BTK Inhibitors for the Treatment of B-Cell Malignancies: Clinical Updates for Specialty Pharmacists

This live broadcast is a part of Asembia's 2020 Specialty Pharmacy Summit Virtual Experience and takes the place of the continuing education satellite program originally scheduled at Asembia's 2020 live event.

SPECIALTY PHARMACY 2020 summit

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Kirollos S. Hanna, PharmD, BCPS, BCOP has the following relationships with commercial interests to disclose:

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BTK Inhibitors for the Treatment of B-Cell Malignancies:

Clinical Updates for Specialty Pharmacists

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Educational Objectives

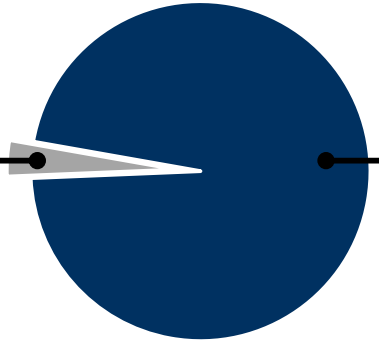
At the completion of this activity, participants will be able to:

- Explain the link between the BCR pathway in the pathophysiology of B-cell malignancies and the role of BTK inhibition for treatment of B-cell malignancies
- Determine the recommended treatment for a given B-cell malignancy based on patient- and disease-specific characteristics
- Develop a counseling and monitoring plan for a patient who is newly started on therapy with a BTK inhibitor for the treatment of a B-cell malignancy

Lymphoma

Hodgkin Lymphoma
New cases: 8480 (10%)

Not discussing today

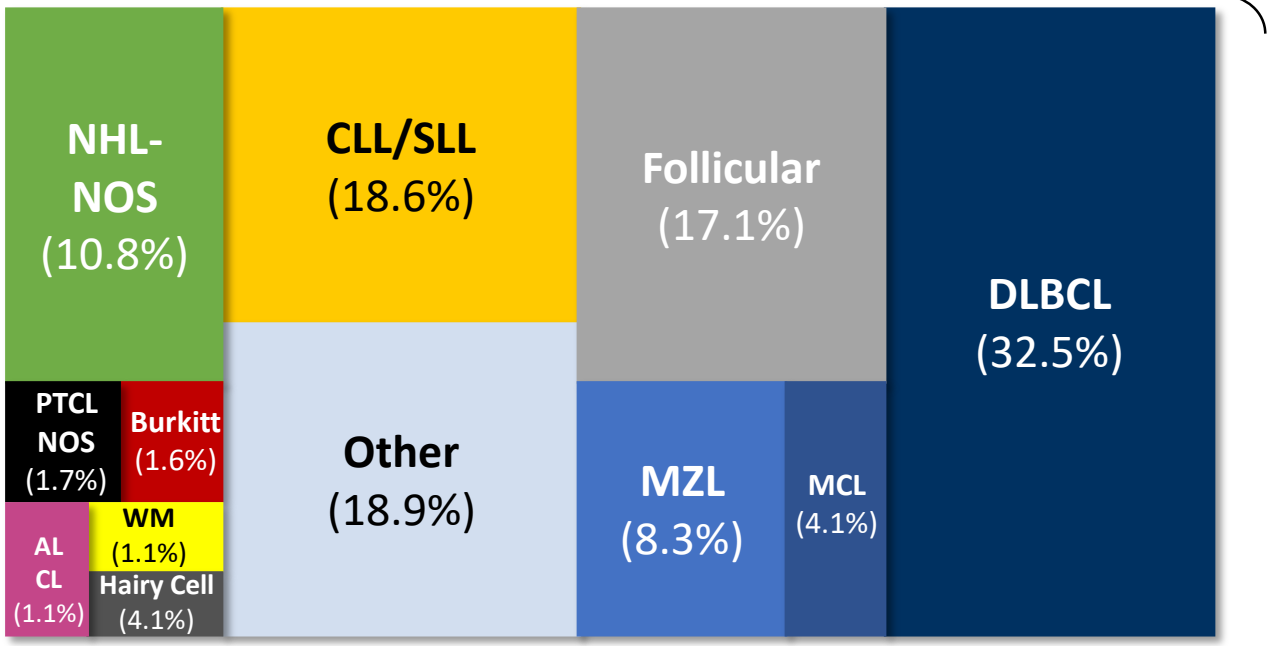


Non-Hodgkin Lymphoma (NHL)
New cases: 77,240 (90%)

+21,040 new cases of CLL

T-Cell Lymphoma

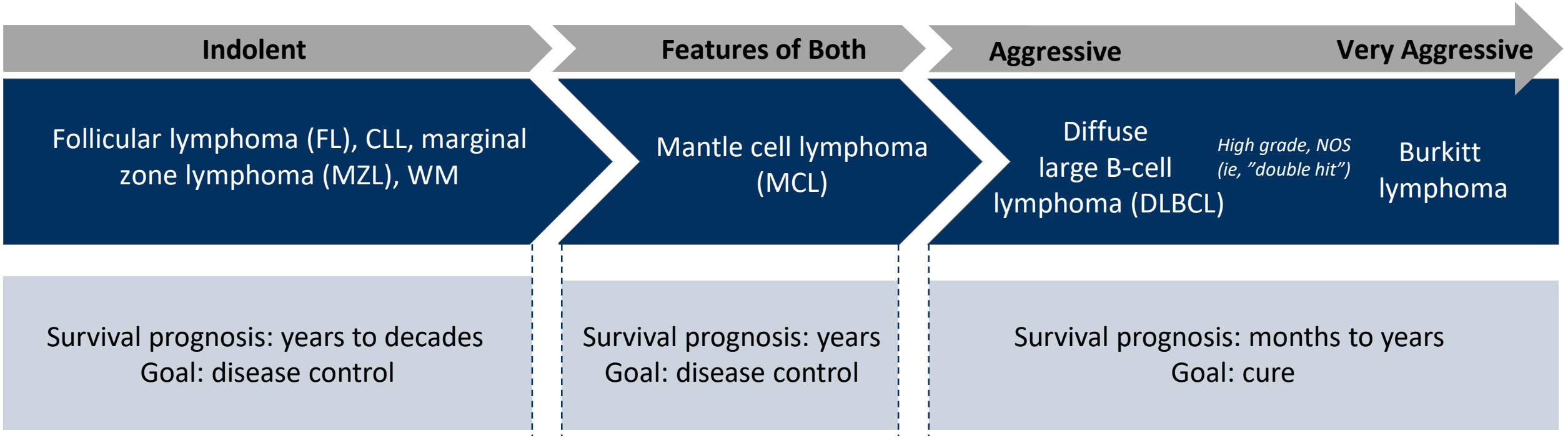
B-Cell Lymphoma



DLBCL, diffuse large-B-cell lymphoma
CLL, chronic lymphocytic leukemia;
SLL, small lymphocytic leukemia;
MZL, marginal zone lymphoma
MCL, mantle cell lymphoma
ALCL, anaplastic large-cell
PTCL-NOS, peripheral T-cell lymphoma not other-wise specified
WM, Waldenström macroglobulinemia/lymphoplasmacytic.

Siegel RL, et al. *CA Cancer J Clin*. 2020;70(1):7-30;
Al-Hamadani M, et al. *Am J Hematol*. 2015;90(9):790-795.

B-Cell NHL



Siegel RL, et al. *CA Cancer J Clin*. 2020;70(1):7-30; Al-Hamadani M, et al. *Am J Hematol*. 2015;90(9):790-795.

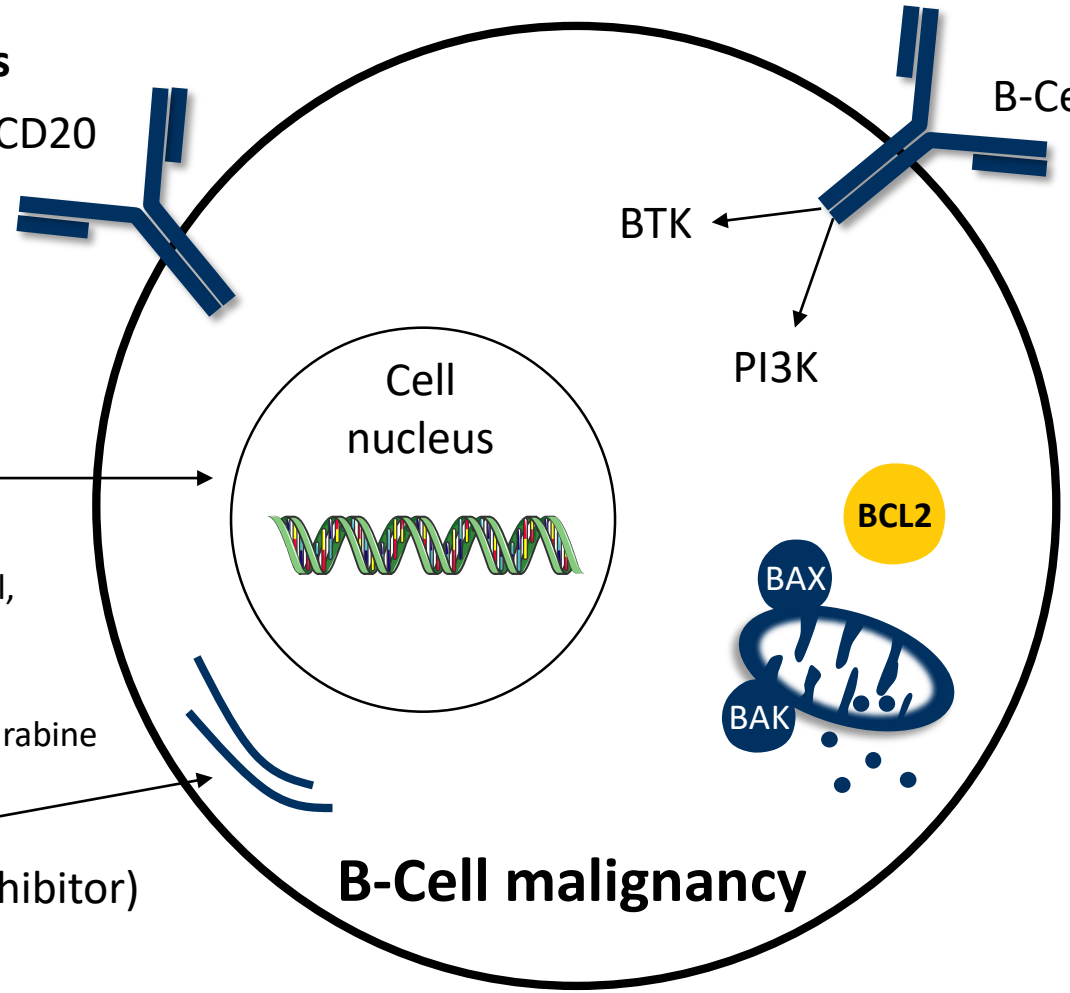
Therapies in B-Cell Malignancies

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 akyloids (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 combinations (FCR, BR, CHOP, PI3Ki + anti-CD20).

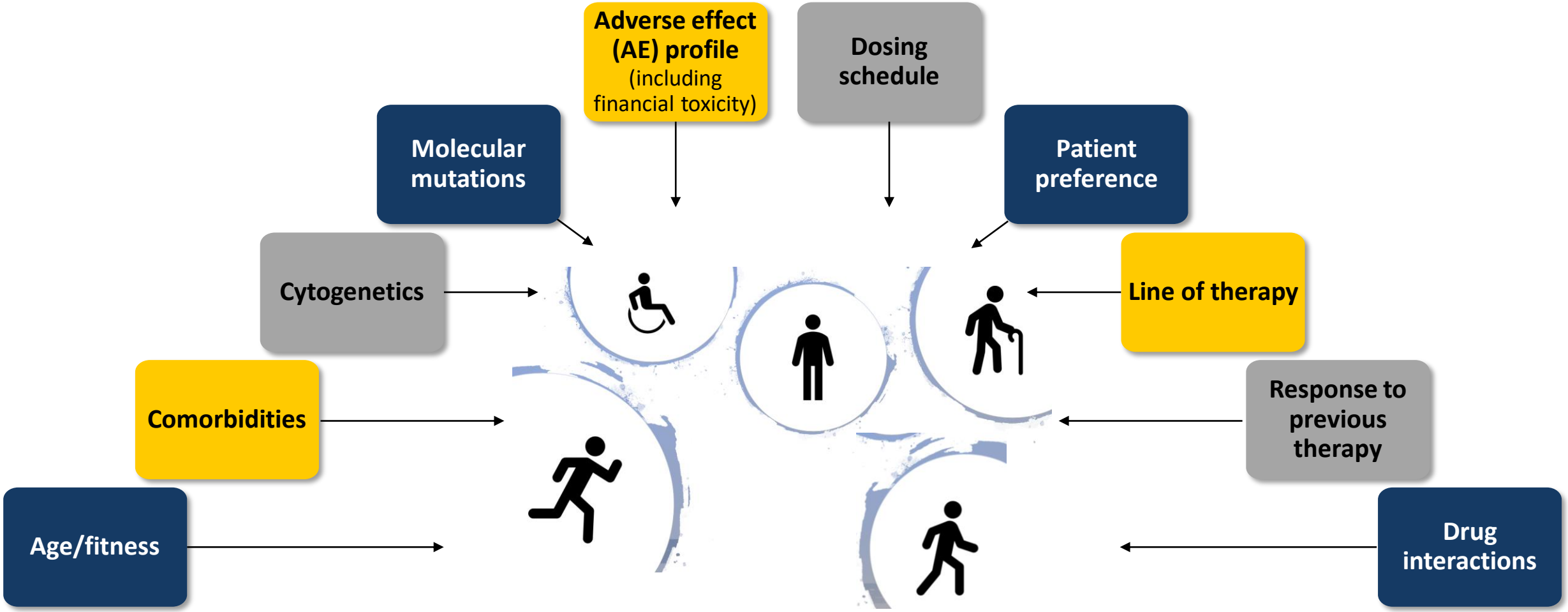
Ongoing studies to determine optimal sequence or combinations.

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

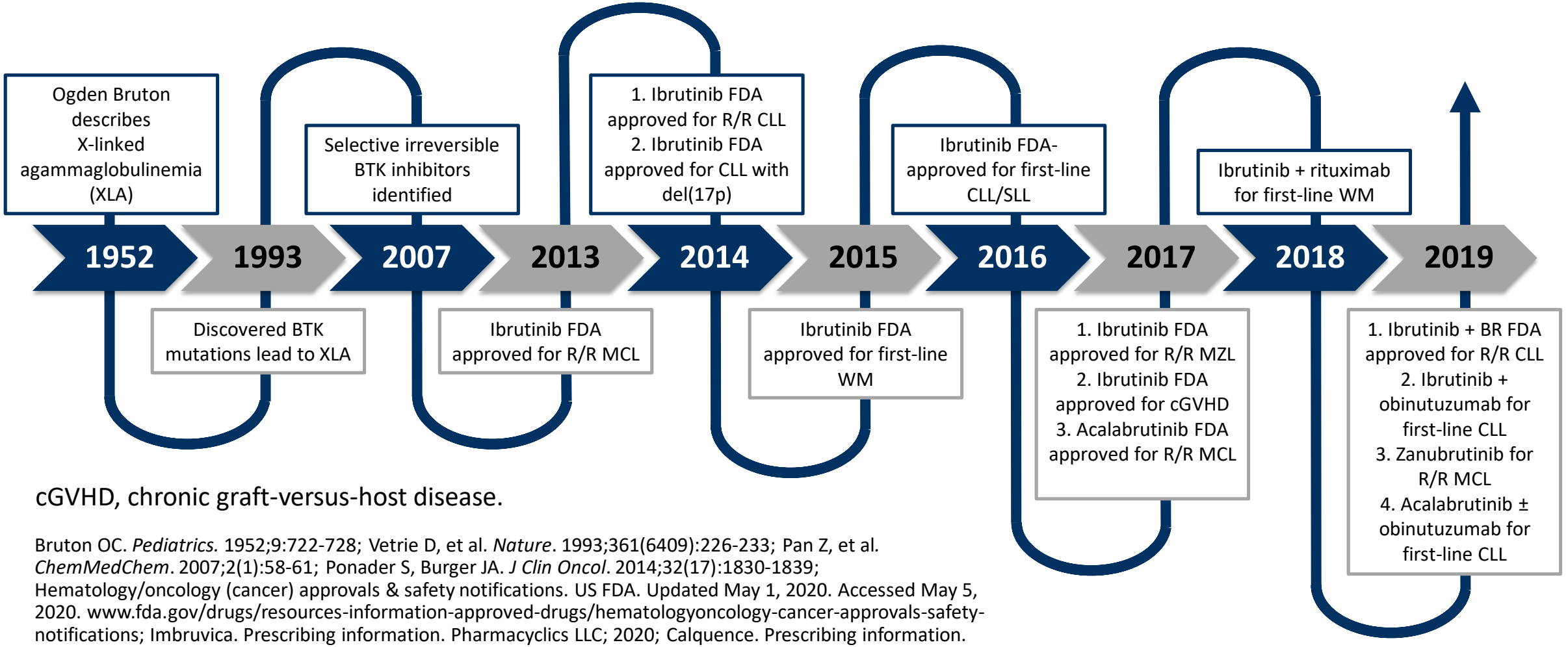
Regimen Acronym Key

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

Considerations When Selecting Therapies



FDA Approval of BTK Inhibitors



cGVHD, chronic graft-versus-host disease.

