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# ADVANCING THE GOLD STANDARD

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**Amer Zeidan, MBBS; and more**

MAIL TO:

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Highlighting Recent CLL Research for World CLL Day

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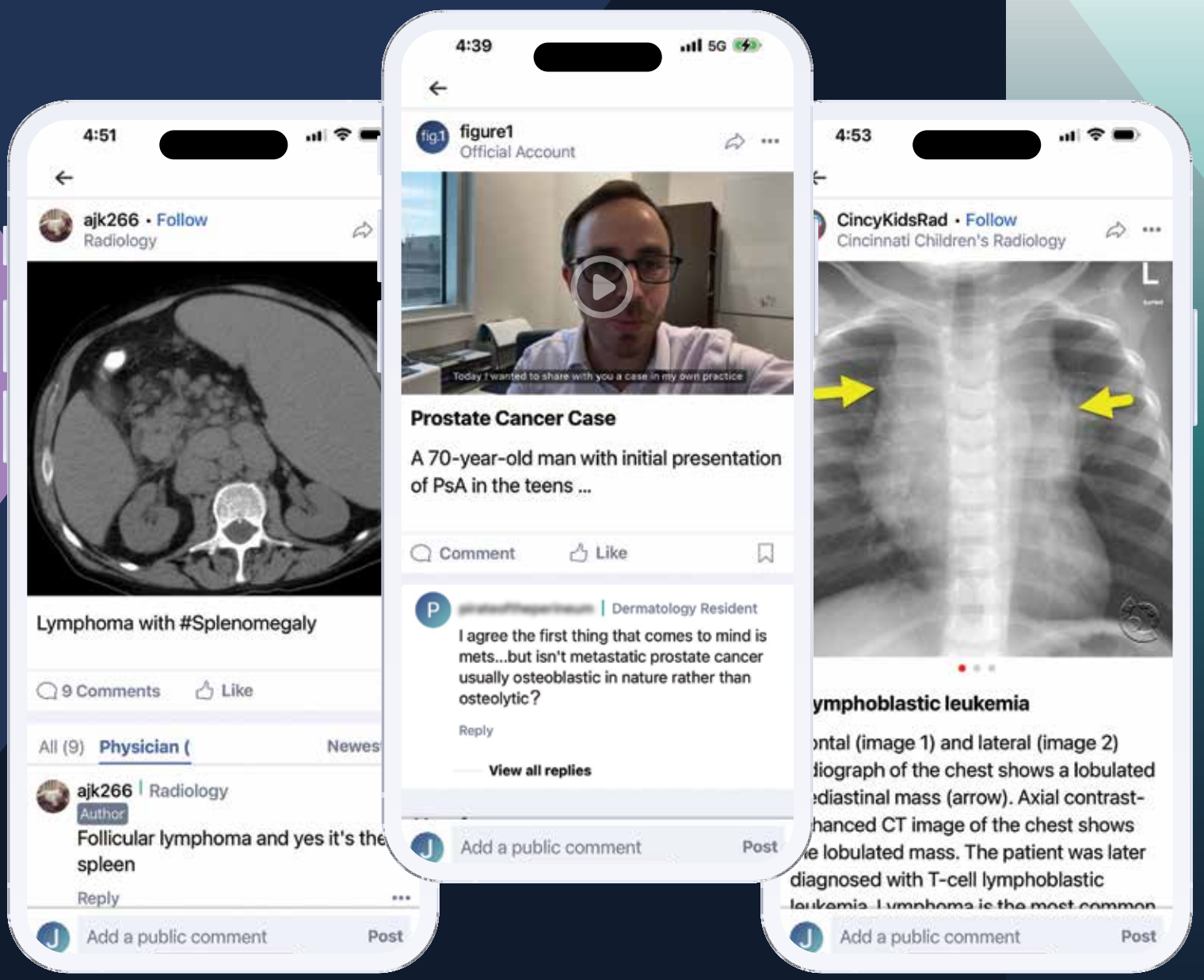

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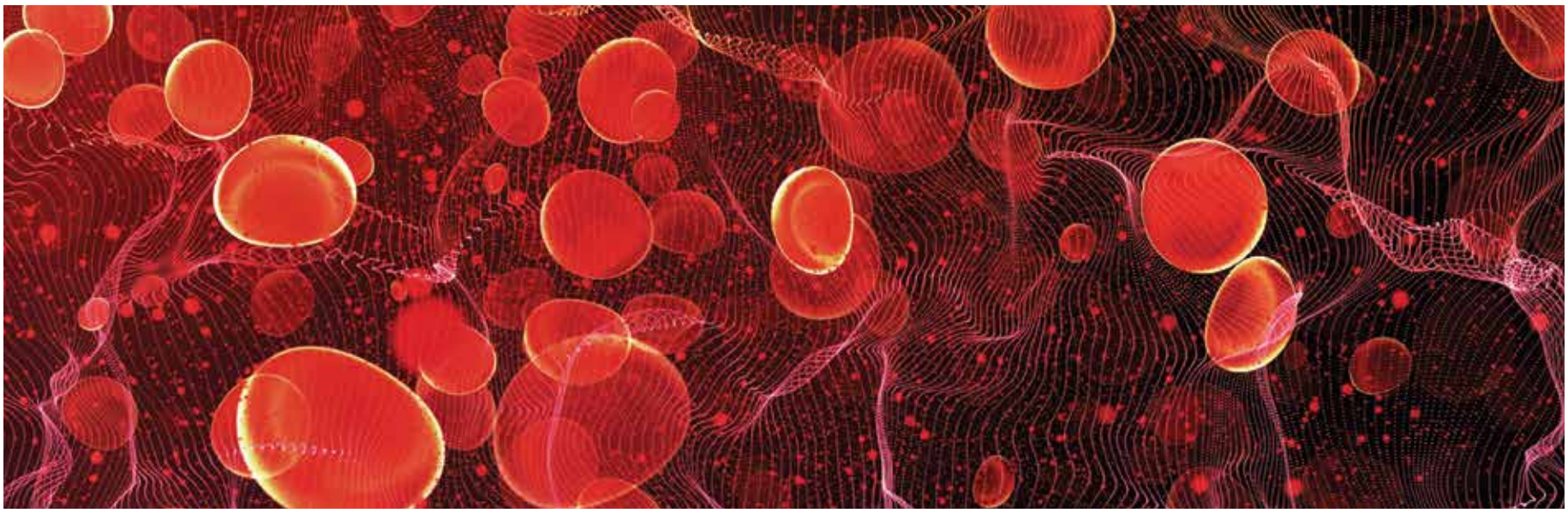
# Get to Know

*Learn more about the leaders, innovators, and educators in hematologic oncology*



# Idoroenyi Amanam, MD

**Idoroenyi Amanam, MD, has moved cities throughout most of his childhood. Now, he's planted roots in Duarte, California, as an assistant professor in the Division of Leukemia, Department of Hematology & Hematopoietic Cell Transplantation at the City of Hope. Dr. Amanam sat down with *Blood Cancers Today* to share his research in cellular therapy, his passion for improving transplant access for all patients, and his love for both science and science fiction.**

*By **Melissa Badamo***

**Where did you grow up, and how did you know you wanted to be a hematologist-oncologist?**
Growing up, I moved around a lot. In that experience, I was forced to figure out myself a little bit. My parents are Nigerian immigrants. When you move around a lot, you're very close to your family, but you might not have many friends. As a kid, you want to have friends and build those relationships.

In my field, I build connections with patients, and unfortunately, some of those patients die. For each of my patients, I'm happy that I had an opportunity to contribute to their journey. My experience growing up has been very helpful in my career journey.

Starting medical school, I wasn't sure what I wanted to do. As a medical student, you have great opportunities to be exposed to all subspecialties. There were tumor boards once a week, and the hematology tumor board offered free lunch. Eventually, I picked up an interest. We were looking at pathology slides and the molecular cell biology and genetics that we must understand to make a diagnosis for specific patients. That was interesting to me. After the second or third month, one of the attendings connected me with research opportunities for medical students, and the rest is history!

This field is forever rapidly changing, and these patients are clinically challenging. We are at the forefront of science and medicine, and being able to take care of these challenging patients is interesting and exciting.

**How has the field changed from when you were in medical school to now?**
In 2013, we were still utilizing 7+3 [chemotherapy] for most patients with AML [acute myeloid leukemia]. Fast forward to now, we still have 7+3. We have hypomethylating agents plus venetoclax. We have targeted therapies. We have immunotherapy and allogeneic stem cell transplant. We have other cellular therapies that target acute leukemias. It's been a rapid change, but I think the most exciting part is giving patients more of an opportunity to get rid of this disease that has unfortunately taken many lives.

**Can you please share your current research?**
From a basic science perspective, we are very interested in targeting myeloproliferative disorders with bispecific antibodies and cellular therapy. I have focused some of my research into developing novel therapeutics that are targeting new targets and other targets that have already been identified in myeloproliferative disorders. At City of Hope, we are one of the largest allogeneic stem cell transplant centers for myeloproliferative disorders.

Even though our outcomes are better than before, I think we can do better. We're identifying better conditioning regimens, better graft-versus-host prophylaxis regimens, and optimizing the donor. We are interested in ensuring that every patient has a good donor, but we also want to make sure that depending on the type of conditioning regimen or the

**"We are at the forefront of science and medicine, and being able to take care of these challenging patients is interesting and exciting."**

graft-versus-host prophylaxis regimen that we identify, these regimens still offer the same benefit.

The third arm of my research interests is looking at how we can improve access to transplant[s] for all patients. Once we get a patient tied into our system and get them through transplant, the outcomes are equal across the board for socioeconomic groups, race, and other factors. But, there's still an issue with patients getting referred or getting an opportunity to be evaluated for transplant. That's where some work needs to be done to improve that access.

**How can access to transplant be improved?**

Unfortunately, there's no easy answer. When we think about race and social determinants of health, those are factors that are more defined by a patient's insurance, neighborhood, and societal factors. One thing we can improve upon is combining a patient's genomic and ancestry factors with societal factors to identify who may be higher risk early on. Then we can pair them and link them with navigators, which is what we do at our center.

Transplant patients are very tied into social workers and navigators who can help them make it through. That's why we have very good outcomes for all patients. For other diseases outside of transplant, we should be able to consider doing the same thing.

Lodging, transportation, and caregiving are necessities for transplant. Unfortunately, CMS [Centers for Medicare and Medicaid Services] and insurance companies look at these items as optional. That leads to a situation where a patient may need a transplant, but they don't have transportation to get to the visits. They don't have a caregiver to assist them. They don't have stable housing. How do we incentivize insurance companies to ensure that patients have all these necessary components? There needs to be a policy involved because financially, for an insurance company, there is a bottom line there.

Transplant is a lifesaving treatment. We should look at scientific data, identify high-risk patients, then show that we can improve outcomes if we link a navigator, provide housing, give them transportation. Hopefully, we can work with payers to cover those components.

**What do you hope to see in the field over the next 10 years?**

It's clear that we can't save all our patients. Transplant is still a very intense regimen treatment with a lot of toxicities. We need more therapies for all patients. We need to continue to improve transplant outcomes.

Hopefully, maybe there's a day that transplant may not be the curative approach for these myeloproliferative disorders. Unfortunately, we may not get there in 10 years, but I think there's a lot of work in identifying disease-modifying drugs, drugs that get rid of the underlying nidus for the disease. I think in the next 10 years, we'll see a lot more therapies that have disease-modifying capabilities.

**What advice would you give to younger physicians or trainees in the field?**

My biggest piece of advice is to identify a subset of cancer patients you have an interest in. Being able to do something that you love is key. If you really enjoy taking care of a subset of patients and improving their outcomes, everything else will come. If you're interested in improving outcomes, you will be doing the research to try to figure that out. Patients will gravitate towards you because they can feel that natural energy of you really wanting to help them and give them the best opportunity to fight their disease.

My dad, who was a businessman, used to tell my two siblings and me to find something that we love to do. Life is more than work, but I think unfortunately as a physician, a good percent of your life will be connected to your job. Enjoying what you do is key to enjoy other things in life.

**"Even though our outcomes are better than before, I think we can do better."**

**What hobbies do you enjoy outside of work?**

I like going to the gym and working out. Aside from the health benefits, it's an opportunity for escape. I also love biking and day hikes. The great thing about being in Southern California is that there's a lot of different places [where] you can hike for 10 or 12 hours and go back home the same day. I love that aspect of being here in SoCal.

Duarte is right by the San Gabriel Mountains. The San Gabriel Mountain range is a very long range in California, but they have a lot of different trails that go up to middle high altitude or mid altitude.

**What's a fun fact most people would be surprised to learn about you?**

Most people don't know that I love sci-fi, fantasy, and adventure films. *Star Wars* and Indiana Jones are my top movies. I do love sci-fi books, too. I read a lot of Michael Crichton, like *Jurassic Park*. For someone who has an interest in science and biology, it's really intriguing to see the mind of a writer who can think beyond what we have available to us today. I'm impressed with all writers and artists. Since I love science, reading science fiction books give me that "wow" feeling when a writer creates a cool, unique idea of how our future would be or how we can utilize DNA to treat patients.

Blood Cancers Today *spotlights the latest research from medical residents and fellows in the field of hematologic malignancies.*

# Older Woman With LGL Leukemia

As in most medical institutions, hematology-oncology teams at Moffitt Cancer Center follow standardized treatment pathways informed by clinical guidelines. However, for patients in certain disease states, those guidelines may not reflect the variability seen in real-world clinical settings, challenging physicians to apply a more individualized approach to care.

A recent case report, published in *Leukemia Research,* included a systematic review of studies on large granular lymphocytic leukemia (LGLL). Although WHO classification for LGLL requires the identification of at least 2,000 large granular lymphocytes per microliter and confirmation of T-cell receptor (TCR) β and/or γ gene clonality, the authors, including hematology-oncology fellow **M. Bakri Hammami, MD**, observed that clinical presentations often fall outside these parameters. Their findings underscore the importance of a comprehensive diagnostic process that includes clinical assessment as well as immunohistopathologic and molecular evaluation of peripheral blood, bone marrow, and, in some cases, skin biopsy specimens to establish an accurate diagnosis.

