Growing Role for New Targeted Therapies and Immunotherapies in Treating Blood Cancers

Chemotherapy-free approaches could offer comparable efficacy with less toxicity.

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ORLANDO — Targeted therapies and immunotherapies are increasingly offering viable alternatives to the chemotherapies that have stood for decades as a mainstay of treatment for individuals living with blood cancers, according to studies presented at the 67th American Society of Hematology (ASH) Annual Meeting and Exposition.

“These studies point to the departure of traditional chemotherapy and shedding traditional approaches,” said Laura Michaelis, MD, professor of medicine at the Medical College of Wisconsin in Milwaukee, who moderated the press briefing Emerging Therapies and Immunotherapies in Blood Cancers. “Researchers are focused on therapeutic approaches that can offer the same or better responses with less toxicity – meaning fewer early deaths, less organ damage, and better quality of life for patients.”

In the first study, a combination regimen of azacitidine [Vidaza, Onureg] and venetoclax [Venclexta] led to better responses and improved event-free survival in patients who were fit enough to undergo conventional induction chemotherapy for newly diagnosed acute myeloid leukemia. The results suggest the combination can lead to better outcomes with substantially less hospitalization and a lower symptom burden for patients with intermediate-to-high-risk disease.

The second study reports that a chemotherapy-free combination of epcoritamab [Epkinly], a bispecific antibody, and rituximab [Rituxan] and lenalidomide [Revlimid], an immunotherapeutic combination, brought a robust and lasting response, showing promise as a chemotherapy alternative for patients with relapsed or refractory follicular lymphoma.

The third and fourth studies reflect the expanding role of tyrosine kinase inhibitors, which target particular enzymes to inhibit cancer cell growth. One study suggests a non-covalent Bruton tyrosine kinase (BTK) inhibitor, pirtobrutinib [Jaypirca], may offer equivalent or better outcomes compared with the older covalent BTK inhibitor, ibrutinib [Imbruvica], for patients with chronic lymphocytic leukemia and small lymphocytic lymphoma. The final study – focused on a

combination therapy that included ponatinib [Iclusig], a tyrosine kinase inhibitor, and blinatumomab [Blincyto], an immunotherapy – offers evidence that chemotherapy can be omitted from frontline treatment for Ph+ acute lymphoblastic leukemia without sacrificing efficacy or safety.

Azacitidine–Venetoclax Combination Outperforms Standard Care in Acute Myeloid Leukemia Patients Eligible for Intensive Chemotherapy
6: Results from paradigm - a phase 2 randomized multi-center study comparing azacitidine and venetoclax to conventional induction chemotherapy for newly diagnosed fit adults with acute myeloid leukemia

In a new trial, patients newly diagnosed with acute myeloid leukemia (AML) fared significantly better with a combined regimen of azacitidine and venetoclax compared with conventional induction chemotherapy. The azacitidine–venetoclax combination (known as aza-ven) is the standard of care for older adults who are not fit enough for intensive chemotherapy. The trial is the first to test the superiority of this regimen to intensive induction chemotherapy, the current standard for fit patients.

“Our study met its primary endpoint, demonstrating that aza-ven improves event-free survival. It also leads to higher rates of overall response and composite complete response than intensive induction chemotherapy in younger, intensive-chemotherapy-eligible patients,” said lead study author Amir Fathi, MD, director of the Center for Leukemia at Mass General Brigham Cancer Institute and associate professor of medicine at Harvard Medical School in Boston. “A greater proportion of patients successfully proceeded to transplant following response with less early mortality, significantly improved quality of life during initial treatment, and less time in the hospital.”

AML is a cancer of the bone marrow that causes an overabundance of abnormal white blood cells and impedes the production of healthy blood cells. Hematopoietic stem cell transplantation can cure AML, but this option is not available to everyone, and almost all patients must undergo initial treatments to reduce cancer in the bone marrow before proceeding to transplant. Intensive induction chemotherapy with cytarabine and anthracyclines has long stood as the standard frontline treatment, but this treatment requires patients to spend about a month in the hospital and carries a high risk of infection, bleeding, and other complications and side effects.