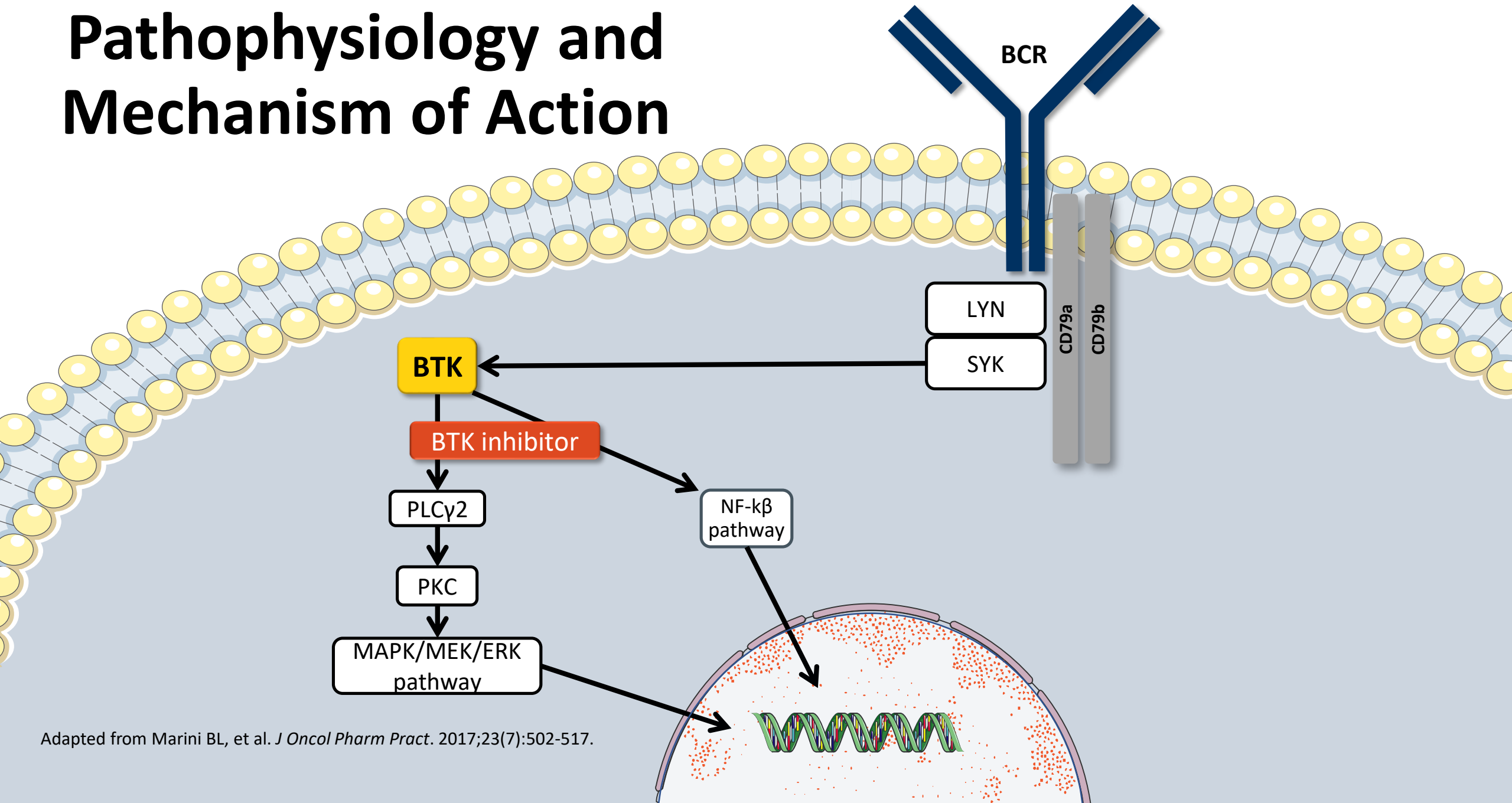
Bruton OC. *Pediatrics.* 1952;9:722-728; Vetrie D, et al. *Nature*. 1993;361(6409):226-233; Pan Z, et al. *ChemMedChem*. 2007;2(1):58-61; Ponader S, Burger JA. *J Clin Oncol*. 2014;32(17):1830-1839; Hematology/oncology (cancer) approvals & safety notifications. US FDA. Updated May 1, 2020. Accessed May 5, 2020. www.fda.gov/drugs/resources-information-approved-drugs/hematologyoncology-cancer-approvals-safety-notifications; Imbruvica. Prescribing information. Pharmacyclics LLC; 2020; Calquence. Prescribing information. AstraZeneca Pharmaceuticals LP; 2019; Brukinsa. Prescribing information. BeiGene USA, Inc; 2019.

BTK Inhibitors in B Cell Malignancies

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 (2nd gen)	100 mg twice daily	Oral	100-mg capsule
Zanubrutinib	MCL (2nd+)	BTKi (2nd gen)	160 mg twice daily or 320 mg daily	Oral	80-mg capsule

Imbruvica. Prescribing information. Pharmacyclics LLC; 2020; Calquence. Prescribing information. AstraZeneca Pharmaceuticals LP; 2019; Brukinsa. Prescribing information. BeiGene USA, Inc; 2019.

Pathophysiology and Mechanism of Action



Adapted from Marini BL, et al. *J Oncol Pharm Pract*. 2017;23(7):502-517.

BTK Inhibitors Not Created Equal

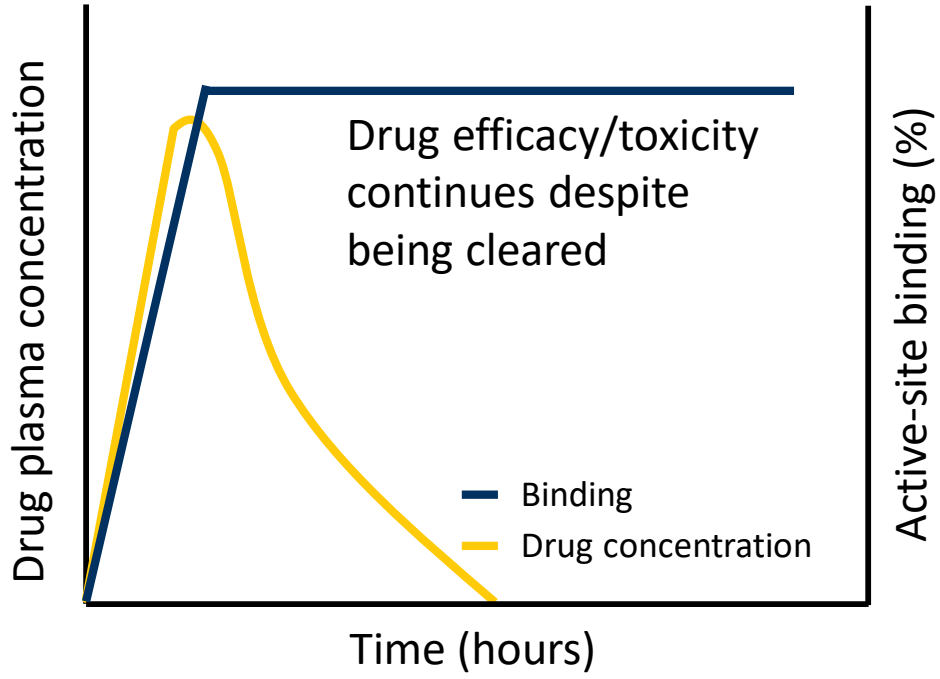
IC_{50}/EC_{50} (nM)

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

Irreversible vs Reversible BTK Inhibitors

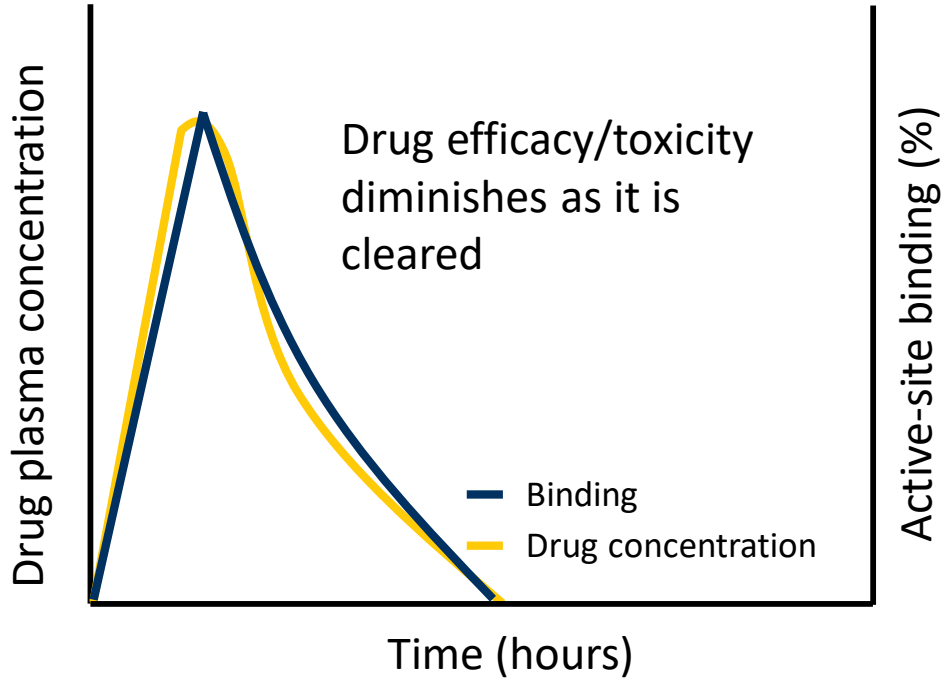
Irreversible inhibitor

- Most drugs are not irreversible inhibitors due to toxicity
- Ibrutinib, acalabrutinib, zanubrutinib, tirabrutinib
  - Irreversibly bind to some non-BTK kinases as well



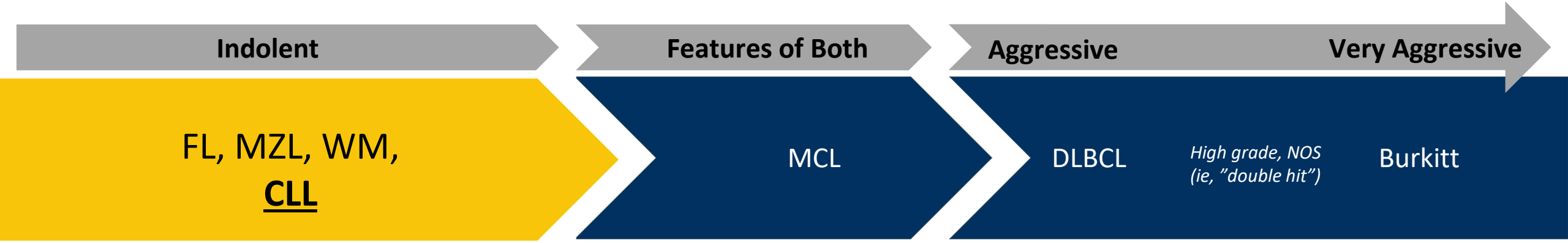
Reversible inhibitor

- Being developed to be more BTK selective, have fewer off-target effects, and allow for persistent binding to mutated BTK (or different BTK binding site) to overcome resistance
- ARQ-531, LOXO-305, ICP-022, SNS-062



Berglöf A, et al. *Scand J Immunol*. 2015;82(3):208-217.

Chronic Lymphocytic Leukemia (CLL)



- **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

IGHV, immunoglobulin heavy chain variable.

Siegel RL, et al. *CA Cancer J Clin*. 2020;70(1):7-30; SEER cancer stat facts: leukemia - chronic lymphocytic leukemia (CLL). National Cancer Institute. Accessed May 5, 2020. seer.cancer.gov/statfacts/html/clyl.html; NCCN Clinical Practice Guidelines in Oncology. Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma v4.2020.

First-Line Treatment in CLL: Pre-BTKi

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

ECOG 1912 Trial: Ibrutinib + R vs FCR

End point	IGHV status	Ibrutinib-R	FCR	*P*-value
PFS	All Patients	89.4%	72.9%	<0.001
	Unmutated	90.7%	62.5%	
OS	---	98.8%	91.5%	

Conclusions

Ibrutinib + R improved PFS compared with FCR, especially in IGHV unmutated CLL

PFS, progression-free survival;
OS, overall survival.

Shanafelt TD, et al. *N Engl J Med*. 2019;381(5):432-443.

First-Line Treatment in CLL: Changing Landscape

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

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

Alliance A041202 Trial

Ibrutinib + rituximab vs ibrutinib alone vs bendamustine + rituximab

Treatment arm	Median PFS	2-year PFS	*P*-value
Ibrutinib	**Not reached**	**87%**	<0.001
Ibrutinib + R	**Not reached**	**88%**	
BR	43 months	74%	

Conclusions

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

Woyach JA, et al. *N Engl J Med*. 2018;379(26):2517-2528.

First-Line Treatment in CLL: Changing Landscape

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

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

ELEVATE-TN Trial

Acalabrutinib + obinutuzumab vs acalabrutinib alone vs chlorambucil + obinutuzumab

Treatment arm	PFS at 30 months	*P*-value
Acalabrutinib	90%	Not reported
Acalabrutinib + obininutuzumab	82%	
Chlorambucil+ obininutuzumab	34%	

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)

ORR, overall response rate.

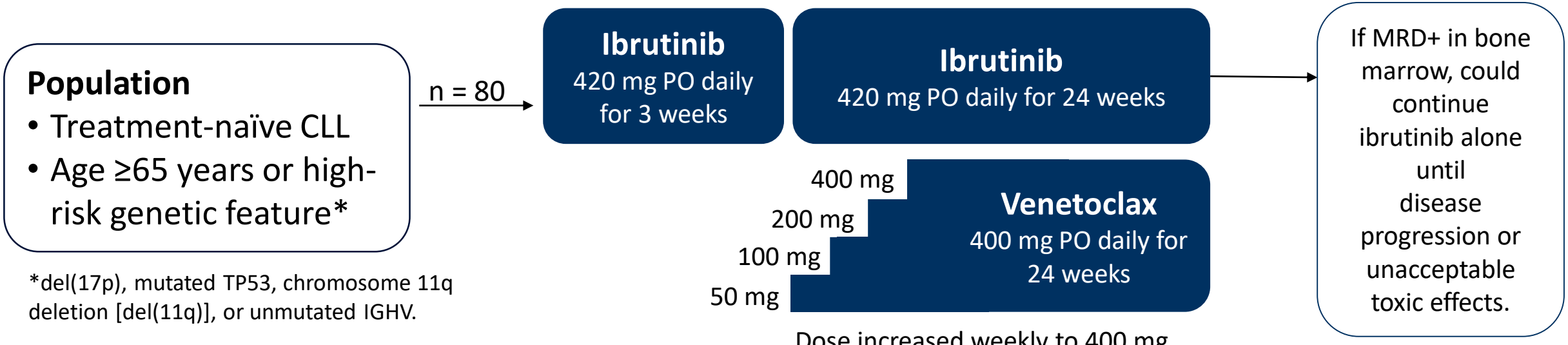
Sharman JP, et al. Presented at 2019 ASH Annual Meeting, December 7-10, 2019. Abstract 31.

First-Line Treatment in CLL: Changing Landscape

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

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

Future Directions: Phase 2 Ibrutinib With Venetoclax



*del(17p), mutated TP53, chromosome 11q deletion [del(11q)], or unmutated IGHV.

