CLL PATIENT CASE STUDY

NAVIGATING A COMPLEX TREATMENT LANDSCAPE

Start Case Study

This is a hypothetical patient case.
This presentation was commissioned by Lilly Medical and is intended to be used by HCPs for medical, scientific and educational purposes.

Instructions

- This activity is an unfolding hypothetical CLL patient case designed to reflect on-label use of approved CLL products per current FDA guidance and guideline-directed management of CLL.
- During this activity, you will have the opportunity to navigate a treatment path that mimics a CLL patient's course of disease and progression through therapy lines via an interactive patient case.
- The activity will begin by introducing the patient and presentation of disease. You will then select from options for next steps in patient management and treatment selection.

These interactive elements appear throughout this slide deck, and the text below indicates what they can be used for. When you are familiar with them, use the "Begin the Activity" button below to proceed.

Click on either option to learn more and advance the patient case

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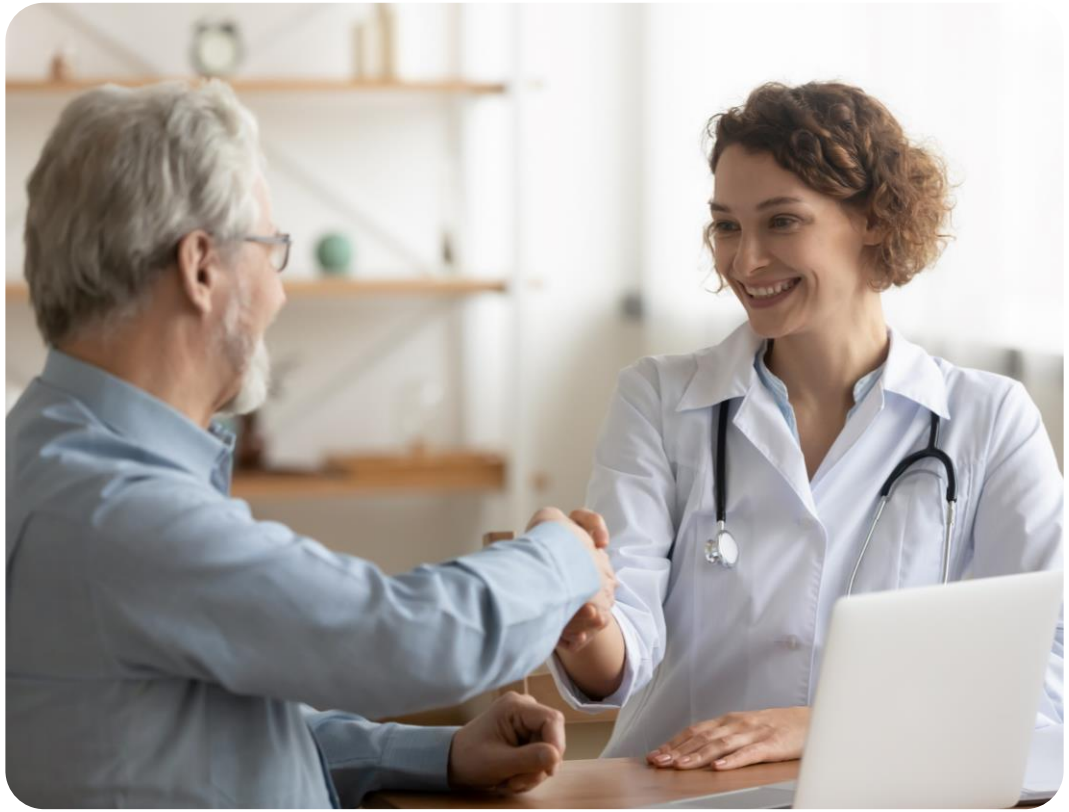
Clinical Patient Case Overview



The patient is a 65-year-old man with mild, well-managed hypertension and no other comorbidities who has been diagnosed with CLL.

At the time of diagnosis, the patient presented with complaints of worsening fatigue and lymph node enlargement over a period of several months. Physical examination revealed the presence of extensive cervical and axillary lymphadenopathy ranging between 3 and 5 cm in various areas. Laboratory results indicated leukocytosis with lymphocytosis, severe anemia, and mild thrombocytopenia.

Complete Blood Count (CBC) Panel	
• White Blood Cell (WBC) count – 125,000/µL	• Hemoglobin – 9.8 g/dL
• Lymphocytes – 75%	• Hematocrit – 31%
• Red Blood Cell (RBC) count – 2.80 × 10^6/µL	• Platelet count – 110,000/µL

Based on these findings, select an option below on the timing of the patient's treatment course:

Watch and Wait Approach

Initiate Therapy

Watch and Wait Approach

Not quite - According to the **International Workshop on Chronic Lymphocytic Leukemia (iwCLL) guidelines**, this patient matches the criteria for treatment initiation based on the presence of symptoms, lymphadenopathy, and laboratory results indicating lymphocytosis, anemia, and thrombocytopenia, all of which indicate active and advanced stage disease (eg, Rai Stage III/IV and Binet Stage C). This patient does **not** match the criteria for watch and wait or active monitoring without therapy.[1]

