AMCP MARKET INSIGHTS

BTKis in Chronic Lymphocytic Leukemia

FINDINGS FROM AN AMCP MARKET INSIGHTS PROGRAM

Meeting Objectives

- Understand the role of BTKi use in CLL
- Prioritize BTKi safety, efficacy, and tolerability in treatment choices
- Define differentiating attributes of medications used in CLL for making utilization management decisions
- Gain insight into future payer management considerations for BTKis in CLL

Introduction

Chronic lymphocytic leukemia (CLL) is characterized by a progressive accumulation of leukemic cells in the peripheral blood, bone marrow, and lymphoid tissues.[1] Diagnosis of CLL requires a B lymphocyte concentration of at least 5×10^9/L in the peripheral blood for 3 months or more.[1,2] It is estimated that in the US there will be 20,160 new cases of CLL in 2022 and 4,410 deaths, making it the most prevalent leukemia type with the third highest mortality.[3]

Recommendations for treatment initiation in CLL are stratified by disease stage using either the Rai staging system, which defines disease as low-, intermediate-, or high-risk; or the Binet staging system, which defines disease as stage A, B, or C based on the number of lymphoid areas involved and the presence of anemia or thrombocytopenia.[2] Generally, treatment should be initiated in patients with active or progressive disease who are intermediate- or high-risk, or stage B or C.[1,2]

Treatment regimen recommendations are also stratified and are based on the presence of a deletion in the short arm of chromosome 17 (del[17p]) or a *TP53* gene mutation.[1,2] NCCN preferred and category 1 regimens across groups include the Bruton's tyrosine kinase inhibitors (BTKis) acalabrutinib (with or without the anti-CD20 monoclonal antibody obinutuzumab), zanubrutinib, and ibrutinib, and the B-cell lymphoma-2 inhibitor (BCL-2i) venetoclax (with or without an anti-CD20 monoclonal antibody; Table 1).[1]

Due to the relatively recent growth in the number of treatment options for CLL, especially among BTKis, and ongoing research into treating this condition, it

Table 1. Current Recommended Treatments in CLL

Mechanism of action	BTK inhibitor			BCL-2 inhibitor	Anti-CD20 monoclonal antibody	
Drug	**Ibrutinib**	**Acalabrutinib**	**Zanubrutinib**	**Venetoclax**	**Obinutuzumab**	**Rituximab**
FDA-approval in CLL	February 2014[22]	November 2019[23]	sNDA accepted February 2022[24]	April 2016[25]	November 2013[26]	October 2009[27]
Clinical studies[a]; [5,12,13,28-30]	**Treatment naïve:** • A041202 (± rituximab vs BR) • E1912 (+ rituximab vs FCR) • iLLUMINATE (+ obinutuzumab vs chlorambucil + obinutuzumab) • RESONATE-2 (vs chlorambucil) **Previously treated:** • 1102 (no comparator) • HELIOS (+ BR vs placebo + BR) • RESONATE (vs ofatumumab)	**Treatment naïve:** • ELEVATE-TN (± obinutuzumab vs chlorambucil + obinutuzumab) **Previously treated:** • ASCEND (vs idelalisib + rituximab or BR) • ELEVATE-RR (vs ibrutinib)	**Treatment naïve:** • SEQUOIA (vs BR) **Previously treated:** • ALPINE (vs ibrutinib)	**Treatment naïve:** • CLL14 (+ obinutuzumab vs obinutuzumab + chlorambucil) **Previously treated:** • MURANO (+ rituximab vs BR) • M13-982 (no comparator) • M12-175 (no comparator) • M14-032 (no comparator)	**Treatment naïve:** • CLL11 (+ chlorambucil vs chlorambucil ± rituximab)	**Treatment naïve:** • CLL Study 1 (+ FC vs placebo + FC) • CLL Study 2 (+ FC vs placebo + FC)
Key safety issues[b]	• Hypertension • Atrial fibrillation • Arthralgias • Bleeding • Infection	Headache	Neutropenia	Tumor lysis syndrome	**First-line + BTKi:** • Hematopoietic effects • B-cell depletion • Potential worse outcomes with COVID-19	None discussed
Special considerations[c]	• NCCN downgraded from preferred regimen • Tolerability often leads to discontinuation • PI update strengthened cardiovascular risk	NCCN preferred regimen	NCCN preferred regimen	• Time-limited regimen • Requires dose escalation protocol	None discussed	Biosimilars available