Insights From

**M. Bakri Hammami, MD**

Hematology/Oncology Fellow at
H. Lee Moffitt Cancer Center

## Case Information Table

| Category | Details |
|---|---|
| Patient Demographics | 66-year-old female |
| Medical History | Rheumatoid arthritis |
| Presenting Symptom | Persistent fatigue |
| Physical Findings | 3-cm ulcerated, nodular lesion in right axilla (noticed ~6 months ago) |
| Lesion Description | Raised with dusky base, soft surface, erythematous halo |
| Laboratory Results | **WBC:** 14.2 × $10^3$/μL<br>**Hemoglobin:** 14.9 g/dL |
| | **ANC:** 0.01 × $10^3$/μL **ALC:** 13.1 × $10^3$/μL<br>**Platelets:** 88,000/μL |
| Infectious/Autoimmune Workup | No significant findings |
| Bone Marrow Biopsy | 90% cellularity 60%-70% atypical CD3+ small lymphocytes |
| Bone Marrow Immunophenotype | CD2+, CD3+, CD4-, CD5+, CD7-, CD8-, TCR γδ+ |
| Peripheral Blood Flow Cytometry | Neoplastic lymphocytes = 86.5% CD3+, CD5+ (dim), CD7+ (dim), TCR γδ+ |
| Genetic Findings | STAT3 p.Y640F mutation VAF: 41% |
| Imaging (PET/CT) | Subtle FDG-avid right axillary nodes<br>Mild diffuse splenic uptake |
| Skin Biopsy (Ulcer) | Size: 0.4 × 0.4 × 0.7 cm ulceration, acute inflammation in dermis/subcutis |
| Skin IHC Staining | CD2+, CD3+, CD7+ lymphocytes |
| Skin Flow Cytometry | 42% Clonal T cells γδ-TCR phenotype consistent with γδ T-LGLL |
| Clinical Course | Complete resolution of lesion days after biopsy |

**"This case and review show that LGL leukemia can present in unexpected ways, including diverse skin presentations. The takeaway is to maintain a broad differential and pursue biopsy and immunophenotyping early for new or unusual skin changes, particularly in patients with cytopenia or autoimmune features. At Moffitt, we take a multidisciplinary approach to LGLL diagnosis, starting with diagnostic confirmation via flow cytometry, TCR rearrangement, STAT3 mutation testing, and bone marrow biopsy."**

# Venetoclax Leads the Way in Redefining CLL Treatment

*By* ***Nichole Tucker***

Dr. Huang is a senior hematology and oncology fellow at Fred Hutch Cancer Center and the University of Washington, where she also served as chief fellow. She received her medical and doctoral degrees from Duke University and completed her internal medicine residency at Washington University in St. Louis. Her research interests include clinical and translational investigations at the intersection of lymphoma and cellular therapy. She is currently leading a clinical trial evaluating the efficacy and safety of combination therapies with chimeric antigen receptor (CAR) T-cell therapy for patients with chronic lymphocytic leukemia and conducting translational projects on the impact of Bruton's tyrosine kinase inhibitors on CAR T-cell and immune function in patients with lymphoma. Dr. Huang will join the faculty as an assistant professor at Fred Hutch Cancer Center and the University of Washington in January 2026.

Over the past decade, the treatment landscape for chronic lymphocytic leukemia (CLL) and small lymphocytic lymphoma (SLL) has undergone a dramatic transformation. Chemoimmunotherapy, once the standard of care, has been steadily replaced by targeted agents that offer deeper and more durable responses. At the forefront of this shift is the BCL-2 inhibitor venetoclax, which, whether used as monotherapy or in combination with other therapies, has delivered impressive efficacy and is poised to redefine the treatment paradigm.

At Fred Hutchinson Cancer Center in Seattle, Washington, **Mazyar Shadman, MD, MPH,** professor, Clinical Research Division, medical director, and Cellular Immunotherapy, Innovators Network Endowed Chair led a review of CLL clinical trials exploring venetoclax combinations for the treatment of CLL/SLL along with **Jennifer Huang, MD, PhD,** a hematology/oncology fellow and recent recipient of the Young Investigator Award research grant from Conquer Cancer.

In an interview with *Blood Cancers Today,* Dr. Huang emphasized the growing role of venetoclax in reshaping CLL treatment, underscoring its impact across multiple patient populations.

Beginning with earlier studies of venetoclax in CLL, Drs. Shadman and Huang demonstrate that chemoimmunotherapy is no longer an appropriate treatment. First, in a study of venetoclax combined with anti-CD20 monoclonal antibodies like rituximab or obinutuzumab, the BCL-2/anti-CD20 combinations outperformed chemoimmunotherapy in fit and frail patients. Researchers then explored the combination of venetoclax plus obinutuzumab in the GAIA-CLL13 study. Again, it outperformed chemoimmunotherapy, this time in the fit, untreated CLL population.

Other studies that investigated the combination of venetoclax and obinutuzumab, including CLL14 and CRISTALLO, solidified the role of targeted therapies over chemoimmunotherapy with better responses, including in subsets of patients with measurable residual disease (MRD) positivity at baseline and those with *TP53*-altered CLL.

Venetoclax with the first-generation BTK inhibitor, ibrutinib, was the combination of choice across many clinical trials. For example, the GLOW study investigated the combination in fit and unfit patients with CLL and demonstrated improvements in progression-free survival (PFS), complete response (CR) rates, and undetectable MRD rates compared with chemoimmunotherapy. Venetoclax/ibrutinib demonstrated similar superiority following a time-limited approach in the CAPTIVATE study.

The pivot to using second-generation BTK inhibitors like acalabrutinib and zanubrutinib in combination with venetoclax revealed even more impressive efficacy. The most recent studies investigating venetoclax and second-generation BTK inhibitors include AMPLIFY and SEQUOIA.

> **"There are new generations of drugs in the same BCL-2 inhibitor class, such as sonrotoclax or lisaftoclax, that are being studied in clinical trials that may be both more effective and [have] more tolerable safety profile[s]."**
>
> *—Jennifer Huang, MD, PhD, Fred Hutch Cancer Center*

According to results presented at recent medical meetings, the doublet combination of zanubrutinib and venetoclax showed promising efficacy and tolerability in treatment-naive patients, including those with *TP53* alterations. The fixed-duration triplet composed of acalabrutinib, venetoclax, and obinutuzumab also demonstrated activity in previously untreated, high-risk patients with CLL and was well tolerated.

Despite the growing number of chemotherapy-free options, including all-oral regimens, Drs. Huang and Shadman noted that no consensus has been reached on the optimal combination. "There are many choices for a partner for venetoclax, but the best partner is yet unknown," said Dr. Huang.

Multiple clinical trials are now underway to answer this question. Investigators are also looking beyond venetoclax to further enhance efficacy outcomes.

"While venetoclax has been an important option in the toolbox for treating CLL, there are new generations of drugs in the same BCL-2 inhibitor class, such as sonrotoclax or lisaftoclax, that are being studied in clinical trials that may be both more effective and [have] more tolerable safety profile[s]," Dr. Huang added.

**Reference**

Huang J, et al. *Hematol Oncol Clin North Am.* 2025;1:S0889-8588(25)00079-6. doi:10.1016/j.hoc.2025.05.007


*By* ***Melissa Badamo***

Double-blind, placebo-controlled trials are considered the "gold standard" in scientific research due to their value in determining the efficacy and safety of a particular treatment.[1] However, as per FDA guidance, using a placebo alone is not considered ethical for patients with hematologic malignancies for which standard effective therapy is currently available.[2]

Placing a patient in a placebo arm without active treatment delays their receipt of an effective drug, prevents entry into another clinical trial, and exposes them to increased symptoms, pain, and risk for death.[2,3] Rather, investigators should opt for an open-label trial design using standard therapy as an active control, according to the FDA.[2]

*Blood Cancers Today* spoke with several investigators to explore when and why placebos are used in blood cancer trials, the challenges of designing trials, and their hopes for future innovations in blood cancer trials.

### The Value of Placebo

The use of a placebo, combined with randomization and double blinding, helps reduce bias in clinical trials.

"In terms of trial design, placebo control is really important," said **Aaron Gerds, MD,** a hematologist-oncologist at the Cleveland Clinic. "We're all full of biases. We jump to conclusions; it's human nature. We don't want to be hindered from finding the truth by our biases. That's one of the ideas behind placebo control."

"There is physician- and patient-associated biases when we do a single-arm study. We have our own preconceived notions of things, and patients do too," added **John DiPersio, MD, PhD,** Virginia E and Sam J Golman Professor and section director of cellular therapy at Washington University Medicine. "You have to test something in the context of a randomized trial."

### "Add-On" Trials

Many blood cancer clinical trials utilize an "add-on" design, in which both arms receive standard therapy plus either the experimental treatment or the placebo. This prevents patients in the placebo arm from being left untreated.[3]

For example, the phase 3 MANIFEST-2 study evaluated pelabresib plus ruxolitinib versus placebo plus ruxolitinib in Janus kinase inhibitor–naive patients with myelofibrosis.

"The placebo portion of this trial wasn't placebo in the sense of not getting the study drug, but all patients did get a standard-of-care therapy as the backbone of their therapy, which to me is absolutely the right thing," said **Raajit K. Rampal, MD, PhD,** investigator of the MANIFEST-2 study and a leukemia specialist at the Memorial Sloan Kettering Cancer Center. "The question being asked is if the combination is better than the single agent, so this is the appropriate design. If this had been a study versus completely placebo, that to me is unethical at this point."

Dr. Rampal and colleagues found that 56.5% of patients in the pelabresib plus ruxolitinib arm achieved a reduction in spleen volume of at least 35% at 48 weeks, compared with 37.5% of patients in the ruxolitinib plus placebo arm.[4]

### The Role of Standard of Care

Standard of care is typically used in addition to a placebo, but what if the standard of care is considered ineffective?

Dr. Gerds is the lead investigator of the REVIVE trial, which compared rusfertide with placebo in patients with polycythemia vera (PV).[5] Both arms received standard-of-care phlebotomy to maintain hematocrit levels under 45%, but this treatment is considered outdated, according to Dr. Gerds.

"Phlebotomy is commonly used. It's a really old therapy. It's about time we have something new for the treatment of PV. There are studies showing that with phlebotomy, we're keeping the hematocrit under the mark of 45% a third of the time, maybe half the time in some studies. It's woefully inadequate," Dr. Gerds explained. "There's a difference between inadequate and standard of care. It is a standard of care treatment, and although inadequate, we use it because we don't have a lot else."

Both the phase 2 REVIVE trial and phase 3 VERIFY trial successfully showed that rusfertide eliminated the need for phlebotomies, Dr. Gerds explained.

"There are a lot of standard-of-care treatments that are relatively toxic and ineffective that we use all the time," Dr. DiPersio added. "For patients with acute leukemia that have resistant disease, of course, they want to try the new drug against what's considered standard-of-care. Maybe the patient has already received multiple treatments, and the standard of care is only going to cause some level of harm and toxicity and not any level of efficacy. Sometimes, supportive care is an option that may actually be better for the patient."

While supportive care may be an appropriate option, Dr. DiPersio explained, offering standard therapy is ultimately based on the notion that it provides some benefit to the patient.

### iMERGE Trial

The randomized, double-blind, placebo-controlled phase 3 iMERGE trial by **Amer Zeidan, MBBS,** a professor of medicine at Yale School of Medicine, and colleagues compared imetelstat with placebo in patients with red blood cell transfusion-dependent, lower-risk myelodysplastic syndromes (MDS) who are not responding to or are ineligible for erythropoiesis-stimulating agents.[6]

In iMERGE, an outlier in contemporary cancer trials, investigators utilized placebo as the sole control—but only due to a matter of timing.

Luspatercept, the current standard of care for lower-risk MDS, was not FDA-approved at the start of the trial, Dr. Zeidan explained. Luspatercept was approved in August 2023 as a first-line treatment of anemia in adult patients with lower-risk MDS based on results of the COMMANDS trial.[7]

"There are other available drugs that are used but are not technically standard of care," Dr. Zeidan explained. For example, while hypomethylating agents are occasionally used in lower-risk MDS, they are not globally available for lower-risk MDS and are mostly used for higher-risk disease.

"If you are to design a trial using a hypomethylating agent as a control, then you have to supply the drugs," Dr. Zeidan added. "The dosing is also not established for lower-risk MDS. We generally would use shorter courses and lower doses of hypomethylating agents. Other drugs like lenalidomide are used off-label outside of deletion 5q lower-risk MDS. So, I think this has been always a challenge. However, nowadays you have imetelstat and luspatercept. There are options to use now compared to back when the iMERGE trial was designed."

### Patient Conversations

When clinicians speak to patients about enrolling in clinical trials, the first question patients ask is whether they will receive a placebo, Dr. Rampal explained.

"Patients are afraid of that, and justifiably so," he said. "We have to be really careful about what we mean if we're going to use a placebo, and we have to make sure patients absolutely understand that it does not mean that they're not getting a treatment. They are getting a treatment, but they may not get the investigational drug."

In a survey of 6,000 patients with cancer, 31% "reported the fear of receiving a placebo as a major factor in their decision" to not participate in a clinical trial.[8]

"Patients want to make sure they're getting a new and innovative therapy that might be potentially better than what they're getting," Dr. Gerds added.

While the possibility of a placebo deters some patients from enrollment, others are inspired to play an active role in advancing research and helping future patients.

"Every patient wants to live and get a treatment that might help them," Dr. Dipersio said. "The second most important thing to a lot of patients is the notion of participating in a study that might help others after them. There's amazing interest when you bring that issue up with the patients."

### Crossover Trials

One method of increasing patient enrollment and ensuring they eventually receive the investigational drug is through crossover trials, in which eligible patients can cross over to the active treatment from a placebo.

"That helps accrue immensely and helps those discussions with the patients," Dr Gerds said.

Patients in the REVIVE study were also eligible to roll over to the phase 2 THRIVE OLE study, which is continuing to assess the safety and efficacy of rusfertide for up to 5.8 years.[5]

However, one downside to crossover trials is that they can obscure results, Dr. Gerds noted.

"If you're doing a survival study for a particular drug, when there's crossover, it will lessen the survival advantage of the better therapy," he said. "At that point, patients are getting both arm A and the control arm. You lose the ability to do a rigorous long-term survival analysis."

This downside has less of an impact for PV trials in which patients live more than 25 years and take 15 years to progress to myelofibrosis, Dr Gerds explained. Therefore, it would not be feasible to conduct a survival study.

"It's okay to let them cross over because the main point of the trial was to determine if rusfertide can eliminate the need for phlebotomies. Once you've proven that it does or doesn't depending on the arm, patients can cross over. It's not going to obscure the main results of the trial," Dr. Gerds added.

"When you design a trial, you power to answer one question. Once you've answered that question, everything else is gravy. It gives you a lot more wiggle room in your design for allowing for things like crossover."

Another placebo "workaround" is shifting the balance by randomly assigning patients 2:1 to the treatment arm rather than 1:1, Dr. Zeidan mentioned. This way, there's a higher chance that more patients will receive the active drug.

### Future Clinical Trial Innovations

Finally, the investigators outlined their hopes for future designs and innovations in blood cancer clinical trials.

"We need better end points," Dr. Gerds said. "The end point of spleen volume reduction in myelofibrosis is important, but we want to go beyond that. We want to start looking at survival as an end point, like progression-free survival and durability of therapy. We need to design trials that will answer that question as the primary result, like the ongoing phase 3 trial with imetelstat. We need better biomarkers to help us do better trials."

