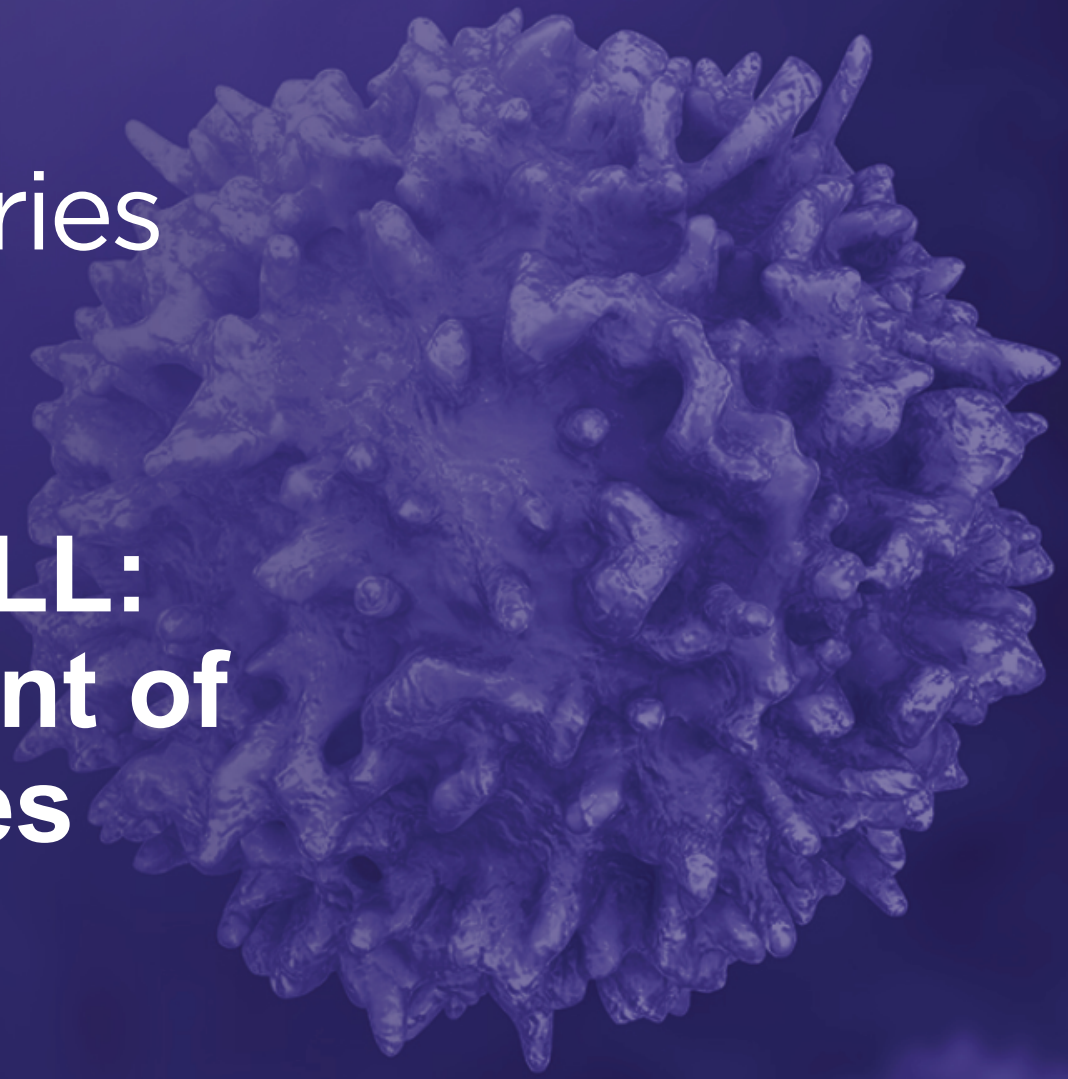
JADPRO Clinical Case Series

BTK Inhibitors Beyond CLL: Their Role in the Treatment of Select B-Cell Malignancies



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PRESENTER

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Objectives

- Understand the management of patients with mantle cell lymphoma (MCL), marginal zone lymphoma (MZL), and Waldromström macroglobulinemia (WM) on ibrutinib therapy.
- Discuss the role of advanced practitioners (APs) in the treatment of these patients
- Review case studies to understand treatment decision-making

