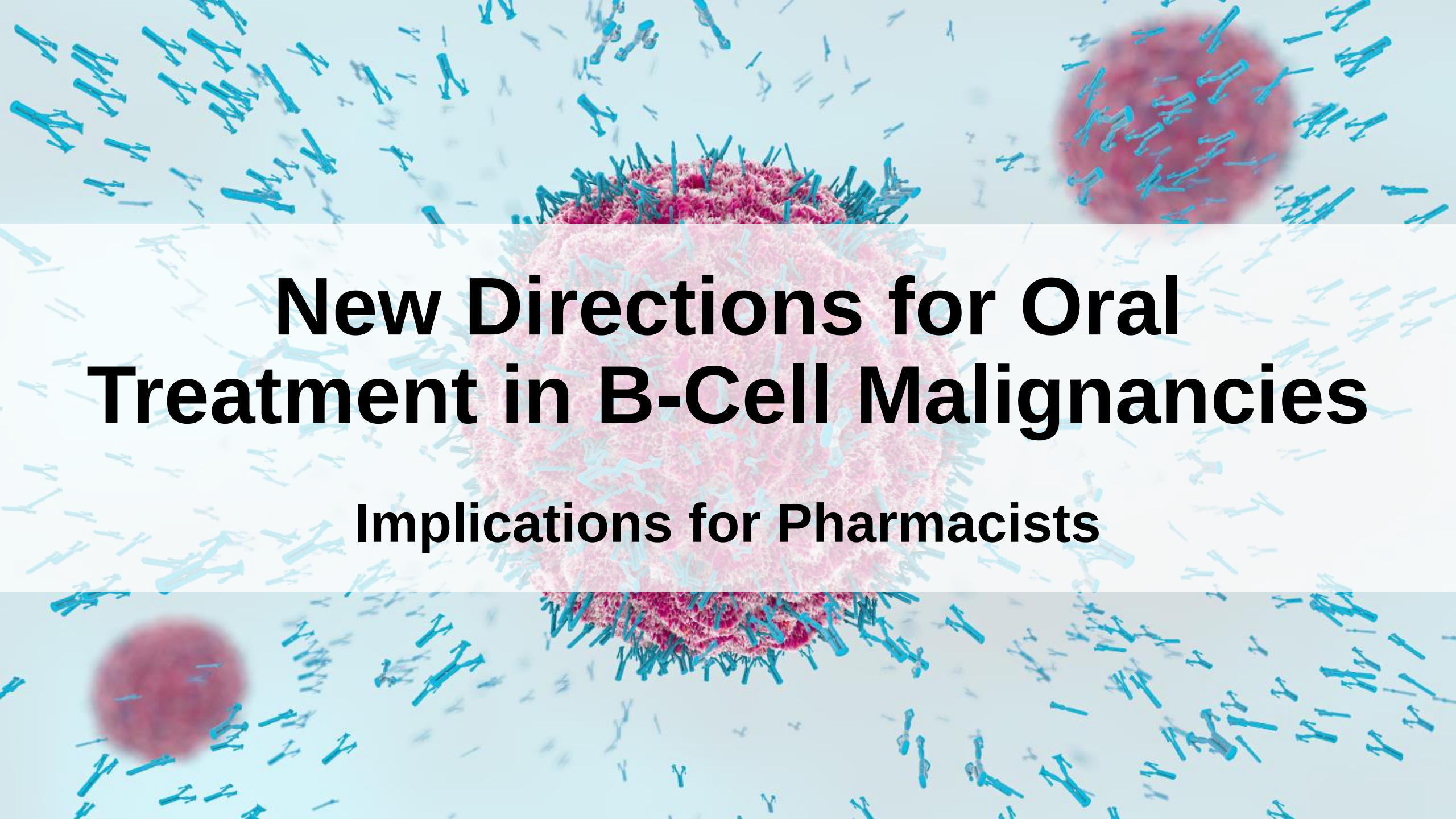
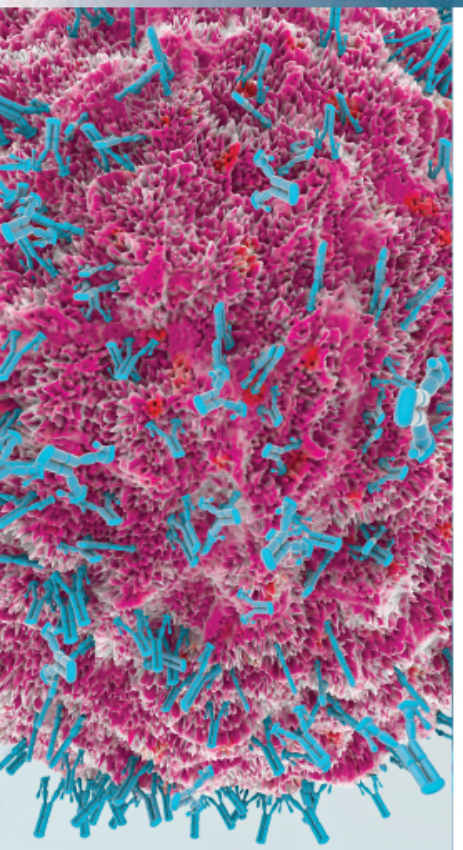


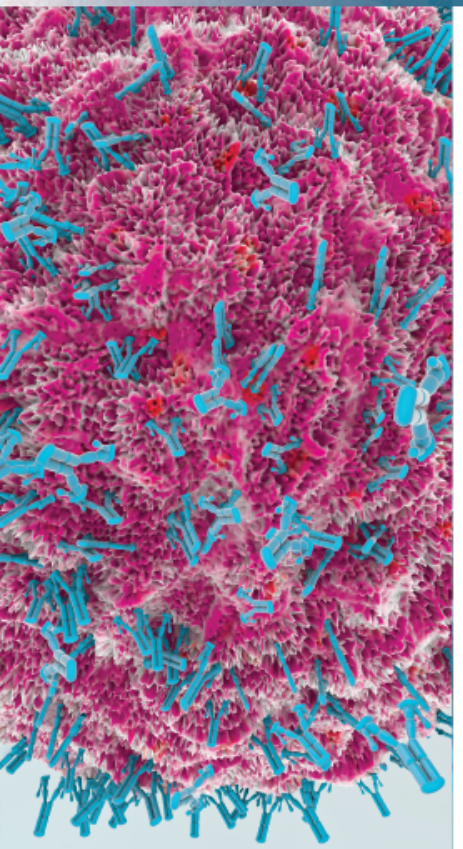
New Directions for Oral Treatment in B-Cell Malignancies

Implications for Pharmacists

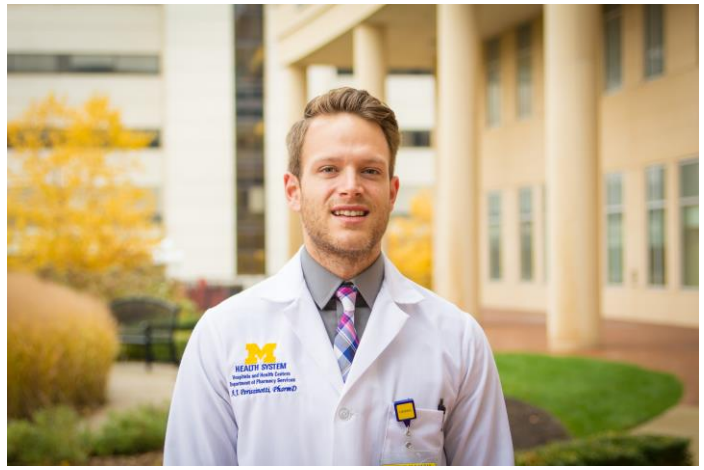


This educational activity is accredited by Purdue University, sponsored by Postgraduate Healthcare Education, LLC, and supported by educational grants from AbbVie Inc. and Janssen Pharmaceuticals Inc.

Faculty

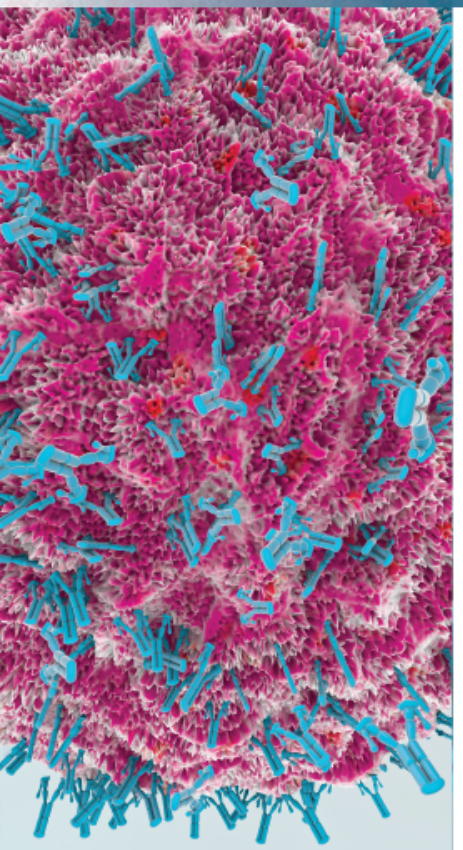


Anthony J. Perissinotti, PharmD, BCOP
Clinical Team Lead, Hematology/Oncology
Clinical Pharmacist Specialist, Inpatient Hematology
The University of Michigan – Michigan Medicine
Adjunct Clinical Assistant Professor
The University of Michigan College of Pharmacy
Ann Arbor, MI



Dr. Perissinotti is a hematology clinical pharmacist specialist at the University of Michigan, Michigan Medicine, clinical team leader of hematology/oncology, and adjunct clinical assistant professor at the University of Michigan College of Pharmacy in Ann Arbor, Michigan. He obtained his Doctor of Pharmacy degree from Wayne State University in Detroit, Michigan. He completed his first year of postgraduate residency training at the Detroit Medical Center, Harper University Hospital in Detroit, and his second year of postgraduate residency training at The University of Texas MD Anderson Cancer Center in Houston, Texas. Dr. Perissinottti is a Board Certified Hematology/Oncology Pharmacist.

Faculty



Victoria Nachar, PharmD, BCOP
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Ambulatory Hematology Oncology
University of Michigan – Michigan Medicine,
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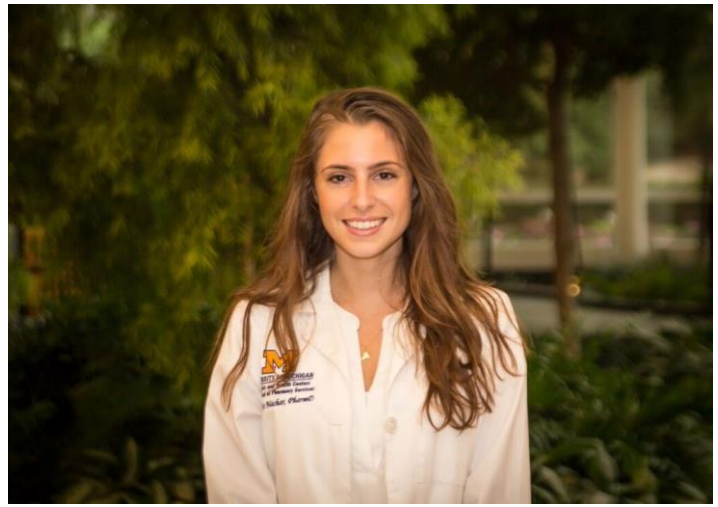
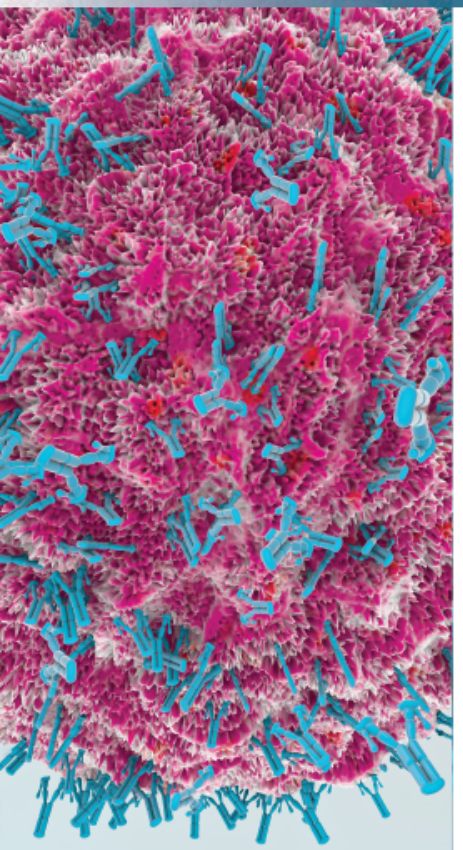
Adjunct Clinical Assistant Professor
The University of Michigan College of Pharmacy
Ann Arbor, MI



Dr. Nachar is a hematology/oncology clinical pharmacist specialist at the Michigan Medicine Rogel Cancer Center and an adjunct clinical assistant professor at the University of Michigan College of Pharmacy. She completed her Doctor of Pharmacy degree at the University at Buffalo, followed by residency training at the University of Michigan. She is a Board Certified Hematology/Oncology Pharmacist. She primarily cares for patients with both hematological and oncologic malignancies in Ann Arbor and at the Rogel Cancer Center satellite in Brighton, Michigan. Her professional interests include lymphoma, multiple myeloma, and clinical research.

Disclosures



Drs. Perissinotti and **Nachar** have disclosed that they have no actual or potential conflict of interest in relation to this program.

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

Susanne Batesko, RN, BSN, Robin Soboti, RPh, and Susan R. Grady, MSN, RN-BC, as well as the planners, managers, and other individuals, not previously disclosed, who are in a position to control the content of Postgraduate Healthcare Education (PHE) continuing education activities hereby state that they have no relevant conflicts of interest and no financial relationships or relationships to products or devices during the past 12 months to disclose in relation to this activity. PHE is committed to providing participants with a quality learning experience and to improve clinical outcomes without promoting the financial interests of a proprietary business.

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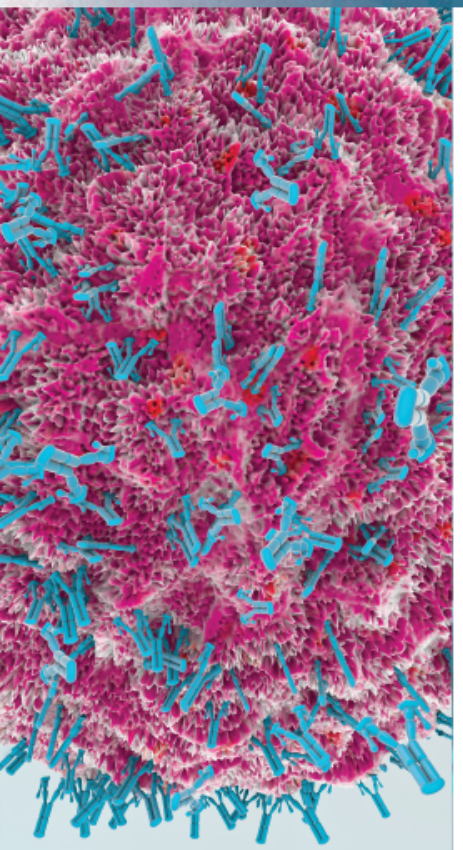

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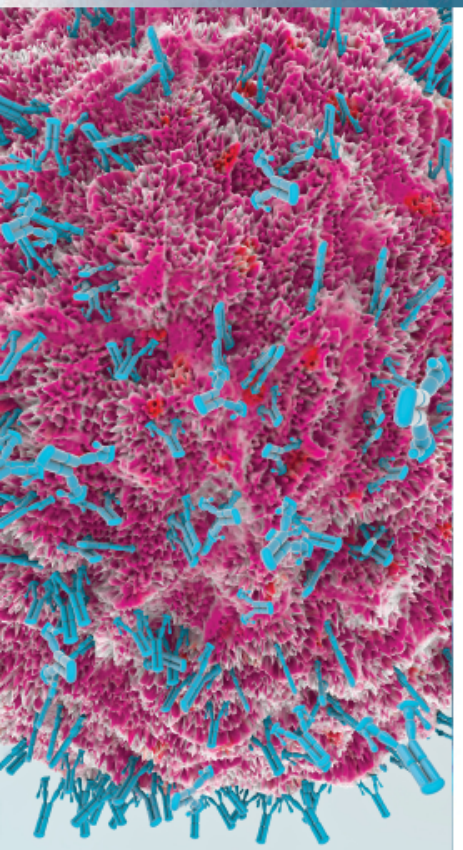
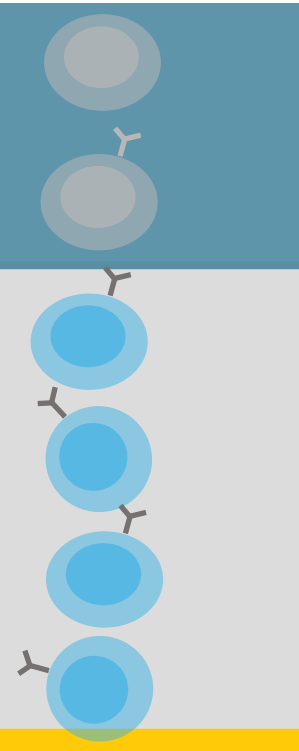
UAN: 0018-9999-20-020-H01-P
Credits: 1.0 hour (0.1 CEU)
Type of Activity: Application

Learning Objectives



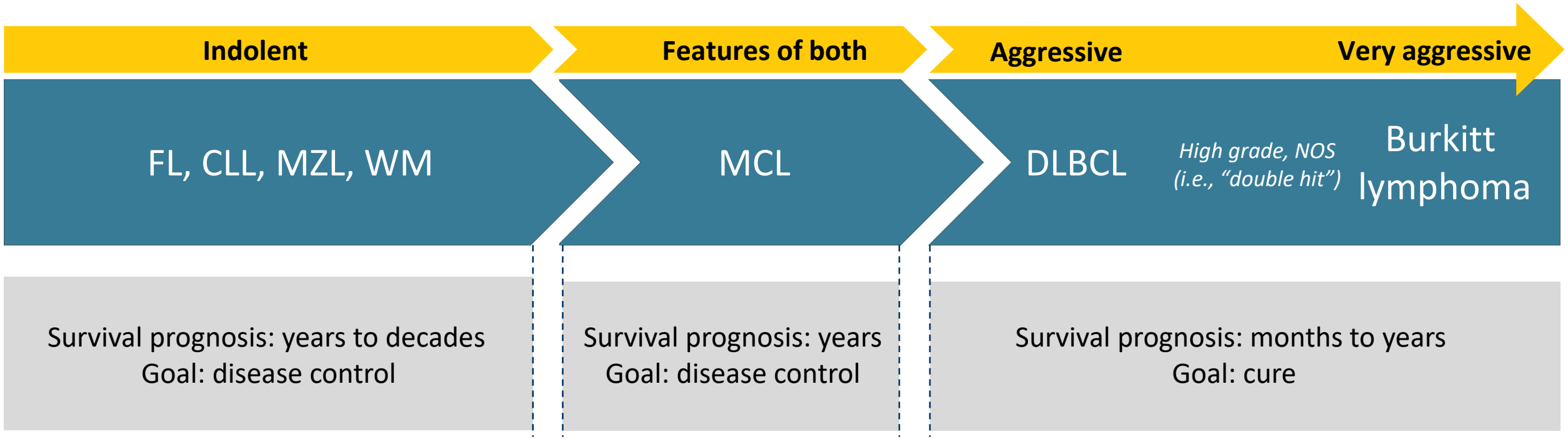
- **Discuss** the current guideline recommendations for the treatment of B-cell malignancies
- **Appraise** the mechanism of action, efficacy, and safety of current and emerging oral treatment options for B-cell malignancies
- **Demonstrate** strategies to effectively counsel patients receiving oral therapy for the treatment of B-cell malignancies, including assessment and management of adverse effects, and education for promoting safe use and adherence to treatment

B-Cell Malignancy Cell of Origin

BLOOD AND MARROW	Lymphoid progenitor		Acute lymphoblastic leukemia
	Pre-B-cell		
SECONDARY LYMPHOID TISSUE	Naïve B-cell		**Mantle cell lymphoma (MCL)**, Marginal zone lymphoma (MZL), **Chronic lymphocytic leukemia (CLL)**
	Activated B-Cell		Diffuse large b-cell lymphoma (DLBCL)
	Germinal center B-cell		**Follicular lymphoma (FL)**
	Memory B-cell		Burkitt lymphoma, **CLL**
BONE MARROW	Plasmablast		**Waldenstrom's macroglobulinemia (WM)**
	Plasma cell		Multiple myeloma, Amyloidosis

Hardy RR, Hayakawa K. B cell development pathways. *Annu Rev Immunol.* 2001;19:595-621.

B-Cell Non-Hodgkin Lymphoma (NHL)



Al-Hamadani M, et al. *Am J Hematol*. 2015;90(9):790-5.; Siegel RL, et al. *CA Cancer J Clin*. 2020;70(1):7-30.

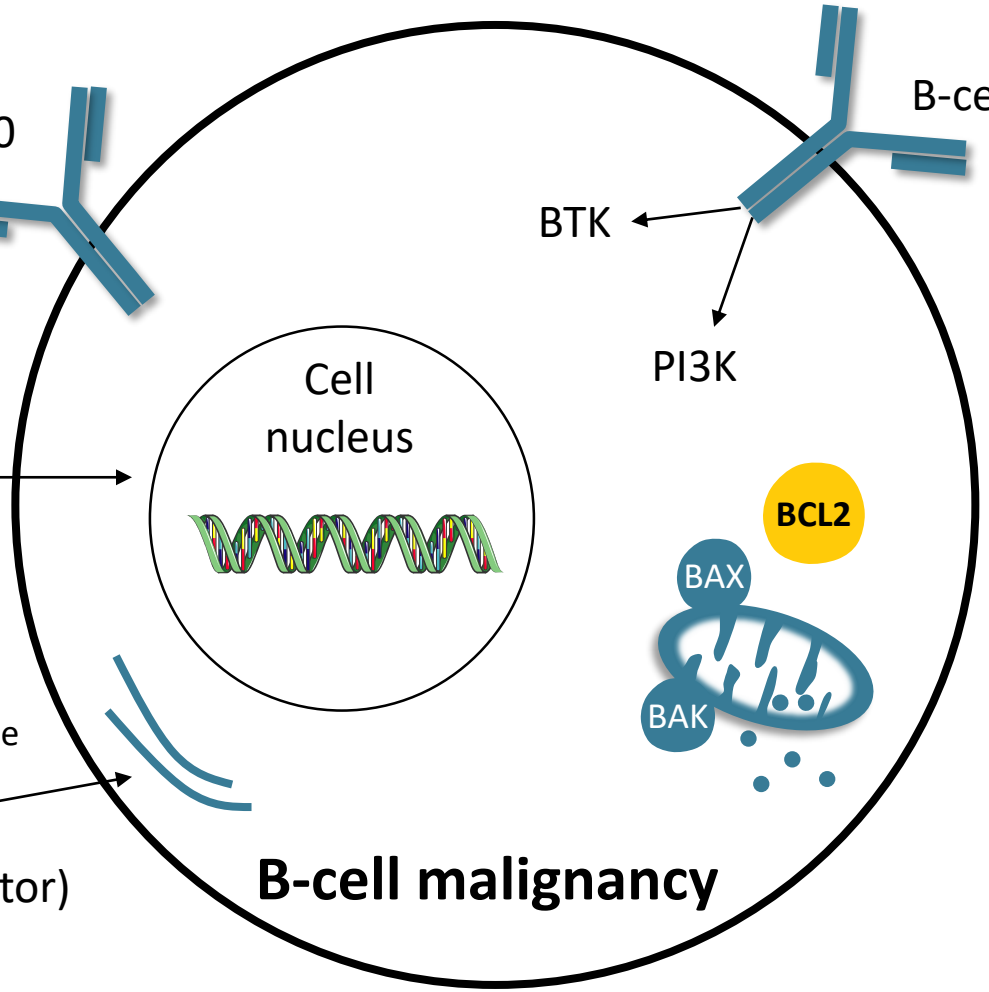
Therapies in B-Cell Malignancies

Anti-CD20 monoclonal antibodies

1. Rituximab
2. Obinutuzumab
3. Ofatumomab

Traditional chemotherapy

1. Alkylating agents
   - Cyclophosphamide, chlorambucil, bendamustine
2. Purine/pyrimidine analogues
   - Fludarabine, bendamustine, cytarabine
3. Anthracyclines
   - Doxorubicin
4. Vinca alkyloids (microtubule inhibitor)
   - Vincristine



BTK inhibitors

1. Ibrutinib
2. Acalabrutinib
3. Zanubrutinib

PI3K inhibitors

1. Idelalisib
2. Duvelisib
3. Copanlisib

BCL2 inhibitor

1. Venetoclax

Variety of standard regimens

Ongoing studies to determine optimal sequence or combinations

National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology: B-Cell Lymphomas v1.2020.

