Newer Drugs for ALL Are Hitting the U.S. Market, Potentially Filling Unmet Need

The FDA has approved multiple new agents for the treatment of acute lymphoblastic leukemia (ALL) — which is also known as acute lymphocytic leukemia — and recently converted an accelerated approval it had given one of them to full. However, even with all these options, respondents to a Zitter Insights survey said that unmet need exists in treating the disease.

On June 21, 2023, the FDA granted full approval to Amgen Inc.'s Blincyto (blinatumomab) for the treatment of adults and pediatric patients with CD19-positive B-cell precursor ALL first or second complete remission with minimal residual disease (MRD) greater than or equal to 0.1%. The agency first approved the CD19-directed CD3 T-cell engager on Dec. 3, 2014; the accelerated approval for MRD-positive B-cell ALL was granted on March 29, 2018.

Dosing consists of 28 days of continuous intravenous infusion via an infusion pump and then a 14-day treatment-free interval. For a treatment course of four cycles, people weighing at least 45 kg are administered 28 mcg/day for the first 28 days of each cycle. People weighing less than 45 kg are given 15 mcg/m^2/day on the same schedule. Drugs.com lists the price of one 35 mcg lyophilized powder in a single-dose vial as more than $5,169.

In Amgen's press release on the most recent approval, David M. Reese, M.D., executive vice president of research and development for the manufacturer, notes that Blincyto is the first CD19-directed CD3 T-cell engager BiTE — or Bispecific T cell Engager — immunotherapy that the FDA has approved and the first approved for MRD.

The Phase II BLAST study found that more than 81% of adults receiving Blincyto had a complete MRD response finding, says Andy Szczotka, Pharm.D., chief pharmacy officer at AscellaHealth. He adds that people who were MRD negative and were treated with a combination of Blincyto and chemotherapy lived longer than people who were treated with chemotherapy monotherapy.

"It should be noted that nearly 70% of patients in the study…underwent allogeneic hematopoietic stem cell transplantation following Blincyto therapy," he tells AIS Health, a division of MMIT. "These results may indicate that MRD negative patients may be good candidates for therapy with Blincyto. The drug cost for the nine cycles of additional Blincyto therapy is greater than $1.2 million, so the additional therapy cost will be a consideration in the treatment decision pathway."

Study Findings May Make Case for Earlier-Line Use

Szczotka adds that data from the trial was presented at the 2022 American Society of Hematology (ASH) annual meeting. The person leading the study revealed that many participants could not continue since chemotherapy failed to help "the patient achieve complete remission. However, the study leader noted that this may raise the question whether there could be a place for immunotherapy earlier in the course of treatment. Studies would need to be conducted to support this placement, and if conclusive results are confirmed, immunotherapy, such as Blincyto, may play a larger role in ALL treatment pathways."

Results from additional confirmatory Phase III trials "reinforc[e] Blincyto as the standard of care for patients with MRD following remission," asserts Winston Wong, Pharm.D., president of W-Squared Group. He notes that the "B-cell lineage is the most prevalent type of the ALL malignancies, which is the most common cancer in children. Unfortunately, the incidence of ALL in children also appears to be increasing. The exact cause is unknown, but there has been an association with environmental and genetic risk factors."

The level of MRD directly correlates to the possibility of long-term, relapse-free survival, he says, adding that children with detectable MRD have lower rates of disease-free survival and overall survival. "While general chemotherapy is used for induction and consolidation therapy, immunotherapy is indicated in patients who are still MRD positive at the end of induction. Blincyto is the only immunotherapy treatment options approved for the first or second remission with an elevated MRD."

Blincyto's anti-CD19/CD3 effect makes it unique, claims Wong. "Two other immunotherapies are an anti-CD22 directed antibody-drug conjugate and a CD19 CAR-T that are indicated for relapsing/refractory disease." This means that due to Blincyto's mechanism of action and its indication, it "fills an unmet need in the treatment of B-cell ALL with no true competitors.

"In some respects," he continues, "payers have no choice but to cover Blincyto, and they will most likely continue to manage to [FDA-approved] indication. The use of immunotherapies is restricted to these niche indications for the time being due to their adverse effective profiles; however, they are being studied as first-line induction/consolidation treatment to assess their benefits and toxicity."

With so much scrutiny of the FDA's accelerated approval pathway, the conversion of an agent from accelerated to full approval is "significant," maintains Wong. Based upon confirmatory trial results, the agency can either grant full approval or withdraw the accelerated indication from a drug's label. "Although there is scrutiny of the accelerated approval pathway," says Szczotka, "the basis of it is to fulfill an unmet medical need in patients suffering from diseases without current therapeutic alternatives."