Case 1

Introduction to Case 1: Diagnosis of WM

- Mr. Jones is a 71-year-old man who presents with early satiety
- Past medical history (PMH): hypertension well-controlled with losartan
- Splenomegaly found during physical exam

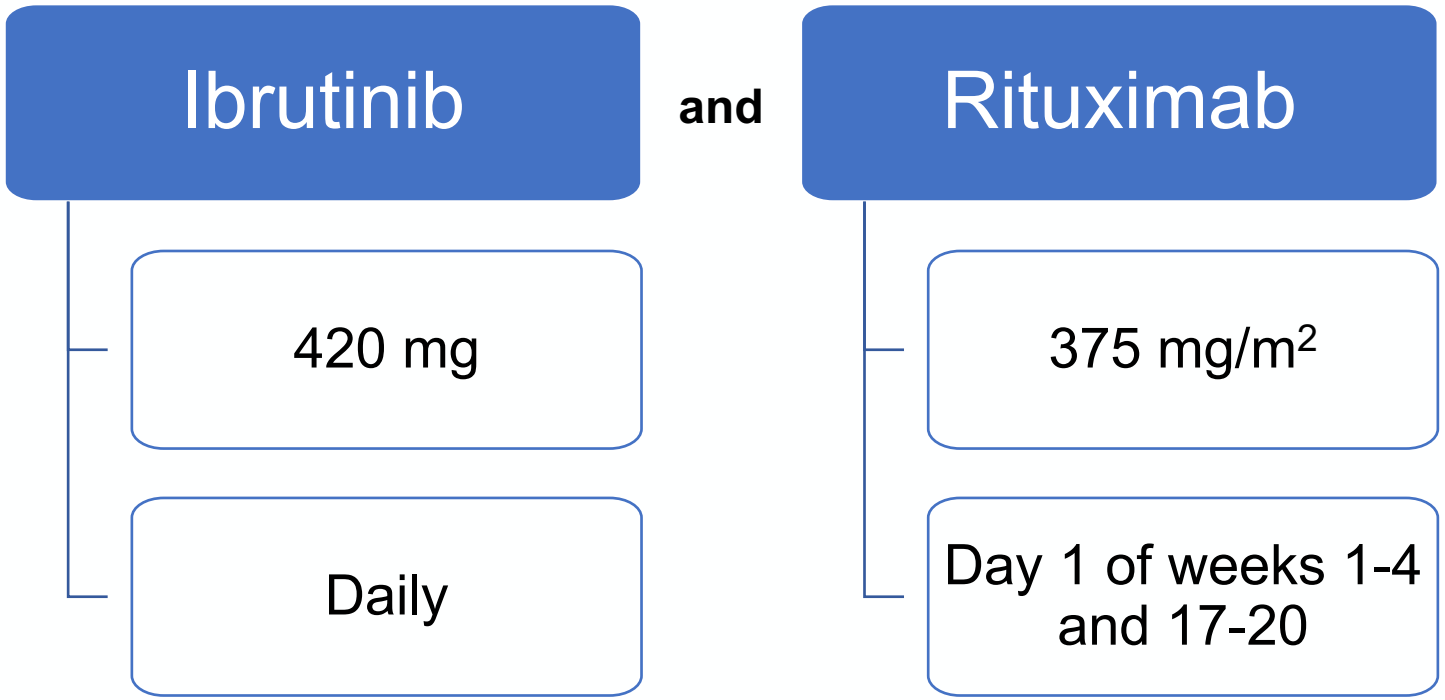
Laboratory Values at Initial Visit

Parameters	Initial Values
Hemoglobin	10.3 g/dL
Monoclonal IgM	3200 mg/dL
Bone marrow	25% lymphoplasmacytic infiltration
MYD88 mutation	Positive