Regimen Definitions

BR	Bendamustine, rituximab
FCR	Fludarabine, cyclophosphamide, rituximab
Clb + Obi	Chlorambucil, obinutuzumab
CHOP	Cyclophosphamide, doxorubicin, vincristine, prednisone
HiDAC	High-dose cytarabine
Nordic regimen	Maxi-CHOP alternating with HiDAC
CVP	Cyclophosphamide, vincristine, prednisone
VR-CAP	Bortezomib, rituximab, cyclophosphamide, doxorubicin, prednisone
DRC	Dexamethasone, rituximab, cyclophosphamide
BDR	Bortezomib, dexamethasone, rituximab
Hyper-CVAD	Cyclophosphamide, vincristine, doxorubicin, dexamethasone alternating with HiDAC, methotrexate
CVP	Cyclophosphamide, vincristine, prednisone

Chronic Lymphocytic Leukemia (CLL)

- **Indolent lymphoma**
- **Incidence:**
  - Estimated 21,040 Americans in 2020
- **Deaths:**
  - 4060 in 2020
- **Median age:** 70 years

- **Most prevalent leukemia**
- **Prognostic factors:**
  - del(17p)/TP53 mutation, unmutated IGHV, complex karyotype
- **CLL and SLL (same malignancy)**
  - CLL: > 5000 clonal lymphocytes in blood
  - SLL: < 5000 clonal lymphocytes in blood but presence of lymphadenopathy and/or splenomegaly

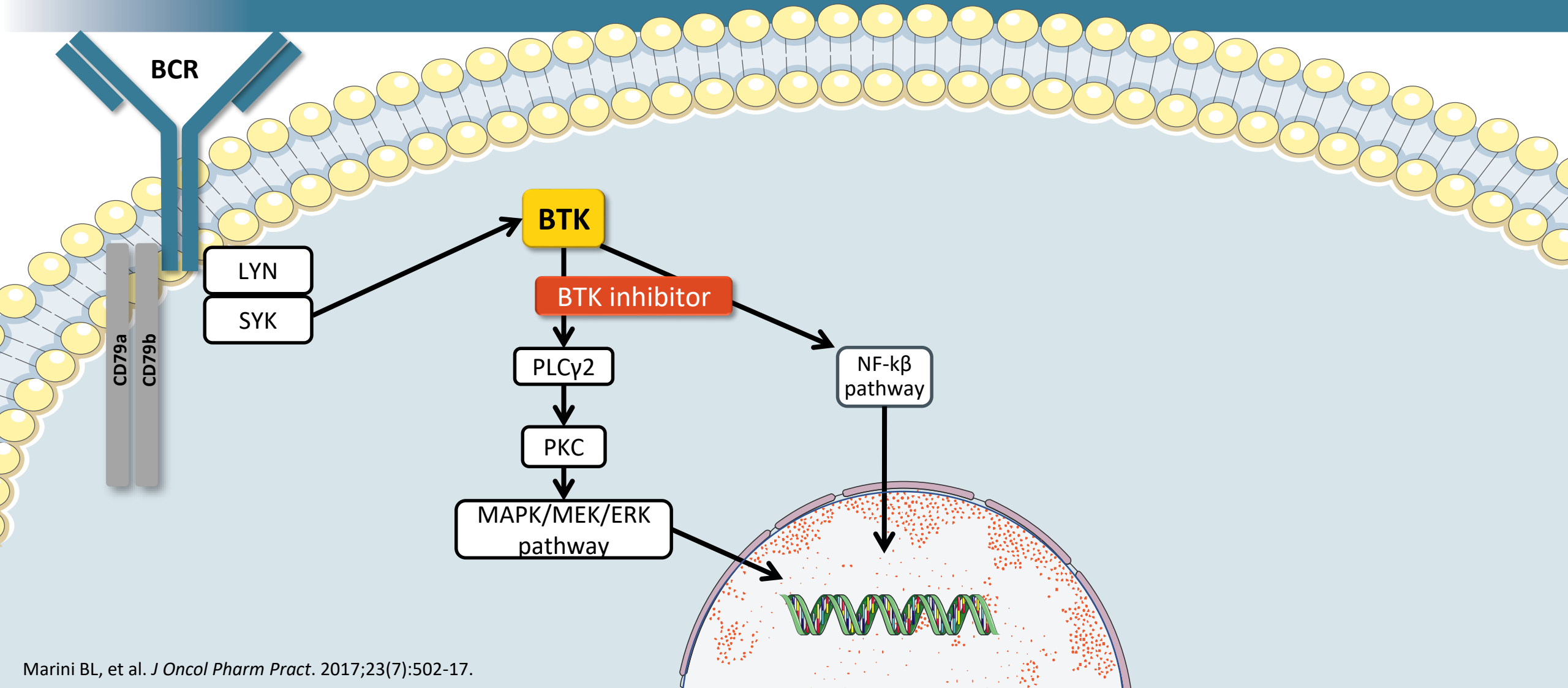
National Cancer Institute. seer.cancer.gov/statfacts/html/clyl.html. Accessed June 2nd, 2020.;
National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology: Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma v4.2020.; Siegel RL, et al. *CA Cancer J Clin*. 2020;70(1):7-30.

IGHV, immunoglobulin heavy chain variable.

First-Line Treatment in CLL: Pre-BTK Inhibitors

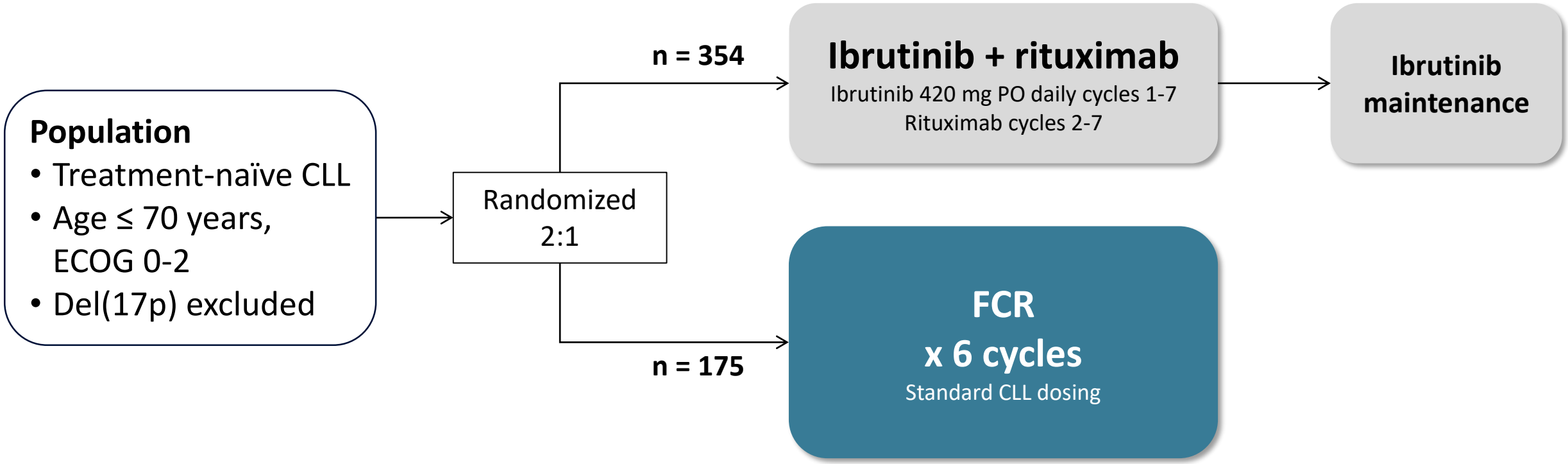
Population	Old standard	New standard
Young/fit	Mutated IGHV: FCR Unmutated IGHV: FCR or BR	
Older/fit	Bendamustine + rituximab	
Elderly/comorbidities	Chlorambucil + Obi	

BTK Inhibitor Mechanism of Action



Marini BL, et al. *J Oncol Pharm Pract*. 2017;23(7):502-17.

ECOG 1912 Trial: Study Schema



Study design

- Phase III, multicenter, open-label, randomized controlled trial (RCT)

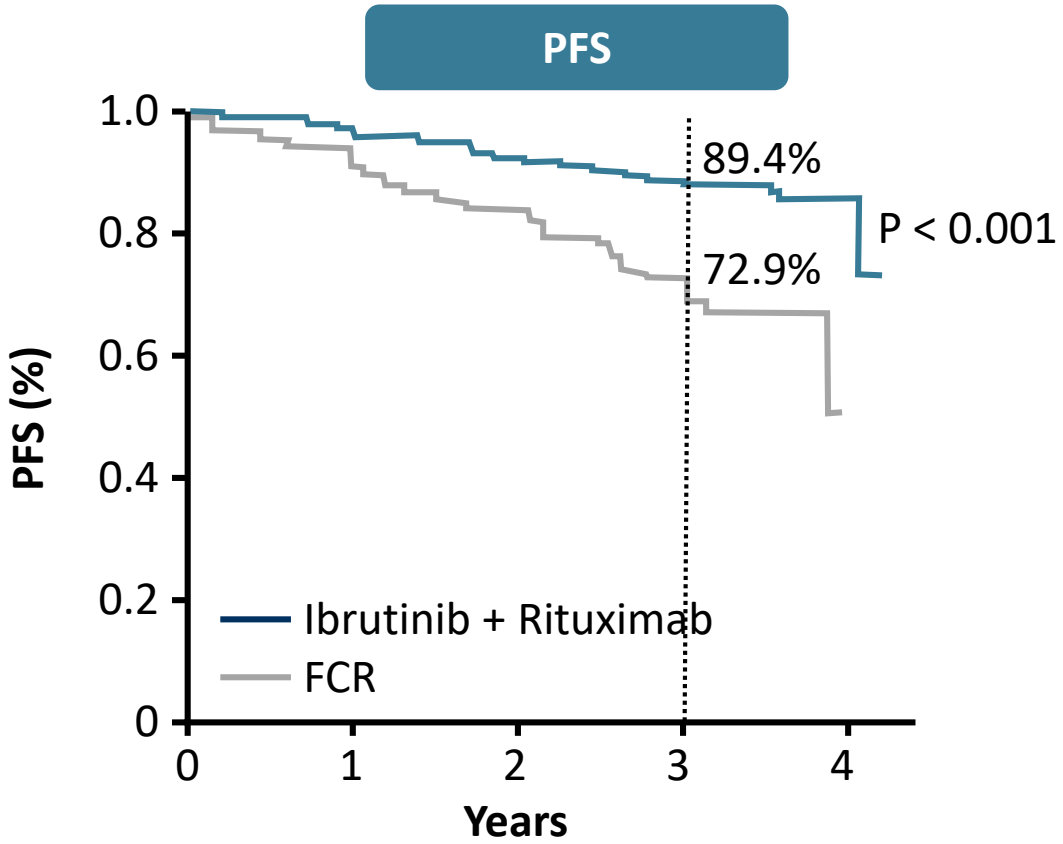
Primary outcome

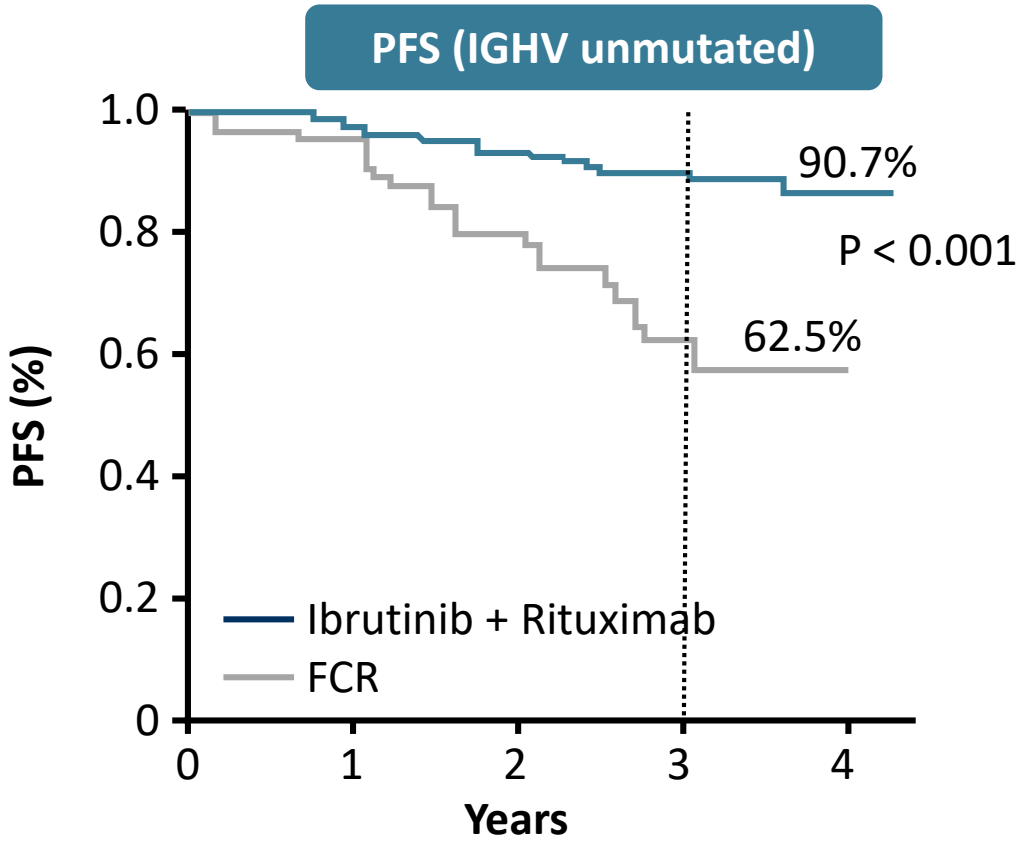
- Progression-free survival (PFS)

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

ECOG 1912 Trial: Results

Ibrutinib + Rituximab (IR) vs. FCR





Conclusions

IR improved PFS vs. FCR, especially in IGHV unmutated CLL

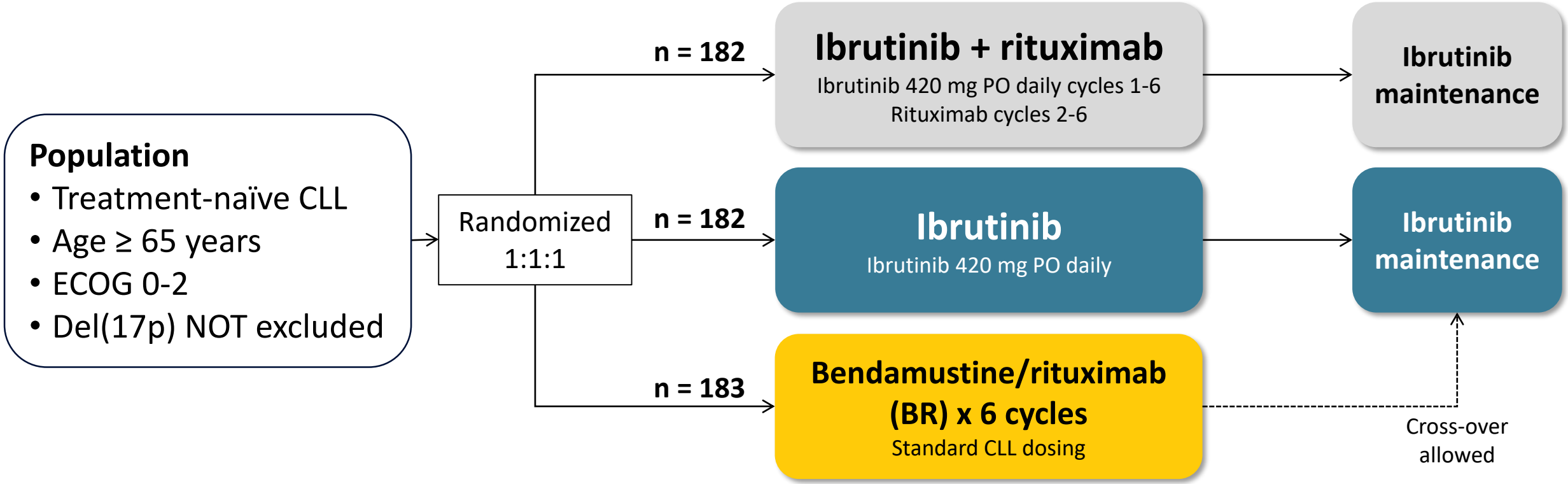
Shanafelt TD, et al. *N Engl J Med*. 2019;381(5):432-43.

First-Line Treatment in CLL: Changing Landscape

Population	Old standard	New standard
Young/fit	Mutated IGHV: FCR Unmutated IGHV: FCR or BR	Ibrutinib + rituximab*
Older/fit	Bendamustine + rituximab	
Elderly/comorbidities	Chlorambucil + Obi	

*Mutated IGHV without del(17p)/TP53 mutation can consider FCR.

Alliance A041202 Trial: Study Schema



Study design

- Phase III, multicenter, open-label, RCT

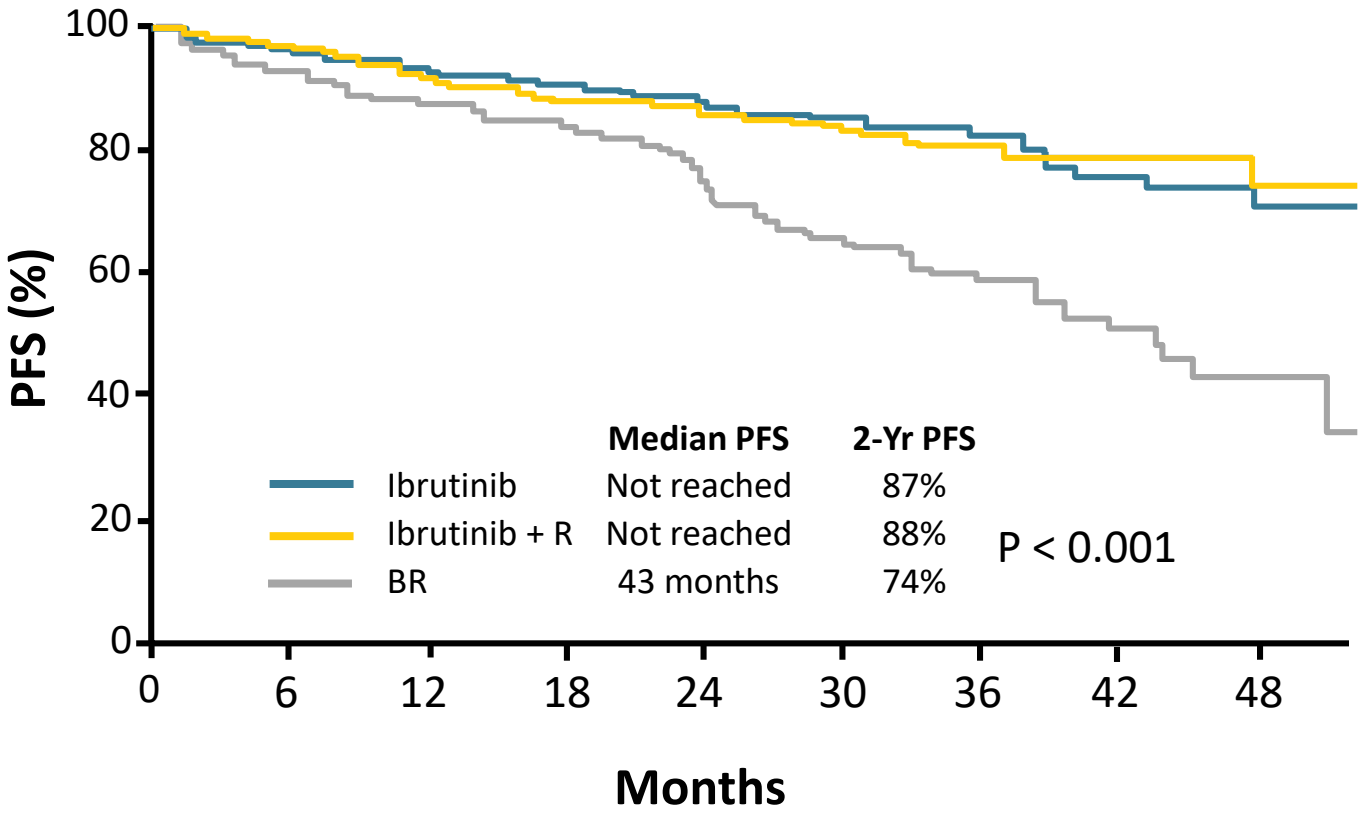
Primary outcome

- PFS

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

Alliance A041202 Trial: Results

Ibrutinib + Rituximab (IR) vs. Ibrutinib Alone vs. Bendamustine + Rituximab (BR)



Conclusions

- Ibrutinib ± rituximab improved PFS vs. BR
- No improvement with adding rituximab to ibrutinib
- Vast majority of patients with CLL no longer need chemotherapy

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

First-Line Treatment in CLL: Changing Landscape

Population	Old standard	New standard
Young/fit	Mutated IGHV: FCR Unmutated IGHV: FCR or BR	Ibrutinib + rituximab*
Older/fit	Bendamustine + rituximab	Ibrutinib
Elderly/comorbidities	Chlorambucil + Obi	

*Mutated IGHV without del(17p)/TP53 mutation can consider FCR; can consider no rituximab with ibrutinib based on ALLIANCE trial (but now FDA approved).

FDA, United States Food and Drug Administration.

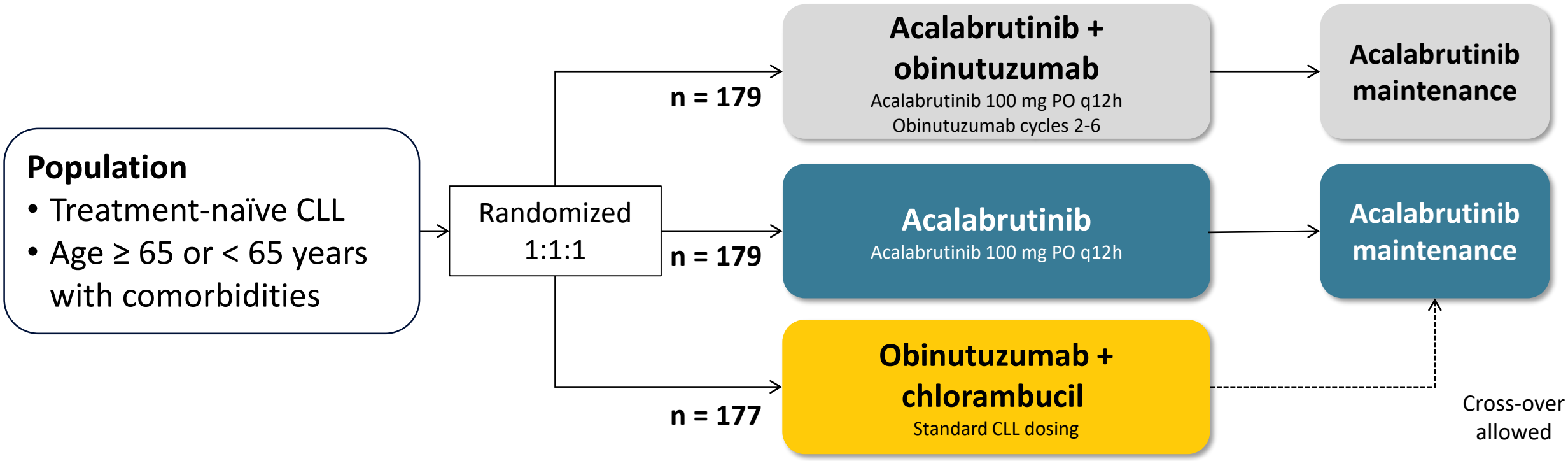
BTK Inhibitors Not Created Equal

IC_{50}/EC_{50} (nM)

Kinase	Ibrutinib	Acalabrutinib	Zanubrutinib
BTK	1.5	5.1	0.5
TEC	10	126	44
ITK	4.9	> 1000	50
BMX	0.8	46	1.4
EGFR	5.3	> 1000	21
ERBB4	3.4	16	6.9
JAK3	32	> 1000	1377
BLK	0.1	> 1000	2.5

Kaptein A, et al. *Blood.* 2018;132(Suppl 1):1871.