In addition, Dr. DiPersio thinks it's time to modify the traditional "3+3" design—which is used to determine the recommended phase 2 dose—and shift to simultaneous dosing.

"A lot of the traditional 3+3 designs can be modified so that you have a much faster Bayesian statistical approach to trials, which is single patient or simultaneous patients at different doses moving ahead at the same time," he said. "There are better statistical designs that can enhance the enrollment of patients, especially at lower doses. You can move through these lower doses much faster, which saves months or years."

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# FDA's ODAC Votes Belantamab Mafodotin at Proposed Dosing Unfavorable in Multiple Myeloma

*By **Melissa Badamo***

The FDA's Oncologic Drugs Advisory Committee (ODAC) has determined that the overall benefit-risk of belantamab mafodotin (Blenrep) in combination with bortezomib and dexamethasone (BVd) or pomalidomide and dexamethasone (BPd) is not favorable at the proposed dosage in patients with relapsed or refractory multiple myeloma (MM).

The Committee convened on July 17, 2025, at the Center for Drug Evaluation and Research (CDER) on the FDA White Oak Campus in Silver Spring, Maryland, to discuss the Biologics License Application submitted in November 2024 by GlaxoSmithKline LLC (GSK) for the following regimens:

- Belantamab mafodotin in combination with BVd for adult patients who have received at least one prior line of therapy
- Belantamab mafodotin in combination with BPd for patients who have received at least one prior line of therapy, including lenalidomide

In introductory remarks, **Deepti Telaraja, MD,** of the FDA's division of hematologic malignancies II, raised concerns about the high rates of ocular toxicity and uncertainty regarding the proposed dosages in the DREAMM-7 and DREAMM-8 trials.[1]

Patients in DREAMM-7 received a dosage of 2.5 mg/kg every 3 weeks, and patients in DREAMM-8 received a starting dose of 2.5 mg/kg every 3 weeks in cycle 1, followed by 1.9 mg/kg every 4 weeks on cycle 2.[1]

In DREAMM-7, the rates of ocular events were 79% with BVd versus 29% with daratumumab, bortezomib, and dexamethasone (DVd). In DREAMM-8, the rates were 89% with BPd versus 30% with pomalidomide, bortezomib, and dexamethasone (PVd). In both trials, ocular events were managed by dose modification of belantamab mafodotin.[3,4]

"The toxicity is caused by damage to the corneal epithelium manifesting as corneal changes and visual acuity changes," Dr. Telaraja explained.[1]

Despite the high rate of ocular events, the drug met its primary end point of progression-free survival (PFS) in both trials.

In DREAMM-7, BVd showed superior PFS compared with DVd among patients with MM progression after one or more lines of therapy, having produced a median PFS of 36.6 months versus 13.4 months, respectively ($P<0.001$).[3]

In DREAMM-8, the 12-month estimated PFS was 71% with BPd and 51% with PVd ($P<0.001$) among lenalidomide-exposed patients with relapsed or refractory MM after one or more lines of therapy.[4]

"Ocular events are reversible with time and effectively managed with dose modifications, allowing patients to remain on treatment and derive benefit," said **Hesham A. Abdullah, MD, MSc, RAC,** senior vice president and global head of oncology at GSK.[1] "The dose and schedule of Blenrep has been extensively studied in almost 400 patients. The proposed 2.5 mg/kg starting dose and use of dose reductions and delays to manage ocular events is the most optimal approach for dosing to gain maximal benefit-risk."

**Natalie Afshari, MD,** chief of cornea and refractive surgery and professor of ophthalmology at Shiley Eye Center, University of California, San Diego, explained the pathophysiology behind belantamab mafodotin-related ocular events.

"Blenrep causes microcyst-like changes in the corneal epithelium…these may occur without symptoms but can affect vision depending on severity and location. They begin in the peripheral epithelium then move toward the center, where they may impact vision. As new cells grow from the periphery inwards, older cells are replaced, and vision recovers. It's this pathophysiology that supports the resolution of ocular events associated with Blenrep," Dr. Afshari explained.[1]

Results from a patient questionnaire presented at the meeting showed that 50% of patients who experienced ocular adverse events while receiving belantamab mafodotin reported at least moderate symptoms, and 20% reported severe symptoms.[1]

"More than 10% of patients in both trials experienced a very severe change in best corrected visual acuity to 20/200 or worse, which qualifies as legal blindness," said **Andrea Baines, MD, PhD,** a clinical reviewer at the FDA's division of hematologic malignancies II. "This degree of vision loss would be expected to greatly impair a patient's independence and ability to perform everyday tasks."

Regarding other safety findings from the two trials, grade 3 or higher adverse events (AEs) occurred more frequently with BVd than with DVd, at 95% versus 78%, respectively, and with BPd versus PVd, at 94% versus 76%, respectively.[3,4]

**Sagar Lonial, MD,** chair and chief medical officer at the Winship Cancer Institute, Emory University School of Medicine, concurred that dose adjustments provide patients with a more tolerable safety profile with continued efficacy.

"The results were consistently improved across all end points, including overall response rate, duration of response, MRD [measurable residual disease] negativity, PFS, and overall survival," he said.[1] "These results validate the dose modification scheme outlined in DREAMM-7 and DREAMM-8 and are among the longest PFS seen in any randomized phase 3 trials in early relapsed myeloma. This magnitude of benefit is not observed with most currently available treatment combinations."

However, according to **Ankit Shah, PhD,** clinical pharmacology team leader at the FDA's Division of Cancer Pharmacology, the dose modifications may not be adequately optimized. "The applicant conducted very limited dose exploration in a small number of patients to support selection of the belantamab mafodotin dosages in DREAMM-7 and DREAMM-8," he said.[1] "The available data also suggest that lower exposure of belantamab mafodotin may result in fewer dose modifications and corneal adverse events without necessarily affecting the efficacy."

Following a public hearing, three committee members voted "Yes" and five voted "No" to the question of whether the overall benefit-risk of belantamab mafodotin in combination with BVd is favorable at the proposed dosage in the proposed patient population.

Additionally, one Committee member voted "Yes" and seven voted "No" to the question of whether the overall benefit-risk of belantamab mafodotin in combination with BPd is favorable at the proposed dosage in the proposed dosage in the proposed patient population.

Lack of early dose optimization was identified as a large factor for those who voted "No."

"This was a challenging decision because the efficacy data were strong, but the toxicity data were also very strong," said **Neil Vasan, MD, PhD,** acting chairperson of ODAC, who voted "No" to both questions.[1] "I took a textualist interpretation to this question, and I'd like to emphasize the words 'at the proposed dosage.' This was what swayed the decision. This was just a missed opportunity over the course of many years of development at the drug to explore these different dosages."

"Based on the clinical experience of the researchers and the testimonies we heard, this is an amazing drug for an incurable disease," said **John DeFlice, MD,** who voted "Yes" to both questions.[1]

"The question asked do we have a safe and effective dose, and I think there needs to be more work done," added **Paul Beringer, PharmD,** who voted "No" to both questions.[1]

Despite the outcome of the meeting, many committee members expressed hope for the drug to become optimized and available in the US.

Belantamab mafodotin-blmf was FDA approved in 2020 for use in adults with relapsed or refractory MM who have received at least four prior therapies, including an anti-CD38 monoclonal antibody, a proteasome inhibitor, and an immunomodulatory agent.[5] However, the drug was voluntarily withdrawn from the US market in February 2024 due to a failed confirmatory trial.[1]

The recommendations that ODAC generates for the FDA are not legally binding. However, the FDA usually has adopted these ODAC-issued recommendations.

### References

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# CARVYKTI®
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*Give your adult patients with RRMM who have received a PI and an immunomodulatory agent, and are lenalidomide-refractory, a chance for*

# POWERFUL RESULTS AS EARLY AS 2L[1]

PRESCRIBED CAR-T CELL THERAPY FOR RRMM[2*] #1

*CARVYKTI® demonstrated a*

**↓59%** **Reduction in the risk of disease progression or death vs standard therapy (DPd or PVd)[1†]**
(HR=0.41; 95% CI: 0.30-0.56; *P*<0.0001)

## CARTITUDE-4 STUDY DESIGN

CARTITUDE-4 is a randomized, open label, multicenter controlled study evaluating the efficacy and safety of CARVYKTI® for the treatment of adult patients with relapsed and lenalidomide-refractory multiple myeloma, who previously received at least 1 prior line of therapy including a PI and an immunomodulatory agent. A total of 419 patients were randomized 1:1 to receive either CARVYKTI® (n=208) or standard therapy, which included daratumumab, pomalidomide, and dexamethasone (DPd) or pomalidomide, bortezomib, and dexamethasone (PVd) selected by physician prior to randomization based on patient's prior antimyeloma therapy (n=211). The primary efficacy measure was PFS analyzed based on the Intent-to-Treat Analysis Set.[1]

2L=second-line; CAR-T=chimeric antigen receptor-T cell; CI=confidence interval; HR=hazard ratio; PFS=progression-free survival; PI=proteasome inhibitor; RRMM=relapsed or refractory multiple myeloma.

*From January 2021 to November 2024.
†15.9 month median follow-up (Intent-To-Treat Analysis Set).

## INDICATIONS AND USAGE

CARVYKTI® (ciltacabtagene autoleucel) is a B-cell maturation antigen (BCMA)-directed genetically modified autologous T cell immunotherapy indicated for the treatment of adult patients with relapsed or refractory multiple myeloma, who have received at least 1 prior line of therapy, including a proteasome inhibitor and an immunomodulatory agent, and are refractory to lenalidomide.

## IMPORTANT SAFETY INFORMATION

**WARNING: CYTOKINE RELEASE SYNDROME, NEUROLOGIC TOXICITIES, HLH/MAS, PROLONGED and RECURRENT CYTOPENIA, and SECONDARY HEMATOLOGICAL MALIGNANCIES**

**Cytokine Release Syndrome (CRS), including fatal or life-threatening reactions, occurred in patients following treatment with CARVYKTI®. Do not administer CARVYKTI® to patients with active infection or inflammatory disorders. Treat severe or life-threatening CRS with tocilizumab or tocilizumab and corticosteroids.**

**Immune Effector Cell-Associated Neurotoxicity Syndrome (ICANS), which may be fatal or life-threatening, occurred following treatment with CARVYKTI®, including before CRS onset, concurrently with CRS, after CRS resolution, or in the absence of CRS. Monitor for neurologic events after treatment with CARVYKTI®. Provide supportive care and/or corticosteroids as needed.**

**Parkinsonism and Guillain-Barré syndrome (GBS) and their associated complications resulting in fatal or life-threatening reactions have occurred following treatment with CARVYKTI®.**

**Hemophagocytic Lymphohistiocytosis/Macrophage Activation Syndrome (HLH/MAS), including fatal and life-threatening reactions, occurred in patients following treatment with CARVYKTI®. HLH/MAS can occur with CRS or neurologic toxicities.**

**Prolonged and/or recurrent cytopenias with bleeding and infection and requirement for stem cell transplantation for hematopoietic recovery occurred following treatment with CARVYKTI®.**

**Secondary hematological malignancies, including myelodysplastic syndrome and acute myeloid leukemia, have occurred in patients following treatment with CARVYKTI®. T-cell malignancies have occurred following treatment of hematologic malignancies with BCMA- and CD19-directed genetically modified autologous T-cell immunotherapies, including CARVYKTI®.**

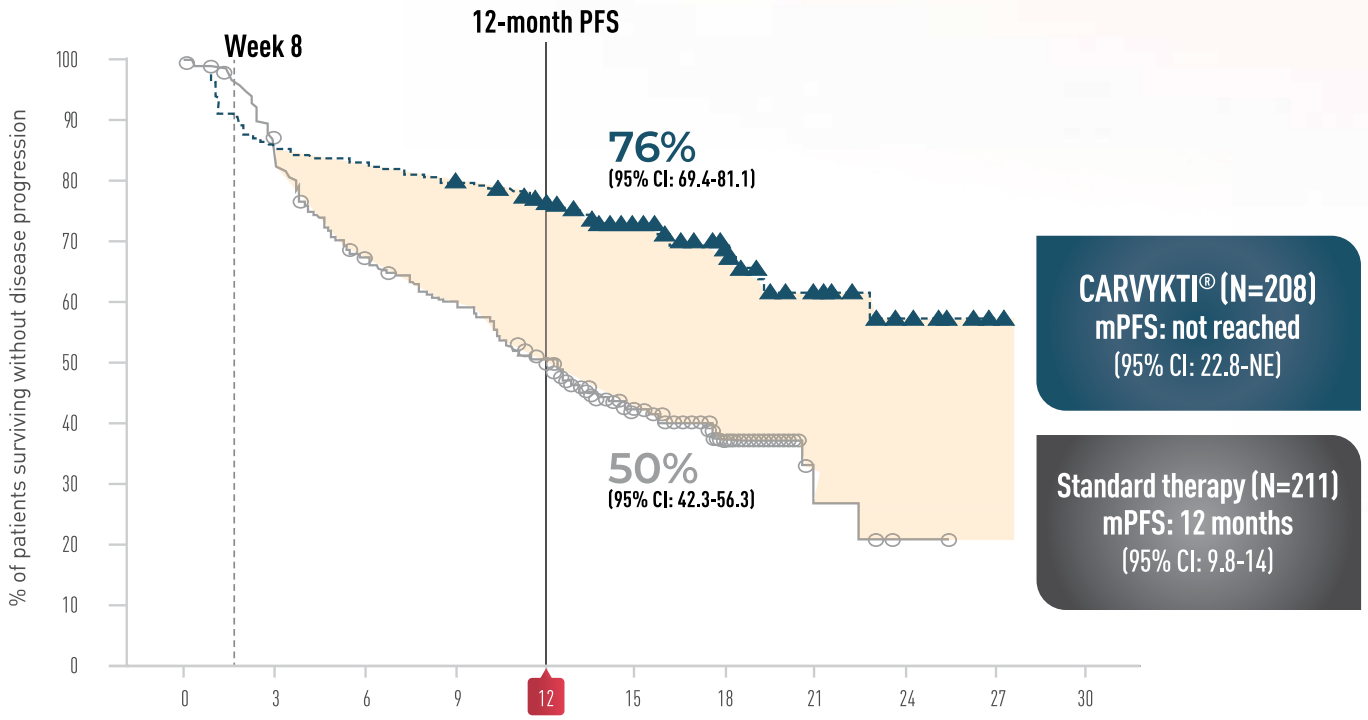
**CARVYKTI® is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called the CARVYKTI® REMS Program.**

# POWERFUL RESULTS

## CARTITUDE-4 median follow-up of 15.9 months

## CARVYKTI® SIGNIFICANTLY PROLONGED PROGRESSION-FREE SURVIVAL (PRIMARY ENDPOINT) vs STANDARD THERAPY (DPd or PVd)

### PROGRESSION-FREE SURVIVAL[1,3*]




15.9-month median follow-up (Intent-to-Treat Analysis Set)

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| CARVYKTI® arm | 208 | 177 | 172 | 166 | 146 | 94 | 45 | 22 | 9 | 1 | 0 |
| Standard therapy arm | 211 | 176 | 133 | 116 | 88 | 46 | 20 | 4 | 1 | 0 | 0 |

CARVYKTI® arm — Standard therapy arm

*CARVYKTI® demonstrated a*

**59%**

**Reduction in the risk of disease progression or death vs standard therapy (DPd or PVd)**
(HR=0.41; 95% CI: 0.30-0.56; *P*<0.0001)[1*]

## DEEP RESPONSES[2]

### 85% overall response rate was achieved with CARVYKTI®

### 81% of patients achieved a deep response with CARVYKTI®[1,3*]

- Deep response is defined as ≥VGPR
- **With CARVYKTI® (N=208): 85% ORR[†] (95% CI: 79.0-89.2), 74% ≥CR (95% CI: 67.5-79.9), 81% ≥VGPR** (66% sCR, 8% CR, 8% VGPR), and 3% PR
- With standard therapy (DPd or PVd) (N=211): 68% ORR[†] (95% CI: 61.0-74.0), 22% ≥CR (95% CI: 16.8-28.5), 46% ≥VGPR (18% sCR, 4% CR, 23% VGPR), and 22% PR

## DURABLE RESPONSES

### Median duration of response for CARVYKTI® was not reached[1*]

- **mDOR was not reached with CARVYKTI® in patients who achieved PR or better or in patients who achieved CR or better** vs 16.6 months with standard therapy (95% CI: 12.9-NE)[1*‡]

Percentages rounded to nearest whole number.