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Initiate Therapy

Correct - According to **iwCLL guidelines**, this patient matches the criteria for treatment initiation based on the presence of symptoms, lymphadenopathy, and laboratory results indicating lymphocytosis, anemia, and thrombocytopenia, all of which indicate active and advanced stage disease (eg, Rai Stage III/IV and Binet Stage C). Therapy should be initiated.[1]

Proceed to Next Step in Treatment Journey

Prognostic Biomarker Testing in CLL

Based on evidence of active disease, this patient will need to start therapy immediately.[1] While the Rai and Binet clinical staging systems indicate high-risk disease in this patient, these systems only account for laboratory and physical examination findings. Cytogenetic and molecular genetic evaluation of CLL cells have introduced additional prognostic factors associated with time to treatment initiation and overall survival.[2,3] In addition, biomarker results can be used to help inform treatment selection.[2,3]

Select an option below for appropriate biomarker testing at this time point of evaluation:

- **Prior to the Start of Therapy, Test for Select Cytogenetic and Molecular Biomarkers (eg, del(11q), del(17p), *TP53* mutations, *IGHV* mutational status, and karyotype)**
- **Wait Until Patient Progression or Relapse to Test for Biomarkers**

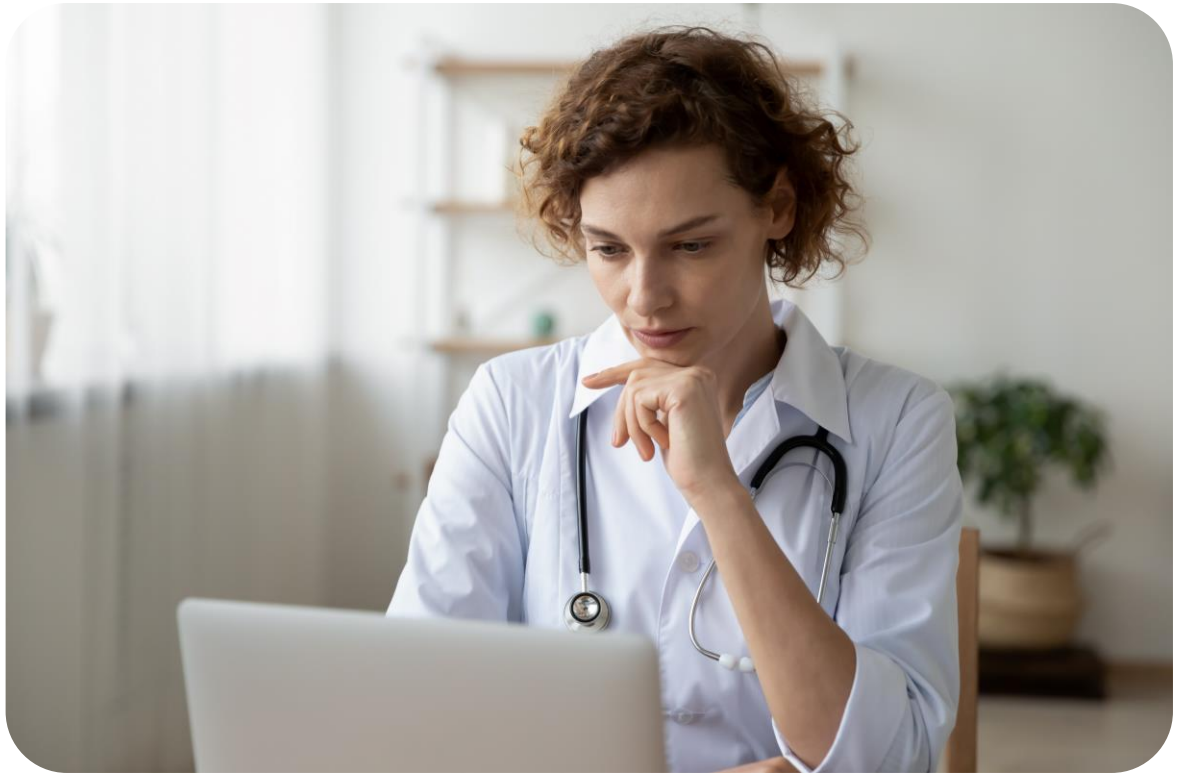
Test for Select Cytogenetic and Molecular Biomarkers Prior to Initiation of Therapy

Correct - Cytogenetic and molecular biomarkers provide complementary prognostic information that is valuable prior to selection and initiation of therapy. **For this patient**, cytogenetic and molecular biomarkers identified del(17p), a *TP53* missense mutation, and unmutated *IGHV.*

- *TP53* aberrations (including del(17p) and *TP53* mutations) are currently the most important prognostic factors in CLL predicting resistance to chemoimmunotherapy (CIT) and shorter time to progression with targeted therapies. Testing is recommended prior to the initiation of first-line therapy and before each additional line of therapy.[3,4]
- *IGHV* mutational status is an established independent prognostic factor for survival outcomes in CLL and remains consistent throughout the disease and treatment course and, therefore, doesn't need to be retested at subsequent relapses. Unmutated *IGHV* is associated with a poor prognosis and worse response to CIT.[5,6]
- Complex karyotype and chromosomal aberrations, including del(11q), have also been associated with a poor prognosis and should be tested prior to initiation of therapy.[3,6]