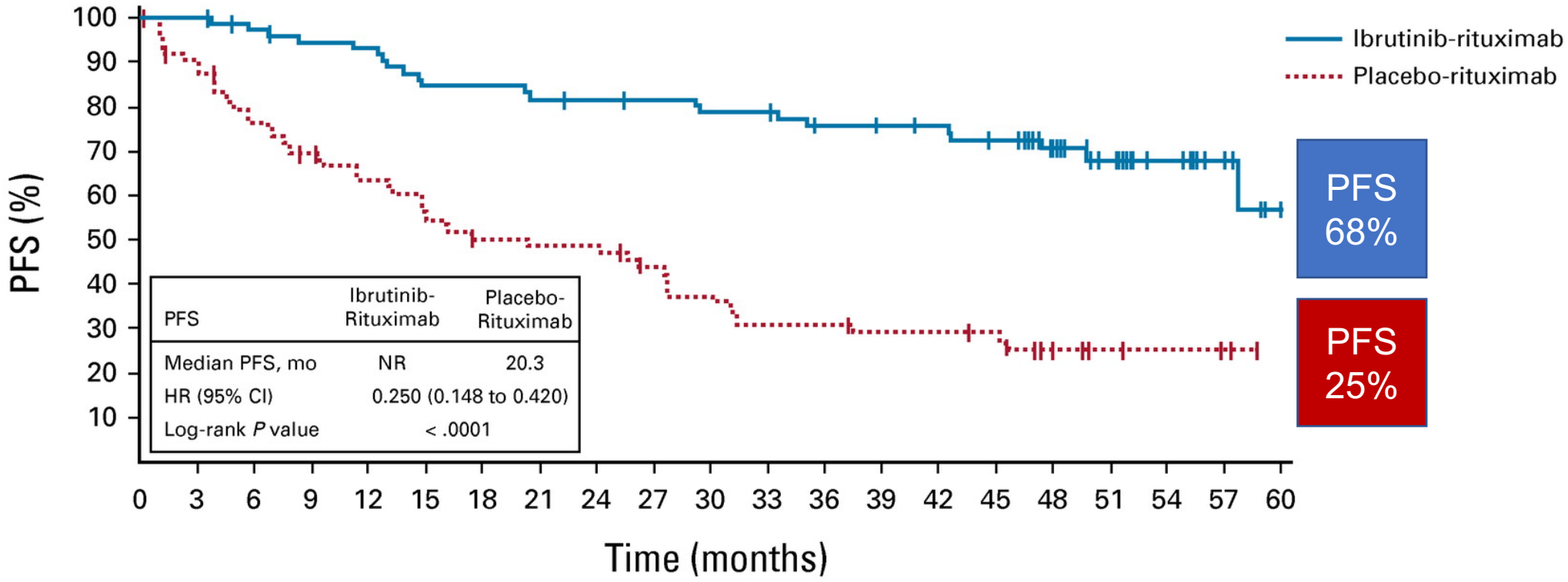
Diagnosis: WM

Case 1: Treatment Selection

- Recommend initiation of therapy because Mr. Jones is symptomatic



Addition of Ibrutinib to Rituximab Decreased Risk of Progression By 75%



CI, confidence interval; HR, hazard ratio; NR, not reached; PFS, progression-free survival

Buske C, et al. *J Clin Oncol*. 2021;40:52-62.

Case 1: 6-Month Follow-up

- Very good partial response to therapy
  - Splenomegaly resolved
  - IFE: + IgM monoclonal protein
- Continued ibrutinib with monthly visits with AP

Laboratory Values

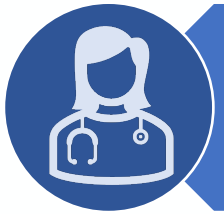
Parameters	Initial	6 Months
Hemoglobin	10.3 g/dL	12.1 g/dL
Monoclonal IgM	3200 mg/dL	214 mg/dL

IFE, immunofixation electrophoresis

Case 1: 2.5-Year Follow-up

- Mr. Jones reports that home blood pressure readings have been increasing

Blood Pressure Readings



143/88 mmHg

140-150 / 80-90 mmHg

Risk of Cardiovascular Events With Ibrutinib

Grade ≥3 N (%)	Year 0-1 (n=75)	Year 1-2 (n=69)	Year 2-3 (n=58)	Year 3-4 (n=54)	Year 4-5 (n=40)	Overall (N=75)
Hypertension	5 (7)	7 (10)	6 (10)	3 (6)	1 (3)	11 (15)
Atrial fibrillation	6 (8)	5 (7)	1 (2)	2 (4)	1 (3)	12 (16)

Grade 3 hypertension:
systolic BP ≥160 mm Hg or diastolic BP ≥100 mm Hg

Buske C, et al. *J Clin Oncol*. 2021;40:52-62.