MRD, minimal residual disease.

Study design

- Phase 2, single-center, open-label

Primary end point

- Complete response (CR) rate (with or without blood count recovery)

Jain N, et al. *N Engl J Med*. 2019;380(22):2095-2103.

Phase 2 Ibrutinib With Venetoclax: Results

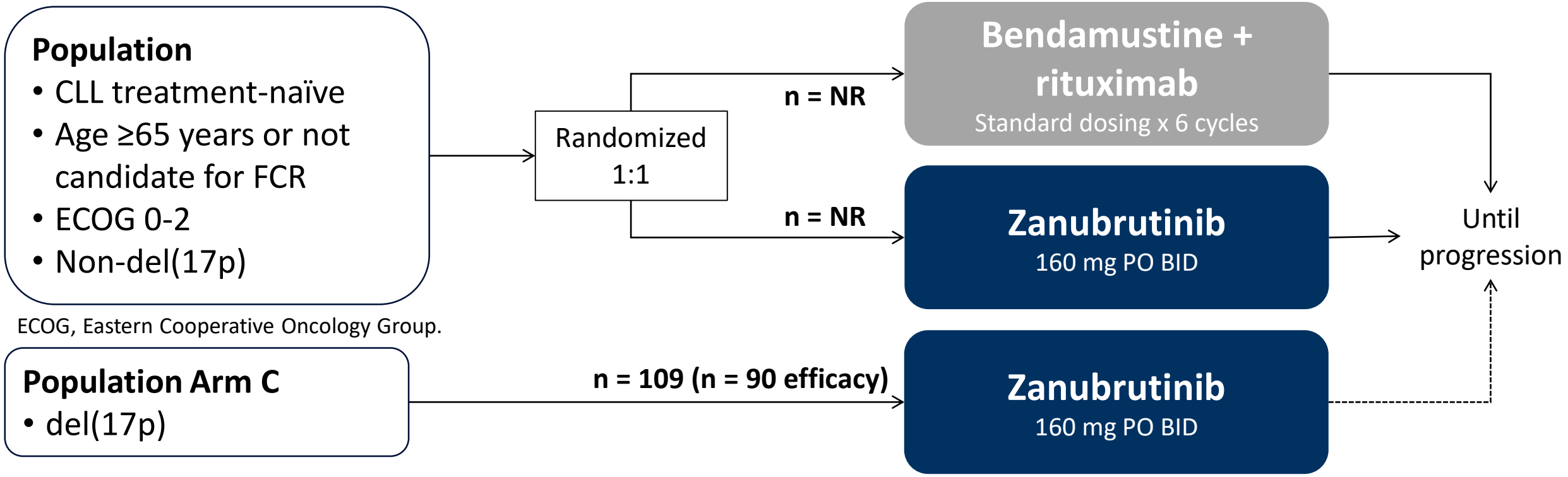
Treatment arm	n	Undetectable MRD in bone marrow (%)	CR (%)	Partial response (PR) (%)
3 cycles ibrutinib	75	--	--	96
3 cycles ibrutinib + Ven	72	17	57	43
6 cycles ibrutinib + Ven	70	40	73	27
9 cycles ibrutinib + Ven	60	52	83	17
12 cycles ibrutinib + Ven	33	61	88	12
18 cycles ibrutinib + Ven	26	69	96	4

Conclusions

- Ibrutinib + Ven leads to high CR rates and high MRD negativity
- PFS at 1 year was 98% and OS at 1 year was 99%
- Multicenter phase 3 trial eagerly awaited

Jain N, et al. *N Engl J Med*. 2019;380(22):2095-2103.

Future Directions: SEQUOIA Trial



ECOG, Eastern Cooperative Oncology Group.

Study design

- Phase 3, multicenter, open-label, randomized, controlled trial

Primary outcome

- PFS

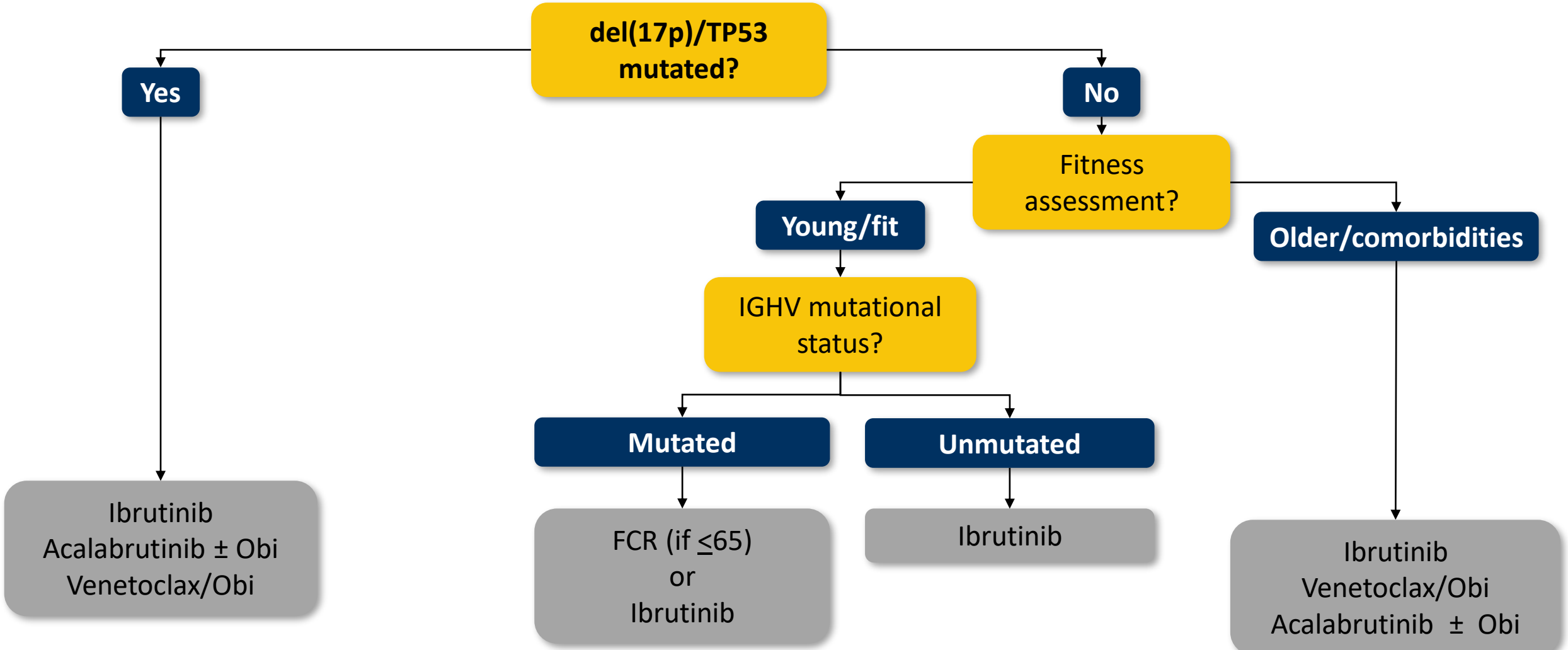
Tam CS, et al. Presented at 2019 ASH Annual Meeting, December 7-10, 2019. Abstract 499.

SEQUOIA Trial: Arm C Results

	Treatment-naïve del(17p) CLL/SLL (N = 90)
Median follow-up, mo (range)	7 (2.9-14.5)
Efficacy (best response)	
Overall response rate	92.2%
CR	0%
PR	75.6%
PR with lymphocytosis	16.7%
Stable disease	6.7%
Progressive disease	1.1%

Tam CS, et al. Presented at 2019 ASH Annual Meeting, December 7-10, 2019. Abstract 499.

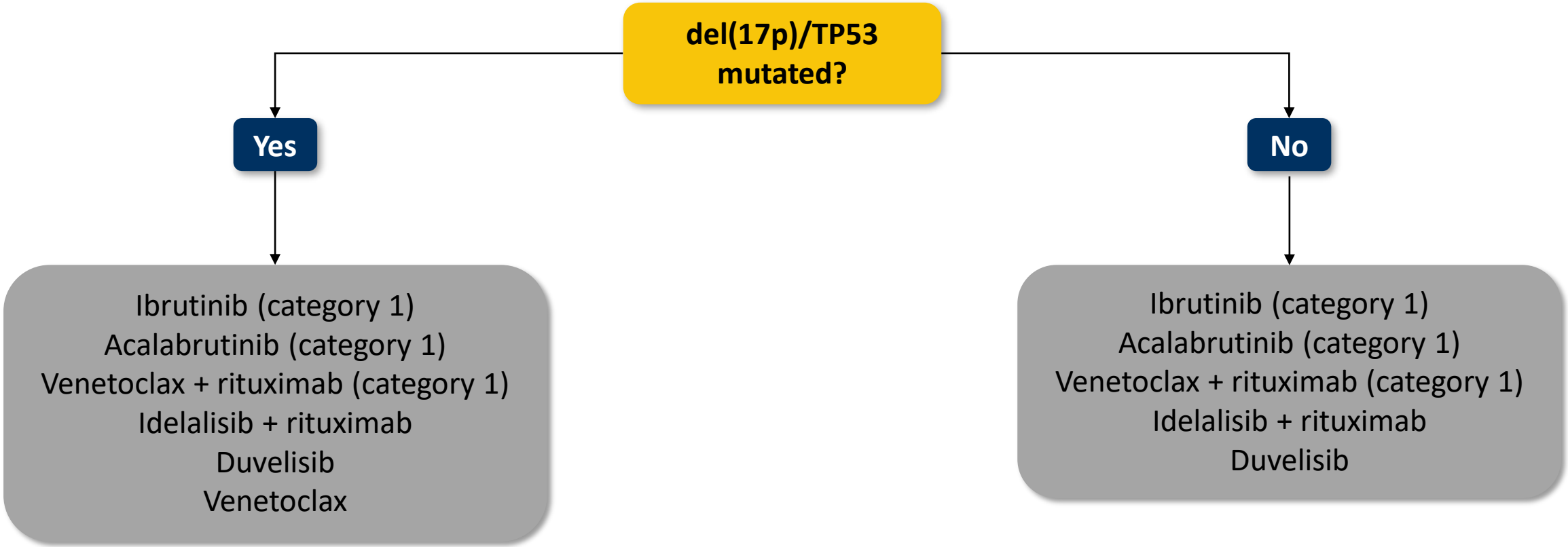
CLL Treatment 2020: First-Line Therapy



*NCCN Clinical Practice Guidelines in Oncology. Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma v4.2020.

* Select regimens are included. More therapies are included in the guidelines and may be selected based on patient- and disease-specific factors.

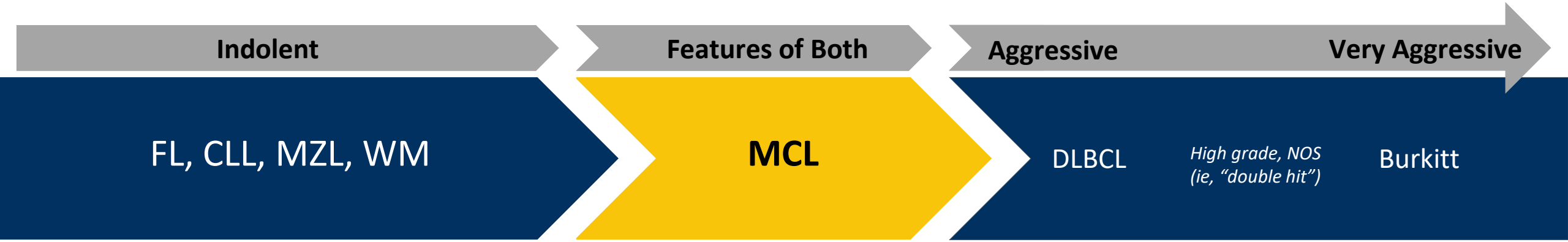
CLL Treatment 2020: Relapsed/Refractory



*NCCN Clinical Practice Guidelines in Oncology. Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma v4.2020.

* Select regimens are included. More therapies are included in the guidelines and may be selected based on patient- and disease-specific factors.

Mantle Cell Lymphoma (MCL)



- **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

NCCN Clinical Practice Guidelines in Oncology. B-Cell Lymphomas v1.2020; Armitage JO, Weisenburger DD. *J Clin Oncol*. 1998;16(8):2780-2795; Hoster E, et al. *Blood*. 2008;111(2):558-565; SEER Cancer Stat Facts: non-Hodgkin lymphoma. National Cancer Institute. Accessed May 5, 2020. seer.cancer.gov/statfacts/html/nhl.htm; Eskelund CW, et al. *Blood*. 2017;130(17):1903-1910; Jain P, Wang M. *Am J Hematol*. 2019;94(6):710-725; Tiemann M, et al. *Br J Haematol*. 2005;131(1):29-38; Herrmann A, et al. *J Clin Oncol*. 2009;27(4):511-518.

MCL Treatment 2020

First-line therapy

"Watch and wait"/observation

Transplant eligible

Intensive therapy
R-CHOP/HiDAC based therapy (ie, 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

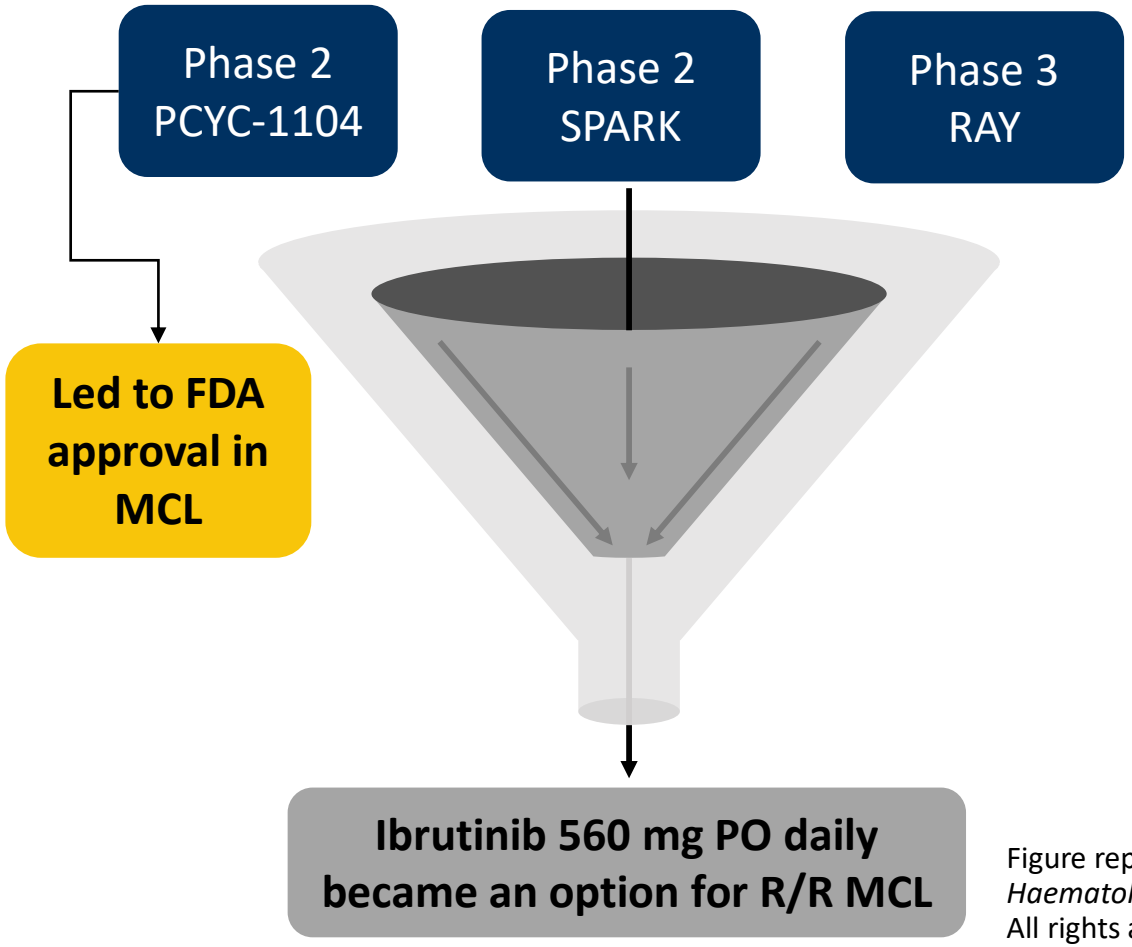
Second line:
- R-chemotherapy
- Bortezomib ± R
- Lenalidomide ± R
- **BTK inhibitors:**
  - **Ibrutinib ± R**
  - **Acalabrutinib**
  - **Zanubrutinib**
- Venetoclax ± ibrutinib

