# Optimizing Safety and Efficacy of BTK Inhibitors Within the Health System With the Use of Digital Strategies



PTce ONCOLOGY

# Faculty Information

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# Educational Objectives

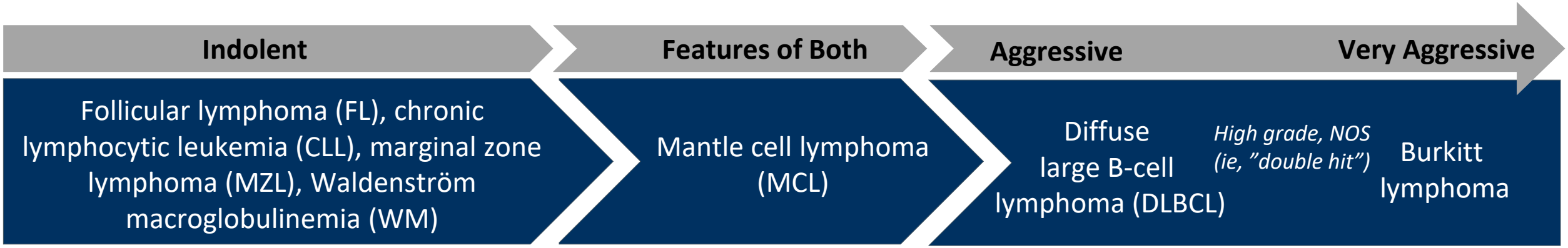
*After completion of this activity, participants will be able to:*

- Compare the efficacy of oral BTK inhibitors across B-cell malignancies including a focus on emerging clinical data
- Identify pharmacists' responsibilities for monitoring and managing cardiac adverse effects specific to different health-system practice types
- Determine the pharmacist's role in implementing digital and telemedicine technologies within the health system to improve adherence and provide remote patient monitoring and management

# Setting the Stage

*The Shifting Treatment Paradigm in B-cell Malignancies*

# Overview of B-cell Non-Hodgkin Lymphoma (NHL)




**102,810**

**estimated new cases** of NHL + CLL diagnosed in the United States, 2021

**25,040**

**estimated deaths** from NHL + CLL in the United States, 2021

NOS, not otherwise specified.

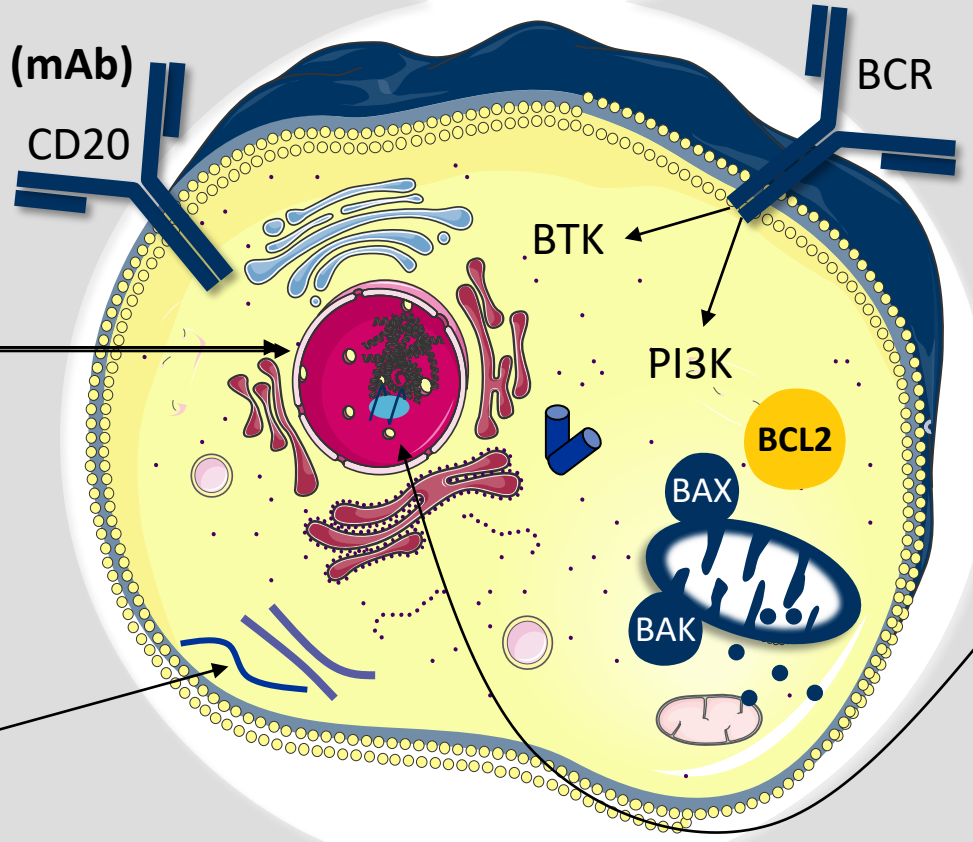
Siegel RL, et al. *CA Cancer J Clin.* 2021;71(1):7-33; Al-Hamadani M, et al. *Am J Hematol*. 2015;90(9):790-795.

# Trends in Oral Oncolytic Use

**Intravenous (IV) Therapies** → **Oral Therapies**

**Anti-CD20 Monoclonal Antibodies (mAb)**
1. Obinutuzumab (O)
2. Ofatumumab
3. Rituximab (R)

**Traditional Chemotherapy**
1. Alkylating agents
   - Cyclophosphamide, chlorambucil, bendamustine
2. Anthracyclines
   - Doxorubicin
3. Purine/pyrimidine analogs
   - Fludarabine, bendamustine, cytarabine
4. Vinca alkaloids (microtubule inhibitor)
   - Vincristine




**BTK Inhibitors**
1. Acalabrutinib
2. Ibrutinib
3. Zanubrutinib

**PI3K Inhibitors**
1. Copanlisib (IV)
2. Duvelisib
3. Idelalisib
4. Umbralisib

**BCL2 Inhibitor**
1. Venetoclax

**EZH2 Inhibitor**
1. Tazemetostat

BCR, B-cell receptor.

National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology. B-Cell Lymphomas, v2.2021.