ELEVATE-TN Trial: Study Schema



Study design

- Phase III, multicenter, open-label, RCT

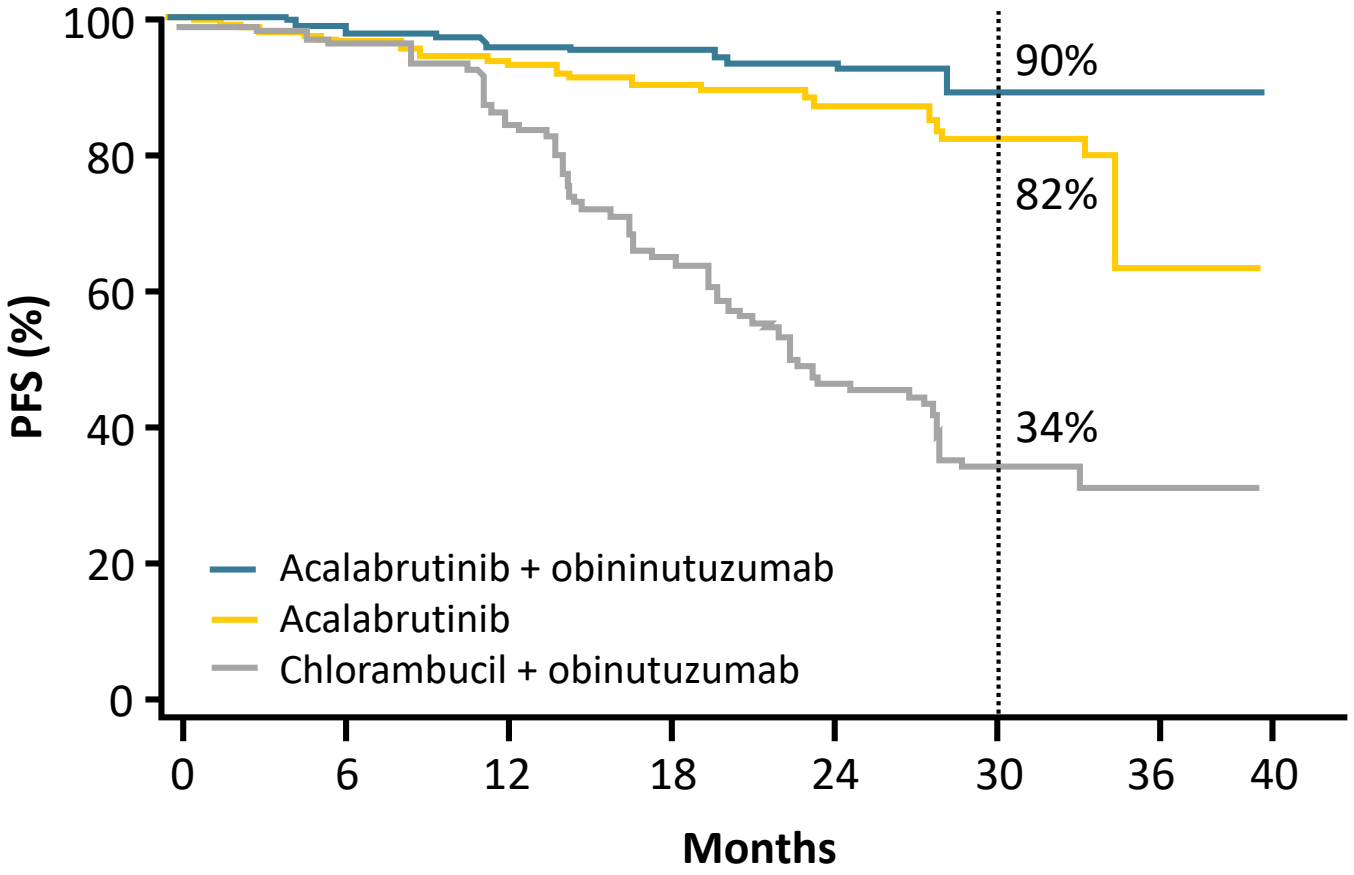
Primary outcome

- PFS

Sharman JP, et al. *Lancet*. 2020;395(10232):1278-91.

ELEVATE-TN Trial: Results

Acalabrutinib + Obinutuzumab vs. Acalabrutinib Alone vs. Chlorambucil + Obinutuzumab



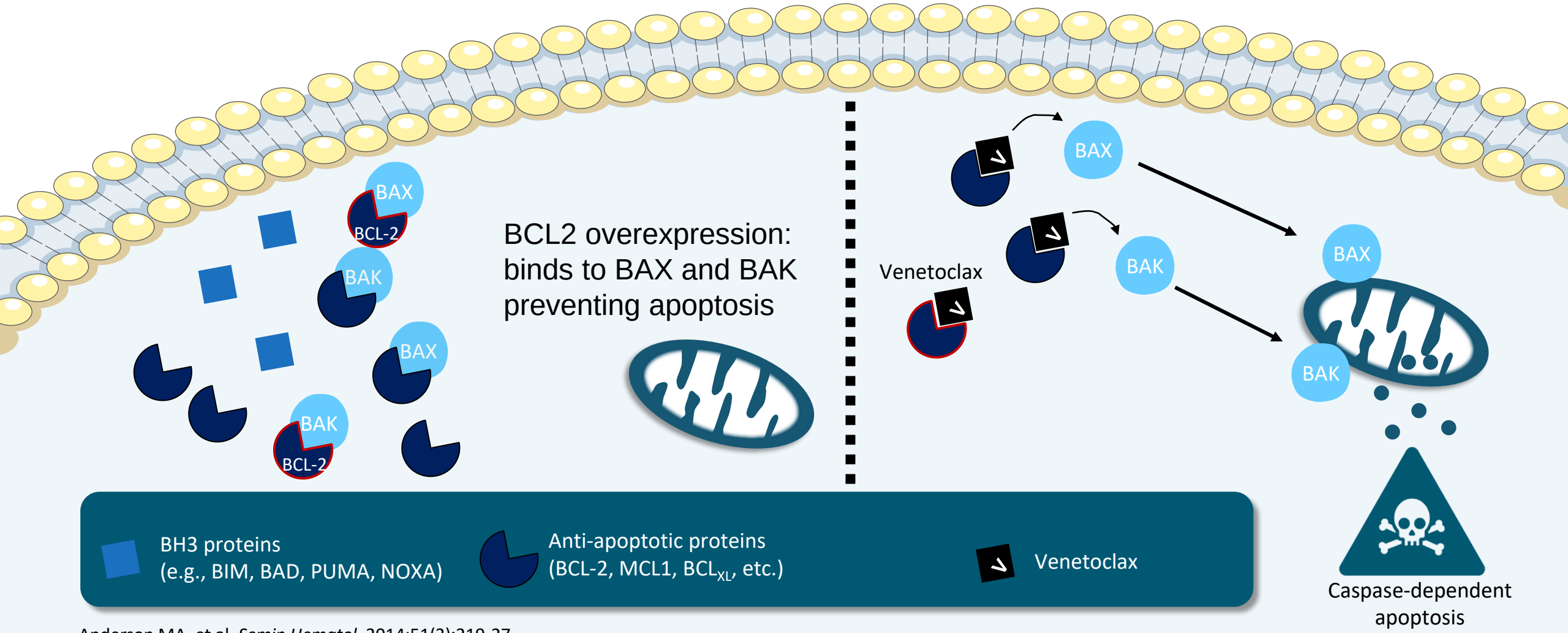
Conclusions

- Acalabrutinib ± Obi improved PFS vs. chlorambucil + Obi
- No significant PFS improvement with adding Obi to acalabrutinib
- Higher ORR with adding Obi to acalabrutinib (94% vs. 79%; p<0.0001)

Sharman JP, et al. *Lancet*. 2020;395(10232):1278-91.

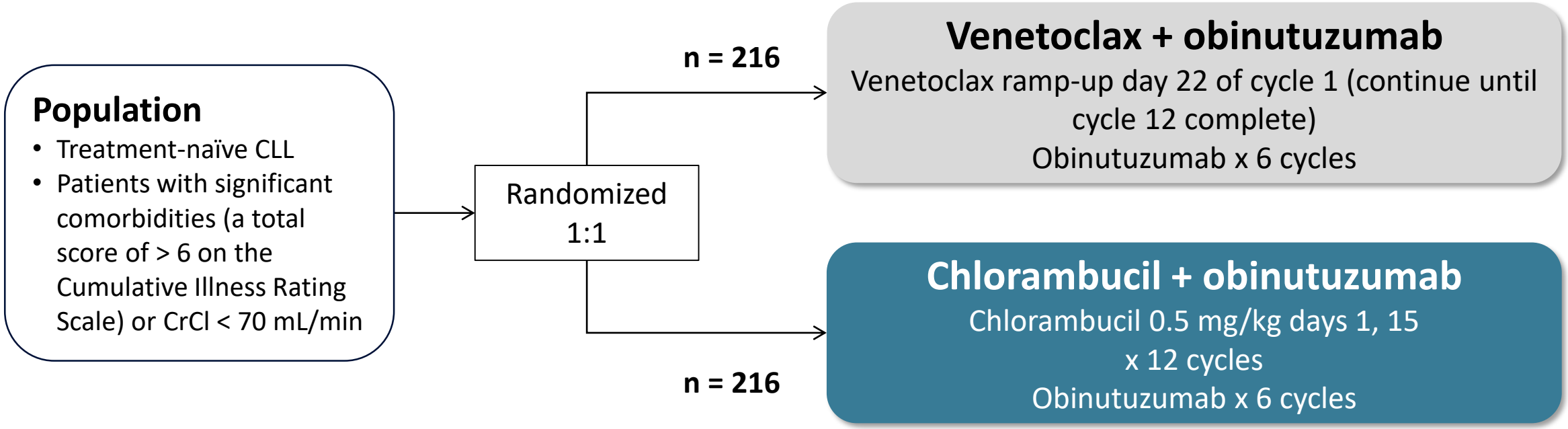
ORR, overall response rate.

BCL2 Inhibitor Mechanism of Action



Anderson MA, et al. *Semin Hematol*. 2014;51(3):219-27.

CLL14 Trial: Study Schema



Study design

- Phase III, multicenter, open-label, RCT

Primary outcome

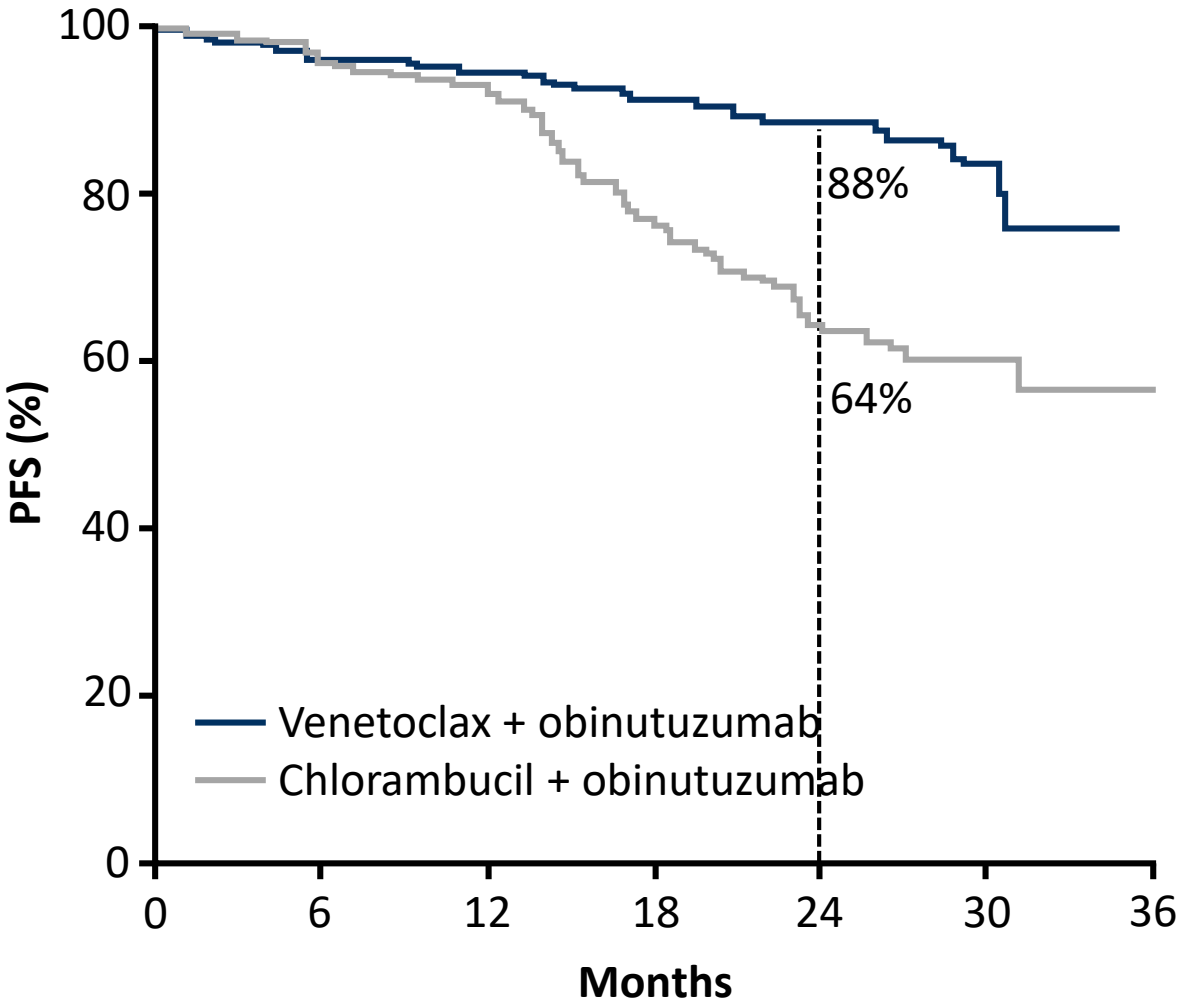
- PFS

Fischer K, et al. *N Engl J Med*. 2019;380(23):2225-36.

CrCl, creatinine clearance.

CLL14 Trial: Results

Venetoclax + Obinutuzumab vs. Chlorambucil + Obinutuzumab



Conclusions

- Venetoclax ± Obi improved PFS vs. chlorambucil + Obi
- Provides a targeted therapy option with a fixed duration (1 year then stop)
- Low rate of tumor lysis; no different between the 2 groups

Fischer K, et al. *N Engl J Med*. 2019;380(23):2225-36.

First-Line Treatment in CLL: Changing Landscape

Population	Old standard	New standard
Young/fit	~~Mutated IGHV: FCR Unmutated IGHV: FCR or BR~~	Ibrutinib + rituximab*
Older/fit	~~Bendamustine + rituximab~~	Ibrutinib
Elderly/comorbidities	~~Chlorambucil + Obi~~	Acalabrutinib +/- Obi Ibrutinib Venetoclax + Obi

*Mutated IGHV without del(17p)/TP53 mutation can consider FCR; can consider no rituximab with ibrutinib based on ALLIANCE trial (but now FDA approved).

Mantle Cell Lymphoma (MCL)

- **Indolent with aggressive features**
- **Incidence:** 6% of NHL
- **Deaths:**
  - Low risk: 5-year OS 60%
  - Intermediate risk: median 51-month OS
  - High risk: median 29-month OS
- **Median age:** 63 years

- **Hallmark:**
  - t(11;14)
- **Prognostic factors:**
  - p53 mutations, ATM, CCND2 or 3, SOX11, IGHV
- **Cytologic variants**
  - Classic, small-cell, blastoid, pleomorphic

Armitage JO, Weisenburger DD. *J Clin Oncol*. 1998;16(8):2780-95.; Eskelund CW, et al. *Blood*. 2017;130(17):1903-10.; Herrmann A, et al. *J Clin Oncol*. 2009;27(4):511-8.; Hoster E, et al. *Blood*. 2008;111(2):558-65.; Jain P, Wang M. *Am J Hematol*. 2019;94(6):710-25.; National Cancer Institute. seer.cancer.gov/statfacts/html/nhl.htm. Accessed June 2, 2020.; National Comprehensive Cancer Center. NCCN Clinical Practice Guidelines in Oncology: B-Cell Lymphomas v1.2020.; Tiemann M, et al. *Br J Haematol*. 2005;131(1):29-38.

OS, overall survival.

MCL Treatment 2020

First-line therapy

"Watch and wait"/observation

Transplant eligible

Intensive therapy
R-CHOP/HiDAC-based therapy (i.e., Nordic, Hyper-CVAD)

Autologous stem cell transplant

Non-transplant eligible

Less intensive therapy
BR, R-CHOP, VR-CAP, R-lenalidomide

Maintenance rituximab

Relapsed/refractory therapy

Second line:

- R-chemotherapy
- Bortezomib ± R
- Lenalidomide ± R
- **BTK inhibitors:**
  - **Ibrutinib ± R**
  - **Acalabrutinib**
  - **Zanubrutinib**
- **Venetoclax ± ibrutinib**

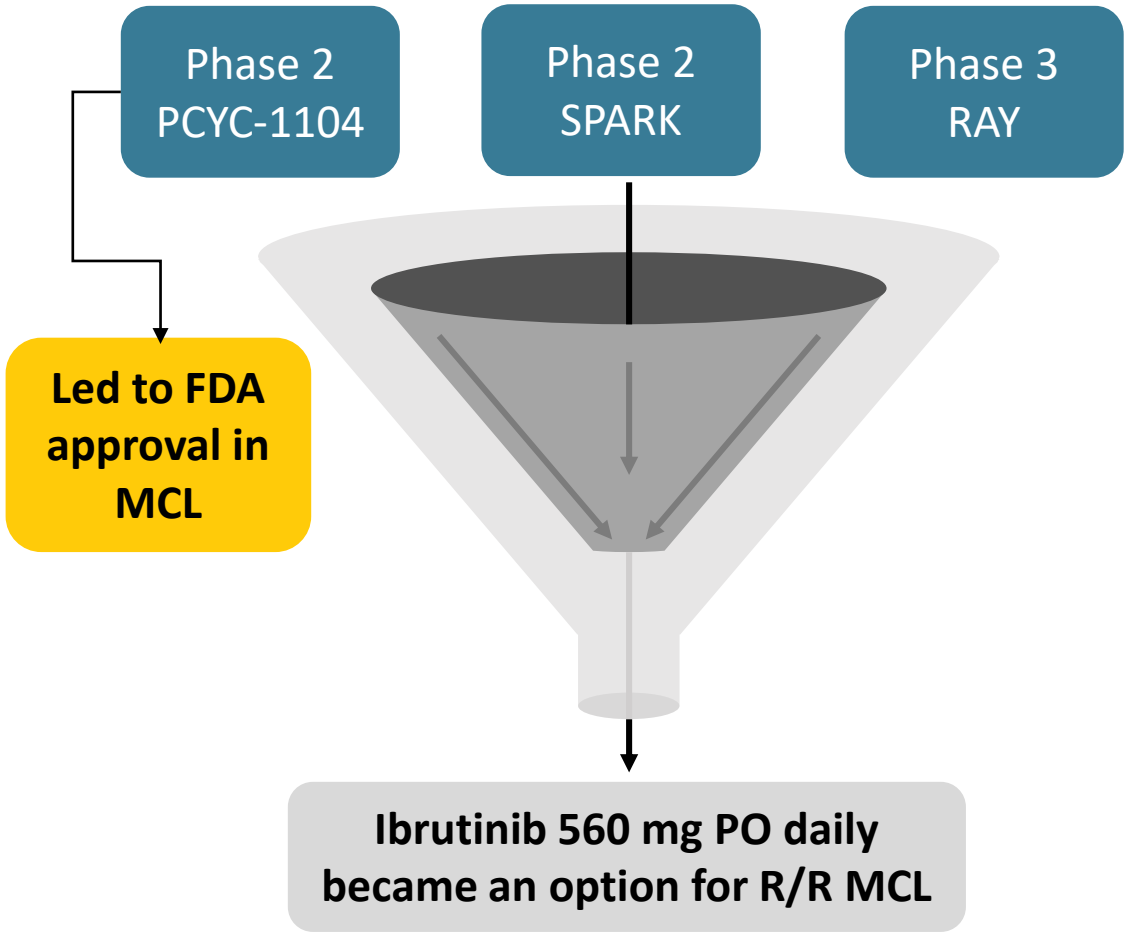
Third line:

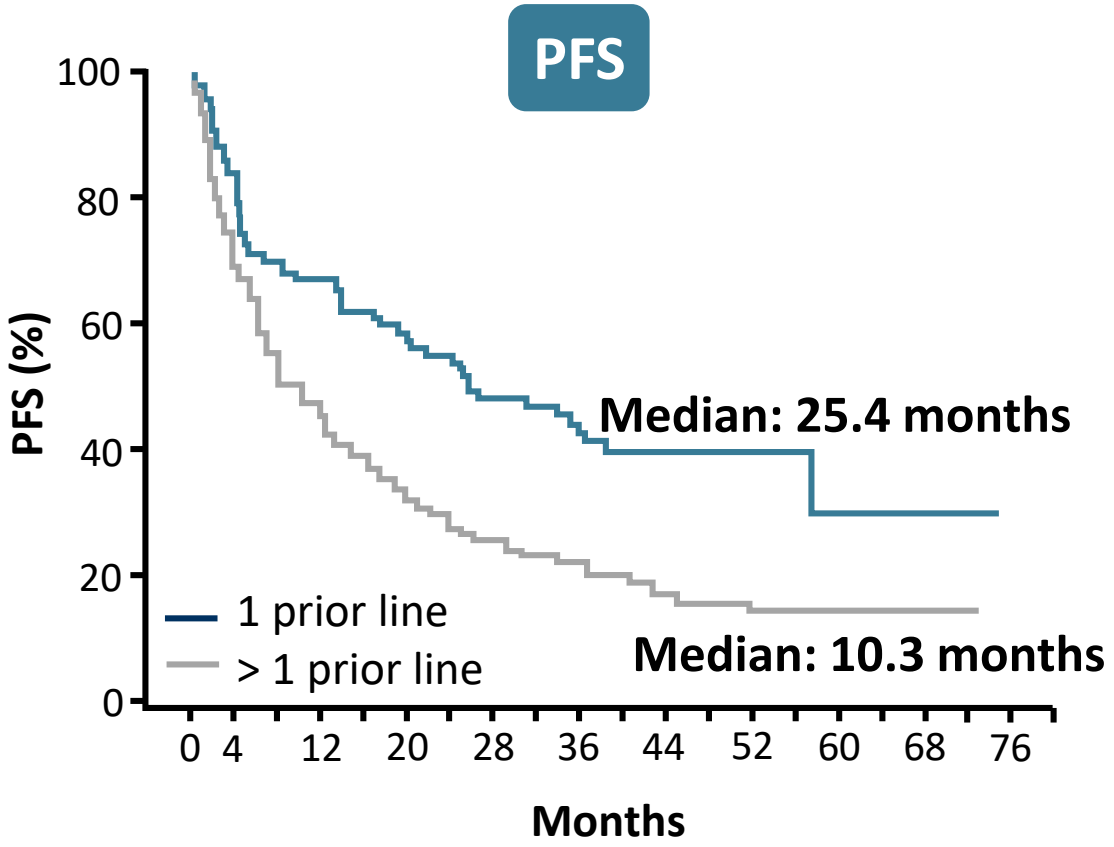
- Treatment based on prior therapies

Factors to consider: response and duration of response to previous therapy, patient age, and comorbidities.

NCCN Clinical Practice Guidelines in Oncology: B-Cell Lymphomas v1.2020.

Ibrutinib Pooled Analysis: Relapsed/Refractory (R/R) MCL





Rule S, et al. *Haematologica*. 2019;104(5):e211-4.