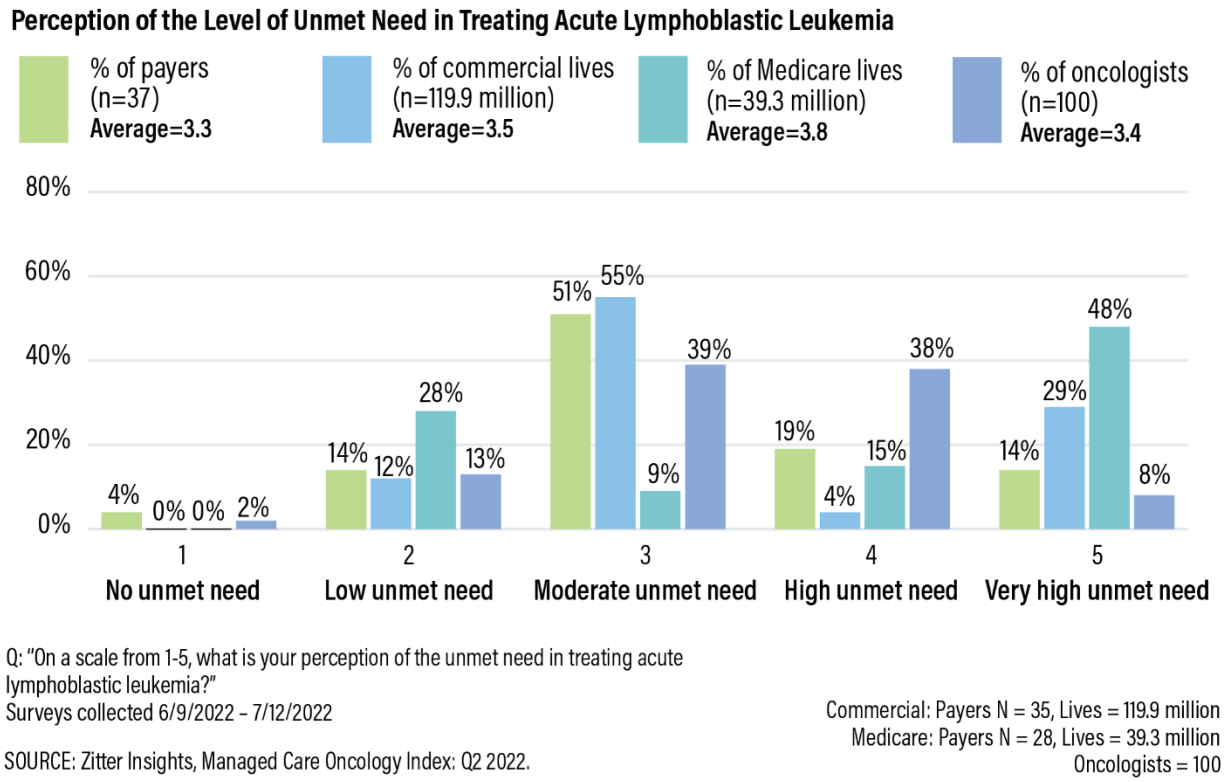
Survey Finds CLL Management Is Average Priority for Payers

For the Managed Care Oncology Index: Q2 2022, from June 9, 2022, to July 12, 2022, Zitter Insights polled 35 commercial payers covering 119.9 million lives, 28 Medicare payers representing 39.3 million lives and 100 oncologists about their management and prescribing of ALL therapies. Out of 11 agents in the class, Blincyto was used on the largest number of unique patients — 47% — in the year prior to the survey.

Payers covering 62% of commercial lives and 58% of Medicare lives said that managing branded treatments for ALL is an average priority. Those representing almost 90% of commercial beneficiaries and 95% of Medicare lives reported that they are slightly or somewhat aggressive in their management of branded ALL agents.

Zitter Insights also is a division of MMIT.

Commercial payers with 78% of lives and Medicare payers with 67% of lives expressed average satisfaction with the current treatments compared with 44% of oncologists. However, opinions vary on how respondents perceive the unmet need in the treatment of the disease (see chart).



Q: "On a scale from 1-5, what is your perception of the unmet need in treating acute lymphoblastic leukemia?"
Surveys collected 6/9/2022 - 7/12/2022

SOURCE: Zitter Insights, Managed Care Oncology Index: Q2 2022.