# Foundations of Evidence for the Use of BTK Inhibitors in B-cell Malignancies

# BTK Inhibitor Mechanism of Action

## The B-cell Receptor (BCR)

-Regulates differentiation, proliferation, and chemotaxis

## Overactivation

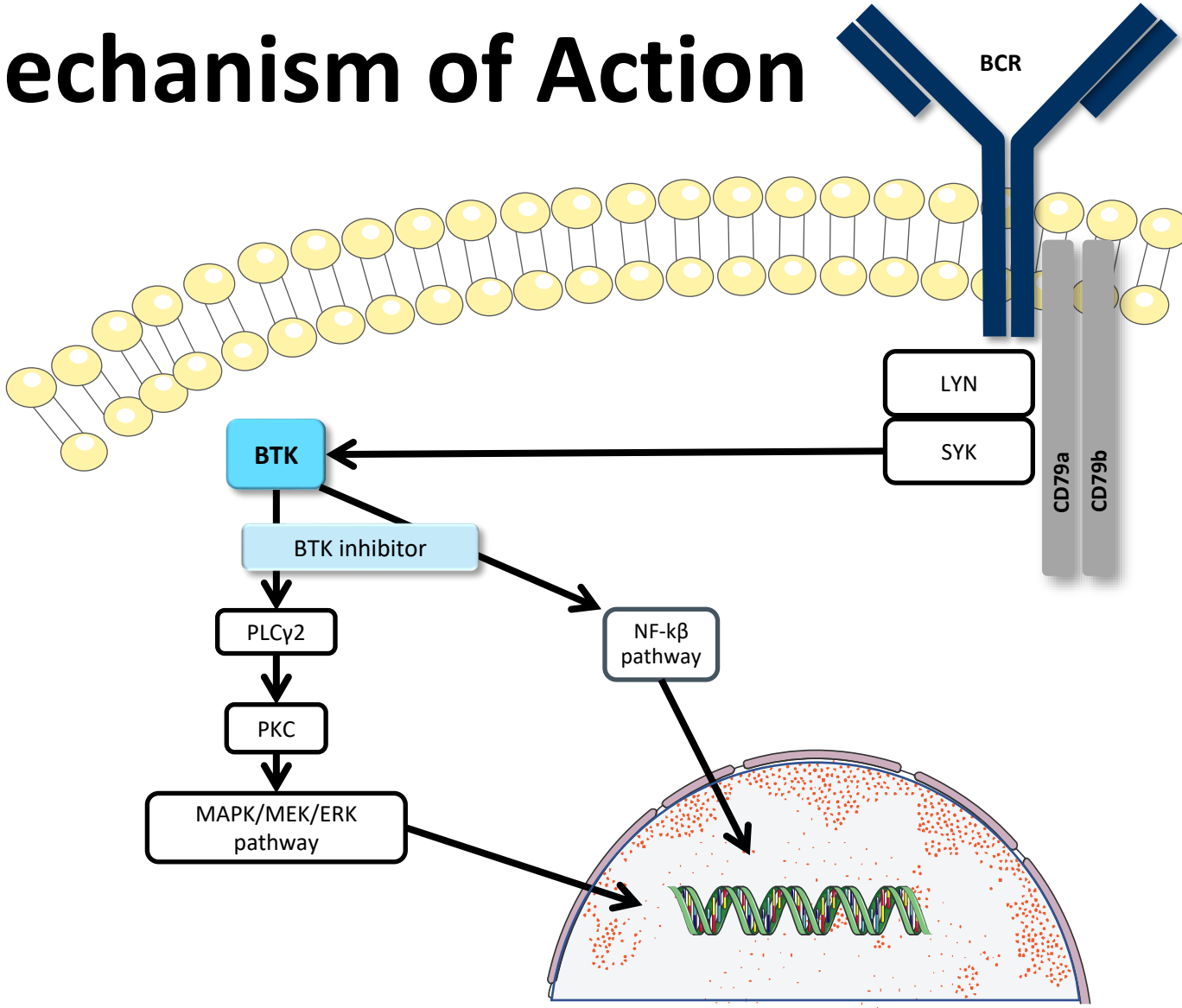
-The BCR in B-cell malignancies is overstimulated and B cells are protected by the microenvironment

## Bruton's Tyrosine Kinase (BTK)

-The overactivated BCR signals through BTK leading to uncontrolled proliferation/malignant B cell

## Ibrutinib/Acalabrutinib/Zanubrutinib

-Covalently binds to a cysteine residue at position 481 on BTK, which abrogates downstream signaling through BTK




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

# BTK Inhibitors in NHL

| Agent | FDA Approval | Class | Dose | Route | Supplied |
|---|---|---|---|---|---|
| **Acalabrutinib** | MCL (2nd+)<br>CLL (1st+) | BTK inhibitor (2nd generation) | 100 mg twice daily | Oral | 100-mg capsule |
| **Ibrutinib** | CLL (1st+), MCL (2nd+)<br>WM (1st+), MZL (2nd+) | BTK inhibitor | MCL: 560 mg daily<br>CLL: 420 mg daily | Oral | 70- and 140-mg capsules; 140-, 280-, 420-, and 560-mg tablets |
| **Zanubrutinib** | MCL (2nd+) | BTK inhibitor (2nd generation) | 160 mg twice daily or 320 mg daily | Oral | 80-mg capsule |

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

# Drug and Comorbidity Interactions With BTK Inhibitors

| Agent | Metabolism | CYP Inhibitors | CYP Inducers | Renal | Hepatic |
|---|---|---|---|---|---|
| ***Acalabrutinib** | CYP3A4 (major)<br>P-gp, BCRP | Strong: avoid<br>Moderate: ↓ 100 mg daily | Avoid (↑ 200 mg twice daily if cannot be avoided) | No changes | No changes<br>Avoid in severe |
| **Ibrutinib** | CYP3A4 (major)<br>CYP2D6 (minor) | Voriconazole: ↓ 140 mg daily?<br>Posaconazole: ↓ 70 mg daily<br>Moderate: ↓ 280 mg daily | Avoid | No changes | Child-Pugh A: ↓ 140 mg<br>Child-Pugh B: ↓ 70 mg<br>Child-Pugh C: Avoid |
| **Zanubrutinib** | CYP3A4 (?) | Strong: ↓ 80 mg daily<br>Moderate: ↓ 80 mg twice daily | Avoid | No changes | Severe: ↓ 80 mg twice daily |

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

*Avoid proton pump inhibitors; take acalabrutinib 2 hours before $H_2$RAs and antacids (reduces acalabrutinib AUC 40%-50%).

# BTK Inhibitors: Past and Present

| Disease State | Past Treatment | Pivotal Study | Present Treatment |
|---|---|---|---|
| **CLL (1st line)** | Chemotherapy (FCR or BR)<br>Obinutuzumab/chlorambucil | Phase 3: ELEVATE-TN<br>Phase 3: E1912 and A041202<br>Phase 3: CLL14 | Acalabrutinib +/- O<br>Ibrutinib +/- anti-CD20 mAb<br>Venetoclax + O |
| **MCL (2nd line)** | Intensive chemotherapy (Nordic)<br>Less intensive chemotherapy (BR) | Phase 2: ACE-LY-004<br>Phase 2: PCYC-1104<br>Phase 2: BGB-3111-206 | Acalabrutinib<br>Ibrutinib +/- R<br>Zanubrutinib |
| **MZL (2nd line)** | Chemotherapy (BR) | Phase 2: PCYC-1121-CA<br><br>Phase 2: UNITY-NHL | Ibrutinib<br>Lenalidomide + R<br>Umbralisib |
| **WM (1st line)** | Chemotherapy (BR)<br>Rituximab<br>Bortezomib-based | Phase 3: iNNOVATE<br><br>Phase 3: ASPEN | Bortezomib-based<br>BTK inhibitor (Ibrutinib or zanubrutinib*)<br>Bendamustine/R<br>Rituximab |

*Zanubrutinib is not FDA approved or included within the NCCN Guidelines. It is utilized in clinical practice off-label. A PDUFA date of October 2021 is expected.

Shanafelt TD, et al. *N Engl J Med*. 2019;381(5):432–443; Woyach JA, al. *N Engl J Med*. 2018;379(26):2517–2528; Sharman JP, et al. *Lancet*. 2020;395(10232):1278-1291; Fischer K, et al. *N Engl J Med*. 2019;380(23):2225-2236; Wang M, et al. *Lancet*. 2018;391(10121):659-667; Wang M, et al. *Leukemia*. 2019;33(11):2762-2766; Song Y, et al. *Clin Cancer Res*. 2020;26(16):4216-4224; Noy A, et al. *Blood*. 2017;129(16):2224-2232; Noy A, et al. *Blood Adv*. 2020;4(22):5773-5784; Fowler NSF, et al. *J Clin Oncol*. 2019;37:7506; Dimopoulos MA, et al. *N Engl J Med*. 2018;378(25):2399–2410; Owen RG, et al. *Lancet Haematol*. 2020;7(2):e112–e121; Tam CS et al. *Blood*. 2020;136(18):2038-2050.

