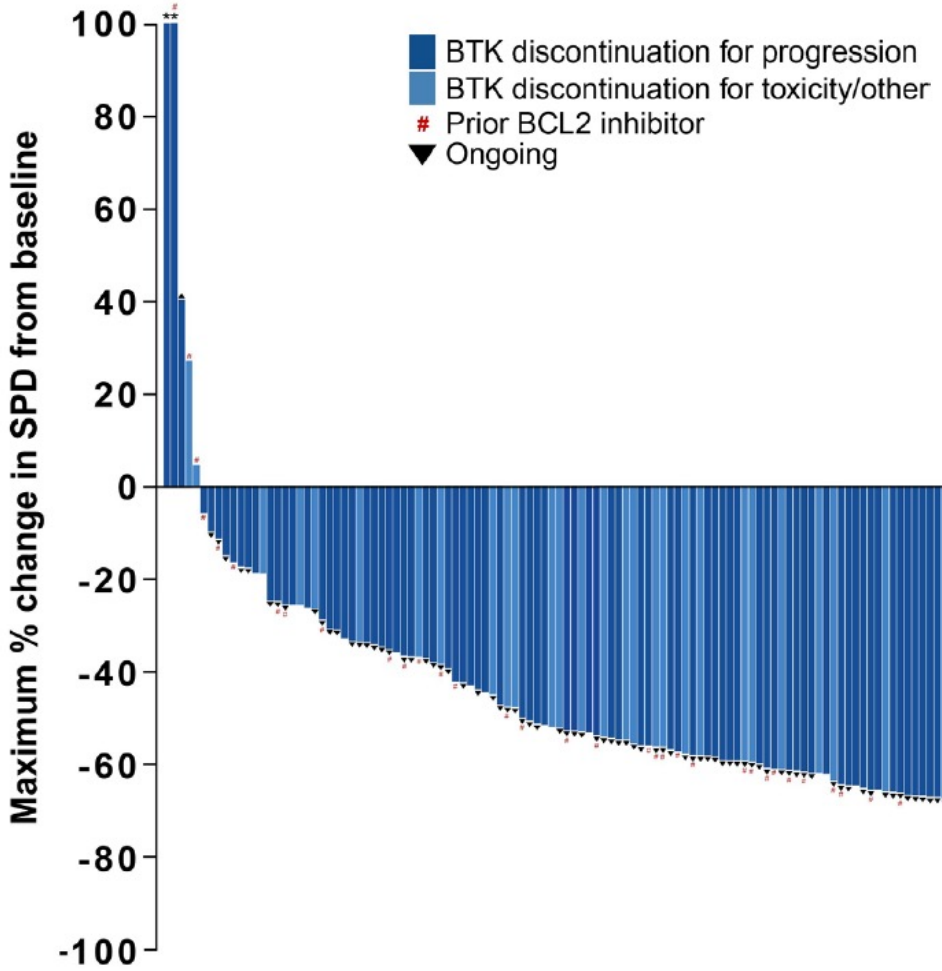
Pirtobrutinib, a Next Generation, Highly Selective, Non-Covalent BTK Inhibitor in Previously Treated CLL/SLL: Updated Results from the Phase 1/2 BRUIN Study

Mato AR et al.

ASH 2021;Abstract 391.

BRUIN: Pirtobrutinib Efficacy in Patients with BTK-Pretreated CLL or Small Lymphocytic Lymphoma (SLL)

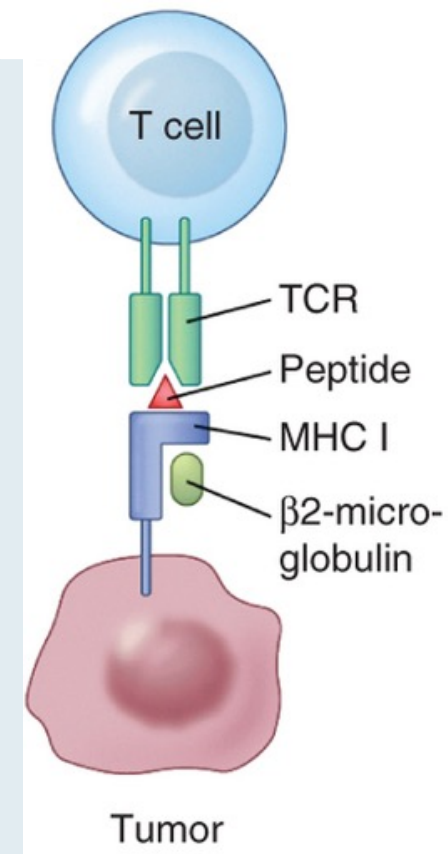


Efficacy evaluable BTK pre-treated CLL/SLL Patients[a]	n = 252
Overall Response Rate, % (95% CI)[b]	**68 (62 – 74)**
Best response	
CR, n (%)	2 (1)
PR, n (%)	137 (54)
PR-L, n (%)	32 (13)
SD, n (%)	62 (25)

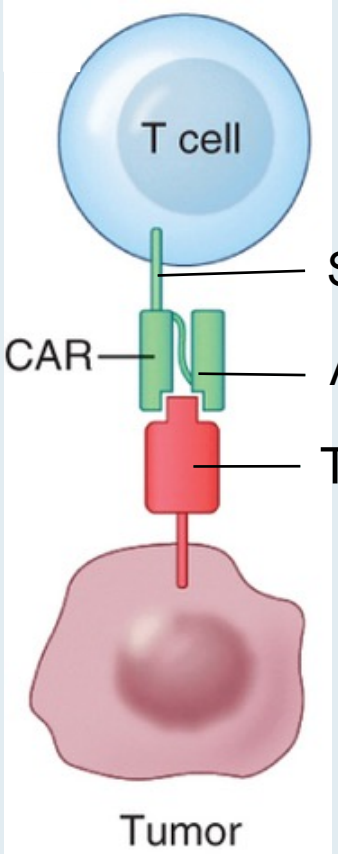
Mato AR et al. ASH 2021;Abstract 391.

Chimeric Antigen Receptor (CAR) Modified T Cells

Normal T cell



CAR T cell



- **Genetically engineered T cells altered to express an artificial receptor, CAR**