CI=confidence interval; CR=complete response; DPd=daratumumab, pomalidomide, and dexamethasone; HR=hazard ratio; mDOR=median duration of response; mPFS=median progression-free survival; NE=not estimable; ORR=overall response rate; PFS=progression-free survival; PR=partial response; PVd=pomalidomide, bortezomib, and dexamethasone; sCR=stringent complete response; VGPR=very good partial response.

*Median follow-up was 15.9 months in the Intent-to-Treat Analysis Set.
[†]Includes patients who achieved PR or better.
[‡]Estimated mDOR.

**Please read accompanying Brief Summary of the full Prescribing Information, including Boxed Warning, for CARVYKTI®.**

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# OVERALL SURVIVAL

## CARTITUDE-4 median follow-up of 15.9 months

### MEDIAN OVERALL SURVIVAL WAS NOT REACHED WITH CARVYKTI® OR STANDARD THERAPY[1]

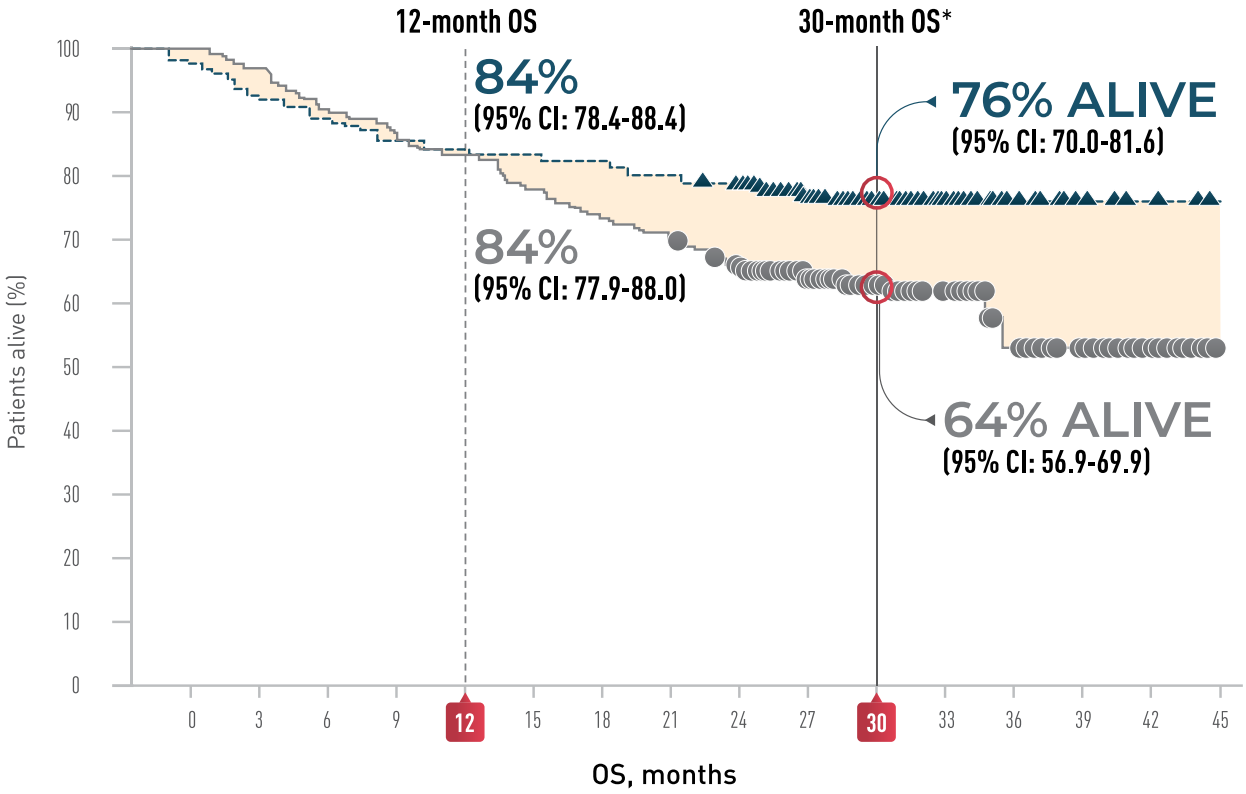
- 34% of the planned OS events have occurred
- Within the first 10 months of randomization, a higher proportion of patients in the CARVYKTI® arm died compared with the standard therapy arm

## CARTITUDE-4 median follow-up of 33.6 months

### OVERALL SURVIVAL FOR CARVYKTI® vs STANDARD THERAPY IN 2L+

You are now viewing a subsequent follow-up analysis of the CARTITUDE-4 trial. This information is not included in the current USPI and should be interpreted with caution. The data are presented here for descriptive purposes only.

### OVERALL SURVIVAL[1-4*†]




CARVYKTI® (N=208)
mOS: not reached
(95% CI: NE-NE)

Standard therapy (N=211)
mOS: not reached
(95% CI: 37.75-NE)

| | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| CARVYKTI® arm | 208 | 201 | 190 | 183 | 175 | 173 | 171 | 167 | 163 | 159 | 146 | 93 | 44 | 24 | 9 | 0 |
| Standard therapy arm | 211 | 207 | 196 | 184 | 173 | 163 | 154 | 147 | 137 | 133 | 127 | 71 | 35 | 13 | 4 | 0 |

CARVYKTI® arm — Standard therapy group

*CARVYKTI® demonstrated a*

**↓45%**

**Reduction in the risk of death vs standard therapy (DPd or PVd)** (HR=0.55; 95% CI: 0.39-0.79[4*†])

Percentages rounded to nearest whole number.
2L=second-line; CI=confidence interval; DPd=daratumumab, pomalidomide, and dexamethasone; HR=hazard ratio; mOS=median overall survival; NE=not estimable; OS=overall survival; PVd=pomalidomide, bortezomib, and dexamethasone; USPI=US Prescribing Information.
*Median follow-up was 33.6 months in the Intent-to-Treat Analysis Set.
†HR and 95% CI from a Cox proportional hazards model with treatment as the sole explanatory variable.

**Please read accompanying Brief Summary of the full Prescribing Information, including Boxed Warning, for CARVYKTI®.**

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## WARNINGS AND PRECAUTIONS

**Increased early mortality** - In CARTITUDE-4, a (1:1) randomized controlled trial, there was a numerically higher percentage of early deaths in patients randomized to the CARVYKTI® treatment arm compared to the control arm. Among patients with deaths occurring within the first 10 months from randomization, a greater proportion (29/208; 14%) occurred in the CARVYKTI® arm compared to (25/211; 12%) in the control arm. Of the 29 deaths that occurred in the CARVYKTI® arm within the first 10 months of randomization, 10 deaths occurred prior to CARVYKTI® infusion, and 19 deaths occurred after CARVYKTI® infusion. Of the 10 deaths that occurred prior to CARVYKTI® infusion, all occurred due to disease progression, and none occurred due to adverse events. Of the 19 deaths that occurred after CARVYKTI® infusion, 3 occurred due to disease progression, and 16 occurred due to adverse events. The most common adverse events were due to infection (n=12).

**Cytokine release syndrome (CRS)**, including fatal or life-threatening reactions, occurred following treatment with CARVYKTI® Among patients receiving CARVYKTI® for RRMM in the CARTITUDE-1 & 4 studies (N=285), CRS occurred in 84% (238/285), including ≥Grade 3 CRS (ASTCT 2019) in 4% (11/285) of patients. Median time to onset of CRS, any grade, was 7 days (range: 1 to 23 days). CRS resolved in 82% with a median duration of 4 days (range: 1 to 97 days). The most common manifestations of CRS in all patients combined (≥10%) included fever (84%), hypotension (29%) and aspartate aminotransferase increased (11%). Serious events that may be associated with CRS include pyrexia, hemophagocytic lymphohistiocytosis, respiratory failure, disseminated intravascular coagulation, capillary leak syndrome, and supraventricular and ventricular tachycardia. CRS occurred in 78% of patients in CARTITUDE-4 (3% Grade 3 to 4) and in 95% of patients in CARTITUDE-1 (4% Grade 3 to 4).

Identify CRS based on clinical presentation. Evaluate for and treat other causes of fever, hypoxia, and hypotension. CRS has been reported to be associated with findings of HLH/MAS, and the physiology of the syndromes may overlap. HLH/MAS is a potentially life-threatening condition. In patients with progressive symptoms of CRS or refractory CRS despite treatment, evaluate for evidence of HLH/MAS.

Ensure that a minimum of two doses of tocilizumab are available prior to infusion of CARVYKTI®.

Of the 285 patients who received CARVYKTI® in clinical trials, 53% (150/285) patients received tocilizumab; 35% (100/285) received a single dose, while 18% (50/285) received more than 1 dose of tocilizumab. Overall, 14% (39/285) of patients received at least one dose of corticosteroids for treatment of CRS.

Monitor patients at least daily for 10 days following CARVYKTI® infusion at a REMS-certified healthcare facility for signs and symptoms of CRS. Monitor patients for signs or symptoms of CRS for at least 4 weeks after infusion. At the first sign of CRS, immediately institute treatment with supportive care, tocilizumab, or tocilizumab and corticosteroids.

Counsel patients to seek immediate medical attention should signs or symptoms of CRS occur at any time.

**Neurologic toxicities**, which may be severe, life-threatening, or fatal, occurred following treatment with CARVYKTI®. Neurologic toxicities included ICANS, neurologic toxicity with signs and symptoms of parkinsonism, GBS, immune mediated myelitis, peripheral neuropathies, and cranial nerve palsies. Counsel patients on the signs and symptoms of these neurologic toxicities, and on the delayed nature of onset of some of these toxicities. Instruct patients to seek immediate medical attention for further assessment and management if signs or symptoms of any of these neurologic toxicities occur at any time.

Among patients receiving CARVYKTI® in the CARTITUDE-1 & 4 studies for RRMM, one or more neurologic toxicities occurred in 24% (69/285), including ≥Grade 3 cases in 7% (19/285) of patients. Median time to onset was 10 days (range: 1 to 101) with 63/69 (91%) of cases developing by 30 days. Neurologic toxicities resolved in 72% (50/69) of patients with a median duration to resolution of 23 days (range: 1 to 544). Of patients developing neurotoxicity, 96% (66/69) also developed CRS. Subtypes of neurologic toxicities included ICANS in 13%, peripheral neuropathy in 7%, cranial nerve palsy in 7%, parkinsonism in 3%, and immune mediated myelitis in 0.4% of the patients.

Immune Effector Cell-associated Neurotoxicity Syndrome (ICANS): Patients receiving CARVYKTI® may experience fatal or life-threatening ICANS following treatment with CARVYKTI®, including before CRS onset, concurrently with CRS, after CRS resolution, or in the absence of CRS.

Among patients receiving CARVYKTI® in the CARTITUDE-1 & 4 studies, ICANS occurred in 13% (36/285), including Grade ≥3 in 2% (6/285) of the patients. Median time to onset of ICANS was 8 days (range: 1 to 28 days). ICANS resolved in 30 of 36 (83%) of patients with a median time to resolution of 3 days (range: 1 to 143 days). Median duration of ICANS was 6 days (range: 1 to 1229 days) in all patients including those with ongoing neurologic events at the time of death or data cut off. Of patients with ICANS 97% (35/36) had CRS. The onset of ICANS occurred during CRS in 69% of patients, before and after the onset of CRS in 14% of patients respectively.

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## IMPORTANT SAFETY INFORMATION (cont'd)

**Neurologic toxicities** (cont'd)

Immune Effector Cell-associated Neurotoxicity Syndrome occurred in 7% of patients in CARTITUDE-4 (0.5% Grade 3) and in 23% of patients in CARTITUDE-1 (3% Grade 3). The most frequent ≥2% manifestations of ICANS included encephalopathy (12%), aphasia (4%), headache (3%), motor dysfunction (3%), ataxia (2%) and sleep disorder (2%).

Monitor patients at least daily for 10 days following CARVYKTI® infusion at the REMS-certified healthcare facility for signs and symptoms of ICANS. Rule out other causes of ICANS symptoms. Monitor patients for signs or symptoms of ICANS for at least 4 weeks after infusion and treat promptly. Neurologic toxicity should be managed with supportive care and/or corticosteroids as needed.

Parkinsonism: Neurologic toxicity with parkinsonism has been reported in clinical trials of CARVYKTI®. Among patients receiving CARVYKTI® in the CARTITUDE-1 & 4 studies, parkinsonism occurred in 3% (8/285), including Grade ≥ 3 in 2% (5/285) of the patients. Median time to onset of parkinsonism was 56 days (range: 14 to 914 days). Parkinsonism resolved in 1 of 8 (13%) of patients with a median time to resolution of 523 days. Median duration of parkinsonism was 243.5 days (range: 62 to 720 days) in all patients including those with ongoing neurologic events at the time of death or data cut off. The onset of parkinsonism occurred after CRS for all patients and after ICANS for 6 patients.