# BTK Inhibitors: Recent Data and Future

## ASPEN Trial
Population: 1st Line WM
Treatment: Zanubrutinib vs ibrutinib
Efficacy: no significant differences (OS, PFS, response rates)
Safety: ↓ atrial fibrillation, hemorrhage, pneumonia; ↑ neutropenia

## GENUINE Trial
Population: R/R high-risk CLL
Treatment: Ibrutinib +/- ublituximab
Efficacy: Improved ORR and PFS with combo
Safety: No unexpected AEs

## MAGNOLIA Trial
Population: R/R MZL
Treatment: Zanubrutinib
Efficacy: 60% ORR
Safety: 7.3% grade ≥3 neutropenia

## AVO Trial
Population: 1st line CLL
Treatment: Acalabrutinib + obinutuzumab + venetoclax
Efficacy: 100% ORR
Safety: No TLS from venetoclax

## SEQUOIA Trial (Arm C)
Population: 1st line CLL with del(17p)
Treatment: Zanubrutinib
Efficacy: 94.5% ORR; 18-month PFS: 88.6%
Safety: 12.9% grade ≥3 neutropenia

## ELEVATE-RR Trial
Population: R/R high-risk CLL
Treatment: Acalabrutinib vs ibrutinib
Efficacy: Noninferior PFS
Safety: ↓ atrial fibrillation

AE, adverse effect; PFS, progression-free survival; ORR, overall response rate; R/R, relapsed/refractory; TLS, tumor lysis syndrome.

Brown JR, et al. ASH 2020: Abstract 1306; Opat S, et al. ASH 2020: Abstract 339; Tam CS, et al. *Blood*. 2020;136(18):2038-2050; Sharman JP, et al. *Lancet Haematol*. 2021:S2352-3026(20)30433-6; Davids MS, et al. ASH 2020: Abstract 2216; Calquence met primary efficacy endpoint in head-to-head trial against ibrutinib in chronic lymphocytic leukaemia. News release. AstraZeneca; January 25, 2021. Accessed March 18, 2021. astrazeneca.com/media-centre/press-releases/2021/calquence-met-primary-endpoint-against-ibrutinib.html

# Hot off the Press in CLL!

## 1st Line Combination Studies

**GLOW Trial (Phase III)**
Treatment: Ibrutinib + Venetoclax versus Clb + O
Efficacy: PFS not reached vs 21 months
Safety: Neutropenia, diarrhea, hypertension

**CAPTIVATE Trial (Phase II)**
Treatment: Ibrutinib + Venetoclax
Efficacy: PFS 95% and OS was 98% @ 2 years
Safety: Neutropenia, hypertension

## Relapsed/Refractory Comparative Studies

**ELEVATE-RR Trial (Phase III)**
Treatment: Acalabrutinib vs Ibrutinib
Efficacy: Non-inferior PFS (both 38 months)
Safety: ↓ a.fib, hypertension, arthralgia, diarrhea, bleeding; ↑ headache and cough

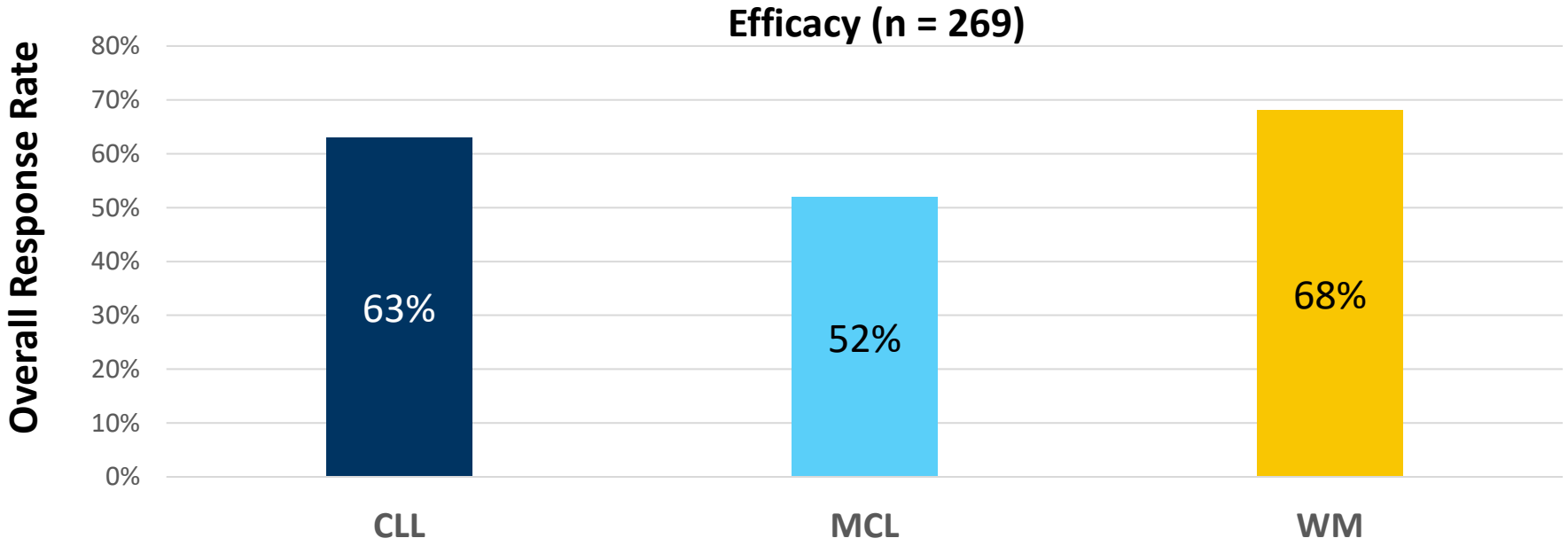
**ALPINE Trial (Phase III)**
Treatment: Zanubrutinib vs Ibrutinib
Efficacy: PFS 94.9% vs 84.0% @ 1 year
Safety: ↓ a. fib, major bleeding, infections, AEs leading to DC; ↑ neutropenia

Clb, chlorambucil

Kater A, et al. EHA 2021. Abstract LB1902; Ghia P, et al. ASCO 2021. Abstract 7501; Byrd JC, et al. ASCO 2021. Abstract 7500; Hillmen P, et al. EHA 2021. Abstract LB1900.

# Future Approaches: Pirtobrutinib (Loxo-305)

- Highly potent and selective noncovalent BTK inhibitor
  - >300-fold selectively for BTK vs 370 other kinases
- Phase 1/2 BRUIN study (R/R B-cell malignancies; many with prior BTK inhibitor exposure)
  - Safety (n = 323): covalent BTK inhibitor-associated toxicities rarely observed (longer follow-up needed)