Courtesy of Sattva S Neelapu, MD

Adapted from Hinrichs & Restifo. Nat Biotech 2013

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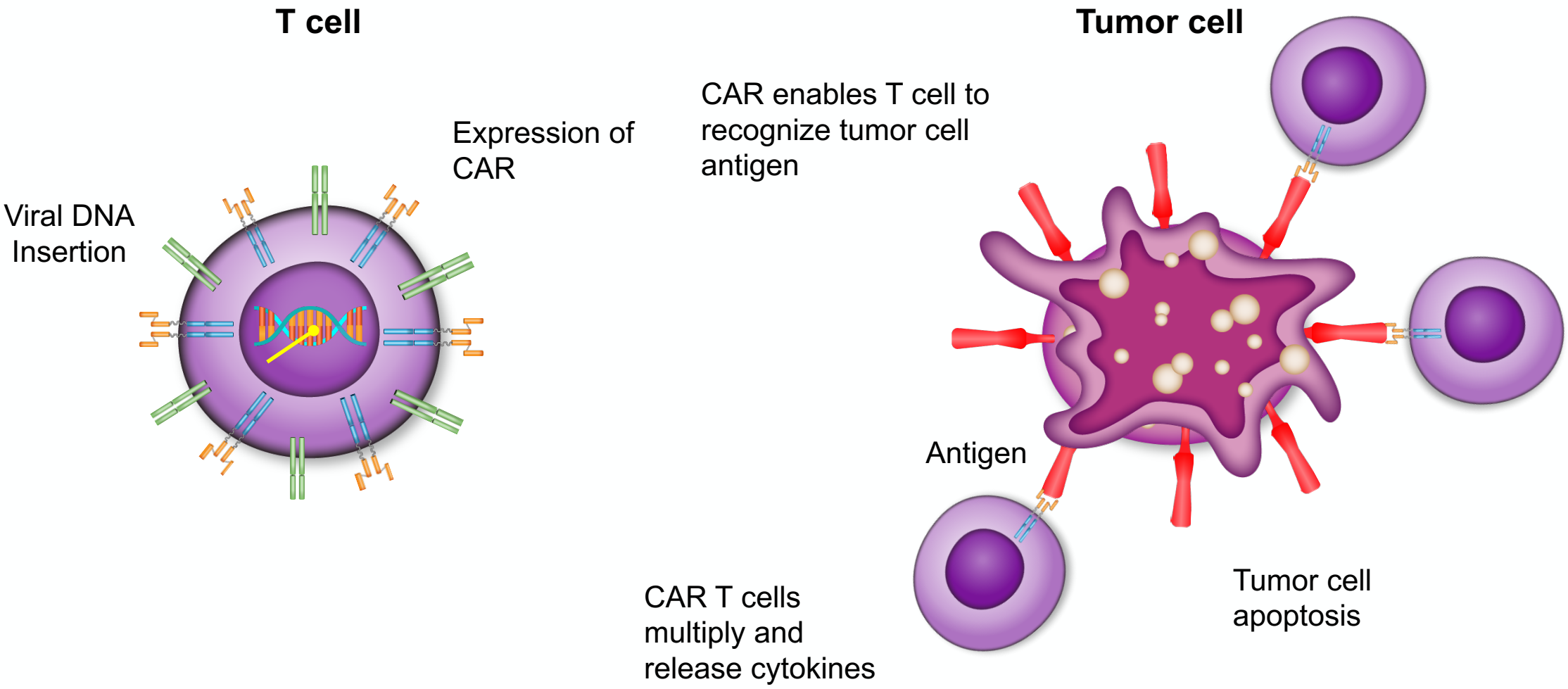
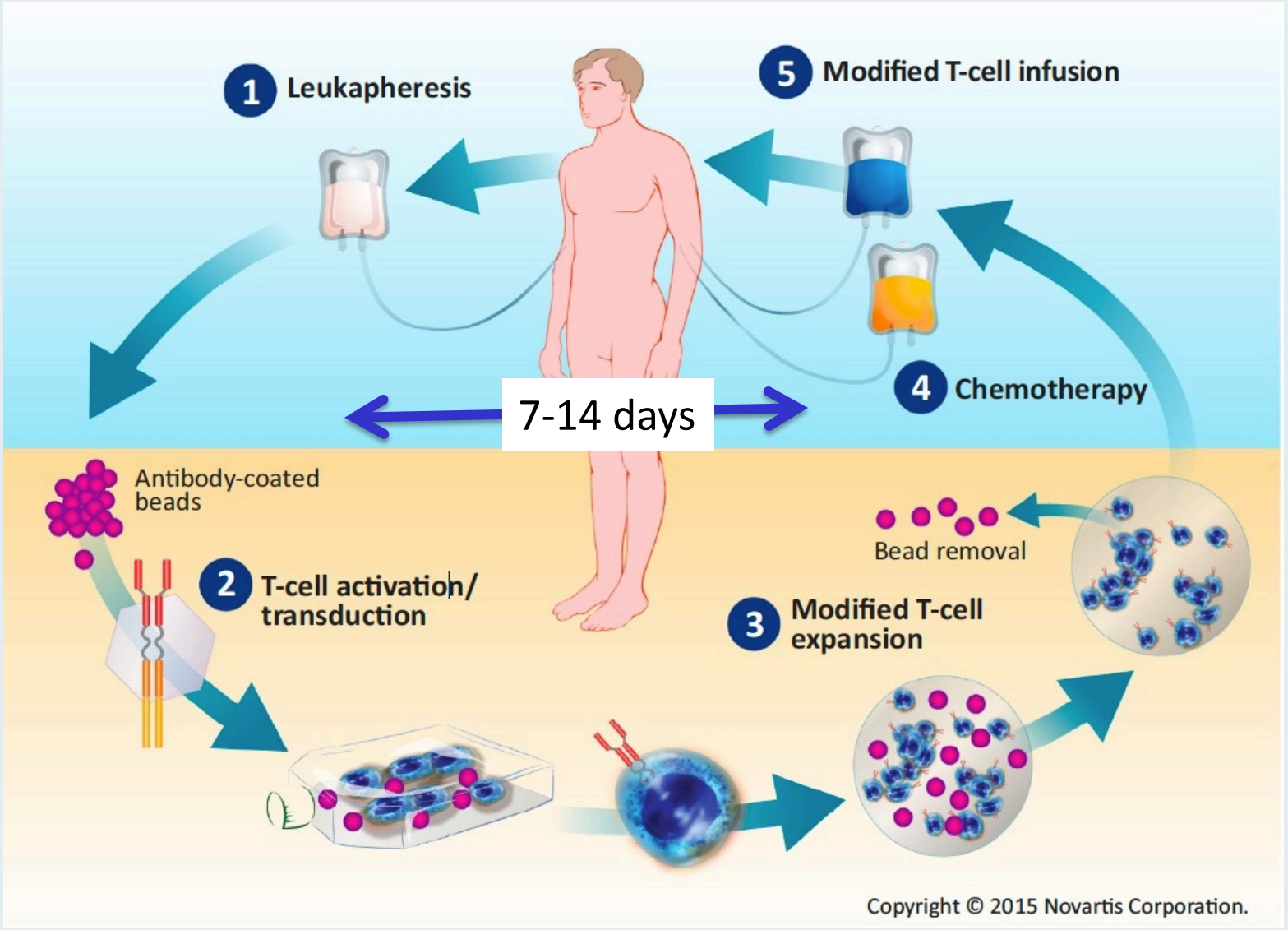
CAR T Cells: Mechanism of Action



Overview of CAR T-Cell Therapy



Modification, Courtesy, David Porter, MD

Questions — Anthony R Mato, MD, MSCE

Patients with CLL who have exhausted all approved treatment options: Future directions

- **What are your thoughts about these novel strategies: pirtobrutinib, CAR T-cell therapy and bispecific antibodies?**
- **How do you explain to patients who are eligible for clinical trials with these agents how they work?**

Commentary — Anthony R Mato, MD, MSCE

Patients with CLL who have exhausted all approved treatment options: Future directions

- **What are your thoughts about these novel strategies: pirtobrutinib, CAR T-cell therapy and bispecific antibodies?**
  - Discuss emerging data for Pirtobrutinib in terms of clinical activity / safety profile from BRUIN trial
    - Focus on low discontinuation rate due to AEs and BTK specific toxicities
    - Focus on data for Pirtobrutinib in cBTK treated patients
    - Focus on data for Pirtobrutinib in double exposed patients
    - Discuss emerging mechanisms of resistance to Pirtobrutinib and emerging strategies to address resistance
  - Discuss data for CAR-T (Liso-Cel) in R/R CLL
  - Discuss data for Epcoritamab in R/R CLL
- **How do you explain to patients who are eligible for clinical trials with these agents how they work?**
  - Discuss MOA for ncBTK (focus on Pirtobrutinib) and how it is both similar and different

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Commentary — Anthony R Mato, MD, MSCE

Actual clinical experiences with patients who have exhausted all approved treatment options