Blood Pressure Control Reduces Risk of Cardiovascular Events

- Hypertension is a common side effect and can potentiate other cardiac AEs
- In a large review of 562 patients treated with ibrutinib:
  - Approximately 80% of patients developed new or worsening hypertension with SBP ≥130 mmHg on 2 separate visits within 3 months
  - Higher baseline SBP was associated with higher risk of ibrutinib-associated hypertension
  - New or worsened hypertension was associated with increased risk of major cardiovascular events (AF, HF, CVA, MI, ventricular arrhythmia or death)

AE, adverse event; AF, atrial fibrillation; CVA, coronary vascular disease; HF, heart failure, MI, myocardial infarction; SBP, systolic blood pressure

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

Recommendations

- Patients should monitor blood pressure at home while taking ibrutinib, as hypertension can occur late in the course of therapy
- Initiate antihypertensive or increase current antihypertensive therapy for SBP >130 mmHg
- No preferred class of antihypertensives specific to treat ibrutinib-associated hypertension
- CYP3A inhibitors, such as verapamil and diltiazem, should be avoided because they increase ibrutinib concentrations, increasing risk of toxicity

CYP, cytochrome P450 enzyme

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

Polling Question

How do you manage hypertension in your patients treated with ibrutinib?

A. Refer to cardiology **17%**

B. Refer to their primary care provider **11%**

C. Treat when blood pressure is ≥130/80 mmHg **44%**

D. Treat when blood pressure is ≥160/90 mmHg **28%**

Case 1: Hypertension Management

- Mr. Jones had been taking losartan 25 mg daily
- In the setting of worsening hypertension, losartan was increased to 50 mg daily
  - BP improved to <130/80 mmHg at subsequent follow-up visits

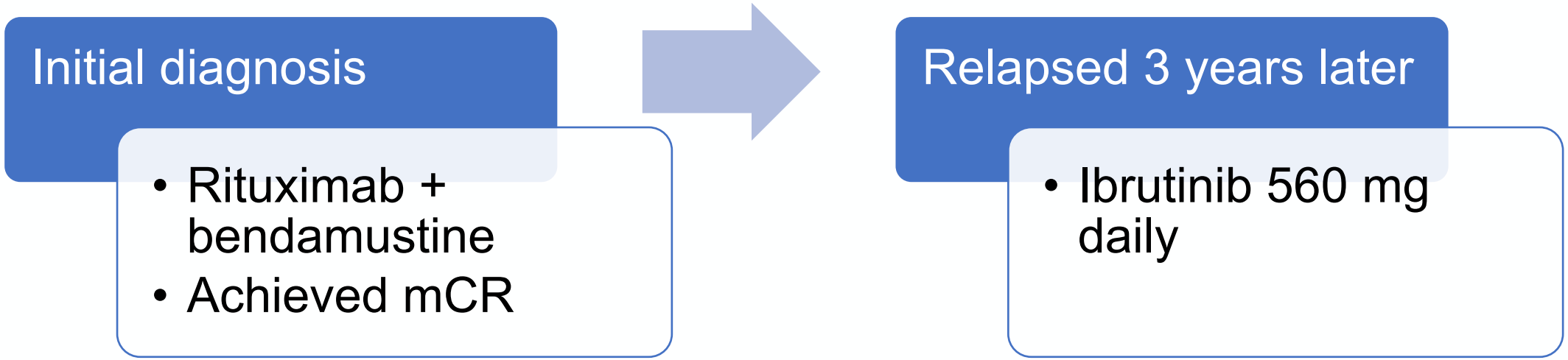
Clinical Pearl

Hypertension is common and can occur anytime during ibrutinib therapy. Treatment of hypertension is associated with decreased risk of cardiovascular events.

Case 2

Introduction to Case 2: Relapsed/Refractory MZL

- Ms. Brown is a 39-year-old woman who was previously diagnosed with extranodal MZL involving the breast, lymph nodes, and presacral lesion



mCR, molecular complete response

Case 2: Managing Side Effects

- At her clinic visit after 1 month on ibrutinib therapy, Ms. Brown reports that she has been experiencing joint pain
  - Interferes with ability to work
  - Skipped a few doses, which provided some relief
- Concerned that treatment team will change her therapy

Options for Arthralgia Management

- Topical creams: arnica, diclofenac gel, camphor, menthol, capsaicin, lidocaine
- Acetaminophen
- Short-course steroids
- NSAIDs
  - Effective in many patients to manage arthralgia[1]
  - Some clinicians recommend avoiding, as they may exacerbate risk of bleeding[2]
  - Use lowest dose possible and monitor for risk of bleeding

NSAIDs, nonsteroidal anti-inflammatory drugs

1. Rhodes J, et al. *Clin Lymphoma Myeloma Leuk*. 2020;20:438-444.e1. 2. Stephens DM, et al. *Blood*. 2019;133:1298-1307.