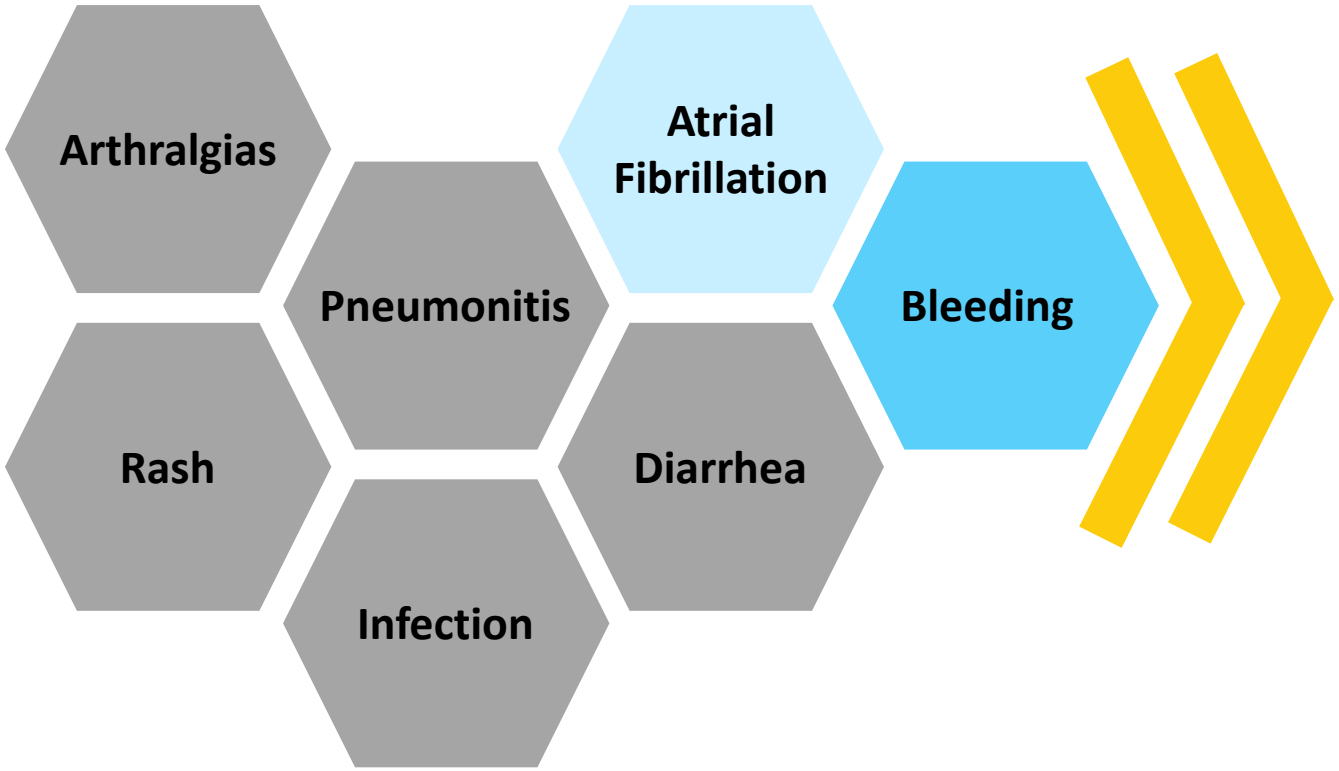



Brandhuber B, et al. *Clin Lymphoma Myeloma Leuk*. 2018;18(suppl 1):S216; Mato AR, et al. *Lancet*. 2021;397(10277):892-901.

# Examining the Approach to Bleeding and Cardiac Toxicities Associated With BTK Inhibitor Therapy

# Discontinuation Rates of Ibrutinib

## Most Common Reasons




**21%**

**ibrutinib discontinuation rate** due to toxicity

**↑ Age**

**strong predictor** for discontinuation due to toxicity

Mato AR, et al. *Haematologica*. 2018;103(5):874-879; Brown JR. *Blood*. 2018;131(4):379-386; Maddocks KJ, et al. *JAMA Oncol*. 2015;1(1):80-87.

# On- and Off-Target Effects

| Kinase | Expression/Toxicity | Ibrutinib | Acalabrutinib | Zanubrutinib |
|---|---|---|---|---|
| BTK | Lymphocytes, cardiac, platelets | +++ | ++ | +++ |
| TEC | Platelet effects, T-cell priming | ++ | – | + |
| EGFR | Rash, cardiac, diarrhea | ++ | – | + |
| BMX | Cardiac | +++ | + | +++ |
| ERBB4 | Cardiac | ++ | + | ++ |

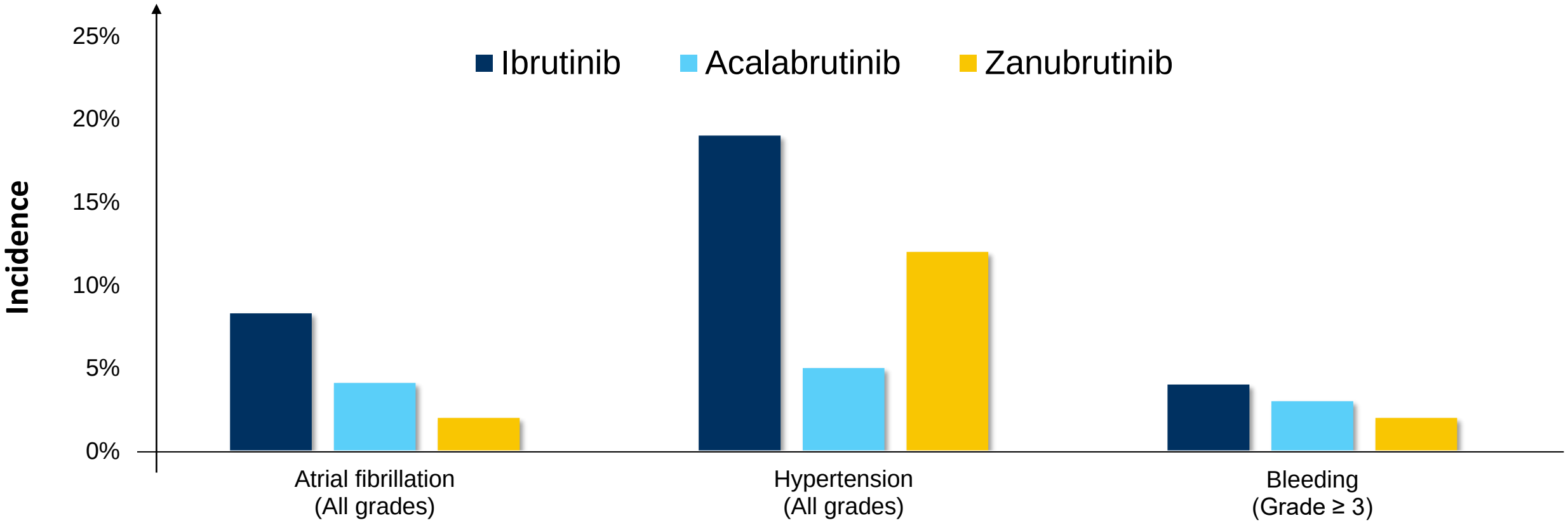
**+** = increased potency

**–** = minimal/no inhibition

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; Kaptein A, et al. *Blood*. 2018;132:1871.

# Toxicity Comparison:

## *Bleeding and Cardiac AEs from Prescribing Information**




AE, adverse effect.

*Cross trial comparisons should be interpreted with caution.

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

# Atrial Fibrillation With BTK Inhibitors: Incidence

## Overall Risk

1. ≈10% incidence at 3 years (with ibrutinib)
2. Median time to onset: ≈8 months

## 2nd Generation BTK Inhibitor

1. Incidence lower with acalabrutinib and zanubrutinib
2. ASPEN (WM): 15% ibrutinib vs 2% zanubrutinib
3. ELEVATE-RR (CLL): ibrutinib > acalabrutinib

## Scoring Tool for Individual's Risk

| Factor | Points |
|---|---|
| Age (years) | |
| • 65-74 | 2 |
| • ≥75 | 3 |
| Male | 1 |
| Valvular disease | 2 |
| Hypertension | 1 |

## Calculating Individual's Risk

| Risk Score | 5-Year Atrial Fibrillation Rate |
|---|---|
| 0-1 | 0.4% |
| 2-3 | 2.8% |
| 4 | 7.6% |
| ≥ 5 | 17.9% |