- > 100 pts treated with Pirtobrutinib at MSKCC as monotherapy and in combination
- Discuss experience as lead PI on BRUIN trial
- US lead for Epcoritamab in R/R CLL study. Discuss patient with R/R CLL who is on Epo > 12 months and is MRD undetectable
- Discuss clinical data for Liso-Cel in R/R CLL – particular focus on patients with double refractory CLL

Questions — Amy Goodrich, CRNP

Patients with CLL who have exhausted all approved treatment options: Future directions

- **What do you say about potential benefits to patients who are considering clinical trial participation?**
- **How do you dispel common misperceptions of clinical trial participation?**
- **What are some of the psychosocial issues that arise in this situation?**

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Commentary — Amy Goodrich, CRNP

Patients with CLL who have exhausted all approved treatment options: Future directions

What I say about clinical trials

- **New drug classes/targets have changed the outlook for patients with CLL**
- **New generations of agents have been successful in many drug classes**
- **Many patients have been on and have had benefit from drugs that were not FDA approved when they were initially diagnosed**
- **Opportunity to get something new, balanced with standard of care options, including sequencing**
- **Can withdraw at any time**

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Commentary — Amy Goodrich, CRNP

Dispelling common misperceptions

- **Chronic nature of CLL allows for repeated discussions about trials, new agents, new combinations**
- **Many R/R patients have been on agents/regimens that did not exist when they were initially diagnosed**
- **For TN patients, the observation period allows for questions, education, patients doing their own research**
- **Can withdraw at any time**

Commentary — Amy Goodrich, CRNP

Patient #2 with benefit from clinical trial participation

- 42 yo diagnosed with CLL in 1997, 17p deletion
- FCR (1997)
- Allo transplant (1998)
- DLI (2009)
- Lenalidomide on trial 2010
- Bendamustine 2010
- Ofatumumab 2010
- DLI 2010
- CAR-T on trial 4 infusions 2011-2012
- Bendamustine 2012
- Ibrutinib on trial 2013-2018
- Venetoclax 2018, obinutuzumab added 2019
- Chlorambucil + prednisone 2021
- Alemtuzumab 2021
- Died at age 66 of infection trying to get on another CAR-T study

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Commentary — Amy Goodrich, CRNP

Psychosocial issues

- **Multiple providers across the country**
- **In constant contact with most of his providers**
- **Ultra educated on disease and trials (open and coming)**
- **Minimized symptoms and side effects**
- **Single, estranged from siblings, no children, little social support**
- **Never believed he would run out of treatment options**

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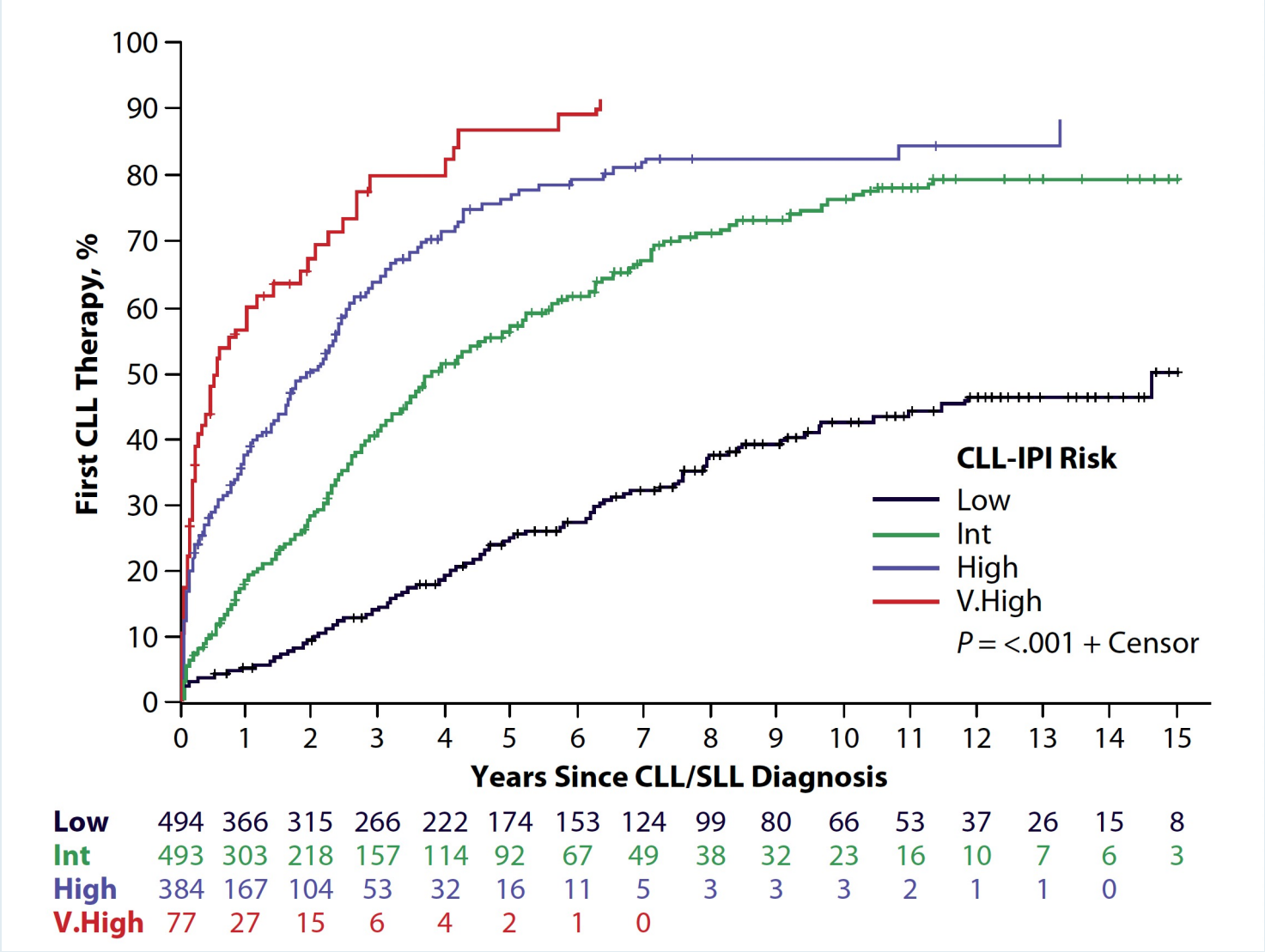
Appendix

Time to First Therapy Since Chronic Lymphocytic Leukemia (CLL)/Small Cell Lymphoma (SLL) Diagnosis According to CLL-IPI



Muchtar E et al. *Clin Adv Hematol Oncol* 2021;19(2):92-103.

Patient Education: Ibrutinib

Teaching points

- Common side effects
  - Nausea, diarrhea, arthralgias, fatigue, minor bleeding
  - Prescription and OTC meds to manage; lifestyle/diet changes; holding for procedures
- Uncommon side effects
  - Major bleeding
  - A-fib/flutter
- Potential for lymphocytosis
- Contact/emergency numbers
- Monitoring schedule
  - I see/touch base weekly until good symptom management
  - Frequent initial labs, we did TLS monitoring due to bulky adenopathy

Courtesy of Amy Goodrich, CRNP

Patient Education: Ibrutinib

1. Adverse events are common and are often managed by briefly holding for 7 days or less or with supportive care. These include cutaneous toxicities, increased risk for infection (fungal infections), headaches, and myalgias and arthralgias.
2. During the first 4-6 weeks patients tend to feel fatigued. It is usually better tolerated after the first month.
3. Weekly labs for the first month to monitor for tumor lysis and organ function. Peripheralization is common in the first weeks to months. Patients should not be alarmed if WBC count increases.
4. There is an increased bleeding risk. Will have to hold ibrutinib at least 3-7 days prior to procedures and inform the medical team.
5. Hypertension and atrial fibrillation can occur at any time. New medications should be reported to avoid drug interactions, especially antiplatelet medications.