Ibrutinib-Induced Arthralgias

- Occurs in approx. 35%
- Median onset is 34.5 months in real-world data
- Most cases grade 1-2
- Risk factors: female, younger age, frontline therapy, history of autoimmune disease
- Low-grade arthralgias may be self-limiting
  - If not, may respond to dose reduction
- Treatment should be discontinued for grade 3 events

Rhodes J, et al. *Clin Lymphoma Myeloma Leuk*. 2020;20:438-444.e1..

Approach to Managing Arthralgias

Grade 1-2, not affecting ADLs	• Continue ibrutinib at current dose • Monitor closely for symptom progression
Grade 1-2, affecting ADLs	• Consider ibrutinib dose reduction
Grade 3	• Hold ibrutinib dose until resolution • Rechallenge with dose reduction
Recurrence with rechallenge	• Switch to alternative agent

ADLs, activities of daily living

Rhodes J, et al. *Clin Lymphoma Myeloma Leuk*. 2020;20:438-444.e1..

Case 2: Managing Arthralgia

Acetaminophen + topical arnica

- No improvement after 1 week

Ibuprofen 400 mg 3 times per day

- No improvement after 1 week
- Interfering with daily activities

Prednisone 20 mg daily for 5 days

- Symptoms resolve
- Recur few weeks later

Ibrutinib dose reduction to 420 mg daily

- Symptoms resolve

Clinical Pearl

Dose holds or dose reductions are commonly used to manage arthralgias that don't respond to supportive care

Polling Question

When a patient on ibrutinib develops non–life-threatening side effects, but their disease is responding to therapy, what is your preferred initial course of action?

A. Continue treatment at current dose, and try to manage toxicity with supportive care **54%**

B. Decrease the dose, and try to manage toxicity with supportive care **31%**

C. Interrupt therapy, and try to manage toxicity with supportive care **8%**

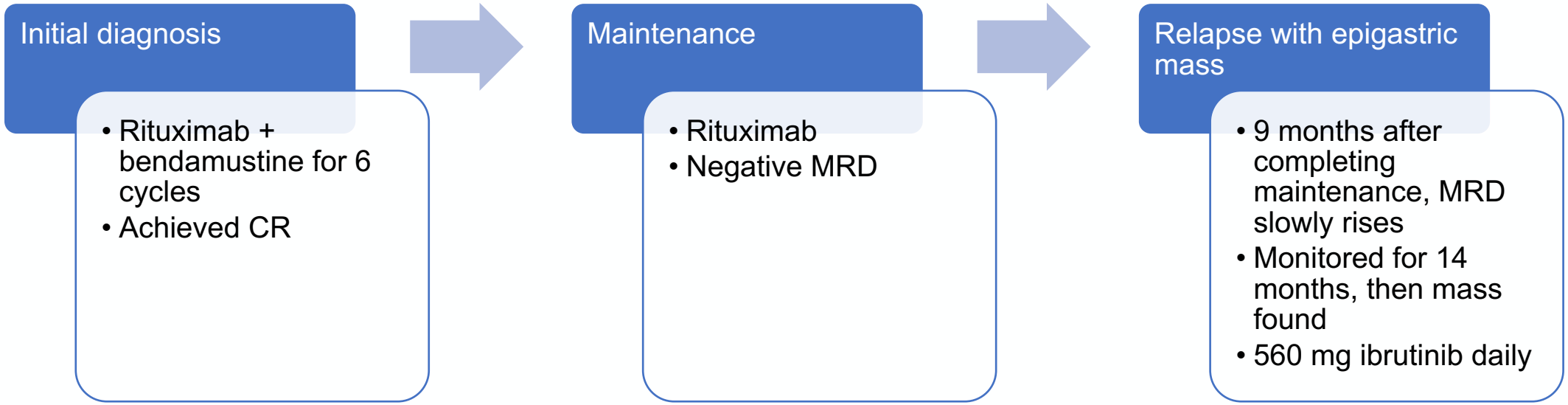
D. Switch to a treatment with the same mechanism of action but a different toxicity profile **8%**