ACE-LY-004 Trial: Study Schema

Population

- R/R MCL
- 1-5 prior lines of therapy
- No notable CVD*
- No concurrent use of warfarin/equivalent vitamin K antagonists
- No prior BTK or BCL-2 inhibitors

n = 124

Acalabrutinib
100 mg PO BID in 28-day cycles

Until progression or unacceptable toxicity

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

Study design

- Phase II, multicenter, open-label

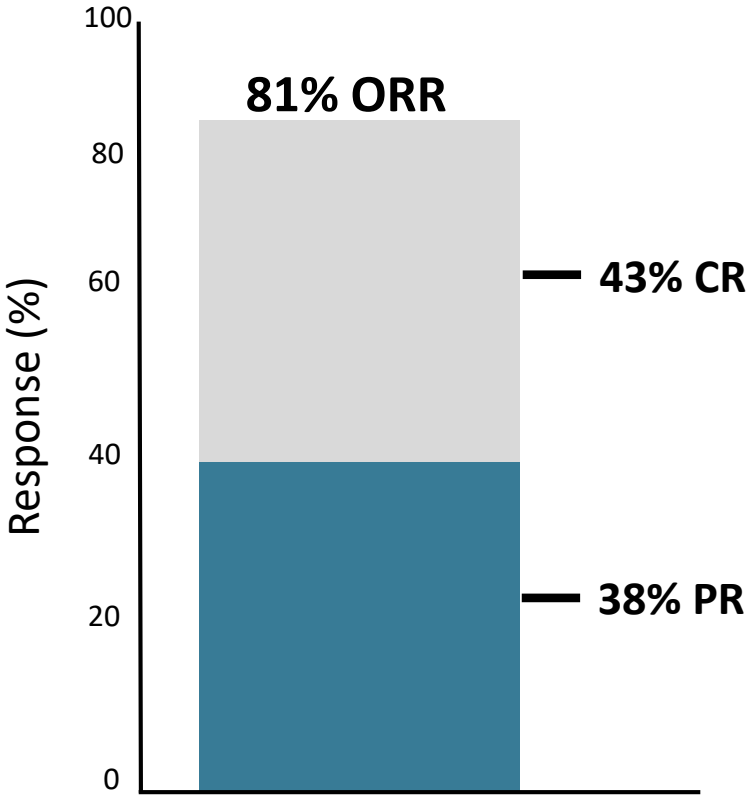
Primary endpoint

- ORR

Wang M, et al. *Lancet*. 2018;39(10121)1:659-67.

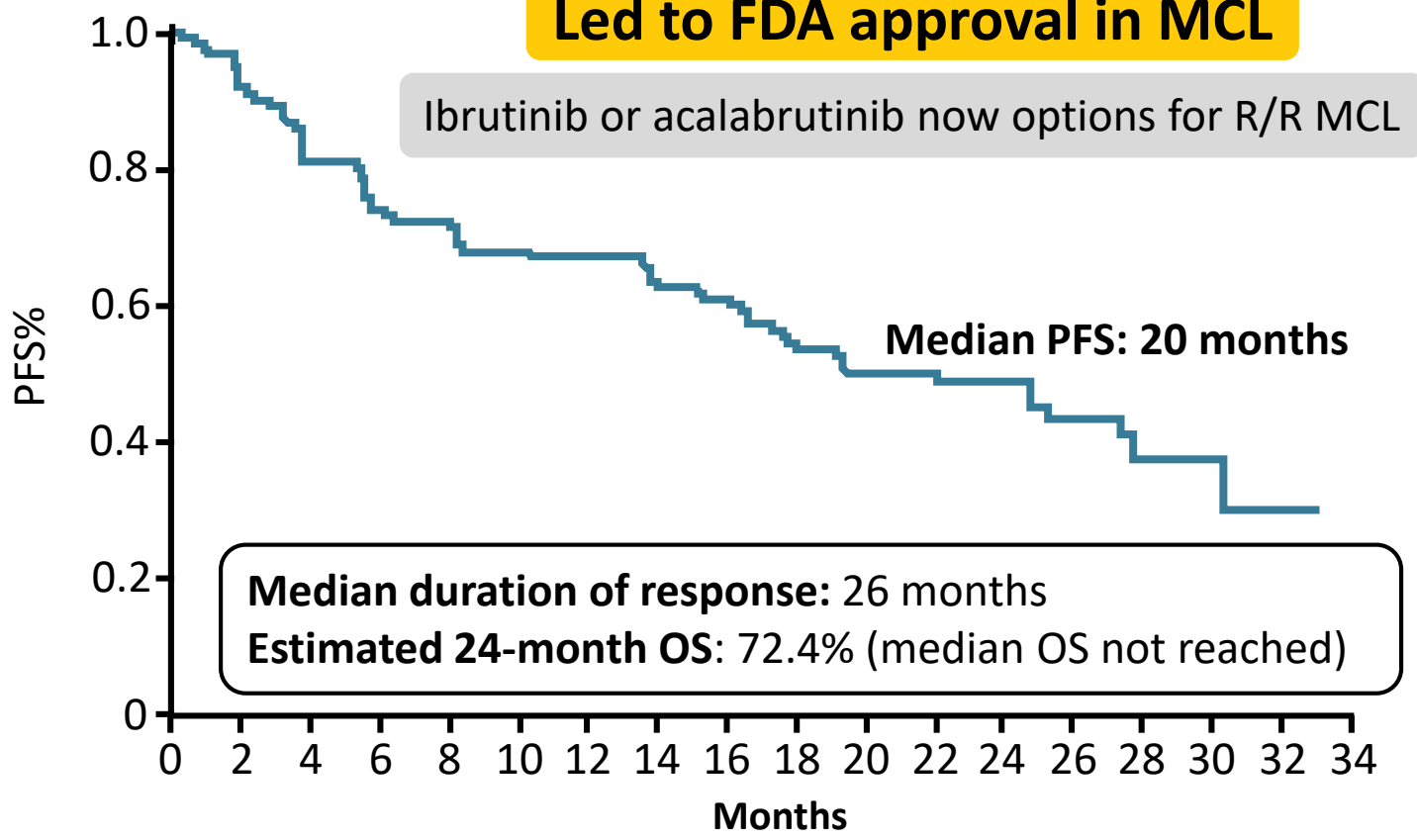
CHF, congestive heart failure; CVD, cardiovascular disease; MI, myocardial infarction; NYHA, New York Heart Association.

ACE-LY-004 Trial: Acalabrutinib for R/R MCL Results



Led to FDA approval in MCL

Ibrutinib or acalabrutinib now options for R/R MCL

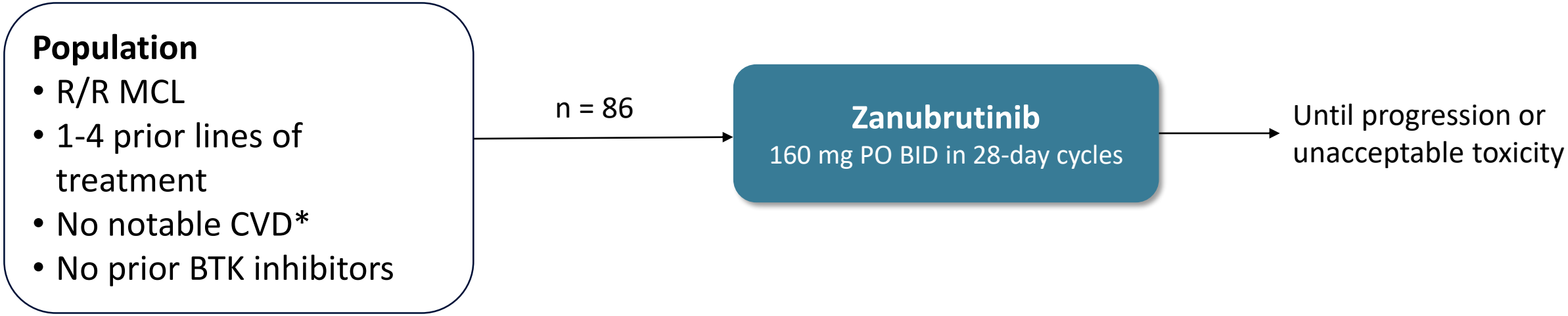


Median duration of response: 26 months
Estimated 24-month OS: 72.4% (median OS not reached)

Wang M, et al. *Lancet*. 2018;391(10121):659-67.; Wang M, et al. *Leukemia*. 2019;33(11):2762-6.

CR, complete response; PR, partial response.

BCG-3111-206 Trial: Study Schema



*Clinically significant CVD; patients with history of cardiac arrythmia that was adequately controlled at time of enrollment were eligible

Study design

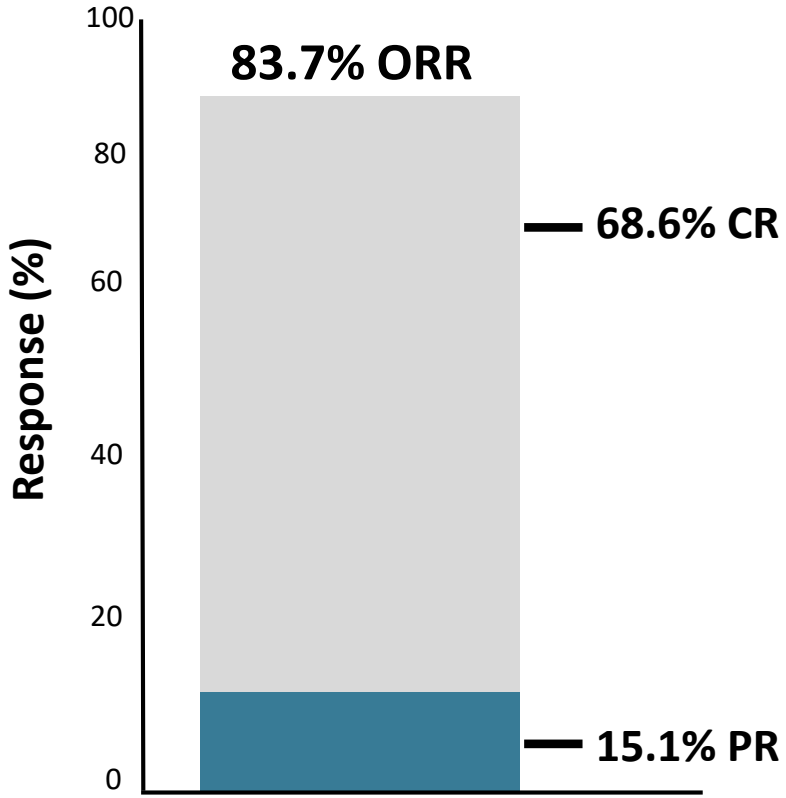
- Phase II, multicenter, open-label

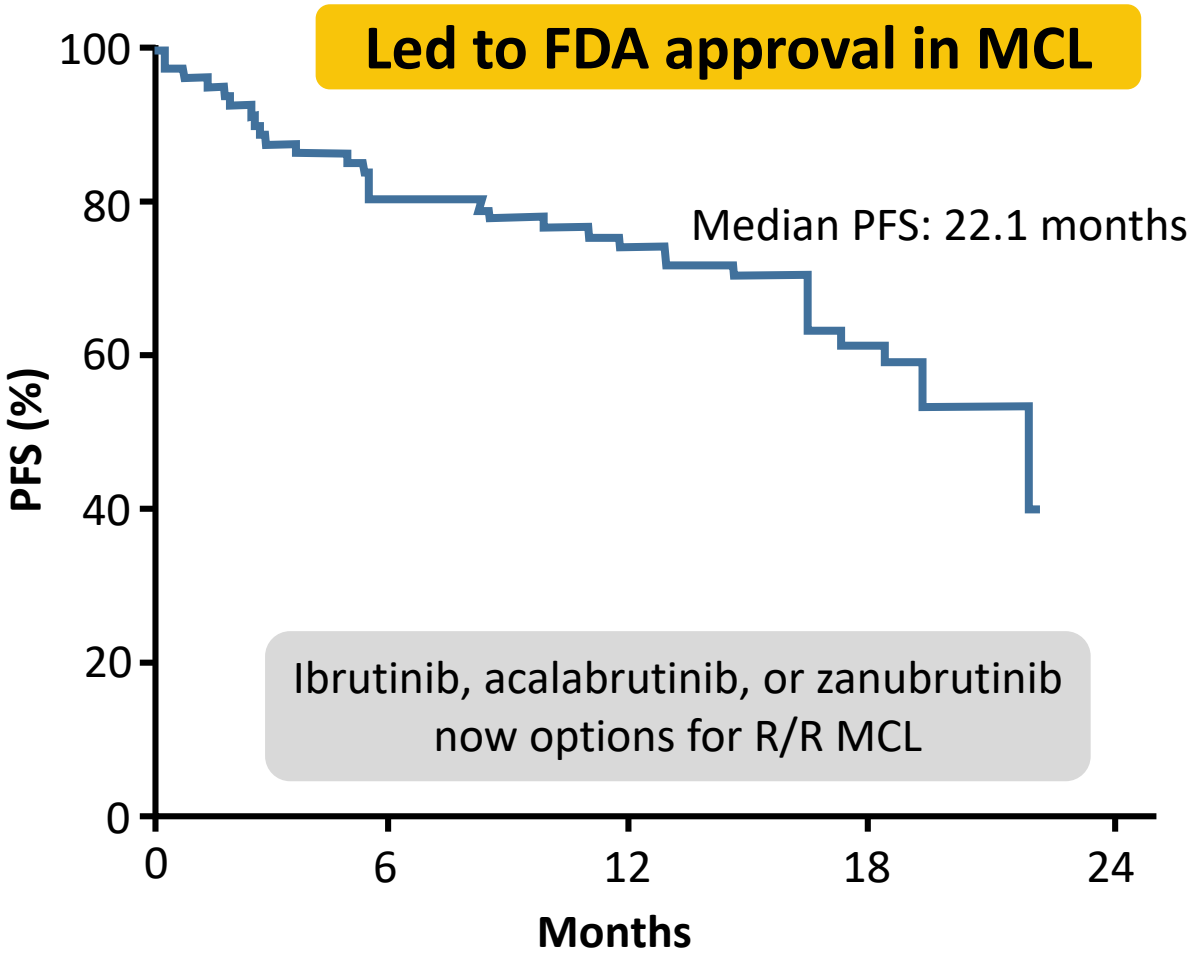
Primary endpoint

- ORR

Song Y, et al. *Clin Cancer Res*. 2020;clincanres.3703.2019.

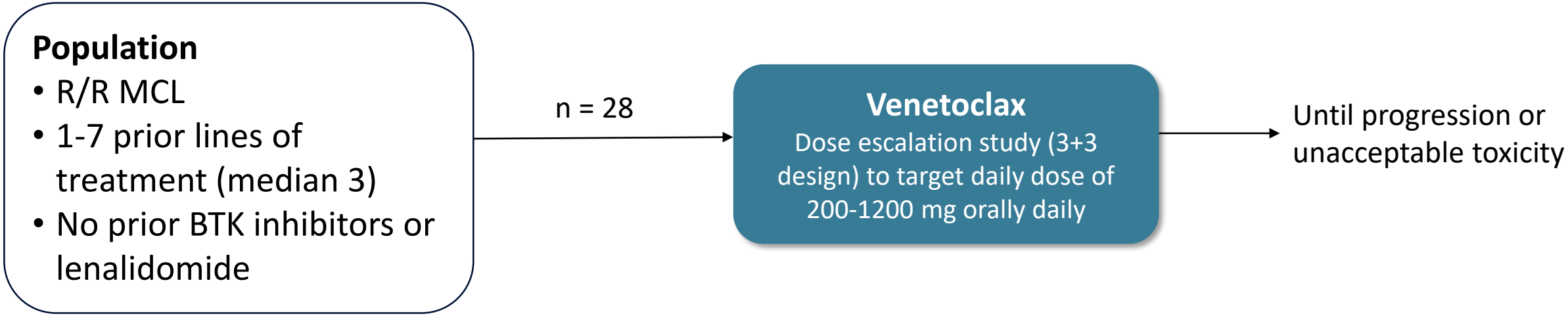
BCG-3111-206 Trial: Zanubrutinib for R/R MCL Results





Song Y, et al. *Clin Cancer Res*. 2020;clincanres.3703.2019.

M12-175 Trial: Study Schema



Study design

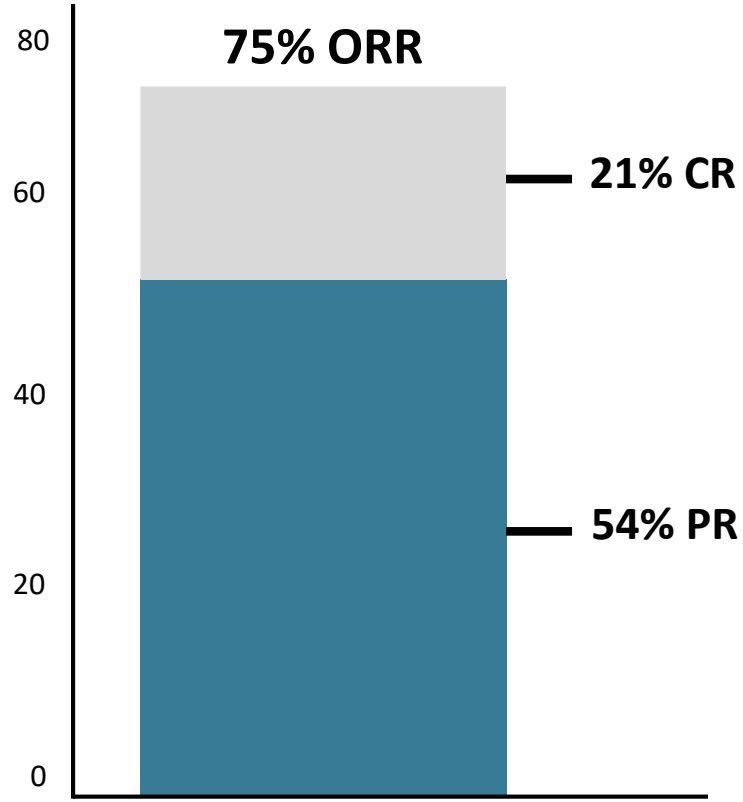
- Phase I multicenter, open-label

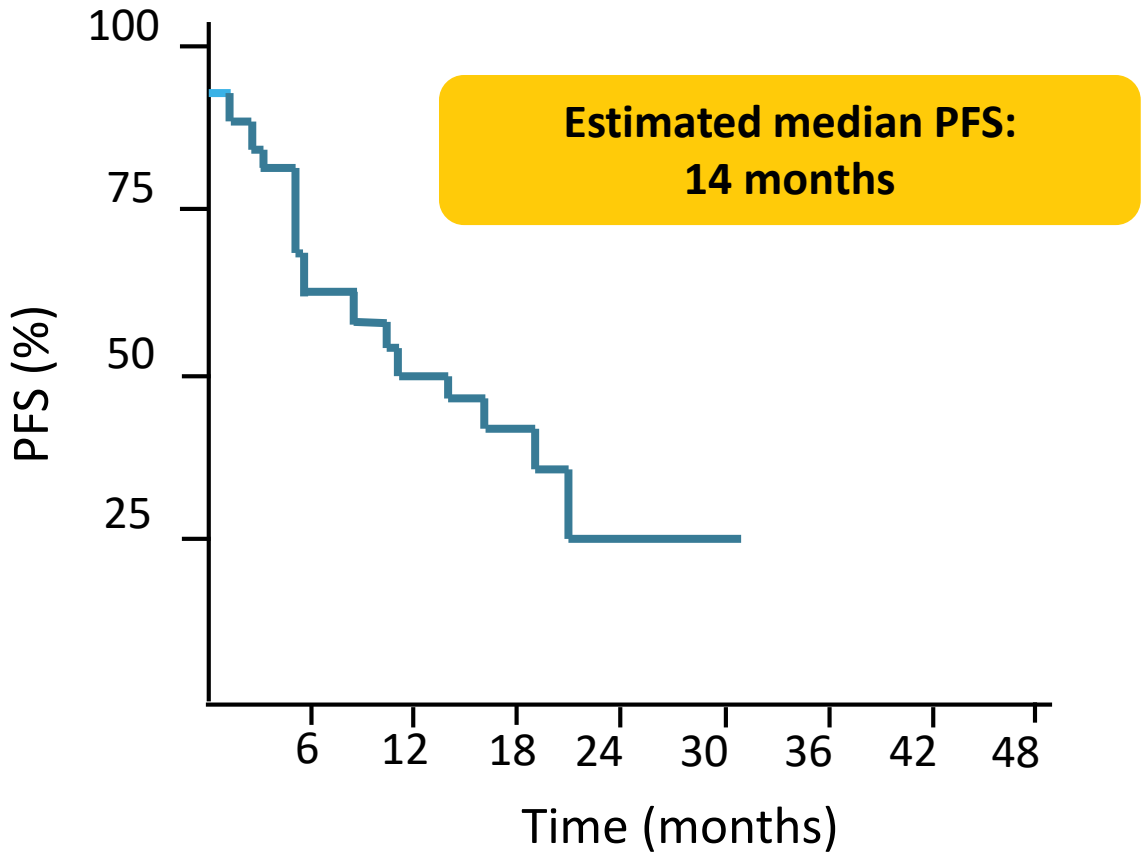
Primary endpoint

- Safety

Davids MS, et al. *J Clin Oncol*. 2017;35(8):826-33.

Venetoclax: R/R MCL





Davids MS, et al. *J Clin Oncol*. 2017;35(8):826-33.

Future Directions: AIM Trial
Ibrutinib + Venetoclax for R/R MCL

Population
- R/R MCL or treatment-naïve not candidate for chemoimmunotherapy
- No notable CVD*
- No prior BTK inhibitors

n = 24

Ibrutinib
560 mg PO daily for 4 weeks

Ibrutinib
560 mg PO daily

Venetoclax
400-800 mg PO daily

50 mg → 100 mg → 200 mg → 400 mg → 800 mg

Dose increased weekly to 400 mg; increased to 800 mg if no CR by week 16.

Until progression or unacceptable toxicity

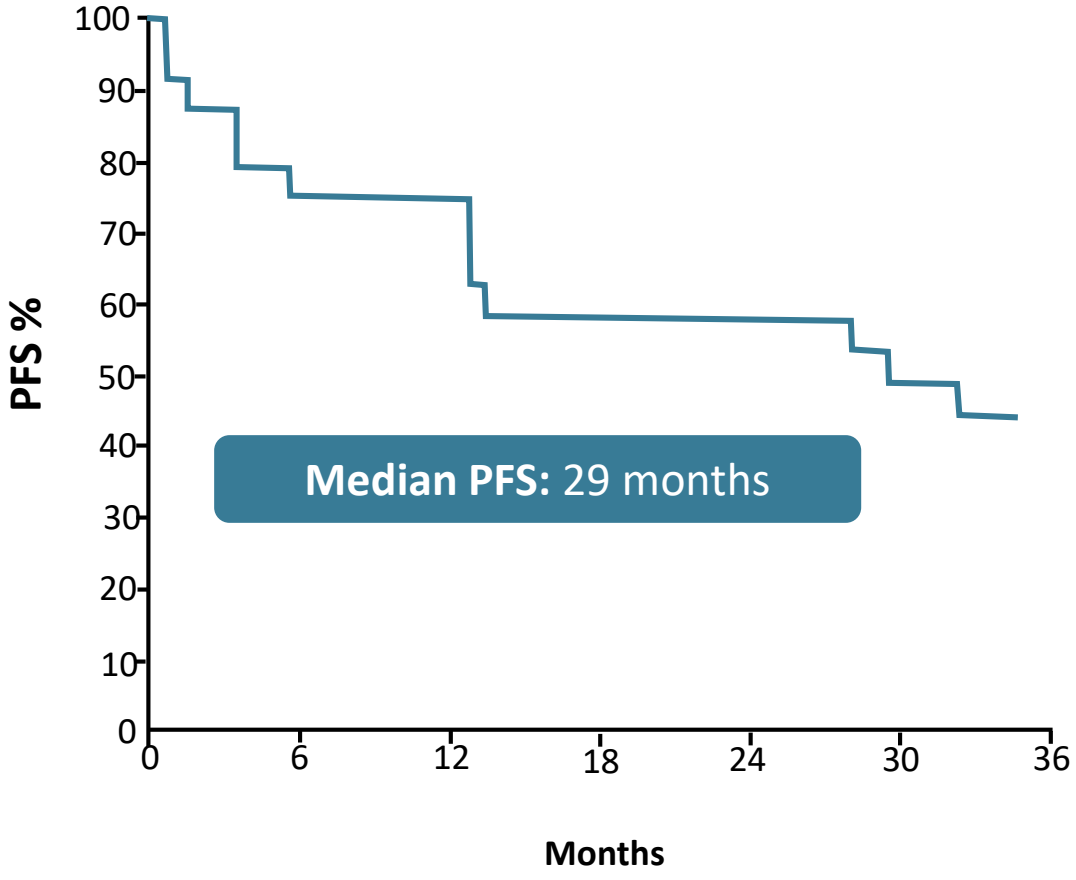
*Uncontrolled or symptomatic arrhythmias, CHF, or MI within 6 months of screening, or any class 3/4 cardiac disease per NYHA Functional Classification.