Brown J, et al. *Haematologica*. 2017;102(10):1796-1805; Wiczer TE, et al. *Blood Adv.* 2017;1(20):1739-1748; Tam CS, et al. *Blood*. 2020;136(18):2038-2050; Calquence met primary efficacy endpoint in head-to-head trial against ibrutinib in chronic lymphocytic leukaemia. News release. AstraZeneca; January 25, 2021. Accessed March 18, 2021. astrazeneca.com/media-centre/press-releases/2021/calquence-met-primary-endpoint-against-ibrutinib.html

# Atrial Fibrillation With BTK Inhibitors: Management

## Mechanism

- Not fully elucidated
  - Off-target
    - Cardiac PI3K inhibition and TEC
  - On-target
    - BTK
- Risks include cardiac risk factors, acute infections, prior history of atrial fibrillation

## Management

- Educate patient on risk and when to call
- Rate control (β blocker preferred as verapamil and diltiazem are CYP inhibitors)
  - Monitor digoxin level if used with P-gp inhibitor
  - Rhythm control (careful selection due to drug interactions)
- Controllable atrial fibrillation: continue therapy (some consider switching to alternative BTK inhibitor)
- Uncontrollable atrial fibrillation: consider alternative therapy

**Common questions:** Can ibrutinib be used in a patient who already has atrial fibrillation? How often is atrial fibrillation controlled versus need to be switch therapy? Do dose reductions help? Should therapy be held?

Imbruvica. Prescribing information. Pharmacyclics LLC; December 2020; Calquence. Prescribing information. AstraZeneca Pharmaceuticals LP; November 2019. Brukinsa. Prescribing information. BeiGene USA, Ltd; November 2019; McMullen JR, et al. *Blood*. 2014;124(25):3829-3830; de Weerdt I, et al. *Haematologica*. 2017;102(10):1629-1639; Brown JR. *Blood*. 2018;131(4):379-386.

# Anticoagulation Management Considerations


**Prevent Stroke**

$CHA_2DS_2$-VASc ≥2: consider anticoagulation

**Calculate Risk**

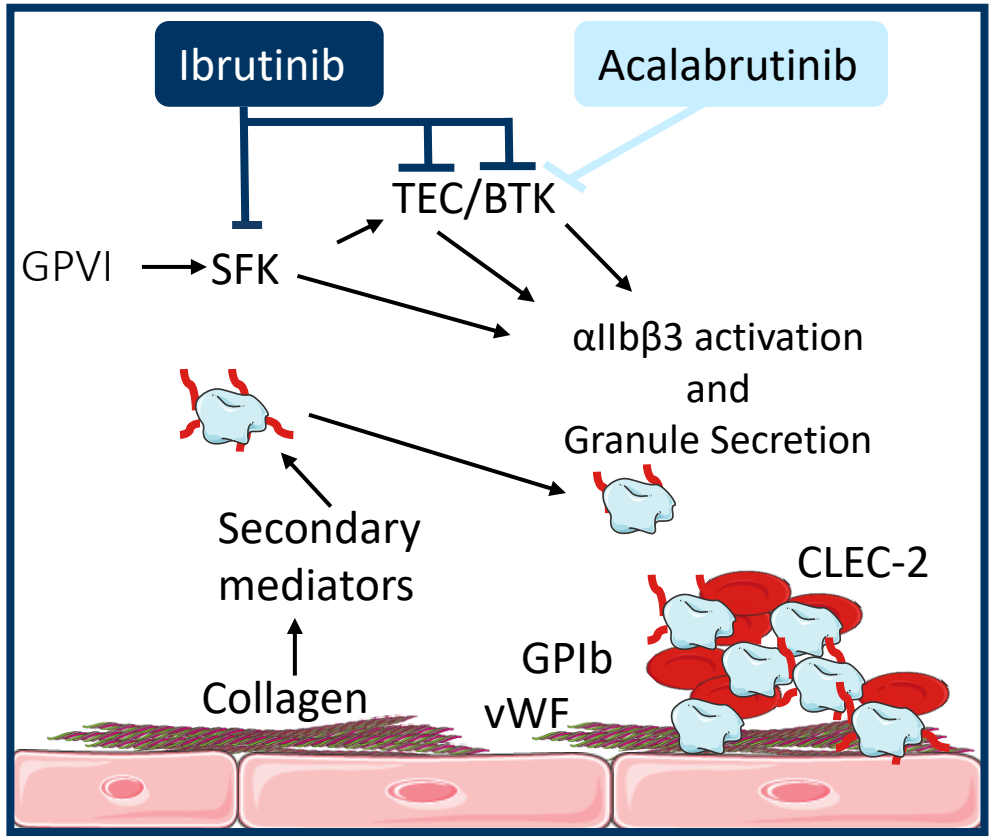
Calculate $CHA_2DS_2$-VASc
Calculate HAS-BLED score
*(neither scoring system has been validated in patients receiving BTK inhibitors)*

**Prevent Bleeding**

Discuss risk vs benefit based on HAS-BLED score and other factors
**avoid warfarin**

de Weerdt I, et al. *Haematologica*. 2017;102(10):1629-1639; Brown JR. *Blood*. 2018;131(4):379-386.

# Major Bleeding: Mechanism




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):2610-2623.

# Bleeding With BTK Inhibitors: Management

## Real-World Risk (Multivariable Analysis)

Elevated INR (>1.5)
**4.6x**

Antiplatelet plus anticoagulant vs neither
**20x**

Conflicting data: Jones JA, et al → low bleed incidence despite antiplatelet and/or anticoagulant (comorbidities may be more predictive).

## Management

- Hold prior to and after invasive procedures for 3 (minor) to 7 days (major)
  - Reversible impact within 1 week of discontinuation
  - Platelet transfusion may reverse antiplatelet effects
- Anticoagulants/antiplatelets are not contraindications
  - Avoid warfarin
  - Consider stopping other medications

**Common questions:** Does ibrutinib need to be discontinued for mild bleeding? Should acalabrutinib or zanubrutinib be started in a patient at high risk for bleed?

Imbruvica. Prescribing information. Pharmacyclics LLC; December 2020; Calquence. Prescribing information. AstraZeneca Pharmaceuticals LP; November 2019. Brukinsa. Prescribing information. BeiGene USA, Ltd; November 2019; Mock J, et al. *Clin Lymphoma Myeloma Leuk*. 2018;18(11):755-761; Jones JA, et al. *Br J Haematol*. 2017;178(2):286-291; de Weerdt I, et al. *Haematologica*. 2017;102(10):1629-1639; Brown JR. *Blood*. 2018;131(4):379-386.

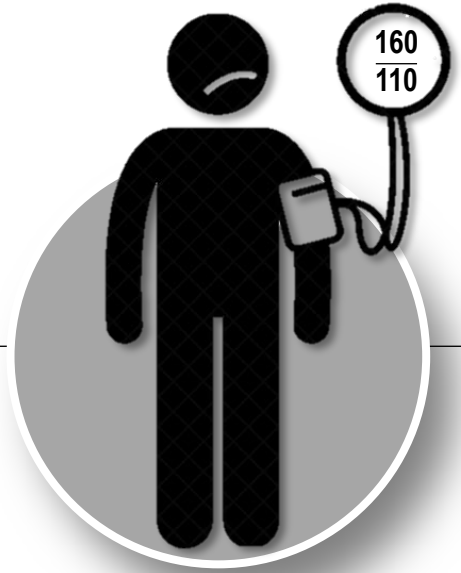
# Hypertension from BTK Inhibitors: Incidence

## Take-Home Points

01 BTK inhibitor may ↑ HTN risk 13x

02 New or worsened HTN ↑ major CV events

03 Control with antihypertensive ↓ major CV events




04 Median onset, 4 months (risk continues for years)

05 40% may require antihypertensive; 18% require >1 BP med

06 2nd generation BTK inhibitor may reduce risk?