Proceed to Next Step in Treatment Journey

Wait Until Patient Progression or Relapse to Test for Biomarkers



Not quite - Testing for cytogenetic and molecular biomarkers, including del(11q), del(17p), and *TP53* mutations; *IGHV* mutational status; and karyotype is recommended prior to initiation of first-line therapy to help inform treatment decisions and predict likely response to therapy.[2,4]

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Clinical Decision Making in CLL

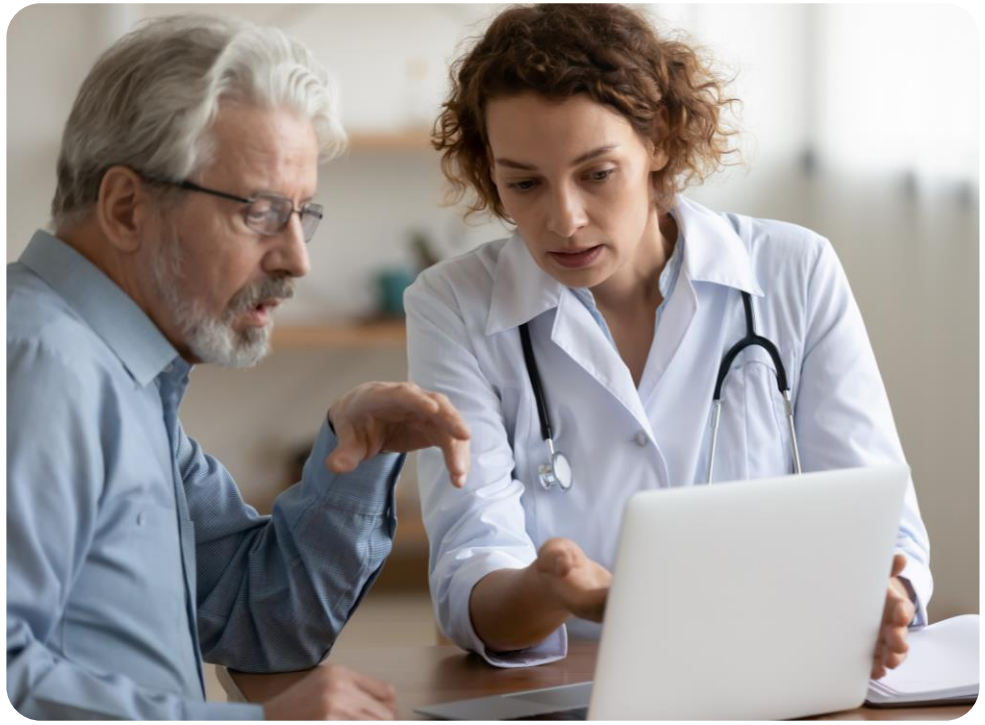
- This patient had evidence of active disease requiring treatment, and biomarker testing identified del(17p), a *TP53* missense mutation, and unmutated *IGHV* that can help inform treatment selection.
- Treatment decisions may be informed in a traditional clinician-directed approach that relies on the physician's previous experience and knowledge in therapy selection, or it may be informed by shared decision making, in which both the patient and physician work together to make a decision incorporating evidence-based information, the clinician's knowledge and experiences, and the patient's values and preferences.[7,8]

Select an option below that helps inform the treatment decision:

Shared Decision Making

Clinician-Directed Decision Making

Shared Decision Making

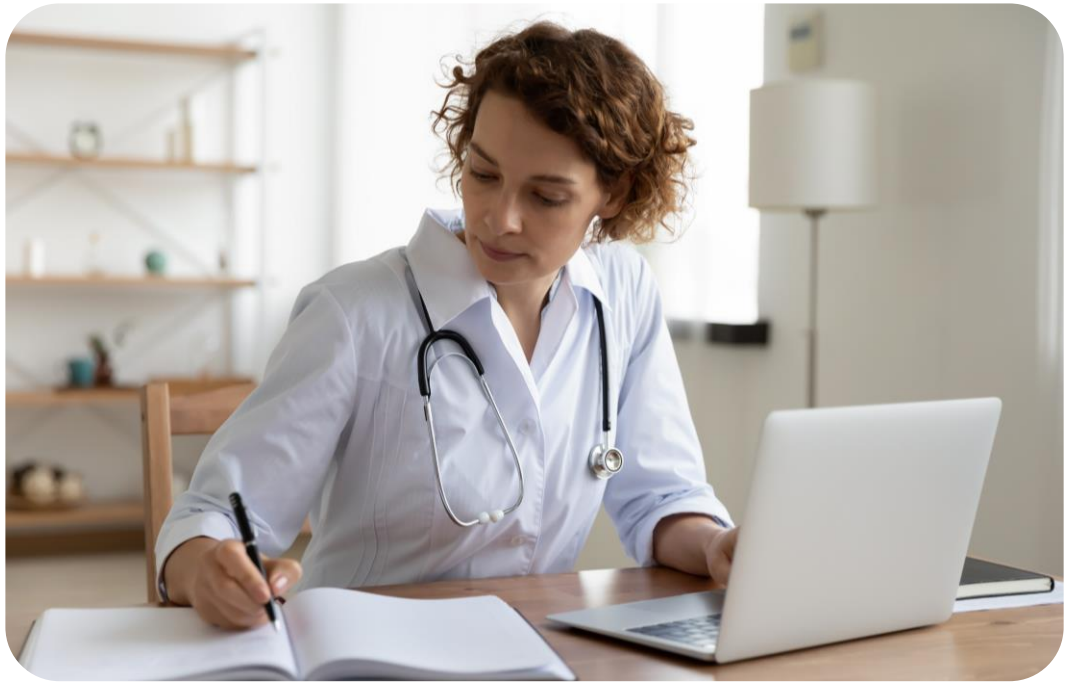


Correct - Shared decision-making (SDM) has been recognized as an important component of patient-centered care, and studies across disease states have highlighted potential benefits of this approach, including improvement in adherence, a decrease in patient decisional regret, and a decrease in health care costs.[9]

