Patient Management Strategies for Newly Diagnosed CLL

Report Date: February 3, 2025

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for BeiGene

INTRODUCTION

As the most prevalent type of leukemia that continues to have an increasing global incidence, chronic lymphocytic leukemia (CLL) represents a hematologic malignancy that most oncology health care providers will encounter.[1] Appropriate choice of treatment coupled with multidisciplinary supportive and survivorship care are critical to optimizing outcomes for patients with CLL. To better understand the CLL treatment paradigm through the perspective of recognized thought leaders, NCODA members were invited to participate in a survey to obtain their insights into CLL management, including a focus on identifying patients with early signs of resistance or intolerance to current first-line treatments and exploring alternative agents within the same drug class.

A total of 97 NCODA members completed the survey. Responses were anonymously collected, and findings were aggregated into the data reported herein.

CHRONIC LYMPHOCYTIC LEUKEMIA (CLL) OVERVIEW

BACKGROUND

CLL is a hematologic malignancy characterized by the clonal proliferation and accumulation of mature, typically CD5-positive, B-cells within the blood, bone marrow, lymph nodes, and spleen.[2] CLL is the most prevalent adult leukemia in Western countries; in the United States alone, an estimated 20,700 people were diagnosed with CLL and an estimated 4,440 people died from the disease in 2024.[3] The average age at diagnosis is 70 years, and men have a slightly higher risk of CLL than women.[4]

The genetic and mutational landscape of CLL is heterogeneous and plays an important role in the prognosis and evolution of CLL.[5,6] The Rai and Binet staging systems are used for the evaluation of patients with CLL, and rely on physical assessments and blood parameters to evaluate the degree of tumor burden.[6] However, progress in CLL therapy necessitated a more adequate way to distinguish prognostic subgroups. Hence, the CLL International Prognostic Index (CLL-IPI), which combines genetic, biochemical, and clinical parameters into a prognostic model (discriminating four prognostic subgroups) was developed.[7]

TREATMENT LANDSCAPE

The initiation of treatment for CLL depends on the presence of active or symptomatic disease.[2,6] Patients with early-stage, asymptomatic disease are monitored without therapy unless there is evidence of rapid disease progression, whereas treatment should be initiated in patients who progress or present with progressive or symptomatic disease. Outside of a clinical trial, treatment of CLL has largely evolved from conventional chemotherapeutic agents combined with anti-CD20 antibodies to individualized therapy with targeted agents.

In the first-line setting, high risk characteristics (eg, del(17p), *TP53* mutation) and age/fitness level are the main determinants for therapy selection.[4] National Comprehensive Cancer Network (NCCN) suggested treatment regimens in the first-line CLL setting are displayed in Table 1.[8] Considerations for determining choice of first-line treatment include patient preference, toxicity profile of the regimens, and logistics for each therapy. Bruton tyrosine kinase (BTK) inhibitor (BTKi) therapy with or without a CD20 monoclonal antibody is administered until disease progression, whereas the venetoclax and obinutuzumab combination is administered for a fixed duration. Venetoclax is less preferred in patients with a high tumor burden or reduced creatinine clearance; BTKi are less preferred in patients with a history of cardiac arrythmia, on therapeutic anticoagulation, or with difficult-to-control hypertension.

Table 1. NCCN Suggested First-Line CLL Treatment Regimens

Preferred Regimens	Other Recommended Regimens	Useful in Certain Circumstances
CLL Without del(17p)/*TP53* Mutation		
• Acalabrutinib ± obinutuzumab[a] • Zanubrutinib[a] • Venetoclax + obinutuzumab[a]	• Ibrutinib[a] • Ibrutinib + venetoclax	• FCR: consider for IGHV-mutated CLL in patients <65 yo without significant comorbidities • Ibrutinib + anti-CD20 mAb • Bendamustine + anti-CD20 mAb[b] • Obinutuzumab ± chlorambucil[b] • HDMP + anti-CD20 mAb[b]
CLL With del(17p)/*TP53* Mutation		
• Acalabrutinib ± obinutuzumab • Zanubrutinib • Venetoclax + obinutuzumab	• Ibrutinib • Ibrutinib + venetoclax	• HDMP + anti-CD20 mAb[b] • Obinutuzumab[b]

[a]category 1.
[b]Consider when cBTKi and venetoclax not available or contraindicated or rapid disease debulking needed
cBTKi, covalent BTK inhibitor; FCR, fludarabine, cyclophosphamide, rituximab; HDMP, high-dose methylprednisolone; mAb, monoclonal antibody.

