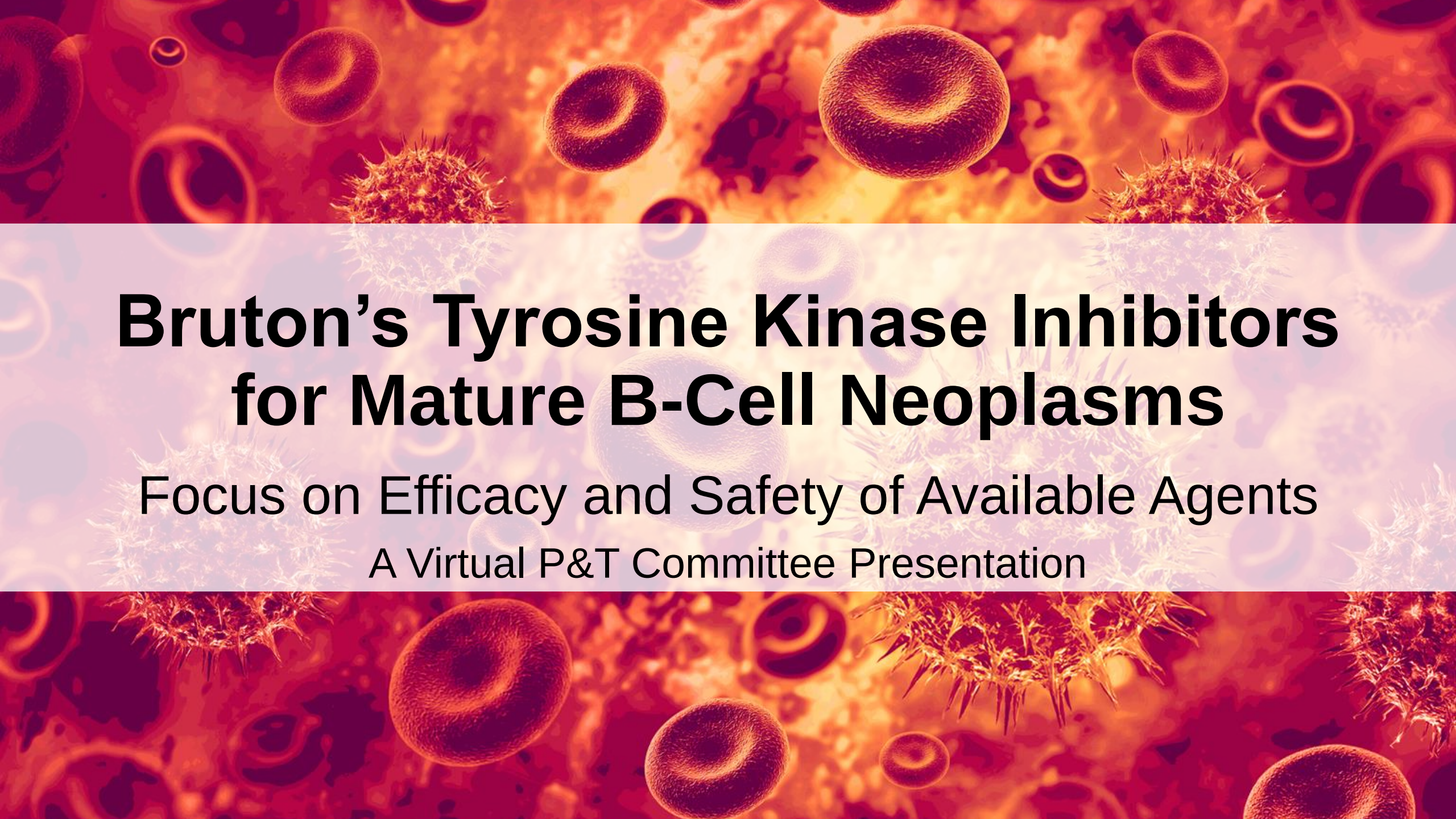
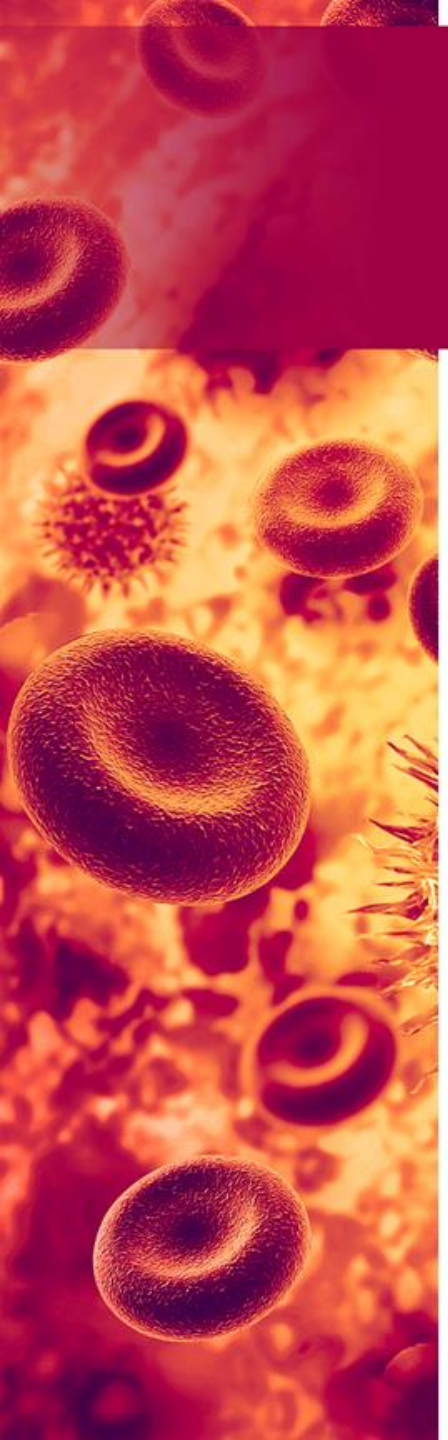


Bruton's Tyrosine Kinase Inhibitors for Mature B-Cell Neoplasms

Focus on Efficacy and Safety of Available Agents

A Virtual P&T Committee Presentation



This educational activity is sponsored by Postgraduate Healthcare Education, LLC and supported by an educational grant from AstraZeneca Pharmaceuticals LP.

Moderator

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Clinical Manager, Oncology Pharmacy
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Dr. Fausel is the Clinical Manager of the Oncology Pharmacy at the Indiana University Simon Cancer Center in Indianapolis and oversees clinical and dispensing activities for oncology pharmacy services at Indiana University Health academic health center. He also serves as Chairman of the Board of the Hoosier Cancer Research Network, a non-profit organization that conducts clinical trials and translational research in cancer and serves as the administrative headquarters of the Big Ten Cancer Research Consortium. Dr. Fausel is the Chair of a biomedical Institutional Review Board (IRB) and serves on the IRB Executive Committee for Indiana University.

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Faculty

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Professor, Department of Hematology and Medical Oncology and
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Dr. Harvey is Professor of Hematology and Medical Oncology at the Winship Cancer Institute of Emory University. He serves as director of the Winship Cancer Institute's Phase I Clinical Trials Unit and Section and as chair of the Data and Safety Monitoring Committee. He is a Fellow of the American College of Clinical Pharmacy and a Fellow of the Hematology/Oncology Pharmacy Association.

Dr. Harvey obtained his Bachelor’s of Pharmacy and Doctor of Pharmacy degrees at the University of North Carolina at Chapel Hill (UNC). He completed subsequent training at the University of Kentucky Medical Center and School of Pharmacy and specialized in Hematology/Oncology at UNC.

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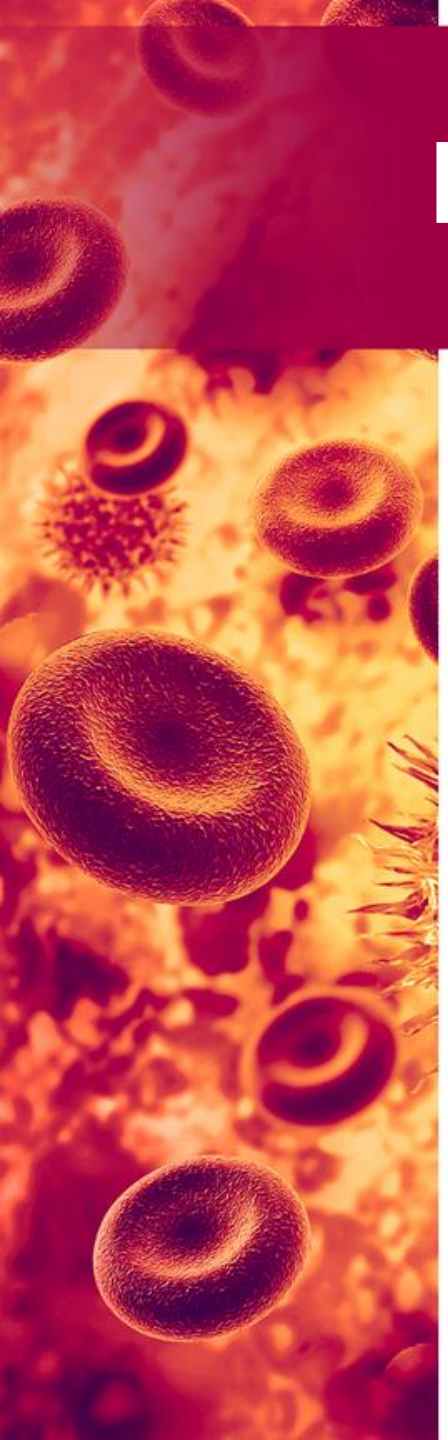

Disclosures

Drs. Fausel and Whited have no relevant affiliations or financial relationships with a commercial interest to disclose.

Dr. Buie has disclosed that he serves/has served as a consultant for Amgen, Pfizer, and Jazz Pharmaceuticals.

Dr. Harvey has disclosed that he has served as a consultant for BMS, Genentech, and Takeda and that his institution has received research funding from Abbvie, Amgen, Arqule, AstraZeneca, Boston Biomedical, Bristol-Myers Squibb, Calithera, Celgene, Cleave, Corvus, Eli Lilly, Five Prime Therapeutics, GenMab, Halozyme, Ignyta, Incyte, Merck, Nektar, Pfizer, Regeneron, Rgenix, Sanofi, Syndax, Takeda, Tesaro, Vertex, and Xencor that supports his salary.

The clinical reviewer, Megan May, PharmD, BCOP, has no actual or potential conflict of interest in relation to this program.

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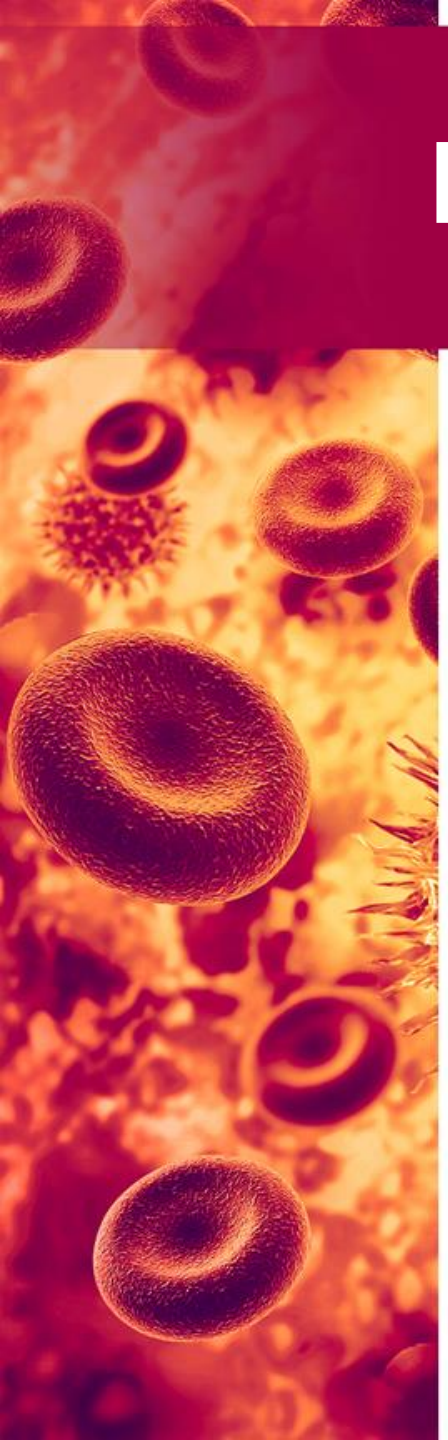
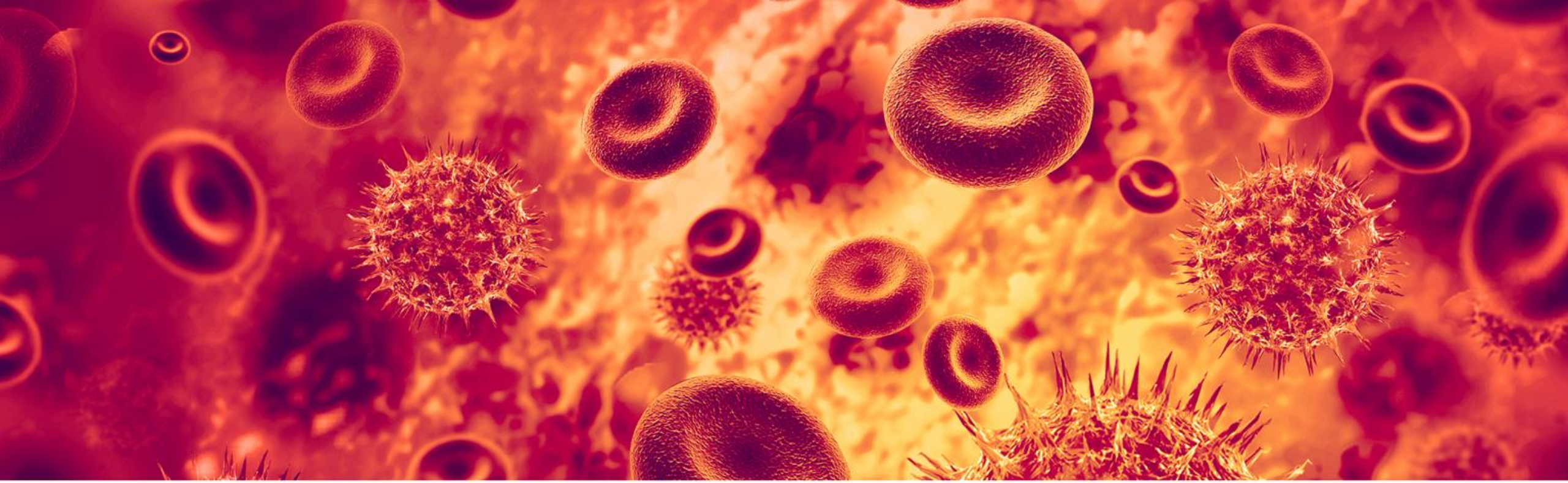
Type of Activity: Application



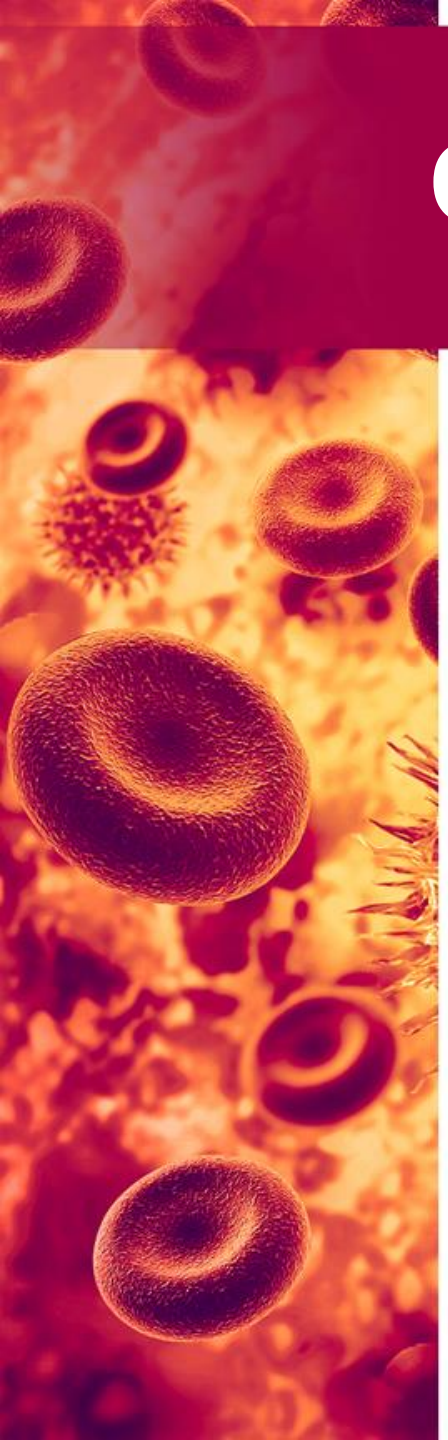
Learning Objectives

- **Compare and contrast** the Bruton's tyrosine kinase (BTK) inhibitors, including their pharmacological differences
- **Discuss** key published clinical trials, ongoing clinical trials, and guideline recommendations for BTK inhibitors in mantle cell lymphoma (MCL) and chronic lymphocytic leukemia (CLL)
- **Design** a treatment plan involving an appropriate BTK inhibitor and corresponding safety considerations
- **Formulate** effective strategies for ensuring the proper selection and use of BTK inhibitors in the care of individual patients and patient populations



Overview of CLL & MCL

Chris Fausel

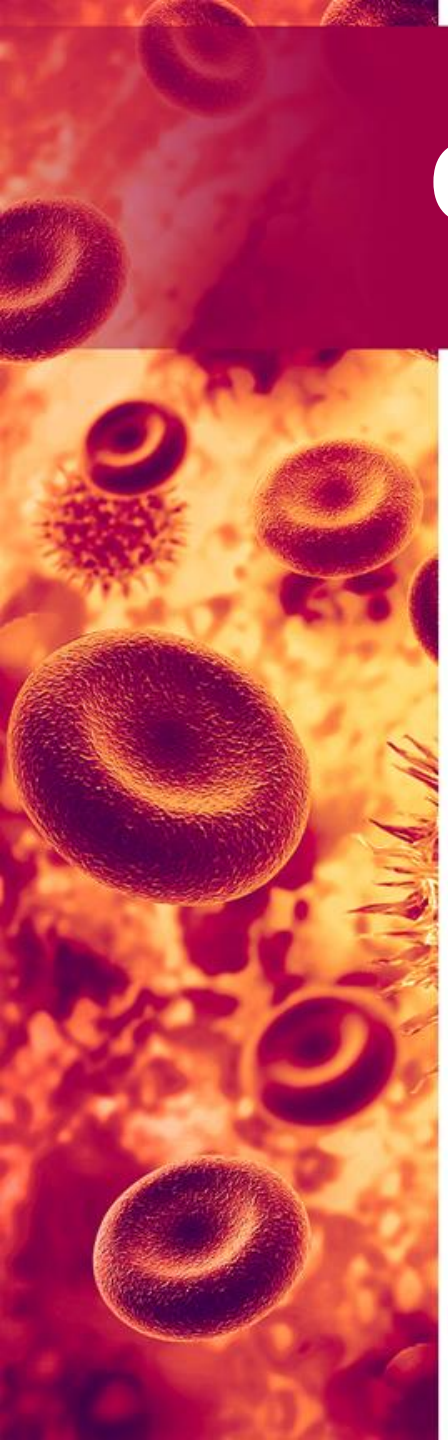


Chronic Lymphocytic Leukemia

- Most common leukemia in Western countries
- 20,720 estimated new cases in United States (U.S.) in 2019
  - 3930 estimated annual deaths
- 5-year overall survival (OS) = 85%
- Median age at diagnosis = 70 years

National Cancer Institute. https://seer.cancer.gov/statfacts/html/clyl.html. Accessed July 30, 2019.