- The patient in this hypothetical case scenario lives in a rural area, making frequent visits to the clinic difficult. He prefers an approved oral regimen that he can manage independently without frequent clinic visits and doesn't mind taking a pill every day. He is not interested in clinical trial participation during this SDM encounter.

Proceed to Next Step in Treatment Journey

Clinician-Directed Decision Making



Not quite - It is appropriate to incorporate both the clinician's knowledge and experience and the patient's values and preferences when making treatment decisions. Shared decision-making (SDM) has been recognized as an important component of patient-centered care, and studies across disease states have highlighted potential benefits of this approach, including improvement in adherence, a decrease in patient decisional regret, and a decrease in health care costs.[9]

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Selection of First-Line Therapy

Cytogenetic and molecular testing identified del(17p), a *TP53* missense mutation, and unmutated *IGHV* in this patient, features associated with high-risk CLL. Considering the genetic disease profile, the patient's history and physical examination findings, and the patient's preferences (as expressed via SDM), select the most appropriate first-line treatment option for this patient.

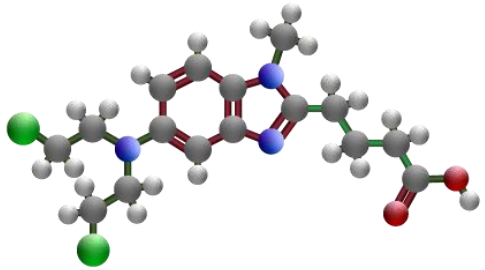
Select an appropriate first-line treatment option below for this patient:

- BR (Bendamustine + Rituximab)
- Ibrutinib
- Second-Generation Covalent BTK Inhibitor
- Venetoclax + Obinutuzumab

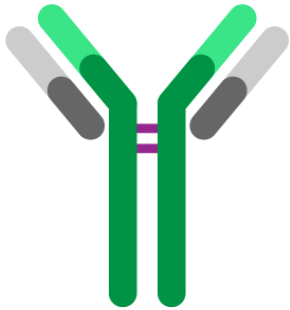
BR (Bendamustine + Rituximab)

CIT is **not** considered standard management in patients with *TP53* aberrations, who require drugs that promote cell death independently of p53.[10,11] With the availability of nonchemotherapeutic targeted treatments, the role of CIT in the management of CLL is now limited; it remains a recommended option only for patients with mutated *IGHV*, unaltered *TP53*, and noncomplex karyotype.[11]

Bendamustine



Rituximab



Return to Previous Step to Explore Other Treatment Options

Ibrutinib

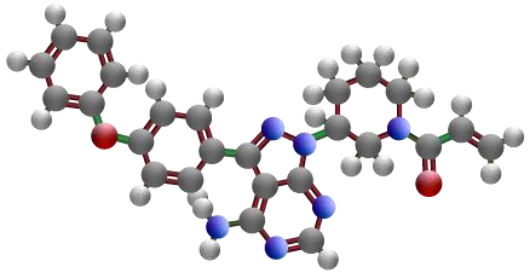
This is an FDA-approved treatment for front-line CLL

First-generation covalent BTK inhibitor ibrutinib is approved for use in adult patients with CLL.[12] **However**, second-generation covalent BTK inhibitors acalabrutinib and zanubrutinib are now clinical guideline–preferred regimens due to their potential for less off-target effects and a more favorable safety profile.[13]

- In ELEVATE-RR, a head-to-head trial of acalabrutinib vs ibrutinib in patients with relapsed/refractory (R/R) CLL, all-grade atrial fibrillation/atrial flutter was significantly less frequent with acalabrutinib compared with ibrutinib.[14] In the ALPINE trial, a head-to-head trial of zanubrutinib vs ibrutinib in patients with R/R CLL, zanubrutinib demonstrated a numerically lower rate of all-grade atrial fibrillation or flutter compared with ibrutinib in patients with R/R CLL.[15]

- Zanubrutinib has shown superior efficacy to ibrutinib in the ALPINE trial,[15] and acalabrutinib has been shown to be noninferior to ibrutinib in the ELEVATE-RR trial.[14]

Ibrutinib



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Second-Generation Covalent BTK Inhibitor

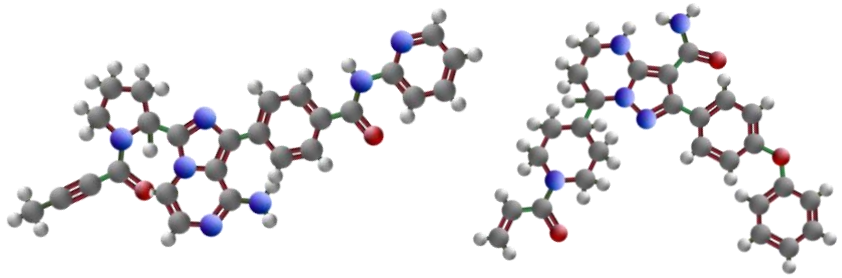
This is an FDA-approved treatment for front-line CLL

Second-generation covalent BTK inhibitors, including acalabrutinib and zanubrutinib, have become a **commonly accepted standard** for first-line treatment of patients with symptomatic CLL with or without *TP53* loss and/or mutation.[10,13] This would be an **acceptable** first-line treatment option for this patient.