Courtesy of Kristen E Battiato, AGNP-C

Acalabrutinib

- 2nd Generation BTK inhibitor
  - More selective kinase inhibitor = less AE's
- Highly effective
  - Activity appears comparable to ibrutinib
  - No 5 year follow up at this point
- Better tolerated (my opinion)
  - Less arthralgia, myalgia, HTN, Afib, Bleeding
  - Does cause headache – caffeine helps
- Other issues
  - 100 mg po BID
  - Can't be on proton pump inhibitor
  - Should take on empty stomach

Courtesy of Brad S Kahl, MD

Patient Education: Acalabrutinib/Obinutuzumab

Pharmacy consultation re potential drug interactions

- **CYP3A4 interactions - Avoid strong inhibitors & inducers**
  - **Azole antifungals, mycin antibiotics, protease inhibitors, etc**
  - **Moderate – consider dose adjustment**
  - **Avoid grapefruit/juice and Seville oranges**
- **Avoid antacids or calcium supplements and H2 receptor antagonists for 2 hours before and after acalabrutinib**
- **Avoid proton pump inhibitors due to potential decrease in drug exposure**

Take with water, with or without food

Possible tumor lysis syndrome

- **Allopurinol x 10 days at start of therapy**

Courtesy of Robin Klebig, APRN, CNP, AOCNP

Patient Education: Acalabrutinib/Obinutuzumab

Acalabrutinib is typically very well tolerated

Bleeding tendency with BTK inhibitors

- **May note easy bleeding/bruising/petechiae**
- **Avoid NSAIDs, ASA, vitamin E, fish oil**
- **Hold acalabrutinib 3 days prior to and 3 days following minor procedure; 7 days for major procedure**

Headache is likely

- **Usually temporary, first month or so**
- **Typically easily managed with acetaminophen**

Courtesy of Robin Klebig, APRN, CNP, AOCNP

Patient Education: Acalabrutinib/Obinutuzumab

Risk for atrial fibrillation

- **Watch for palpitations, lightheadedness, syncope, dyspnea, irregular rapid pulse**

Risk for hypertension

Diarrhea

- **Loperamide prn**
- **Record # stools per day at baseline**

Myalgia/arthralgia

- **Recommend increase activity, movement, stretching**
- **Treat symptomatically**

Nausea

Rash

Cytopenias

- Anemia
  - Typically not transfusion requiring
- Leukopenia, neutropenia, lymphocytopenia
  - Increased infection risk
- Thrombocytopenia
- Monitor weekly during 1st month
- Consider dose adjustment if limiting

Take acalabrutinib *indefinitely*, as long as responding if no CR

Courtesy of Robin Klebig, APRN, CNP, AOCNP

RTP RESEARCH TO PRACTICE

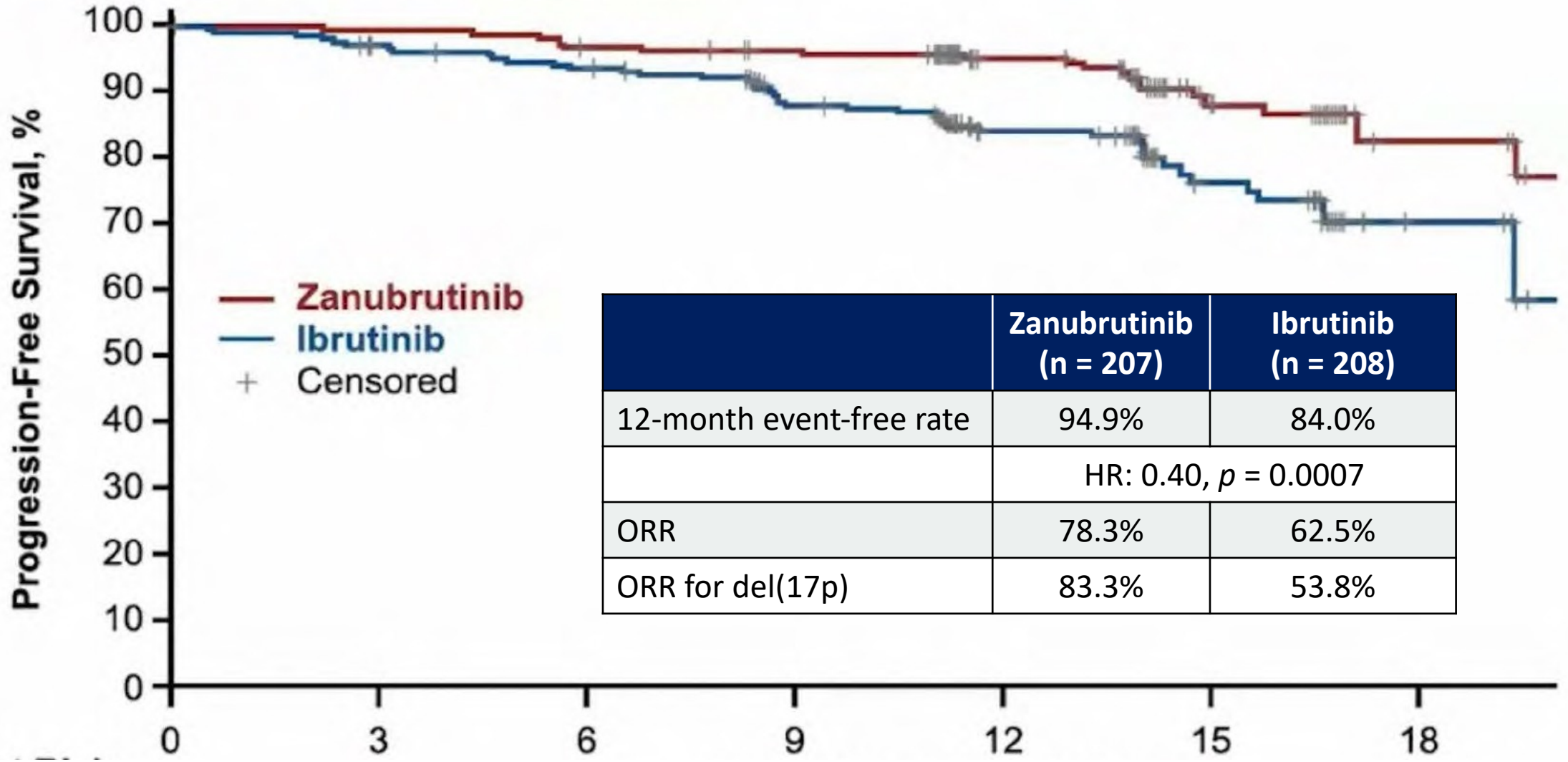
ELEVATE-RR: Characterization of Adverse Events with Acalabrutinib versus Ibrutinib