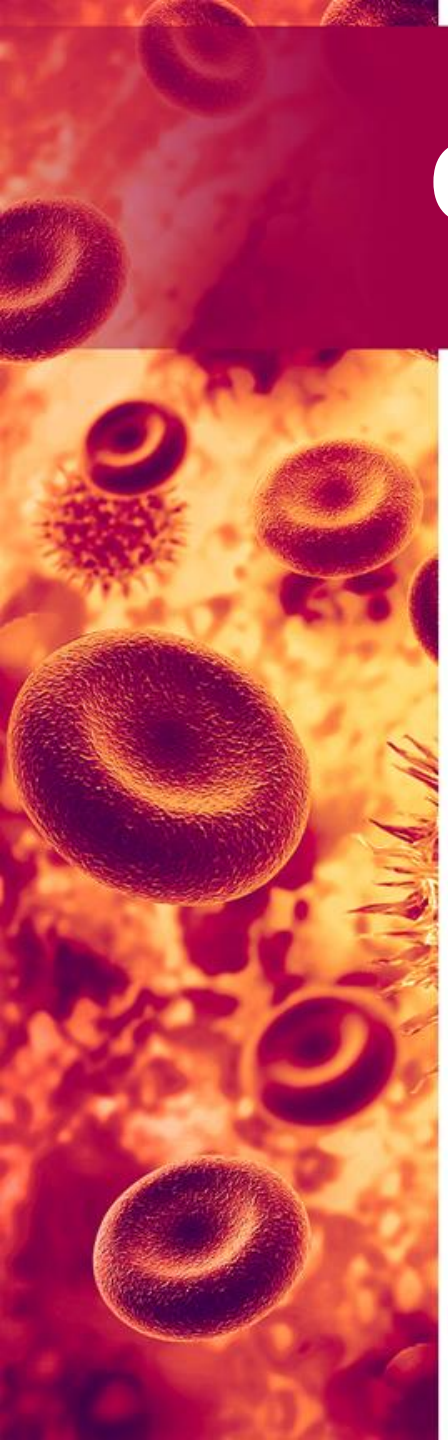
CLL: Diagnosis



- Presence of > 5000/µL monoclonal lymphocytes in the peripheral blood by flow for at least 3 months
- CD5-, CD23-, CD19-, and CD20-positive cells
- Expression of surface immunoglobulin is typically lower than normal B-cells

Hallek M. *Am J Hematol*. 2017;92(2):946-65.

CLL: Disease Course



- Indolent disease
- Survival ranges from 1 to 20 years following diagnosis
- Survival depends on stage of disease
  - **Rai Stage 0: > 15 years**
  - **Rai Stage IV: 3 – 4 years**
- Richter's transformation = transformation to diffuse large cell lymphoma (< 5%)

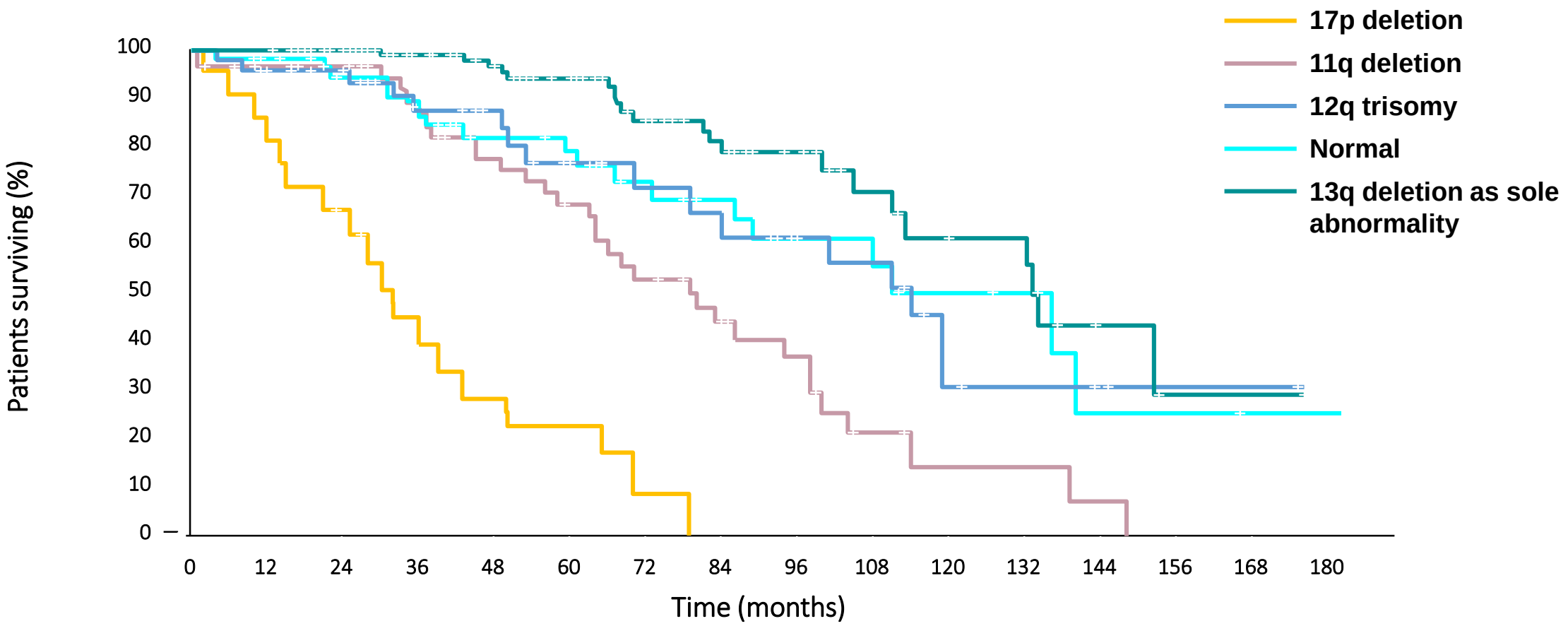
Chiorazzi N, et al. *N Engl J Med*. 2005;352(8):804-15.

CLL: Presence of Cytogenetic Abnormalities

Aberration	No. of Patients (%)
13q deletion	178 (55)
11q deletion	58 (18)
12q trisomy	53 (16)
17p deletion	23 (7)
6q deletion	21 (6)
8q trisomy	16 (5)
t(14q32)	12 (4)
3q trisomy	9 (3)
Clonal abnormalities	268 (82)
Normal karyotype	57 (18)

Döhner H, et al. *N Engl J Med*. 2000;343(26):1910-6.

Cytogenetics and Overall Survival



Döhner H, et al. *N Engl J Med*. 2000;343(26):1910-6.

CLL International Prognostic Index (IPI)

- 3472 treatment-naïve patients
  - Median age: 61 years (range, 27-86 years)
- 5 independent prognostic factors impacting **OS**:
  - ***TP53* status/del(17p)**
  - ***IGHV* mutational status**
  - **Serum β2-microglobulin (≤ 3.5 mg/L vs. > 3.5 mg/L)**
  - **Clinical stage (Binet A/Rai 0 vs. Binet B-C/Rai I – IV)**
  - **Age (≤ 65 years vs. > 65 years)**

International CLL-IPI Working Group. *Lancet Oncol*. 2016;17(6):779-90.

CLL-IPI: Prognostic Scoring

Prognostic Variable	Assigned Risk Score
TP53 status/del(17p)	4
IGHV mutational status	2
Serum β2-microglobulin (≤ 3.5 mg/L vs. > 3.5 mg/L)	2
Clinical stage (Binet A/Rai 0 vs. Binet B-C/Rai I – IV)	1
Age (≤ 65 years vs. > 65 years)	1

International CLL-IPI Working Group. *Lancet Oncol*. 2016;17(6):779-90.

CLL-IPI: Overall Survival

Prognostic Category	CLL-IPI Risk Score	5-Year OS	10-Year OS
Low	0 - 1	93.2%	79%
Intermediate	2 - 3	79.3%	39.2%
High	4 - 6	63.3%	21.9%
Very high	7 - 10	23.3%	3.5%

International CLL-IPI Working Group. *Lancet Oncol*. 2016;17(6):779-90.

Indications for Treatment

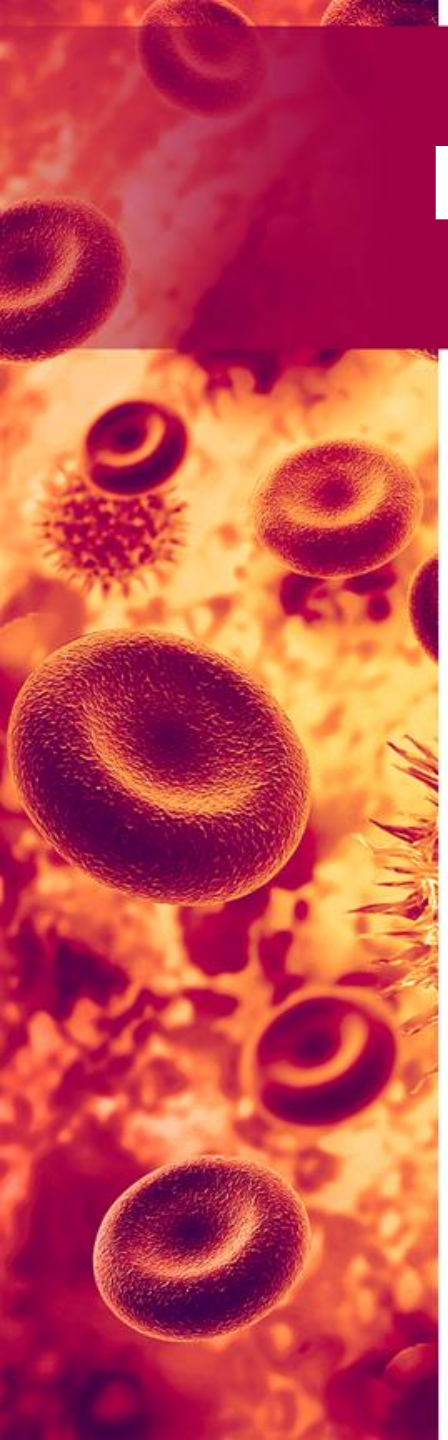
Clinical Scenario	Comment
Progressive bone marrow failure	Anemia/thrombocytopenia
Massive or progressive symptomatic splenomegaly	≥ 6 cm below the costal margin
Massive or progressive lymphadenopathy	≥ 10 cm in longest diameter
Progressive lymphocytosis	Increase of > 50% over 2 months
Lymphocyte doubling time of < 6 months	< 30,000 µL may require longer observation
Autoimmune anemia or thrombocytopenia	Poorly responsive to corticosteroids or other therapies
Disease-related symptoms	Weight loss, fatigue, fevers, night sweats

Hallek M, et al. *Blood*. 2008;111(12):5446-56.

Historical Treatments for CLL

Traditional Chemotherapy	Immunotherapy	Targeted Therapy
Bendamustine Chlorambucil Cladribine Corticosteroids Fludarabine Pentostatin Combination chemotherapy: • Cyclophosphamide, doxorubicin, vincristine, prednisone (CHOP) • Cyclophosphamide, doxorubcin, prednisone	Rituximab Alemtuzumab Ofatumumab Obinutuzumab	Idelalisib Ibrutinib Lenalidomide Venetoclax Duvelisib Acalabrutinib

Halleck M. *Am J Hematol*. 2017;92(9):946-65.;
National Comprehensive Cancer Network. https://www.nccn.org/professionals/physician_gls/pdf/cll.pdf. Published August 23, 2019.

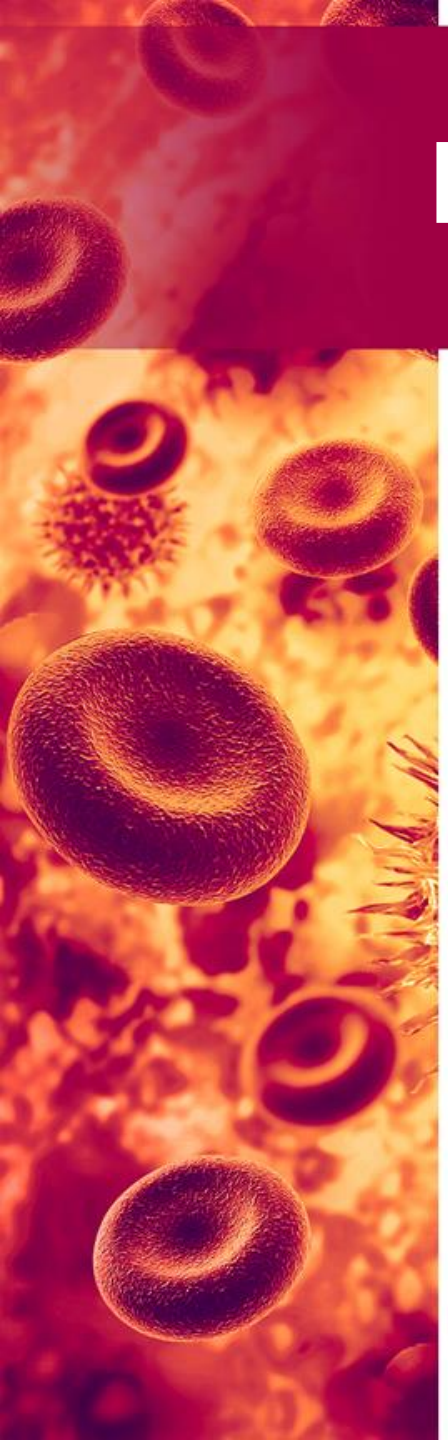


Mantle Cell (non-Hodgkin) Lymphoma

- Approximately 4400 estimated new cases in U.S. in 2019
  - 3% – 10% of all non-Hodgkin lymphoma (NHL) cases
- 5-year OS = 77%
- Median age at diagnosis = 68 years

Jain P, Wang M. *Am J Hematol*. 2019;94(6):710-25.;
National Cancer Institute. https://seer.cancer.gov/statfacts/html/nhl.html. Accessed July 30, 2019.

MCL: Diagnosis

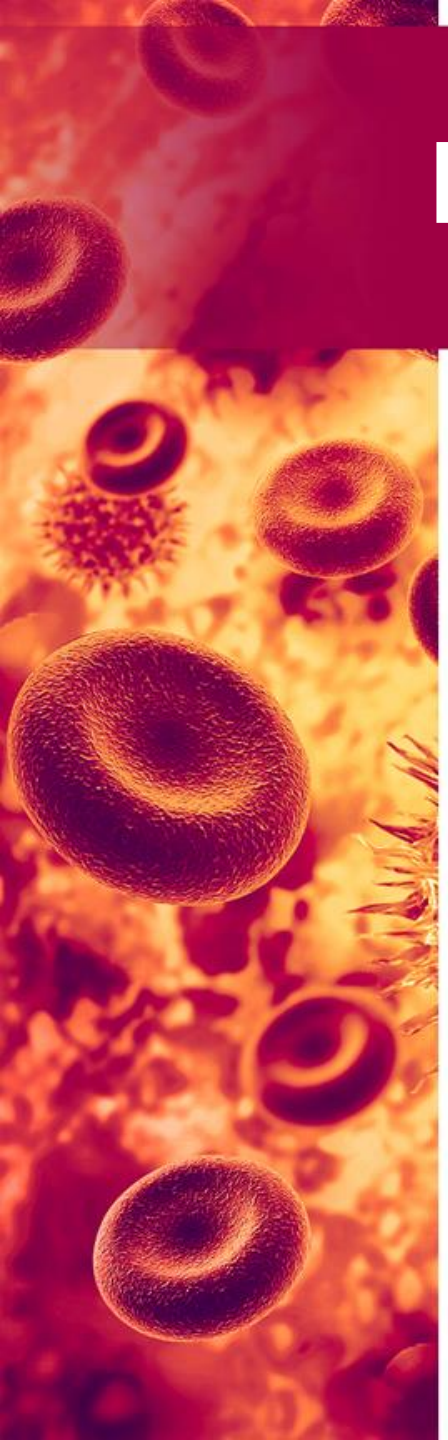


- Disease presentation includes lymphadenopathy (75%) and often extranodal involvement secondary to the aggressive growth profile of the disease
- Excisional biopsy of involved lymph node
  - Histologic pattern: may be nodular, diffuse, pleomorphic, or blastoid
  - Immunophenotyping:
    - **Positive**: CD19, CD20, CD22, CD43, CD79a, CD5, and FMC7
    - **Negative**: CD23, CD10, CD200, and BCL6
- Staging: CBC, β-2 microglobulin, LDH, unilateral bone marrow biopsy, CT from neck to pelvis/PET may be useful
- GI tract is involved in most cases
  - Pathogenic confirmation is not generally necessary

Cheah CY, et al. *J Clin Oncol*. 2016;34(11):1256-69.

CBC, complete blood count; CT, computed tomography; GI, gastrointestinal; LDH, lactate dehydrogenase; PET, positron emission tomography.

MCL: Disease Course



- Aggressive disease
- Typically responds well to initial therapy only to relapse later
- Survival:
  - **Initial therapy:**
    - **OS: 5 – 10 years**
    - **Progression-free survival (PFS): 3 – 7 years**
  - **Relapsed disease:**
    - **OS: 12 – 36 months**
    - **Duration of response (DOR): 6 – 16 months**

Cheah CY, et al. *J Clin Oncol*. 2016;34(11):1256-69.

Simplified MIPI Calculations

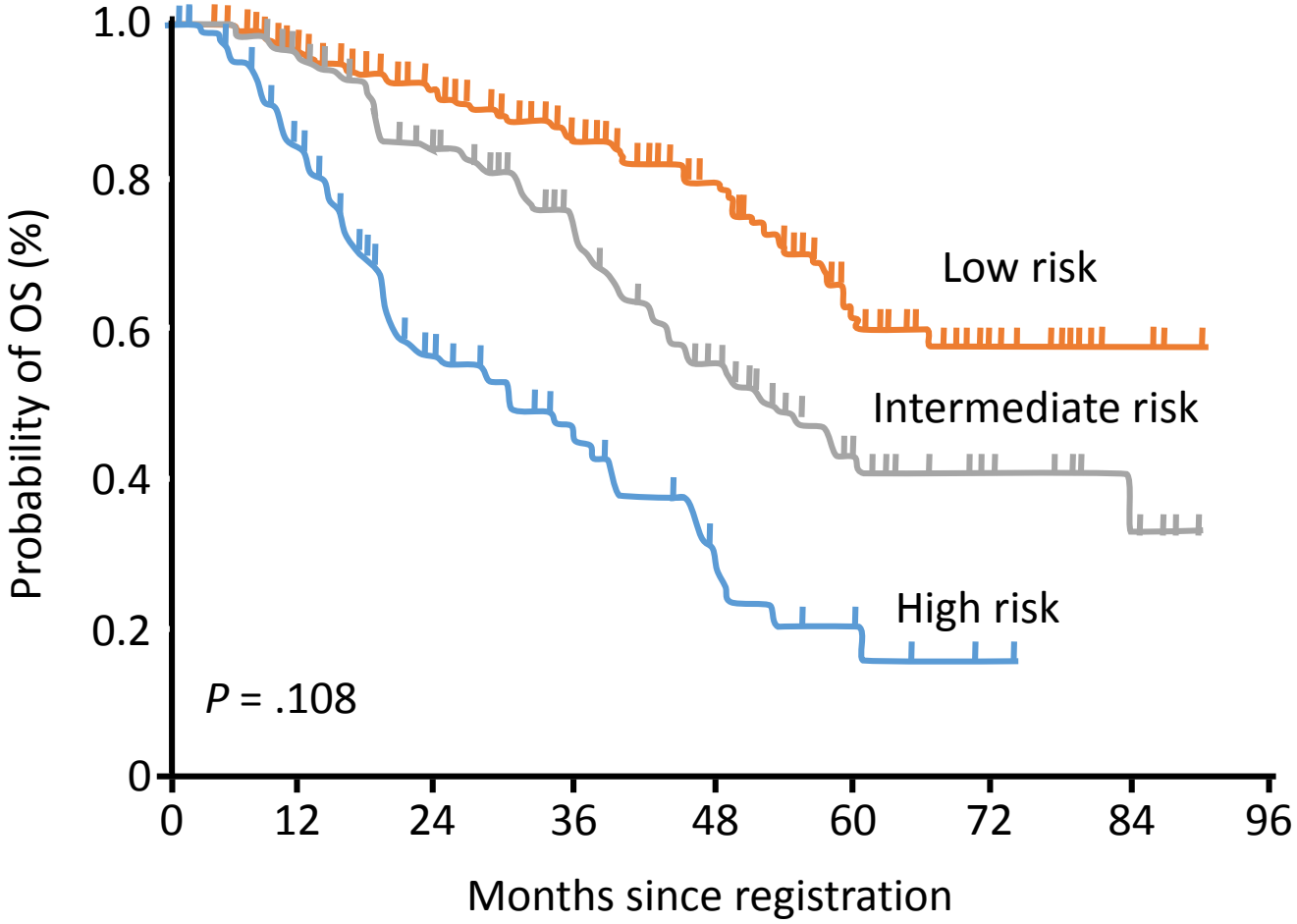
- 4 prognostic factors for survival
  - Age, PS, LDH, leukocyte counts
- Risk groups are well separated
  - Low: 0-3 points
  - Intermediate: 4-5 points
  - High: 6-11 points

Points	Age, years	ECOG PS	LDH x ULN	WBC, 10^9/L
0	< 50	0-1	< 0.67	< 6.7
1	50-59	--	0.68-0.99	6.7 < 10
2	60-69	2-4	1.0-1.49	10 < 15
3	≥ 70	--	≥ 1.5	≥ 15

ECOG, Eastern Cooperative Oncology Group; PS, performance status; ULN, upper limit of normal; WBC, white blood cell.