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: R/R MCL



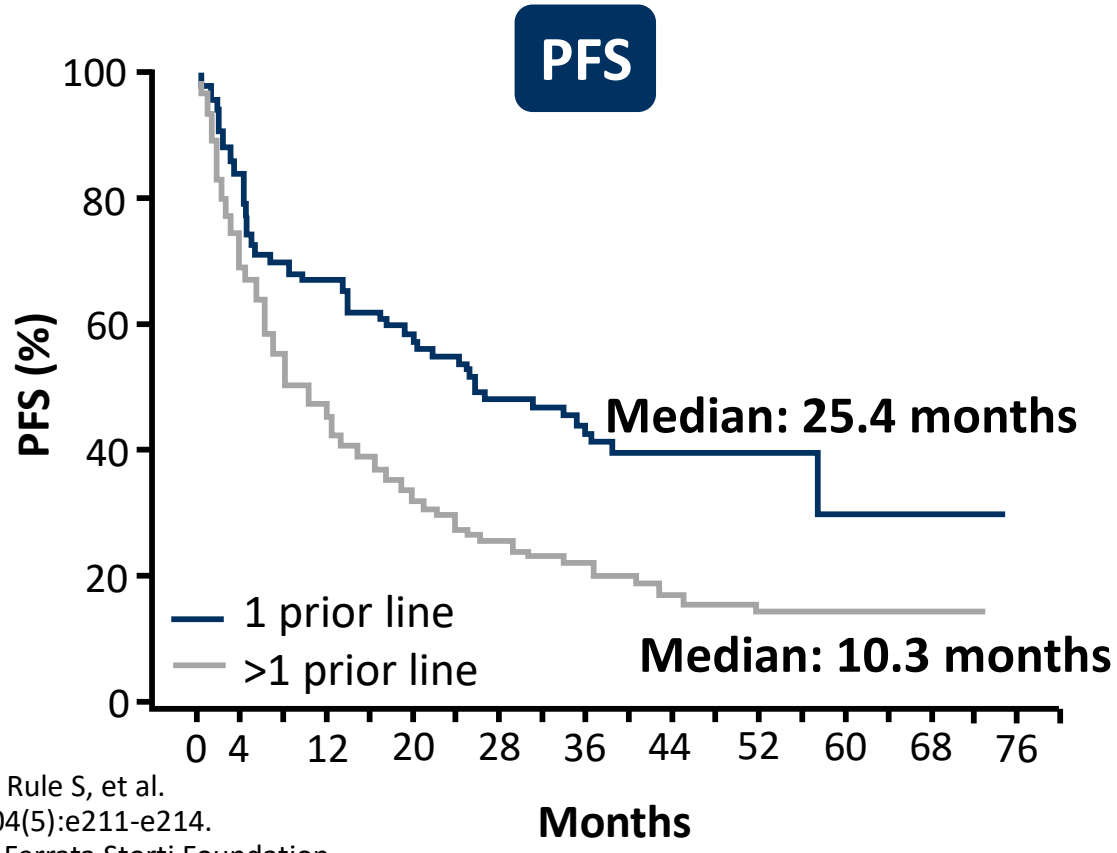
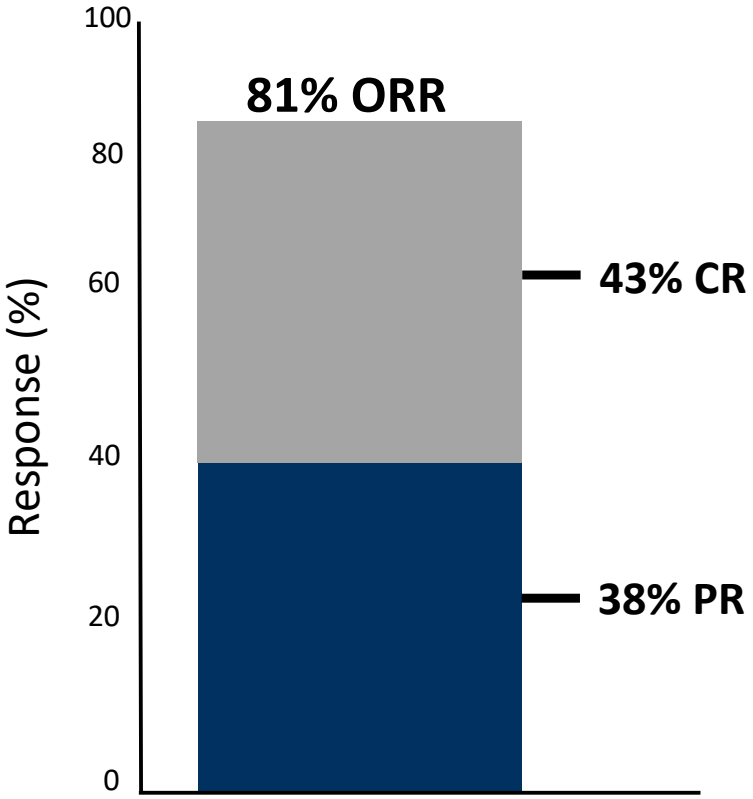


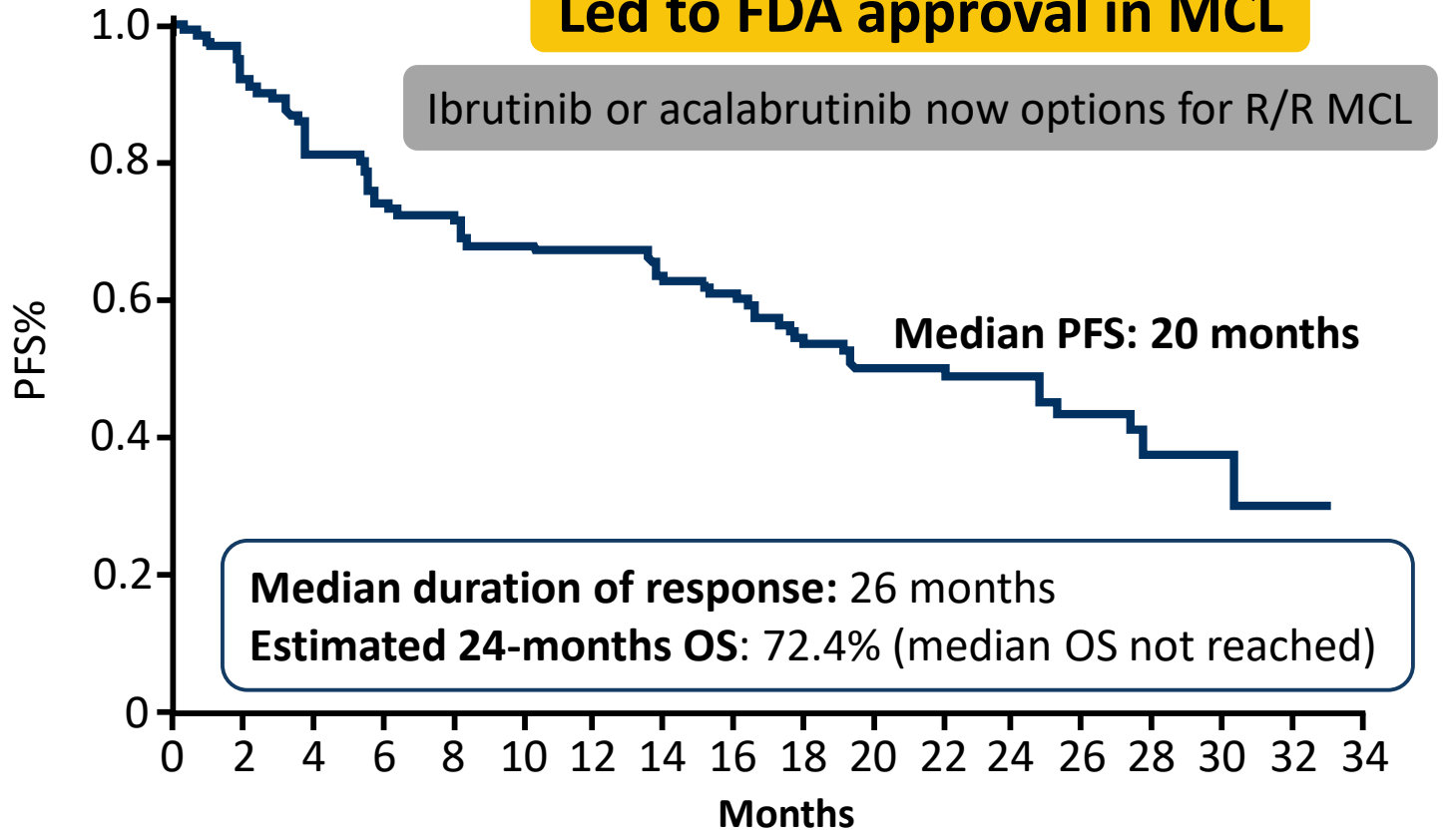
Figure republished from Rule S, et al. *Haematologica*. 2019;104(5):e211-e214.

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



Led to FDA approval in MCL

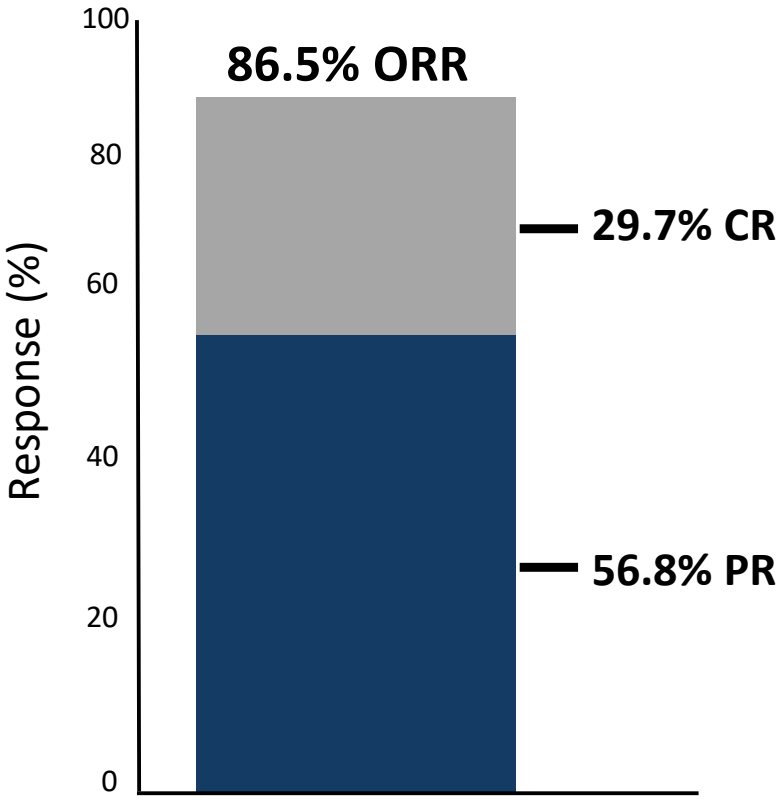
Ibrutinib or acalabrutinib now options for R/R MCL



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

Wang M, et al. *Lancet*. 2018;391(10121):659-667; Wang M, et al. *Leukemia*. 2019;33(11):2762-2766.

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



Led to FDA approval in MCL

Conclusions

Median PFS: 16.7 months

Median duration of response: 14 months

Ibrutinib, acalabrutinib, or zanubrutinib now options for R/R MCL

Song Y, et al. *Hematol Oncol.* 2019;37:45-46.

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

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

n = 24

Ibrutinib
560 mg PO daily for 4 weeks

Ibrutinib
560 mg PO daily

800 mg
400 mg
200 mg
100 mg
50 mg

Venetoclax
400-800 mg PO daily

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

Until progression or unacceptable toxicity

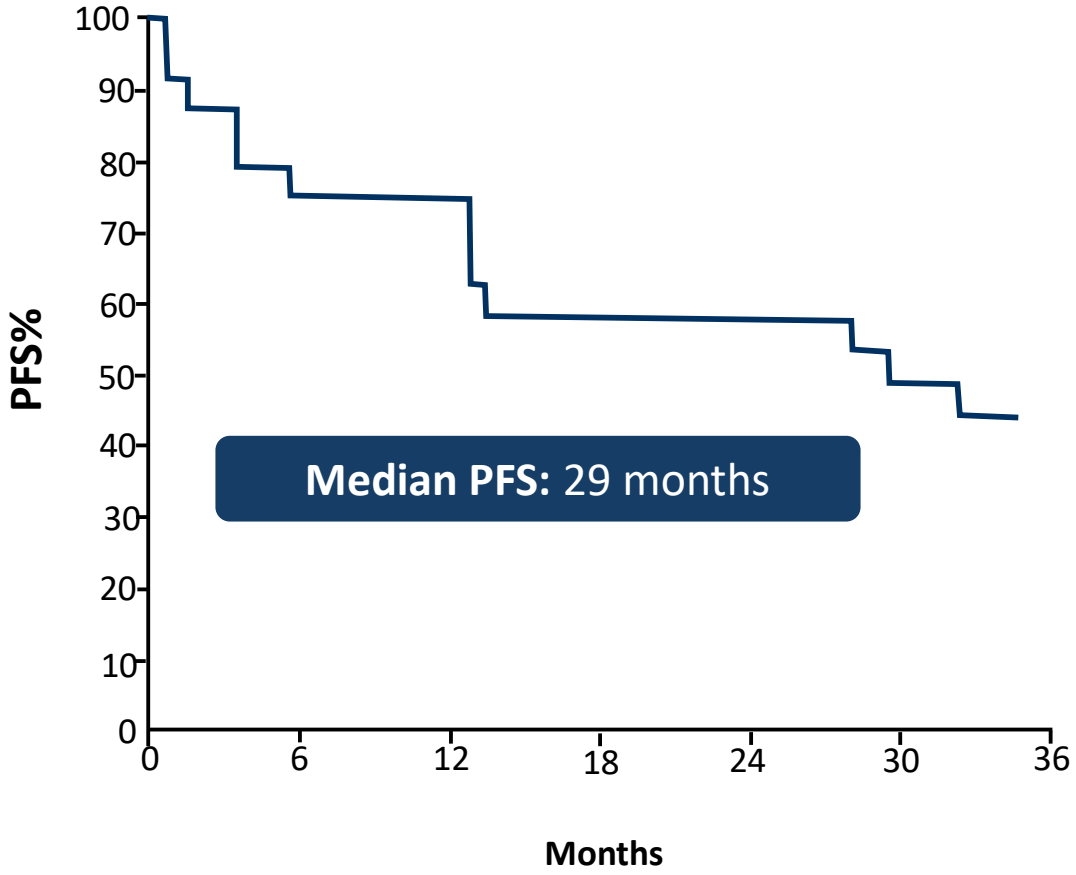
*Uncontrolled or symptomatic arrhythmias, congestive heart failure, or myocardial infarction within 6 months of screening, or any class 3/4 cardiac disease per NYHA Functional Classification.