- Based on results from the ELEVATE-TN and ASCEND trials, **acalabrutinib** is approved for treatment either as a single agent or in combination with obinutuzumab for adult patients with CLL.[16] A progression free survival (PFS) benefit for **acalabrutinib ± obinutuzumab** compared with obinutuzumab-chlorambucil has been demonstrated in previously untreated patients with or without del(17p) or *TP53* mutation.[17]

- Based on results from the SEQUOIA and ALPINE trials, **zanubrutinib** is approved for adult patients with CLL.[18] Single-agent **zanubrutinib** has demonstrated clinically meaningful activity in previously untreated patients with CLL including del(17p) and/or *TP53* mutation in the prospectively enrolled, nonrandomized cohort of SEQUOIA.[19]

Acalabrutinib ***Zanubrutinib***



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Proceed to Next Step in Treatment Journey

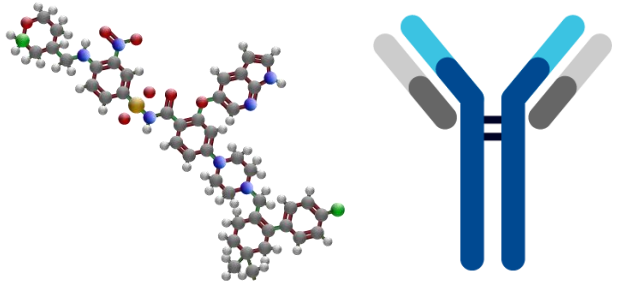
Venetoclax + Obinutuzumab

This is an FDA-approved treatment for front-line CLL

Based on results from the CLL14 trial, fixed-duration venetoclax + obinutuzumab is approved for use in previously untreated patients with CLL.[20,21] A fixed-duration regimen of venetoclax + obinutuzumab involves 6 cycles of obinutuzumab intravenous (IV) infusions (complete after 6 months) and venetoclax oral tablets administered in a 5-week dose ramp-up to 400 mg daily to gradually reduce tumor burden and decrease risk of tumor lysis syndrome (completed after 12 months).[21]

- This regimen can also be considered for patients who are not good candidates for BTK inhibitors (eg, significant or uncontrolled cardiac comorbidities)[10] or based on a patient's preference for a fixed-duration option. Evidence supporting first-line use of venetoclax in patients with *TP53* aberrations remains limited.[11,22]
- In this hypothetical case scenario, an SDM encounter revealed that the patient preferred a single-agent oral treatment option that he could take independently, so this would **not** be the best treatment option when factoring in patient/physician shared decision making.

Venetoclax ***Obinutuzumab***



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First-Line Treatment Journey and Relapse

Shared decision-making with the patient led to selection of a **second-generation covalent BTK inhibitor**. Therapy was initiated with **acalabrutinib**. Within 4 months, the patient experienced a partial response to therapy and was able to maintain long-term disease control.

- Shortly after initiating therapy, the patient experienced low-grade headache and diarrhea that were mitigated at home with over-the-counter (OTC) medications. After 2 years on therapy, the patient experienced grade 1 atrial fibrillation and was closely monitored for increased severity and symptoms of arrythmia. No dosage modifications were needed.
- After 4 years on acalabrutinib, the patient began experiencing worsening fatigue and night sweats, and a CBC confirmed rapidly progressive disease in the form of anemia and lymphocytosis. Considering prior first-line therapy, duration of remission, and progression on treatment, select an appropriate second-line therapy.

Select an appropriate second-line treatment option below for this patient:

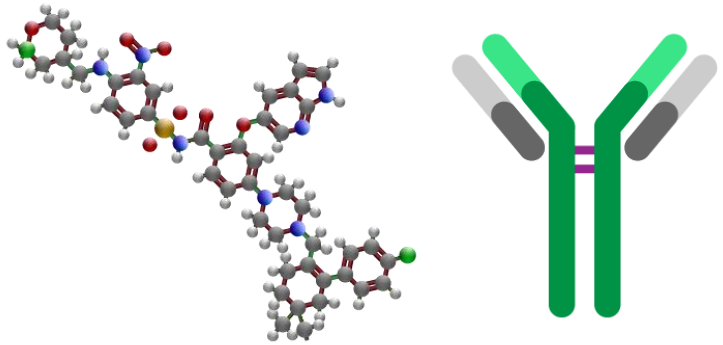
- **Venetoclax + Rituximab**
- **Covalent BTK Inhibitor**
- **Idelalisib + Rituximab**