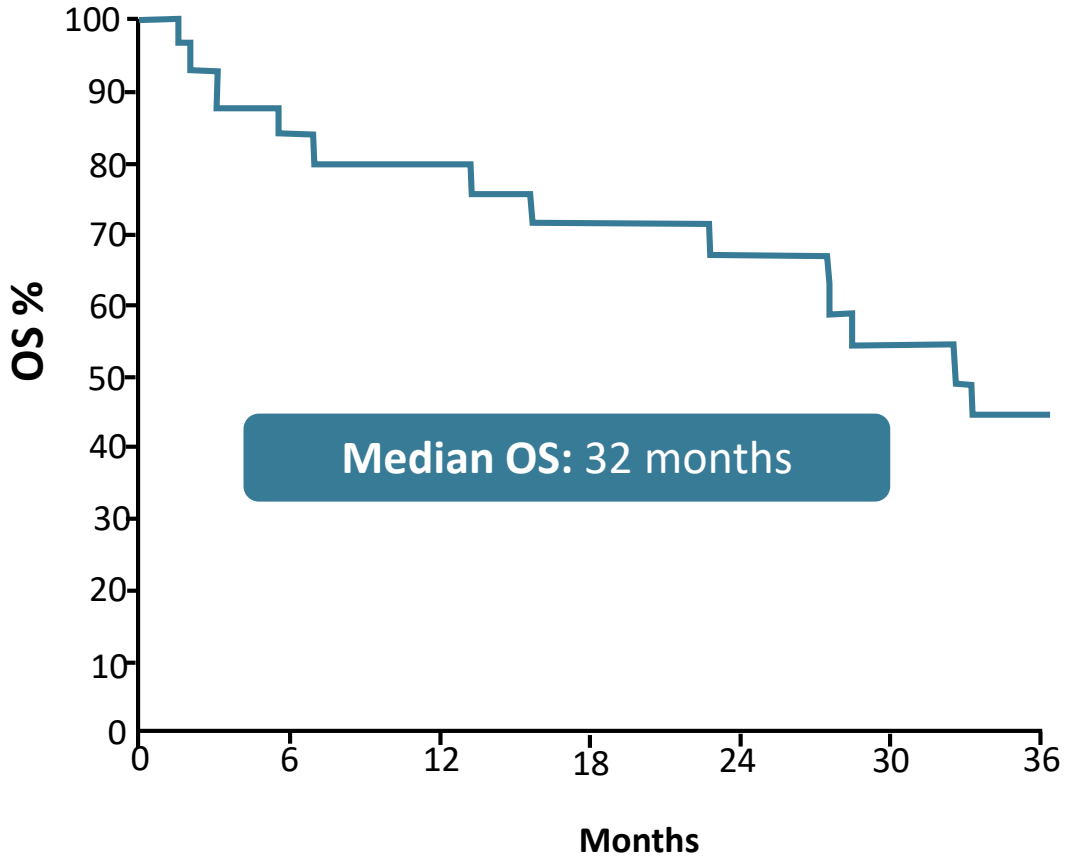
Study design
- Phase 2, multicenter, open-label

Primary endpoint
- CR at week 16

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

AIM Trial:
Ibrutinib + Venetoclax for R/R MCL Results





Handunnetti SM, et al. *Blood*. 2019;134(suppl 1):756.; Tam CS, et al. *N Engl J Med*. 2018;378(13):1211-23.

Waldenström Macroglobulinemia (WM)

- **Indolent lymphoma**
- **Incidence:**
  - < 1% of NHL; 100-1500 new cases/year
- **Deaths:**
  - 60% OS at 5 years
- **Median age:** 63 years

- **Hallmark:**
  - $MYD88^{L265P}$ (> 90%), high IgM
- **Prognostic factors:**
  - $MYD88^{WT}$ and CXCR4 mutations
- **Presentation**
  - Hyperviscosity, neuropathy, adenopathy or organomegaly, amyloidosis, cryoglobulinemia, cold agglutin disease, and cytopenias

American Cancer Society. cancer.org/cancer/waldenstrom-macroglobulinemia/about/key-statistics.html. Published July 19, 2018. Accessed June 2, 2020.; Castillo JJ, Treon SP. *Leukemia*. 2019;33(11):2555-62.; National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology: Waldenström Macroglobulinemia/Lymphoplasmacytic Lymphoma v1.2020.

WM Treatment 2020

First line:
Significantly symptomatic

- Bulky disease
- Profound cytopenias
- Constitutional symptoms
- Hyperviscosity symptoms

Hyperviscosity symptoms

Yes → Plasmapheresis

No

BR
Ibrutinib ± ritixumab*
DRC (if no need for fast response)
BDR (no baseline neuropathy)

Relapsed/refractory
> 3 years from previous therapy

Yes → Repeat original therapy

No

BTK inhibitor*^
- **Ibrutinib**
- **Acalabrutinib**

BDR if baseline PN < grade 2*
BR*
DRC*

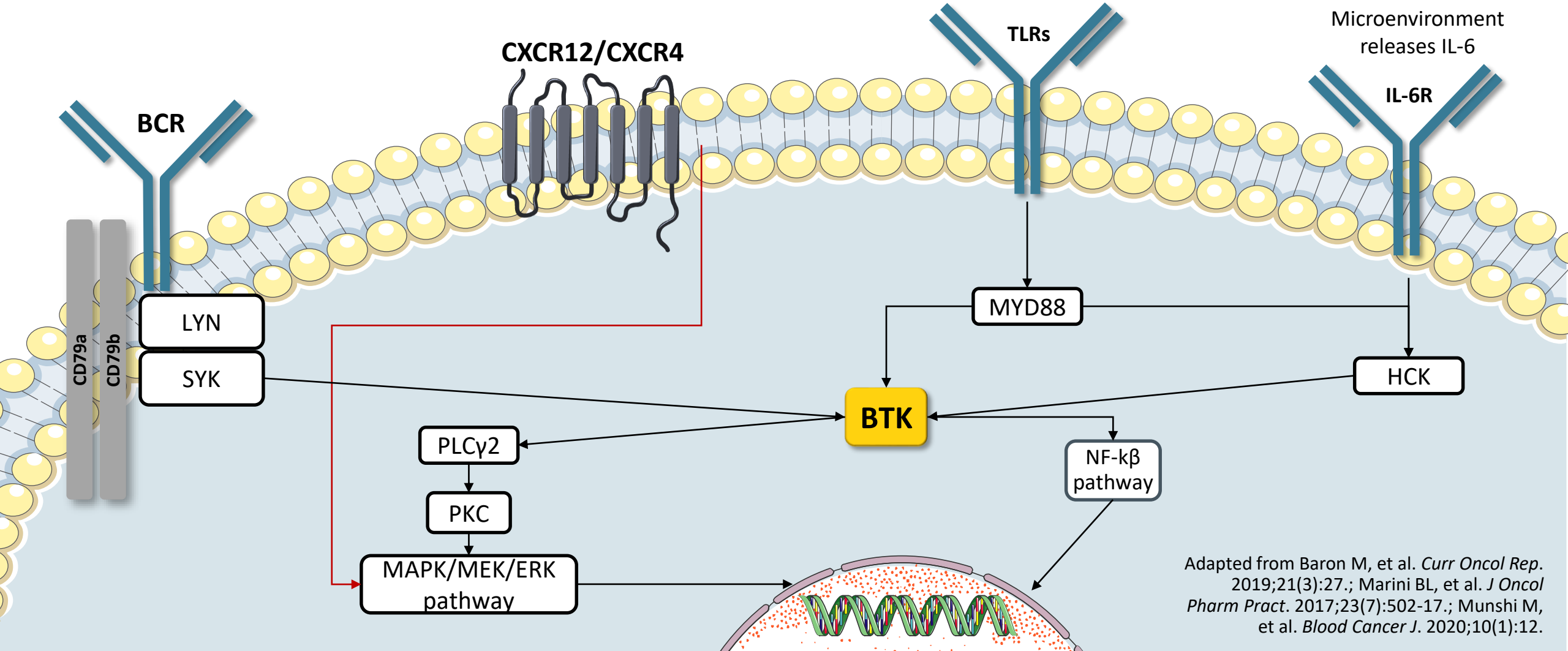
*If not previously received

^Patients with MYD88^{WT} and/or CXCR4 mutations have lower and slower responses.

PN, peripheral neuropathy.

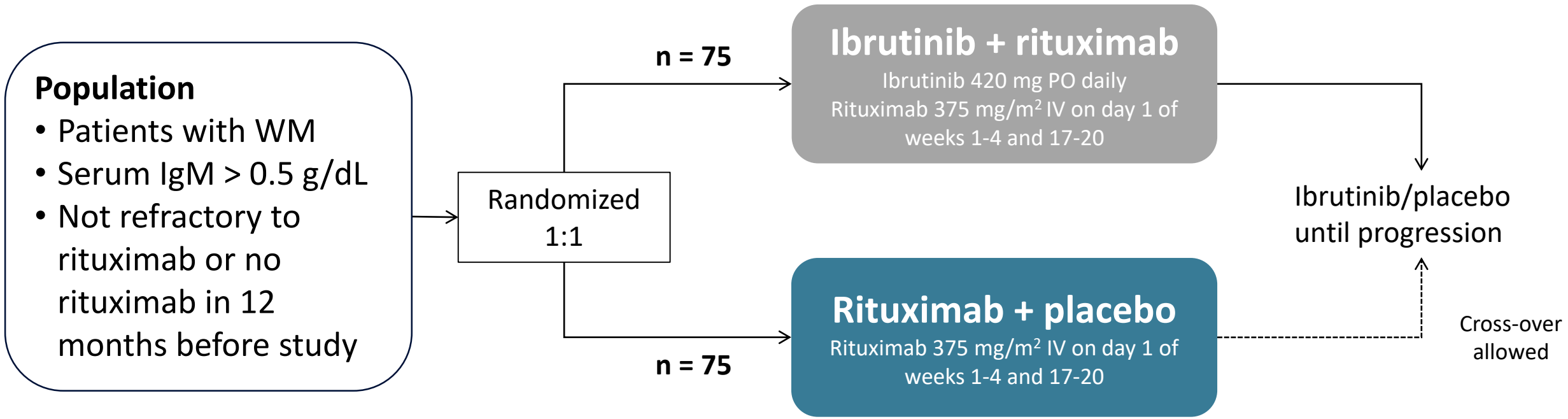
National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology: Waldenström Macroglobulinemia/Lymphoplasmacytic Lymphoma v1.2020.; Vaxman I, Gertz M. *Leuk Lymphoma*. 2020;1-13.

Revisited: Pathophysiology and Mechanism of Action in WM



Adapted from Baron M, et al. *Curr Oncol Rep*. 2019;21(3):27.; Marini BL, et al. *J Oncol Pharm Pract*. 2017;23(7):502-17.; Munshi M, et al. *Blood Cancer J*. 2020;10(1):12.

iNNOVATE Trial: Study Schema



Study design

- Phase III, multicenter, placebo-controlled, RCT

Primary outcome

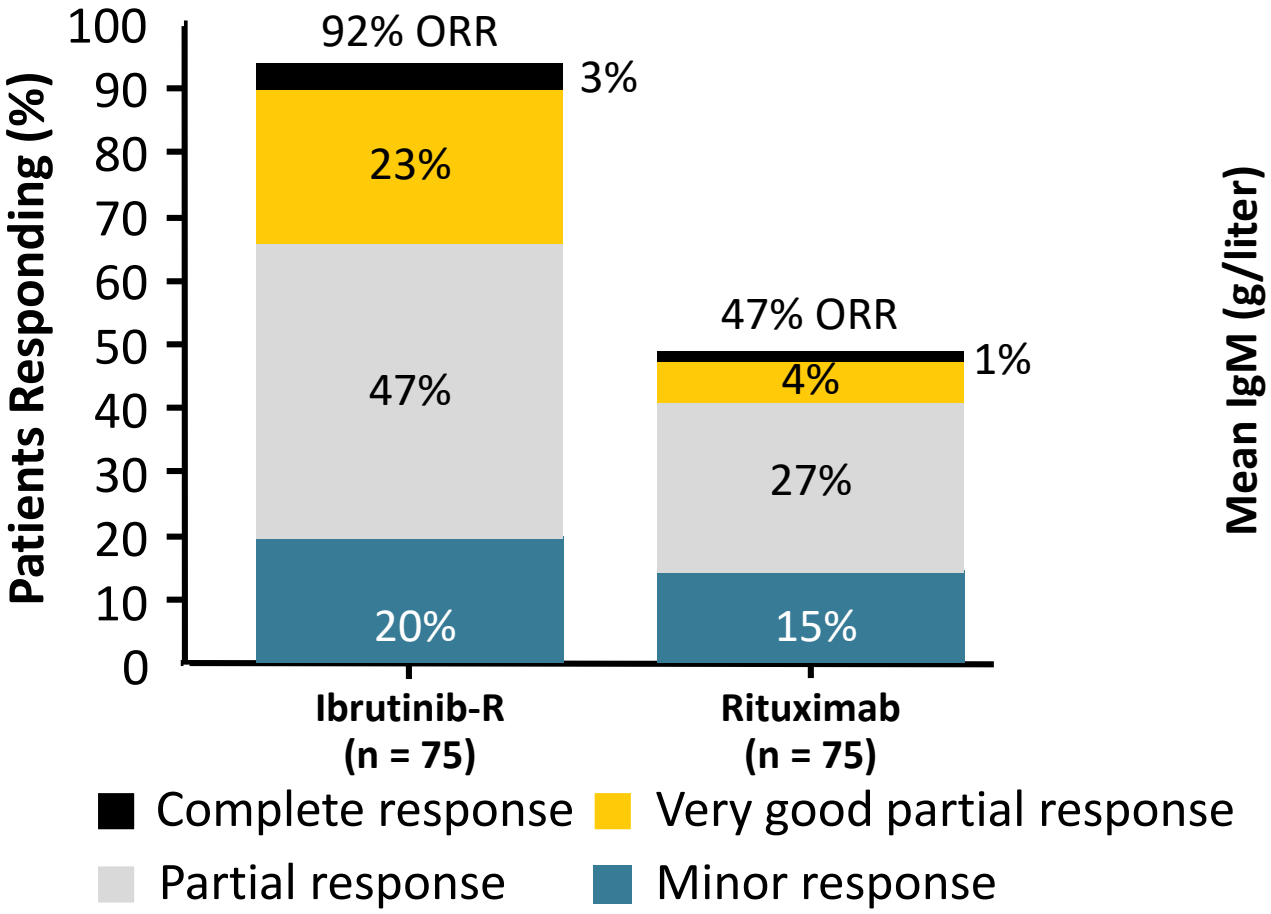
- PFS

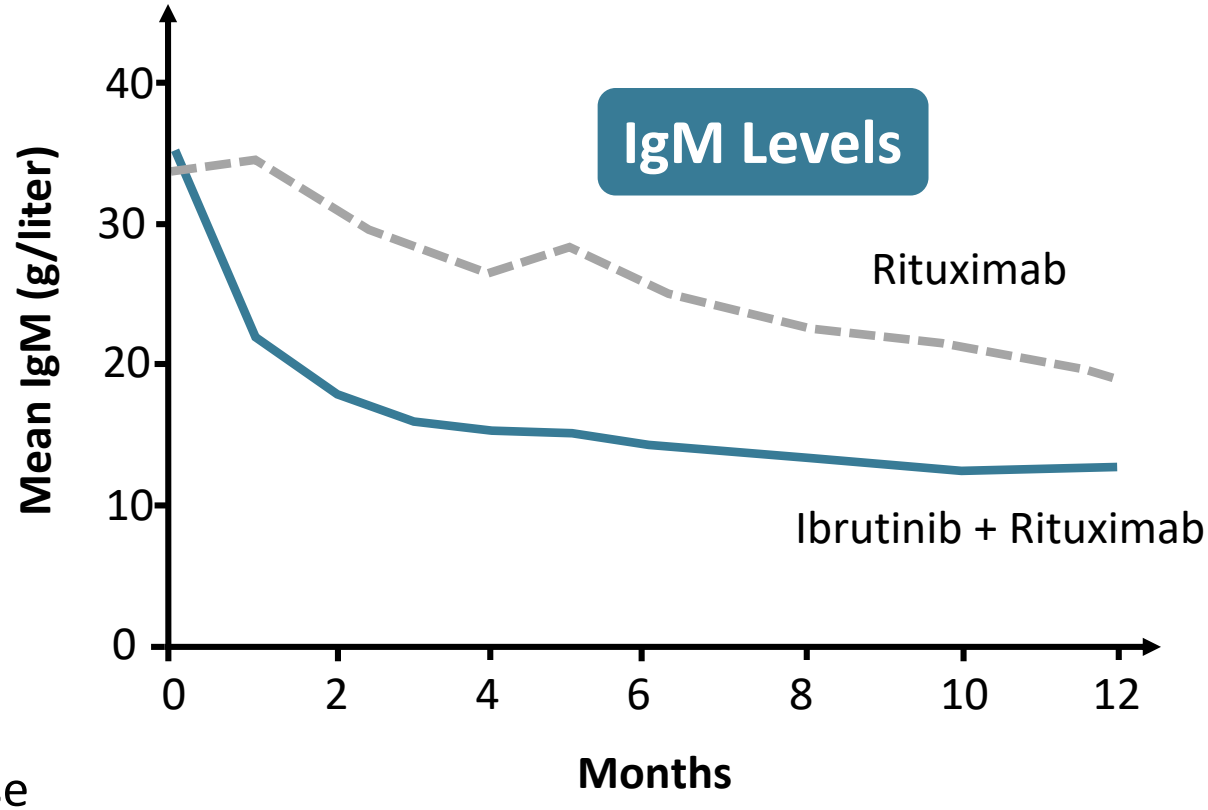
Dimopoulos MA, et al. *N Engl J Med*. 2018;378(25):2399-410.

IgM, immunoglobulin M.

iNNOVATE Trial: Results

Ibrutinib + Rituximab vs. Rituximab for First-Line WM

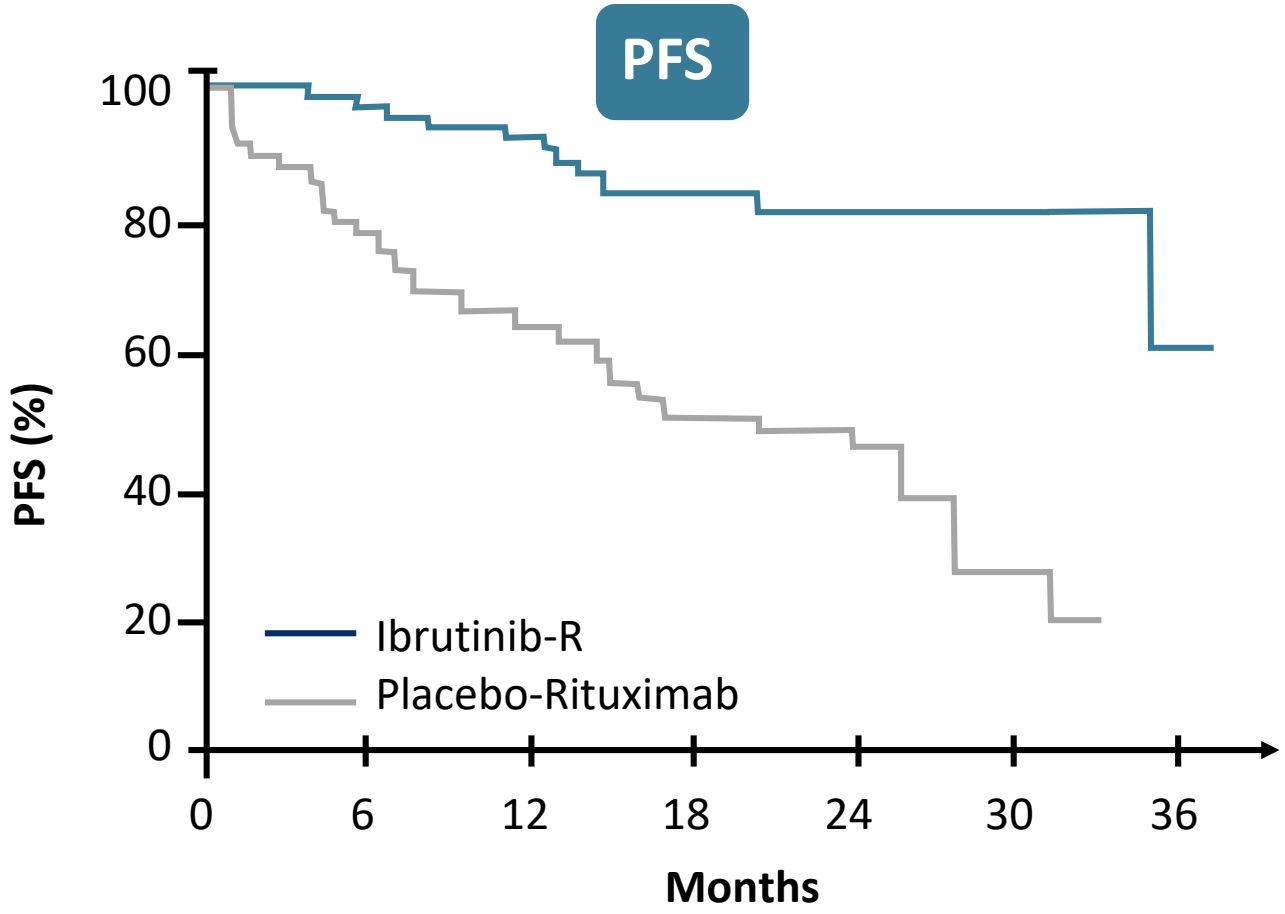




Dimopoulos MA, et al. *N Engl J Med*. 2018;378(25):2399-410.

iNNOVATE Trial: Results

Ibrutinib + Rituximab vs. Rituximab for First-Line WM



Led to FDA approval in WM

Conclusions

Ibrutinib + rituximab improves PFS over rituximab alone

- Median PFS: NR vs. 20.3 months; HR 0.2 (95% CI, 0.11-0.38); $p < 0.001$

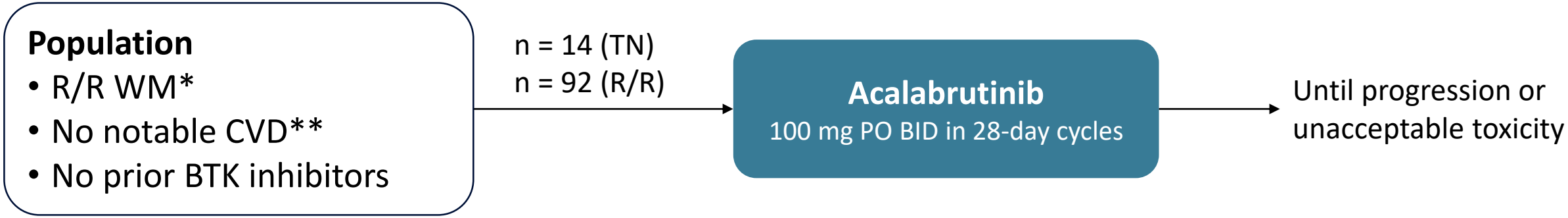
- 30-month PFS: 82% vs. 28%
- 30-month OS: 94% vs. 92%

Patients with mutations in CXCR4 or $MYD88^{WT}$ have lower and slower responses

HR, hazard ratio; NR, not reached.

Dimopoulos MA, et al. *N Engl J Med*. 2018;378(25):2399-410.

ACE-WM-001 Trial: Study Schema



*Or treatment-naïve patients who declined or had comorbidities that would preclude treatment with chemoimmunotherapy, such as symptomatic hyperviscosity with ≥ IgM 5000 mg/dL, or disease-related neuropathy

**Uncontrolled or symptomatic arrhythmias, CHF, or MI within 6 months of screening; any class 3 or 4 cardiac disease as defined by the NYHA Functional Classification; or QTc > 480 ms; patients with previous or concurrent atrial fibrillation could participate.