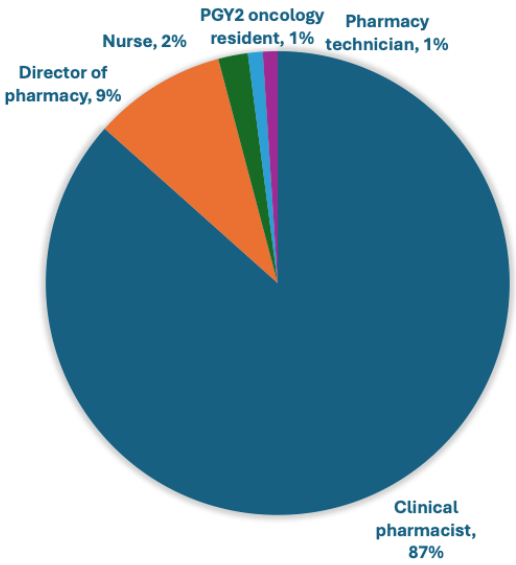
The type of initial treatment, response and duration, and acquired resistance to treatment play a role in choice of treatment for second-line and subsequent CLL therapy as well as relapsed or refractory disease.[8] Acalabrutinib, zanubrutinib, and venetoclax ± rituximab are preferred treatment options for second-line and subsequent therapy. Ibrutinib is used less frequently due to its toxicity profile.

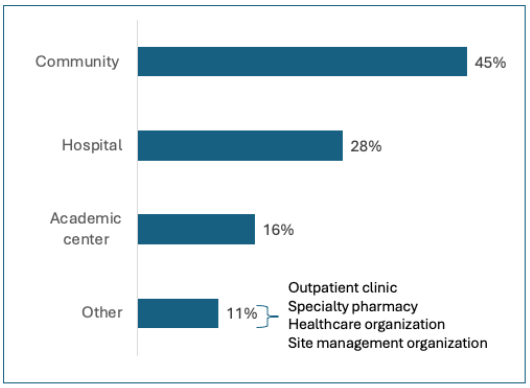
Understanding regimen tolerance and time to disease progression in patients previously treated with venetoclax + obinutuzumab can help determine whether to switch to a different class of therapy or continue venetoclax. Also, patients with a durable response to venetoclax + obinutuzumab may be considered for retreatment if >12 months off therapy. Switching to BTKi-based therapy is recommended for patients who did not tolerate venetoclax-based treatment well or had disease progression on or shortly after treatment. Switching to a venetoclax-based regimen is recommended for patients who received a BTKi and had disease progression. In patients with poor tolerance to a BTKi, switching to a different BTKi may be appropriate.

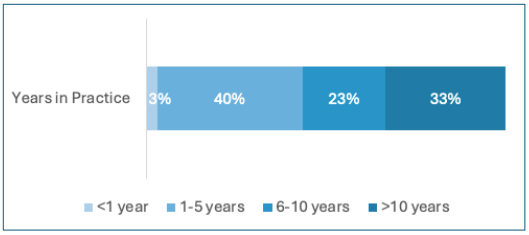
Pirtobrutinib is an effective alternative for the management of intolerance or resistance to a covalent BTKi. Pirtobrutinib and lisocabtagene maraleucel are also options for relapsed/refractory CLL after prior treatment with BTKi and/or venetoclax-based regimens.

SURVEY PARTICIPANTS

Ninety-seven participants answered the survey. Breakdown of participant role, years in practice, and practice setting are displayed in the chart.