Azacitidine is a chemotherapy drug that has been used for years, in injectable forms, for older patients with AML. Venetoclax is an oral targeted therapy that inhibits the BCL-2 protein, which is involved in cancer cell survival. The two agents are generally well tolerated and can be administered and managed safely on an outpatient basis over time.

In the trial, 172 adult patients were randomly assigned to receive either aza-ven or standard intensive induction chemotherapy. The results were significantly better in the aza-ven arm for the trial’s primary endpoint, event-free survival (EFS), with events defined as relapse, disease progression, disease refractoriness prompting change in therapy, or death. With a median follow-

up of just under 22 months, EFS was significantly longer in the aza-ven arm; the median EFS was more than 14 months among those receiving aza-ven compared with a median of just over six months for those receiving induction chemotherapy. The effect of aza-ven remained protective even after adjusting for other variables, and at one year, 53% of those in the aza-ven arm met criteria for EFS compared with 36% of those in the control arm.

Patients whose cancer had certain characteristics, including core binding factor fusions, FLT3 mutations, or NPM1 mutations (unless age 60 or over), were excluded from the trial. As a result, the study reflects a patient population of predominantly intermediate-to-high-risk AML, although all patients were fit enough to undergo intensive induction chemotherapy.

“I believe the data support the use of this treatment in this population,” said Dr. Fathi. “It applies to adverse risk and intermediate risk patients who don’t have FLT3 mutations. That doesn’t mean that other patient populations may not benefit, but they require their own focused study.”

Participants receiving aza-ven experienced a higher overall response to treatment than those receiving induction chemotherapy, with 88% of those in the aza-ven arm seeing an overall response and 78% seeing a composite complete response, compared with 62% and 54% in the control arm, respectively. They were also more likely to progress to a transplant, which occurred in 61% of those receiving aza-ven and 40% of those receiving induction chemotherapy.

The rate of grade 3 or 4 therapy-related adverse events was similar between study arms. No patients who received aza-ven died within 60 days, while 5% of those in the control group died by this timepoint. Hospitalization was also longer among patients in the control group. Ten percent of patients in the induction arm required admission to the intensive care unit during their index hospitalization, compared with zero in the aza-ven arm. Patients in the aza-ven arm also reported a lower symptom burden and lower rates of depression at two weeks, according to quality of life assessments.

The researchers plan to conduct further analyses to compare costs, the rate of infectious complications, and other factors that may inform treatment decisions for this patient population. In addition, they will assess the use of measurable residual disease status to provide key prognostic and predictive information across arms of the study and inform the optimal amount of treatment needed for aza-ven prior to transplant.

The study was investigator-initiated; Genentech and AbbVie Inc. (maker of venetoclax), provided the study drug and funding to support research staff.

Amir Fathi, MD, of Mass General Brigham Cancer Institute and Harvard Medical School will present this study on Sunday, December 7, 2025, at 3:45 p.m. Eastern time during the Plenary Scientific Session in West Hall D2 of the Orange County Convention Center.

Adding Epcoritamab to Standard Second-Line Therapy Improves Follicular Lymphoma Outcomes
466: Primary Phase 3 results from the epcore FL-1 trial of epcoritamab with rituximab and

lenalidomide (R2) versus R2 for relapsed or refractory follicular lymphoma

In a new trial, patients with follicular lymphoma had a significantly higher response to treatment and a nearly 80% reduction in the risk of death or disease progression if they received epcoritamab in addition to the standard second-line regimen versus the standard regimen alone. The study is the first reported randomized controlled trial to test a bispecific antibody combination in follicular lymphoma and suggests the combination could offer an effective alternative to chemotherapy that can be safely administered on an outpatient basis.

Based on the study results, the U.S. Food and Drug Administration (FDA) approved epcoritamab with rituximab and lenalidomide for relapsed or refractory follicular lymphoma in November 2025.

“The addition of epcoritamab to rituximab and lenalidomide very substantially increased the response rates, depth of response, and duration of benefit and therefore may represent a new standard of care in patients with follicular lymphoma,” said lead study author Lorenzo Falchi, MD, assistant attending physician in the lymphoma service at Memorial Sloan Kettering Cancer Center in New York. “We are at a point in time when chemo-free approaches based on immunotherapy can seriously challenge chemotherapy as the standard of care. We will not know for a long time if [this regimen] is curative, but it’s certainly the beginning of a bright era for chemo-free therapy for follicular lymphoma.”