Hoster E, et al. *Blood*. 2008;111(2):558-65.

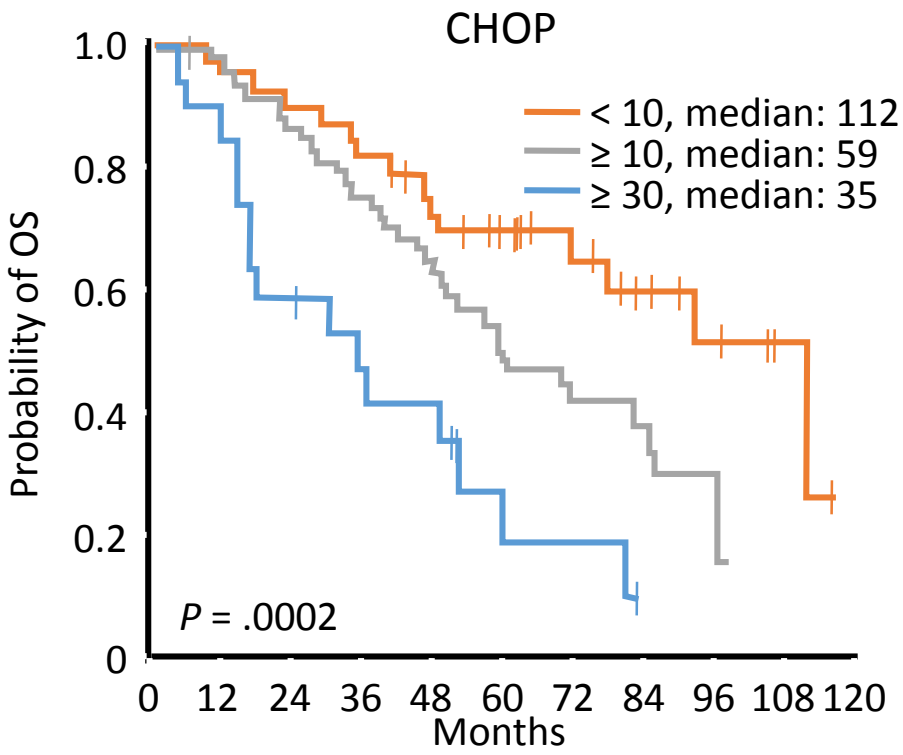
MCL OS According to MCL-IPI (MIPI)

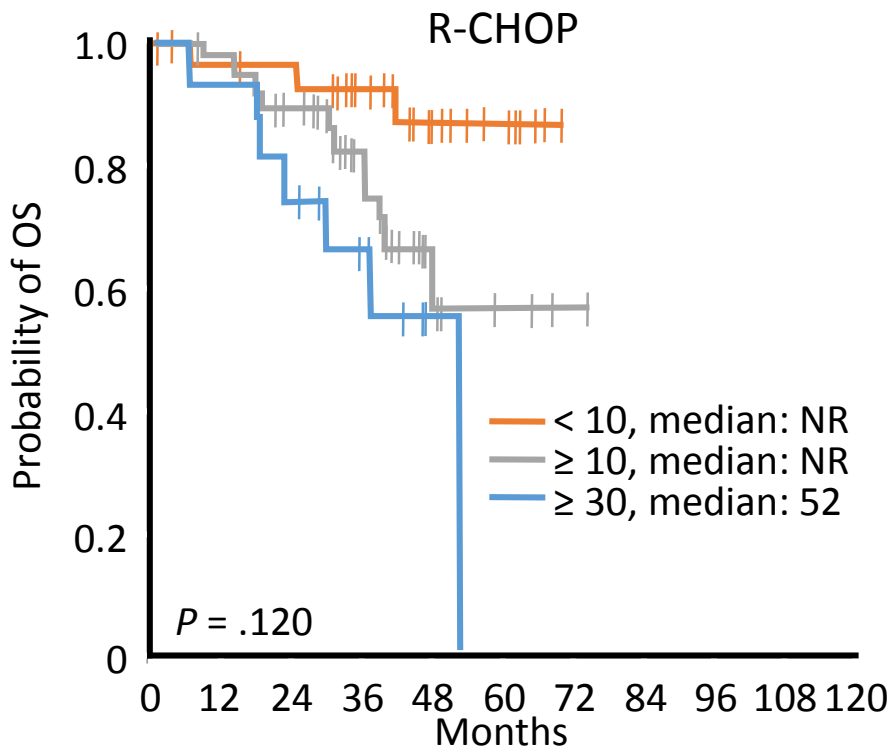


Hoster E, et al. *Blood*. 2008;111(2):558-65.

Ki-67 Index: Prognostic Value in MCL

- Proliferation index measured by the percentage of Ki67-positive cells
- Performed on diagnostic tissue
- Strong prognostic relevance for OS

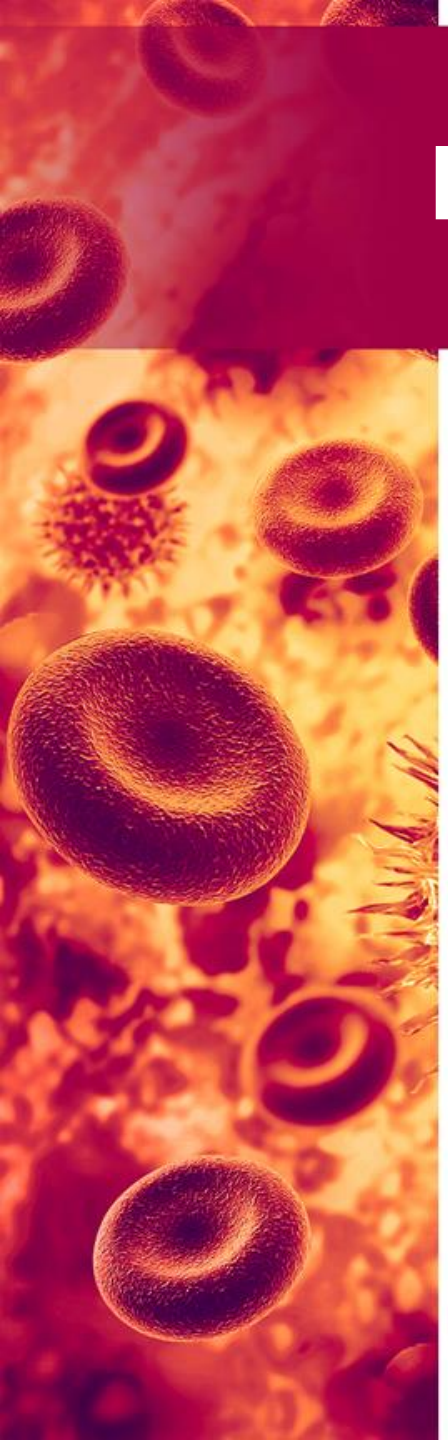




Bertoni F, Ponzoni M. *Int J Biochem Cell Biol*. 2007;39(1):1747-53.; Determann O, et al. *Blood*. 2008;111(4):2385-7.

NR, not reached; R-CHOP, cyclophosphamide/doxorubicin/vincristine/prednisone plus rituximab.

Presence of Cytogenetic Abnormalities



- Molecular hallmark: t(11;14)(q13;q32)
- Transposes the cell cycle regulator CCND1 (11q13) leading to constitutive expression of cyclin D1
  - Cyclin D1 binds to cyclin-dependent kinases 4 and 6 (CDK4/6) and causes cell cycle dysregulation
  - Cyclin D1 induces chromosomal instability, transcriptional regulation, and epigenetic modulation
- Acquisition of secondary genetic alterations contribute to aggressive disease course
  - SOX11, PAX5

Cheah CY, et al. *J Clin Oncol*. 2016;34(11):1256-69.

Historical Treatments for MCL

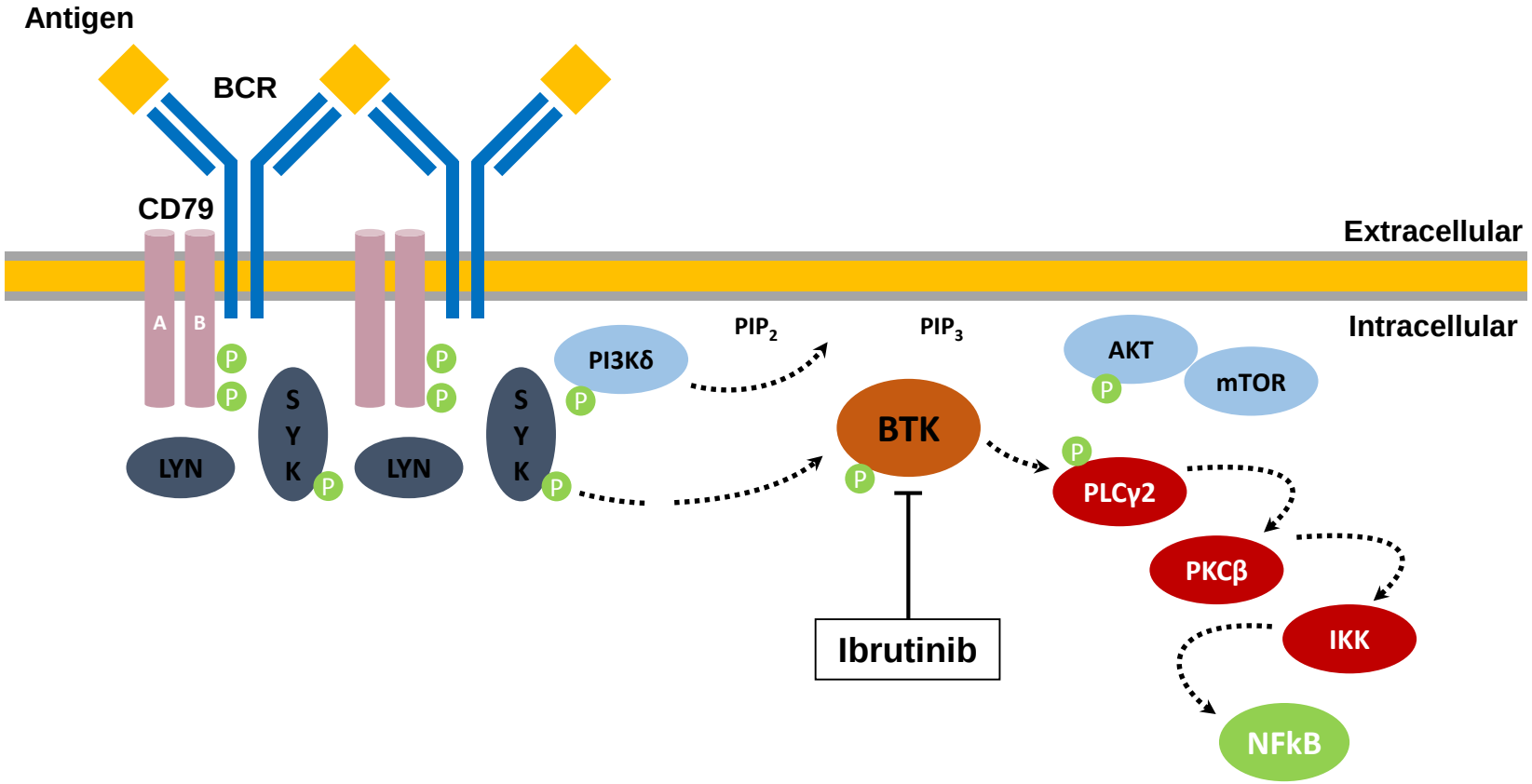
First-Line Therapy*	Relapsed Disease
R-CHOP	Bortezomib
R-hyperCVAD	Ibrutinib ± rituximab
R-DHA	Lenalidomide ± rituximab
Bendamustine-rituximab	Venetoclax
R-DHAP	Acalabrutinib
R-maxiCHOP	Allogeneic stem cell transplant
VR-CAP	

**Often followed by consolidation high-dose chemotherapy with autologous hematopoietic stem cell transplant (autoHCT) and/or rituximab maintenance*

R-DHAP, rituximab, dexamethasone, cytarabine, cisplatin; R-HyperCVAD, rituximab, cyclophosphamide, vincristine, doxorubicin, dexamethasone alternating with methotrexate, cytarabine, methylprednisolone; VR-CAP, bortezomib, rituximab, cyclophosphamide, doxorubicin, prednisone.

Cheah CY, et al. *J Clin Oncol*. 2016;34(11):1256-69.;
National Comprehensive Cancer Network. https://www.nccn.org/professionals/physician_gls/pdf/b-cell.pdf. Published June 18, 2019.

BTK Inhibition



Buchner M, Muschen M. *Curr Opin Hematol*. 2014;21(4):341-9.; Wiestner A. *J Clin Oncol*. 2013;31(1):128-30.

Ibrutinib Overview

Dose: 420 – 560 mg PO daily until disease progression	
Lymphocytosis	Transient: occurs during the first weeks to months of therapy Should not be confused with disease progression
Surgery interruptions	Hold 3 days before and after a minor surgical procedure Hold 7 days before and after a major surgical procedure
Drug interactions	CYP3A inhibitors: modify dose as needed, depending on strength of inhibitor CYP3A inducers: should be avoided when possible
Warnings	Hemorrhage, infections, cytopenias, cardiac arrhythmias, hypertension, second primary malignancies, tumor lysis syndrome

CYP, cytochrome P450; PO, by mouth.

Imbruvica [package insert]. Sunnyvale, CA: Pharmacyclics; 2019.

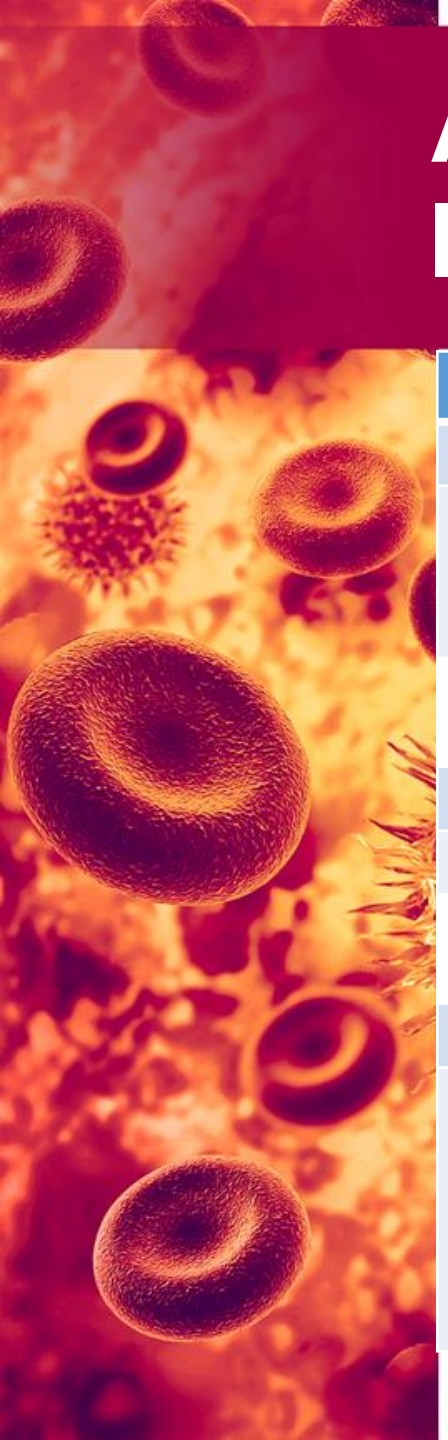
Acalabrutinib Overview

FDA Approval: October 31, 2017	
FDA-labeled indication	Treatment of adult patients with MCL with at least 1 prior line of therapy
Pharmacology	Small-molecule BTK inhibition: forms covalent bond with cysteine residue in the BTK active site, leading to inhibition of BTK enzymatic activity. BTK inhibition results in decreased B-cell proliferation, trafficking, chemotaxis, and adhesion.
Dosing	100 mg by mouth every 12 hours with or without food
Drug interactions	CYP3A inhibitors: avoid strong inhibitors (e.g., itraconazole); moderate inhibitors, reduce acalabrutinib dose to 100 mg/day CYP3A inducers (e.g., rifampin): avoid inducers or increase dose to 200 mg by mouth twice daily Gastric acid-reducing agents: avoid PPIs; separate dosing of acalabrutinib and H2-antagonists or antacids by at least 2 hours

FDA, U.S. Food and Drug Administration; H2, histamine 2 receptors; PPIs, proton pump inhibitors.

Calquence [package insert]. Wilmington, DE: AstraZeneca Pharmaceuticals LP; 2017.

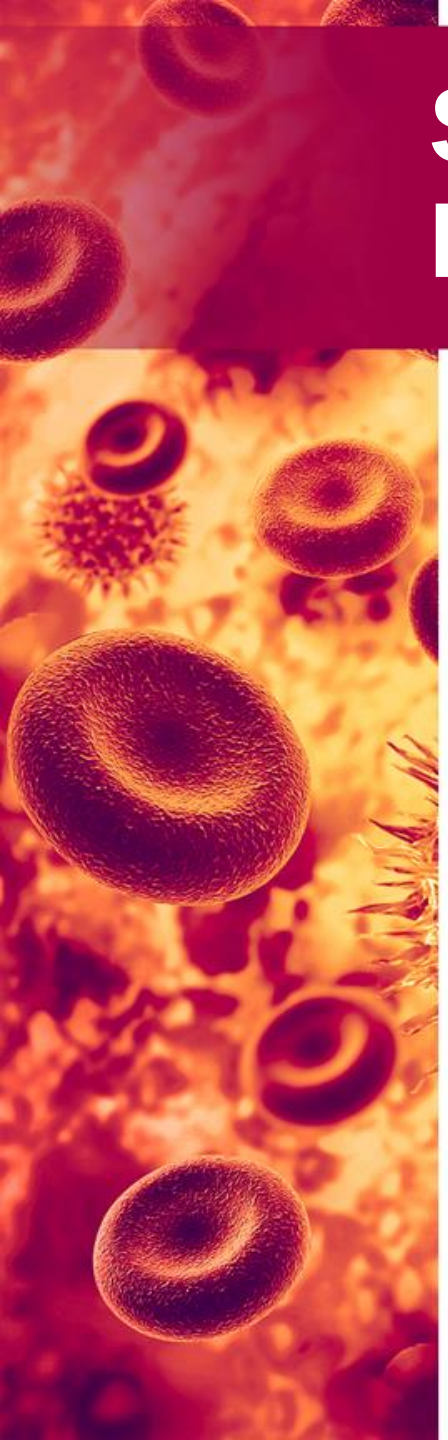
Adverse Events of Available BTK Inhibitors



Ibrutinib	Acalabrutinib
Cytopenias (grade 3/4)	
Neutropenia, 13% to 29% (with risk of febrile neutropenia) Thrombocytopenia, 5% to 17% Anemia, 0% to 13%	Neutropenia, 10% to 23% Thrombocytopenia, 5% to 8% Anemia, 5% to 11%
Hold BTK inhibitors for grade 3 neutropenia with infection or fever or grade 4 cytopenia	
Infection (grade 3-5)	
14% to 29% of patients	11% to 18% of patients
Consider prophylaxis in patients who are at increased risk for opportunistic infections	
Other notable adverse events (all grades)	
Cardiac arrhythmia, 1% Bleeding/bruising, 19 to 39% Rash, 12 to 36% Diarrhea (early, self-limited, typically responds to loperamide), 28 to 59% Muscle cramping (late, can be very bothersome), 14 to 40% Pneumonitis (rare but serious; discontinue ibrutinib), 11 to 21%	Cardiac arrhythmia, 3% Bleeding/bruising, 8 to 21% Rash, 18% Headaches, 39% Diarrhea, 31%

Calquence [package insert]. Wilmington, DE: AstraZeneca Pharmaceuticals LP; 2017.; Imbruvica [package insert]. Sunnyvale, CA: Pharmacyclics; 2019.