Parkinsonism occurred in 1% of patients in CARTITUDE-4 (no Grade 3 to 4) and in 6% of patients in CARTITUDE-1 (4% Grade 3 to 4).

Manifestations of parkinsonism included movement disorders, cognitive impairment, and personality changes. Monitor patients for signs and symptoms of parkinsonism that may be delayed in onset and managed with supportive care measures. There is limited efficacy information with medications used for the treatment of Parkinson's disease for the improvement or resolution of parkinsonism symptoms following CARVYKTI® treatment.

Guillain-Barré syndrome: A fatal outcome following GBS occurred following treatment with CARVYKTI® despite treatment with intravenous immunoglobulins. Symptoms reported include those consistent with Miller-Fisher variant of GBS, encephalopathy, motor weakness, speech disturbances, and polyradiculoneuritis.

Monitor for GBS. Evaluate patients presenting with peripheral neuropathy for GBS. Consider treatment of GBS with supportive care measures and in conjunction with immunoglobulins and plasma exchange, depending on severity of GBS.

Immune mediated myelitis: Grade 3 myelitis occurred 25 days following treatment with CARVYKTI® in CARTITUDE-4 in a patient who received CARVYKTI® as subsequent therapy. Symptoms reported included hypoesthesia of the lower extremities and the lower abdomen with impaired sphincter control. Symptoms improved with the use of corticosteroids and intravenous immune globulin. Myelitis was ongoing at the time of death from other cause.

Peripheral neuropathy occurred following treatment with CARVYKTI®. Among patients receiving CARVYKTI® in the CARTITUDE-1 & 4 studies, peripheral neuropathy occurred in 7% (21/285), including Grade ≥3 in 1% (3/285) of the patients. Median time to onset of peripheral neuropathy was 57 days (range: 1 to 914 days). Peripheral neuropathy resolved in 11 of 21 (52%) of patients with a median time to resolution of 58 days (range: 1 to 215 days). Median duration of peripheral neuropathy was 149.5 days (range: 1 to 692 days) in all patients including those with ongoing neurologic events at the time of death or data cut off.

Peripheral neuropathies occurred in 7% of patients in CARTITUDE-4 (0.5% Grade 3 to 4) and in 7% of patients in CARTITUDE-1 (2% Grade 3 to 4). Monitor patients for signs and symptoms of peripheral neuropathies. Patients who experience peripheral neuropathy may also experience cranial nerve palsies or GBS.

Cranial nerve palsies occurred following treatment with CARVYKTI®. Among patients receiving CARVYKTI® in the CARTITUDE-1 & 4 studies, cranial nerve palsies occurred in 7% (19/285), including Grade ≥3 in 1% (1/285) of the patients. Median time to onset of cranial nerve palsies was 21 days (range: 17 to 101 days). Cranial nerve palsies resolved in 17 of 19 (89%) of patients with a median time to resolution of 66 days (range: 1 to 209 days). Median duration of cranial nerve palsies was 70 days (range: 1 to 262 days) in all patients including those with ongoing neurologic events at the time of death or data cut off. Cranial nerve palsies occurred in 9% of patients in CARTITUDE-4 (1% Grade 3 to 4) and in 3% of patients in CARTITUDE-1 (1% Grade 3 to 4).

The most frequent cranial nerve affected was the 7$^{th}$ cranial nerve. Additionally, cranial nerves III, V, and VI have been reported to be affected.

Monitor patients for signs and symptoms of cranial nerve palsies. Consider management with systemic corticosteroids, depending on the severity and progression of signs and symptoms.

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## IMPORTANT SAFETY INFORMATION (cont'd)

**Hemophagocytic Lymphohistiocytosis (HLH)/Macrophage Activation Syndrome (MAS)**: Among patients receiving CARVYKTI® in the CARTITUDE-1 & 4 studies, HLH/MAS occurred in 1% (3/285) of patients. All events of HLH/MAS had onset within 99 days of receiving CARVYKTI®, with a median onset of 10 days (range: 8 to 99 days) and all occurred in the setting of ongoing or worsening CRS. The manifestations of HLH/MAS included hyperferritinemia, hypotension, hypoxia with diffuse alveolar damage, coagulopathy and hemorrhage, cytopenia and multi-organ dysfunction, including renal dysfunction and respiratory failure.

Patients who develop HLH/MAS have an increased risk of severe bleeding. Monitor hematologic parameters in patients with HLH/MAS and transfuse per institutional guidelines. Fatal cases of HLH/MAS occurred following treatment with CARVYKTI®.

HLH is a life-threatening condition with a high mortality rate if not recognized and treated early. Treatment of HLH/MAS should be administered per institutional standards.

**CARVYKTI® REMS**: Because of the risk of CRS and neurologic toxicities, CARVYKTI® is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called the CARVYKTI® REMS.

Further information is available at https://www.carvyktirems.com/ or 1-844-672-0067.

**Prolonged and Recurrent Cytopenias**: Patients may exhibit prolonged and recurrent cytopenias following lymphodepleting chemotherapy and CARVYKTI® infusion.

Among patients receiving CARVYKTI® in the CARTITUDE-1 & 4 studies, Grade 3 or higher cytopenias not resolved by day 30 following CARVYKTI® infusion occurred in 62% (176/285) of the patients and included thrombocytopenia 33% (94/285), neutropenia 27% (76/285), lymphopenia 24% (67/285) and anemia 2% (6/285). After Day 60 following CARVYKTI® infusion 22%, 20%, 5%, and 6% of patients had a recurrence of Grade 3 or 4 lymphopenia, neutropenia, thrombocytopenia, and anemia respectively, after initial recovery of their Grade 3 or 4 cytopenia. Seventy-seven percent (219/285) of patients had one, two or three or more recurrences of Grade 3 or 4 cytopenias after initial recovery of Grade 3 or 4 cytopenia. Sixteen and 25 patients had Grade 3 or 4 neutropenia and thrombocytopenia, respectively, at the time of death.

Monitor blood counts prior to and after CARVYKTI® infusion. Manage cytopenias with growth factors and blood product transfusion support according to local institutional guidelines.

**Infections:** CARVYKTI® should not be administered to patients with active infection or inflammatory disorders. Severe, life-threatening, or fatal infections, occurred in patients after CARVYKTI® infusion.

Among patients receiving CARVYKTI® in the CARTITUDE-1 & 4 studies, infections occurred in 57% (163/285), including ≥Grade 3 in 24% (69/285) of patients. Grade 3 or 4 infections with an unspecified pathogen occurred in 12%, viral infections in 6%, bacterial infections in 5%, and fungal infections in 1% of patients. Overall, 5% (13/285) of patients had Grade 5 infections, 2.5% of which were due to COVID-19. Patients treated with CARVYKTI® had an increased rate of fatal COVID-19 infections compared to the standard therapy arm.

Monitor patients for signs and symptoms of infection before and after CARVYKTI® infusion and treat patients appropriately. Administer prophylactic, pre-emptive and/or therapeutic antimicrobials according to the standard institutional guidelines. Febrile neutropenia was observed in 5% of patients after CARVYKTI® infusion and may be concurrent with CRS. In the event of febrile neutropenia, evaluate for infection and manage with broad-spectrum antibiotics, fluids and other supportive care, as medically indicated. Counsel patients on the importance of prevention measures. Follow institutional guidelines for the vaccination and management of immunocompromised patients with COVID-19.

Viral Reactivation: Hepatitis B virus (HBV) reactivation, in some cases resulting in fulminant hepatitis, hepatic failure and death, can occur in patients with hypogammaglobulinemia. Perform screening for Cytomegalovirus (CMV), HBV, hepatitis C virus (HCV), and human immunodeficiency virus (HIV) or any other infectious agents if clinically indicated in accordance with clinical guidelines before collection of cells for manufacturing. Consider antiviral therapy to prevent viral reactivation per local institutional guidelines/clinical practice.

**Hypogammaglobulinemia**: can occur in patients receiving treatment with CARVYKTI®. Among patients receiving CARVYKTI® in the CARTITUDE-1 & 4 studies, hypogammaglobulinemia adverse event was reported in 36% (102/285) of patients; laboratory IgG levels fell below 500mg/dl after infusion in 93% (265/285) of patients. Hypogammaglobulinemia either as an adverse reaction or laboratory IgG level below 500mg/dl, after infusion occurred in 94% (267/285) of patients treated. Fifty six percent (161/285) of patients received intravenous immunoglobulin (IVIG) post CARVYKTI® for either an adverse reaction or prophylaxis.

CARVYKTI®
(ciltacabtagene autoleucel) Suspension for IV Infusion

## IMPORTANT SAFETY INFORMATION (cont'd)

### Hypogammaglobulinemia (cont'd)

Monitor immunoglobulin levels after treatment with CARVYKTI® and administer IVIG for IgG <400 mg/dL. Manage per local institutional guidelines, including infection precautions and antibiotic or antiviral prophylaxis.

Use of Live Vaccines: The safety of immunization with live viral vaccines during or following CARVYKTI® treatment has not been studied. Vaccination with live virus vaccines is not recommended for at least 6 weeks prior to the start of lymphodepleting chemotherapy, during CARVYKTI® treatment, and until immune recovery following treatment with CARVYKTI®.

**Hypersensitivity Reactions** occurred following treatment with CARVYKTI®. Among patients receiving CARVYKTI® in the CARTITUDE-1 & 4 studies, hypersensitivity reactions occurred in 5% (13/285), all of which were ≤Grade 2. Manifestations of hypersensitivity reactions included flushing, chest discomfort, tachycardia, wheezing, tremor, burning sensation, non-cardiac chest pain, and pyrexia.

Serious hypersensitivity reactions, including anaphylaxis, may be due to the dimethyl sulfoxide (DMSO) in CARVYKTI®. Patients should be carefully monitored for 2 hours after infusion for signs and symptoms of severe reaction. Treat promptly and manage patients appropriately according to the severity of the hypersensitivity reaction.

**Secondary Malignancies:** Patients treated with CARVYKTI® may develop secondary malignancies. Among patients receiving CARVYKTI® in the CARTITUDE-1 & 4 studies, myeloid neoplasms occurred in 5% (13/285) of patients (9 cases of myelodysplastic syndrome, 3 cases of acute myeloid leukemia, and 1 case of myelodysplastic syndrome followed by acute myeloid leukemia). The median time to onset of myeloid neoplasms was 447 days (range: 56 to 870 days) after treatment with CARVYKTI®. Ten of these 13 patients died following the development of myeloid neoplasms; 2 of the 13 cases of myeloid neoplasm occurred after initiation of subsequent antimyeloma therapy. Cases of myelodysplastic syndrome and acute myeloid leukemia have also been reported in the post marketing setting. T-cell malignancies have occurred following treatment of hematologic malignancies with BCMA- and CD19-directed genetically modified autologous T-cell immunotherapies, including CARVYKTI®. Mature T-cell malignancies, including CAR-positive tumors, may present as soon as weeks following infusions, and may include fatal outcomes.

Monitor life-long for secondary malignancies. In the event that a secondary malignancy occurs, contact Janssen Biotech, Inc. at 1-800-526-7736 for reporting and to obtain instructions on collection of patient samples.

**Effects on Ability to Drive and Use Machines**: Due to the potential for neurologic events, including altered mental status, seizures, neurocognitive decline or neuropathy, patients receiving CARVYKTI® are at risk for altered or decreased consciousness or coordination in the 8 weeks following CARVYKTI® infusion. Advise patients to refrain from driving and engaging in hazardous occupations or activities, such as operating heavy or potentially dangerous machinery during this initial period, and in the event of new onset of any neurologic toxicities.

### ADVERSE REACTIONS

The most common nonlaboratory adverse reactions (incidence greater than 20%) are pyrexia, cytokine release syndrome, hypogammaglobulinemia, hypotension, musculoskeletal pain, fatigue, infections-pathogen unspecified, cough, chills, diarrhea, nausea, encephalopathy, decreased appetite, upper respiratory tract infection, headache, tachycardia, dizziness, dyspnea, edema, viral infections, coagulopathy, constipation, and vomiting. The most common Grade 3 or 4 laboratory adverse reactions (incidence greater than or equal to 50%) include lymphopenia, neutropenia, white blood cell decreased, thrombocytopenia, and anemia.

**Please read accompanying full Prescribing Information, including Boxed Warning, for CARVYKTI®.**

cp-258862v9

**References: 1.** CARVYKTI®. Prescribing information. Horsham, PA: Janssen Biotech, Inc. **2.** Data on file. Janssen Biotech, Inc. **3.** San-Miguel J, Dhakal B, Yong K, et al. Cilta-cel or standard care in lenalidomide-refractory multiple myeloma. *N Engl J Med.*2023;389(4):335-347. doi:10.1056/NEJMoa2303379 **4.** Mateos MV, San-Miguel J, Dhakal B, et al. Overall survival with ciltacabtagene autoleucel versus standard of care in lenalidomide-refractory multiple myeloma: phase 3 CARTITUDE-4 study update. Presented at the 21st International Myeloma Society (IMS) Annual Meeting; September 25-28, 2024; Rio de Janeiro, Brazil. Oral Presentation. **5.** Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Multiple Myeloma V.1.2025. © National Comprehensive Cancer Network, Inc. 2024. All rights reserved. Accessed January 31, 2025. To view the most recent and complete version of the guideline, go online to NCCN.org. NCCN makes no warranties of any kind whatsoever regarding their content, use or application and disclaims any responsibility for their application or use in any way.

CARVYKTI®
(ciltacabtagene autoleucel) Suspension for IV Infusion

*Give your adult patients with RRMM who have received a PI and an immunomodulatory agent, and are lenalidomide-refractory, a chance for results that are*

# POWERFUL. DEEP. DURABLE.
## After a One-Time Infusion[1,2]*

### CARTITUDE-4 primary analysis demonstrated†:

**POWERFUL**

**mPFS not reached with CARVYKTI®** (95% CI: 22.8-NE) **vs 12 months with standard therapy (DPd or PVd)** (95% CI: 9.8-14)

**59% reduction in the risk of disease progression or death vs standard therapy‡**
(HR=0.41; 95% CI: 0.30-0.56) *P*<0.0001

**DEEP**

**85% ORR** and **74% ≥CR** with **CARVYKTI®** vs 68% ORR and 22% ≥CR with standard therapy

81% of patients achieved a deep response of VGPR or better

**DURABLE**

**mDOR not reached with CARVYKTI® in patients who achieved PR or better or in patients who achieved CR or better** vs 16.6 months with standard therapy

DISCOVER MORE AT
**CARVYKTIHCP.com**
Data rates may apply.