Venetoclax + Rituximab

This is an FDA-approved treatment for R/R CLL

Based on the MURANO trial, **venetoclax in combination with rituximab is approved** for use in patients with CLL who have progressed after receiving at least 1 previous treatment regardless of *TP53* mutational status.[23,24] A regimen of fixed-duration venetoclax + rituximab involves venetoclax oral tablets administered in a 5-week dose ramp-up to 400 mg daily to gradually reduce tumor burden and decrease risk of tumor lysis syndrome (complete after 24 months) and 6 cycles of rituximab IV infusions that are started after the initial venetoclax dose ramp-up (complete after 6 months).[21] Current evidence supports using a venetoclax-based regimen in patients with CLL who experience disease progression on a covalent BTK inhibitor.[25-28]

Venetoclax ***Rituximab***



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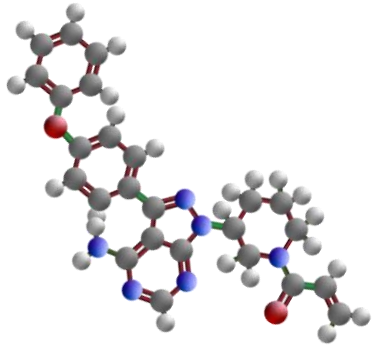
Proceed to Next Step in Treatment Journey

Covalent BTK Inhibitor

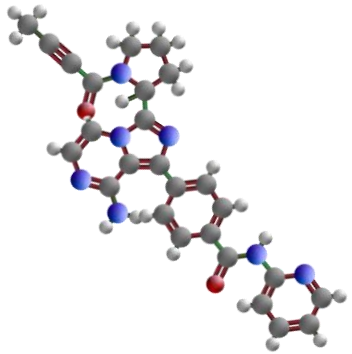
This is an FDA-approved treatment for R/R CLL

Current guidelines **do not** recommend sequencing a second covalent BTK inhibitor after progression following first-line treatment with a covalent BTK inhibitor since mutations may have developed that would confer resistance to other covalent BTK inhibitors, such as a mutation in the BTK cysteine 481 residue to which the inhibitors covalently bind.[25,26,28]

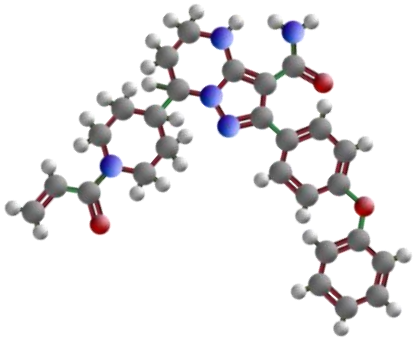
Ibrutinib



Acalabrutinib



Zanubrutinib



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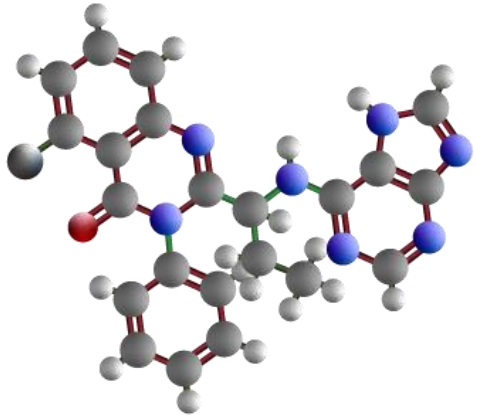
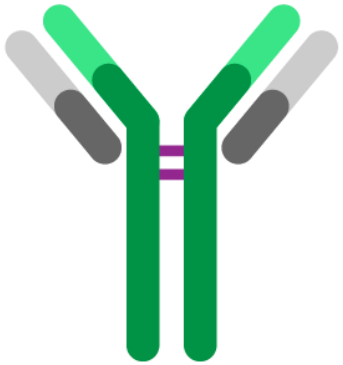
Idelalisib + Rituximab

The use of PI3K inhibitor idelalisib + rituximab would **not** be appropriate for this patient. Toxicity concerns with the use of PI3K inhibitors have **limited their use to patients with progressive disease after at least 2 lines of therapy**.[3,29,30] Idelalisib is currently approved for the treatment of relapsed CLL in combination with rituximab, in patients for whom rituximab alone would be considered appropriate therapy due to other comorbidities based on results from a randomized phase 3 study of idelalisib + rituximab vs placebo + rituximab in patients with R/R CLL.[29,30]

Idelalisib



Rituximab



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Second-Line Treatment Journey and Relapse

Following progression on front-line therapy with acalabrutinib, the patient was switched to a **fixed-duration regimen of venetoclax + rituximab**.

- During therapy, the patient experienced grade 3 neutropenia with a fever that resulted in a dose interruption until resolution to grade 1. The patient achieved a partial response within ≈4 weeks of initiating the full dose of venetoclax.

- However, after 2 years, the patient experienced disease progression again manifesting as anemia, thrombocytopenia, and enlarged axillary lymph nodes. During this time, the patient's Eastern Cooperative Oncology Group (ECOG) performance score increased to 2. **Considering that progression has now occurred on both a BTK inhibitor and BCL-2 inhibitor, select an appropriate third-line therapy**.