Commercial: Payers N = 35, Lives = 119.9 million
Medicare: Payers N = 28, Lives = 39.3 million
Oncologists = 100

VIEW LARGER IMAGE

In their management of ALL agents, payers often implement traditional utilization management strategies such as prior authorization and step therapy and also turn to guideline-based tactics, says Szczotka. The latter approach includes review of "available pivotal clinical trials, peer-reviewed published clinical literature, the approved FDA

label, nationally known guidelines" — for example, the American Society of Clinical Oncology (ASCO) and the National Comprehensive Cancer Network (NCCN) — "consultation with the specialist and other treatment-specific compendia as support for use in treatment." And while treatments for adults may vary from those for pediatric patients, the management steps taken to determine a drug's place in treatment are similar, he adds.

In situations where clinical pathways are not in place, Wong says that management of the agents will be informed by their FDA-approved labels. He tells AIS Health that Blincyto will contribute to ALL's cost burden, "especially since the bulk of the induction and consolidation chemotherapy is still relatively inexpensive [compared] to other targeted cancer treatments. However, we are also in a period of transition, moving away from the use of the narrow scope of treatment pathways and guidelines to more of a comprehensive partnering with the oncology practices." He credits this to CMS "leading the way" via the Oncology Care Model, which health plans have learned from, "creating similar, improved programs and financial arrangement with practices."

Szczotka also cites new, emerging strategies that are helping payers with oncology management. "Some of these newer strategies include programs that review the value of each drug to determine pricing and have shared risk among all parties, including the pharmaceutical industry. Additionally, a proposed alternative payment model, termed the Patient-Centered Oncology Payment: Payment Reform to Support Higher Quality, More Affordable Patient Care, ensures that the full range of services needed by patients is supported within a value-based reimbursement system that increases patient satisfaction and cost savings." He also points to the Oncology Care Model, which "aims to provide higher quality, more highly coordinated oncology care at the same or lower cost to Medicare."

Szczotka and Wong agree that managing oncology drugs in general is a high priority for payers due to their high costs in both the medical and the pharmacy benefit. The class consistently falls within the top three categories of specialty drug spend.

But ALL itself "may not be as high of a concern as other cancers, mainly due to the induction and consolidation regimens utilizing general chemotherapy agents; however, common to other cancers, the treatment of relapsing/refractory and residual cancer can get relatively expensive," observes Wong.

ALL comorbidities usually occur in older patients, says Szczotka, and they "can limit the patient's tolerability to aggressive therapies and predispose to treatment-related adverse effects, ultimately affecting survival. Standard ALL treatment includes intensive induction and post-remission therapy. This can be challenging for older adults because of comorbidities such as diabetes, cardiac dysfunction, pulmonary abnormalities, neuropathy, polypharmacy and decline in performance status. Increased age has also been associated with higher risk of infections during induction and more dose reductions."

These toxicities related to standard chemotherapy have led some oncologists to consider newer ALL drugs for older patients who have relapsed, including Blincyto, Pfizer Inc.'s Besponsa (inotuzumab ozogamicin) and Tecartus (brexucabtagene autoleucel) from Kite Pharma, Inc., a division of Gilead Sciences, Inc., a chimeric antigen receptor T-cell (CAR-T) therapy approved for use in adults with relapsed or refractory B-cell precursor ALL.

Another CAR-T, Kymriah (tisagenlecleucel) from Novartis Pharmaceuticals Corp., is approved for B-cell precursor ALL that is refractory or in second or later relapse but only for use in people 25 years old or younger. The CAR-Ts, asserts Szczotka, citing multiple published clinical trials, have shown promising outcomes for many people with ALL. "CAR-T therapies provide another new therapy option with potential to advance the treatment of ALL."

The American Cancer Society estimates that there are approximately 6,000 new ALL cases in the U.S. in 2023. It's also a rare cancer, representing less than half of all cancers in the country. Yet "there has been a rise in the number of drug approvals for the treatment of ALL, as well as several agents in the pipeline," Szczotka notes. "According to a recent study, around 412,000 people worldwide are likely to be diagnosed with some type of leukemia, with ALL accounting for about 12% of those cases. The rise in prevalence is likely to increase the demand for all therapies, including the newer agents, in the treatment of ALL. Multiple therapy options are available for the treatment of ALL and often are used in combination based on the disease and treatment stage. The chosen treatment will be driven by the clinical results, regardless of the therapeutic class of the particular therapy agent."

For more information on the Zitter Insights data, contact Jill Brown Kettler at jkettler@mmitnetwork.com. Contact Szczotka via Caroline Chambers at cchambers@cpronline.com and Wong at w2sqgroup@gmail.com.

By Angela Maas