Follicular lymphoma is a slow-growing non-Hodgkin lymphoma that can progress to a more aggressive form. Patients who see their cancer return after an initial round of treatment have limited options and often experience subsequent relapses.

The immunotherapeutic combination rituximab and lenalidomide (known as R2) has become a standard second-line treatment for follicular lymphoma, while epcoritamab, a bispecific antibody, was more recently approved for follicular lymphoma that is relapsed or refractory (R/R) after two or more lines of systemic therapy. R2 and epcoritamab operate through different mechanisms to enhance the ability of a patient’s immune system to recognize and eradicate cancer cells.

The study randomized 488 patients with R/R follicular lymphoma to receive epcoritamab plus R2 or R2 alone for up to 12 cycles. At a median follow-up of just under 15 months, the group receiving epcoritamab plus R2 showed a significantly higher overall response rate (95.1% versus 79.2% among the control group) and a significantly longer progression-free survival (85.5% versus 40.2% at 16 months), meeting both of the trial’s primary endpoints.

Epcoritamab plus R2 also outperformed R2 alone for the trial’s secondary endpoints, with 82.7% of patients in this arm seeing a complete response (CR) to treatment versus 49.8% among those who received R2 alone. Participants who received epcoritamab plus R2 also showed a significantly longer duration of response and CR. The results were consistent across all subgroups analyzed.

Additionally, researchers noted that very few patients who received epcoritamab required subsequent treatments during the study period, suggesting that the new regimen can help

patients avoid or delay further treatments and their associated toxicities. At 16 months, 92.8% of patients in this group remained free from new anti-lymphoma treatments, compared with 64.9% among those who received R2 alone.

“A time-limited therapy that is not followed by another therapy for a long time is certainly a very good value for patients,” said Dr. Falchi.

Participants who received epcoritamab plus R2 experienced a higher rate of adverse events, with grade 3 or 4 treatment-related adverse events occurring in 90.1% of patients receiving epcoritamab and 67.6% of patients in the control group. This increase was driven largely by a higher rate of low white blood cell counts and infections among those receiving epcoritamab. There was no evidence of neurological toxicity and no reports of grade 3 or 4 cytokine release syndrome (CRS). According to researchers, this suggests that the combined regimen is safe to administer in a variety of medical settings.

“There has been some hesitancy to use bispecific antibodies in a community setting because of CRS,” said Dr. Falchi. “The prospect of a subcutaneous, completely outpatient treatment that does not result in a significant rate of CRS is good news for giving more patients the best opportunity for a response.”

The study also tested two different step-up dosing regimens for the epcoritamab–R2 combination, showing that three initial smaller doses resulted in a reduced rate of low-grade CRS compared with a course of just two initial smaller doses.

Given the study’s relatively short median follow-up time to date, the researchers will continue to track participants to assess longer-term outcomes. In addition, a separate study is underway to test the epcoritamab–R2 combination in a frontline setting. Dr. Falchi added that epcoritamab could also be investigated as a single-agent treatment for patients who are not candidates for R2.

The study was funded by Genmab and AbbVie Inc. The results were simultaneously published in The Lancet.

Lorenzo Falchi, MD, of Memorial Sloan Kettering Cancer Center, will present this study on Sunday, December 7, 2025, at 10:15 a.m. Eastern time in West Hall D2 of the Orange County Convention Center.

Non-Covalent BTKi Pirtobrutinib Shows Promise as Frontline Therapy for CLL/SLL
683: Pirtobrutinib vs ibrutinib in treatment-naïve and relapsed/refractory CLL/SLL: Results from the first randomized phase III study comparing a non-covalent and covalent BTK inhibitor

Pirtobrutinib, a non-covalent Bruton tyrosine kinase (BTK) inhibitor, met the primary endpoint for non-inferiority in terms of overall response rate in the first head-to-head comparison with ibrutinib, a covalent BTK inhibitor. Based on the study results, researchers suggest pirtobrutinib shows promise as initial BTK inhibitor therapy, including in the frontline setting, for patients with chronic

lymphocytic leukemia (CLL) and small lymphocytic lymphoma (SLL).