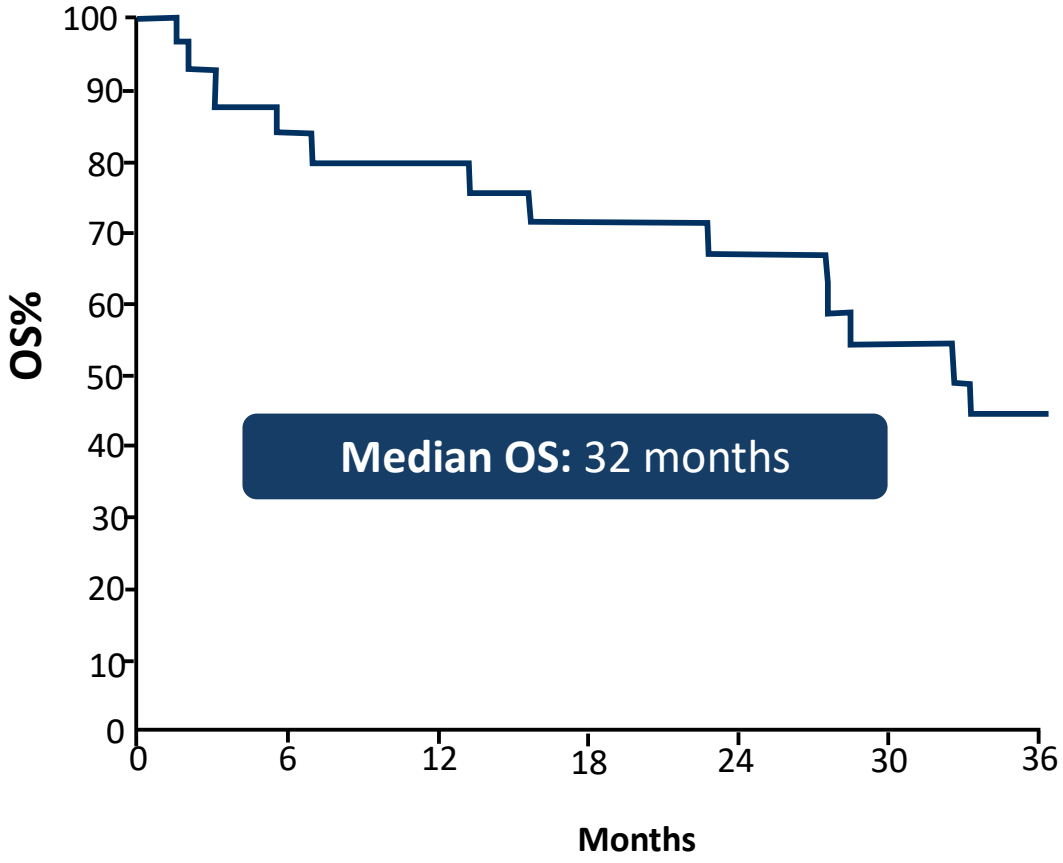
Study design
- Phase 2, multicenter, open-label

Primary end point
- CR at week 16

Tam CS, et al. *N Engl J Med*. 2018;378(13):1211-1223.

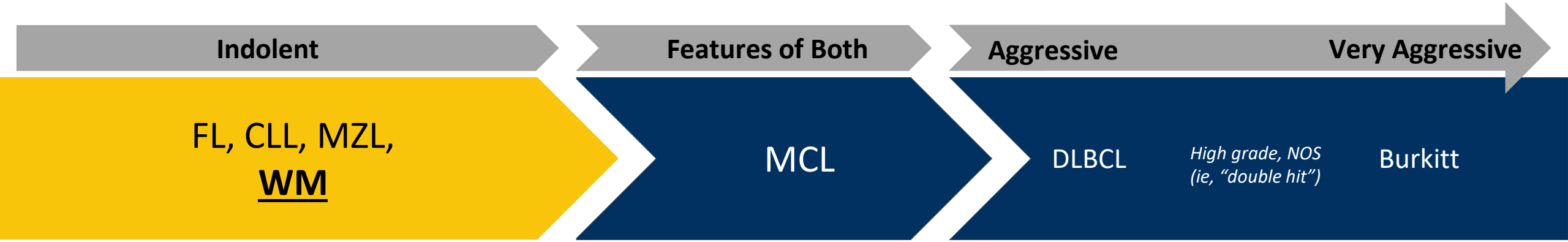
AIM Trial:
Ibrutinib + Venetoclax for R/R MCL Results





Tam CS, et al. *N Engl J Med*. 2018;378(13):1211-1223; Handunnetti SM, et al. *Blood*. 2019;134(suppl 1):756.

Waldenström Macroglobulinemia (WM)

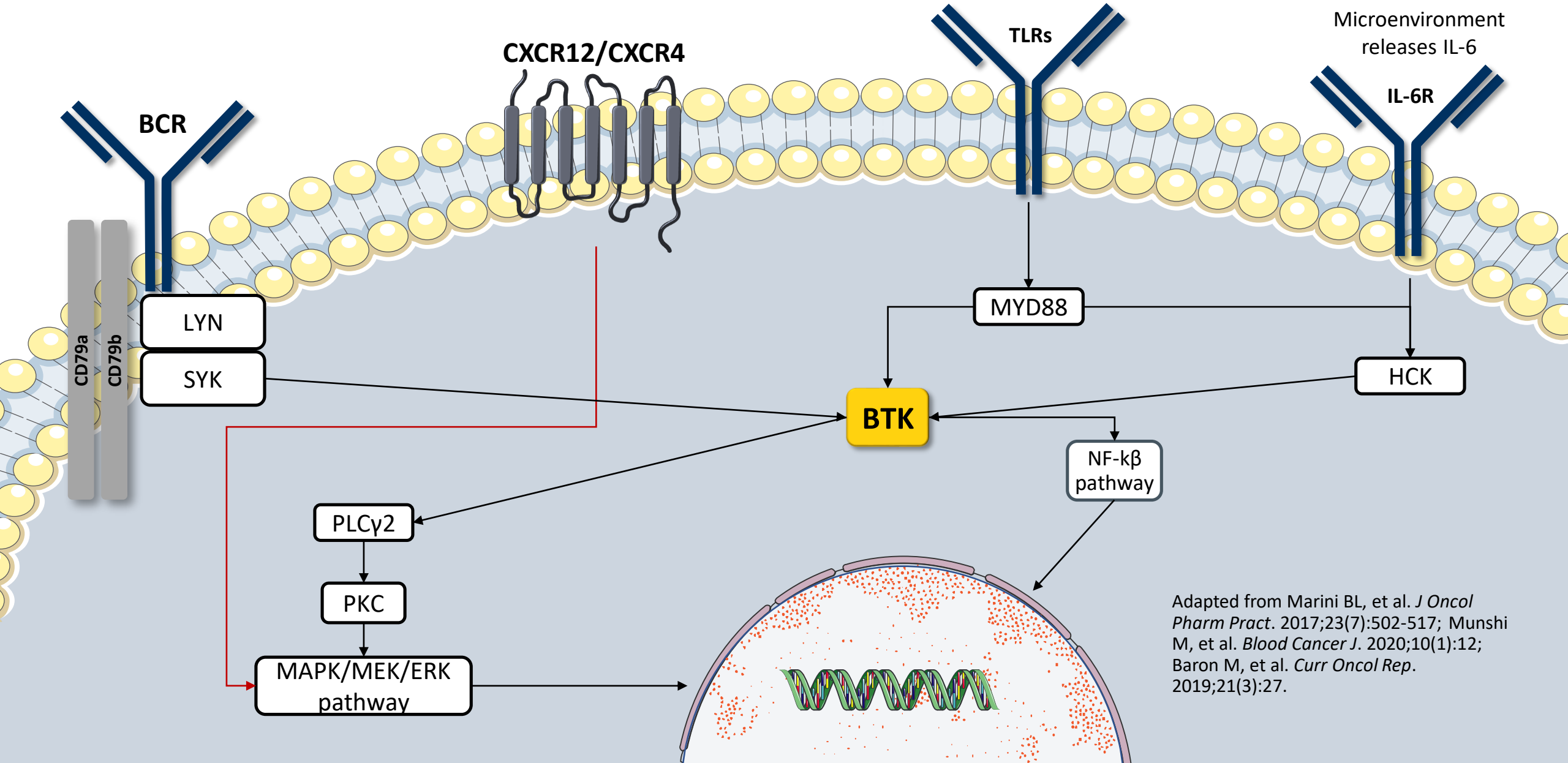


- **Incidence:**
  - <1% of NHL; 100-1500 new cases/year
- **Deaths:**
  - 60% OS at 5-years
- **Median age:** 63 years

- **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

NCCN Clinical Practice Guidelines in Oncology. Waldenström Macroglobulinemia/Lymphoplasmacytic Lymphoma v1.2020; Key statistics about Waldenstrom macroglobulinemia. American Cancer Society. Published July 19, 2018. Accessed May 5, 2020. cancer.org/cancer/waldenstrom-macroglobulinemia/about/key-statistics.html; Castillo JJ, Treon SP. *Leukemia*. 2019;33(11):2555-2562.

Revisited: Pathophysiology and Mechanism of Action in WM



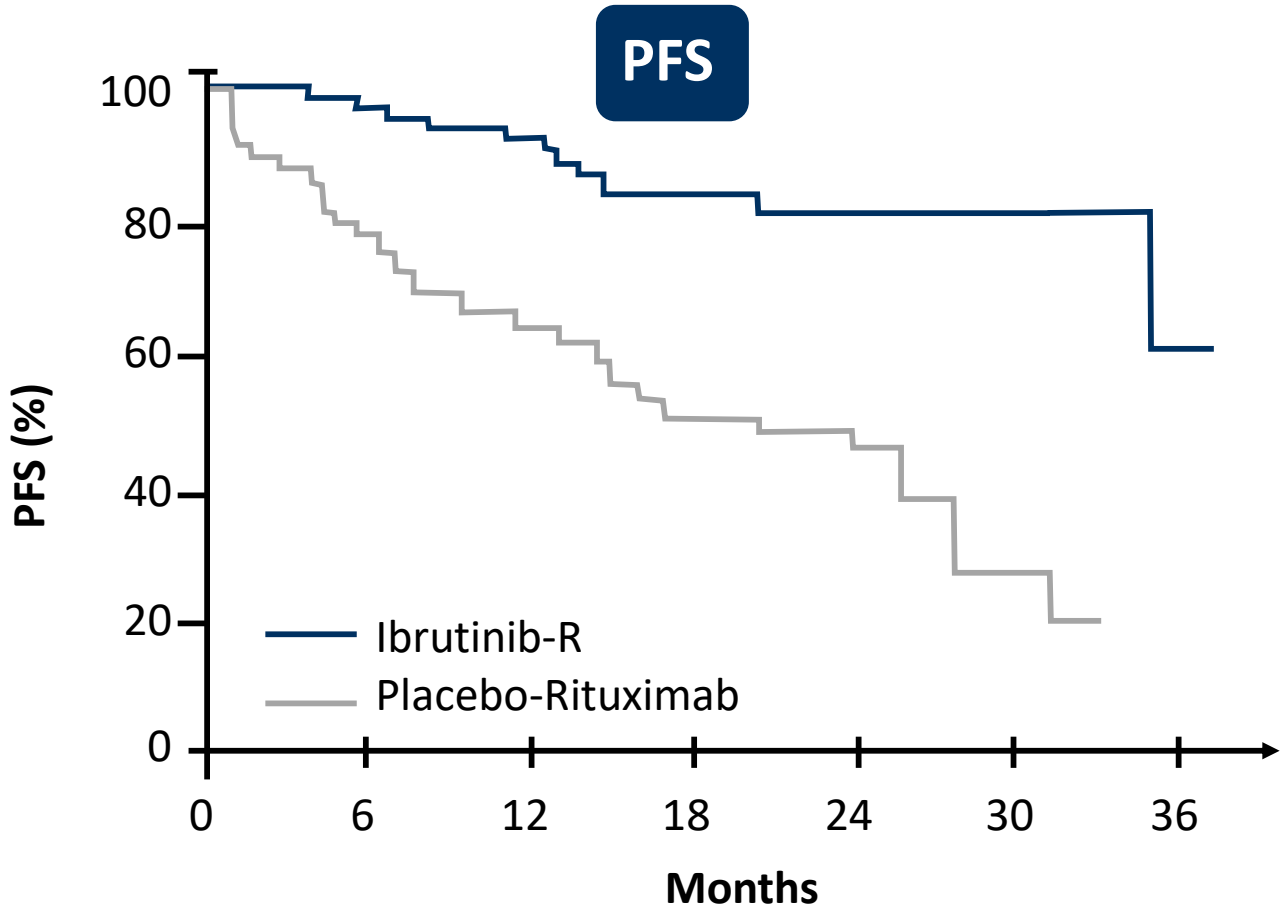
Adapted from Marini BL, et al. *J Oncol Pharm Pract*. 2017;23(7):502-517; Munshi M, et al. *Blood Cancer J*. 2020;10(1):12; Baron M, et al. *Curr Oncol Rep*. 2019;21(3):27.

iNNOVATE Trial
Ibrutinib + Rituximab vs Rituximab

End point	Ibrutinib-R (n = 75), %	Rituximab (n = 75), %	
ORR	92	47	p<0.001
CR	3	1	p<0.001
Very good PR	23	4	
PR	47	27	
Minor response	20	15	
Median serum IgM level	Decreased by 56%	Increased by 6%	

Dimopoulos MA, et al. *N Engl J Med*. 2018;378(25):2399-2410.

iNNOVATE Trial
Ibrutinib + Rituximab vs Rituximab



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

Dimopoulos MA, et al. *N Engl J Med*. 2018;378(25):2399-2410.

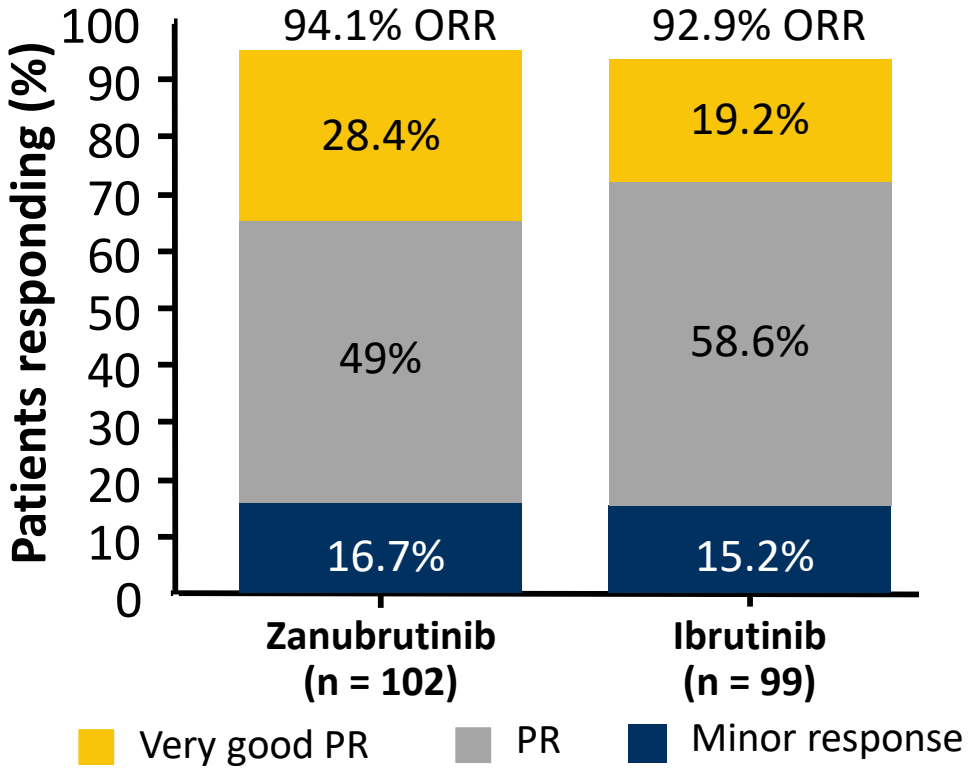
ACE-WM-001 Trial: Acalabrutinib for WM Results

End point	Treatment naïve (n = 14), %	R/R (n = 92), %
ORR	93	93
Very good PR	--	9
PR	79	72
Minor response	14	13

End point	$MYD88^{L265P}$ (n = 36)	$MYD88^{WT}$ (n = 14)
ORR	94	79
Very good PR	11	--
PR	69	64
Minor response	14	14

Owen RG, et al. *Lancet Haematol*. 2020;7(2):e112-e121.