Side Effects of Available BTK Inhibitors: Bruising and Hemorrhage

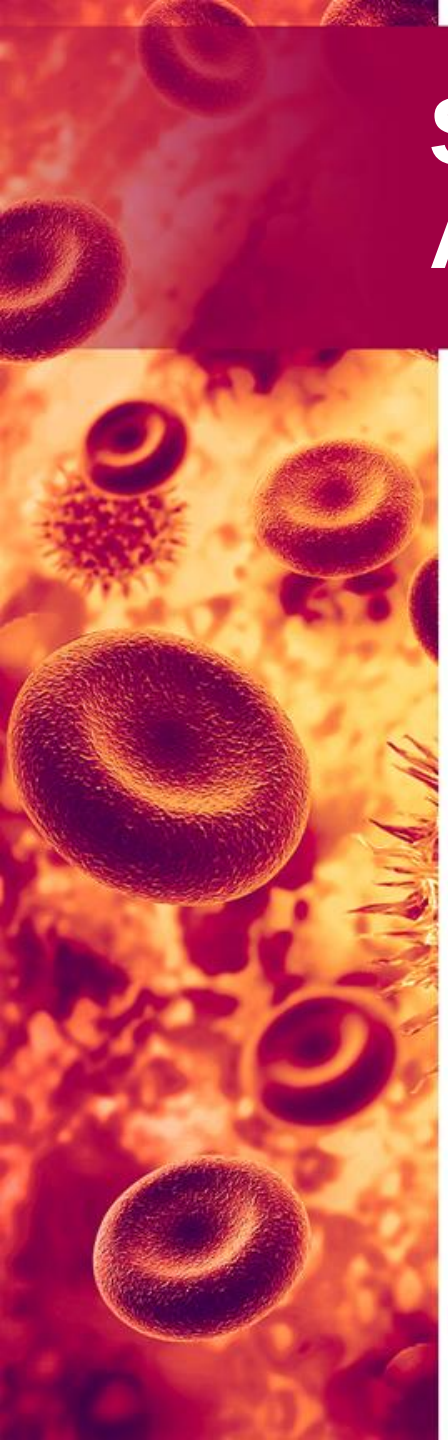


Ibrutinib	Acalabrutinib
• Bleeding consistent with "hemostatic failure" with bruising and subcutaneous bleeding with minor trauma in up to 50% of patients • Grade ≥ 3 hemorrhage: up to 6%	• Overall, bleeding events, including bruising and petechiae of any grade, occurred in approximately 50% of patients • Grade ≥ 3 hemorrhage: up to 3%

Clinical Management
• Impact of platelet aggregation is reversible within 1 week of discontinuation • Recommend holding BTK inhibitor prior to and after invasive procedures for 3 (minor) to 7 (major) days • Blood thinner or antiplatelet agents (e.g., aspirin, clopidogrel, prasugrel, ticagrelor) may increase bleeding risk • Anticoagulants may increase bleeding risk by impacting multiple hemostatic pathways

Calquence [package insert]. Wilmington, DE: AstraZeneca Pharmaceuticals LP; 2017.; Imbruvica [package insert]. Sunnyvale, CA: Pharmacyclics; 2019.

Side Effects of Available BTK Inhibitors: Atrial Fibrillation and Other Cardiac Events



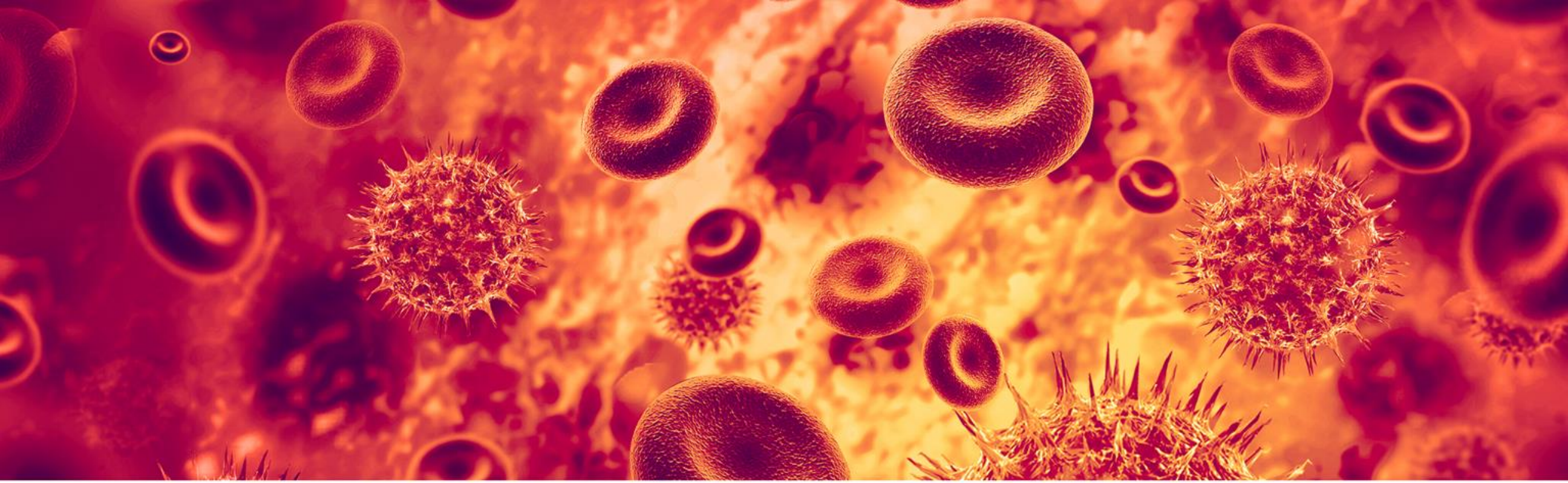
Ibrutinib	Acalabrutinib

• Incidence of AF:
  • 11% in MCL
  • 5% in CLL (8% all cardiac dysfunction)
  • 2% in WM (7% all cardiac dysfunction)
	• Incidence of AF:
	  • 0 in MCL (8% other cardiac dysfunction)
	  • 3% in CLL
	  • 5% in WM

Clinical Management
• Risks include cardiac risk factors, acute infections, prior history of AF • AF is not an absolute indication to discontinue BTK inhibitors • Anticoagulation should be used with caution • If AF persists, consider the risks and benefits of treatment and dose modification

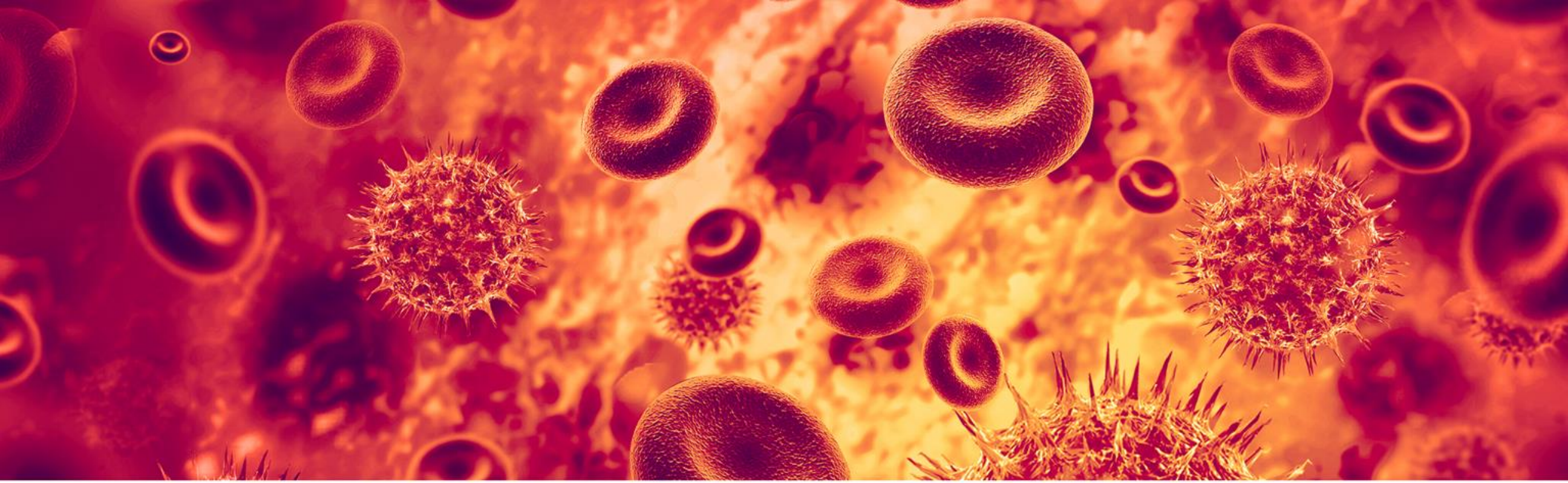
AF, atrial fibrillation; WM, Waldenström macroglobulinemia.

Calquence [package insert]. Wilmington, DE: AstraZeneca Pharmaceuticals LP; 2017.; Imbruvica [package insert]. Sunnyvale, CA: Pharmacyclics; 2019.



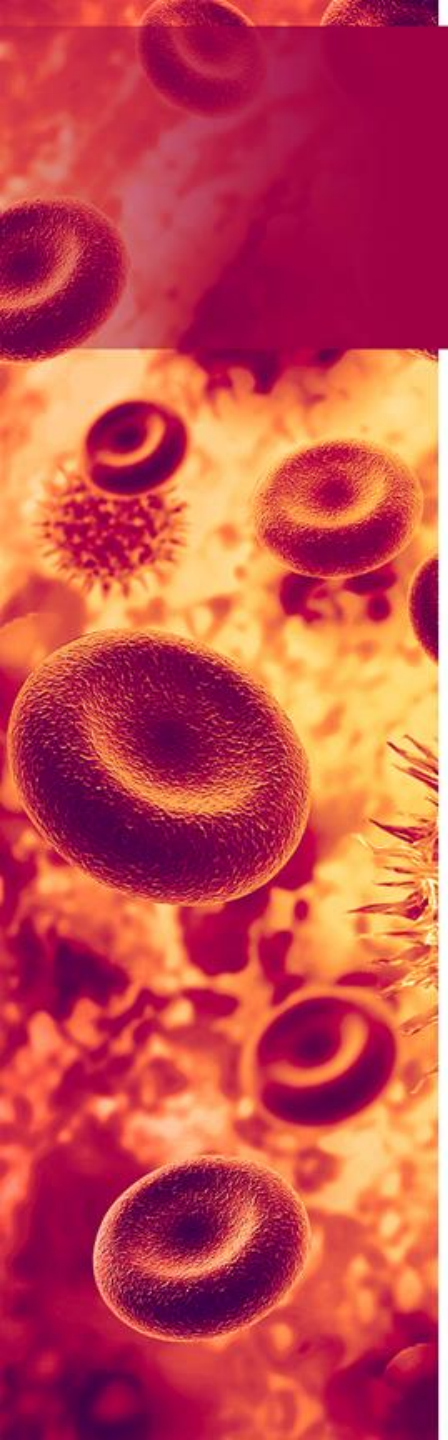
Ibrutinib Drug Overview & CLL

Larry Buie



Front-Line Ibrutinib in CLL

CLL Without del(17p)/TP53 Mutation: First-Line Therapy



Frail patient with significant comorbidity

Patients age ≥ 65 years and younger patients with comorbidities

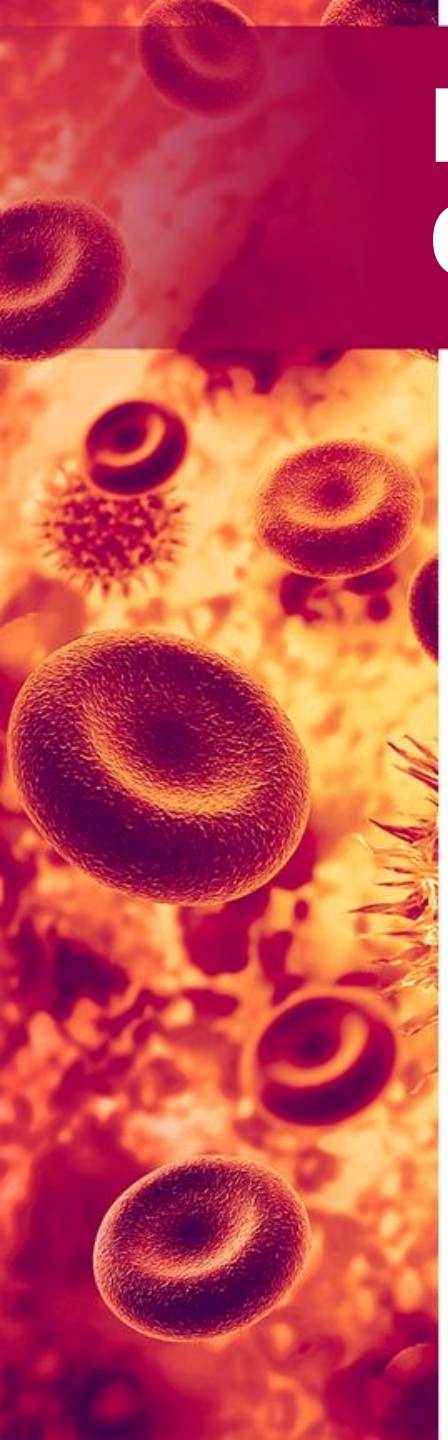
→ Category 1/Preferred **Ibrutinib** Venetoclax + obinutuzumab

Patients age < 65 years without significant comorbidities

→ Category 1/Preferred **Ibrutinib**

National Comprehensive Cancer Network. https://www.nccn.org/professionals/physician_gls/pdf/cll.pdf. Published August 23, 2019.

Resonate-2: Ibrutinib Versus Chlorambucil



International, phase III, open-label, randomized clinical trial

N=269

Untreated CLL/SLL
≥ 65 years old
ECOG ≤ 2

Ibrutinib 420 mg PO daily, continuous (N=136)

Chlorambucil 0.5-0.8 mg/kg D1 and D15 of 28-day cycle (N=133)

PFS
OS
ORR
HI
QOL

Barr PM, et al. *Haematologica.* 2018;103(9):1502-10.;
Burger JA, et al. *N Engl J Med.* 2015;373(25):2425-37.

ORR, overall response rate; HI, hematologic improvement; QOL, quality of life; SLL, small lymphocytic leukemia.

Ibrutinib Superior to Chlorambucil

Extended follow-up of 29 months:
Median PFS (NR vs. 15 months, HR 0.12, p<0.0001)
PFS was better at 24 months (89% vs. 34%, p<0.0001)
Higher ORR (92% vs. 36%, p<0.0001))

24-month OS (95% vs. 84%, HR 0.43, p=0.0145)
Improved QOL

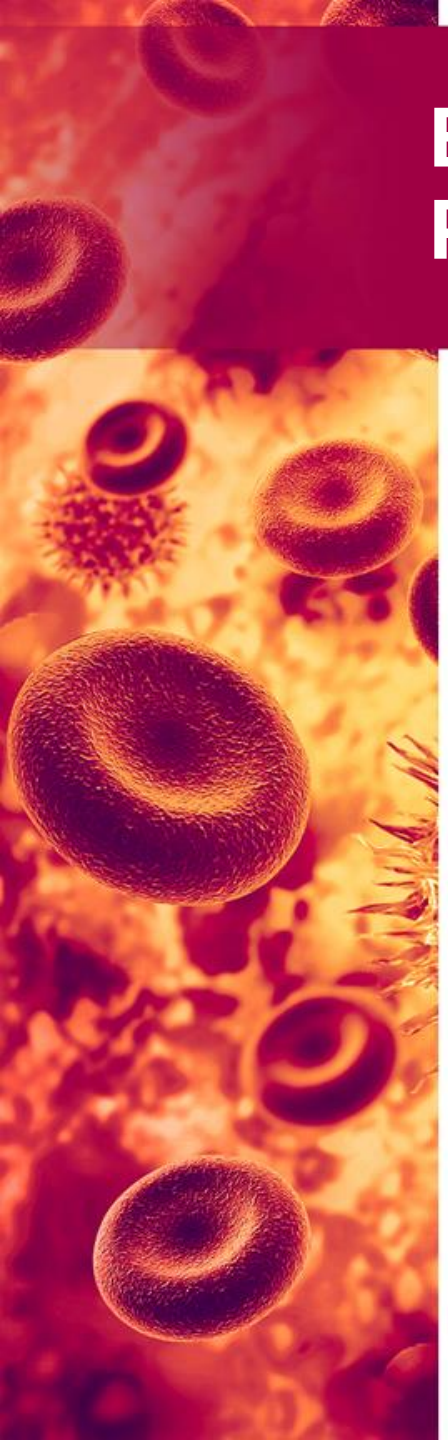
Ibrutinib outperformed chlorambucil across all subgroups, including patients with advanced or bulky disease

NCCN Category 1 recommendation for upfront treatment with ibrutinib in patients ≥ 65 years without del(17p)

HR, hazard ratio; NCCN, National Comprehensive Cancer Network.

Barr PM, et al. *Haematologica.* 2018;103(9):1502-10.; Burger JA, et al. *N Engl J Med.* 2015;373(25):2425-37.

ECOG-E1912: A Paradigm Shift for Younger Patients



Phase III, multicenter, international clinical trial

N=529

Treatment-naïve CLL
≤ 70 years old

Ibrutinib 420 mg daily, continuous
PLUS
rituximab
(N=354)

Fludarabine, cyclophosphamide, and rituximab
X 6 cycles
(N=175)

PFS
OS

Shanafelt TD, et al. *Blood*. 2018;132:LBA-4.; Shanafelt TD, et al. *N Engl J Med*. 2019;381(5):432-43.

Ibrutinib + Rituximab is Superior to FCR

Median follow-up: 33.6 months

3-year PFS is better in patients receiving ibrutinib plus rituximab (89.4% vs. 72.9%, HR 0.35, p<0.001)

Especially in patients with unmutated IGHV

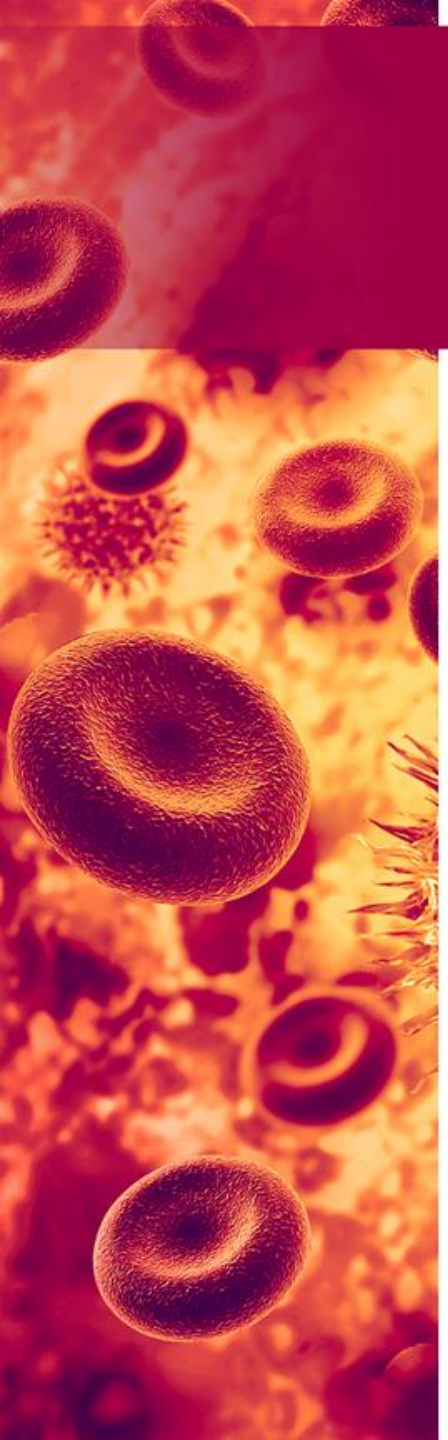
3-year OS improved with ibrutinib + rituximab (98.8% vs. 91.5%, HR 0.17, p<0.001)

NCCN Category 1 recommendation for patients < 65 years without del(17p) or TP53 mutation
FCR downgraded to a category 2A recommendation for patients < 65 years without significant comorbidities

FCR, fludarabine, cyclophosphamide, and rituximab; IGHV, immunoglobulin heavy chain gene.

Shanafelt TD, et al. *Blood*. 2018;132:LBA-4.; Shanafelt TD, et al. *N Engl J Med*. 2019;381(5):432-43.

Alliance



International, phase III, randomized clinical trial

N=547

≥ 65 years old
Untreated CLL

- Bendamustine plus rituximab X 6 cycles (N=183)
- Ibrutinib 420 mg PO daily (N=182)
- Ibrutinib 420 mg daily plus rituximab X 6 cycles (N=182)

PFS
OS
ORR

Woyach JA, et al. *N Engl J Med.* 2018;379(26):2517-28.