Dickerson T, et al. *Blood*. 2019;134 (22):1919-1928.

BP, blood pressure; CV, cardiovascular; HTN, hypertension.

# Hypertension from BTK Inhibitors: Management

## Mechanism

- Several hypotheses (likely on- and off-target)
  - PI3K-p110α inhibition
  - VEGF downregulation
  - Nitric oxide reduction
  - Endothelial cell dysfunction
- Risks include cardiac risk factors, prior history of HTN

## Management

- Monitor BP throughout treatment
- Standard management (no specific agent)
- Treatment discontinuation not necessary in most
- Adequate management of hypertension mitigates CV events
- Check drug interactions (MV analysis):
  - 2-fold increase risk of developing HTN
  - 3-fold increase risk of worsening HTN

**Common questions:** Should an anti-hypertensive be started pre-emptively? How often should blood pressure be monitored?

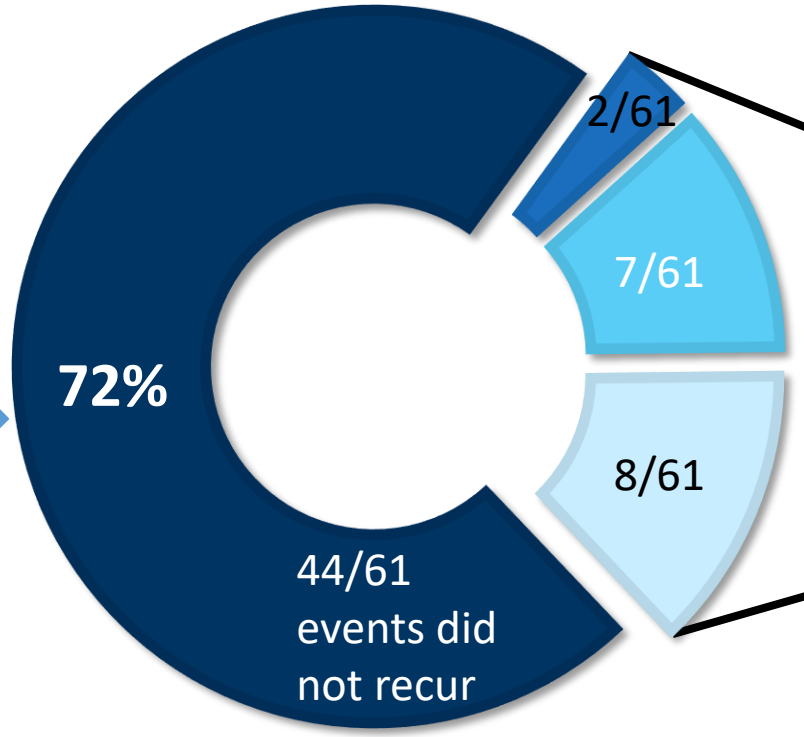
VEGF, vascular endothelial growth factor.

Imbruvica. Prescribing information. Pharmacyclics LLC; December 2020; Calquence. Prescribing information. AstraZeneca Pharmaceuticals LP; November 2019. Brukinsa. Prescribing information. BeiGene USA, Ltd; November 2019; Dickerson T, et al. *Blood*. 2019;134 (22):1919-1928.

# Switching to Another BTK Inhibitor: Acalabrutinib for Ibrutinib-Intolerant Patients

33 patients were intolerant to ibrutinib and experienced a total of 61 AEs.

These patients were switched to acalabrutinib and recurrence of AEs was evaluated.




**27.9% AEs Recurred**

- 3.3% higher grade
- 11.5% same grade
- 13.1% lower grade

AE, adverse effect.

**Lingering questions:** Did all ibrutinib "intolerance" need to be stopped (definition was vague)? With management discussed, could ibrutinib have been restarted with similar success?

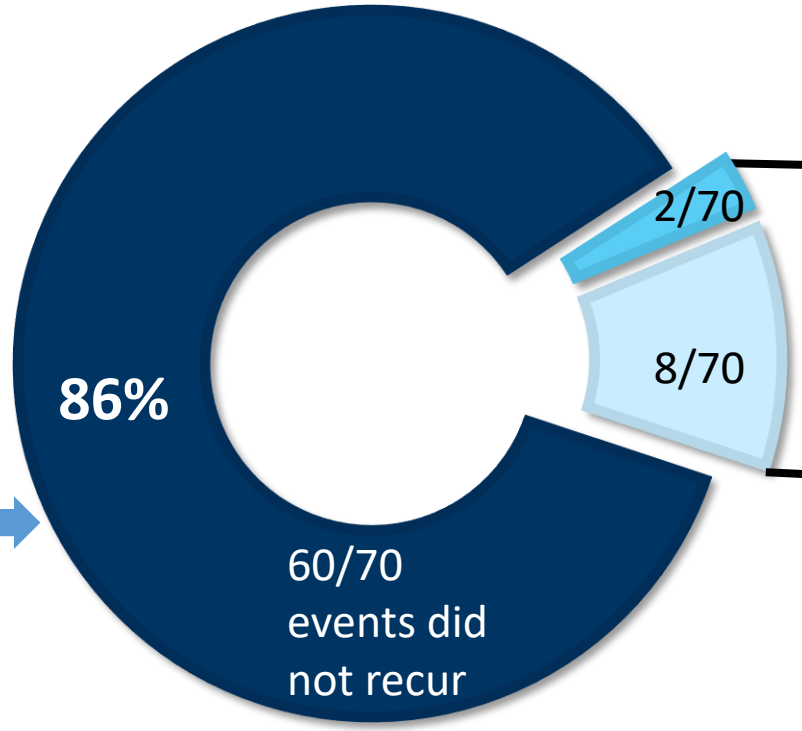
Awan, FT et al. *Blood Adv*. 2019;3(9):1553-1562.

# Switching to Another BTK Inhibitor: Zanubrutinib for Ibrutinib- or Acalabrutinib-Intolerant Patients

32 patients were intolerant to ibrutinib or acalabrutinib and experienced a total of 70 AEs.*

*4 events from acalabrutinib.

These patients were switched to zanubrutinib and recurrence of AEs was evaluated.




**14% AEs Recurred**

- 0% higher grade
- 2.6% same grade
- 11.4% lower grade

**Lingering question:** Which agent is better tolerated – acalabrutinib or zanubrutinib?

Shadman M. ASH 2020: Abstract 2947. Accessed March 18, 2021. www.beigenemedical.com/CongressDocuments/Shadman%20Zanubrutinib%20BGB-3111-215%20ASH%20Poster%202020.pdf

# Dose Modifications for Nonhematologic AEs

**STARTING DOSE**

**Ibrutinib:** 420-560 mg QD
**Acalabrutinib:** 100 mg BID
**Zanubrutinib:** 320 mg QD
(or 160 mg BID)

1st grade 3/4 occurrence
***INTERRUPT*** then

**Once symptoms resolve to grade 1, restart at starting dose**

2nd grade 3/4 occurrence
***INTERRUPT*** then

**Ibrutinib:** reduce by 140 mg
**Acalabrutinib:** starting dose
**Zanubrutinib:** 160 mg QD
(or 80 mg BID)

3rd grade 3/4 occurrence
***INTERRUPT*** then

**Ibrutinib:** reduce by 140 mg
**Acalabrutinib:** 100 mg QD
**Zanubrutinib:** 80 mg QD

4th grade 3/4 occurrence
***INTERRUPT*** then

**DISCONTINUE**
if toxicity persists

**No dose adjustments or discontinuations required for grade 1/2***

*Would consider if persistent/impacting quality of life.