Future Directions: ASPEN Trial
Zanubrutinib vs Ibrutinib



Look for future FDA guidance

Conclusions

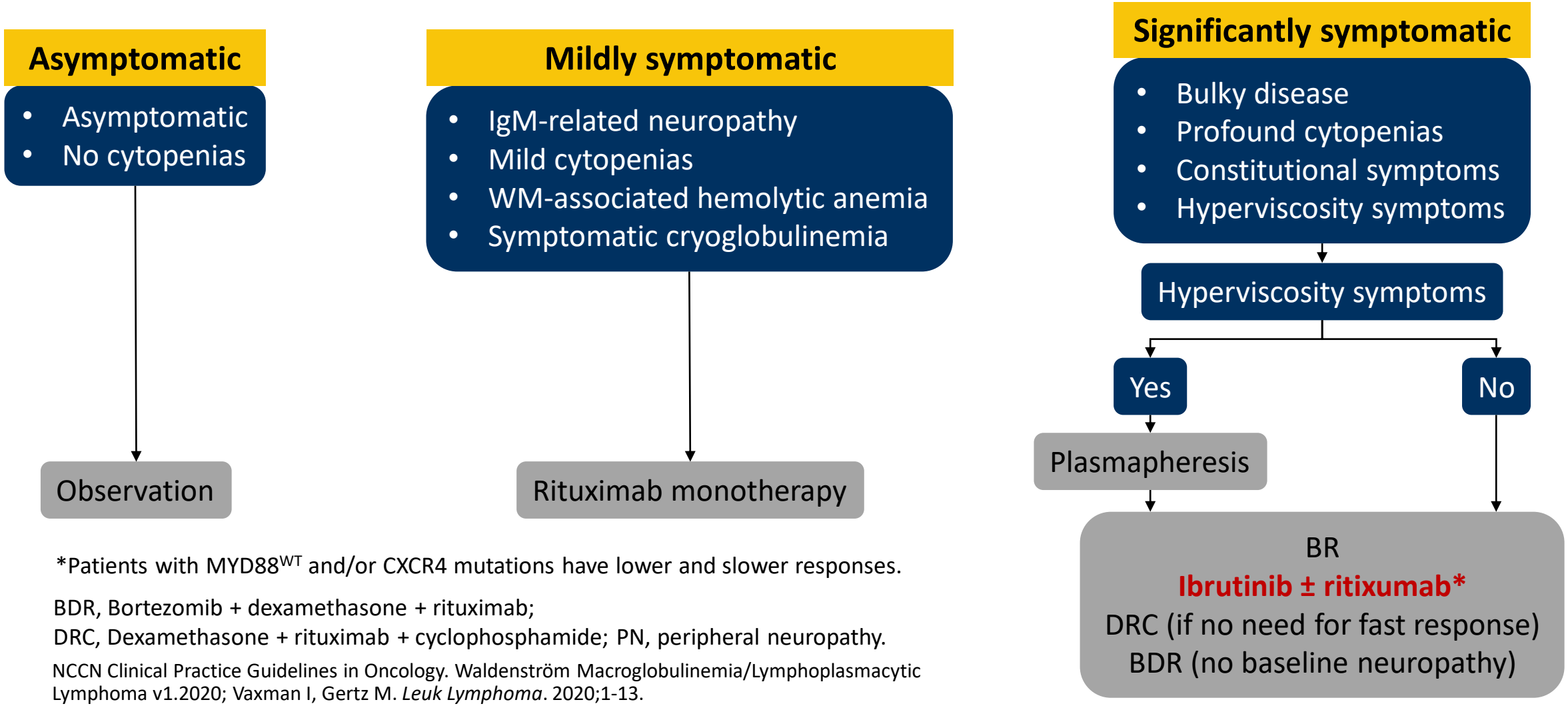
First randomized trial comparing 2 BTK inhibitors

Improved toxicity profile with zanubrutinib (not shown)

No significant differences in ORR, PFS, or OS

A Study Comparing BGB-3111 and Ibrutinib in Participants With Waldenström's Macroglobulinemia (WM) (ASPEN). ClinicalTrials.gov identifier: NCT03053440. Updated April 24, 2020. Accessed May 5, 2020. clinicaltrials.gov/ct2/show/NCT03053440?term=NCT03053440&draw=2&rank=1; BeiGene. News release. Published December 16, 2019. Accessed May 5, 2020. globenewswire.com/news-release/2019/12/16/1960839/0/en/BeiGene-Announces-Results-of-Phase-3-ASPEN-Trial-of- Zanubrutinib-Compared-to-Ibrutinib-for-the-Treatment-of-Patients-with-Waldenstr%C3%B6m-s-Macroglobulinemia.html

WM Treatment 2020 (First-Line Therapy)

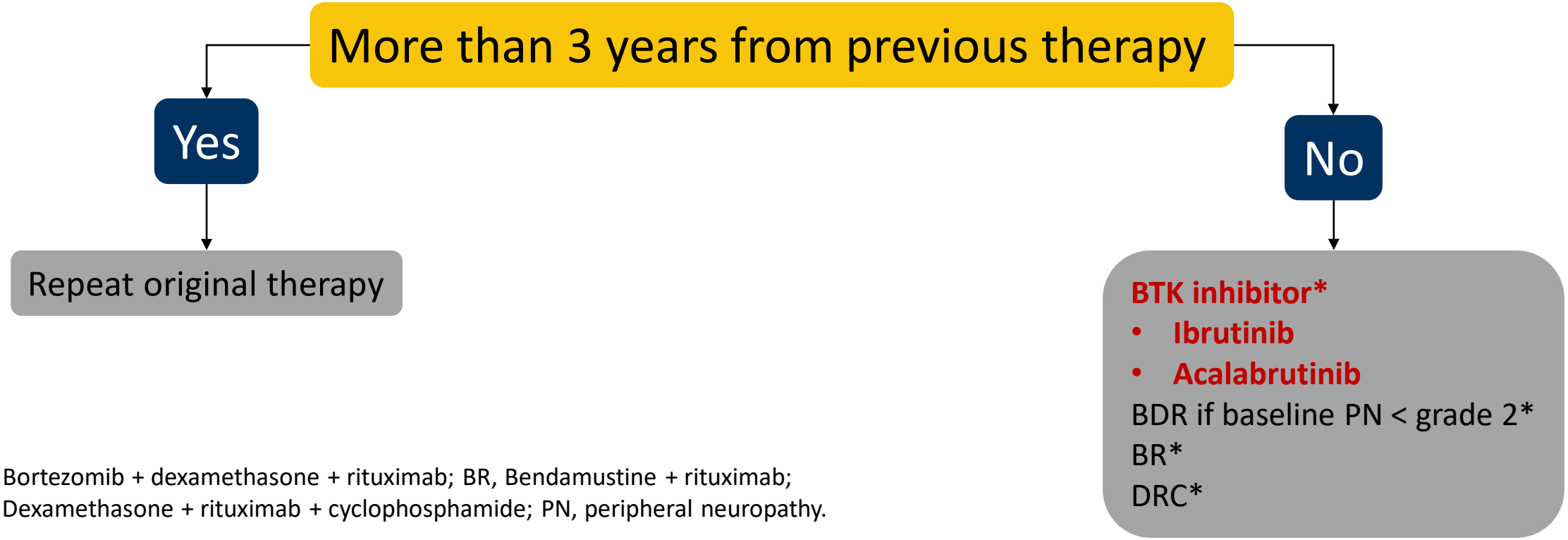


*Patients with MYD88^{WT} and/or CXCR4 mutations have lower and slower responses.

BDR, Bortezomib + dexamethasone + rituximab;
DRC, Dexamethasone + rituximab + cyclophosphamide; PN, peripheral neuropathy.

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

WM Treatment 2020 (R/R Therapy)



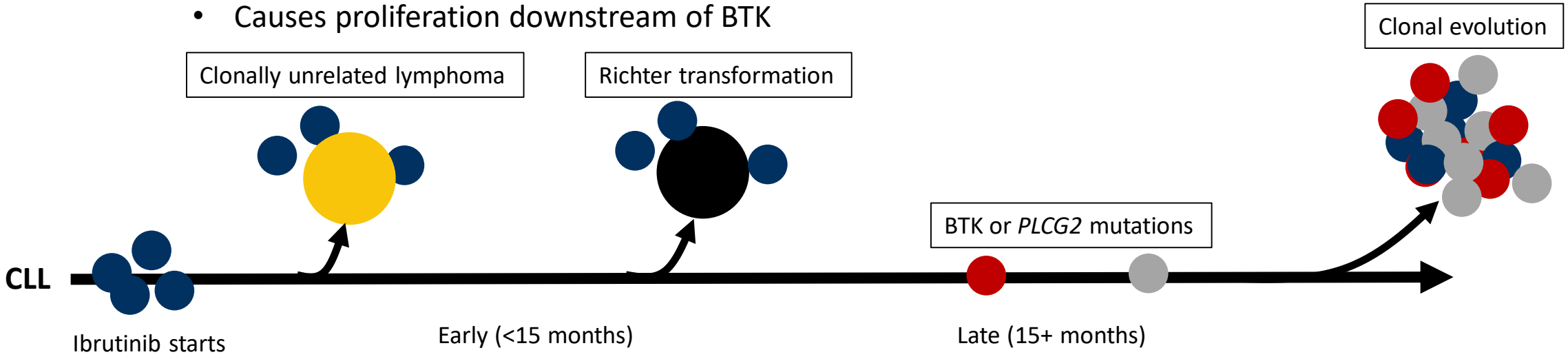
BDR, Bortezomib + dexamethasone + rituximab; BR, Bendamustine + rituximab; DRC, Dexamethasone + rituximab + cyclophosphamide; PN, peripheral neuropathy.

*If not previously received.

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

BTK Inhibitor Resistance

- Resistance in CLL more well described than MCL and WM
- 2 primary mediators of resistance
  - BTK point mutation (ie, BTK^{C481S}; others: C481R, C481F, and C481Y)
    - Changes irreversible BTK inhibitor to reversible inhibitor with decreased BTK binding affinity
  - *PLCG2* mutation (ie, R665W, S707Y, L845F)
    - Causes proliferation downstream of BTK



Woyach JA, et al. *N Engl J Med*. 2014;370(24):2286-2294; Woyach JA, et al. *J Clin Oncol*. 2017;35(13):1437-1443; Ahn IE, et al. *Blood*. 2017;129(11):1469-1479; Woyach JA, et al. *Blood*. 2019;134(suppl 1):504; Furman RR, et al. *N Engl J Med*. 2014;370(24):2352-2354; Jain P, et al. *Br J Haematol*. 2018;183(4):578-587; Jiménez C, et al. *Br J Haematol*. Published online February 27, 2020. doi: 10.111/bjh.16463

Novel Approaches to BTK Inhibitor Resistance/Progression

Approach	Agent
Reversible BTK inhibitors	ARQ-531, Loxo-305, ICP-022 (Orelabrutinib), SNS-062 (Vecabrutinib)
Different target	Venetoclax, CAR-T, idelalisib, duvelisib
Chemotherapy	Depends on clinical scenario and disease (ie, R-BAC for MCL)

Reiff SD, et al. *Blood.* 2016;128(22):Abstract 3232; Binnerts ME, et al. 2015 AACR-NCI-EORTC International Conference on Molecular Targets and Cancer Therapeutics. Abstract C186; Brandhuber B, et al. SOHO 2018. Abstract CLL-200; McCulloch R, et al. *Br J Haematol*. Published online February 3, 2020. doi: 10.1111/bjh.16416; Wang M, et al. *N Engl J Med*. 2020;382(14):1331-1342.

BTK Inhibitors for the Treatment of B-Cell Malignancies: Clinical Updates for Specialty Pharmacists

Kirollos S. Hanna, PharmD, BCPS, BCOP

Oncology Pharmacy Manager

M Health Fairview Maple Grove Minnesota

Assistant Professor of Pharmacy

Mayo Clinic College of Medicine

Rochester, Minnesota

Patient Case

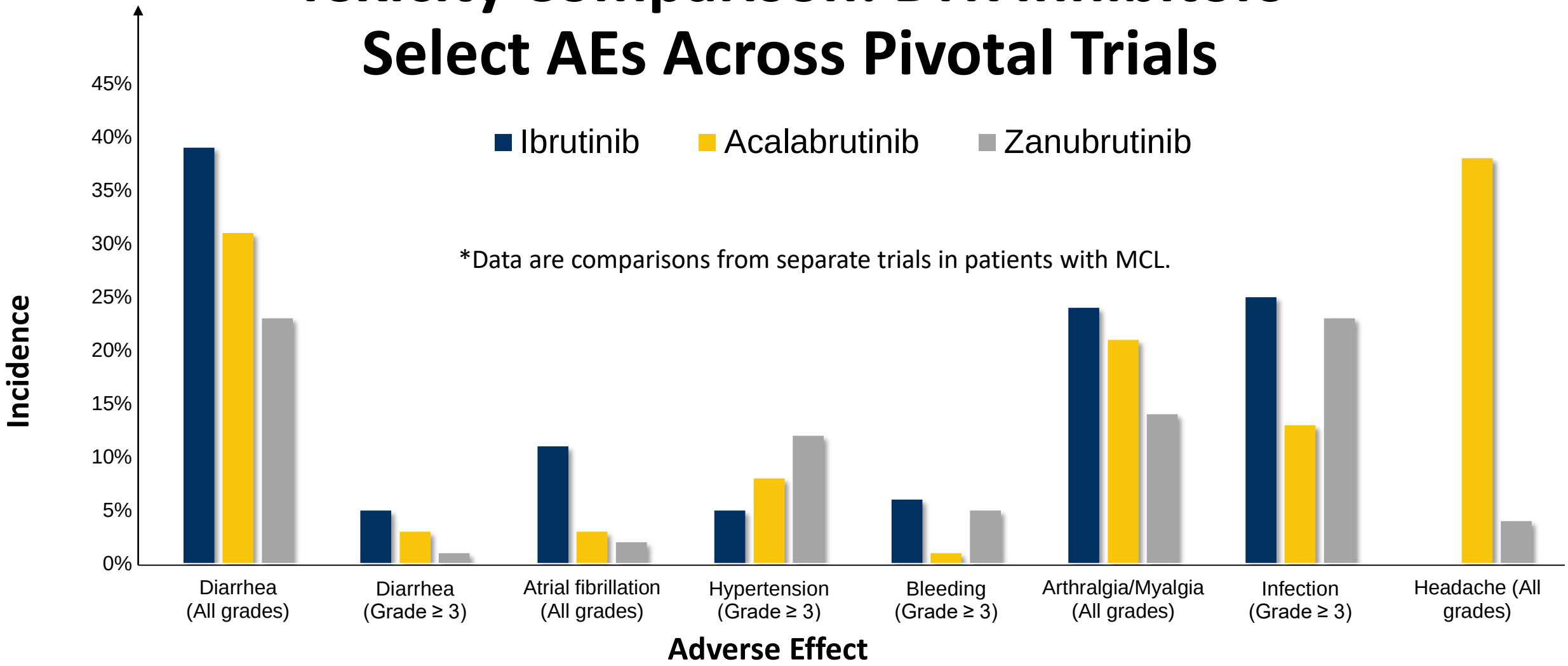
AJ is a 64-year-old man with relapsed MCL who is initiating therapy with zanubrutinib.

- **On what adverse effects would you counsel the patient?**
- **What supportive care recommendations would you make?**
- **How do we best coordinate efforts between the stakeholders in this patient's care including the primary oncology team and specialty pharmacy?**

Patient Counseling and Monitoring Plans

BTK Inhibitors for the Treatment of B-Cell Malignancies: Clinical Updates for Specialty Pharmacists

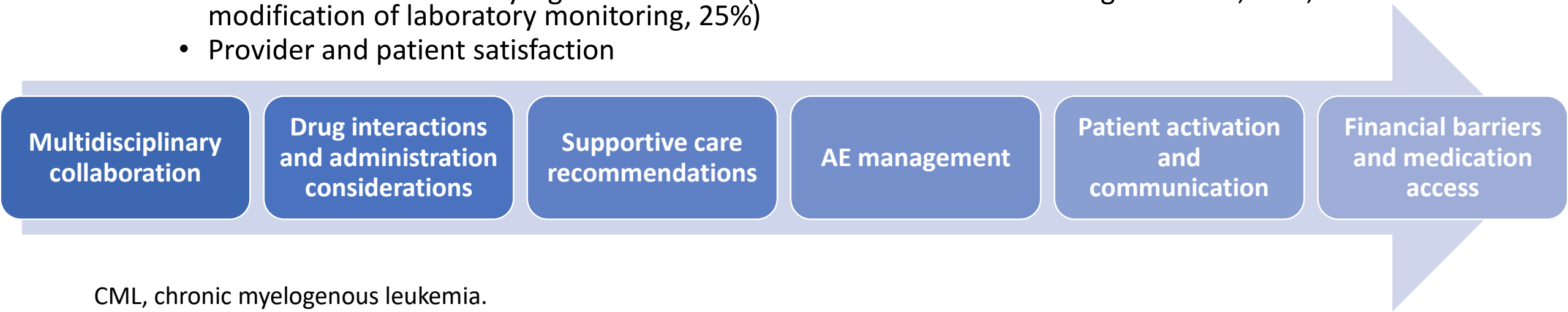
Toxicity Comparison: BTK Inhibitors Select AEs Across Pivotal Trials



Rule S, et al. *Haematologica*. 2019;104(5):e211-e214; Tam CS, et al. *Hematol Oncol*; 2019;37:245-247; Wang M, et al. *Lancet*. 2018;391(10121):659-667; Imbruvica. Prescribing information. Pharmacyclics LLC; 2020. Brukinsa. Prescribing information. BeiGene USA, Inc; 2019; Calquence. Prescribing information. AstraZeneca Pharmaceuticals LP; 2019.