Ibrutinib is Better Option than Chemoimmunotherapy Among Elderly

Median PFS only reached in BR group

No significant PFS differences between ibrutinib monotherapy and ibrutinib plus rituximab arms

ORR 93% and 94% with ibrutinib and ibrutinib plus rituximab, respectively, compared with 81% for BR

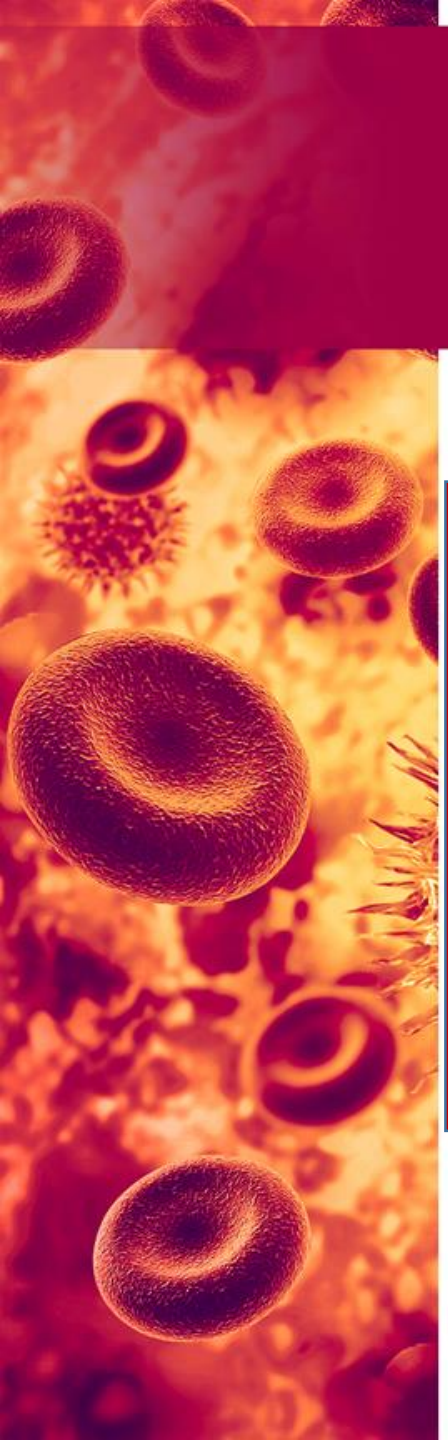
No significant differences in OS among the 3 groups

NCCN panel concensus was that longer PFS was the result of continuous ibrutinib and not the combination of ibrutinib plus anti-CD20 MAB

BR, bendamustine plus rituximab; MAB, monoclonal antibody.

Woyach JA, et al. *N Engl J Med.* 2018;379(26):2517-28.

CLL With del(17p)/TP53 Mutation: Front-Line Therapy



Del(17p) and TP53 mutations have been independently associated with poor outcomes, shortened survival, and resistance to purine-based chemoimmunotherapy regimens

Category 1/Preferred

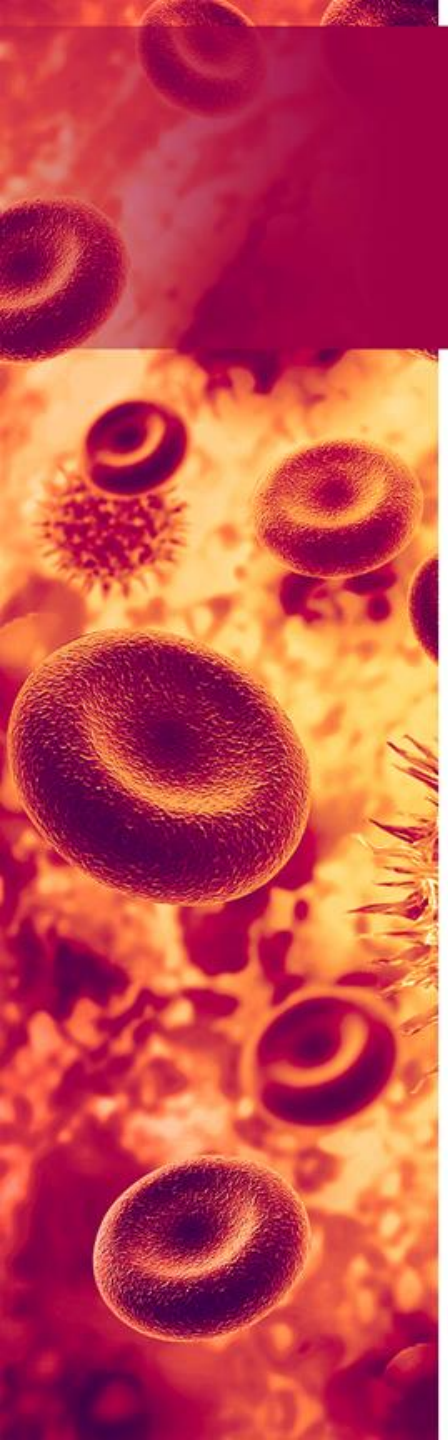
Ibrutinib

Venetoclax/obinutuzumab

Clinical trial

National Comprehensive Cancer Network. https://www.nccn.org/professionals/physician_gls/pdf/cll.pdf. Published August 23, 2019.

Ibrutinib as Front-Line Therapy in High-Risk Patients



Phase II, multicenter, international, open-label, single-arm study

N=51
(TP53 cohort)

≥ 18 years old
TP53 mutation

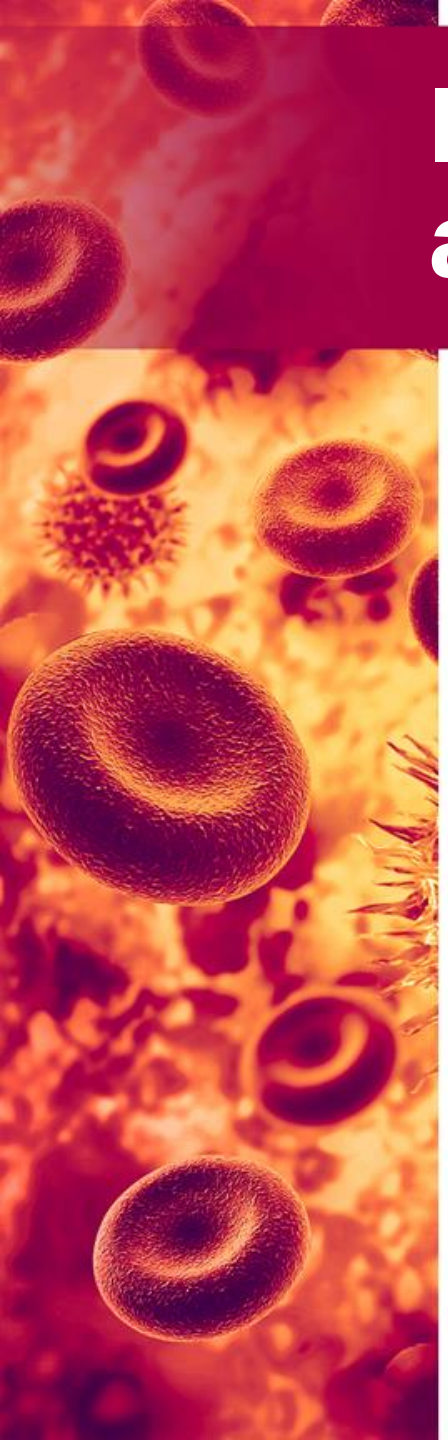
Treatment-naïve (TN) and relapsed or refractory (R/R) CLL

Ibrutinib 420 mg PO daily until disease progression/toxicity

ORR
PFS
OS

Ahn IE, et al. *Blood*. 2018;131(21):2357-66.

Ibrutinib Extends Disease Progression and OS in Patients with TP53 Mutations



- ORR at 6 months: 95.8% in TP53 cohort
- Depth of response improved with time
- 29.2% had a CR
- 5-year PFS was 74.4% for TN CLL vs. 19.4% for R/R CLL (p=0.0002)
- 5-year OS was 85.3% for TN CLL vs. 53.7% for R/R CLL (p=0.023)

Long-term administration of ibrutinib is well tolerated and provides durable disease control

in patients with high-risk disease

CR, complete response.

Ahn IE, et al. *Blood*. 2018;131(21):2357-66.

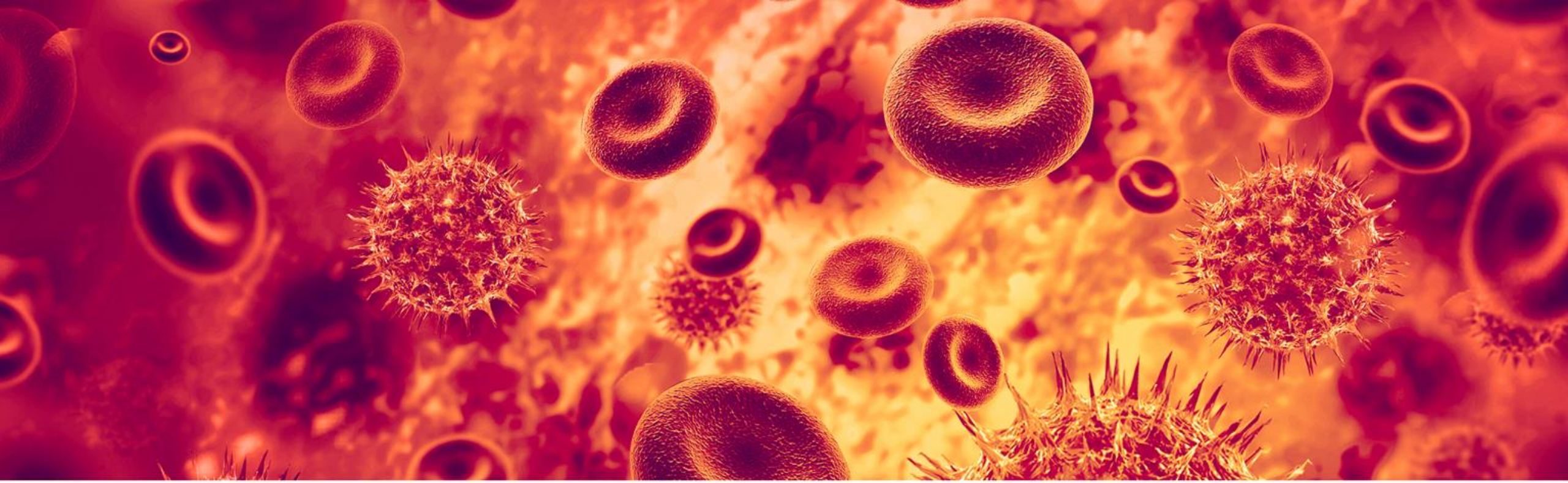
Ibrutinib + Venetoclax*: Phase II First-Line CLL – High-Risk Patients

Parameter	(N=80)
CR following 3 cycles of ibrutinib lead-in	1%
PR following 3 cycles of ibrutinib lead-in	96%
CR following 18 cycles	96%
PR following 18 cycles	4%
Undetectable MRD in bone marrow	69%
PFS at 1 year	98%
OS at 1 year	99%
CLL progression	0%

*Ibrutinib 420 mg PO daily x 3 cycles then venetoclax 400 mg PO daily added
Patients had either 17p deletion, mutated TP53, chromosome 11q deletion, unmutated IGHV, or age ≥ 65 years
Median follow-up: 14.8 months

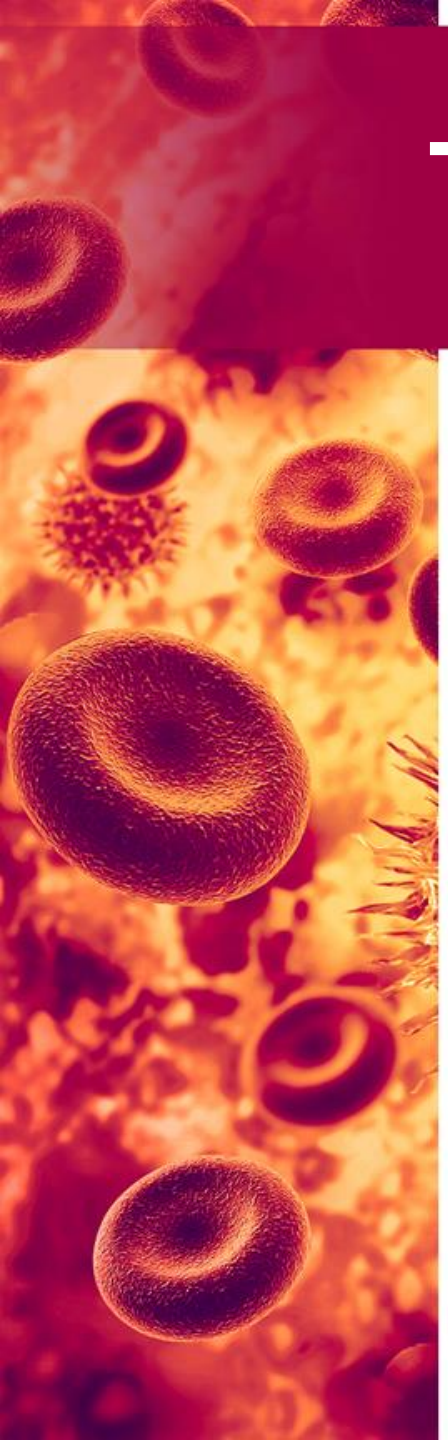
Jain N, et al. *N Engl J Med.* 2019;380(22):2095-103.

MRD, minimum residual disease; PR, partial response.



Relapsed & Refractory CLL

Treatment Options R/R CLL Patients



Without del(17p)/TP53 mutation

Frail with significant comorbidity	Category 1/Preferred Ibrutinib Acalabrutinib Venetoclax + rituximab Duvelisib Idelalisib + rituximab
≥ 65 years and younger patients with significant comorbidities	
Patients < 65 years without significant comorbidities	

With del(17p) or TP53 mutation

Category 1/Preferred Ibrutinib Acalabrutinib Venetoclax +/- rituximab Duvelisib Idelalisib + rituximab

National Comprehensive Cancer Network. https://www.nccn.org/professionals/physician_gls/pdf/cll.pdf. Published August 23, 2019.

Resonate

Phase III, multicenter, open-label, randomized clinical tiral

N=391

R/R CLL
At least 1 prior therapy
Inappropriate for purine analogue-based therapy

Ibrutinib 420 mg PO daily until disease progression/toxicity (N=195)

Ofatumumab dose escalation and continuation X 24 weeks (N=196)

PFS
OS
ORR

Byrd JC, et al. *N Engl J Med*. 2014;371(3):213-23.

Ibrutinib Improves PFS and OS in R/R CLL

Median PFS not reached in ibrutinib arm vs. 8.1 months in ofatumumab arm (HR 0.22, p<0.001)
PFS benefit retained among patients with 17p deletion, bulky disease, or refractory to purine analogues

Median OS not reached in either group,

but was significantly better with ibrutinib at 12 months (90% vs. ofatumumab 81%, HR 0.43, p=0.005)

ORR significantly higher in ibrutinib-treated patients (42.6% vs. 4.1%. P<0.001)

NCCN Category 1 recommendation for R/R CLL

Byrd JC, et al. *N Engl J Med*. 2014;371(3):213-23.; Byrd JC, et al. *Blood.* 2019;133(19):2031-42.

Resonate-17

Phase II, multicenter, international, open-label, single-arm study

N=144

≥ 18 years old
Del17p
Previously-treated
R/R CLL

Ibrutinib 420 mg PO daily until disease progression/toxicity

ORR
DOR
PFS
OS
HI
Immunologic improvement

O'Brien S, et al. *Lancet Oncol.* 2016;17(10):1409-18.

Ibrutinib is Efficacious in Most Difficult-to-Treat Patients: R/R with del(17p)

ORR was 83%

24-month PFS and 24-month OS were 63% and 75%, respectively

Hematologic improvement was noted in 79% of patients who had baseline cytopenias

Further evidence supporting ibrutinib in the most difficult subset of CLL patients

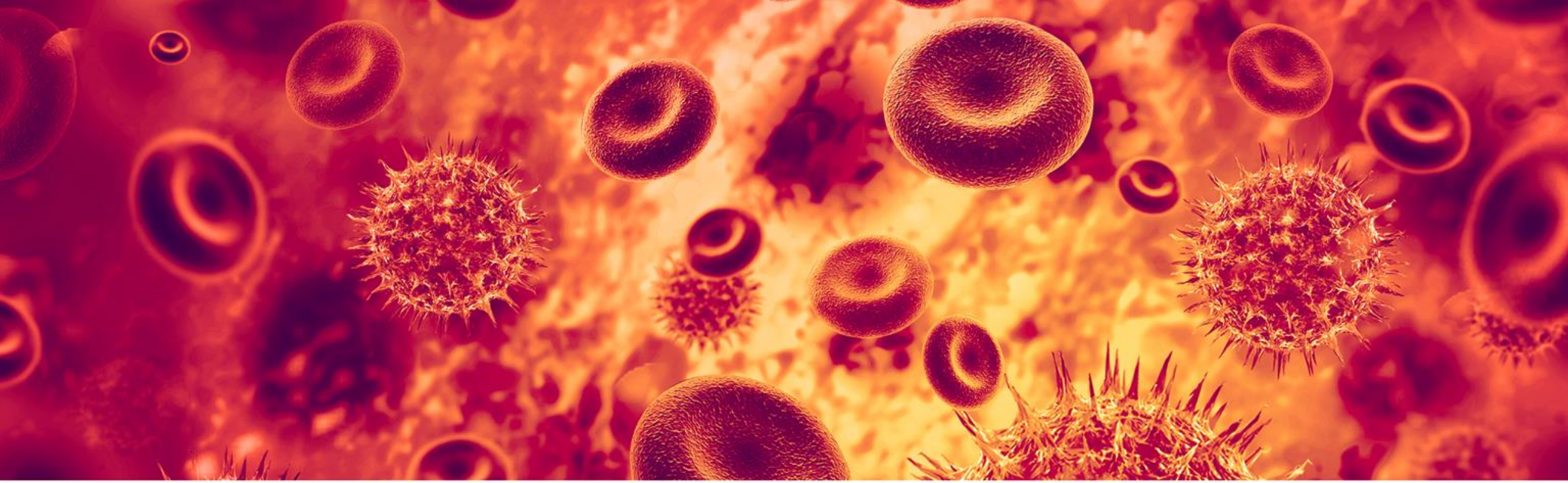
O'Brien S, et al. *Lancet Oncol.* 2016;17(10):1409-18.

Ibrutinib + Venetoclax*: Phase II R/R CLL – High-Risk Patients

Efficacy Parameter	(n=53)
MRD negativity in blood at 12 months[+]	53%
MRD negativity in bone marrow at 12 months[+]	36%
ORR	89%
CR	42%
CLL progression	0%
OS at last follow-up	100%

*Ibrutinib 420 mg PO daily x 8 weeks then venetoclax added and ramped up over 5 weeks to 400 mg PO daily
[+]Indicates primary study endpoint
Median follow-up: 21.1 months

Hillmen P, et al. *J Clin Oncol.* 2019. DOI: 10.1200/JCO.19.00894.



Acalabrutinib Overview & CLL

Chris Fausel

Dosing : Acalabrutinib

- 100 mg twice daily (every 12 hours)
- Can be taken with or without food
- If dose is missed by **more than 3 hours**, skip that dose and take the next one at the regularly scheduled time
  - Do not take an extra dose to make up for a missed dose
- Drug-drug interactions with CYP3A inhibitors/inducers AND gastric acid-reducing agents/PPIs

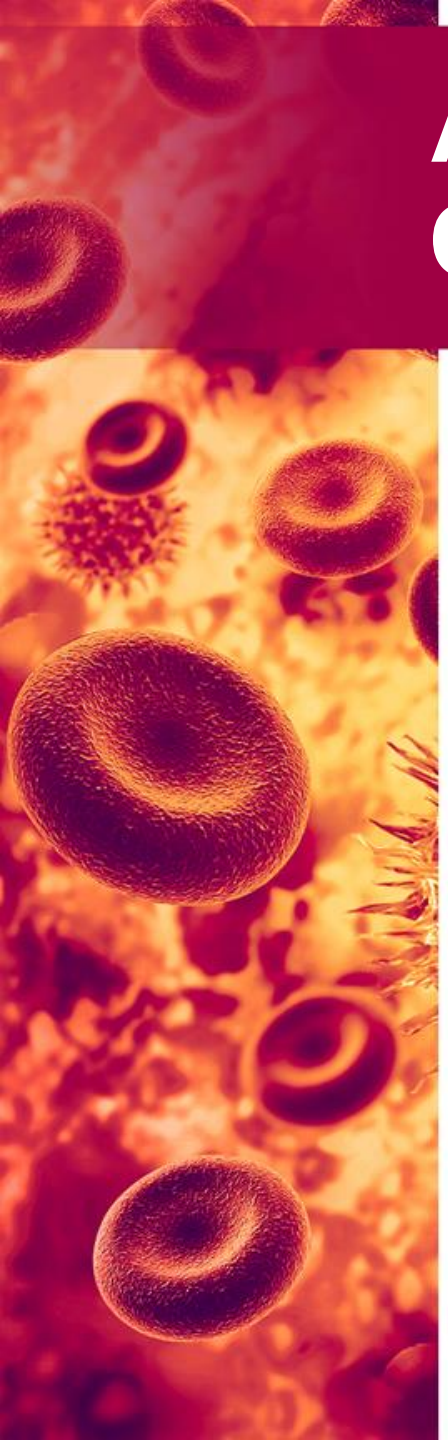
Dose Modifications

Any grade 3+ non-heme AEs, grade 3 thrombocytopenia + bleeding, grade 4 thrombocytopenia, grade 4 neutropenia > 7 days
1st or 2nd occurrence: Stop acalabrutinib until resolves to grade 1 or better Resume acalabrutinib at 100 mg twice daily
3rd occurrence: Stop acalabrutinib until resolves to grade 1 or better Resume acalabrutinib at 100 mg once daily
4th occurrence: Stop acalabrutinib permanently

Calquence [package insert]. Wilmington, DE: AstraZeneca Pharmaceuticals LP; 2017.