Select an appropriate third-line treatment option below for this patient:

- **Lisocabtagene Maraleucel (CAR T-Cell Therapy)**
- **Pirtobrutinib**
- **Enrollment in a Clinical Trial**

Pirtobrutinib

This is an FDA-approved treatment for R/R CLL in the post-BTK and post–BCL-2 inhibitor setting

This is an **appropriate treatment** option for this patient. Based on results from the BRUIN trial, **pirtobrutinib** has received accelerated approval for the treatment of patients with CLL who have progressed on or been intolerant to at least 2 prior lines of therapy, including a BTK inhibitor and a BCL-2 inhibitor.[31,32] Eligibility for therapy also includes having an ECOG PS of 0 to 2.[31,32] Pirtobrutinib is administered at 200 mg orally once daily.[31] Pirtobrutinib is a noncovalent (reversible) BTK inhibitor that does not engage on the cysteine 481 binding site and inhibits both cysteine 481-mutant and unmutated BTK with similar efficacy. Pirtobrutinib has demonstrated efficacy and tolerability in patients who progressed on or were intolerant (eg, cardiotoxicity) to a prior covalent BTK or BCL-2 inhibitor.[31,32]

Pirtobrutinib

Return to Previous Step to Explore Other Treatment Options

Proceed to Next Step in Treatment Journey

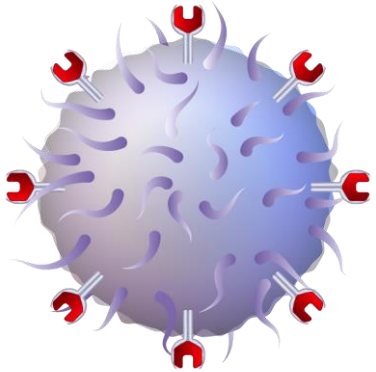
Lisocabtagene Maraleucel (CAR T-Cell Therapy)

This is an FDA-approved treatment for R/R CLL in the post-BTK and post–BCL-2 inhibitor setting

Lisocabtagene maraleucel (liso-cel) is an approved treatment option for patients with progressive CLL after several lines of targeted therapies. The FDA granted accelerated approval to liso-cel for patients with R/R CLL who have received at least 2 prior lines of therapy, including a BTK inhibitor and a BCL-2 inhibitor based on data from the TRANSCEND CLL 004 trial, in which liso-cel demonstrated efficacy and tolerability in this patient population.[33,34] Eligibility for therapy also includes having an ECOG PS of 0 or 1.[33,34] The treatment process can take ≈2 to 3 months and includes leukapheresis, manufacturing, administration, and adverse event (AE) monitoring.

- In this hypothetical case scenario, the HCP and patient decided this was **not** the best option at this time due to the need for the patient to start a therapy immediately, the patient's clinical fitness (ECOG PS of 2), and the distance required to travel to an authorized treatment center from the patient's home.

Lisocabtagene maraleucel



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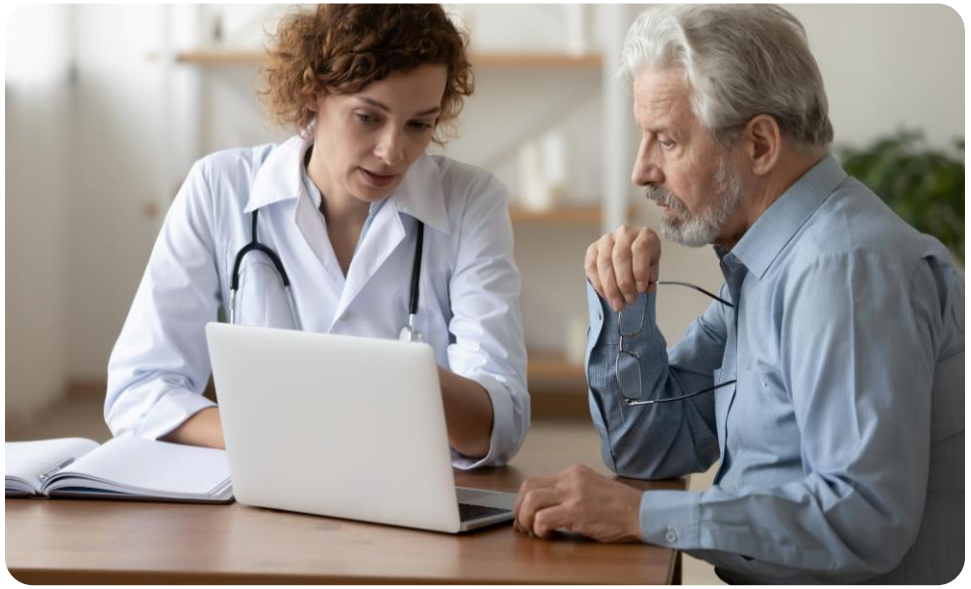
Enrollment in a Clinical Trial

This is a guideline-recommended approach for R/R CLL

Enrollment in a suitable, well-designed clinical trial exploring novel therapeutics is a reasonable option for patients with double-refractory CLL due to the limited approved treatment options. **However**, in this hypothetical patient case scenario, the patient preferred to use one of the currently FDA-approved treatment options in the R/R setting.