Multidisciplinary Collaboration

- **Pharmacy-led oral chemotherapy management programs improved**
  - Patient knowledge, adherence rates that exceeded nationally established thresholds, superior response outcomes in CML
  - Adherence to national oral chemotherapy prescribing standards
  - Time to medication access
  - Identification of clinically significant issues (most common: adverse drug reactions, 40%; modification of laboratory monitoring, 25%)
  - Provider and patient satisfaction



CML, chronic myelogenous leukemia.

Hansen EA, et al. *J Pharm Pract*. 2016;29(3):206-211; Holle LM, et al. *J Oncol Pharm Pract*. 2016;22(3):511-516; Lam MS, et al. *J Oncol Pharm Pract*. 2016;22(6):741-748; Muluneh B, et al. *J Oncol Pract*. 2018;14(6):e324-e334; Perez A, et al. *J Hematol Oncol Pharm.* 2015;5:99-108; Mancini R, et al. *J Clin Oncol.* 2012;30(suppl):Abstract 44; Koselke E, et al. *J Hematol Oncol Pharm.* 2015;5:62-68; Mackler E, et al. *J Oncol Pract.* 2019;15(4):e346-e355.

Characteristics of BTK Therapies

Agent	Metabolism and transport	Concurrent CYP3A4 inhibitor	Concurrent CYP3A4 inducer	Concurrent acid suppression
Ibrutinib	Substrate: CYP2D6 (minor), CYP3A4 (major)	Moderate: Reduce to 280 mg PO daily Strong (posaconazole): Reduce to 70 mg PO daily Strong (other): Avoid	Strong: Avoid	N/A
Acalabrutinib	Substrate: CYP3A4 (major), P-gp, BCRP/ABCG2	Strong: Avoid Moderate: Reduce to 100 mg PO daily	Strong: Increase to 200 mg PO bid	Separate antacids by 2 hours; take acalabrutinib 2 hours prior to H2RAs; avoid PPIs
Zanubrutinib	Substrate: CYP3A4 (major)	Strong: Reduce to 80 mg PO daily Moderate: Reduce to 80 mg PO twice daily	Moderate or Strong: avoid	N/A

BCRP, breast cancer resistance protein; H2RA, H2 receptor antagonist; PPI, proton pump inhibitor.

Imbruvica. Prescribing information. Pharmacyclics LLC; 2020. Brukinsa. Prescribing information. BeiGene USA, Inc; 2019; Calquence. Prescribing information. AstraZeneca Pharmaceuticals LP; 2019.

Administration of Oral BTK Therapies

Agent	Pill burden	Frequency	Effect of food	Missed dose recommendations
Ibrutinib	1 tablet	Daily	Administer with **OR** without food	Same day ASAP
Acalabrutinib	1 capsule (100 mg)	BID	Administer with **OR** without food; high-fat, high-calorie meal decreases C_{max} by 73% and T_{max} delayed 1 or 2 hours	Within 3 hours otherwise skip
Zanubrutinib	2-4 capsules (80 mg)	Daily or BID	Administer with **OR** without food	Same day ASAP

Imbruvica. Prescribing information. Pharmacyclics LLC; 2020. Brukinsa. Prescribing information. BeiGene USA, Inc; 2019; Calquence. Prescribing information. AstraZeneca Pharmaceuticals LP; 2019.

Infection Prophylaxis: No Standard for BTK Inhibitor

CLL agent	*Pneumocystis jirovecii* pneumonia (PJP)	Herpes simplex virus (HSV)	Cytomegalovirus (CMV)	Hepatitis B (HepB)
Agent for prophylaxis or monitoring	Sulfamethoxazole/ trimethoprim or equivalent	Acyclovir or equivalent	CMV PCR Q2-3W	High-risk: prophylaxis and monitoring
Acalabrutinib				
Ibrutinib				
Zanubrutinib				
Duvelisib	X		X	
Idelalisib	X		X	
Purine analog	X	X	X	
Venetoclax				
Bendamustine	X	X	X	
Alemtuzumab	X	X	X	
Anti-CD20				X

Consider prophylaxis with BTK inhibitor for "high-risk" patients

HepB
Fungal PNA
PJP
EBV
CMV

EBV, Epstein-Barr virus; PNA, pneumonia.

NCCN Clinical Practice Guidelines in Oncology. Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma v4.2020; Imbruvica. Prescribing information. Pharmacyclics LLC; 2020; Brukinsa. Prescribing information. BeiGene USA, Inc; 2019; Calquence. Prescribing information. AstraZeneca Pharmaceuticals LP; 2019; Copiktra. Prescribing information. Verastem Oncology; 2019; Zydelig. Prescribing information. Gilead Sciences Inc; 2018; Venclexta. Prescribing information. AbbVie Inc; 2019.

Adverse Effect Management

BTK Inhibitors for the Treatment of B-Cell Malignancies:
Clinical Updates for Specialty Pharmacists

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

PMN, polymorphonuclear leukocyte.

Berglöf A, et al. *Scand J Immunol*. 2015;82(3):208; Shatzel JJ, et al. *J Thromb Haemost*. 2017;15(5):835-847; Bye AP, et al. *Blood Adv.* 2017;1(26):2610-2623; Ghez D, et al. *Blood*. 2018;131(17):1955-1959; Woyach JA. *Blood*. 2018;132(18):1869-1870; Rogers K. *Blood*. 2018;131(17):1882-1884; Ruchlemer R, et al. *Mycoses*. 2019;62(12):1140-1147; Rogers KA, et al. *Leukemia*. 2019;33(10):2527-2530; Bose P, et al. *Expert Opin Drug Metab Toxicol*. 2016;12(11):1381-1392.

Ibrutinib Safety in the "Real World"

- Multicenter, retrospective analysis of patients with CLL treated in clinics and clinical trials (N = 616)

Discontinuation rate: 42% after median follow-up of 17 months

Reasons for discontinuation (%)	
Front line	**Relapsed**
Arthralgias (42)	Atrial fibrillation (12.3)
Atrial fibrillation (25)	Infection (11)
Rash (16)	Pneumonitis (10)
	Bleeding (9)
	Diarrhea (7)

- Of note, BTK C481S mutations render patients refractory to BTK therapies

Mato AR, et al. *Haematologica*. 2018;103(5):874-879; Dickerson T, et al. *Blood*. 2019;134(22):1919-1928.

Retrospective review from Ohio State

- 78.3% new or worsened hypertension (HTN) over a median of 30 months
- New HTN in 71.6% of ibrutinib users; 17.7% developed high-grade HTN (BP >160/100 mm Hg)
- 50% cumulative incidence of 4.2 months
- New or worsened HTN was associated with increased major adverse cardiovascular effects (HR, 2.17; 95% CI, 1.08-4.38)
- No single antihypertensive class was associated with prevention or control of ibrutinib-related HTN

Safety of Acalabrutinib from ASCEND

Adverse reaction	Acalabrutuinib (n = 154)		Idelalisib + R (n = 118)		BR (n = 35)	
	All grades (%)	Grade ≥3 (%)	All grades (%)	Grade ≥3 (%)	All grades (%)	Grade ≥3 (%)
Infections	56	15	65	28	49	11
Neutropenia	48	23	79	53	80	40
Anemia	47	15	45	8	57	17
Thrombocytopenia	33	6	41	13	54	6
Lymphocytosis	26	19	23	18	2.9	2.9
Headache	22	0.6	6	0	0	0
Diarrhea	18	1.3	49	25	14	0
Hemorrhage	16	1.3	5	1.7	6	2.9
Fatigue	15	1.9	13	0.8	31	6
Musculoskeletal pain	15	1.3	15	1.7	2.9	0

Calquence. Prescribing information. AstraZeneca Pharmaceuticals LP; 2019.

Safety of Zanubrutinib from BGB-3111 Trials

Adverse reaction	Zanubrutinib (n = 118)	
	All grades (%)	Grade ≥3 (%)
Neutropenia	38	15
Thrombocytopenia	27	5
WBC decrease	25	5
Anemia	14	8
URTI	39	0
Pneumonia	15	10
Urinary tract infection	11	0.8
Rash	36	0
Diarrhea	23	0.8
Hypertension	12	3.4
Hemorrhage	11	3.4

URTI, upper respiratory tract infection.

Brukinsa. Prescribing information. BeiGene USA, Inc; 2019.

Management of Ibrutinib AEs and Pearls

Ibrutinib

- Muscle cramps: magnesium and calcium tablets
- Hypertension: standard management, discontinue if 2-3 meds required
  - Median time to onset, 5.9 months (range, 0.03–24 months)
- Arthralgias/myalgias
  - Acetaminophen, prednisone, quinine/tonic water, discontinue
- Leg lymphedema: discontinue
- Fatigue: reduce dose/discontinue

- For patients who experience grade 3/4 nonhematologic AEs, ibrutinib should be held until resolution to baseline or grade 1
- Once resolved, restart at:
  - 1st occurrence: **starting dose of 420 mg PO daily for CLL or WM; 560 mg PO daily for MCL or MZL**
  - 2nd/3rd recurrence: **decrease dose by 140 mg per recurrence**
  - 4th recurrence: **discontinue**
- Mid-cycle trade-in program available

Weerdt I, et al. *Haematologica*. 2017;102(10):1629-1639; Imbruvica. Prescribing information. Pharmacyclics LLC; 2020.

Management of Acalabrutinib AEs and Pearls

Acalabrutinib

- Headaches
  - Acetaminophen, caffeine, hydration
- Arm skin thickening/lymphedema
  - Discontinue
- HTN
  - Standard management: discontinue if 2-3 meds required

- For patients who experience grade 3/4 nonhematologic AEs, acalabrutinib should be held until resolution to baseline or grade 1
- Once resolved, restart at:
  - 1st or 2nd recurrence: restart at **starting dose (100 mg twice daily)**
  - 3rd recurrence: restart **at 100 mg once daily**
  - **4th recurrence:** acalabrutinib should be discontinued
- Mid-cycle trade-in program available

Calquence. Prescribing information. AstraZeneca Pharmaceuticals LP; 2019.

Management of Zanubrutinib AEs

Zanubrutinib

- Rash: topical emollients or corticosteroids
- Diarrhea: if no evidence of infection, antidiarrheals as needed
- Infection: monitor and treat as needed
- Hypertension: standard management, discontinue if 2-3 meds required

- For grade 3/4 nonhematologic AEs, zanubrutinib should be held until resolution to baseline or grade 1
- Once resolved, restart at:
  - 1st occurrence: **320 mg PO once daily (or 160 mg PO BID)**
  - 2nd recurrence: **160 mg PO once daily (or 80 mg PO BID)**
  - 3rd recurrence: **80 mg PO once daily**
  - 4th recurrence: discontinue
- Mid-cycle trade-in program available

Brukinsa. Prescribing information. BeiGene USA, Inc; 2019.

Other AEs of Interest: Atrial Fibrillation

All Grades:
Ibrutinib (8.4%) > Acalabrutinib (4.1%) > Zanubrutinib (2%)

Prevention

- Monitor for signs and symptoms: palpitations, lightheadedness, dizziness, fainting, shortness of breath, chest discomfort

Management

- If CHA_2DS_2-VASc score ≥2, guidelines recommend anticoagulation
- Consider non-warfarin anticoagulation
  - In combination with ibrutinib, prefer rivaroxaban or apixaban
- Monitor carefully; if uncontrolled, consider switching to alternative therapy

Weerdt I, et al. *Haematologica*. 2017;102(10):1629-1639; Imbruvica. Prescribing information. Pharmacyclics LLC; 2020; Chai LK, et al. *Leuk Lymphoma*. 2017;58(12):2811-2814; Calquence. Prescribing information. AstraZeneca Pharmaceuticals LP; 2019; Jones JA, et al. *Br J Haematol*. 2017;178(2):286-291; Brukinsa. Prescribing information. BeiGene USA, Inc; 2019.

Other AEs of Interest: Bleeding

Major Bleeding:
Ibrutinib (4%) > Acalabrutinib (3%) > Zanubrutinib (2%)

Prevention

- Impact of platelet aggregation is reversible within 1 week of discontinuation
- Clinical trials excluded patients receiving warfarin
- Consider risks and benefits with antiplatelet and anticoagulation therapy
- Monitor for signs of bleeding
- Surgery: Evaluate risk and benefit
  - All BTK inhibitors
    - Hold for 3 days pre and 3 days post surgery; consider the benefit-risk for 3-7 days pre and post surgery
    - Minor surgery: hold for 3 days pre and 3 days post surgery
    - Major surgery: hold for 7 days pre and 7 days post surgery

Weerdt I, et al. *Haematologica*. 2017;102(10):1629-1639; Imbruvica. Prescribing information. Pharmacyclics LLC; 2020; Chai LK, et al. *Leuk Lymphoma*. 2017;58(12):2811-2814; Calquence. Prescribing information. AstraZeneca Pharmaceuticals LP; 2019; Jones JA, et al. *Br J Haematol*. 2017;178(2):286-291; Brukinsa. Prescribing information. BeiGene USA, Inc; 2019.

Treatment-Related Lymphocytosis

Lymphocytosis does <u>NOT</u> indicate progressive disease.

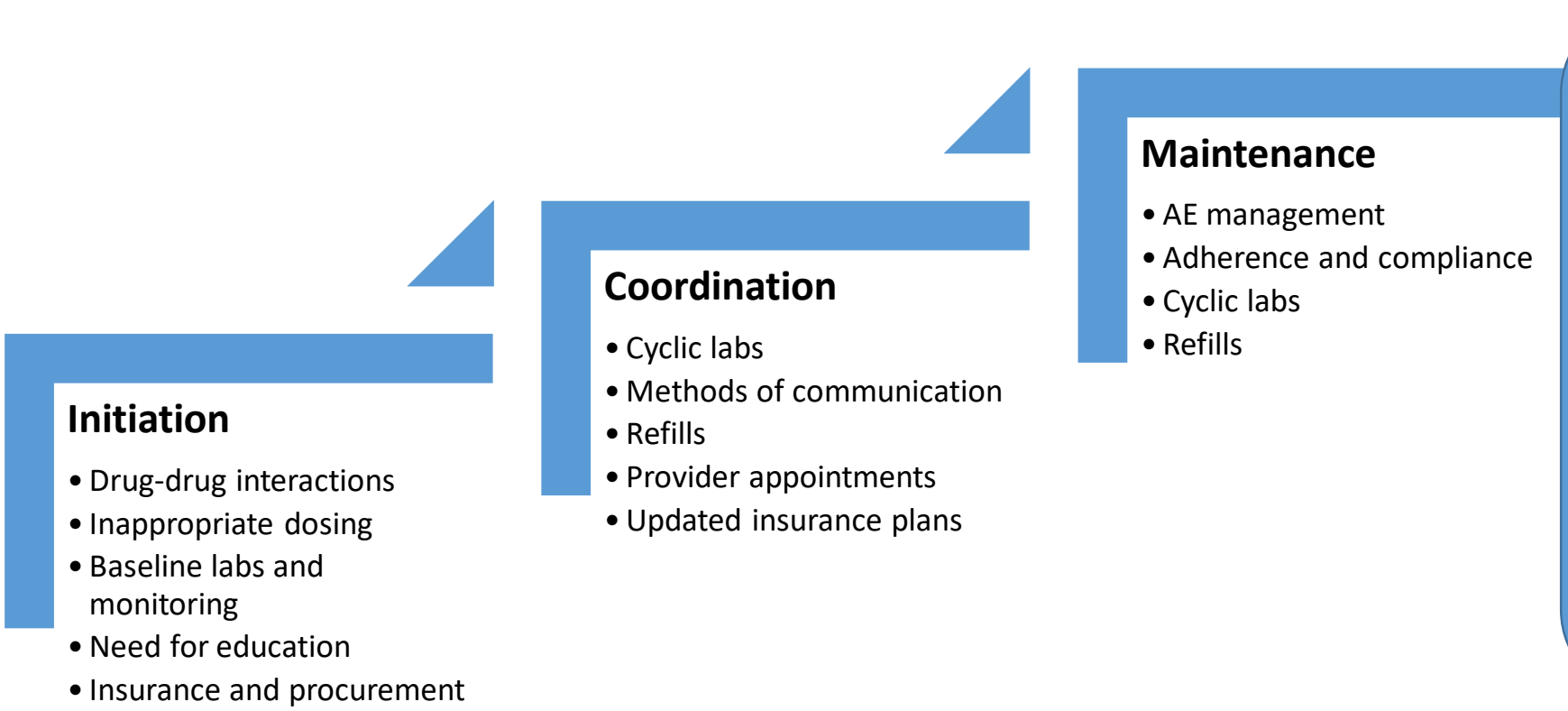
- Lymphocytosis occurs with many therapies used to treat B-cell malignancies
- BTK inhibitors lead to transient lymphocytosis due to redistribution or release of cells from lymph nodes to peripheral blood
- Often resolves within 8 months from <u>treatment initiation</u> (prolonged durations have been reported)

Chanan-Khan A, et al. *Cancer*. 2011;117(10):2127-2135; Woyach JA, et al. *Blood*. 2014;123(12):1810-1817; Brown JR, et al. *Blood.* 2014;123(22):3390-3397; NCCN Clinical Practice Guidelines in Oncology. Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma v4.2020.