AE, adverse event.

ACP-196 (Acalabrutinib) in Relapsed CLL: Phase I - II



Patients with relapsed CLL or SLL (n=61)

Study endpoints

Phase 1:
MTD, PK, PD

Phase 2:
ORR

Median follow-up:
14.3 months

ENROLL

Dose escalation for Phase 1:
100 mg, 175 mg, 250 mg, 400 mg PO once daily

Dose-expansion cohort:
Acalabrutinib 100 mg PO twice daily

Byrd JC, et al. *N Engl J Med.* 2016;374(4):323-32.

MTD, maximum tolerated dose; PD, pharmacodynamics; PK, pharmacokinetics.

Toxicity Results

Adverse Event	Grade 3/4
Hypertension	7%
Fatigue	3%
Pyrexia	3%
Arthralgia	2%
Diarrhea	2%
Increased weight	2%

Hemorrhage, infection, cytopenias, atrial fibrillation/flutter, and second primary malignancies reported in other clinical trials.

Byrd JC, et al. *N Engl J Med.* 2016;374(4):323-32.

Efficacy Results

Parameter	Result
ORR	95%
PR	85%
PR with lymphocytosis	10%
PFS	96% at 18 months
Lymphadenopathy reduction	98%
Treatment-related lymphocytosis (ALC > 5000/µL)	61%
Improvement in low baseline platelet count	62%
Improvement in low baseline hemoglobin	76%
Improvement in low baseline ANC	80%
Resolution of baseline B-symptoms	88% (by cycle 3) 100% (by cycle 9)

ALC, absolute lymphocyte count; ANC, absolute neutrophil count.

Byrd JC, et al. *N Engl J Med.* 2016;374(4):323-32.

Update from American Society of Hematology

Efficacy Parameter	Result (n=99)
ORR	97%
CR	5%
PR	92%
Median DOR	Not reached
36-month DOR	96%
Median PFS	Not reached
36-month PFS	97%

Byrd JC, et al. *Blood*. 2018;132:Abstract 692.

Relapsed/Refractory CLL

Primary endpoint: PFS

Relapsed/ Refractory CLL
(≥ 1 regimen)
(N=310)

Median follow-up: 16.1 months

Median age: 67 years
Stratification: del(17p), ECOG PS, prior lines of therapy

Acalabrutinib 100 mg PO BID

Investigator's choice*:
Rituximab (375 or 500 mg/m^2) plus idelalisib 150 mg PO twice daily **OR** bendamustine (70 mg/m^2) on days 1 and 2 every 28 days up to 6 cycles

*Patients could cross-over to acalabrutinib

Ghia P, et al. *EHA Library.* 2019;Abstract LB2606.

BID, twice daily.

Efficacy Results

Parameter	Acalabrutinib (n=155)	Investigator's choice (n=155)
PFS	Not reached	16.5 months
PFS at 1 year	88%	68%
ORR	81%	76%
CR	0%	2%
PR	81%	74%
OS at 12 months	94%	91%
DOR at 12 months	Not reached	13.6 months

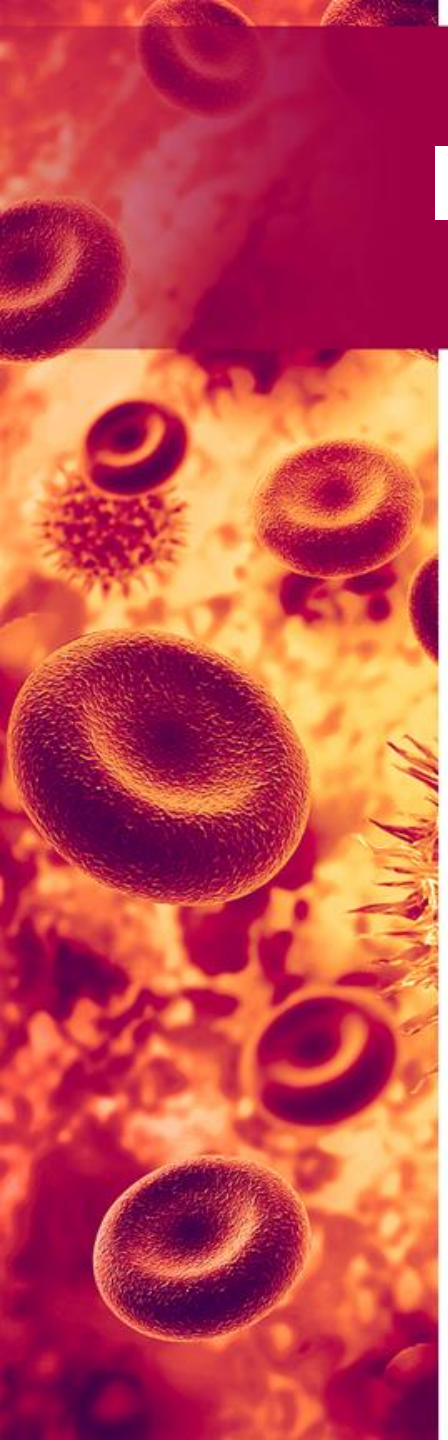
Ghia P, et al. *EHA Library.* 2019;Abstract LB2606.

Toxicity Results (≥ Grade 3)

Parameter	Acalabrutinib (n=155)	Idelalisib/rituximab (n=118)	Bendamustine/ rituximab (n=35)
Neutropenia	49%	90%	49%
Anemia	12%	40%	31%
Pneumonia	5%	8%	3%
Diarrhea	1%	24%	0%
Thrombocytopenia	4%	8%	3%
ALT increased	1%	8%	3%
Infection	15%	33%	11%
Bleeding	2%	3%	1%
AF	1%	1%	1%
Second primary malignancy	3%	0%	3%

ALT, alanine aminotransferase.

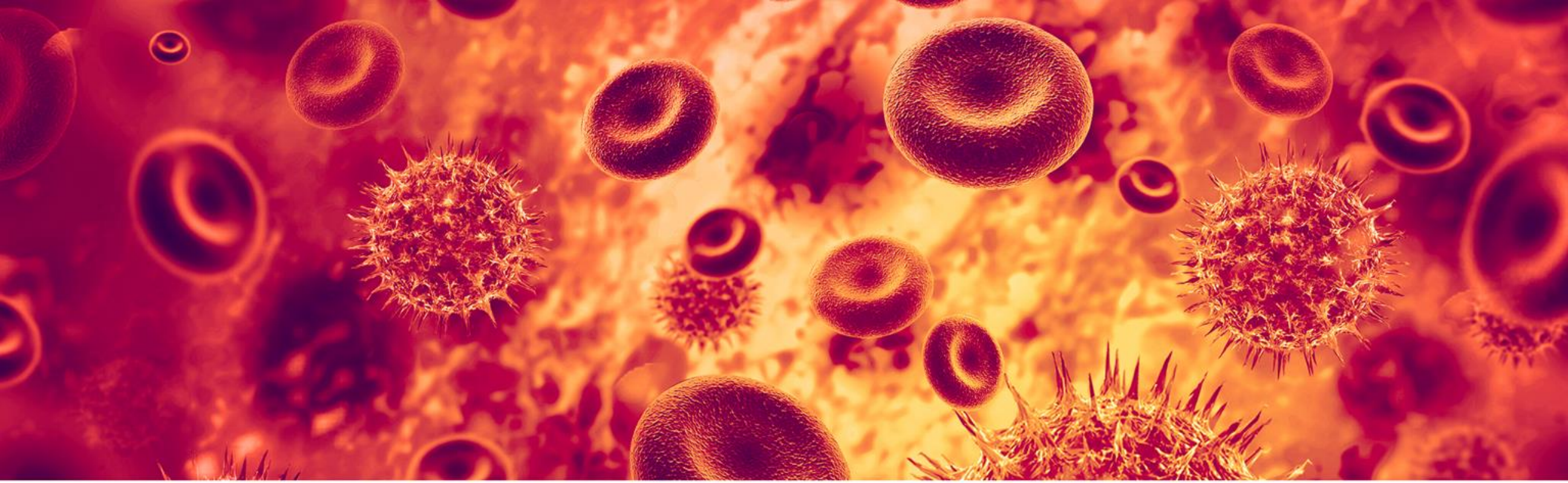
Ghia P, et al. *EHA Library.* 2019;Abstract LB2606.



Investigational BTK Inhibitors in CLL

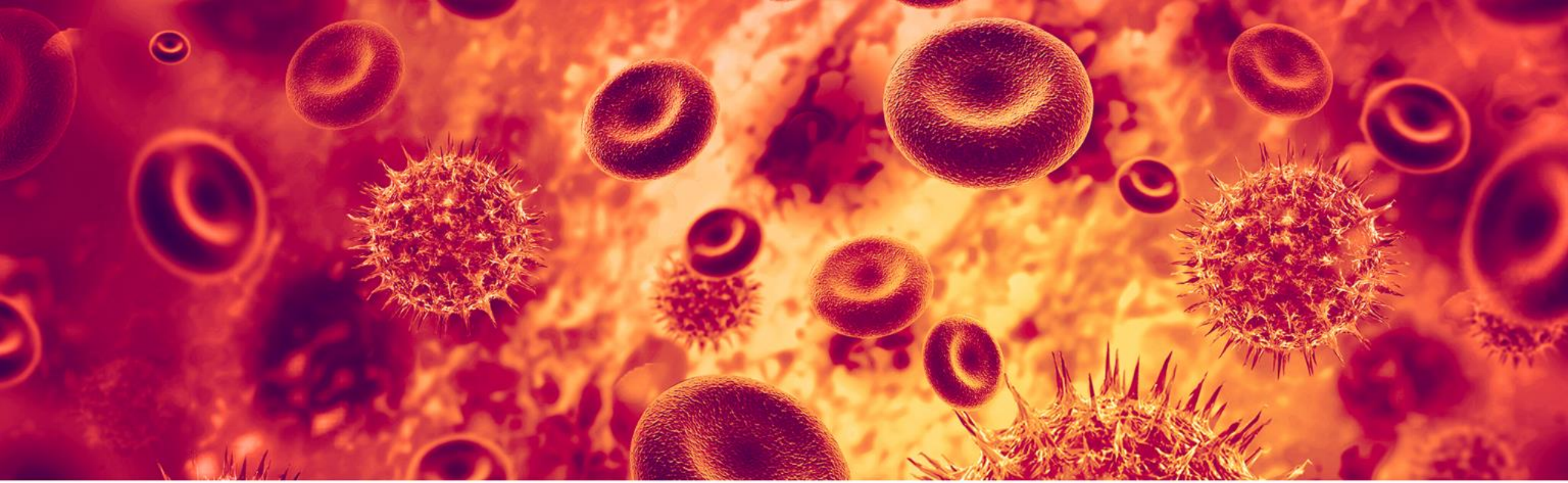
- Zanubrutinib
  - Phase I experience in CLL now published
  - No dose-limiting toxicity experienced during dose escalation with > 90% ORR
- Tirabrutinib
  - Phase I experience in Japan for CLL/NHL
  - Myelosuppression and pneumonitis were notable toxicities
  - Both CLL and NHL had documented clinical response

Munakata W, et al. *Cancer Sci.* 2019;110(5):1686-94.; Tam CS, et al. *Blood.* 2019;134(11):851-9.



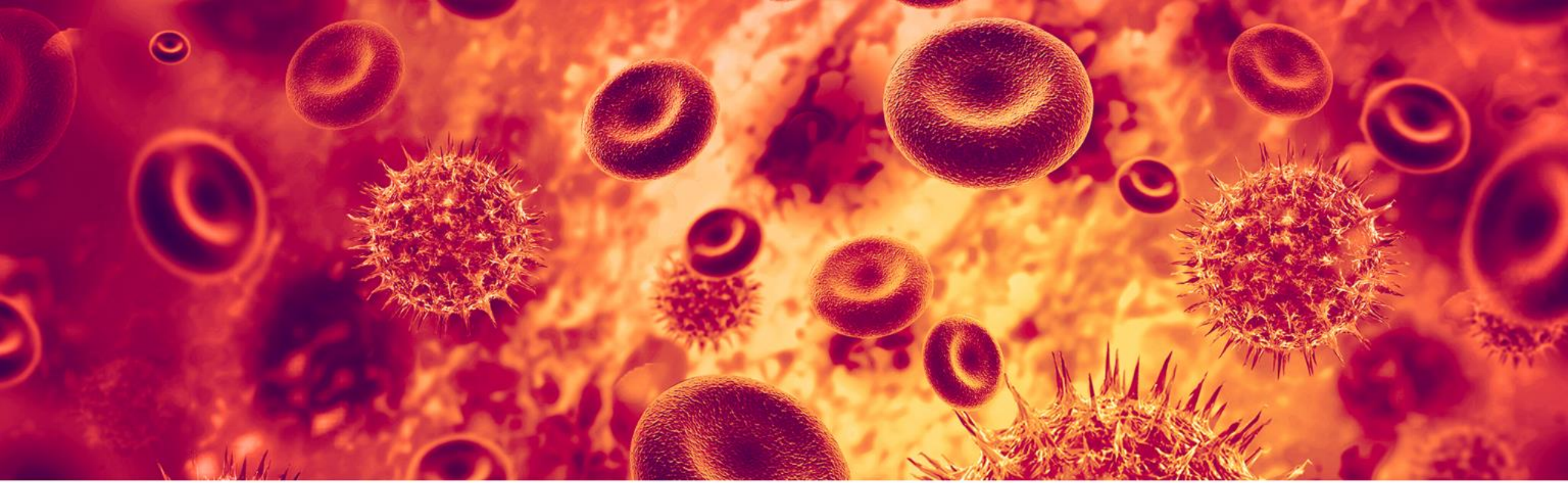
Discussion

Ibrutinib and Acalabrutinib in CLL



Ibrutinib & MCL

Laura Whited

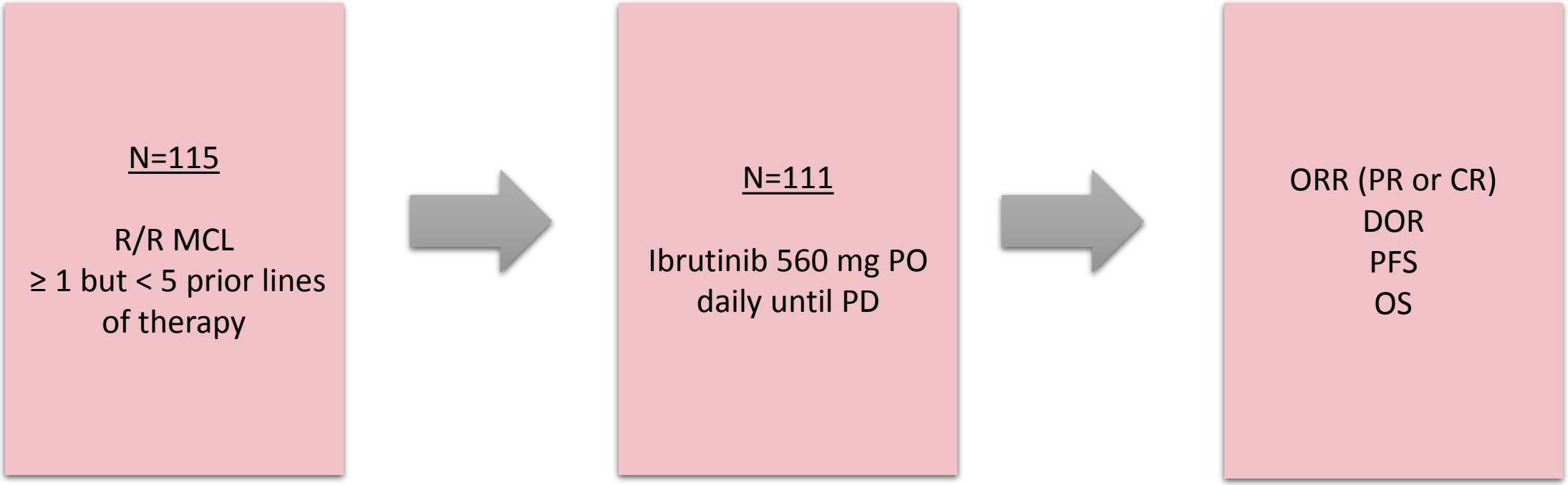


Relapsed & Refractory MCL

Monotherapy

Targeting BTK with Ibrutinib in R/R MCL

International, open-label, phase II clinical trial



Wang ML, et al. *N Engl J Med.* 2013;369(6):507-16.

PD, progressive disease.

Targeting BTK with Ibrutinib in R/R MCL

- ORR 68% in patients who had no prior bortezomib exposure
  - Median time to response was 1.9 months
  - DOR: 15.8 – 17.5 months

- Long-term follow-up of MCL patients treated with single-agent ibrutinib
  - ORR for all patients was 67% at ~2-year follow-up
    - CR 23% (95% CI: 15.1% - 31.4%)
  - Median PFS was 13 months and median OS was 22.5 months
  - Response was durable at 17.5 months

Long-term administration of ibrutinib is well tolerated and provides durable disease control in patients with highly refractory MCL

Wang ML, et al. *N Engl J Med.* 2013;369(6):507-16.; Wang ML, et al. *Blood.* 2015;126(6):739-45.

Phase III: Ibrutinib vs. Temsirolimus in Patients with R/R MCL (RAY Study)

- Primary endpoint: PFS

N=280

R/R MCL
(≥ 1 rituximab-containing regimen)

RANDOMIZED

Ibrutinib arm (n=139)
560 mg PO daily until PD

Temsirolimus arm (n=141)
175 mg for D1,8,15 on C1 →
75 mg q3weeks

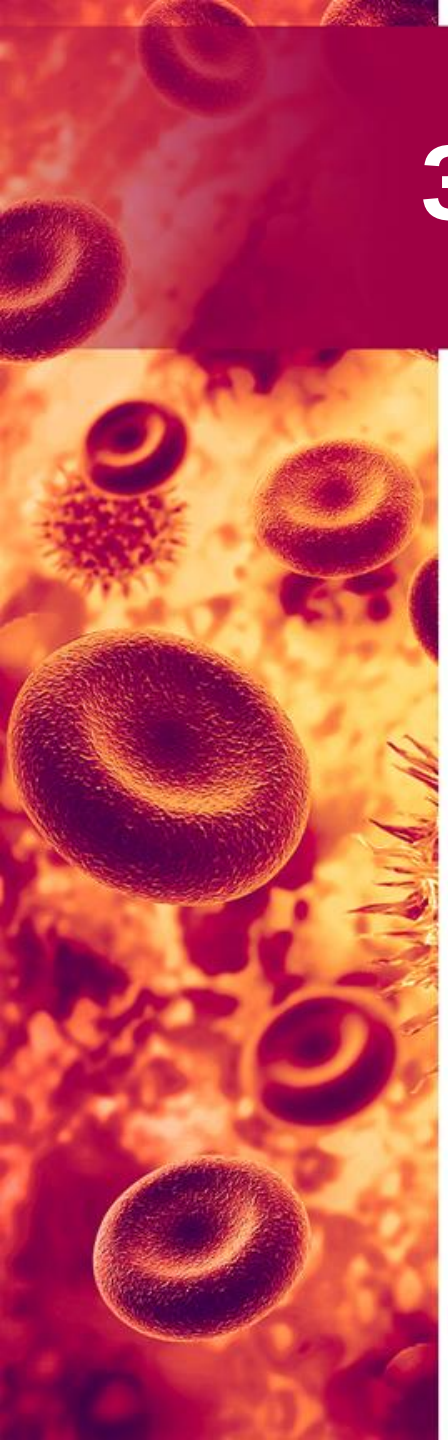
Median follow-up: 20 months
Median age: 68 years
Intermediate risk disease = 49%
More patients in temsirolimus arm had refractory disease (33%)

RESULTS

- **Median PFS**
  14.6 vs. 6.2 months
  (95% CI: 10.4-NR)
- 57% reduction in risk of progression (HR 0.45 [95% CI: 0.32-0.58])
- 2-year PFS: 41% vs. 7%
- ORR: 72% vs. 40% (95% CI: 20.5-42.5)
- mOS: NR vs. 21.3 months

Dryeling M, et al. *Lancet.* 2016;387(10020):770-8.