Of the 97 survey participants, 87% were clinical pharmacists. The majority of respondents have been in practice for 1-5 (40%) or >10 years (33%). All practice settings were represented among participants, with the majority from a community or hospital practice.

Practice setting characteristics elucidated in the survey were as follows:

- 82% have a pharmacist working in the clinic areas (of these 39% community, 27% hospital, 20% academic, 14% other).
- 86% have a medically integrated pharmacy (MIP; of these 48% community, 27% hospital, 15% academic, 9% other).
- 91% of practices have a process for coordinating regimens that include both intravenous and oral medications.

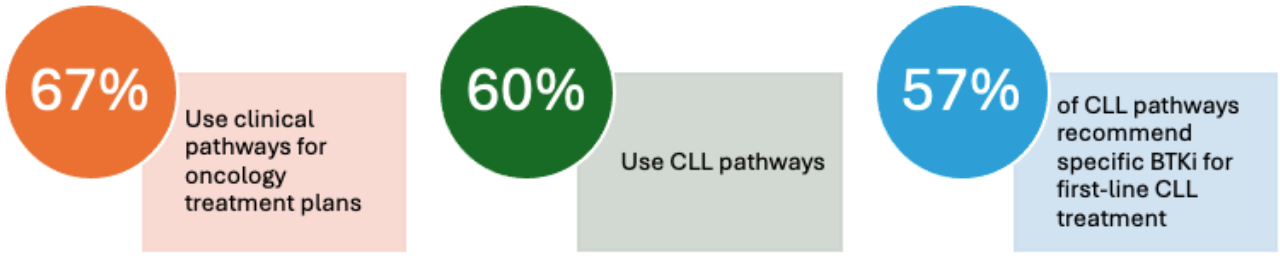
PATHWAYS FOR CLL

Most participants' (67%) practices utilize clinical pathways (see chart for types utilized) for oncology treatment plans; of these, practice setting was predominantly community (43%) or hospital (31%), followed by academic center (15%) and other (11%). Pathways utilized are mostly internally developed (71%).

The majority (55%) of participants have pathways integrated within the electronic medical record (EMR)(8% unsure); practice settings for those with pathway EMR integration generally followed participant demographics, with mostly community (45%) or hospital (30%), followed by academic center (13%) and other (11%).

Participants were asked about pathways for CLL. Most (60%) participants use CLL clinical pathways (13% were unsure). Of those utilizing CLL pathways, practice setting reflected participant demographics with predominantly community (47%) or hospital (25%), followed by academic center (17%) and other (5%). Though most (60%) participants indicated that they were unsure about pathway adherence for first-line treatment of CLL, 22% and 11% indicated high adherence rates of 80% and 60-79%, respectively. Most participants (57%) indicated that specific BTKi products are recommended for first-line CLL treatment within pathways (22% were unsure); practice setting was mostly community (52%) or hospital (28%), followed by academic center (11%) or other (9%).

KEY TAKEAWAYS



- Community and hospital practice settings are the most predominant users of clinical pathways, approximately half of which are integrated into the EMR.