Patient Activation and Communication

BTK Inhibitors for the Treatment of B-Cell Malignancies: Clinical Updates for Specialty Pharmacists

Oral Chemotherapy Logistics



Need for medically integrated model

Pharmacists provide **clinical considerations** and **operational best practices** to optimize oral chemotherapy dispensing and management.

Timmers L, et al. *BMC Cancer*. 2017;17(1):122; Mulkerin DL, et al. *J Oncol Pract*. 2016;12(10):e912-e923; Battis B, et al. *J Oncol Pharm Pract*. 2017;23(8):582-590.

Barriers: Medication Persistence

The first year is critical.

Time to 

4.1 months
- Severe AE/intolerance

5.6 months
- Non-severe AE/intolerance

9.1 months
- Disease progression

Mato AR, et al. *Cancer Biol Ther*. 2018;19(7):636-643.

Impact of Adherence on Efficacy

Study design	Retrospective sub-analysis from RESONATE trial evaluating effect of ibrutinib dose adherence on patient outcomes

Methods	• Treatment adherence measured by overall dose intensity ($DI_{overall}$) and 8-week DI ($DI_{8\text{-week}}$)
	  • DI defined as proportion of administered vs planned doses
	  • Patients with DI below mean considered “low DI”

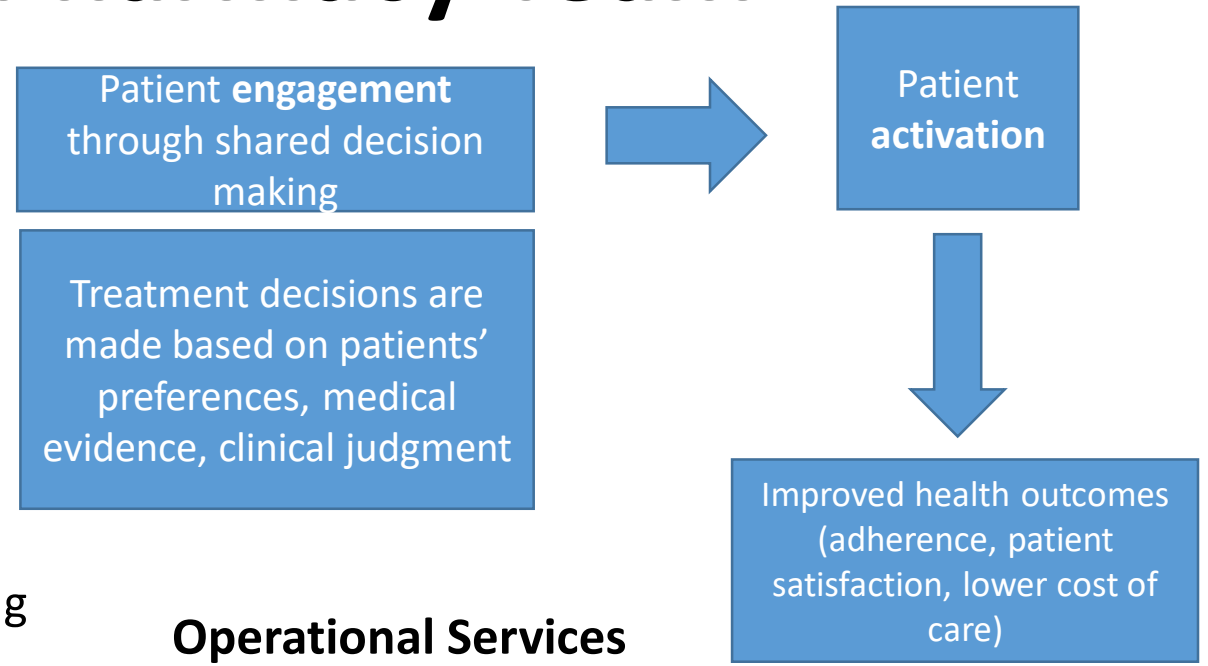
Results	• Fewer PFS events in patients with high $DI_{overall}$ vs low $DI_{overall}$ (12% vs 33%) • Patients who missed ≥8 consecutive days experienced more PFS events (30% vs 12%) with decrease in PFS (10.9 months vs NR, *P* = 0.0151) than those who missed <8 days

Barr PM, et al. *Blood*. 2017;129(19):2612-2615.

Role of the Pharmacy Team

Clinical Services

- Adherence
- Education/counseling
  - Disease state
  - Medication
  - Storage, handling, administration, and disposal
  - When and whom to contact with questions/concerns
- Comprehensive medication review (ie, drug-drug interactions, concurrent CLL therapies)
- Monitoring
  - Efficacy
  - Safety: toxicity management



Operational Services

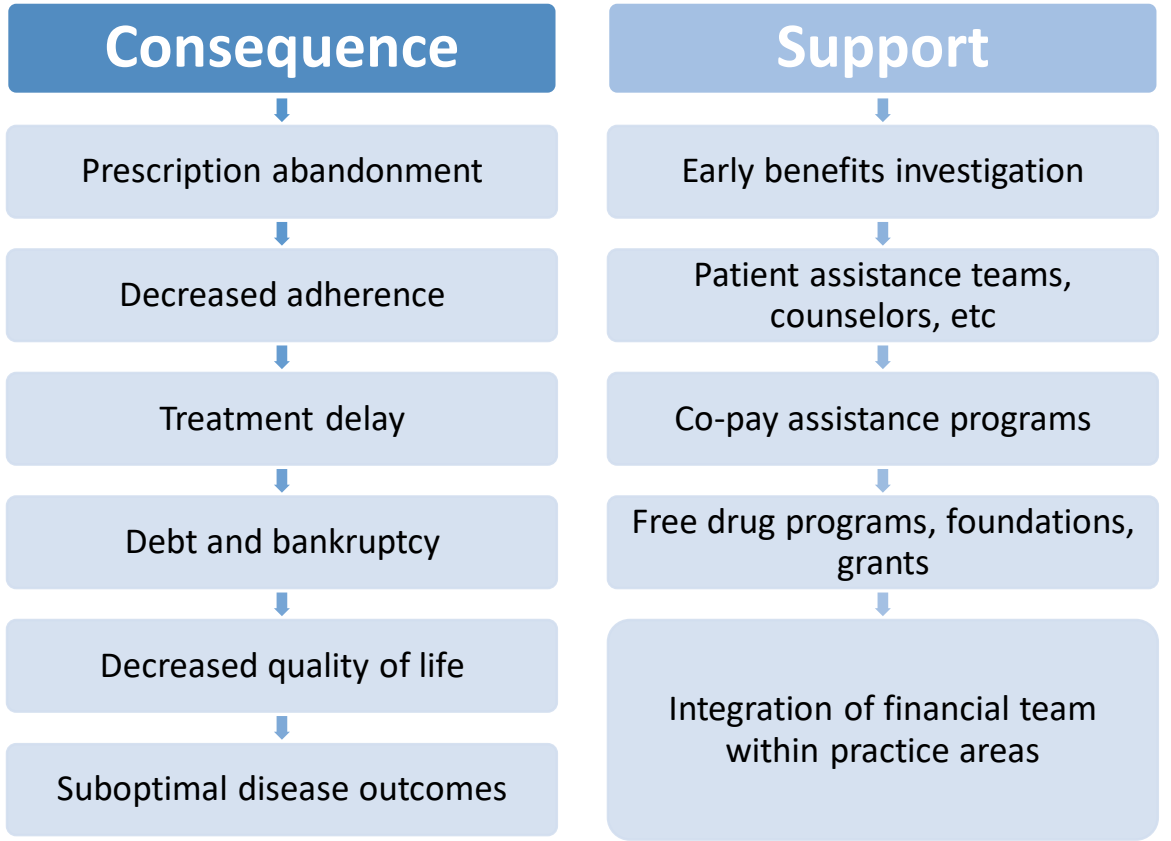
- Benefits investigation
- Patient assistance programs
- Dispensing and shipping
- Refills and renewals

Hibbard JH, et al. *Health Aff (Millwood)*. 2013;32(2):207-214; Hibbard JH, et al. *Health Aff (Millwood).* 2013;32(2):216-222; Carman KL, et al. *Health Aff (Millwood).* 2013;32(2):223-231.

Financial Burden

Agent	AWP for 30 days of therapy
Acalabrutinib (100 mg PO bid)	$16,876.80
Zanubrutinib (320 mg PO daily)	$15,522.00
Ibrutinib (420 mg PO daily)	$14,616.00

AWP, average wholesale price.

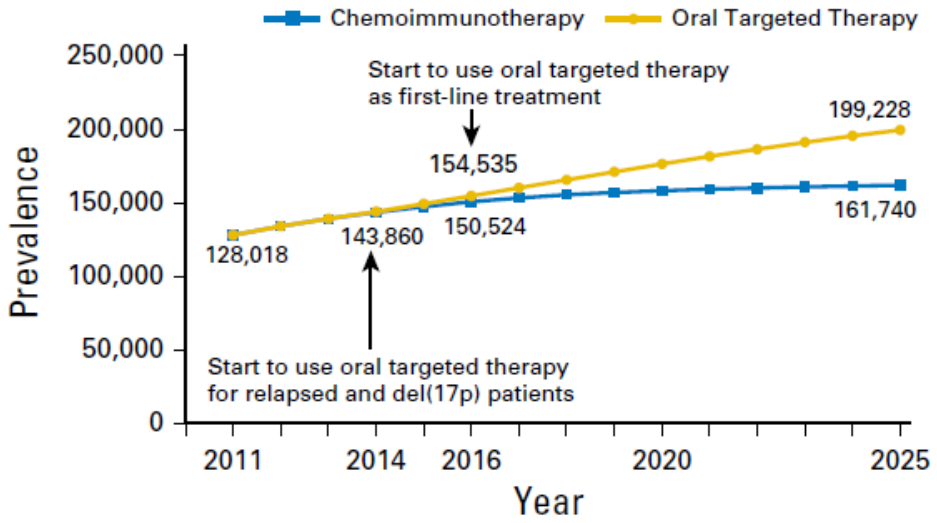


Acalabrutinib: drug information. Lexicomp database. Accessed February 24, 2020; Zanubrutinib: drug information. Lexicomp database. Accessed February 24, 2020; Ibrutinib: drug information. Lexicomp database. Accessed February 24, 2020; Doshi JA, et al. *J Clin Oncol*. 2018;36(5):476-482; Doshi JA, et al. *J Clin Oncol*. 2018;36(5):476-482; Niccolai JL, et al. *J Oncol Pract*. 2017;13(1):e29-e36; Tran G, et al. *Ann Transl Med.* 2018;6(9):166.

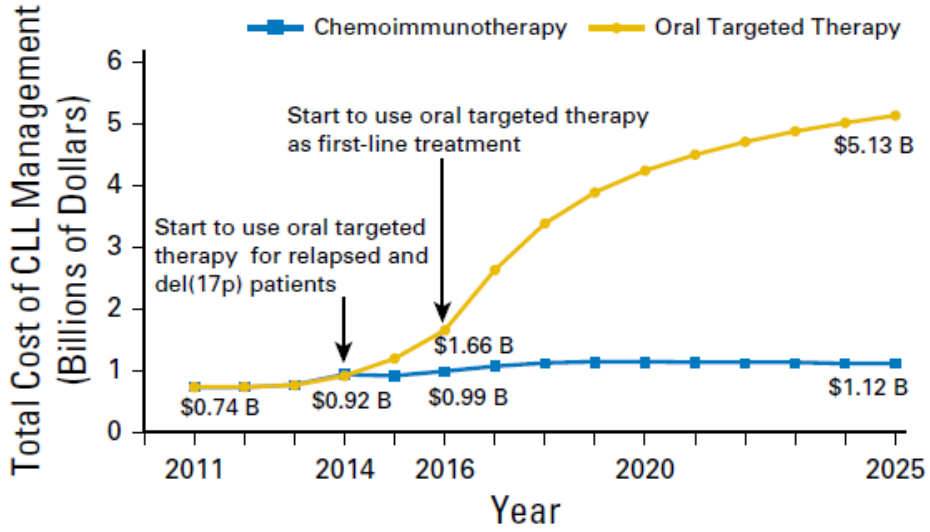
Economics of Novel Agents in CLL

Trend in disease and cost burden of CLL for the chemoimmunotherapy and the oral targeted therapy scenarios.

A: Number of patients with CLL



B: Annual management costs of CLL



- **Prevalence 2011-2025:** Increasing by **55%** (128K-199K)
- **Annual cost of CLL management:** Increasing by **590%** ($0.74B-$5.13B)
- **Per-patient lifetime cost of therapy:** Increasing by **310%** ($147K-$604K)
  - **Medicare total out-of-pocket cost:** Increasing by **520%** ($9.2K-$57K)

Chen Q, et al. *J Clin Oncol.* 25(2), 2016:166-174. Reprinted with permission © 2017 American Society of Clinical Oncology. All rights reserved.

Patient Case Discussion

AJ is a 64-year-old man with relapsed MCL who is initiating therapy with zanubrutinib.

- On what adverse effects would you counsel the patient?
- What supportive care recommendations would you make?
- How often should be this patient be monitored?

Patient Case Discussion

AJ is a 64-year-old man with relapsed MCL who is initiating therapy with zanubrutinib.

- **How do we best coordinate efforts between the stakeholders in this patient's care including the primary oncology team and specialty pharmacy?**
  - Who will provide education?
  - Who will review financial assistance and access?
  - Who will provide monitoring?
  - Who is responsible for follow-up and continual assessment?

Conclusion

- **B-cell malignancies are hematologic malignancies that differ greatly based on the stage of maturation of the cancerous cell and include CLL/SLL, NHLs, and WM**
  - Patients with CLL/SLL may never require treatment and others require aggressive therapy up front
  - MCL and MZL often require treatment at diagnosis with intensive therapies ± stem cell transplant
  - WM, a rare subtype, is often treated when patients become symptomatic
- **BTK inhibitors have demonstrated strong efficacy and a well-tolerated safety profile in the management of B-cell malignancies**
  - Treatment with ibrutinib, acalabrutinib, and zanubrutinib should be tailored to the specific malignancy, patient comorbidities, and ability to adhere to oral therapy
  - In select scenarios, BTK inhibitors may be combined with other agents such as anti-CD20 monoclonal antibodies
- **Pharmacists play an integral role in the management of patients with B-cell malignancies through education, AE management, drug–drug interactions, adherence and compliance, and financial procurement**

Additional Resources

- Armitage JO, Gascoyne RD, Lunning MA, et al. Non-Hodgkin lymphoma. *Lancet*. 2017;390(10091):298-310.
- Vose JM. Mantle cell lymphoma: 2017 update on diagnosis, risk-stratification, and clinical management. *Am J Hematol*. 2017;92(8):806-813.
- Khan N, Moskowitz AJ. Where do the new drugs fit in for relapsed/refractory Hodgkin lymphoma? *Curr Hematol Malig Rep*. 2017;12(3):227-233.
- Dimopoulos MA, Kastritis E. How I treat Waldenström macroglobulinemia. *Blood*. 2019;134(23):2022-2035.
- Lee SQ, Raamkumar AS, Li J, et al. Reasons for primary medication nonadherence: a systematic review and metric analysis. *J Manag Care Spec Pharm*. 2018;24(8):778-794.
- Kavookjian J, Wittayanukorn S. Interventions for adherence with oral chemotherapy in hematological malignancies: a systematic review. *Res Social Admin Pharm*. 2015;11(3):303-314.
- Oral chemotherapy education sheets. Available at: oralchemoedsheets.com

THANK YOU!

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