Study design

- Phase II, multicenter, open-label

Primary endpoint

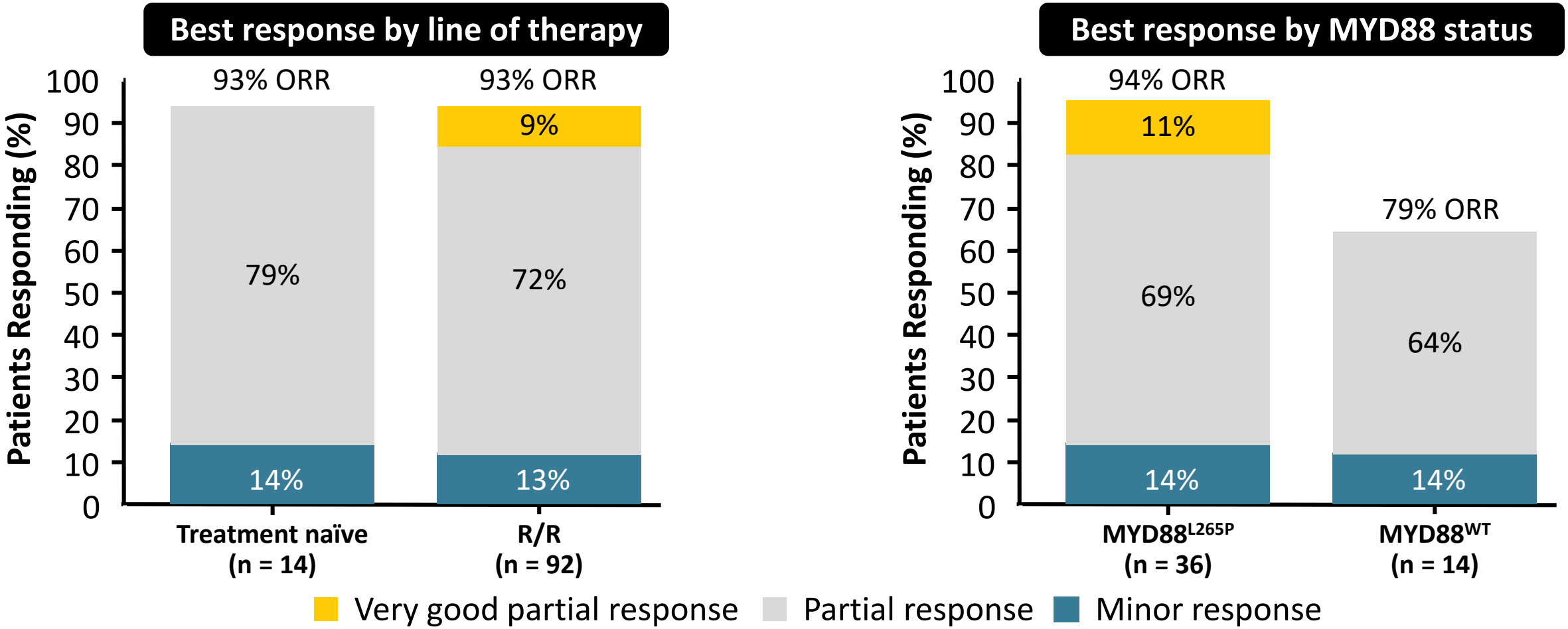
- ORR

Owen RG, et al. *Lancet Haematol*. 2020;7(2):e112-21.

TN=Treat Naive

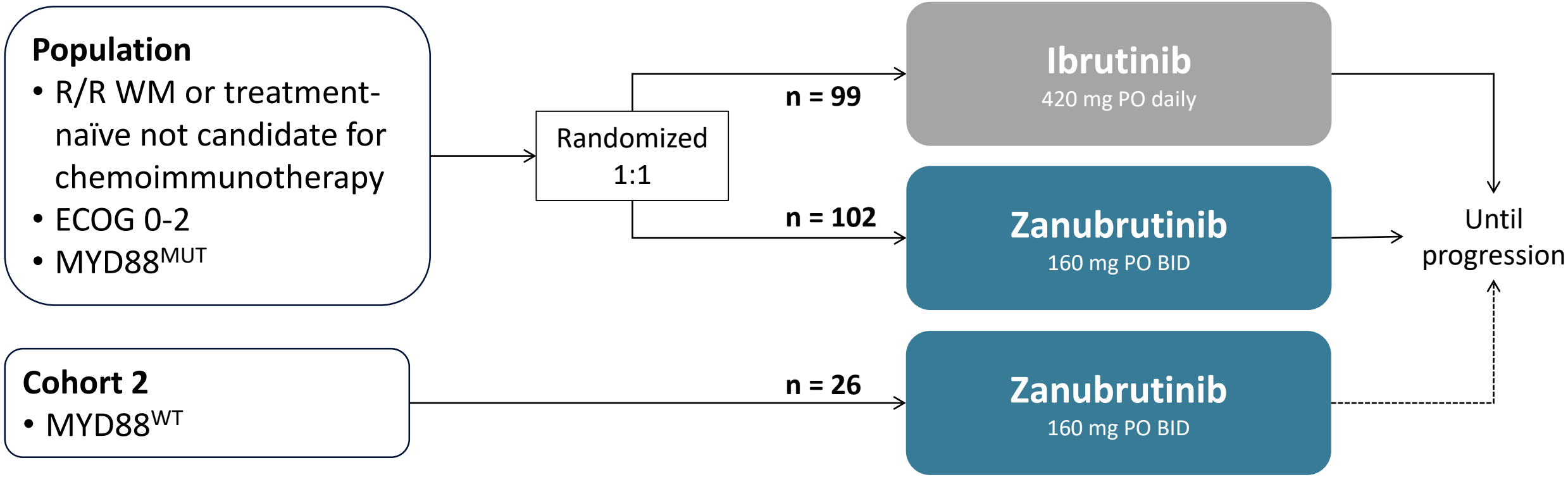
ACE-WM-001 Trial: Results

Acalabrutinib for WM



Owen RG, et al. *Lancet Haematol*. 2020;7(2):e112-21.

ASPEN Trial: Study Schema



Study design

- Phase III, multicenter, open-label, RCT

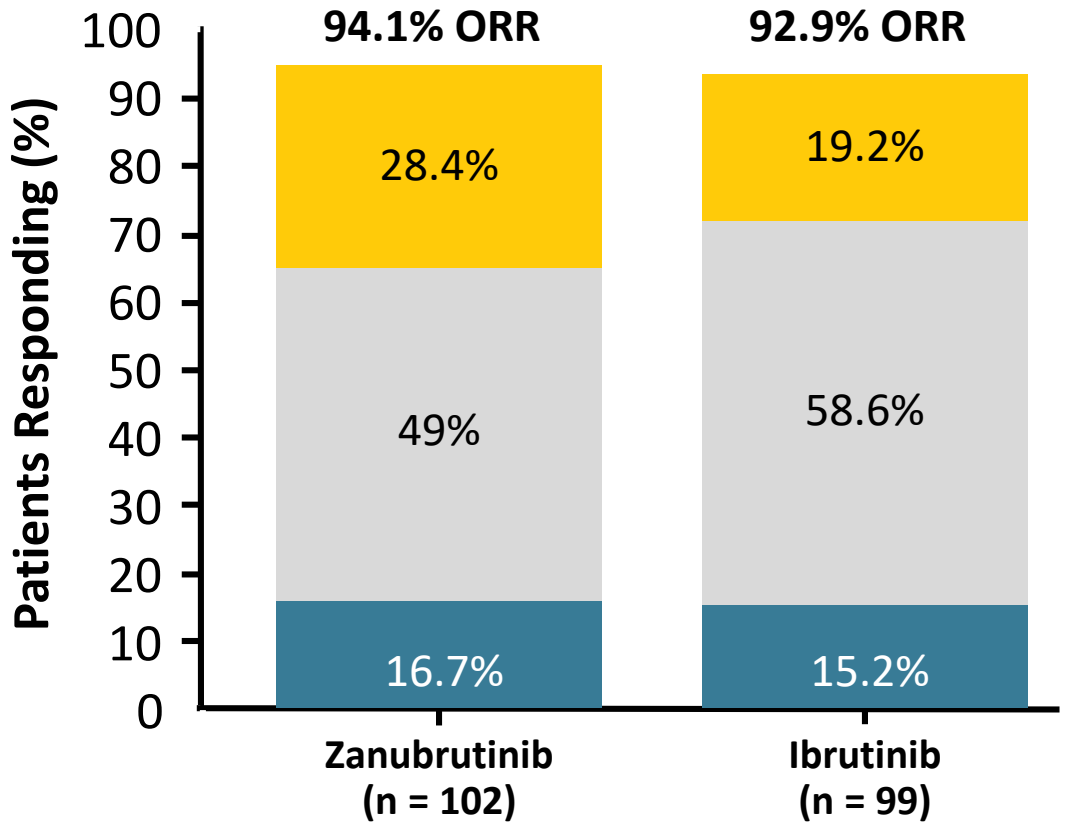
Primary outcome

- Complete response or very good partial response (superiority)

Tam C, et al. *J Clin Oncol.* 2020;(38 suppl):abstr 8007.

Future Directions: ASPEN Trial

Zanubrutinib vs. Ibrutinib for WM



Look for Future FDA Guidance

Conclusions

First randomized trial comparing 2 BTK inhibitors

Improved toxicity profile with zanubrutinib (not shown)

No significant differences in ORR, PFS, or OS

Tam C, et al. *J Clin Oncol.* 2020;(38 suppl):abstr 8007.

Follicular Lymphoma (FL)

- **Indolent lymphoma**
- **Incidence:**
  - 22% of NHL
- **Deaths:**
  - 60% OS at 10 years
- **Median age:** 60 years

- **Hallmark:**
  - BCL2 translocation; t(14;18)
- **Prognostic factors:**
  - FLIPI Score, Grade 3 histology
- **Presentation**
  - Heterogenous (can be asymptomatic)
  - B-symptoms, diffuse lymphadenopathy, bone marrow involvement, splenomegaly, other extra nodal sites

Al-Hamadani M, et al. *Am J Hematol.* 2015;90(9):790-5.; Federico M, et al. *.J Clin Oncol.* 2009;27(27):4555-62.; Junlen HR, et al. *Leukemia*. 2015;29(3):668-76.; National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology: B-cell Lymphomas v1.2020.; Solal-Celigny P, et al. *Blood*. 2004;104:1258-65.; Swerdlow SH, et al. World Health Organization Classification of Tumours of Haematopoietic and Lymphoid Tissues. 2008. IARC Press.

Current Treatment Landscape in FL

Diagnosis

Asymptomatic / No indication

"Watch and wait"
Anti-CD20 mAb
ISRT

Factors to consider: patient preference and tumor burden

Mild symptoms Low tumor burden

Anti-CD20 mAb
ISRT

Factors to consider: patient age and comorbidities

High tumor burden

Anti-CD20 mAb +
- Bendamustine
- CHOP
- CVP
- Lenalidomide

+/- anti-CD20 mAb maintenance
Radioimmunotherapy

Factors to consider: patient age and comorbidities

Relapsed/Refractory

*Rule out histologic transformation to DLBCL

Anti-CD20 mAb +
- Bendamustine
- CHOP
- CVP

Radioimmunotherapy
Lenalidomide +/- anti-CD20 mAb
PI3K inhibitors (2 or more prior therapies)
- **Idelalisib, copanlisib, duvelisib**

+/- anti-CD20 mAb maintenance

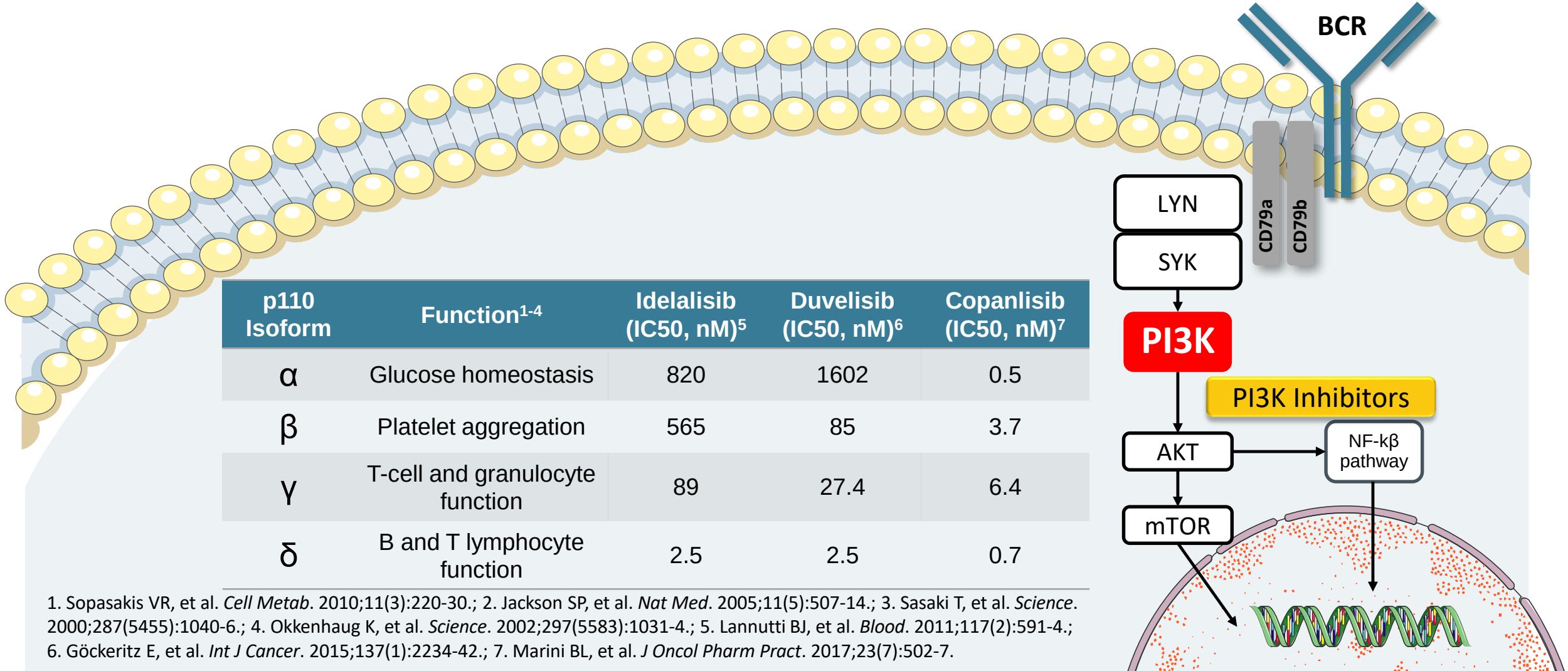
Factors to consider: response and duration of response to previous therapy, patient age, and comorbidities

National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology. B-cell Lymphomas v1.2020.

ISRT, involved-site radiation therapy.

PI3K Inhibitor Mechanism of Action

p110 Isoform	Function[1-4]	Idelalisib (IC50, nM)[5]	Duvelisib (IC50, nM)[6]	Copanlisib (IC50, nM)[7]
α	Glucose homeostasis	820	1602	0.5
β	Platelet aggregation	565	85	3.7
γ	T-cell and granulocyte function	89	27.4	6.4
δ	B and T lymphocyte function	2.5	2.5	0.7



1. Sopasakis VR, et al. *Cell Metab*. 2010;11(3):220-30.; 2. Jackson SP, et al. *Nat Med*. 2005;11(5):507-14.; 3. Sasaki T, et al. *Science*. 2000;287(5455):1040-6.; 4. Okkenhaug K, et al. *Science*. 2002;297(5583):1031-4.; 5. Lannutti BJ, et al. *Blood*. 2011;117(2):591-4.; 6. Göckeritz E, et al. *Int J Cancer*. 2015;137(1):2234-42.; 7. Marini BL, et al. *J Oncol Pharm Pract*. 2017;23(7):502-7.

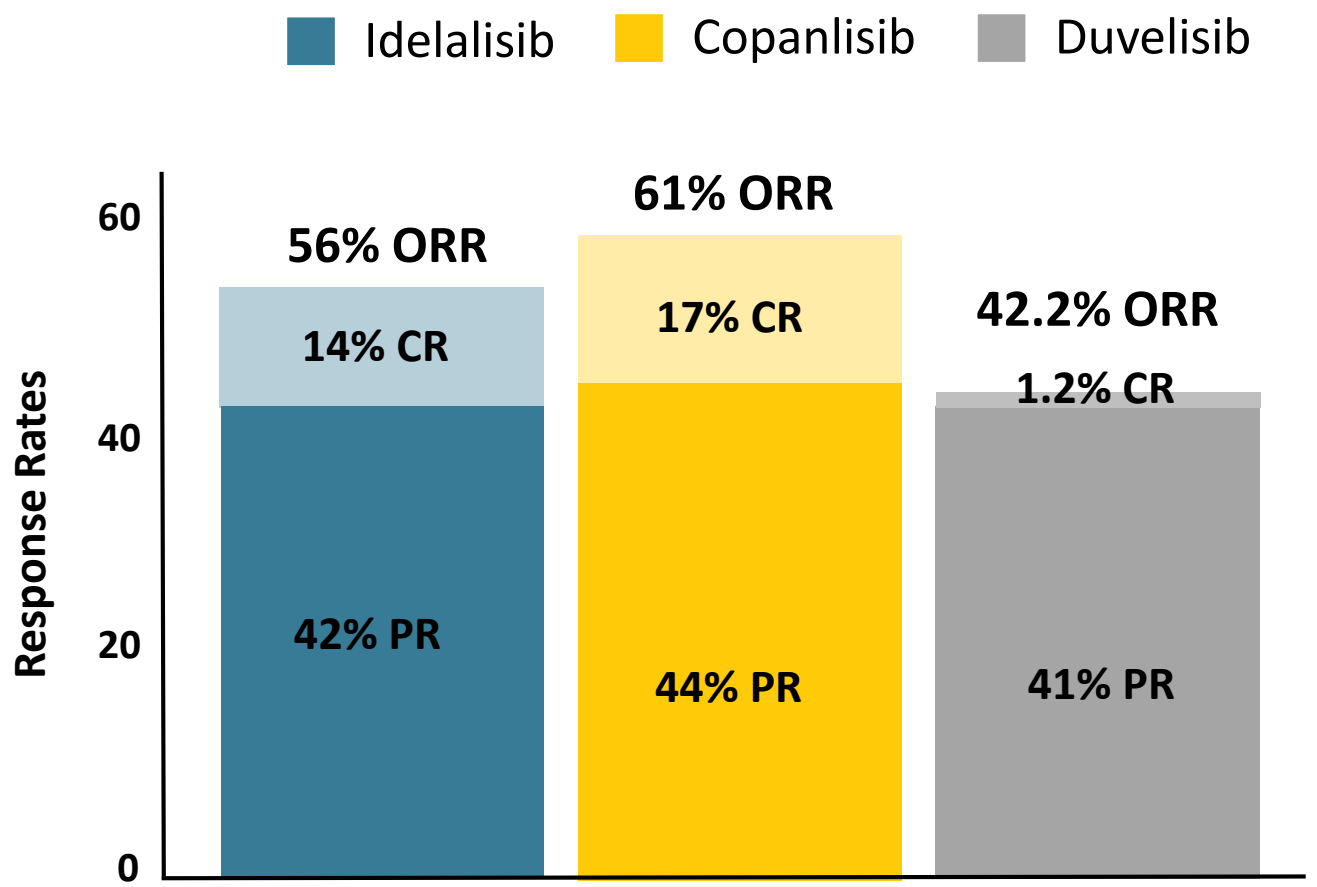
PI3K Inhibitor Pivotal Trial Design

Double refractory NHL (failed to respond or relapsed within 6 months following rituximab and an alkylator)	Single-arm, open-label, phase 2 study **Idelalisib** 150 mg PO BID (N = 72 FL)	Primary endpoint: ORR
Relapsed or refractory after 2 or more lines of therapy	Single-arm, open-label, phase 2 study **Copanlisib** 60 mg IV over 60 minutes on days 1, 8, and 15 of 28-day cycle (N = 104 FL)	Primary endpoint: ORR
▪ Refractory to both rituximab and chemotherapy or RIT ▪ Previously received an alkylating agent or purine analogue	Single-arm, open-label, phase 2 study **Duvelisib** 25 mg PO BID (N = 83 FL)	Primary endpoint: ORR

Continuous until disease progression or unacceptable toxicity

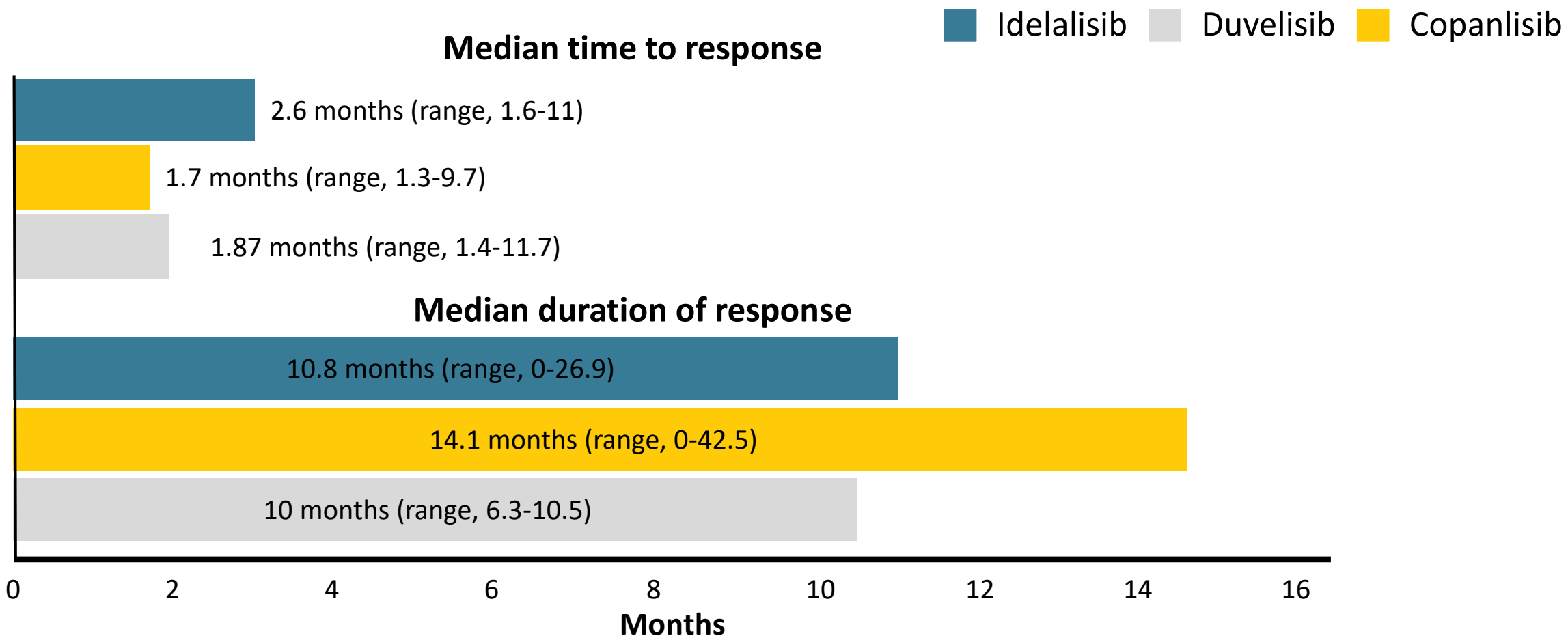
Dreyling M, et al. *J Clin Oncol.* 2017;35(35):3898-905.; Dreyling M, et al. *Am J Hematol*. 2020;1-10.; Flinn IW, et al. *J Clin Oncol.* 2019;37(11):912-22.; Gopal AK, et al. *N Engl J Med.* 2014;370(11):1008-18.; Salles G, et al. *Haematologica.* 2017;102(4):e156-9.