	Incidence, %				Exposure-Adjusted Incidence[b]				Exposure-Adjusted Time With Event[c]			
	Any grade		Grade ≥3		Any grade		Grade ≥3		Any grade		Grade ≥3	
	Acala[d]	Ibru[e]	Acala[d]	Ibru[e]	Acala[d]	Ibru[e]	Acala[d]	Ibru[e]	Acala[d]	Ibru[e]	Acala[d]	Ibru[e]
ECIs												
Cardiac events	24%	30%	9%	10%	1.2	1.9	0.4	0.5	7.1	13.0	0.4	0.2
Afib/flutter	9%	**16%***	5%	4%	0.4	0.7	0.2	0.1	1.3	3.8	0.3	0.1
HTN[f]	9%	**23%***	4%	**9%***	0.4	1.2	0.1	0.4	4.1	15.0	1.6	4.0
Bleeding events[g]	38%	**51%***	4%	5%	2.4	3.8	0.1	0.2	13.7	24.6	0.1	0.1
Major bleeding events[h]	5%[i]	5%[j]	4%	5%	0.2	0.2	0.1	0.2	0.1	0.3	0.1	0.1
Infections[k]	78%	81%	31%	30%	8.9	10.4	1.6	2.0	14.6	15.6	1.5	1.1
Selected Common AEs (preferred term)												
Diarrhea	35%	**46%***	1%	**5%***	1.9	2.8	<0.1	0.2	6.7	9.6	<0.1	0.1
Headache	**35%***	20%	**2%***	0	1.8	1.1	<0.1	0	7.8	5.4	<0.1	0
Cough	**29%***	21%	1%	<1%	1.3	1.1	<0.1	<0.1	5.6	4.9	<0.1	<0.1
Fatigue	20%	17%	**3%***	0%	0.9	0.9	0.1	0	7.4	7.0	0.6	0
Arthralgia	16%	**23%***	0	1%	0.6	1.3	0	<0.1	7.5	10.4	0	<0.1
Back pain	8%	**13%***	0	1%	0.3	0.5	0	<0.1	1.9	3.2	0	0.1
Muscle spasms	6%	**13%***	0	1%	0.2	0.7	0	<0.1	0.8	10.0	0	0.1
Dyspepsia	4%	**12%***	0	0	0.1	0.5	0	0	1.0	2.4	0	0

Seymour JF et al. ASH 2021;Abstract 3721.

ALPINE: Zanubrutinib versus Ibrutinib for Relapsed CLL

Response and Investigator-Assessed Progression-Free Survival



	Zanubrutinib (n = 207)	Ibrutinib (n = 208)
12-month event-free rate	94.9%	84.0%
	HR: 0.40, *p* = 0.0007	
ORR	78.3%	62.5%
ORR for del(17p)	83.3%	53.8%

Hillmen P et al. EHA 2021;Abstract LBA1900.

ALPINE: Adverse Events of Special Interest

Safety Analysis Population	Zanubrutinib (n=204), n (%)		Ibrutinib (n=207), n (%)	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3
Cardiac disorders[a]	28 (13.7)	5 (2.5)	52 (25.1)	14 (6.8)
Atrial fibrillation and flutter (key 2º endpoint)	**5 (2.5)**	**2 (1.0)**	**21 (10.1)**	**4 (1.9)**
Hemorrhage	73 (35.8)	6 (2.9)	75 (36.2)	6 (2.9)
Major hemorrhage[b]	6 (2.9)	6 (2.9)	8 (3.9)	6 (2.9)
Hypertension	34 (16.7)	22 (10.8)	34 (16.4)	22 (10.6)
Infections	122 (59.8)	26 (12.7)	131 (63.3)	37 (17.9)
Neutropenia[c]	58 (28.4)	38 (18.6)	45 (21.7)	31 (15.0)
Thrombocytopenia[c]	19 (9.3)	7 (3.4)	26 (12.6)	7 (3.4)
Secondary primary malignancies	17 (8.3)	10 (4.9)	13 (6.3)	4 (1.9)
Skin cancers	7 (3.4)	3 (1.5)	10 (4.8)	2 (1.0)

Hillmen P et al. EHA 2021;Abstract LBA1900.

SEQUOIA: Adverse Events (AEs) of Interest

AE, n (%)	Arm A Zanubrutinib (n=240[a])		Arm B Bendamustine + Rituximab (n=227[a])	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3
Anemia	11 (4.6)	1 (0.4)	44 (19.4)	4 (1.8)
Neutropenia[b]	38 (15.8)	28 (11.7)	129 (56.8)	116 (51.1)
Thrombocytopenia[c]	11 (4.6)	5 (2.1)	40 (17.6)	18 (7.9)
Arthralgia	32 (13.3)	2 (0.8)	20 (8.8)	1 (0.4)
Atrial fibrillation	8 (3.3)	1 (0.4)	6 (2.6)	3 (1.3)
Bleeding[d]	108 (45.0)	9 (3.8)	25 (11.0)	4 (1.8)
Major bleeding[e]	12 (5.0)	9 (3.8)	4 (1.8)	4 (1.8)
Diarrhea	33 (13.8)	2 (0.8)	31 (13.7)	5 (2.2)
Hypertension[f]	34 (14.2)	15 (6.3)	24 (10.6)	11 (4.8)
Infections[g]	149 (62.1)	39 (16.3)	127 (55.9)	43 (18.9)
Myalgia	9 (3.8)	0 (0.0)	3 (1.3)	0 (0.0)
Other cancers	31 (12.9)	17 (7.1)	20 (8.8)	7 (3.1)
Dermatologic other cancers	16 (6.7)	2 (0.8)	10 (4.4)	2 (0.9)

Tam CS et al. ASH 2021;Abstract 396.

Obinutuzumab

- Anti-CD20 MoAb
  - Designed to be a new and improved rituximab
  - Better than rituximab for CLL
- Dosing: 1000 mg flat dose
  - Cycle 1: Day 1 (100mg), 2 (900mg), 8, 15
  - Cycle 2-6 Day 1
- When to use it
  - If using venetoclax 12-month time limited therapy, combine with obinutuzumab
  - If using BTKi obinutuzumab, use is optional
    - Improves outcomes marginally
    - Adds some toxicity (mostly infections)

Courtesy of Brad S Kahl, MD

Venetoclax

- BCL-2 inhibitor
  - No lymphocytosis
- Highly effective
  - Remission “deeper" than with BTKi’s
    - More complete responses. More MRD negativity.
  - Developed as a 12-month “time limited therapy” when used with obinutuzumab in 1st line
  - Responses in ~90%. No 5-year data yet.
- Generally well tolerated
  - GI side effects, cytopenias
- Tumor Lysis Syndrome

Courtesy of Brad S Kahl, MD

Patient Education: Venetoclax

- **Pharmacy consultation re potential drug interactions**
  - **CYP3A4 interactions - Avoid strong inhibitors & inducers**
    - **Azole antifungals, mycin antibiotics, protease inhibitors, etc**
    - **Moderate – consider dose adjustment**
    - **Avoid grapefruit/juice, Seville oranges, and starfruit**

- **Take with food and water, same time each day**

Courtesy of Robin Klebig, APRN, CNP, AOCNP

Patient Education: Venetoclax

Potential for tumor lysis syndrome

- **5 week ramp up to goal dose**
- **Hospitalization for weekly ramp up (bulky)**
- **TLS lab monitoring q8h x 24 hours**
- **Allopurinol**
- **Hydration**

Nausea

- **prn antiemetic**

Diarrhea

- **Loperamide prn**
- **Record # stools per day at baseline**

Cytopenias

- Neutropenia
  - Increased infection risk
- Thrombocytopenia
  - Bleeding risk
- Anemia
  - Typically not transfusion requiring