3-year Follow-Up From the RAY Study



Median PFS was significantly longer for ibrutinib than temsirolimus (15.6 vs. 6.3 months)

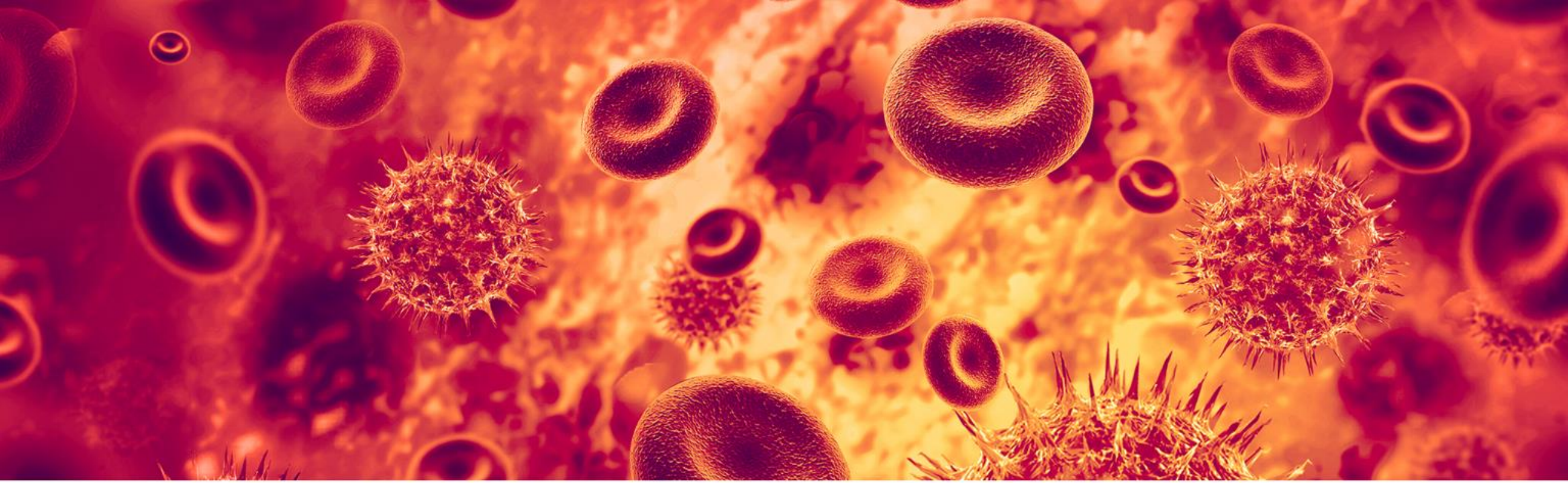
Median OS was not significantly longer for ibrutinib than temsirolimus (30.3 vs. 23.5 months [HR 0.74; 95% CI: 0.54-1.02])

ORR remained consistent at 77% for ibrutinib vs. 47% for temsirolimus

Higher proportion of patients achieved CR in ibrutinib arm (23% vs. 3%)

Most common AEs: diarrhea (33%), fatigue (24%), and cough (23%)

Rule S, et al. *Leukemia* 2018;32(8):1799-803.



Relapsed & Refractory MCL

Combination therapy

Ibrutinib in Combination with Rituximab in R/R MCL

Single-center, open-label, phase II clinical trial

N=50

R/R MCL
(CD20-positive and cyclin D1 over-expression)

Ibrutinib 560 mg PO daily until PD

+

Rituximab 375 mg/m^2 IV weekly x 4, then D1 of C3-8, then every other cycle x 2 years

ORR
DOR
PFS

Wang ML, et al. *Lancet Oncol.* 2016;17(1):48-56.

IV, intravenously.

Ibrutinib in Combination with Rituximab in R/R MCL

- ORR 88% (95% CI: 75.7-95.5) with 44% achieving CR
  - Median follow-up was 16.5 months
  - Median DOR, median PFS, and median OS has not yet been reached
- Patients who had a Ki-67 < 50% were more likely to respond (ORR 100%) than those who had a Ki-67 > 50% (ORR 50%)

- Treatment-related lymphocytosis was rarely observed with ibrutinib/rituximab
- Most common AEs were fatigue (94%), diarrhea (78%), and myalgia (68%)
- AF was reported in 6 patients (12%)

- 4-year follow up study: 68% of patients had DOR ≥ 24 months
- ORR remained at 88% with 7 patients improving from PR to CR
- Median PFS was 43 months with 3-year PFS of 54%

Jain P, et al. *Br J Haematol.* 2018;182(3):404-11.; Wang ML, et al. *Lancet Oncol.* 2016;17(1):48-56.

Ibrutinib Plus Venetoclax for the Treatment of MCL

- Phase II, single-center, open-label, historical control
- Primary endpoint: rate of CR at 16 weeks

n=24

R/R MCL
or
previously
untreated MCL

RANDOMIZED

Ibrutinib 560 mg PO daily
+
Venetoclax started on week 5 at 50 mg/day and increased weekly to 400 mg/day

Median follow-up: 15.9 months
Median age: 68 years
TP53 mutated: 25%
Majority of patients had R/R MCL

RESULTS

- **CR at week 16: 42% (95% CI: 22-63) vs. 9% in historical control (p<0.001)**
- CR with PET: 71% (95% CI: 49-87)
- Median PFS at 15.9 months not yet reached
- 67% had negative MRD at 16 weeks
- Most common AEs
  - Diarrhea (83%)
  - Fatigue (75%)
  - Hemorrhage (54%)

Tam CS, et al. *N Engl J Med.* 2018;378(13):1211-23.

Ibrutinib, Lenalidomide, and Rituximab in R/R MCL (PHILEMON)

- Phase II, multicenter, open-label, single arm
- Primary endpoint: ORR

N=50

R/R MCL
(≥ 1 rituximab-containing regimen)

RANDOMIZED

- **Ibrutinib 560 mg PO daily D1-D28**
- **Lenalidomide 15 mg PO daily D1-D21**
- **Rituximab 376 mg/m^2 IV weekly x 4, then every 8 weeks**

RESULTS

- **ORR (n=50): 76%** (95% CI: 63-86)
- TP53 mutation (n=11): 73%
- Median PFS: 16.0 months
- Median OS: 22 months

Median follow-up: 17.8 months
Median age: 69 years (range, 45-85)
Ann Arbor Stage IV: 84%
Prior autoHCT: 42%

Triplet regimen with ibrutinib, lenalidomide, and rituximab was found to be active but may not be superior to ibrutinib monotherapy with the lower bound of the 95% CI not being above 68%

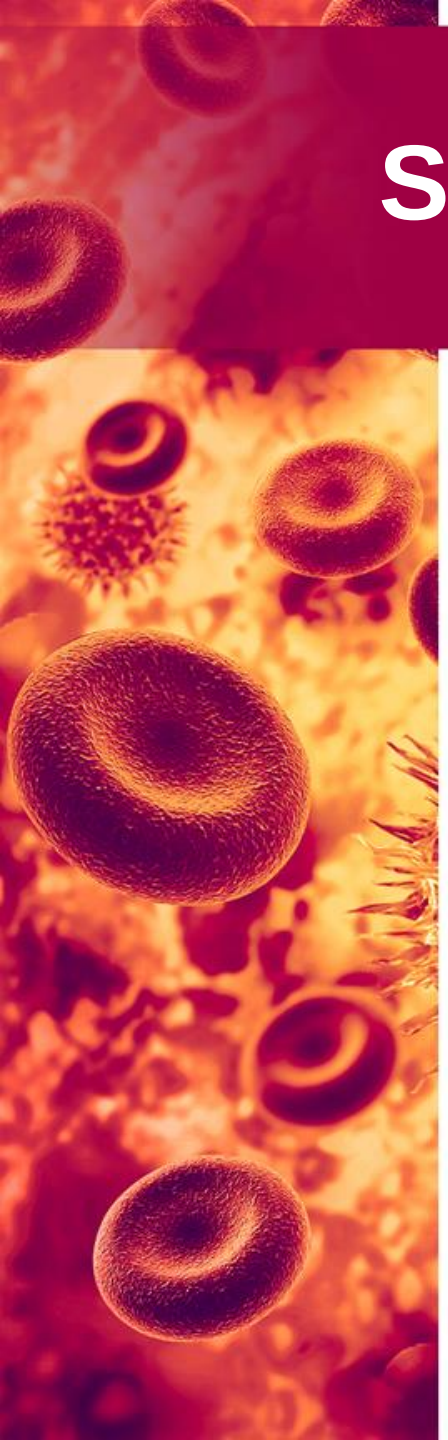
Jerkeman M, et al. *Lancet Haematol.* 2018;5(3):e109-16.

Ibrutinib Safety in Clinical Trials

Adverse Event	Wang, et al (2013) (n=115), %	RAY Study (n=139), %
Neutropenia	20 (18%)	22 (16%)
Thrombocytopenia	20 (18%)	25 (18%)
Diarrhea	56 (50%)	40 (29%)
Fatigue	46 (41%)	31 (22%)
Nausea	34 (31%)	20 (14%)
Upper respiratory infection	26 (23%)	28(20.1%)
Peripheral edema	31 (28%)	18 (13%)
AF	No report	5 (4%)
Bleeding	No report	46 (33%)

Dryeling M, et al. *Lancet.* 2016;387(10020):770-8.; Wang ML, et al. *Blood.* 2015;126(6):739-45.; Wang ML, et al. *N Engl J Med.* 2013;369(6):507-16.

Second-Line Treatment Options for MCL



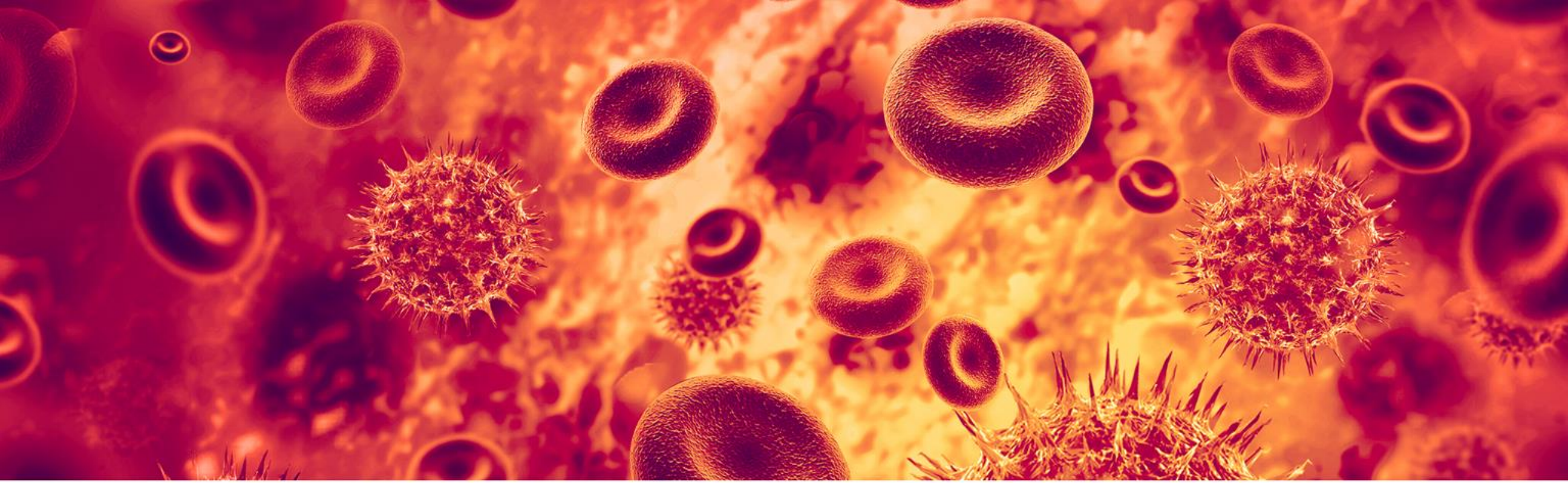
Short response duration to prior chemotherapy (< expected median PFS)	**Category 2A recommendations** • Ibrutinib ± rituximab • Acalabrutinib • Lenalidomide ± rituximab • Venetoclax
	Category 2B recommendations • Ibrutinib, lenalidomide, rituximab • Venetoclax + ibrutinib

National Comprehensive Cancer Network. https://www.nccn.org/professionals/physician_gls/pdf/b-cell.pdf. Published June 18, 2019.

Ibrutinib Drug Information in MCL

Dose: 560 mg PO daily until PD	
Lymphocytosis	Transient: occurs during the first weeks and resolves by a median of 8 weeks Should not be confused with disease progression
Bleeding events	Consider risk vs. benefit in patients requiring anti-platelet or anticoagulant therapies Ibrutinib should not be given with concurrent warfarin
Surgery interruptions	Hold 3 days before and after a minor surgical procedure Hold 7 days before and after a major surgical procedure
Drug interactions	CYP3A4 inhibitors: modify dose as needed, depending on strength of inhibitor CYP3A4 inducers: should be avoided when possible
Warnings	Hemorrhage, infections, cytopenias, cardiac arrhythmias, hypertension, second primary malignancies, tumor lysis syndrome

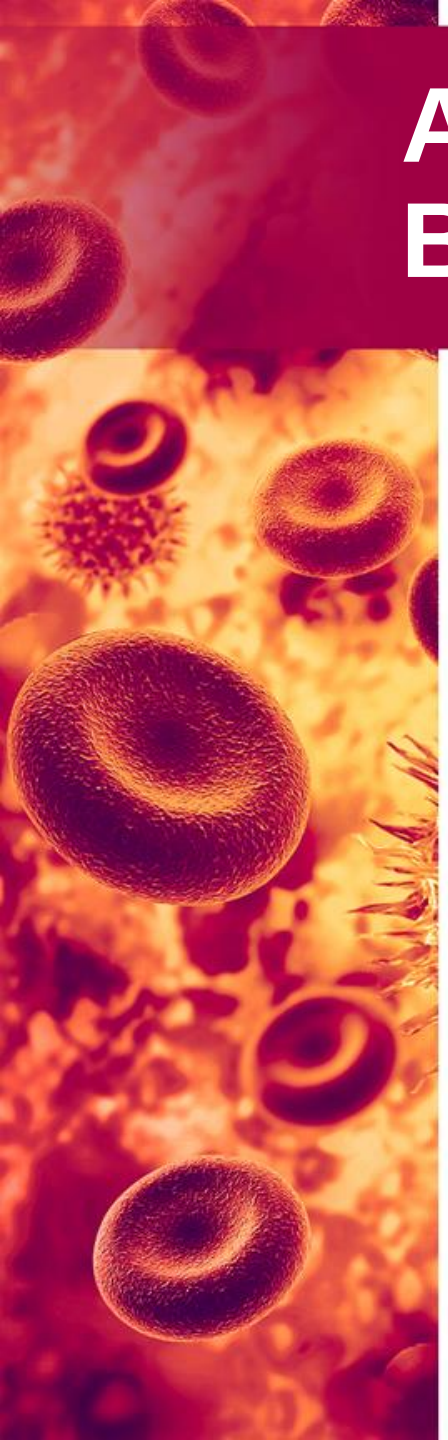
Imbruvica [package insert]. Sunnyvale, CA: Pharmacyclics LLC; 2019.
National Comprehensive Cancer Network. https://www.nccn.org/professionals/physician_gls/pdf/b-cell.pdf. Published June 18, 2019.



Acalabrutinib & MCL

Donald Harvey

Acalabrutinib in R/R MCL (ACE-LY-004): Background



- MCL is a rare form of NHL with a poor prognosis[1]
- Treatment of R/R MCL with the BTK inhibitor ibrutinib is effective, but associated with AF, bleeding, and infection[2,3]
  - Ibrutinib-associated AEs may be due to off-target kinase inhibition[1]
- Acalabrutinib: selective, covalent BTK inhibitor[4,5]
  - Associated with limited off-target effects in preclinical studies
- Current analysis evaluated efficacy and safety of acalabrutinib monotherapy in patients with R/R MCL[6]

1. Stephens DM, Spurgeon SE. *Ther Adv Hematol*. 2015;6(5):242-52.
2. Wang ML, et al. *N Engl J Med.* 2013;369(6):507-16.
3. Imbruvica [package insert]. Sunnyvale, CA: Pharmacyclics LLC; 2019.
4. Byrd JC, et al. *N Engl J Med.* 2016;374(4):323-32.
5. Barf T, et al. *J Pharmacol Exp Ther*. 2017;363(2):240-52.
6. Wang M, et al. *Lancet*. 2018;391(10121):659-67.

ACE-LY-004: Study Design

International, multicenter, open-label phase II trial[1]

N = 124

Adult MCL patients with translocation t(11;14)(q13;q32) and/or cyclin D1 over-expression; R/R to 1-5 prior therapies; measurable nodal disease (≥ 1 LN with longest diameter ≥ 2 cm); ECOG PS 0-2; no notable CVD*; no concurrent use of warfarin/equivalent vitamin K antagonists, no prior BTK inhibitors

*Includes: class 3/4 cardiac disease per NYHA Functional Classification; CHF or MI within 6 months of screening; QTc > 480 ms; uncontrolled/symptomatic arrhythmias

Acalabrutinib 100 mg PO BID in 28-day cycles

until PD

Primary endpoint

Investigator-assessed ORR per 2014 Lugano Classification[1,2]

Secondary endpoints

IRC-assessed ORR, DOR, PFS, OS, PK/PD, safety[1]

Exploratory endpoints

TTR, IRC-assessed ORR per 2007 IHP criteria[1,3]

1. Wang M, et al. *Lancet*. 2018;391(10121):659-67.
2. Cheson BD, et al. *J Clin Oncol*. 2014;32(27):3059-68.
3. Cheson BD, et al. *J Clin Oncol*. 2007;25(5):579-86.

CHF, congestive heart failure; CVD, cardiovascular disease; LN, lymph node; IHP, International Harmonization Project; IRC, independent review committee; MI, myocardial infarction; NYHA, New York Heart Association; TTR, time to response.

Phase II ACE-LY-004 Trial of Acalabrutinib: Investigator-Assessed ORR (Primary Endpoint)

Investigator-assessed ORR concordant with IRC-assessed ORR

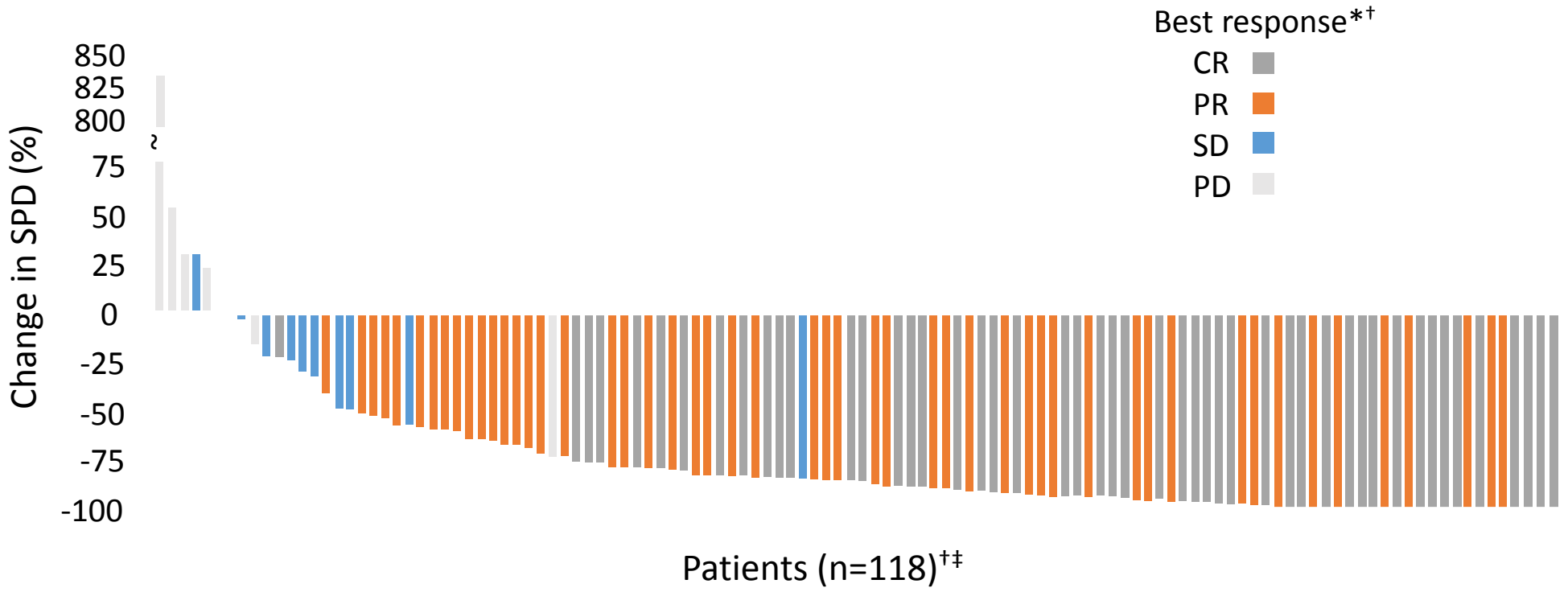
Response, n (%)	Investigator Assessed	IRC Assessed
ORR (CR + PR)	100 (81)	99 (80)
Best response		
CR	49 (40)	49 (40)
PR	51 (41)	50 (40)
SD	11 (9)	9 (7)
PD	10 (8)	11 (9)
Not evaluable	3 (2)	5 (4)

Median follow-up: 15.2 months
Median TTR: 1.9 months (range: 1.5-4.4)
Median DOR: NR (12-month DOR rate: 72%)

Wang M, et al. *Lancet*. 2018;391(10121):659-67.