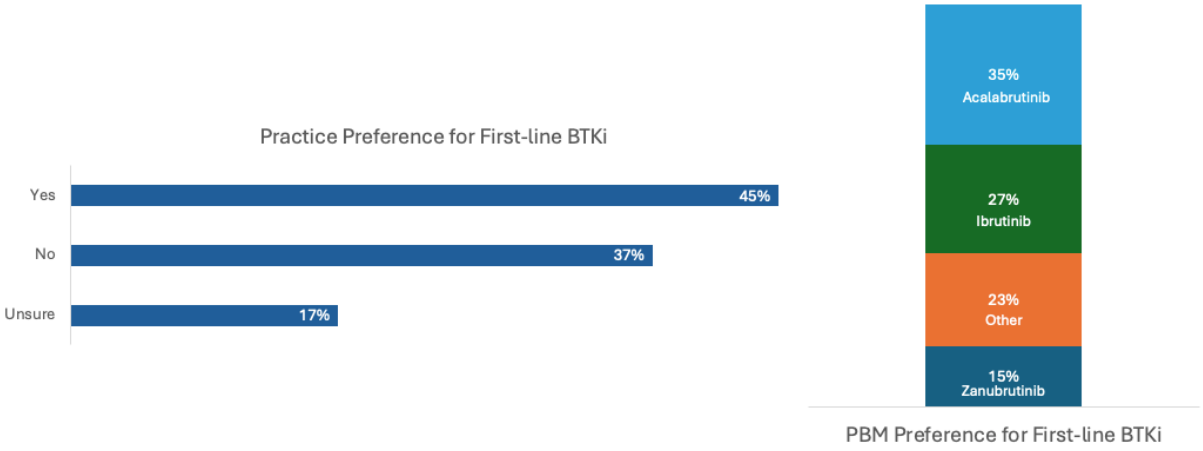
CHOICE OF THERAPY

Participants were asked about first-line treatment options for CLL and choice of treatment. Most respondents indicated that first-line decision making includes branching based on the presence of a del(17p)/*TP53* mutation. Not accounting for participants with an "unsure" response, 92% indicated that BTKi are preferred for patients with del(17p)/*TP53*. In terms of frequency in choice of fixed-duration treatment with venetoclax + obinutuzumab vs continuous BTKi therapy (±anti-CD20 mAb) as first-line treatment, most indicated that fixed duration treatment is preferred most (18%) or some (47%) of the time, though 24% were unsure. Practice setting did not indicate any variance from the participant institutional demographics, with most/some responses as follows: community 46%, hospital 26%, and academic center 20%. See chart summary.

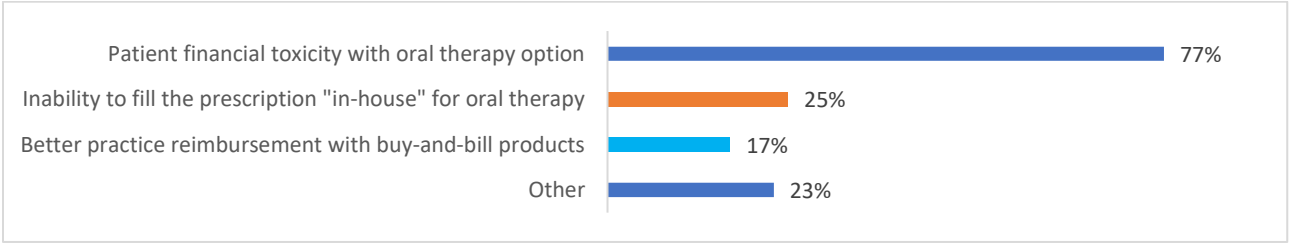
84%	• First-line decision making includes branching based on the presence of a del(17p)/*TP53* mutation • 82% of these practice in community or hospital setting
92%*	• BTKi are preferred for patients with del(17p)/*TP53* mutation • 80% of these practice in a community or hospital setting
65%	• Prefer fixed duration treatment with venetoclax + obinutuzumab vs continuous BTKi (±anti-CD20 mAb) most or some of the time

*Does not account for "unsure" responses.

Survey results indicated that MIPs have relatively full access to dispense BTKi and venetoclax as follows: acalabrutinib (93%), ibrutinib (98%), zanubrutinib (98%), and venetoclax (99%). There was a split in whether practices had a preferred BTKi for first-line treatment (see chart). Forty percent of participants were unsure whether they encounter plans who have step therapy for BTKi therapy. Breakdown of frequency of encountering step BTKi therapy plans was as follows: 5% encountered ≥80% of the time, 9% 60-79% of the time, 15% 40-59% of the time, 12% 20-39% of the time, and 18% <20% of the time. Survey results indicated that acalabrutinib is most frequently preferred BTKi by PBMs for initial therapy and zanubrutinib is least preferred (see chart).