Courtesy of Robin Klebig, APRN, CNP, AOCNP

RTP RESEARCH TO PRACTICE

Patient Education: Venetoclax/Obinutuzumab

Teaching points and challenges

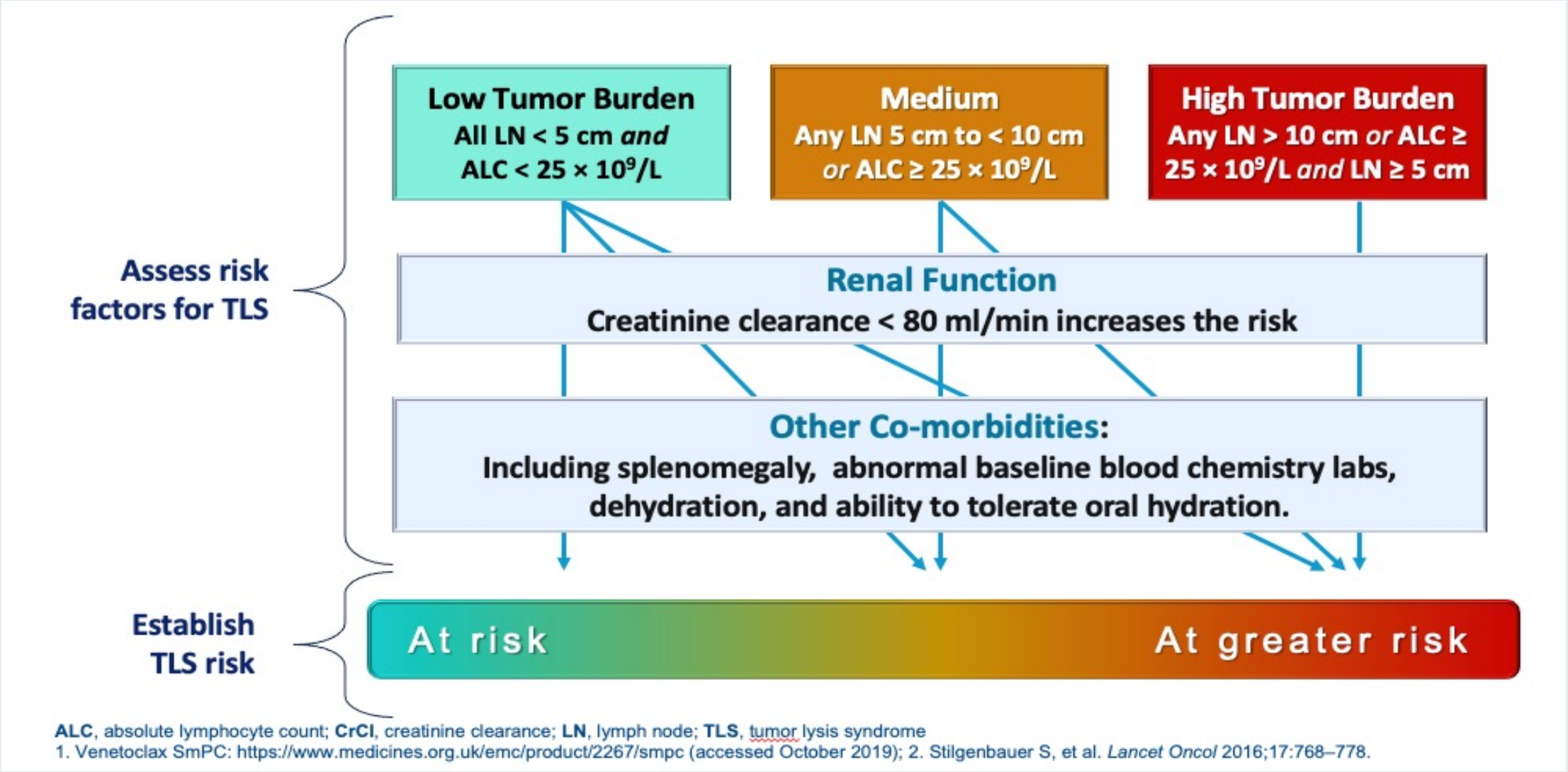
- **Obinutuzumab toxicity (infusion reaction, cytopenias, infection risk)**
- **Venetoclax toxicity (mainly TLS, some nausea)**
- **Relatively new combination regimen, health care teams still gaining expertise on patterns of toxicity and management, not typically using obinutuzumab widely**
- **Mother and children were unaware of diagnosis**
- **Continuing to work full time was a priority**
- **Symptomatic anemia**
- **Daughter active in travel sports, timed transfusions around tournaments**

Courtesy of Amy Goodrich, CRNP

Venetoclax: Drug Interactions

- Strong CYP3A inhibitors: avoid during escalation, later 75% dose reduction
- Moderate CYP3A inhibitor or P-gp inhibitors: avoid during escalation, later 50% dose reduction
- No contra-indication to anticoagulation in general, but will increase serum warfarin concentration

TLS Risk with Venetoclax Is a Continuum Based on Multiple Factors



ALC, absolute lymphocyte count; **CrCl**, creatinine clearance; **LN**, lymph node; **TLS**, tumor lysis syndrome

1. Venetoclax SmPC: https://www.medicines.org.uk/emc/product/2267/smpc (accessed October 2019); 2. Stilgenbauer S, et al. *Lancet Oncol* 2016;17:768–778.

Courtesy of Matthew S Davids, MD, MMSc

GLOW: Safety

	I+V (N = 106)	Clb+O (N = 105)
Median exposure, mos (range)	13.8 (0.7-19.5)	5.1 (1.8-7.9)
Any, %	75.5	69.5
Neutropenia[a]	34.9	49.5
Infections[b]	17.0	11.4
Thrombocytopenia	5.7	20.0
Diarrhea	10.4	1.0
Hypertension	7.5	1.9
Atrial fibrillation	6.6	0
Hyponatremia	5.7	0
TLS	0	5.7

[a]Includes 'neutrophil count decreased'; grade ≥3 febrile neutropenia: 1.9% for I+V vs 2.9% for Clb+O

[b]Includes multiple preferred terms

- After 3 cycles of ibrutinib lead-in, <2% of patients remained at risk for TLS based on high tumor burden
- 2 (1.9%) patients in I+V arm discontinued ibrutinib due to atrial fibrillation
- SAEs in ≥5% of patients for I+V vs Clb+O: Infections (12.3% vs 8.6%) and atrial fibrillation (6.6% vs 0%)
- Rate of secondary malignancies at time of analysis: 8.5% for I+V vs 10.5% for Clb+O
  - NMSC: 3.8% vs 1.9%
  - Other: 4.7% vs 8.6%

Kater A et al. EHA 2021;Abstract LB1902.

CAR T-Cell Therapy-Associated Cytokine Release Syndrome (CRS)