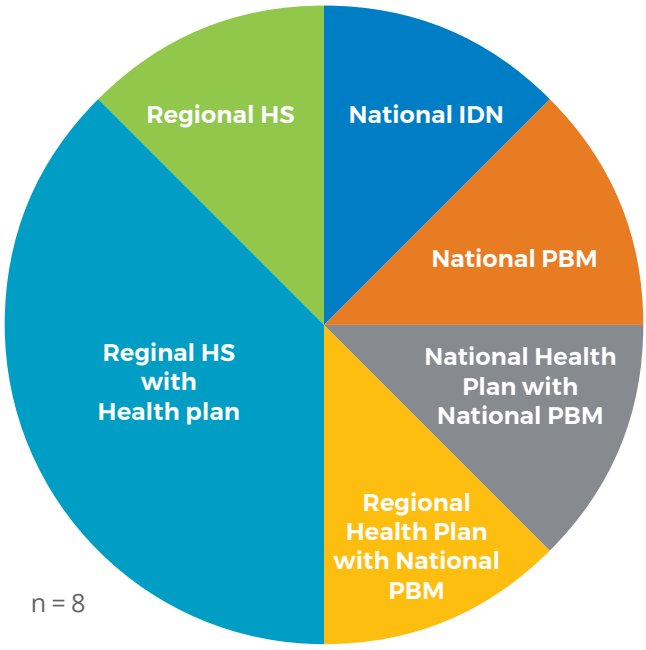
[a]As discussed in the Market Insights program and listed in the prescribing information for each agent in CLL.
[b]Select safety issues of concern as discussed in the Market Insights program.
[c]Select special considerations as discussed in the Market Insights program.
BCL-2=B-cell lymphoma-2; BR=bendamustine/rituximab; BTK=Bruton's tyrosine kinase; CLL=chronic lymphocytic leukemia; COVID=coronavirus disease 2019; FC=fludarabine/cyclophosphamide; FCR=fludarabine/cyclophosphamide/rituximab; FDA=US Food and Drug Administration; NCCN=National Comprehensive Cancer Network; sNDA=supplemental new drug application.

is likely that interest among payers in applying more rigorous management strategies will grow as well. In response, AMCP convened an expert panel of managed care stakeholders to better understand the clinical dynamics of treatment choice in patients with CLL and the key management considerations in CLL with a focus on BTKis.

The program was conducted in a double-blind format with the participants blinded to the program sponsor

and the program sponsor blinded to the participants and their organizations. Panelists included representatives from national and regional health plans, health systems, integrated delivery networks, and pharmacy benefit management. With a guest clinical expert from a leading academic center specializing in the treatment of CLL, participants discussed the role of individual BTKis including important distinctions in their safety, efficacy, and tolerability, and the attributes of CLL and its treatments considered when making management decisions.

Figure 1. Participant Organization Distribution



Clinical Insights

A key clinical insight that emerged from the discussion was that survival and ability to tolerate treatment in patients with CLL has dramatically improved since the introduction of BTKi and BCL-2i therapies. Based on data from the MURANO study, for instance, which demonstrated an overall survival (OS) benefit with a regimen of venetoclax plus rituximab versus chemotherapy in relapsed/refractory CLL, clinical participants confirmed that it is no longer considered clinically appropriate to use chemotherapy in this setting.[4] However, questions remain regarding the order in which to use these newer agents first-line.

> **"No matter what chemotherapy regimen or age group, there are randomized trials against BTKis, and all of them consistently show an advantage for using the BTKi."**
> ***– Clinical expert***

Among the 3 BTKis specifically, clinical participants acknowledged that safety rather than efficacy was the differentiator when the agents were used as monotherapy. Acalabrutinib and zanubrutinib, referred to as second-generation BTKis versus ibrutinib, were highlighted by participants as better tolerated in clinical practice and less likely to cause severe toxicities like cardiovascular adverse effects (e.g., atrial fibrillation, hypertension) seen with ibrutinib.[5] Participants reviewed data that suggests this difference may be due to the relative kinase selectivity of the 3 agents, with ibrutinib having the least selectivity for BTK.[6,7]

> **"It only takes one patient to develop afib [from ibrutinib treatment] for you to get really discouraged."**
> ***– Regional health system***

It was noted by clinical participants that in the case of discontinuation of ibrutinib due to adverse events and switching to either acalabrutinib or zanubrutinib, the adverse events that led to discontinuation did not recur. Data supporting this clinical observation for acalabrutinib was also discussed.[8] Despite this, however, participants stated there continues to be

utilization of ibrutinib first-line based on both clinical experience and claims data and thought this could be due to its place as the first BTKi with the longest history of use in CLL.