Approximately two-thirds of participants (69%) indicated that chemoimmunotherapy treatment options (eg, FCR, bendamustine + anti-CD20) are available first-line treatment options within their EMR. Notably, 18% were unsure of whether these options are available. Practice settings for those with first-line chemoimmunotherapy options were predominantly community (46%) and hospital (31%), followed by academic (16%) and other (6%). Potential reasons for initiating chemoimmunotherapy are displayed in the chart.



Participants were asked about factors that affect the selection of a preferred agent within their practice. Efficacy and safety ranked highest (97% and 95%, respectively), followed by economics/contracting (67%), length of follow-up/data maturity (49%), and manufacturer distribution network (35%).

KEY TAKEAWAYS

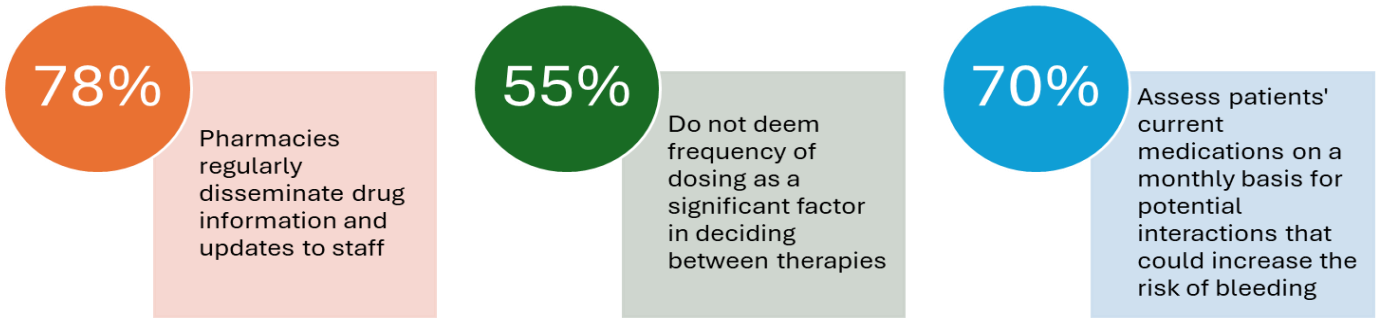
- First-line decision making typically includes branching based on the presence of a del(17p)/*TP53* mutation, and BTKi are preferred for patients with del(17p)/*TP53*.
- Two-thirds (65%) of participants prefer fixed-duration treatment with venetoclax + obinutuzumab over continuous BTKi therapy (±anti-CD20 mAb) as first-line treatment most or some of the time.
- While practices were mostly split regarding whether they have a preferred first-line BTKi, PBMs appear to prefer acalabrutinib most and zanubrutinib least.
- Chemoimmunotherapy treatment options are still available first-line treatment options in 69% of participants' EMR.
- The main factors that impact selection of a preferred agent are efficacy, safety, and economics/contracting.

DRUG ADMINISTRATION

Participants were asked about education, dosing, and administration of CLL treatments. Key findings are summarized herein.

- Most participants' (78%) pharmacies regularly disseminate drug information and updates to staff.
- More than half of participants (55%) do not deem frequency of dosing (ie, once vs twice daily) a significant factor in deciding between therapies. When given the option to dose zanubrutinib one or twice daily, 31% of practices prefer once daily, 16% twice daily, 40% no preference, and 12% unsure.
- Most participants were either unsure of (36%) or indicated that the minority of patients are hospitalized for initiation of first-line venetoclax: 29% answered <20%, 19% answered 20-39%, 15% answered 40-≥80%.
- Most participants (70%) assess a patient's current medications for potential interactions that could increase the risk of bleeding on a monthly basis with assessment/refill calls; 18% assess at patient onboarding only, and 4% each assess quarterly, bi-annually or annually, or never. At onboarding only was predominantly observed in the community and hospital settings (89%).

KEY TAKEAWAYS



MONITORING THERAPY

Participants were asked about various interactions that take place to monitor patients' tolerability to therapy. Key findings are summarized herein.