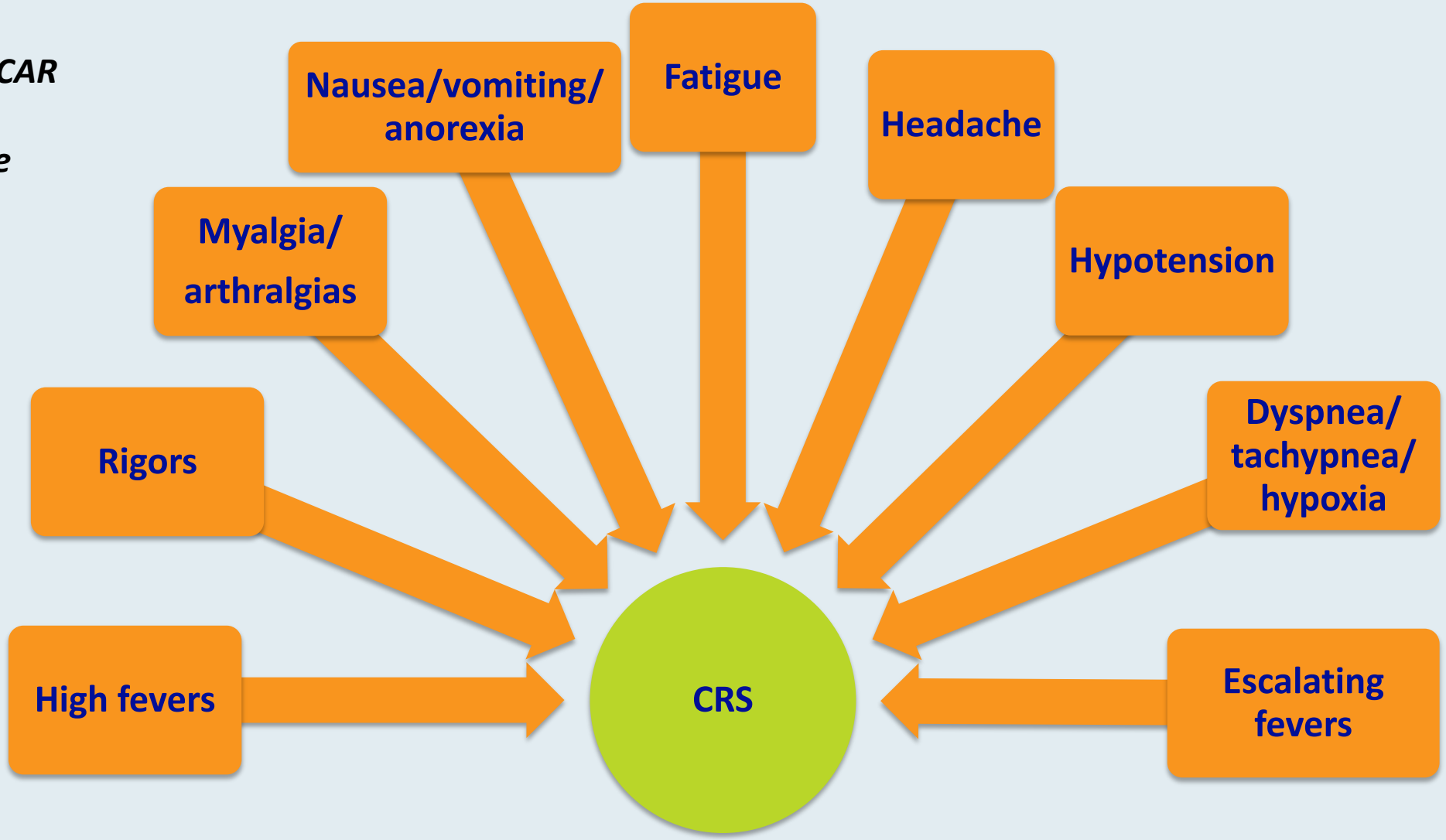
CRS — May be mild or life-threatening

- Occurs with CART19 activation and expansion
- Dramatic cytokine elevations (IL-6, IL10, IFNɣ, CRP, ferritin)
- Fevers initially (can be quite high: 105˚F)
- Myalgias, fatigue, nausea/anorexia
- Capillary leak, headache, hypoxia and hypotension
- CRS-related mortality 3% to 10%

Varadarajan I, Lee DW. *Cancer J* 2019;25(3):223-30.
Abramson JS et al. ASCO 2019 Education Book.

Cytokine Release Syndrome (CRS): Common Symptoms

Based on CAR T-cell experience



Diagnosis based on <u>clinical</u> symptoms and events

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CAR T-Cell Therapy-Associated Neurologic Toxicity

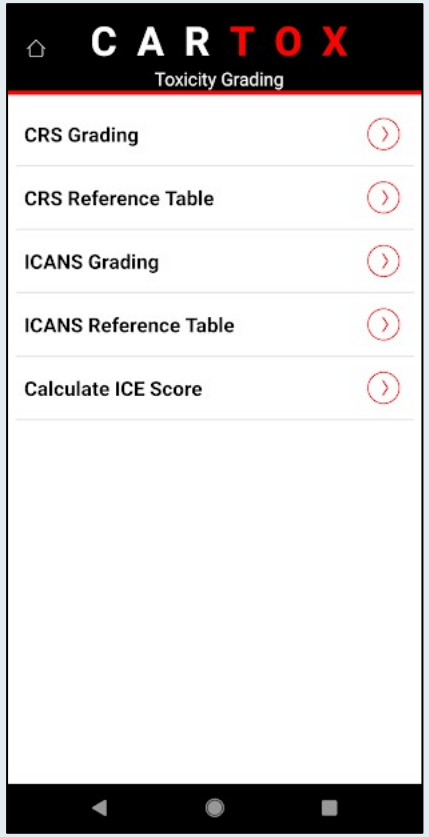
Neurologic toxicity — May be mild or life-threatening

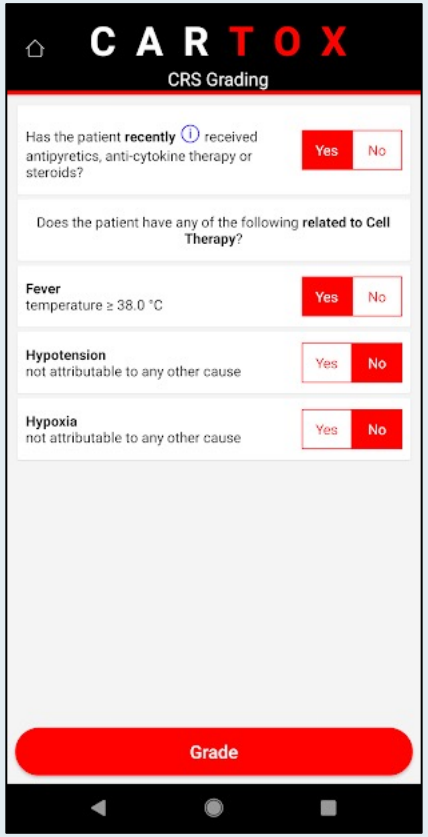
- Mechanism unclear, referred to as immune effector cell-associated neurotoxicity syndrome (ICANS)
- Encephalopathy
- Seizures
- Delirium, confusion, aphasia, agitation, sedation, coma

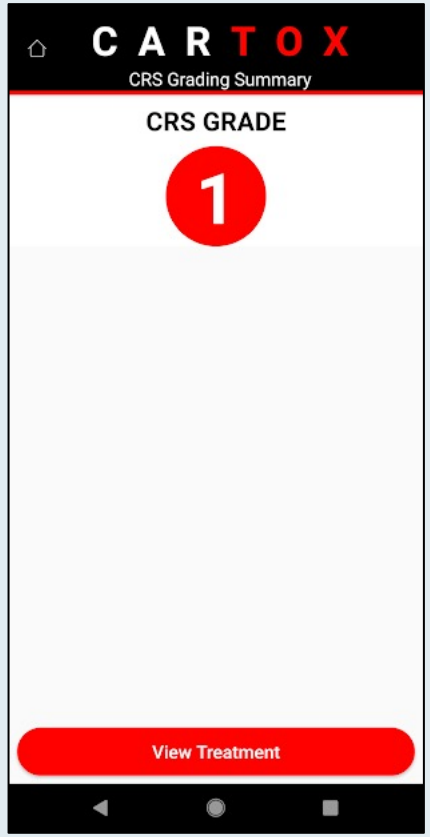
Varadarajan I, Lee DW. *Cancer J* 2019;25(3):223-30.
Abramson JS et al. ASCO 2019 Education Book.