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

# Implementing Digital Technology Tools Within Health-Systems for Improving Adherence and Patient Support

# The Patient Journey and The Pharmacist

### Clinical History

- 63-year-old patient with MCL presents with relapsed disease
- Previously achieved remission following chemotherapy <2 years prior

### Current Medications

- Omeprazole, aspirin, insulin, metoprolol, apixaban, lisinopril

**LYMPHOMA CLINIC**

Diagnosis is made

Pharmacist included in treatment decision

Pharmacist provides education on safety and efficacy

**PHARMACY**

Pharmacist team helps with medication access (co-pay assistance, prior authorization, appeals, delivery, etc)

Education reinforcement

**HOME**

Patient administers oral medication daily

Patient has been educated and empowered to identify AEs

Patient to call/message AEs, new symptoms, and new medications

**MONITORING**

Various touchpoints by pharmacist team:

- Within 1 week
- 14 days later
- Every 3-6 months PRN

Mackler E, et al. *J Oncol Pract*. 2019;15(4):e346-e355.

# Impact of Nonadherence on Outcomes

### History of Present Illness

- Patient began acalabrutinib 100 mg orally twice daily for relapsed MCL 1 month following initial visit
- Often forgets evening dose
- Disease response slower than expected

### Patient Concerns

- Does missing doses impact my response?

***These data should be discussed at each point of patient's treatment journey.***

**Evaluation of ibrutinib nonadherence on outcomes in MCL, CLL, and other B-cell malignancies.**

### Study 1: Barr PM, et al.

1. Higher BTK inhibitor dose intensity improved PFS
2. Missing ≥8 consecutive days = worse PFS

### Study 2: Williams AM, et al.

1. Lower adherence (<80%) = worse PFS and OS
2. Dose interruptions >1 week = worse PFS
3. Nonadherence can occur early (within 8 weeks)

Barr PM, et al. *Blood*. 2017;129(19):2612-2615;
Williams AM, et al. *Clin Lymphoma Myeloma Leuk*. 2019;19(1):41-47.

# Barriers to Adherence

## Patient Characteristics

- Age
- Gender
- Quality of life/ functional status
- Time from diagnosis

## Disease Characteristics

- Complexity
- High prescription burden
- Time from diagnosis
- Concomitant disease

## Treatment Characteristics

- Dose burden
- AEs
- Financial toxicity
- Treatment duration
- Physical properties (shape, size, taste)

## Health Care Factors

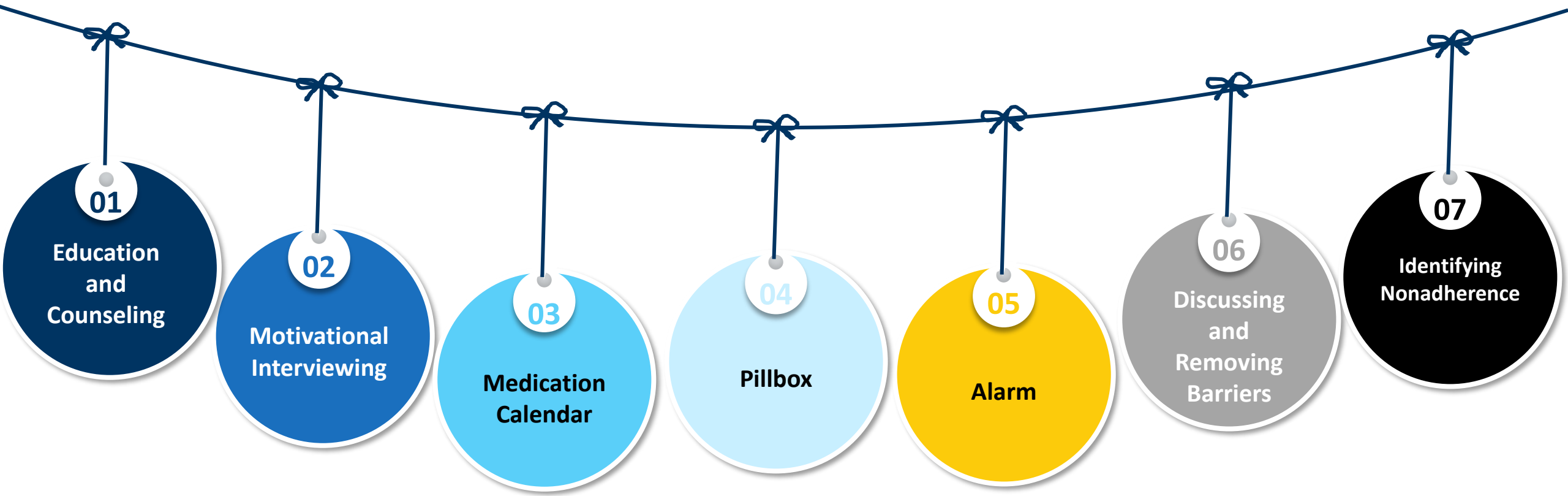
- Quality of the patient-provider relationship
- Communication
- Education
- Medication access

## Socioeconomic Factors

- Financial
- Perception of nonadherence consequences
- Medical literacy
- Faith in physician and treatment
- Perceived benefit

Zackon A, et al. *Leuk Lymphoma*. 2019;60(10):2356-2364; Ruddy K, et al. *CA Cancer J Clin*. 2009;59(1):56-66.

# Traditional Solutions to Promote Adherence



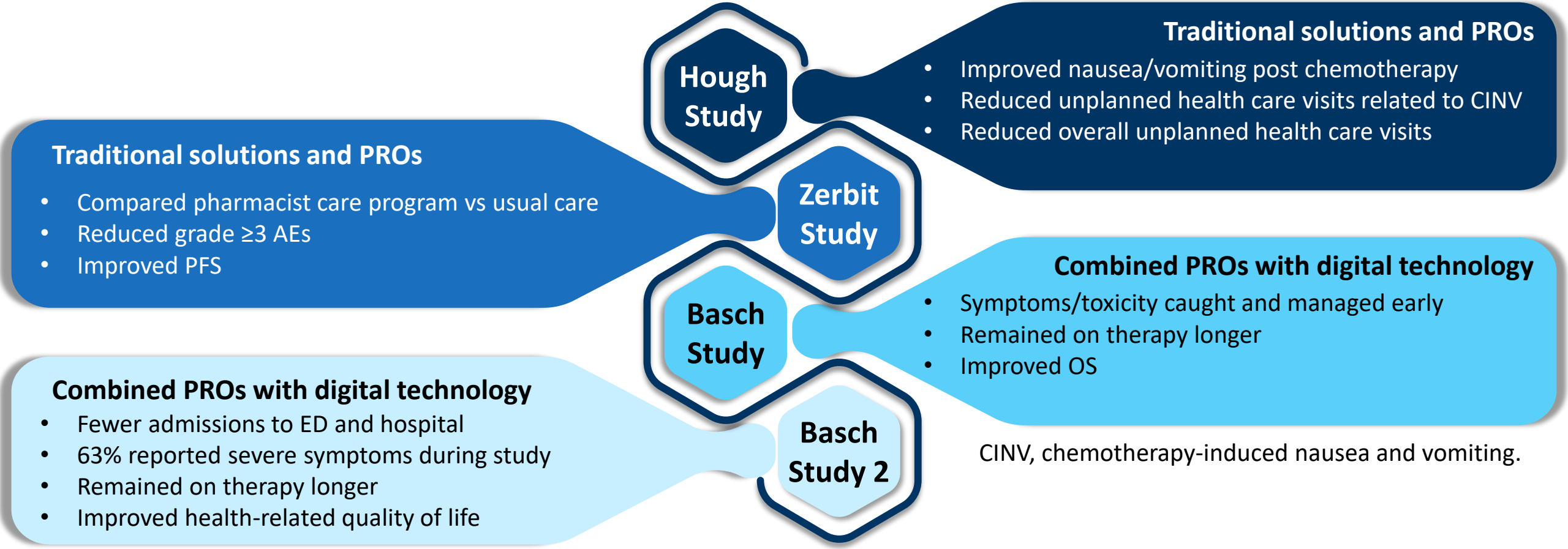

Ryan R, et al. *Cochrane Database Syst Rev*. 2014;2014(4):CD007768.