Non-covalent BTK inhibitors were initially developed to overcome resistance to covalent BTK inhibitors. This study is the first Phase III clinical trial to directly compare a non-covalent BTK inhibitor to a covalent BTK inhibitor in patients with CLL or SLL. It included patients who had not received any previous treatment, a first for any Phase III study directly comparing BTK inhibitors, as well as patients who had their cancer come back (relapse) or not respond (refractory) after receiving treatments other than a covalent BTK inhibitor.

“Pirtobrutinib was clearly non-inferior to ibrutinib, and the response rate actually favors pirtobrutinib in the total cohort,” said lead study author Jennifer Woyach, MD, Bertha Bouroncle, MD, and Andrew Pereny chair of medicine at The Ohio State University College of Medicine. “This shows that pirtobrutinib is a reasonable choice in both the treatment-naive and relapsed/refractory settings.”

CLL and SLL are slow-growing forms of non-Hodgkin lymphoma that develop when lymphocytes grow out of control and abnormal B cells build up in bone marrow (CLL) or lymph nodes (SLL). BTK inhibitors work by blocking the BTK enzyme, which plays a role in B-cell growth and proliferation.

The study enrolled 662 adult patients with CLL or SLL. Of these, 225 had not received any prior treatments, and 437 were R/R to prior treatments and had not received any BTK inhibitors. Participants were randomly assigned to receive either pirtobrutinib or ibrutinib and remain on their assigned therapy unless their disease progressed or they experienced unacceptable side effects.

The study’s primary endpoint, non-inferiority of pirtobrutinib for overall response rate (ORR), was achieved in the full study population. Of 662 participants, the ORR was 87.0% among those receiving pirtobrutinib and 78.6% among those receiving ibrutinib. The results consistently favored pirtobrutinib across the majority of subgroups, including those who were treatment-naive, relapsed/refractory (R/R) to prior treatments, and those with various high-risk disease characteristics.

Survival without disease progression, the study’s secondary endpoint, will be formally assessed at a later time. Early results suggest that pirtobrutinib may offer some benefit over ibrutinib for this endpoint as well, showing 18-month progression-free survival (PFS) rates of 86.9% in the pirtobrutinib arm and 82.3% in the ibrutinib arm. Preliminary results suggest treatment-naive participants saw the most pronounced benefit for this endpoint.

“The PFS is still a little bit immature at this point, but trends toward favoring pirtobrutinib in all of the groups – in the total cohort, in the R/R group, and, importantly, in the treatment-naive cohort,” said Dr. Woyach. “That’s really important, because given the safety of pirtobrutinib, it suggests that this might be a good option in the future for some patients with frontline CLL/SLL.”

The rates of treatment-emergent adverse events (AEs) and treatment discontinuation due to AEs were overall similar between arms. However, those receiving pirtobrutinib experienced lower rates

of AE-related dose reductions, treatment discontinuation due to progressive disease, and certain cardiovascular AEs including hypertension and development of atrial fibrillation or flutter.

These results may indicate pirtobrutinib is especially suitable for use in older or more frail patients. “While the efficacy and safety of pirtobrutinib have been very clearly established when given after a covalent BTK inhibitor, there are likely going to be subgroups of patients where pirtobrutinib is a more attractive option instead of the covalent BTK inhibitors,” said Dr. Woyach.

In addition to continuing to track outcomes from this study, Dr. Woyach said that future clinical trials could help refine the use of pirtobrutinib alone or in combination with other therapies as a frontline treatment. She added that researchers are also continuing to investigate possible mechanisms through which cancer may become resistant to non-covalent BTK inhibitors to further optimize treatment strategies.

This study was funded by Eli Lilly and Company, maker of pirtobrutinib.

Jennifer Woyach, MD, of The Ohio State University College of Medicine, will present this study on Sunday, December 7, 2025, at 5:30 p.m. Eastern time in W224ABEF of the Orange County Convention Center.