NCCN CATEGORY 1

***THE FIRST AND ONLY* CAR-T CELL THERAPY TO BE DESIGNATED AS NCCN CATEGORY 1** in the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for multiple myeloma after 1 prior therapy[5]

Listed under "Therapy for Previously Treated Multiple Myeloma Relapsed/Refractory Disease After 1-3 Prior Therapies" as an option after 1 prior line of therapy, including an IMID and a PI, and refractory to lenalidomide. Additionally, ciltacabtagene autoleucel is designated as Category 2A after 3 prior therapies.[5]

CAR-T=chimeric antigen receptor-T cell; CI=confidence interval; CR=complete response; DPd=daratumumab, pomalidomide, dexamethasone; HR=hazard ratio; IMID=immunomodulatory drug; ISS=International Staging System; mDOR=median duration of response; mPFS=median progression-free survival; NCCN=National Comprehensive Cancer Network; NE=not estimable; ORR=overall response rate; PI=proteasome inhibitor; PR=partial response; PVd=pomalidomide, bortezomib, dexamethasone; RRMM=relapsed or refractory multiple myeloma.

*As part of a 5-step process.
†Median follow-up was 15.9 months in the Intent-to-Treat Analysis Set.
‡Based on a stratified Cox proportional hazards model. An HR <1 indicates an advantage for CARVYKTI® arm. For all stratified analyses, stratification was based on investigator's choice (DPd or PVd), ISS staging (I, II, III), and number of prior lines (1 vs 2 or 3) as randomized.



Johnson&Johnson

LEGEND BIOTECH

**Please read accompanying Brief Summary of the full Prescribing Information, including Boxed Warning, for CARVYKTI®.**

**CARVYKTI® (ciltacabtagene autoleucel) suspension for intravenous infusion**
**Brief Summary of Full Prescribing Information**

**WARNING: CYTOKINE RELEASE SYNDROME, NEUROLOGIC TOXICITIES, HLH/MAS, PROLONGED and RECURRENT CYTOPENIA, and SECONDARY HEMATOLOGICAL MALIGNANCIES**

**Cytokine Release Syndrome (CRS), including fatal or life-threatening reactions, occurred in patients following treatment with CARVYKTI. Do not administer CARVYKTI to patients with active infection or inflammatory disorders. Treat severe or life-threatening CRS with tocilizumab or tocilizumab and corticosteroids *[see Dosage and Administration (2.2, 2.3) in Full Prescribing Information, Warnings and Precautions].***

**Immune Effector Cell-Associated Neurotoxicity Syndrome (ICANS), which may be fatal or life-threatening, occurred following treatment with CARVYKTI, including before CRS onset, concurrently with CRS, after CRS resolution, or in the absence of CRS. Monitor for neurologic events after treatment with CARVYKTI. Provide supportive care and/or corticosteroids as needed *[see Dosage and Administration (2.2, 2.3) in Full Prescribing Information, Warnings and Precautions].***

**Parkinsonism and Guillain-Barré syndrome (GBS) and their associated complications resulting in fatal or life-threatening reactions have occurred following treatment with CARVYKTI *[see Warnings and Precautions].***

**Hemophagocytic Lymphohistiocytosis/Macrophage Activation Syndrome (HLH/MAS), including fatal and life-threatening reactions, occurred in patients following treatment with CARVYKTI. HLH/MAS can occur with CRS or neurologic toxicities *[see Warnings and Precautions].***

**Prolonged and/or recurrent cytopenias with bleeding and infection and requirement for stem cell transplantation for hematopoietic recovery occurred following treatment with CARVYKTI *[see Warnings and Precautions].***

**Secondary hematological malignancies, including myelodysplastic syndrome and acute myeloid leukemia, have occurred in patients following treatment with CARVYKTI. T-cell malignancies have occurred following treatment of hematologic malignancies with BCMA- and CD19-directed genetically modified autologous T-cell immunotherapies, including CARVYKTI *[see Warnings and Precautions].***

**CARVYKTI is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called the CARVYKTI REMS Program *[see Warnings and Precautions].***

## INDICATIONS AND USAGE

CARVYKTI (ciltacabtagene autoleucel) is a B-cell maturation antigen (BCMA)-directed genetically modified autologous T cell immunotherapy indicated for the treatment of adult patients with relapsed or refractory multiple myeloma, who have received at least 1 prior line of therapy, including a proteasome inhibitor and an immunomodulatory agent, and are refractory to lenalidomide.

## CONTRAINDICATIONS

None.

## WARNINGS AND PRECAUTIONS

### Increased Early Mortality

In CARTITUDE-4, a randomized (1:1), controlled trial, there was a numerically higher percentage of early deaths in patients randomized to the CARVYKTI treatment arm compared to the control arm. Among patients with deaths occurring within the first 10 months from randomization, a greater proportion (29/208; 14%) occurred in the CARVYKTI arm compared to (25/211; 12%) in the control arm *[see Clinical Studies (14) in Full Prescribing Information]*. Of the 29 deaths that occurred in the CARVYKTI arm within the first 10 months of randomization, 10 deaths occurred prior to CARVYKTI infusion, and 19 deaths occurred after CARVYKTI infusion. Of the 10 deaths that occurred prior to CARVYKTI infusion, all occurred due to disease progression, and none occurred due to adverse events. Of the 19 deaths that occurred after CARVYKTI infusion, 3 occurred due to disease progression, and 16 occurred due to adverse events. The most common adverse events were due to infection (n=12).

### Cytokine Release Syndrome

Cytokine release syndrome (CRS), including fatal or life-threatening reactions, occurred following treatment with CARVYKTI. Among patients receiving CARVYKTI for relapsed or refractory multiple myeloma in the CARTITUDE-1 and CARTITUDE-4 studies (N=285), CRS occurred in 84% (238/285), including ≥ Grade 3 CRS (ASTCT 2019) in 4% (11/285) of patients. The median time to onset of CRS, any grade, was 7 days (range: 1 to 23 days). Cytokine release syndrome resolved in 82% with a median duration of 4 days (range: 1 to 97 days). The most common manifestations of CRS in all patients combined (≥ 10%) included fever (84%), hypotension (29%) and aspartate aminotransferase increased (11%). Serious events that may be associated with CRS include pyrexia, hemophagocytic lymphohistiocytosis, respiratory failure, disseminated intravascular coagulation, capillary leak syndrome, and supraventricular and ventricular tachycardia *[see Adverse Reactions]*.

Cytokine release syndrome occurred in 78% of patients in CARTITUDE-4 (3% Grade 3 to 4) and in 95% of patients in CARTITUDE-1 (4% Grade 3 to 4).

Identify CRS based on clinical presentation. Evaluate for and treat other causes of fever, hypoxia, and hypotension. CRS has been reported to be associated with findings of HLH/MAS, and the physiology of the syndromes may overlap. HLH/MAS is a potentially life-threatening condition. In patients with progressive symptoms of CRS or refractory CRS despite treatment, evaluate for evidence of HLH/MAS. Please see *Hemophagocytic Lymphohistiocytosis (HLH)/Macrophage Activation Syndrome (MAS)*.

Ensure that a minimum of two doses of tocilizumab are available prior to infusion of CARVYKTI.

Of the 285 patients who received CARVYKTI in clinical trials, 53% (150/285) patients received tocilizumab; 35% (100/285) received a single dose, while 18% (50/285) received more than 1 dose of tocilizumab. Overall, 14% (39/285) of patients received at least one dose of corticosteroids for treatment of CRS.

Monitor patients at least daily for 10 days following CARVYKTI infusion at a REMS-certified healthcare facility for signs and symptoms of CRS. Monitor patients for signs or symptoms of CRS for at least 4 weeks after infusion. At the first sign of CRS, immediately institute treatment with supportive care, tocilizumab, or tocilizumab and corticosteroids, as indicated in Table 1 in Full Prescribing Information *[see Dosing and Administration (2.3) in Full Prescribing Information]*.

Counsel patients to seek immediate medical attention should signs or symptoms of CRS occur at any time *[see Patient Counseling information]*.

### Neurologic Toxicities

Neurologic toxicities, which may be severe, life-threatening or fatal, occurred following treatment with CARVYKTI. Neurologic toxicities included ICANS, neurologic toxicity with signs and symptoms of parkinsonism, GBS, immune mediated myelitis, peripheral neuropathies and cranial nerve palsies. Counsel patients on the signs and symptoms of these neurologic toxicities, and on the delayed nature of onset of some of these toxicities. Instruct patients to seek immediate medical attention for further assessment and management if signs or symptoms of any of these neurologic toxicities occur at any time *[see Patient Counseling Information]*.

Among patients receiving CARVYKTI in the CARTITUDE-1 and CARTITUDE-4 studies for relapsed and refractory multiple myeloma, one or more neurologic toxicities occurred in 24% (69/285), including ≥ Grade 3 cases in 7% (19/285) of patients. The median time to onset was 10 days (range: 1 to 101) with 63/69 (91%) of cases developing by 30 days. Neurologic toxicities resolved in 72% (50/69) of patients with a median duration to resolution of 23 days (range: 1 to 544). Of patients developing neurotoxicity, 96% (66/69) also developed CRS. Subtypes of neurologic toxicities included ICANS in 13%, peripheral neuropathy in 7%, cranial nerve palsy in 7%, parkinsonism in 3%, and immune mediated myelitis in 0.4% of the patients *[see Adverse Reactions]*.

Immune Effector Cell-associated Neurotoxicity Syndrome (ICANS)

Patients receiving CARVYKTI may experience fatal or life-threatening ICANS following treatment with CARVYKTI, including before CRS onset, concurrently with CRS, after CRS resolution, or in the absence of CRS.

Among patients receiving CARVYKTI in the CARTITUDE-1 and CARTITUDE-4 studies, ICANS occurred in 13% (36/285), including Grade ≥ 3 in 2% (6/285) of the patients. The median time to onset of ICANS was 8 days (range: 1 to 28 days). ICANS resolved in 30 of 36 (83%) of patients with a median time to resolution of 3 days (range: 1 to 143 days). The median duration of ICANS was 6 days (range: 1 to 1229 days) in all patients including those with ongoing neurologic events at the time of death or data cut off. Of patients with ICANS 97% (35/36) had CRS. The onset of ICANS occurred during CRS in 69% of patients, before and after the onset of CRS in 14% of patients respectively.

Immune Effector Cell-associated Neurotoxicity Syndrome occurred in 7% of patients in CARTITUDE-4 (0.5% Grade 3) and in 23% of patients in CARTITUDE-1 (3% Grade 3).

The most frequent ≥2% manifestations of ICANS included encephalopathy (12%), aphasia (4%), headache (3%), motor dysfunction (3%), ataxia (2%) and sleep disorder (2%) *[see Adverse Reactions]*.



Monitor patients at least daily for 10 days following CARVYKTI infusion at the REMS-certified healthcare facility for signs and symptoms of ICANS. Rule out other causes of ICANS symptoms. Monitor patients for signs or symptoms of ICANS for at least 4 weeks after infusion and treat promptly. Neurologic toxicity should be managed with supportive care and/or corticosteroids as needed *[see Dosage and Administration (2.3) in Full Prescribing Information]*.

Parkinsonism

Neurologic toxicity with parkinsonism has been reported in clinical trials of CARVYKTI.

Among patients receiving CARVYKTI in the CARTITUDE-1 and CARTITUDE-4 studies, parkinsonism occurred in 3% (8/285), including Grade ≥ 3 in 2% (5/285) of the patients. The median time to onset of parkinsonism was 56 days (range: 14 to 914 days). Parkinsonism resolved in 1 of 8 (13%) of patients with a median time to resolution of 523 days. The median duration of parkinsonism was 243.5 days (range: 62 to 720 days) in all patients including those with ongoing neurologic events at the time of death or data cut off. The onset of parkinsonism occurred after CRS for all patients and after ICANS for 6 patients.

Parkinsonism occurred in 1% of patients in CARTITUDE-4 (no Grade 3 to 4) and in 6% of patients in CARTITUDE-1 (4% Grade 3 to 4).

The manifestations of parkinsonism included movement disorders, cognitive impairment, and personality changes *[see Adverse Reactions]*.

Monitor patients for signs and symptoms of parkinsonism that may be delayed in onset and managed with supportive care measures. There is limited efficacy information with medications used for the treatment of Parkinson's disease for the improvement or resolution of parkinsonism symptoms following CARVYKTI treatment.

Guillain-Barré Syndrome

A fatal outcome following GBS occurred following treatment with CARVYKTI despite treatment with intravenous immunoglobulins. Symptoms reported include those consistent with Miller-Fisher variant of GBS, encephalopathy, motor weakness, speech disturbances, and polyradiculoneuritis.

Monitor for GBS. Evaluate patients presenting with peripheral neuropathy for GBS. Consider treatment of GBS with supportive care measures and in conjunction with immunoglobulins and plasma exchange, depending on severity of GBS.

Immune Mediated Myelitis

Grade 3 myelitis occurred 25 days following treatment with CARVYKTI in CARTITUDE-4 in a patient who received CARVYKTI as subsequent therapy. Symptoms reported included hypoesthesia of the lower extremities and the lower abdomen with impaired sphincter control. Symptoms improved with the use of corticosteroids and intravenous immune globulin. Myelitis was ongoing at the time of death from other cause *[see Adverse Reactions]*.

Peripheral Neuropathy

Peripheral neuropathy occurred following treatment with CARVYKTI.

Among patients receiving CARVYKTI in the CARTITUDE-1 and CARTITUDE-4 studies, peripheral neuropathy occurred in 7% (21/285), including Grade ≥ 3 in 1% (3/285) of the patients. The median time to onset of peripheral neuropathy was 57 days (range: 1 to 914 days). Peripheral neuropathy resolved in 11 of 21 (52%) of patients with a median time to resolution of 58 days (range: 1 to 215 days). The median duration of peripheral neuropathy was 149.5 days (range: 1 to 692 days) in all patients including those with ongoing neurologic events at the time of death or data cut off *[see Adverse Reactions]*.

Peripheral neuropathies occurred in 7% of patients in CARTITUDE-4 (0.5% Grade 3 to 4) and in 7% of patients in CARTITUDE-1 (2% Grade 3 to 4).

Monitor patients for signs and symptoms of peripheral neuropathies.

Patients who experience peripheral neuropathy may also experience cranial nerve palsies or GBS.

Cranial Nerve Palsies

Cranial nerve palsies occurred following treatment with CARVYKTI.

Among patients receiving CARVYKTI in the CARTITUDE-1 and CARTITUDE-4 studies, cranial nerve palsies occurred in 7% (19/285), including Grade ≥ 3 in 1% (1/285) of the patients. The median time to onset of cranial nerve palsies was 21 days (range: 17 to 101 days). Cranial nerve palsies resolved in 17 of 19 (89%) of patients with a median time to resolution of 66 days (range: 1 to 209 days). The median duration of cranial nerve palsies was 70 days (range: 1 to 262 days) in all patients including those with ongoing neurologic events at the time of death or data cut off *[see Adverse Reactions]*.