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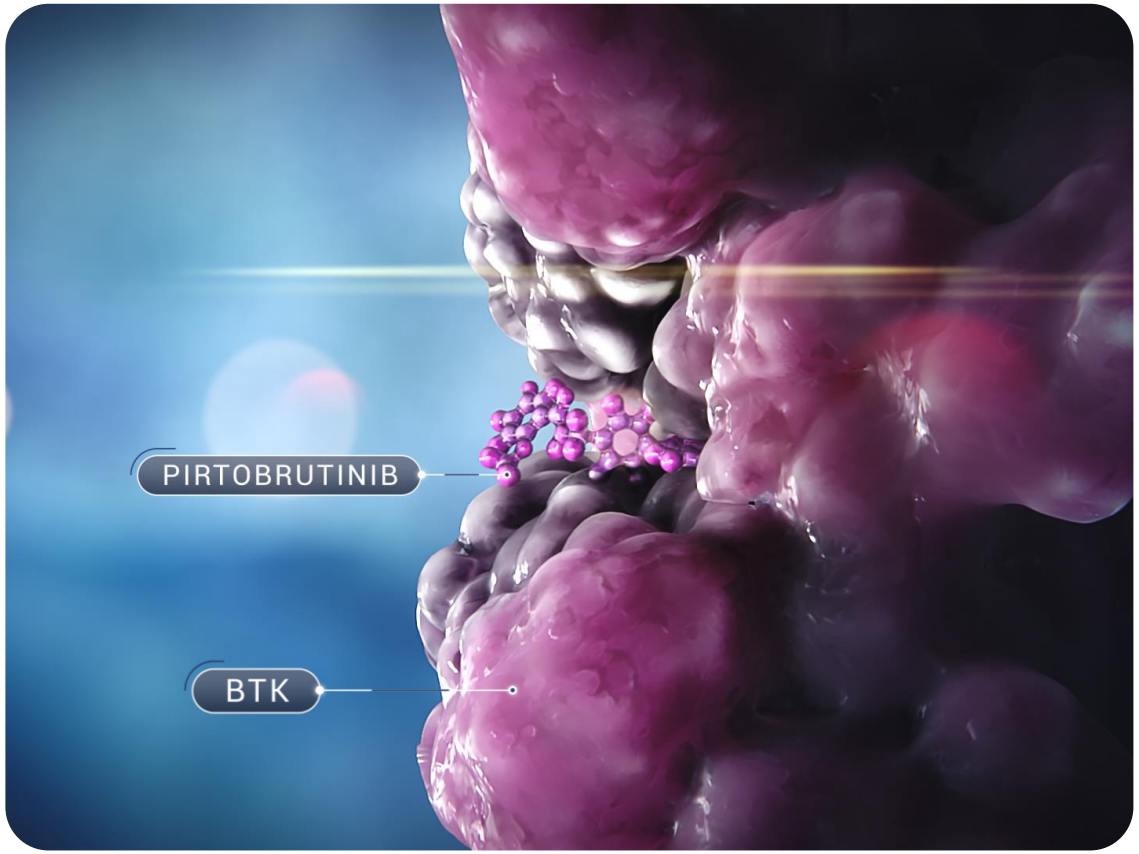
Subsequent Treatment Journey and Pirtobrutinib Response

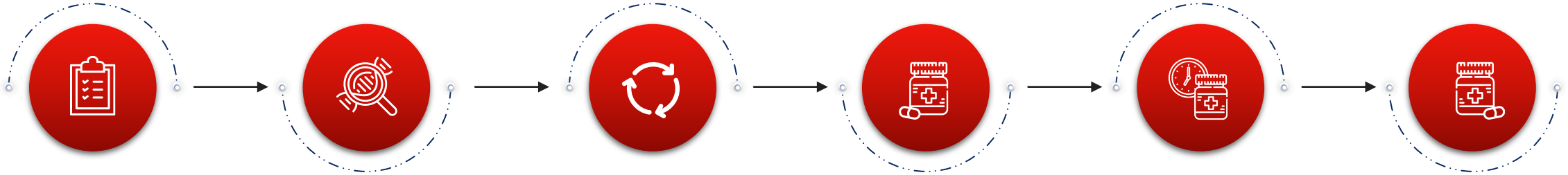


Following progression on both a covalent BTK inhibitor and BCL-2 inhibitor, the patient was placed on **noncovalent BTK inhibitor pirtobrutinib**.

- The patient achieved a partial response ≈8 weeks after initiation of therapy. After 6 months of continuous therapy, the patient is still responding to pirtobrutinib and tolerating the treatment well.
- The patient has reported mild grade 1 and 2 AEs consisting of fatigue, occasional joint pain, bruising, and fever but has been able to maintain the prescribed pirtobrutinib dosing schedule.

Advance to Patient Case Summary

Summary of Patient's Treatment Path



Decision to Initiate Therapy

Need to start therapy based on iwCLL criteria

Biomarker Testing

Revealed high-risk disease (eg, del(17p)/ *TP53* mutation)

Clinical Decision-Making

Shared decision-making to inform treatment selection

Front-Line Therapy

Covalent BTK inhibitor (acalabrutinib)

Second-Line Therapy

Fixed-duration venetoclax + rituximab

Third-Line Therapy

Pirtobrutinib

Selecting the appropriate treatment option to optimize patient outcomes requires consideration of disease characteristics, patient preferences and comorbidities, and prior treatment sequencing.

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