- 55% of participants include potential drug side effects and estimated timing of their onset within pharmacy treatment plans (8% were unsure).
- Most participants always (76%) or sometimes (13%) consider an alternative BTKi for patients intolerant to but not progressing on BTKi therapy.
- Pharmacists proactively reach out to patients initiating a BTKi as follows:
    - Within first 30 days: once within 7 days of therapy initiation (46%) or weekly (8%), with the remainder unsure (20%) or other, not specified (25%).
    - Within 60-90 days: answers were variable and included every 2 weeks, 2-3 times, monthly, seldomly.
- When patients experience grade 3 side effects when taking a BTKi, 76% of participants hold the dose and then restart as indicated in the product label and 35% hold the dose and initiate an alternative BTKi when symptoms are resolved.

Participants were asked about their familiarity with the Lancet publication on the use of zanubrutinib in patients intolerant of ibrutinib or acalabrutinib or both. Two-thirds (67%) had some familiarity (extremely familiar 16%, moderately 15%, somewhat 36%), while 24% and 8% were not so familiar or not at all familiar, respectively.

KEY TAKEAWAYS

Potential drug side effects and timing is included within pharmacy treatment plans 55% of the time.

Alternative BTKi are considered for patients intolerant to but not progressing on BTKi therapy.

Pharmacists and nurses provide proactive outreach to patients on BTKi therapy in variable schedules.

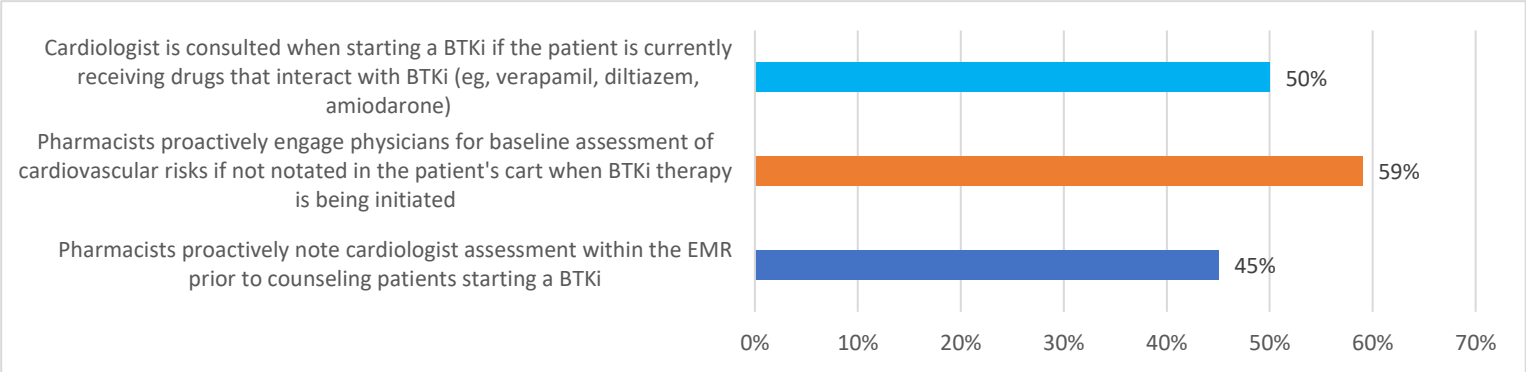
Holding the dose and restarting as indicated on product label is the most common approach for grade 3 BTKi side effects.

CARDIAC MONITORING

Questions related to cardiac history, baseline assessments, and monitoring were included in the survey as follows below.

Cardiac History

Proactive mitigation and monitoring is common in patients with a history of atrial fibrillation and under the care of a cardiologist as shown in the chart.



Most participants (62%) obtain a comprehensive cardiac history before initiating BTKi treatment, though 25% were unsure. Practice setting distribution of these participants reflected the demographics surveyed as follows: 39% community, 31% hospital, 18% academic, and 11% other. In patients with hypertension and/or a history of cardiac arrhythmias, 48% of participants consider anticoagulation therapy (35% were unsure).