Cranial nerve palsies occurred in 9% of patients in CARITUDE-4 (1% Grade 3 to 4) and in 3% of patients in CARTITUDE-1 (1% Grade 3 to 4).

The most frequent cranial nerve affected was the 7th cranial nerve. Additionally, cranial nerves III, V, and VI have been reported to be affected.

Monitor patients for signs and symptoms of cranial nerve palsies. Consider management with systemic corticosteroids, depending on the severity and progression of signs and symptoms.

### Hemophagocytic Lymphohistiocytosis (HLH)/Macrophage Activation Syndrome (MAS)

Among patients receiving CARVYKTI in the CARTITUDE-1 and CARTITUDE-4 studies, HLH/MAS occurred in 1% (3/285) of patients. All events of HLH/MAS had onset within 99 days of receiving CARVYKTI, with a median onset of 10 days (range: 8 to 99 days) and all occurred in the setting of ongoing or worsening CRS. The manifestations of HLH/MAS included hyperferritinemia, hypotension, hypoxia with diffuse alveolar damage, coagulopathy and hemorrhage, cytopenia and multi-organ dysfunction, including renal dysfunction and respiratory failure.

Patients who develop HLH/MAS have an increased risk of severe bleeding. Monitor hematologic parameters in patients with HLH/MAS and transfuse per institutional guidelines. Fatal cases of HLH/MAS occurred following treatment with CARVYKTI *[see Adverse Reactions]*.

HLH is a life-threatening condition with a high mortality rate if not recognized and treated early. Treatment of HLH/MAS should be administered per institutional standards.

### CARVYKTI REMS

Because of the risk of CRS and neurologic toxicities, CARVYKTI is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called the CARVYKTI REMS *[see Boxed Warning, Warnings and Precautions]*. The required components of the CARVYKTI REMS are:

- Healthcare facilities that dispense and administer CARVYKTI must be enrolled and comply with the REMS requirements.
- Certified healthcare facilities must have on-site, immediate access to tocilizumab.
- Ensure that a minimum of 2 doses of tocilizumab are available for each patient for infusion within 2 hours after CARVYKTI infusion, if needed for treatment of CRS.

Further information is available at www.carvyktirems.com or 1-844-672-0067.

### Prolonged and Recurrent Cytopenias

Patients may exhibit prolonged and recurrent cytopenias following lymphodepleting chemotherapy and CARVYKTI infusion.

Among patients receiving CARVYKTI in the CARTITUDE-1 and CARTITUDE-4 studies, Grade 3 or higher cytopenias not resolved by day 30 following CARVYKTI infusion occurred in 62% (176/285) of the patients and included thrombocytopenia 33% (94/285), neutropenia 27% (76/285), lymphopenia 24% (67/285) and anemia 2% (6/285). After Day 60 following CARVYKTI infusion 22%, 20%, 5%, and 6% of patients had a recurrence of Grade 3 or 4 lymphopenia, neutropenia, thrombocytopenia, and anemia respectively, after initial recovery of their Grade 3 or 4 cytopenia. Seventy-seven percent (219/285) of patients had one, two or three or more recurrences of Grade 3 or 4 cytopenias after initial recovery of Grade 3 or 4 cytopenia. Sixteen and 25 patients had Grade 3 or 4 neutropenia and thrombocytopenia, respectively, at the time of death *[see Adverse Reactions]*.

Monitor blood counts prior to and after CARVYKTI infusion. Manage cytopenias with growth factors and blood product transfusion support according to local institutional guidelines.

### Infections

CARVYKTI should not be administered to patients with active infection or inflammatory disorders. Severe, life-threatening, or fatal infections, occurred in patients after CARVYKTI infusion.

Among patients receiving CARVYKTI in the CARTITUDE-1 and CARTITUDE-4 studies, infections occurred in 57% (163/285), including ≥ Grade 3 in 24% (69/285) of patients. Grade 3 or 4 infections with an unspecified pathogen occurred in 12%, viral infections in 6%, bacterial infections in 5%, and fungal infections in 1% of patients. Overall, 5% (13/285) of patients had Grade 5 infections, 2.5% of which were due to COVID-19. Patients treated with CARVYKTI had an increased rate of fatal COVID-19 infections compared to the standard therapy arm *[see Adverse Reactions]*.

Monitor patients for signs and symptoms of infection before and after CARVYKTI infusion and treat patients appropriately. Administer prophylactic, pre-emptive and/or therapeutic antimicrobials according to the standard institutional guidelines. Febrile neutropenia was observed in 5% of patients after CARVYKTI infusion and may be concurrent with CRS. In the event of febrile neutropenia, evaluate for infection and manage with broad-spectrum antibiotics, fluids and other supportive care, as medically indicated.

Counsel patients on the importance of prevention measures. Follow institutional guidelines for the vaccination and management of immunocompromised patients with COVID-19.

Viral Reactivation

Hepatitis B virus (HBV) reactivation, in some cases resulting in fulminant hepatitis, hepatic failure and death, can occur in patients with hypogammaglobulinemia.

Perform screening for Cytomegalovirus (CMV), HBV, hepatitis C virus (HCV), and human immunodeficiency virus (HIV) or any other infectious agents if clinically indicated in accordance with clinical guidelines before collection of cells for manufacturing.

Consider antiviral therapy to prevent viral reactivation per local institutional guidelines/clinical practice.

**Hypogammaglobulinemia**

Hypogammaglobulinemia can occur in patients receiving treatment with CARVYKTI.

Among patients receiving CARVYKTI in the CARTITUDE-1 and CARTITUDE-4 studies, hypogammaglobulinemia adverse event was reported in 36% (102/285) of patients; laboratory IgG levels fell below 500mg/dl after infusion in 93% (265/285) of patients. Hypogammaglobulinemia either as an adverse reaction or laboratory IgG level below 500mg/dl, after infusion occurred in 94% (267/285) of patients treated. Fifty six percent (161/285) of patients received intravenous immunoglobulin (IVIG) post CARVYKTI for either an adverse reaction or prophylaxis *[see Adverse Reactions]*.

Monitor immunoglobulin levels after treatment with CARVYKTI and administer IVIG for IgG <400 mg/dL. Manage per local institutional guidelines, including infection precautions and antibiotic or antiviral prophylaxis.

Use of Live Vaccines

The safety of immunization with live viral vaccines during or following CARVYKTI treatment has not been studied. Vaccination with live virus vaccines is not recommended for at least 6 weeks prior to the start of lymphodepleting chemotherapy, during CARVYKTI treatment, and until immune recovery following treatment with CARVYKTI.

**Hypersensitivity Reactions**

Hypersensitivity reactions occurred following treatment with CARVYKTI.

Among patients receiving CARVYKTI in the CARTITUDE-1 and CARTITUDE-4 studies, hypersensitivity reactions occurred in 5% (13/285), all of which were ≤ Grade 2. Manifestations of hypersensitivity reactions included flushing, chest discomfort, tachycardia, wheezing, tremor, burning sensation, non-cardiac chest pain, and pyrexia.

Serious hypersensitivity reactions, including anaphylaxis, may be due to the dimethyl sulfoxide (DMSO) in CARVYKTI. Patients should be carefully monitored for 2 hours after infusion for signs and symptoms of severe reaction. Treat promptly and manage patients appropriately according to the severity of the hypersensitivity reaction.

**Secondary Malignancies**

Patients treated with CARVYKTI may develop secondary malignancies.

Among patients receiving CARVYKTI in the CARTITUDE-1 and CARTITUDE-4 studies, myeloid neoplasms occurred in 5% (13/285) of patients (9 cases of myelodysplastic syndrome, 3 cases of acute myeloid leukemia, and 1 case of myelodysplastic syndrome followed by acute myeloid leukemia). The median time to onset of myeloid neoplasms was 447 days (range: 56 to 870 days) after treatment with CARVYKTI. Ten of these 13 patients died following the development of myeloid neoplasms; 2 of the 13 cases of myeloid neoplasm occurred after initiation of subsequent antimyeloma therapy. Cases of myelodysplastic syndrome and acute myeloid leukemia have also been reported in the post marketing setting.

T-cell malignancies have occurred following treatment of hematologic malignancies with BCMA- and CD19-directed genetically modified autologous T-cell immunotherapies, including CARVYKTI. Mature T-cell malignancies, including CAR-positive tumors, may present as soon as weeks following infusions, and may include fatal outcomes *[see Boxed Warning, Adverse Reactions, Patient Counseling Information]*.

Monitor life-long for secondary malignancies. In the event that a secondary malignancy occurs, contact Janssen Biotech, Inc. at 1-800-526-7736 for reporting and to obtain instructions on collection of patient samples.

**Effects on Ability to Drive and Use Machines**

Due to the potential for neurologic events, including altered mental status, seizures, neurocognitive decline or neuropathy, patients receiving CARVYKTI are at risk for altered or decreased consciousness or coordination in the 8 weeks following CARVYKTI infusion. Advise patients to refrain from driving and engaging in hazardous occupations or activities, such as operating heavy or potentially dangerous machinery during this initial period, and in the event of new onset of any neurologic toxicities.

## ADVERSE REACTIONS

The following clinically significant adverse reactions are also described elsewhere in the labeling:

- Increased Early Mortality *[see Warnings and Precautions, Clinical Studies (14) in Full Prescribing Information]*.
- Cytokine Release Syndrome *[see Warnings and Precautions]*.
- Neurologic Toxicities *[see Warnings and Precautions]*.
- Hemophagocytic Lymphohistiocytosis (HLH)/Macrophage Activation Syndrome (MAS) *[see Warnings and Precautions]*.
- Prolonged and Recurrent Cytopenias *[see Warnings and Precautions]*.
- Infections *[see Warnings and Precautions]*.
- Hypogammaglobulinemia *[see Warnings and Precautions]*.
- Hypersensitivity Reactions *[see Warnings and Precautions]*.
- Secondary Malignancies *[see Warnings and Precautions]*.

**Clinical Trials Experience**

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The safety data described in the WARNINGS and PRECAUTIONS section reflect exposure to CARVYKTI in 285 patients with relapsed or refractory multiple myeloma: one randomized, open label with 188 patients in CARTITUDE-4 and one single-arm, open label study with 97 patients in CARTITUDE-1.

CARTITUDE-4

The safety of CARVYKTI was evaluated in CARTITUDE-4, a randomized, open label multicenter study, in which patients with relapsed and lenalidomide refractory multiple myeloma received CARVYKTI meeting the product specifications (N=188) or standard therapy (N=211) *[see Clinical Studies (14) in Full Prescribing Information]*. Patients with known active or prior history of central nervous system involvement, patients who exhibit clinical signs of meningeal involvement of multiple myeloma and patients with a history of Parkinson's disease or other neurodegenerative disorder, were excluded from the trial. Patients received CARVYKTI at a median dose of $0.71\times10^6$ CAR-positive viable T-cells/kg (range: 0.41 to $1.08\times10^6$ cells/kg). The median age of the 188 participants was 62 years (range: 27 to 78 years); 40% were 65 years or older, and 57% were male; 76% were White, were 9% Hispanic or Latino, 8% were Asian, and 3% were Black.

The Eastern Cooperative Oncology Group (ECOG) performance status at baseline was 0 in 56%, 1 in 44%. For the details about the study population, see *Clinical Studies (14) in Full Prescribing Information*.

The most common nonlaboratory adverse reactions (≥20%) included pyrexia, CRS, hypogammaglobulinemia, musculoskeletal pain, fatigue, diarrhea, upper respiratory tract infection, viral infections, headache, hypotension, and nausea.

Serious adverse reactions occurred in 34% of patients. The most common nonlaboratory serious adverse reactions (≥5%) were pneumonia (9%), viral infection (6%), CRS (6%), and cranial nerve palsies (5%).

Table 1 summarizes the adverse reactions that occurred in at least 10% of patients treated with CARVYKTI.

**CARVYKTI®** (ciltacabtagene autoleucel)

**Table 1: Adverse reactions observed in at least 10% of patients treated with CARVYKTI (N=188) and standard therapy (N=208) in CARTITUDE-4**

| | CARVYKTI N=188 | | Standard Therapy N=208 | |
|---|---|---|---|---|
| **System Organ Class (SOC) Preferred term** | **Any Grade (%)** | **Grade 3 or higher (%)** | **Any Grade (%)** | **Grade 3 or higher (%)** |
| **Gastrointestinal disorders** | - | - | - | - |
| Diarrhea[a] | 27 | 3 | 27 | 2 |
| Nausea | 20 | 0 | 18 | 1 |
| Constipation | 10 | 0 | 21 | 1 |
| **General disorders and administrative site conditions** | - | - | - | - |
| Pyrexia | 79 | 5 | 16 | 1 |
| Fatigue[b] | 28 | 3 | 50 | 3 |
| Edema[c] | 11 | 1 | 20 | 1 |
| Pain[d] | 10 | 1 | 14 | <1 |
| **Immune system disorders** | - | - | - | - |
| Hypogammaglobulinemia[e] | 94 | 9 | 72 | <1 |
| Cytokine release syndrome | 78 | 3 | <1 | 0 |
| **Infections and infestations** | - | - | - | - |
| Upper respiratory tract infection[f] | 25 | 1 | 40 | 5 |
| Viral infection[g] | 23 | 4 | 31 | 6 |
| Bacterial infection[h] | 15 | 6 | 17 | 4 |
| Pneumonia[i] | 14 | 9 | 18 | 11 |
| **Metabolism and nutrition disorders** | - | - | - | - |
| Decreased appetite | 10 | 0 | 5 | 0 |
| **Musculoskeletal and connective tissue disorders** | - | - | - | - |
| Musculoskeletal pain[j] | 34 | 2 | 47 | 4 |
| **Nervous system disorders** | - | - | - | - |
| Headache[k] | 23 | 0 | 13 | 0 |
| Encephalopathy[l] | 11 | 2 | 4 | 1 |
| **Respiratory, thoracic and mediastinal disorders** | - | - | - | - |
| Cough[m] | 15 | 0 | 18 | 0 |
| Hypoxia | 12 | 3 | 1 | 1 |
| **Vascular disorders** | - | - | - | - |
| Hypotension[n] | 23 | 4 | 3 | 0 |