New Findings Support a Chemo-Free Approach for Treating Ph+ ALL
439: First results of the Phase III GIMEMA ALL2820 trial comparing ponatinib plus blinatumomab to imatinib and chemotherapy for newly diagnosed adult ph+ acute lymphoblastic leukemia patients

A chemotherapy-free combination treatment outperformed a combination of targeted therapy and chemotherapy among patients with Ph+ acute lymphoblastic leukemia (ALL) in a new study. The Phase III trial, which included adult patients with no upper age limit, is the first formal comparison of the efficacy and safety of these two approaches in newly diagnosed patients with Ph+ ALL.

Researchers say the findings offer reassurance that chemotherapy can be omitted without detrimental effects and suggest that a chemo-free targeted agent and immunotherapy combination could become the new standard of care for this patient group.

“The chemo-free approach significantly reduced the rate of death in addition to increasing the rate of complete remission,” said lead study author Sabina Chiaretti, MD, associate professor at Sapienza University of Rome in Italy. “The significance was very impressive, a more than 20% difference in terms of molecular response achievement [a sensitive test for residual cancer cells following treatment], so this approach truly is better.”

ALL is a fast-growing type of leukemia affecting white blood cells, while Ph+ ALL is a genetic subtype characterized by the causal genetic abnormality in the Philadelphia chromosome. Patients with Ph+ ALL have historically faced a poor prognosis and increased resistance to chemotherapy, pointing to a need for improved treatments. In recent years, targeted tyrosine kinase inhibitors (TKIs) and immunotherapies have brought promising results, with good efficacy and fewer side

effects than chemotherapy. Researchers have sought to identify the optimal combination of therapies among TKIs, immunotherapies, and chemotherapy.

For the trial, researchers enrolled 236 adult patients with Ph+ ALL, ranging in age from 19 to 84 years. Two-thirds of participants were randomly assigned to the experimental arm and received a TKI plus immunotherapy; one-third were assigned to the control arm and received a TKI plus chemotherapy. Patients in the experimental group received an initial course of steroids, a 70-day induction with the TKI ponatinib, and two to five cycles of the immunotherapy blinatumomab. Patients in the control group received the TKI imatinib along with either four or six cycles of chemotherapy for patients older or younger than age 65, respectively.

Patients in the chemo-free experimental arm had a significantly higher rate of event-free survival and a better response to treatment. At a median follow-up of 23 months, event-free survival was 87% in the experimental arm and 71% in the control arm, while the rate of death was 3.5% in the experimental arm and 10% in the control arm. The relapse rate was similar among arms (6% in the experimental group and 8% in the control group), although about half of the relapses in the experimental group occurred in patients who had discontinued their treatment.

Complete remission was achieved in 94% of those in the experimental arm and 79% of those in the control group. The chemo-free treatment regimen also resulted in a higher rate of negative measurable residual disease (MRD) status, an indicator that all or nearly all cancer cells have been eradicated. While only 49% of those in the control group achieved MRD-negative status, 71% of those in the experimental group achieved MRD-negative status after two cycles of blinatumomab, and 80% reached this status after five cycles.

“The more cycles with blinatumomab, the more the molecular remission rate increased,” said Dr. Chiaretti. “This suggests that patients really should receive the planned five cycles. This is important because we have been working with blinatumomab for years, but we did not yet know how many cycles should be recommended.”

Participants randomized to the control group were offered the option to cross over to the experimental arm if their disease was MRD-positive. About 37% of patients in the control arm eventually received the experimental treatment regimen, and 62% of these patients subsequently achieved MRD-negative status.

Most of the deaths occurred in older patients, and infections were a primary cause of death among those that occurred in the experimental arm. The safety profiles were consistent with those expected for each therapy involved in the study, and researchers said that most adverse events were successfully addressed by reducing dosage.

While the study was conducted exclusively in Italy, Dr. Chiaretti noted that the results should be applicable in any country. She added that a chemo-free treatment approach can bring economic benefits by reducing the need for hospitalization and allowing patients to continue working while undergoing cancer treatment.

A separate study is now underway to determine whether patients with sustained MRD-negative status can discontinue TKI treatment without raising the risk of a relapse.

Sabina Chiaretti, MD, of Sapienza University of Rome, will present this study on Sunday, December 7, 2025, at 9:30 a.m. Eastern time in W224A-F of the Orange County Convention Center.

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