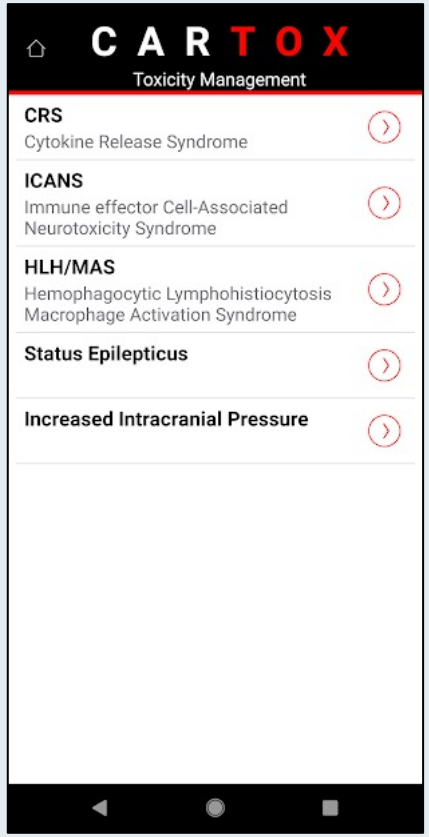
CARTOX App for Grading and Management of CRS and ICANS

Smart phone app available free on both App Store (iPhone) and Google Play (Android)









Sherry Adkins

Courtesy of Sattva S Neelapu, MD

Neelapu et al. *Nat Rev Clin Oncol,* Jan 2018

Lee et al. *Biol Blood Marrow Transplant,* 2019 Apr;25 (4):625-638

RTP RESEARCH TO PRACTICE

Patient Education Regarding CAR T-Cell Therapy

CRS	Neurotoxicity	Management of Toxicities
• Fever • Hypotension • Tachycardia • Hypoxia • Chills	• Tremors • Dizziness • Delirium • Confusion • Agitation • Cerebral Edema	• Tocilizumab • Steroids

Adkins S. *J Adv Pract Oncol 2019;10(Suppl 3):21-8.*

RTP RESEARCH TO PRACTICE

Patient Education Regarding CAR T-Cell Therapy

Logistics	Pancytopenia	Other
• Stay locally for 30 days • Inpatient vs outpatient • Frequent visits to hospital • Local Oncologist to coordinate care • Caregiver 24 hours a day	• Decreased blood counts • Blood and Platelet Transfusions • Growth Factor Support • Infections • Prophylactic Antibiotics	• When to come to ER • When to call the clinic • Ensure caregivers are present • Contact local oncologist

Adkins S. *J Adv Pract Oncol 2019;10(Suppl 3):21-8.*

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Blood 2022;139(12):1794-806

Phase 1 TRANSCEND CLL 004 study of lisocabtagene maraleucel in patients with relapsed/refractory CLL or SLL

Tracking no: BLD-2021-011895R2

Tanya Siddiqi (City of Hope Medical Center, United States) Jacob Soumerai (Massachusetts General Hospital Cancer Center, United States) Kathleen Dorritie (UPMC, United States) Deborah Stephens (University of Utah, United States) Peter Riedell (University of Chicago, United States) Jon Arnason (BIDMC, United States) Thomas Kipps (University of California-San Diego School of Medicine, United States) Heidi Gillenwater (Bristol Myers Squibb, United States) Lucy Gong (Bristol Myers Squibb, United States) Lin Yang (Bristol Myers Squibb, United States) Ken Ogasawara (Bristol Myers Squibb, United States) Jerill Thorpe (Bristol Myers Squibb, United States) William Wierda (University of Texas M.D. Anderson Cancer Center, United States)

TRANSCEND CLL 004: Rates of Cytokine Release Syndrome (CRS), Neurologic Events (NE) and Rehospitalization After Liso-cel Infusion

	All patients (N = 23)	Dose level 1 50×10^6 (n = 9)	Dose level 2 100×10^6 (n = 14)
CRS any grade	17 (74%)	7 (78%)	10 (71%)
CRS Grade ≥3	2 (9%)	0	2 (14%)
NE any grade	9 (39%)	2 (22%)	7 (50%)
NE Grade ≥3	5 (21%)	2 (22%)	2 (14%)
Reasons for patient rehospitalization			
Adverse events	11 (48%)	3 (33%)	8 (57%)
CRS and/or NE	5 (22%)	1 (11%)	4 (29%)
CRS and NE	2 (9%)	0	2 (14%)
NE only	3 (13%)	1 (11%)	2 (14%)

Siddiqi T et al. *Blood* 2022;139(12):1794-806

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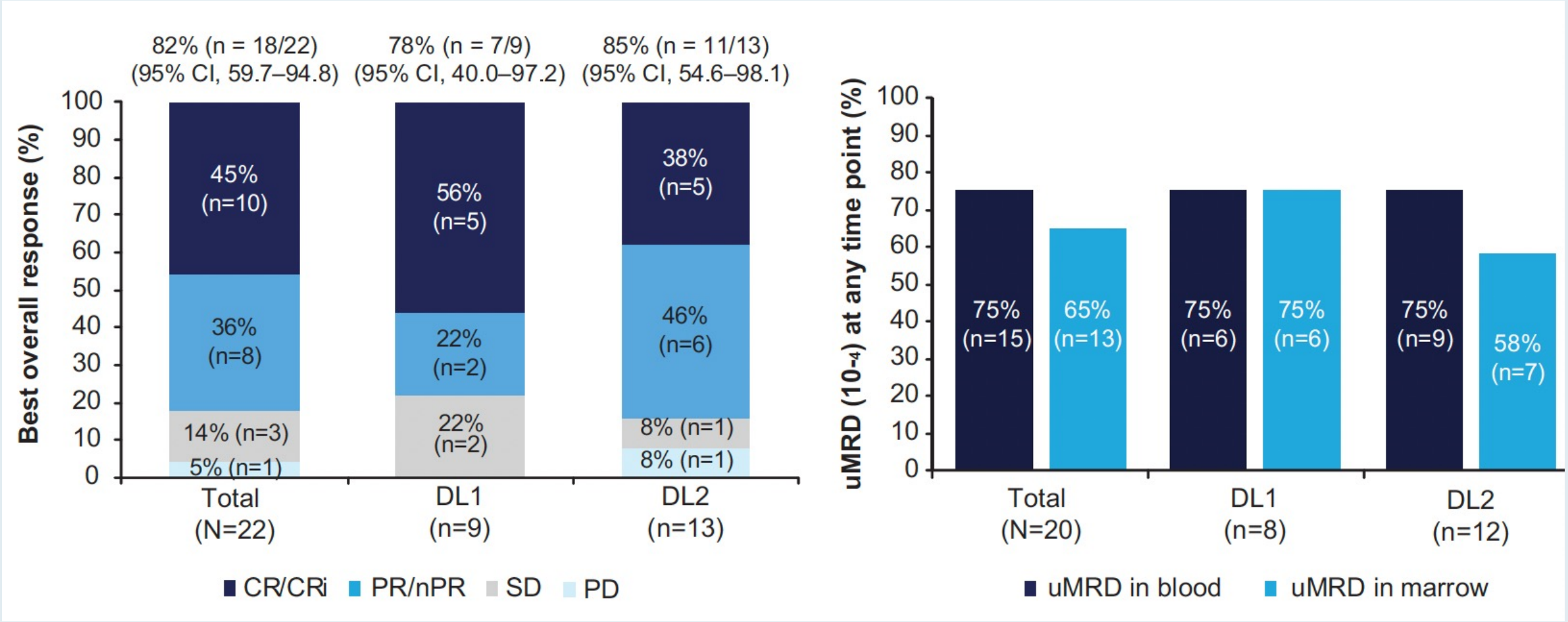
TRANSCEND CLL 004: Response and uMRD (10^{-4}) Rates



Siddiqi T et al. *Blood* 2022;139(12):1794-806

What I Tell My Patients:
New Treatments and Clinical Trial Options

An NCPD Hybrid Symposium Series
Held During the 47th Annual ONS Congress

Breast Cancer

Friday, April 29, 2022
6:00 PM – 8:00 PM PT

Faculty

Jamie Carroll, APRN, MSN, CNP
Sara A Hurvitz, MD
Kelly Leonard, MSN, FNP-BC
Hope S Rugo, MD

Moderator

Neil Love, MD

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