Baseline Assessments

- 86% of participants document a baseline blood pressure prior to initiating BTKi treatment (8% were unsure).
- 58% of participants obtain a baseline ECG prior to initiating BTKi treatment (24% were unsure).

Monitoring

- Most participants (76%) indicated that they obtain a cardiologist consult for patients developing new atrial fibrillation while on BTKi therapy (23% were unsure).
- According to 59% of participants, care plans do not specify timing of anticipated side effects (eg, atrial fibrillation at 2.8 months after zanubrutinib initiation); 21% indicated timing is specified and 20% were unsure.
- 57% of pharmacists routinely ask patients on BTKi about blood pressure monitoring and assess it during proactive outreach calls; this was most prevalent in community (53%) and academic (24%) settings (hospital 15%, other 7%).

KEY TAKEAWAYS

Before BTKi Treatment

- Proactive mitigation and monitoring is common.
- A comprehensive cardiac history is obtained (62%).
- Anticoagulation therapy is considered for hypertension or history of cardiac arrhythmias (48%).
- Baseline blood pressure and ECG are usually obtained (86% and 58%, respectively).

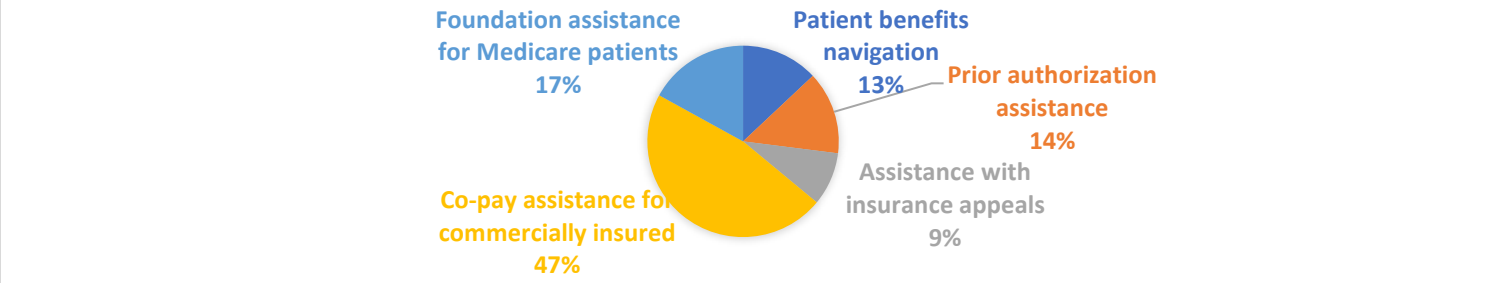
Monitoring BTKi Treatment

- Cardiologist consult is obtained in patients developing new atrial fibrillation on BTKi (76%).
- Pharmacists monitor and assess blood pressure during proactive outreach calls to patients (57%).

RESOURCE UTILIZATION

Participants were asked about resource utilization in several questions as summarized herein.

- Participants indicated their top choice for utilizing myBeiGene as shown in the chart.



- In developing pharmacy treatment plans, 68% of participants utilize manufacturer resources (9% were unsure).
- 54% of participants anticipate manufacturer fair price (MFP) introduction through the IRA in 2026 to have a significant impact on drug utilization and prescribing patterns within the BTKi class; 46% do not anticipate an impact. Anticipated impacts include increased (28%) or decreased (10%) utilization of the MFP product, and 56% were unsure.

CONCLUSION

The management of newly diagnosed CLL is increasingly personalized, focusing on genetic profiles, patient preferences, and treatment tolerability. BTKi therapies dominate first-line treatment preferences, especially for high-risk patients. Effective patient monitoring, integrated care pathways, and economic considerations are pivotal for optimizing treatment outcomes. The anticipated policy changes in 2026 may further influence prescribing patterns, underscoring the need for adaptable and informed treatment strategies.

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