"Most oncologists probably treat one or two patients with CLL a year and get comfortable using treatments they know. They continue to use it because they haven't seen a serious adverse event with ibrutinib and these few patients on it seem to do well."
– Clinical expert

Ongoing research into the use of BTKis in combination with venetoclax, and in combination with venetoclax and the anti-CD20 monoclonal antibody, obinutuzumab, makes the optimal sequencing of these agents even more complex according to participants. For example, the most mature data evaluating combination BTKi and venetoclax is with ibrutinib.[9-11] While participants expressed that from an efficacy perspective one BTKi could likely be substituted with another, such as acalabrutinib or zanubrutinib for ibrutinib, it is currently less clear from a safety perspective. One concern raised by clinical participants was the uncertainty around potentially additive effects such as hemopoietic adverse effects with a combination of zanubrutinib and venetoclax, which are labeled with risk of cytopenias and neutropenia, respectively.[12,13]

Current Coverage Strategies

Payer participants confirmed that coverage of treatments used in oncology is only stratified if their management strategy includes sequencing of products, for instance through step therapy or via a pathway protocol. Without sequencing of products then, clinical factors such as the specific risk category of a patient, do not affect coverage. Currently, only one participant organization has stratified coverage in place for CLL, which is managed via a pathway protocol. However, other participants suggested this would likely change as more agents and regimens become available.

"CLL treatment has historically been just Imbruvica and chemotherapy and management wasn't worth it. Now, given the pipeline and combination regimens, it's worth the effort to develop management strategies."
– National PBM

When determining sequencing of products, payer participants noted safety as a main consideration. Especially relevant to them among BTKis is the development of cardiovascular-related adverse treatment effects like atrial fibrillation and hypertension, as well as neutropenia requiring additional supportive treatment (e.g., colony stimulating factors). They also acknowledged the importance of discontinuation rates – for instance as an endpoint in a value-based contract – especially when the discontinuation rate significant like the 41% reported in one real-world study with ibrutinib.[14] However, they described it as only one consideration of many in developing coverage criteria.

Influence of External Factors

NCCN guideline changes

Participants generally agreed that NCCN treatment guidelines influence coverage decisions from a clinical perspective, although there were different perspectives on whether guideline changes would lead to corresponding formulary or coverage criteria changes. Particularly, participants offered insights on the role of changes like those seen in the current release of the NCCN guidelines in CLL. Key updates in this version included the downgrade of ibrutinib monotherapy from a preferred regimen in some

patient groups due to safety, and the upgrade of the recommendation for zanubrutinib from a category 2A to a category 1, which is the organization's highest.[1,15]

One perspective noted was that the downgrade of a therapy from a preferred regimen, for instance, would likely lead to a change in coverage. Another perspective was that a guideline update alone might not prompt a change as provider network reaction is also a key consideration. Given the uniqueness of oncology patient populations, it was seen as not solely up to payers to direct prescribing when guideline changes occur. From this perspective, whether the guideline change is positive or negative, payer participants felt it was important to ensure that their coverage criteria align to the evidence first and then determine whether and how much it would be appropriate to promote a shift in prescribing.

> **"How much do we want to push the prescriber community and drive them to follow the guidelines, or do we wait to see if they react themselves?"**
> ***– Regional Health Plan***

Prescribing information changes

Regarding a prescribing information update strengthening the warning for risk of cardiac arrhythmias and cardiac failure to include sudden death with ibrutinib, clinical participants did not see it as impactful as it was already a known risk.[5] It might, however, decrease the threshold for switching a patient from ibrutinib to another therapy. Similarly, payer participants suggested this was unlikely to prompt a coverage policy change, but it could be used as supportive if the decision was made to prefer other agents over ibrutinib.

Product reformulation

Dosing of the BTKi acalabrutinib in its originally approved capsule formulation had restrictions around concomitant use and administration with gastric acid reducing agents.[16] Given this, the product was reformulated into tablets that do not carry the same restrictions.[16] There was discussion among participants about this and other product reformulations more broadly.

An internal study from one participant organization found that the co-administration of acalabrutinib capsules with gastric acid reducing agents was not significant enough to require a product reformulation. However, other clinical participants considered patients no longer having to time their dose of acalabrutinib appropriately when also taking gastric acid reducing agents as a sufficient benefit.