Efficacy Outcomes:
PI3K Inhibitors R/R FL

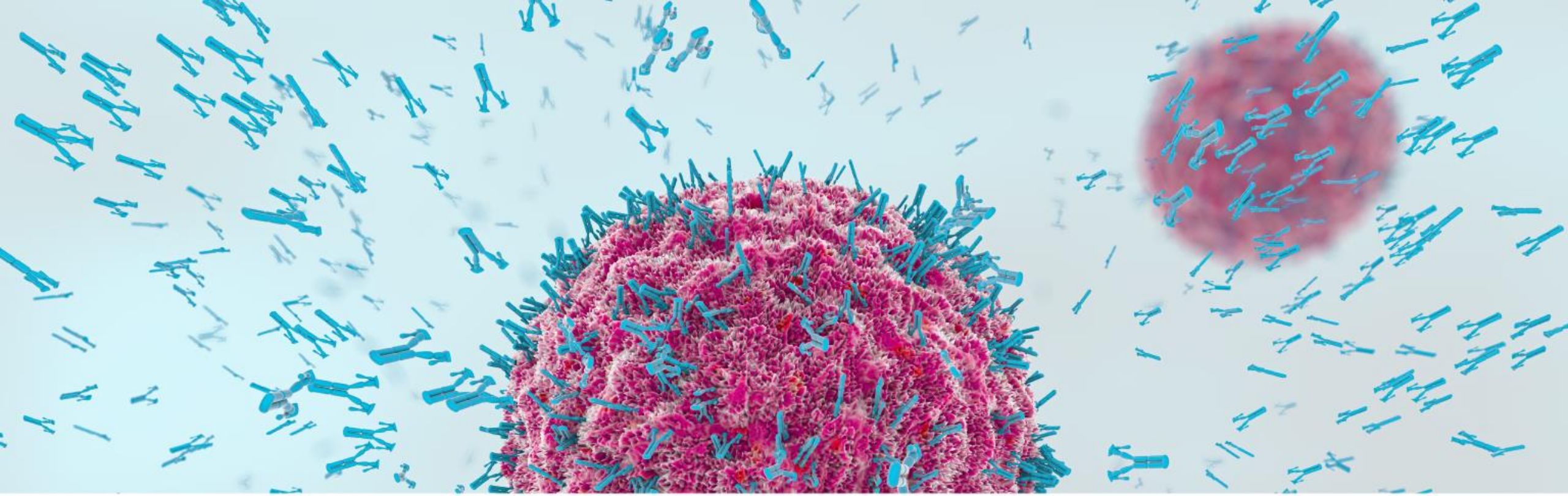


Dreyling M, et al. *J Clin Oncol.* 2017;35(35):3898-905.; Dreyling M, et al. *Am J Hematol*. 2020;1-10.; Flinn IW, et al. *J Clin Oncol.* 2019;37(11):912-22.; Gopal AK, et al. *N Engl J Med.* 2014;370(11):1008-18.; Salles G, et al. *Haematologica.* 2017;102(4):e156-9.

Efficacy Outcomes:
PI3K Inhibitors R/R FL

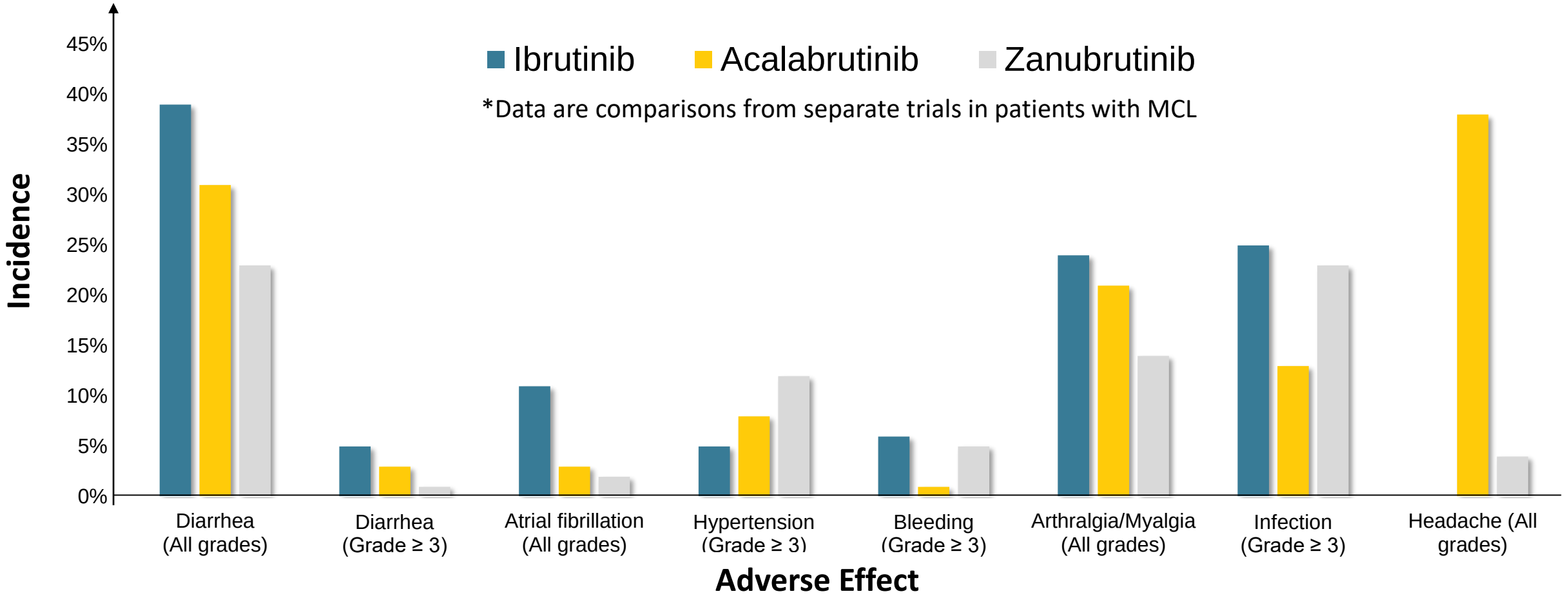


Dreyling M, et al. *J Clin Oncol.* 2017;35(35):3898-905.; Dreyling M, et al. *Am J Hematol*. 2020;1-10.; Flinn IW, et al. *J Clin Oncol.* 2019;37(11):912-22.; Gopal AK, et al. *N Engl J Med.* 2014;370(11):1008-18.; Salles G, et al. *Haematologica.* 2017;102(4):e156-9.



Adverse Effect Management and Patient Monitoring Plans

BTK Inhibitors: Select Adverse Events (AEs) Across Pivotal Trials*



Brukinsa (zanubrutinib) [prescribing information]. 2019.; Calquence (acalabrutinib) [prescribing information]. 2019.; Imbruvica (ibrutinib) [prescribing information]. 2020.; Rule S, et al. *Haematologica*. 2019;104(5):e211-e4.; Tam CS, et al. *Hematol Oncol*; 2019;37:245-7.; Wang M, et al. *Lancet*. 2018;391(10121):659-67.

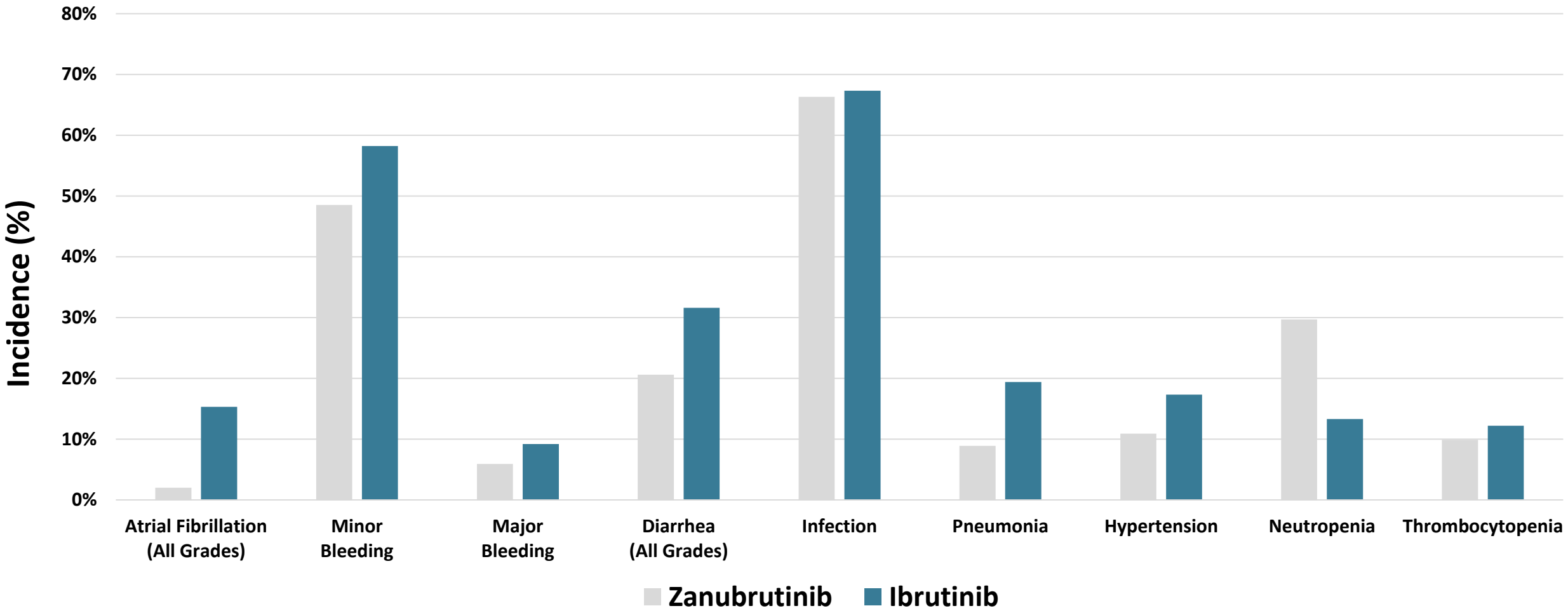
Off-Target Effects

TEC	Platelet effects, T-cell priming
EGFR	Rash, cardiac toxicity, diarrhea
SRC	Platelet effects
BMX	Cardiac toxicity
ITK	Antibody-dependent cellular cytotoxicity, migration of PMN
JAK3	Immune effects
ERBB4	Cardiac toxicity

Berglöf A, et al. *Scand J Immunol*. 2015;82(3):208.; Bose P, et al. *Expert Opin Drug Metab Toxicol*. 2016;12(11):1381-92.; Bye AP, et al. *Blood Adv.* 2017;1(26):2610-23.; Ghez D, et al. *Blood*. 2018;131(17):1955-9.; Rogers K. *Blood*. 2018;131(17):1882-4.; Rogers KA, et al. *Leukemia*. 2019;33(10):2527-30.; Ruchlemer R, et al. *Mycoses*. 2019;62(12):1140-7.; Shatzel JJ, et al. *J Thromb Haemost*. 2017;15(5):835-47.; Woyach JA. *Blood*. 2018;132(18):1869-70.

PMN, polymorphonuclear leukocyte.

ASPEN Trial: Adverse Effects
Only Randomized Trial Comparing BTK inhibitors



Tam C, et al. *J Clin Oncol.* 2020;38(suppl):abstr 8007.

BTK Inhibitors: Hypertension and Atrial Fibrillation

Hypertension

- Risks include cardiac risk factors, prior history of hypertension
- Monitor blood pressure throughout treatment
- Hypertension is not an absolute indication to discontinue BTK inhibitors
- Adequate management of hypertension from BTK inhibitors mitigates cardiovascular events
- If hypertension is persistent or life threatening, consider risks and benefits of treatment and dose modification

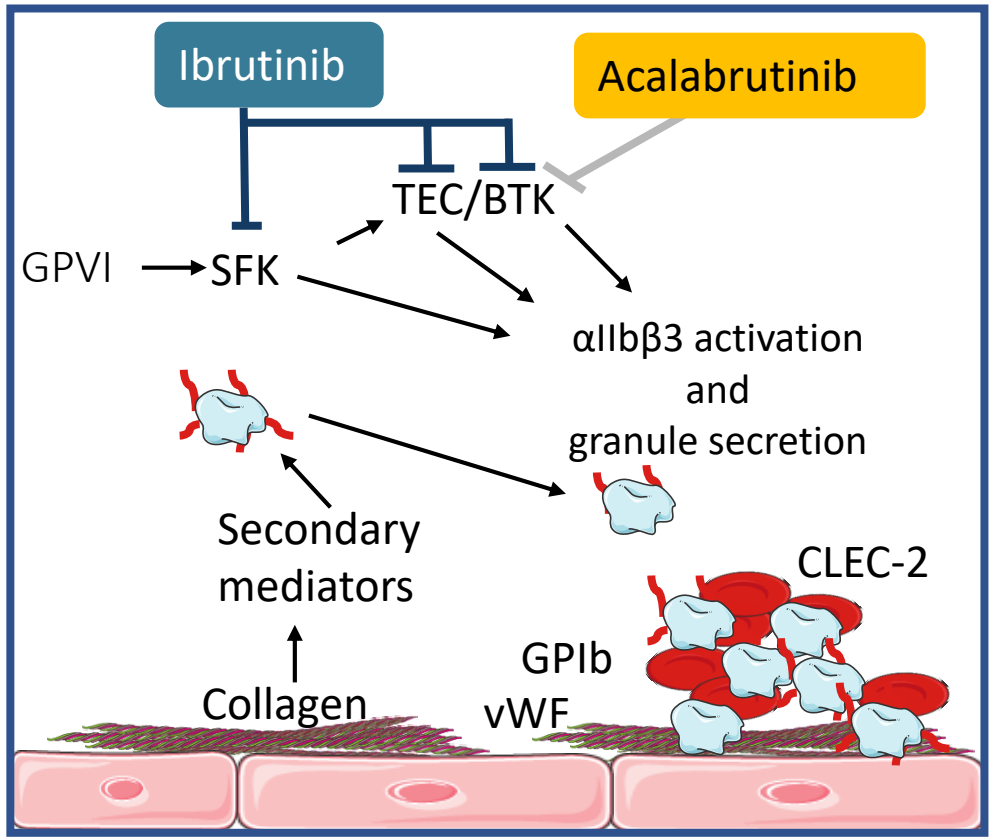
Atrial fibrillation (AF)

- Risks include cardiac risk factors, acute infections, prior history of AF
- Educate patient on risk for AF and what to do in the event of abnormal heart rhythm
- AF is not an absolute contraindication to continuing BTK inhibitors
- Be cautious of drug interactions when managing AF (i.e., diltiazem and CYP3A4)
- Anticoagulation can be used but should be used with caution
  - Avoid vitamin K antagonists
- If AF persists, consider the risks and benefits of treatment and dose modification

Brukinsa (zanubrutinib) [prescribing information]. 2019.; Calquence (acalabrutinib) [prescribing information]. 2019.; Dickerson T, et al. *Blood*. 2019;134 (22):1919-28.; Imbruvica (ibrutinib) [prescribing information]. 2020.

CYP, cytochrome P450.

BTK Inhibitors: Mechanism of Bleeding



Aggregation, adhesion, and stable thrombus formation

- BTK, SFK (src family kinases), and TEC are involved in several platelet activation and adhesion functions:
  - GPVI, CLEC-2, GPIb, integrin αIIbβ3

- TEC compensates when BTK is inhibited/dysfunctional
  - BTK inhibition alone leads to mildly diminished platelet activation
  - Blocking both BTK and TEC leads to significant platelet inhibition, platelet aggregation, and thrombus stability

Bye AP, et al. *Blood Adv*. 2017;1(26):2610-23.

BTK Inhibitors: Bleeding and Bruising Management

Clinical Pearls and Management

- Reversible impact on platelet aggregation within 1 week of discontinuation
- Dose reduction may mitigate platelet aggregation and improve bruising
- Recommend holding BTK inhibitor prior to and after invasive procedures for 3 (minor) to 7 days (major)
- Blood thinner or antiplatelet agents (aspirin, clopidogrel, prasugrel, ticagrelor) increase bleeding risk
- Anticoagulants increase bleeding risk by impacting multiple hemostatic pathways
  - Anticoagulants are not contraindications
  - Avoid concurrent vitamin K antagonists

Real-world risk*

Major bleed (grade ≥ 3)	N=13
Total	18%
Antiplatelet + anticoagulant	54%
Antiplatelet alone	30%
Anticoagulant alone	8%
Interacting medication	8%
None of the above	0%

*Data represented are for ibrutinib.

Imbruvica (ibrutinib) [prescribing information]. 2020.; Kunk PR, et al. *Blood.* 2016;128(22):3229.

BTK Inhibitors: Miscellaneous AE Management

- Muscle cramps
  - Oral magnesium supplements
- Arthralgias/myalgias
  - Acetaminophen, prednisone, tonic water
  - Reduce dose of BTK inhibitor or therapy discontinuation
- Leg lymphedema
  - Therapy discontinuation
- Fatigue
  - Reduce dose of BTK inhibitor or therapy discontinuation
- Headaches
  - Acetaminophen, caffeine, hydration
- Rash
  - Topical emollients or corticosteroids can alleviate symptoms
- Diarrhea
  - If no evidence of infection, antidiarrheals as needed
- Infection
  - Monitor and treat as needed

For all grade 3/4 non-hematologic AEs: hold BTK inhibitor until resolution to baseline or grade 1

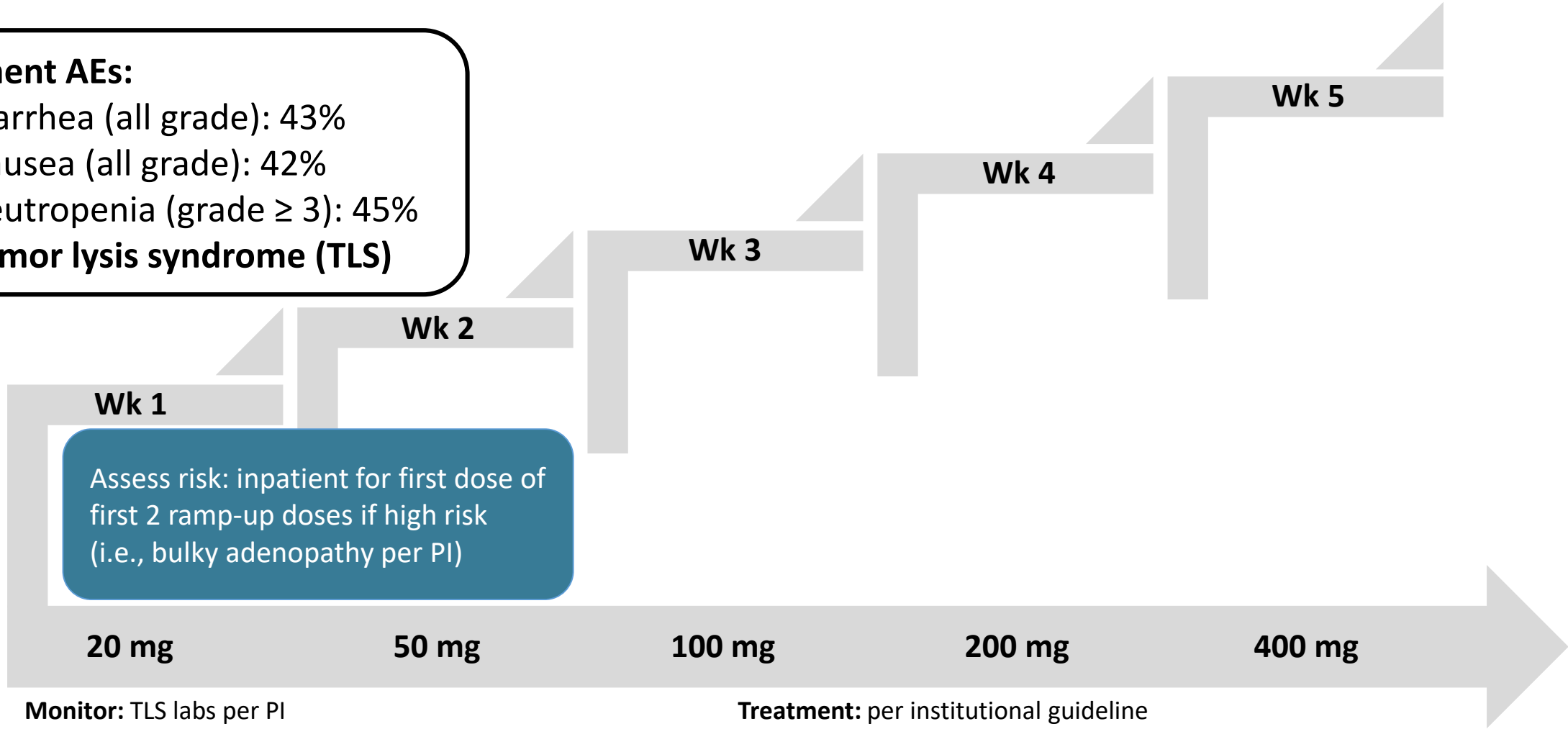
Resume at original dose for first recurrence, refer to package insert for specific dose reductions for second recurrence

Brukinsa (zanubrutinib) [prescribing information]. 2019.; Calquence (acalabrutinib) [prescribing information]. 2019.; Imbruvica (ibrutinib) [prescribing information]. 2019.; Rule S, et al. *Haematologica.* 2019;104:e211-4.; Tam CS, et al. *Hematolog Oncol.* 2019:37:245-7.; Wang M, et al. *Lancet*. 2018;391:659-67.

Venetoclax: AEs and Management

Pertinent AEs:

- Diarrhea (all grade): 43%
- Nausea (all grade): 42%
- Neutropenia (grade ≥ 3): 45%
- **Tumor lysis syndrome (TLS)**



Monitor: TLS labs per PI
Prevention: hydration, antihyperuricemic agents

Treatment: per institutional guideline

PI, prescribing information.
Venclexta (venetoclax) [prescribing information]. 2019.

Venetoclax: TLS Management

1 Assess Risk

TLS risk	Disease characteristics
Low risk	No bulky adenopathy ALC < 25 x 10^9/L
Intermediate risk	Bulky adenopathy: ≥ 5 cm and < 10 cm or ALC: ≥ 25 x 10^9/L
High risk	Bulky adenopathy: ≥ 10 cm or Bulky adenopathy: ≥ 5 cm and ALC ≥ 25 x 10^9/L
Additional factors to consider: baseline uric acid, LDH, potassium, phosphorous, SCr, calcium	

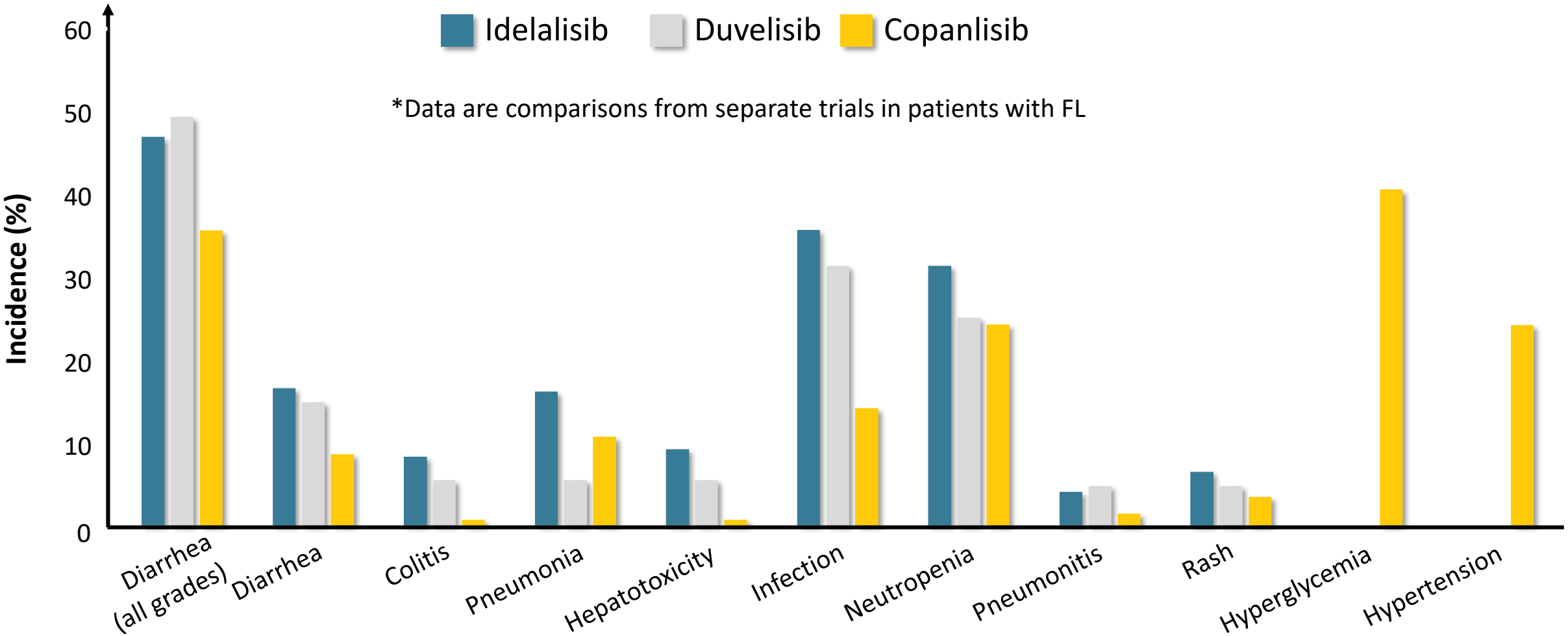
2 Develop a Management Plan

TLS risk	Management plan
Low risk	Outpatient: • Oral hydration (1.5-2 L per day) and allopurinol • Lab monitoring: pre-dose and 6 to 8 hours & 24 hours after first dose of 20 mg and 50 mg and then pre-dose at subsequent ramp-up doses
Intermediate risk	Outpatient: • Oral hydration (1.5-2 L per day), IV (PRN), and allopurinol • Lab monitoring: pre-dose, 6 to 8 hours & 24 hours after first dose of 20 mg and 50 mg and then pre-dose at subsequent ramp-up doses • If creatinine clearance < 80 mL/min, consider inpatient admission for first 2 dose escalations
High risk	Inpatient for first dose of first 2 ramp-up doses: • Oral hydration and IV as tolerated • Allopurinol (consider rasburicase based on baseline uric acid)

ALC, absolute lymphocyte count;
LDH, lactate dehydrogenase;
PRN, as needed; SCr, serum creatinine.