E. Switch to a treatment with a different mechanism of action **0%**

Case 3

Introduction to Case 3: Second-Line Treatment of MCL

- Mrs. Davis is an 80-year-old woman who was previously diagnosed with stage IVA MCL



CR, complete remission; MRD, minimal residual disease

Case 3: Managing Side Effects

- Mrs. Davis' epigastric mass is responding to ibrutinib, and she returns for 3-month follow-up

Reports she has had 3 loose stools with mild abdominal cramping every morning for the past 2 weeks

- She does not leave her house during morning hours because she needs to be close to the bathroom
- After morning episodes, she has no additional diarrhea during the day

She asks what she can do to prevent the diarrhea so she can resume her usual activities?

Case 3: Work-up for Diarrhea

- Infectious gastroenteritis work-up:
  - *Clostridiales difficile*
  - *G*astrointestinal PCR panel that detects *Campylobacter*, *Escherichia coli*, *Salmonella*, Shiga-like toxin–producing *E. coli*, *Shigella*, *Vibrio cholerae*, adenovirus, norovirus, and rotavirus
- No evidence of infectious diarrhea

PCR, polymerase chain reaaction

Diarrhea Among Patients Treated With Ibrutinib

- Occurs in approximately 50% of patients
- Rarely severe
- Incidence highest in first 6 months of treatment
- Typically short-lived, with median duration 6 to 20 days
- Often self-limiting
- Ibrutinib should be held for grade 3 or higher diarrhea

Stephens DM, Byrd JC. *Blood*. 2019;133:1298-1307.

Grading Diarrhea

Grade	Definition
1	Increase of less than 4 stools per day over baseline
2	Increase of 4–6 stools per day over baseline
3	Increase of 7 or more stools per day over baseline
4	Life-threatening consequences or the need for urgent intervention
5	Death

- Mrs. Davis has had 3 loose stools per day
  - 2 more than baseline of 1 stool per day

NIH. Cancer Therapy Evaluation Program. Website Updated September 21, 2020. https://ctep.cancer.gov/protocoldevelopment/electronic_applications/ctc.htm#ctc_50. Accessed December 29, 2021.

Options for the Treatment of Diarrhea

- Low-residue diet
- Antidiarrheal medication
  - Loperamide: 4 mg after first loose stool, then 2 mg after subsequent loose stools, with maximum of 8/day
  - Diphenoxylate/atropine: 1 to 2 tabs 4 times a day, with maximum of 8/day
  - Cholestyramine: 4 g orally twice daily

Case 3: Diarrhea Treatment

- Mrs. Davis continued ibrutinib at current dose
- She began cholestyramine 4 g orally twice daily
- At her 1-week follow-up visit, she said that the diarrhea had resolved, and she resumed her normal morning activities

Clinical Pearl

Ibrutinib-induced diarrhea tends to occur early in the treatment course and usually resolves on its own within the first 1-2 months. Symptoms can be controlled with antidiarrheal medicine, and dose reduction or discontinuation is usually not necessary.

Polling Question

What is your recommendation if a patient develops grade 1 diarrhea with ibrutinib?

A. Initiate infectious gastrointestinal workup; if negative, continue ibrutinib, and manage diarrhea with supportive care **70%**

B. Initiate infectious gastrointestinal workup; if negative, hold ibrutinib until resolution of diarrhea, and manage diarrhea with supportive care **10%**

C. Initiate infectious gastrointestinal workup; if negative, dose-reduce ibrutinib and manage diarrhea with supportive care **20%**

D. Initiate infectious gastrointestinal workup; if negative, switch to an alternative therapy **0%**

Take-Home Messages

- AEs can develop any time during ibrutinib therapy
  - Treatment of hypertension is associated with a decreased risk of cardiac events
- Many AEs can be well managed with appropriate surveillance and early intervention
- Appropriate evaluation of new symptoms (e.g., diarrhea) is essential for correct management
- APs play a crucial role in identifying and managing AEs as well as providing patient education.

Q & A

Please type your questions for Laura Zitella
into the **question box** in the control panel.

Thank You