# Digital Tools to Promote Adherence

| Digital Tool | How It Works | Examples |
|---|---|---|
| **Virtually observed therapy** | Smartphone camera captures patient administration<br>Verified by remote professional or AI/analytics technology | Emocha Mobile Health, sureAdhere |
| **Smart pill bottles** | Sensor on pill bottle or cap tracks medication use | Adhere Tech, glowCap, Pillsy, Medikyu, doseSmart, Nomi |
| **Smart pill dispensers, smart home medication assistant** | Technology to store and dispense medication, integrate data from wearable devices, offer teleservice option with virtual chats with a pharmacist | Pillo, Catalia Health, spencer Health Solutions, mediPENSE |
| **Smart pill organizers** | Pill boxes with sensor tracks use of medication | TowerView Health, medMinder, Vaica, MedSentry, PillDrill, Tricella |
| **Medication adherence apps** | Phone apps remind patient and log administration | Pill monitor, Medisafe pill reminder, Round Health, CareZone, MedHelper pill reminder, Dosecast |
| **Virtual visits** | Scheduled visits to assess response, toxicity, and adherence<br>May be triggered by visits from patient-reported outcomes (PROs) | Video chat integrated into EMR |

Aungst TD. The Digital Apothecary; 2019. Accessed February 9, 2021. thedigitalapothecary.com/pharmacy-innovation-news/2019/2/14/digital-health-for-pharmacists-e-book; ASCO. Other mobile applications. Cancer.Net. Published 2020. Accessed February 9, 2021. cancer.net/navigating-cancer-care/managing-your-care/other-mobile-applications; Charbonneau DH, et al. *Digit Health*. 2020;6:2055207620905413; Marotta R. 5 digital tools for improving medication adherence. PharmacyTimes. Published December 5, 2018. Accessed February 9, 2021. pharmacytimes.com/conferences/ashpmidyear2018/5-digital-tools-for-improving-medication-adherence; Park JYE, et al. *JMIR Mhealth Uhealth*. 2019;7(1):e11919.

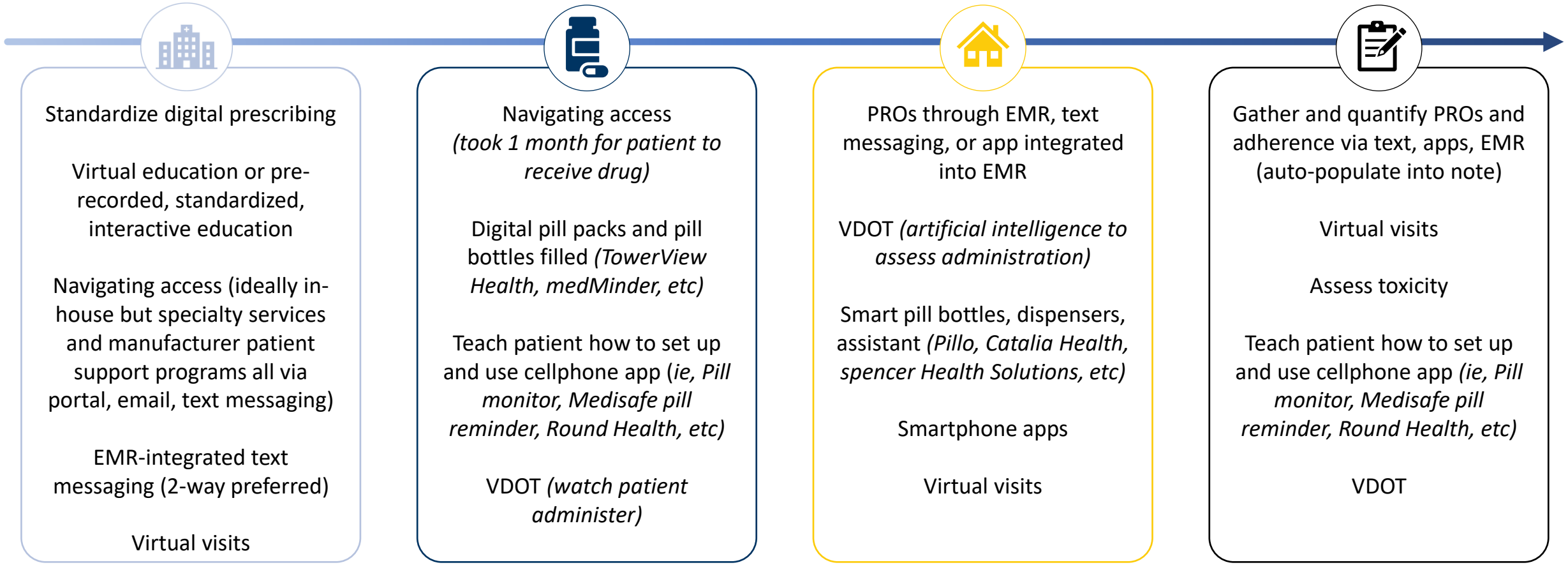
# Traditional Solutions, Digital Tools, and PROs Improve Patient Outcomes




CINV, chemotherapy-induced nausea and vomiting.

Hough S, et al. *J Clin Oncol*. 2020;38(15 suppl):2001; Zerbit J, et al. *Ann Hematol.* 2020;99(7):1615-1625; Basch E, et al. *JAMA*. 2017;318(2):197-198; Basch E, et al. *J Clin Oncol*. 2016;34(6):557-565.

# Incorporating Digital Tools into the Patient Journey




VDOT, video directly observed therapy.

Aungst TD. The Digital Apothecary; 2019. Accessed February 9, 2021. thedigitalapothecary.com/pharmacy-innovation-news/2019/2/14/digital-health-for-pharmacists-e-book; ASCO. Other mobile applications. Cancer.Net. Published 2020. Accessed February 9, 2021. cancer.net/navigating-cancer-care/managing-your-care/other-mobile-applications; Marotta R. 5 digital tools for improving medication adherence. PharmacyTimes. Published December 5, 2018. Accessed February 9, 2021. pharmacytimes.com/conferences/ashpmidyear2018/5-digital-tools-for-improving-medication-adherence

# Conclusion

- BTK inhibitors have revolutionized the treatment of B-cell malignancies
- BTK inhibitors exhibit unique toxicities that are generally manageable
- Cardiac toxicities are a leading contributing cause to nonadherence
- Pharmacists have several tools (traditional methods, PROs, digital technology) available that may improve patient adherence
- Improving adherence improves patient outcomes and quality of life

# Additional Resources

| Journal Articles |
| --- |
| Lasica M, Tam CS. Management of Ibrutinib Toxicities: a Practical Guide. Curr Hematol Malig Rep. 2020 Jun;15(3):177-186. |
| Pineda-Gayoso R, Alomar M, Lee DH, Fradley MG. Cardiovascular Toxicities of Bruton's Tyrosine Kinase Inhibitors. Curr Treat Options Oncol. 2020 Jun 30;21(8):67. |

| Websites | |
| --- | --- |
| The Digital Apothecary | www.thedigitalapothecary.com/ |
| Michigan Oncology Quality Consortium – Oral Oncolytics | MOQC.org/resources/oral-oncolytics/ |