Venclexta (venetoclax) [prescribing information]. 2019.

PI3K Inhibitors: Select Grade ≥ 3 AEs Across Pivotal Trials*



Dreyling M, et al. *J Clin Oncol*. 2017;35(35):3898-905.; Flinn IW, et al. *J Clin Oncol*. 2019;37(11):912-22.; Gopal AK, et al. *New Engl J Med*. 2014;370(11):1008-18.

PI3K Inhibitors: Black Box Warnings

Idelalisib	Duvelisib	Copanlisib
Hepatotoxicity Diarrhea and colitis Intestinal perforation Infection Pneumonitis	Diarrhea and colitis Infection Pneumonitis Cutaneous reactions	None

Immune-related toxicity mechanism: decrease in T-regulatory cells (due to PIK3δ inhibition)

PI3K Inhibitors: Infectious and Respiratory Complications

Idelalisib

- Febrile neutropenia: 3%
- 21% experienced a fatal or serious infection
- *Pneumocystis jirovecii pneumonia* (PJP) or cytomegalovirus (CMV): < 1% of patients
- Pneumonitis: 2%

Duvelisib

- Febrile neutropenia: 9.3%
- 31% experienced a fatal or serious infection
- PJP or CMV: 1% of patients, 1 case of bronchopulmonary aspergillosis
- Pneumonitis: 5%

Copanlisib

- Neutropenia (including febrile neutropenia): 32%
- 19% experienced a fatal or serious infection
- PJP: < 1% of patients, 1 case of bronchopulmonary aspergillosis
- Pneumonitis: 5%

Aliqopa (copanlisib) [prescribing information]. 2019.; Copiktra (duvelisib) [prescribing information]. 2019.; Dreyling M, et al. *J Clin Oncol*. 2017;35(35):3898-905.; Flinn IW, et al. *J Clin Oncol*. 2019;37(11):912-22.; Gopal AK, et al. *New Engl J Med*. 2014;370(11):1008-18.; Zydelig (idelalisib) [prescribing information]. 2018.

PI3K Inhibitors: Infectious and Respiratory Complications

Management

Infection

- Provide PJP prophylaxis during treatment
- Clinical and laboratory monitoring for CMV infection is recommended in patients with history of CMV infection or positive CMV serology at the start of treatment
- Suspected infection, CMV viremia/infection, or PJP infection: interrupt therapy until infection has resolved. Permanent discontinuation if PJP infection is confirmed, consider permanent discontinuation for all infections.

Pneumonitis

- Pneumonitis: Time to onset ranged from < 1 to 15 months
- Monitor for pulmonary symptoms such as cough, dyspnea, hypoxia, interstitial infiltrates on a radiologic exam, or a decline by more than 5% in oxygen saturation
- Discontinue therapy with any severity symptomatic pneumonitis and initiate appropriate treatment with corticosteroids

Aliqopa (copanlisib) [prescribing information]. 2019.; Copiktra (duvelisib) [prescribing information]. 2019.; Dreyling M, et al. *J Clin Oncol*. 2017;35(35):3898-905.; Flinn IW, et al. *J Clin Oncol*. 2019;37(11):912-22.; Gopal AK, et al. *New Engl J Med*. 2014;370(11):1008-18.; Zydelig (idelalisib) [prescribing information]. 2018.

PI3K Inhibitors: Diarrhea and Colitis Management

Time to onset (months)

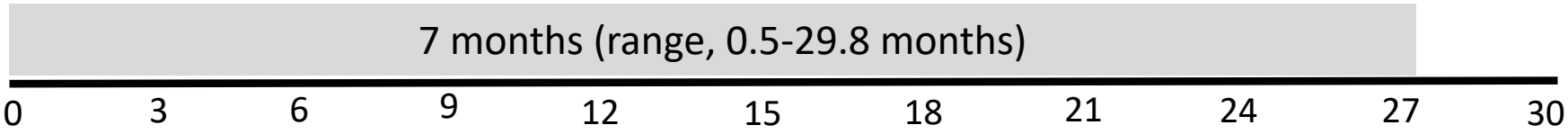
Mild to moderate diarrhea

1.5 months (range, 0-15.2 months)

*Mild: increase of < 4 stools per day over baseline;
Moderate: increase of 4-6 stools per day over baseline

Severe diarrhea

*Severe: increase of ≥ 7 stools per day over baseline



Management

- Patient and provider education
- Mild diarrhea: initiate supportive therapy with antidiarrheal agents, monitor weekly until resolved
- Mild diarrhea unresponsive to intervention and moderate diarrhea: withhold therapy, initiate supportive therapy with enteric-acting steroids (e.g., budesonide); once resolved, resume therapy at reduced dose
- Severe diarrhea or abdominal pain, stool with mucus or blood, change in bowel habits, peritoneal signs: withhold therapy, initiate supportive therapy with enteric-acting steroids or systemic steroids; once resolved, consider resuming therapy at reduced dose
- For any recurrent grade 3+ diarrhea or colitis, permanently discontinue therapy

Aliqopa (copanlisib) [prescribing information]. 2019.; Copiktra (duvelisib) [prescribing information]. 2019.; Coutré SE, et al. *Leuk Lymphoma.* 2015;56(10):2779-86.; Zydelig (idelalisib) [prescribing information]. 2018.

PI3K Inhibitors: Hyperglycemia Management

Transient hyperglycemia

- Peak: 5-8 hours post-infusion
- Permanent BG elevation in approximately 18% of patients, 10% of patients will develop A1C > 6.5%
- Optimize BG control in all patients before starting copanlisib

Management

Pre-dose: fasting BG > 160 mg/dL OR random/non-fasting BG > 200 mg/dL	• Withhold until FBG ≤ 160 mg/dL or a random/non-fasting BG ≤ 200 mg/dL • Close observation with PCP or endocrinology
Pre-dose or post-dose BG ≥ 500 mg/dL or more	• Withhold until FBG ≤ 160 mg/dL or a random/non-fasting BG ≤ 200 mg/dL or less, then reduce dose • Close observation with PCP or endocrinology • If persists at lowest dose, permanently discontinue

A1C, hemoglobin A1C; BG, blood glucose; FBG, fasting blood glucose; PCP, primary care physician.

Aliqopa (copanlisib) [prescribing information]. 2019.; Cheson BD, et al. *Clin Lymphoma Myeloma Leuk*. 2019;19(3):135-41.

PI3K Inhibitors: Hypertension Management

Transient hypertension

- Monitor BP pre- and post-dose
- BP decline starting 2 hours post-infusion but can remain elevated for 6-8 hours
- Optimal BP control should be achieved before starting each infusion

If treating during the infusion, short-acting antihypertensives should be used

Management

Pre-dose BP ≥ 150/90 mmHg	• Withhold until BP is < 150/90 mmHg based on 2 consecutive BP measurements at least 15 minutes apart
Post-dose BP ≥ 150/90 mmHg (non-life-threatening)	• If antihypertensive is not required, continue at previous dose • If antihypertensive is required,* consider dose reduction • Discontinue therapy if BP remains high (> 150/90 mmHg) despite antihypertensive
Post-dose elevated BP (life threatening)	• Permanently discontinue

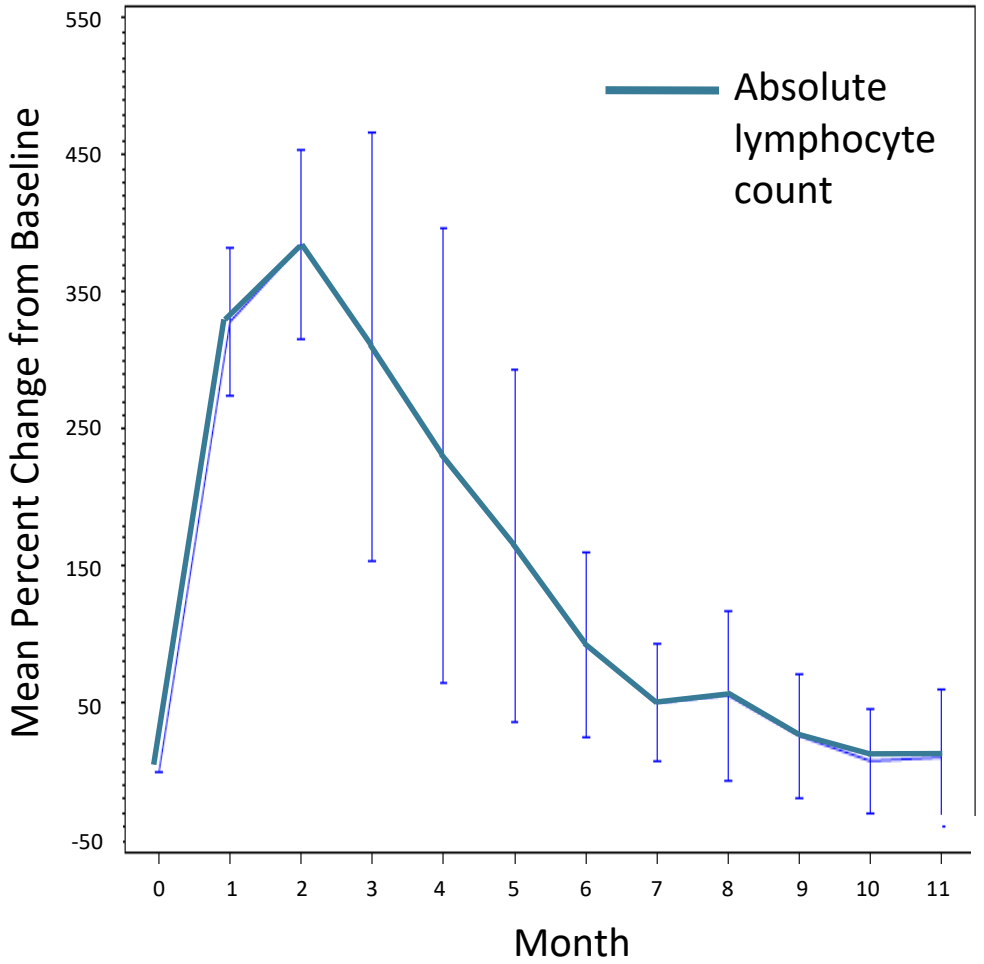
*Decision to treat should be individualized on the basis of several factors, including baseline BP, severity of BP elevation, and pre-existing cardiovascular risk (diabetes, chronic kidney disease) or coronary vascular disease.

Aliqopa (copanlisib) [prescribing information]. 2019.; Cheson BD, et al. *Clin Lymphoma Myeloma Leuk*. 2019;19(3):135-41.

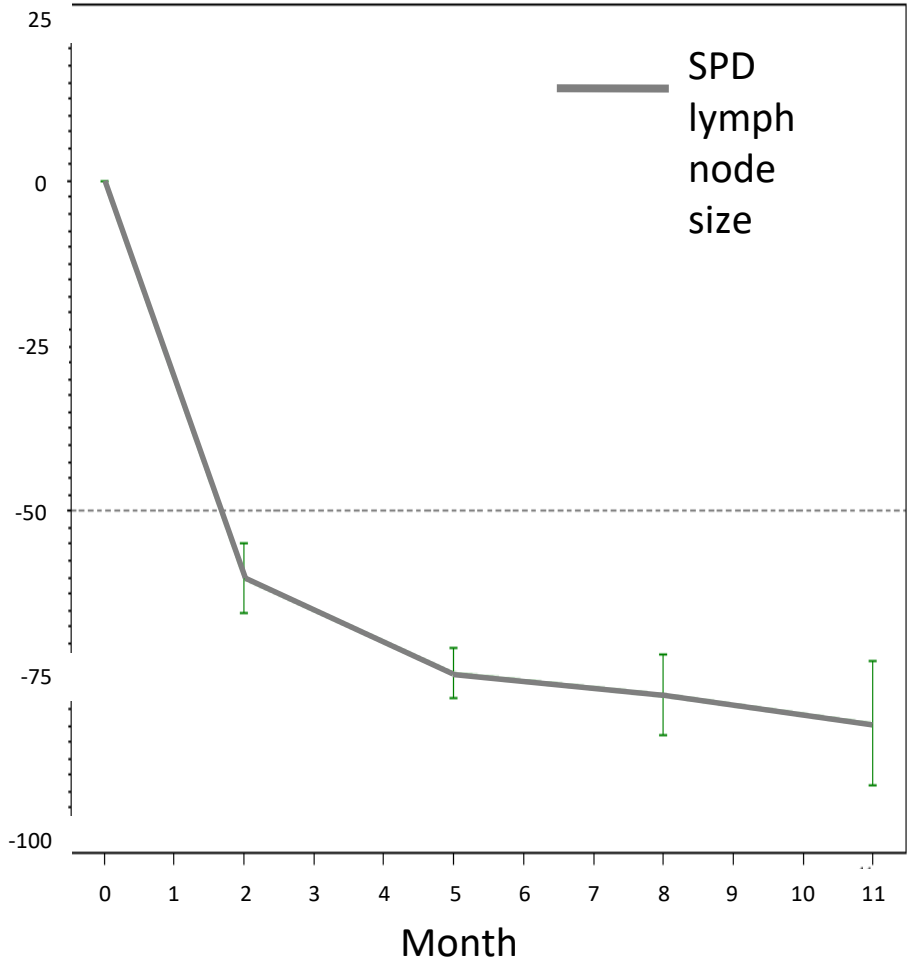
BP, blood pressure.

Transient Lymphocytosis with PI3K Inhibitors/BTK Inhibitors?

Blood Lymphocytes



Lymph Nodes



SPD, sum of products.

Brown JR, et al. *Blood*. 2015;126(23):2952.;
Byrd JC, et al. *New Engl J Med*. 2013;369(1):32-42.

Summary of Novel Agents in Lymphoma

Agent	FDA approval	Class	Dose	Route	Supplied
Ibrutinib	CLL (1st+), MCL (2nd+) WM (1st+), MZL (2nd+)	BTKi	MCL: 560 mg daily CLL: 420 mg daily	Oral	70-, 140-, 280-, 420-, and 560-mg tablets
Acalabrutinib	MCL (2nd+) CLL (1st+)	BTKi	100 mg twice daily	Oral	100-mg capsule
Zanubrutinib	MCL (2nd+)	BTKi	160 mg twice daily or 320 mg daily	Oral	80-mg capsule
Idelalisib	CLL (3rd+), FL (3rd+) CLL with comorbidities (2nd+)	PI3Ki (δ)	150 mg twice daily	Oral	100- and 150-mg tablets
Duvelisib	CLL (3rd+), FL (3rd+)	PI3Ki (γ/δ)	25 mg twice daily	Oral	15- and 25-mg capsules
Copanlisib	FL (3rd+)	PI3Ki (α/δ)	60 mg IV over 1-hour days 1, 8, and 15 (28-day cycle)	Intravenous	60 mg vial
Venetoclax	CLL (1st+)	BCL2i	MCL: 400-800 mg with food CLL: 400 mg with food	Oral	10-, 50-, and 100-mg tablets

Aliqopa (copanlisib) [prescribing information]. 2019.; Brukinsa (zanubrutinib) [prescribing information]. 2019.; Calquence (acalabrutinib) [prescribing information]. 2019.; Copiktra (duvelisib) [prescribing information]. 2019.; Imbruvica (ibrutinib) [prescribing information]. 2020.; Zydelig (idelalisib) [prescribing information]. 2018.

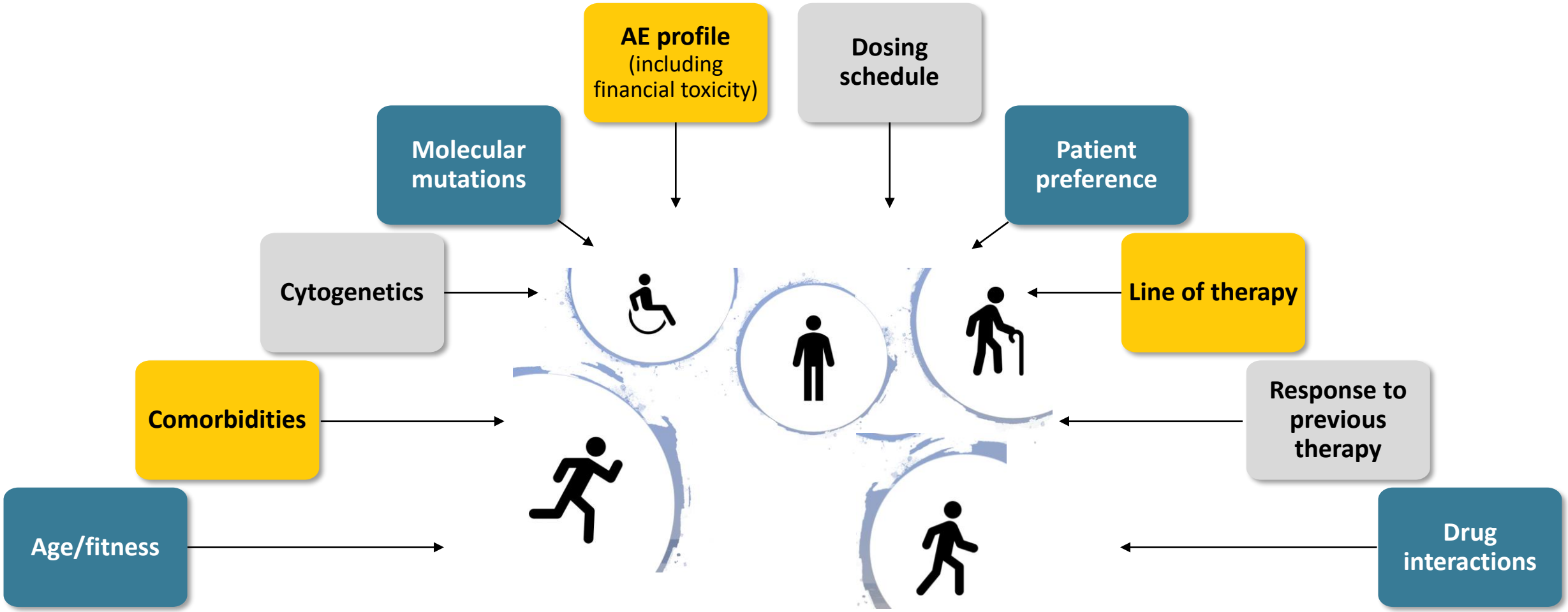
Drug and Comorbidity Interactions with Novel Agents in Lymphoma

Agent	Metabolism	CYP Inhibitors	CYP Inducers	Renal	Hepatic
Ibrutinib	CYP3A4 (major) CYP2D6 (minor)	Voriconazole: ↓ 140 mg daily? Posaconazole: ↓ 70 mg daily Moderate: ↓ 280 mg daily	Avoid	No changes	Child-Pugh A: ↓ 140 mg Child-Pugh B: ↓ 70 mg Child-Pugh C: avoid
***Acalabrutinib**	CYP3A4 (major) P-gp, BCRP	Strong: avoid Moderate: ↓ 100 mg daily	↑ 200 mg twice daily	No changes	No changes Monitor in severe
Zanubrutinib	CYP3A4 (?)	Strong: ↓ 80 mg daily Moderate: ↓ 80 mg twice daily	Avoid	No changes	Severe: ↓ 80 mg twice daily
****Idelalisib**	CYP3A4 (major) P-gp, UGT1A4	Avoid	Avoid	No changes	Caution (1.7x increase AUC)
^Duvelisib	CYP3A4 (major)	Strong: ↓ 15 mg daily	Avoid	No changes	No changes
Copanlisib	CYP3A4 (major) P-gp, BCRP	Strong: avoid or ↓ 45 mg daily	Avoid	No changes	Child-Pugh B: ↓ 45 mg Child-Pugh C: avoid
Venetoclax	CYP3A4 (major) P-gp	Strong: avoid during ramp-up, ↓ 75% thereafter Moderate: ↓ 50%	Avoid	Monitor TLS	Monitor toxicity

*Avoid proton pump inhibitors; take acalabrutinib 2 hrs before H2RAs and antacids (reduces acalabrutinib AUC 40% to 50%). †Idelalisib inhibits CYP3A4 (strong) and UGT1A1. Duvelisib inhibits CYP3A4 (moderate); all agents listed inhibit P-glycoprotein except for acalabrutinib, copanlisib, and duvelisib.

AUC, area under the curve; H2RA, histamine-2 receptor antagonist; TLS, tumor lysis syndrome.
Aliqopa (copanlisib) [prescribing information]. 2019.; Brukinsa (zanubrutinib) [prescribing information]. 2019.; Calquence (acalabrutinib) [prescribing information]. 2019.; Copiktra (duvelisib) [prescribing information]. 2019.; Imbruvica (ibrutinib) [prescribing information]. 2020.; Zydelig (idelalisib) [prescribing information]. 2018.

Considerations When Selecting Therapies



Patient Education

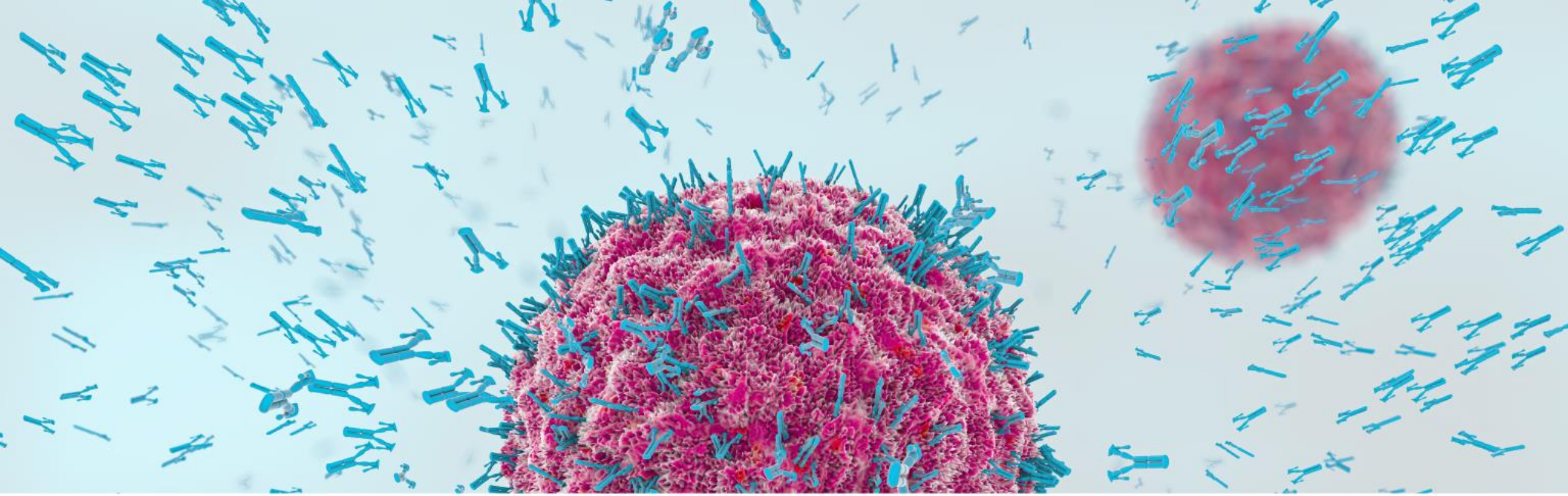
Administration

Adherence

Drug-drug interactions
Contact with new medications, herbals, or supplements

Create a monitoring plan
Highlight key adverse effects, how to self-manage, and when to report

Drug procurement



Thank You!