Payer participants indicated that, in general, they would first try to determine whether the underlying rationale for the reformulation was clinically driven as in this case or whether it was market-driven (e.g., patent extension) before making formulary changes. Additionally, participants commented that market-driven product reformulation is one example of why the cost conversation continues to escalate among payers - especially when it undermines encouraging the use of generic alternatives or allowing broader coverage of innovative, branded products that are clear differentiators. However, because there is not currently a generic alternative available for acalabrutinib and the manufacturer is removing the capsule formulation from the market, this additional consideration was not an issue of concern in this case.

Deriving Value in Chronic Lymphocytic Leukemia

Three elements that participants saw as key to deriving the value of treatments used in CLL were sequencing of therapies, understanding the difference between the benefits in PFS and OS of CLL regimens, and comparing their total cost of care. For each, participants acknowledged current gaps in the available data.

Sequencing of therapies

NCCN treatment guidelines list regimens including the BTKis acalabrutinib and zanubrutinib, and the BCL-2i ventoclax as preferred for CLL.[1] Additionally, ibrutinib is listed under other regimens with the highest evidence rating of category 1.[1] However, participants noted that the guidelines do not address the optimal sequencing of these products. For instance, whether to initiate a BTKi or a BCL-2i first, or, in the case of a BTKi, the ideal agent with which to begin treatment. Given this, they highlighted the importance of additional evidence to determine the optimal sequencing of therapies in CLL, especially head-to-head clinical trials such as the ELEVATE-RR trial evaluating acalabrutinib vs ibrutinib both as monotherapies in previously treated patients, and the similarly designed ALPINE trial with zanubrutinib vs ibrutinib.[17,18]

Differentiating between PFS vs OS benefit

The evidence showing the benefit of treatments in CLL is primarily based on progression-free survival (PFS). PFS is a surrogate endpoint that may predict clinical benefit but is not itself a direct measurement of clinical benefit.[19] While PFS is a surrogate endpoint recognized by the US Food and Drug Administration in oncology, payer participants expressed uncertainty in differentiating between a benefit in PFS and a true clinical outcome such as OS.[19] They also wondered what the future role of PFS would be in approving treatments for CLL and whether there would be an increased demand for OS data to differentiate products as more become available.

"As the treatment landscape continues to evolve, how will we understand the difference between OS and PFS if we just keep chasing PFS moving forward?"
– *Regional health system*

Comparative total cost of care

Currently, there is limited data on the comparative total cost of care of treatment regimens used in CLL. Given this, uncertainty exists, especially among payer participants, about how to account for certain clinical nuances in the treatment of CLL. For instance, the cost avoidance associated with preventing significant cardiovascular-related adverse effects that may require ongoing specialized care, by using a second-generation BTKi versus ibrutinib. Or, how to quantify the savings that may be achieved with a venetoclax-based regimen; a time-limited therapy which may achieve remission and allow treatment discontinuation, but that also requires an initial dose-escalation protocol due to the risk of tumor lysis syndrome.[13]

"We have all these clinical trials which don't really describe the impact of discontinuation, or of serious adverse events. The true story comes from the total cost of care picture when you can see the impact of actually preventing these serious events like afib."
– *Regional health system*

"Any research efforts that will support getting our patients off of therapy and getting the total cost of care down safely and effectively, I'm supportive of it."
– *Regional health system*

One participant organization which has evaluated total cost of care internally, determined that even with its lower wholesale acquisition cost, use of ibrutinib was not appropriate given the totality of the data. Also considered in this evaluation was that once-daily dosing with zanubrutinib, although not yet FDA-approved in CLL, had an adherence benefit

versus twice daily acalabrutinib. Participants referred to data which showed a cost benefit for zanubrutinib versus ibrutinib in Waldenström macroglobulinemia, a type of non-Hodgkin lymphoma characterized by the accumulation of lymphoplasmacytic cells in bone marrow, lymph nodes, and other organs.[20,21]

Payer Response to Emerging Trends

Payer participants underscored the emergence of combination regimens as a top concern in the management of CLL, especially integrated payers who must manage both pharmacy and medical benefits. Questions posed by participants regarding combination regimens included:

- Is there benefit and what is the magnitude of benefit in dual and triple combination regimens versus monotherapies?
- Is the benefit of a dual or triple combination regimen enough to outweigh the additional safety and cost burden versus monotherapies?