ACE-LY-004: Change in Tumor Burden per Best Response Status

94% of patients with reduced lymphadenopathy

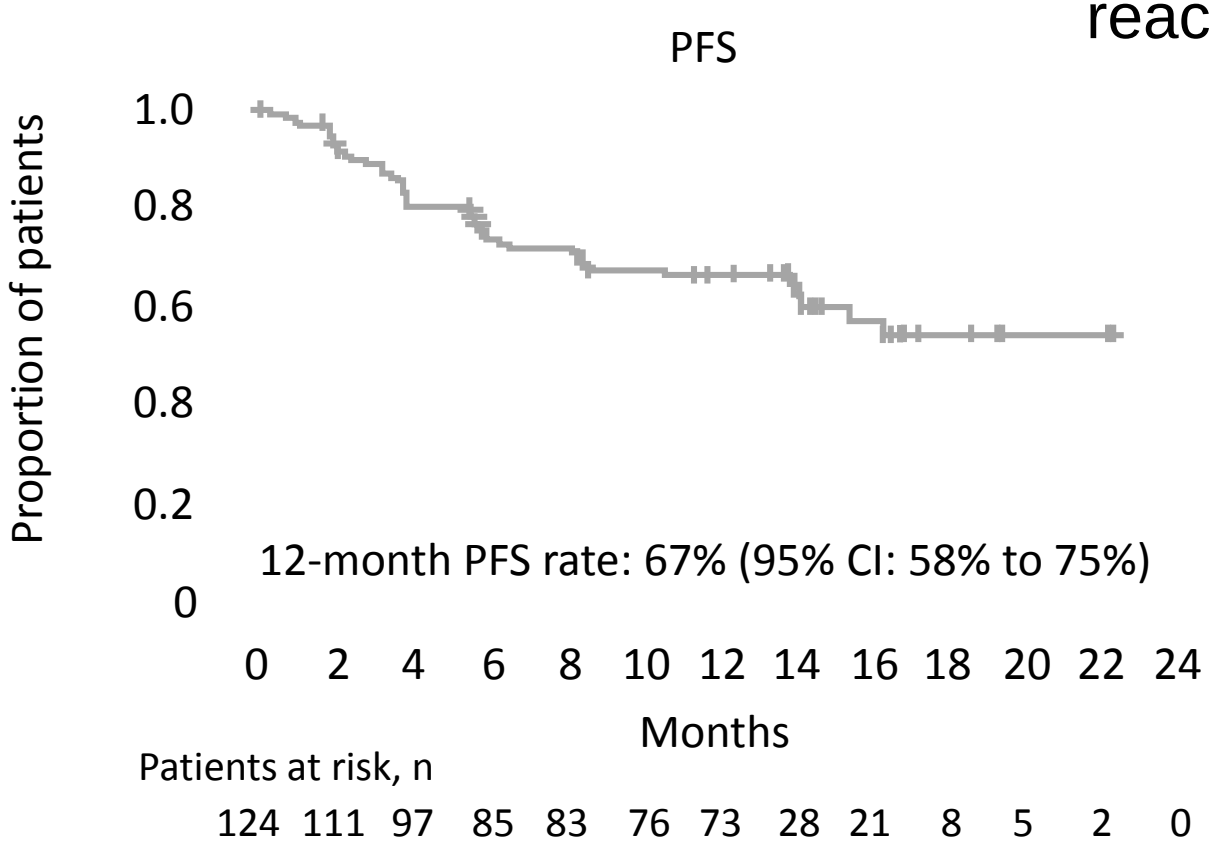


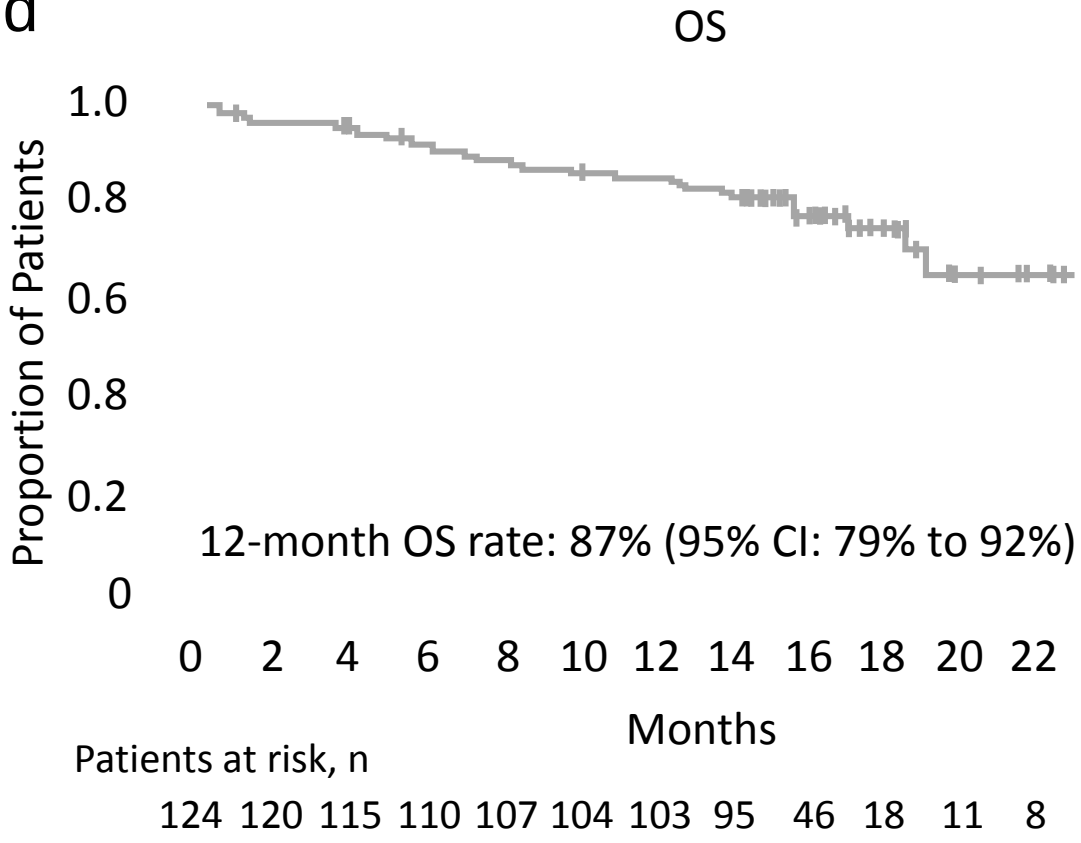
*Per 2014 Lugano Classification. †Best response not evaluable in 3 pts (2%). ‡All treated patients with lesion measurements at baseline and ≥ 1 post baseline; 6 patients excluded (early PD by evidence other than CT [n=4]; began subsequent anticancer treatment [n=1]; death [n=1]).

Wang M, et al. *Lancet*. 2018;391(10121):659-67.

Phase II ACE-LY-004 Trial of Acalabrutinib: Survival

After median follow-up of 15.2 months, neither median PFS nor median OS reached





Wang M, et al. *Lancet*. 2018;391(10121):659-67.

Phase II ACE-LY-004 Trial of Acalabrutinib: Summary of AEs

Most Common AEs (≥ 20% of Patients), %	Any Grade	Grade 3/4
Headache	38	2
Diarrhea	31	3
Fatigue	27	1
Myalgia	21	1

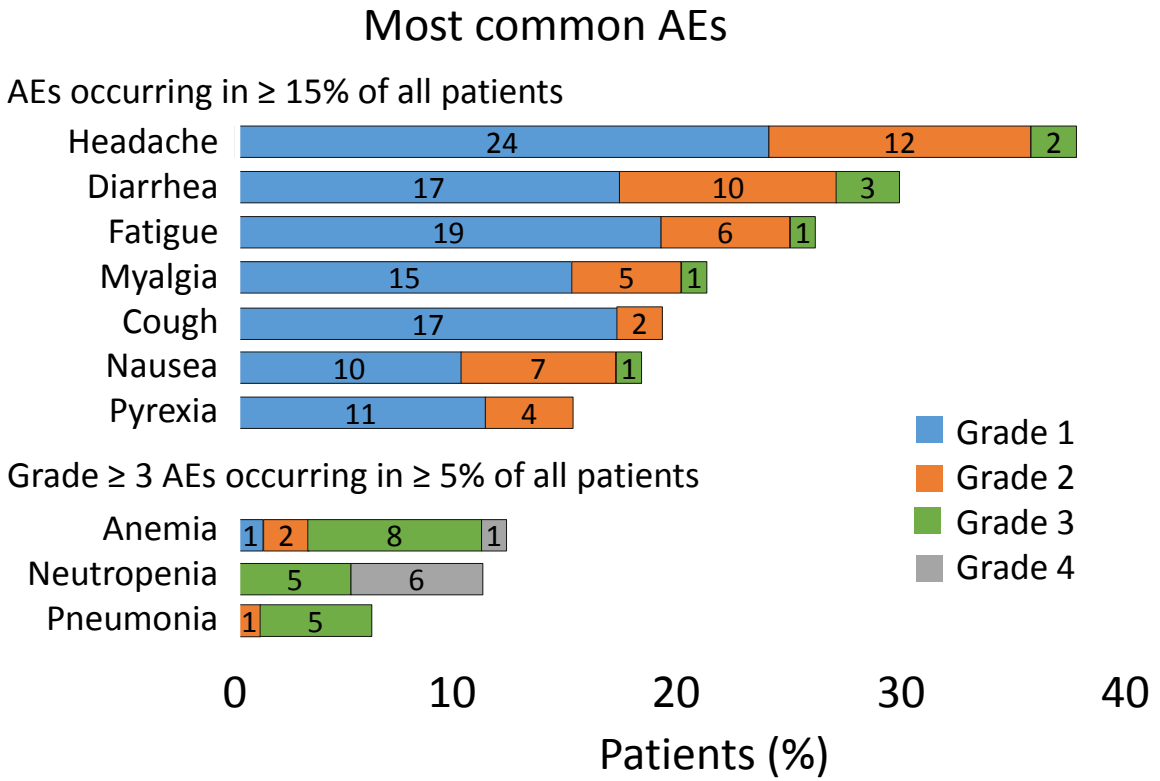
Most Common Grade ≥ 3 Hematologic AEs, %	Grade 3/4
Anemia	9
Neutropenia	11
Thrombocytopenia	5

AEs of Interest

- Infection (all grade): 53%
  - Grade ≥ 3: 13% (5% pneumonia)
- Bleeding/bruising (all grade): 31%
  - Grade ≥ 3: 1% (no grade 5)
- Cardiac (all grade): 8%
  - Grade ≥ 3 cardiac: 2%
  - No AF

Wang M, et al. *Lancet*. 2018;391(10121):659-67.

ACE-LY-004: Safety



Event, n (%)	Patients (N=124)
Serious AEs	48 (39)
Serious AEs in ≥ 2 pts*	
▪ Pneumonia	5 (4)
▪ Anemia	4 (3)
▪ General physical health deterioration	3 (2)
▪ Sepsis	2 (2)
▪ Tumor lysis syndrome	2 (2)
▪ Vomiting	2 (2)
AE-related discontinuation†	7 (6)

*Other serious AEs: grade 3 GI hemorrhage in patient with history of GI ulcer (n=1); grade 5 aortic stenosis in patient with history of non-treatment-related aortic stenosis (n=1)

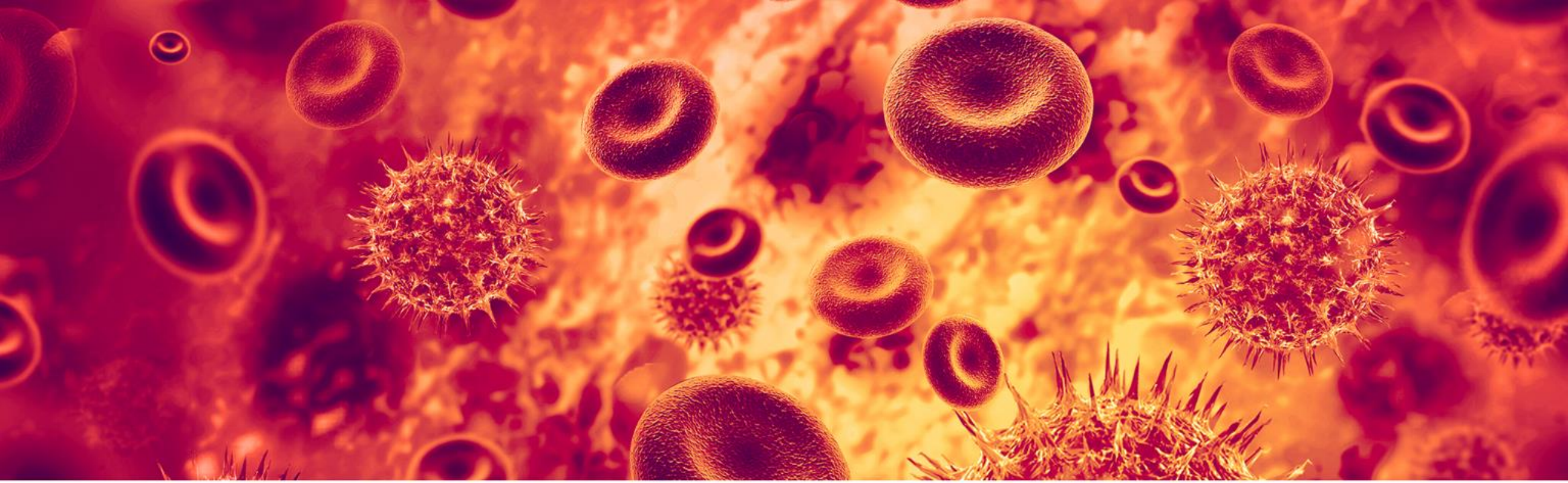
†n=1 each: aortic stenosis, diffuse large B-cell lymphoma, blood blister and petechiae (both in same patient on clopidogrel for grade 3 acute coronary syndrome), dyspnea and leukostasis syndrome, noncardiac chest pain, pulmonary fibrosis, and thrombocytopenia

Wang M, et al. *Lancet*. 2018;391(10121):659-67.

ACE-LY-004: Conclusions

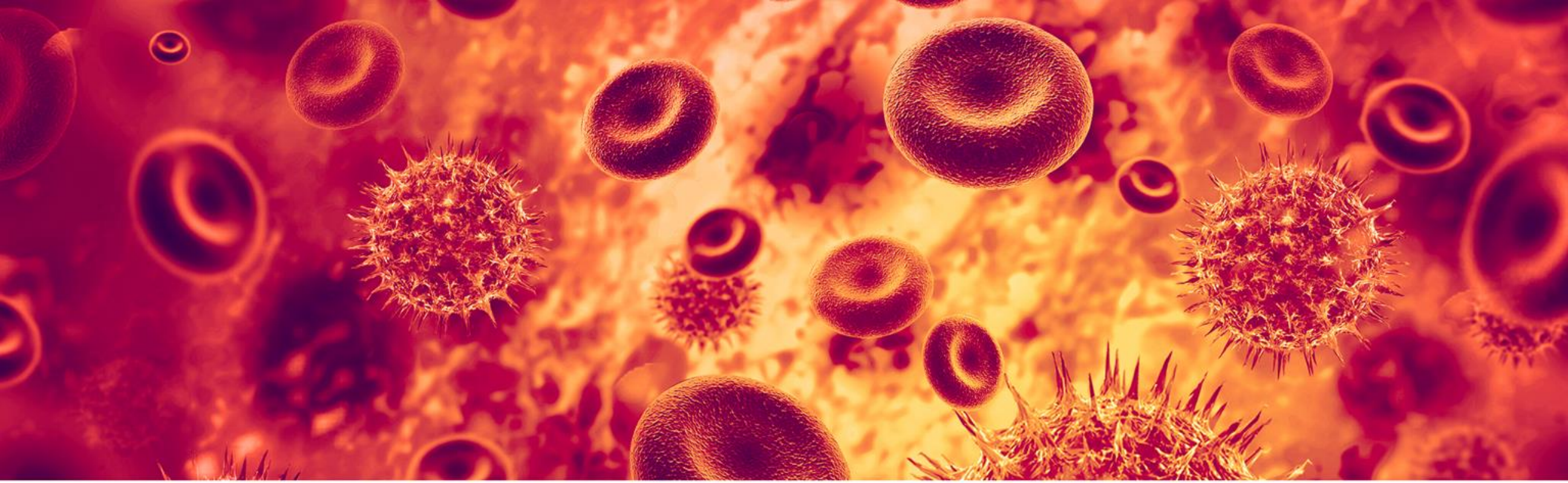
- In patients with R/R MCL, acalabrutinib monotherapy was associated with ORR of 81% and CR of 40%
  - Responses durable with a 12-month DOR rate of 72%
- Safety profile of acalabrutinib was favorable, with mostly low-grade AEs, low rate of AE-related discontinuation (6%), no cases of AF, and low rate of grade ≥ 3 hemorrhage (1%)
- Investigators concluded that acalabrutinib 100 mg BID is an effective therapeutic option with a differentiated safety profile from ibrutinib in patients with R/R MCL
  - Acalabrutinib 100 mg BID was approved by the FDA in October 2017 for adult patients with MCL who received ≥ 1 prior therapy

Calquence [package insert]. Wilmington, DE: AstraZeneca Pharmaceuticals LP; 2017.; Wang M, et al. *Lancet*. 2018;391(10121):659-67.

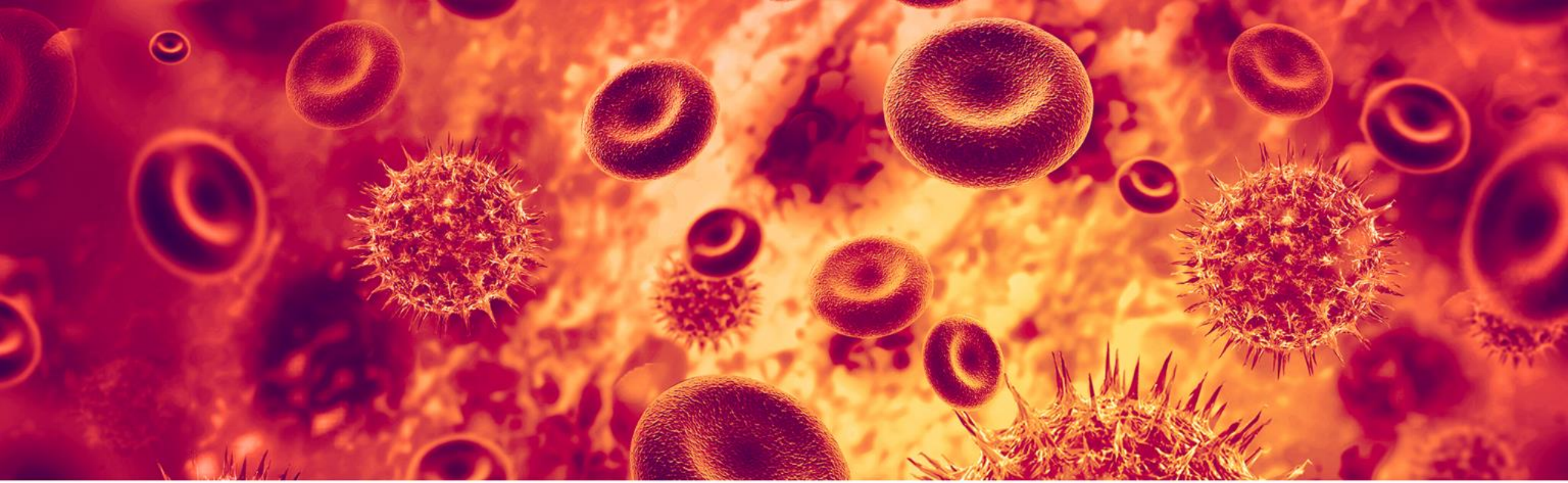


Discussion & Conclusion

Ibrutinib and Acalabrutinib in MCL



Question & Answer



Thank You!