Participants suggested that, from a pathway perspective, it would be unlikely for combinations containing all 3 BTKis to be preferred. Instead, most would try to select either 1 or 2 to prefer based on clinical characteristics and cost-effectiveness. However, both clinical and payer participants agreed that there is not yet enough data to guide these decisions.

"Until there's more data, for instance to know whether combination approaches are better than a sequential monotherapy approach in CLL, it would be hard to pushback against payer management strategies preferring certain agents over others."
– *Clinical expert*

While NCCN was seen by participants as a valuable clinical resource in determining pathway options, the guidelines do not consider cost. The challenge of overall value-based decision-making, including how to incorporate the evidence for an agent that has been downgraded in the guidelines or whether it makes sense to prefer a higher-cost agent that has not shown overall cost offset, remains with payers.

Looking Ahead

Access and affordability

To ensure access and affordability of treatments for patients with CLL, participants emphasized the importance of continuing multi-stakeholder discussions such as this one. Payer participants appreciated the perspective of clinical participants in bringing elements of the data to life, particularly the significance of negative cardiovascular effects with ibrutinib or the benefit of the reformulation of acalabrutinib. Clinical participants learned about the considerations that go into coverage decisions and the challenges faced by payers.

"Our goals continue to be the same, to ensure access to the best therapies that are personalized and that are affordable. It is conversations like these that allow us to be equipped to make the best decisions for patients in partnership with our clinicians."
– *Regional Health Plan*

Building pathways

Participants also discussed key considerations in building pathways for the treatment of CLL as many are considering implementing them. They particularly called for provider guidance and additional data around genetic and biomarker testing, sequencing of therapies, differentiating between PFS and OS, and the utility of dual and triple agent combinations.

One participant with experience building a CLL pathway recommended focusing on front-line

therapy which is the highest percent of CLL patients, as the number of relapsed/refractory patients is low. Additionally, since there are effective monotherapy options for the treatment of CLL, decision-making will likely need to focus on combination regimens as well as on the role of innovative approaches such as chimeric antigen receptor T (CAR T) cell therapies.

Comparative total cost of care

Payer participants stressed the need for comparative total cost of care data to support value-based decision-making. Especially, to understand the nuances of clinical dynamics such as the potential cost avoidance associated with prevention of adverse events, and the effect of time-limited treatment regimens.

Summary

In this double-blind, expert forum, participants discussed important elements in treatment choice and management of agents used in CLL, especially BTKis. BTKi and BCL-2i therapy represent a survival and tolerability benefit in CLL versus chemotherapy; however, the optimal order in which to use these therapies first-line remains unclear. Safety is the primary differentiator in BTKi monotherapy and second-generation acalabrutinib and zanubrutinib have fewer significant safety risks than the first-generation agent ibrutinib. Data on both the safety and efficacy of combination regimens including BTKis are still emerging.

Management of agents used in CLL, including the use of pathways, is likely to increase as more therapies become available and combination regimens become more prevalent. External factors such as guideline changes, prescribing information changes, and product reformulations may affect decision-making, but there are many other considerations. Value-based decision-making in CLL remains a challenge for payers due to limited data for key considerations like sequencing of therapies, differentiating between PFS and OS, and comparative total cost of care.

Actions encouraged by forum participants included continued multi-stakeholder conversations and partnering between clinicians and payers especially as pathways in CLL are considered. Data needs identified include both clinical and cost of care data to inform value-based decision-making.

Disclosures

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Key Summary Findings

- Survival and tolerance have dramatically improved in CLL with BTKi and BCL-2i vs chemotherapy.
- Questions remain about the order in which to use newer agents front-line.
- It is no longer clinically appropriate to use chemotherapy second line.
- Safety rather than efficacy is the differentiator in monotherapy.
- Treatments for CLL are not currently actively managed according to most participants.
- NCCN guideline changes are important from a clinical perspective, but may not lead to formulary or coverage criteria changes; provider network reaction is also a significant consideration in the decision to make a coverage change.
- Three key elements to deriving the value of treatments used in CLL include:
  - Sequencing of therapies
  - Understanding the difference between the benefits in PFS and OS of CLL regimens
  - Comparing the total cost of care of CLL regimens
- Among emerging trends in CLL, combination regimens are a main concern.

Looking Ahead

Actions recommended by this program's participants include:

- Continue multi-stakeholder conversations such as these to understand and partner on access and affordability issues.
- Facilitate provider guidance and data generation to support building pathways.
- Develop comparative total cost of care data to support value-based decision making.