Adverse reactions are reported using MedDRA version 25.0

[a] Diarrhea includes Colitis, and Diarrhea.
[b] Fatigue includes Asthenia, Fatigue, and Malaise.
[c] Edema includes Face edema, Generalized edema, Localized edema, Edema peripheral, Periorbital edema, Peripheral swelling, Pulmonary edema, and Scrotal edema.
[d] Pain includes Anorectal discomfort, Catheter site pain, Flank pain, Inflammatory pain, Pain, Pain in jaw, Pain of skin, Pelvic pain, Rhinalgia, and Sacral pain.
[e] Hypogammaglobulinemia includes subjects with adverse event of hypogammaglobulinemia and/or laboratory IgG levels that fell below 500 mg/dL following CARVYKTI infusion or standard therapy.
[f] Upper respiratory tract infection includes Bronchitis, Nasal congestion, Nasopharyngitis, Pharyngitis, Respiratory tract infection, Rhinitis, Rhinorrhea, Rhinovirus infection, Sinusitis, Upper respiratory tract infection, and Viral pharyngitis.
[g] Viral infection includes Adenovirus infection, Asymptomatic COVID-19, COVID-19, Cytomegalovirus infection, Cytomegalovirus infection reactivation, Cytomegalovirus viremia, Hepatitis B reactivation, Herpes simplex reactivation, Herpes virus infection, Herpes zoster, Human herpesvirus 6 infection, Influenza, Lymphadenitis viral, Metapneumovirus infection, Parainfluenza virus infection, Parvovirus B19 infection, Parvovirus infection, Respiratory syncytial virus infection, Respiratory tract infection viral, and Rotavirus infection.
[h] Bacterial infection includes Bordetella infection, Bronchitis bacterial, Campylobacter infection, Catheter site infection, Cellulitis, Chalazion, Citrobacter infection, Clostridium difficile colitis, Device related infection, Gingivitis, Perichondritis, Pyelonephritis acute, Salmonellosis, Skin infection, Staphylococcal infection, Superinfection bacterial, Vascular access site infection, and Vascular device infection.
[i] Pneumonia includes COVID-19 pneumonia, Lower respiratory tract infection, Metapneumovirus pneumonia, Pneumonia, Pneumonia moraxella, Pneumonia pseudomonal, and Pneumonia streptococcal.
[j] Musculoskeletal pain includes Arthralgia, Back pain, Bone pain, Bursitis, Musculoskeletal chest pain, Musculoskeletal pain, Myalgia, Myositis, Neck pain, Non-cardiac chest pain, Osteoarthritis, Pain in extremity, Plantar fasciitis, Rotator cuff syndrome, Spinal pain, and Tendonitis.
[k] Headache includes Headache and Tension headache.
[l] Encephalopathy includes Amnesia, Bradyphrenia, Confusional state, Depressed level of consciousness, Disturbance in attention, Immune effector cell-associated neurotoxicity syndrome, Lethargy, and Psychomotor retardation.
[m] Cough includes Cough, Productive cough, and Upper-airway cough syndrome.
[n] Hypotension includes Hypotension, and Orthostatic hypotension.

Other clinically important adverse reactions that occurred in less than 10% of patients treated with CARVYKTI include the following:

- *Blood and lymphatic system disorders:* coagulopathy[a] (5%), febrile neutropenia (2%), lymphocytosis (2%),
- *Cardiac disorders:* tachycardia[b] (5%), cardiac arrhythmias[c] (3%)
- *Gastrointestinal disorders:* abdominal pain[d] (6%), vomiting (5%)
- *General disorders and administration site conditions:* chills (6%)
- *Immune system disorders:* HLH (1%)
- *Infections and Infestations:* gastroenteritis[e] (7%), sepsis[f] (9%), urinary tract infection[g] (5%), fungal infection[h] (3%)
- *Investigations:* c-reactive protein increased (6%)
- *Metabolism and Nutrition Disorders:* hypophosphatemia (10%), hyperferritinemia (7%)
- *Neoplasms benign, malignant, and unspecified (incl cysts and polyps):* hematologic malignancy[i] (3%)
- *Nervous system disorders:* dizziness[j] (9%), cranial nerve palsies[k] (9%), motor dysfunction[l] (9%), peripheral neuropathy[m] (7%), sleep disorder[n] (6%), tremor (4%), aphasia[o] (3%), ataxia[p] (3%),
- *Psychiatric disorders:* delirium[q] (2%) personality changes[r] (2%)
- *Renal and urinary disorders:* renal failure[s] (5%)
- *Respiratory, thoracic and mediastinal disorders:* dyspnea[t] (10%)
- *Skin and subcutaneous tissues:* rash[u] (7%)
- *Vascular Disorders:* hemorrhage[v] (9%), hypertension (7%), thrombosis[w] (3%), capillary leak syndrome (1%)

[a] Coagulopathy includes Blood fibrinogen decreased, Coagulation test abnormal, Coagulopathy, Disseminated intravascular coagulation, and Hypofibrinogenemia.
[b] Tachycardia includes Sinus tachycardia, and Tachycardia.
[c] Cardiac arrhythmias includes Atrial fibrillation, and Atrioventricular block second degree.
[d] Abdominal pain includes Abdominal discomfort, Abdominal pain, Abdominal pain lower, Abdominal pain upper, and Dyspepsia.
[e] Gastroenteritis includes Enterocolitis viral, Enterovirus infection, Gastroenteritis, Gastroenteritis rotavirus, Gastroenteritis salmonella, Gastrointestinal infection, and Large intestine infection.
[f] Sepsis includes Bacteremia, Candida sepsis, Device related bacteremia, Enterococcal bacteremia, Hemophilus sepsis, Neutropenic sepsis, Pseudomonal sepsis, Sepsis, Septic shock, Staphylococcal bacteremia, Systemic candida, and Urosepsis.
[g] Urinary tract infection includes Cystitis, Escherichia urinary tract infection, and Urinary tract infection.
[h] Fungal infection includes Candida infection, Oral candidiasis, Tongue fungal infection, and Vulvovaginal candidiasis.
[i] Hematologic malignancy includes Myelodysplastic syndrome, Acute myeloid leukemia, and T-cell lymphoma. Incidence based on cutoff date of 01 November 2022 (median follow-up time of 115.9 months).
[j] Dizziness includes Dizziness, Dizziness postural, Presyncope, Syncope, and Vertigo.

[k] Cranial nerve palsies includes Facial paralysis, Facial paresis, IIIrd nerve paralysis, and Trigeminal palsy.
[l] Motor dysfunction includes Bradykinesia, Coordination abnormal, Dysgraphia, Extrapyramidal disorder, Micrographia, Muscle spasms, Muscular weakness, and Parkinsonism.
[m] Neuropathy peripheral includes Peripheral motor neuropathy, Peripheral sensory neuropathy, and Polyneuropathy.
[n] Sleep disorder includes Insomnia, Sleep disorder, and Somnolence.
[o] Aphasia includes Aphasia, and Dysarthria.
[p] Ataxia includes Ataxia, Balance disorder, Dysmetria, and Gait disturbance.
[q] Delirium includes Agitation, Disorientation, and Hallucination.
[r] Personality changes includes Personality change, and Reduced facial expression.
[s] Renal failure includes Acute kidney injury, Blood creatinine increased, Chronic kidney disease, Renal failure, and Renal impairment.
[t] Dyspnea includes Dyspnea, Dyspnea exertional, Respiratory failure, Tachypnea, and Wheezing.
[u] Rash includes Dermatitis psoriasiform, Drug eruption, Erythema, Pityriasis lichenoides et varioliformis acuta, Rash, Rash erythematous, Rash maculo-papular, Rash papular, and Urticaria.
[v] Hemorrhage includes Catheter site hemorrhage, Conjunctival hemorrhage, Contusion, Epistaxis, Hematemesis, Hematoma, and Hematuria.
[w] Thrombosis includes Deep vein thrombosis, Pulmonary embolism, and Venous thrombosis limb.

Laboratory Abnormalities

Table 2 presents the most common Grade 3 or 4 laboratory abnormalities based on laboratory data, occurring in at least 10% of patients.

**Table 2: Grade 3 or 4 laboratory abnormalities in at least 10% of patients treated with CARVYKTI (N=188) and standard therapy (N=208) in CARTITUDE-4**

| | CARVYKTI (N=188) | Standard Therapy (N=208) |
|---|---|---|
| **Laboratory Abnormality** | **Grade 3 or 4 (%)** | **Grade 3 or 4 (%)** |
| Lymphocyte count decreased | 99 | 62 |
| Neutrophil count decreased | 95 | 88 |
| White blood cell decreased | 94 | 69 |
| Platelet count decreased | 47 | 20 |
| Hemoglobin decreased | 34 | 17 |

Laboratory abnormalities graded using NCI Common Terminology Criteria for Adverse Events version 5.0. Laboratory abnormalities are sorted by decreasing frequency in the Grade column.

Other clinically important Grade 3 or 4 laboratory abnormalities (based on laboratory data) that occurred in less than 10% of patients treated with CARVYKTI include fibrinogen decreased, gamma glutamyl transferase increased, hypokalemia, alanine aminotransferase increased, aspartate aminotransferase increased, alkaline phosphatase increased, hypoalbuminemia, hyponatremia, hypertriglyceridemia, hypomagnesemia, hypocalcemia, and blood bilirubin increased.

CARTITUDE-1

The safety data described in this section reflect the exposure of 97 adult patients with relapsed/refractory multiple myeloma in the CARTITUDE-1 study (USA cohort) to CARVYKTI and includes 17 patients (18%) with manufacturing failures either because they received CARVYKTI that did not meet product release specifications or there were insufficient data to confirm product release specifications for CARVYKTI. Patients received CARVYKTI across a dose range of 0.51 to $0.95\times10^6$ CAR-positive viable T cells/kg body weight *[see Clinical Studies (14) in Full Prescribing Information]*. Patients with a history of CNS disease (such as seizure or cerebrovascular ischemia) or requiring ongoing treatment with chronic immunosuppression were excluded. The median duration of follow-up was 18 months. The median age of the study population was 61 years (range: 43 to 78 years); 36% were 65 years or older, and 59% were men. The Eastern Cooperative Oncology Group (ECOG) performance status at baseline was 0 in 40%, 1 in 56%, and 2 in 4% of patients. Three of the patients treated with CARVYKTI had a creatinine clearance of <45 mL/min at baseline. For the details about the study population, see *Clinical Studies (14) in Full Prescribing Information*.

The most common (greater or equal to 10%) Grade 3 or higher nonlaboratory adverse reactions were infections-pathogen unspecified (19%), pneumonia (13%), hematologic malignancy (10%) and hypotension (10%).

The most common nonlaboratory adverse reactions (incidence greater than or equal to 20%) included pyrexia, CRS, hypogammaglobulinemia, hypotension, musculoskeletal pain, fatigue, infections of unspecified pathogen, cough, chills, diarrhea, nausea, encephalopathy, decreased appetite, upper respiratory tract infection, headache, tachycardia, dizziness, dyspnea, edema, viral infections, coagulopathy, constipation, and vomiting.

Serious adverse reactions occurred in 55% of patients. The most common non-laboratory (greater than or equal to 5%) serious adverse reactions included CRS (21%), sepsis (7%), encephalopathy (10%), and pneumonia (8%). Fatal adverse reactions occurred in 9% of patients.

Table 3 summarizes the adverse reactions that occurred in at least 10% of patients treated with CARVYKTI.

**Table 3: Adverse reactions observed in at least 10% of patients treated with CARVYKTI in CARTITUDE-1 (N=97)**

| System Organ Class (SOC) Preferred term | Any Grade (%) | Grade 3 or higher (%) |
|---|---|---|
| **Blood and lymphatic system disorders** | - | - |
| Coagulopathy[a] | 22 | 2 |
| Febrile Neutropenia | 10 | 9 |
| **Cardiac disorders** | - | - |
| Tachycardia[b] | 27 | 1 |
| **Gastrointestinal disorders** | - | - |
| Diarrhea[c] | 33 | 1 |
| Nausea | 31 | 1 |
| Constipation | 22 | 0 |
| Vomiting | 20 | 0 |
| **General disorders and administrative site conditions** | - | - |
| Pyrexia | 96 | 5 |
| Fatigue[d] | 47 | 7 |
| Chills | 33 | 0 |
| Edema[e] | 23 | 0 |
| **Immune system disorders** | - | - |
| Cytokine release syndrome[f] | 95 | 5 |
| Hypogammaglobulinemia[g] | 93 | 2 |
| **Infections and infestations[h]** | - | - |
| Infections-pathogen unspecified[i] | 41 | 19 |
| Upper respiratory tract infection[j] | 28 | 3 |
| Viral infections[k] | 23 | 7 |
| Pneumonia[l] | 14 | 13 |
| Sepsis[m] | 10 | 7 |
| **Metabolism and nutrition disorders** | - | - |
| Decreased appetite | 29 | 1 |
| **Musculoskeletal and connective tissue disorders** | - | - |
| Musculoskeletal pain[n] | 48 | 2 |
| **Nervous system disorders** | - | - |
| Encephalopathy[o] | 30 | 6 |
| Headache | 27 | 0 |
| Dizziness[p] | 23 | 1 |
| Motor dysfunction[q] | 16 | 3 |

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**Table 3: Adverse reactions observed in at least 10% of patients treated with CARVYKTI in CARTITUDE-1 (N=97) (continued)**

| System Organ Class (SOC) Preferred term | Any Grade (%) | Grade 3 or higher (%) |
|---|---|---|
| **Psychiatric disorders** | - | - |
| Insomnia | 13 | 0 |
| **Respiratory, thoracic and mediastinal disorders** | - | - |
| Cough[r] | 39 | 0 |
| Dyspnea[s] | 23 | 3 |
| Nasal congestion | 15 | 0 |
| Hypoxia | 12 | 4 |
| **Neoplasms benign, malignant, and unspecified (incl cysts and polyps)** | | |
| Hematologic malignancy[t] | 10 | 10 |
| **Vascular disorders** | - | - |
| Hypotension[u] | 51 | 10 |
| Hypertension | 19 | 6 |
| Hemorrhage[v] | 16 | 4 |

Adverse reactions are reported using MedDRA version 23.0
[a] Coagulopathy includes Activated partial thromboplastin time prolonged, Coagulopathy, Disseminated intravascular coagulation, Hypofibrinogenemia, International normalized ratio increased, and Prothrombin time prolonged. Also includes terms reported under investigation SOC.
[b] Tachycardia includes Sinus tachycardia, and Tachycardia.
[c] Diarrhea includes Colitis, and Diarrhea.
[d] Fatigue includes Asthenia, Fatigue, and Malaise.
[e] Edema includes Face edema, Generalized edema, Localized edema, Edema peripheral, Periorbital edema, Peripheral swelling, Pulmonary edema, and Scrotal edema.
[f] Cytokine release syndrome includes CRS, and Systemic inflammatory response syndrome.
[g] Hypogammaglobulinemia includes subjects with adverse event of hypogammaglobulinemia (12%) and/or laboratory IgG levels that fell below 500 mg/dL following CARVYKTI infusion (92%).
[h] Infections and infestations System Organ Class Adverse Events are grouped by pathogen type and selected clinical syndromes.
[i] Infections - pathogen unspecified includes Abscess limb, Atypical pneumonia, Bacteremia, Bronchitis, Conjunctivitis, Enterocolitis infectious, Folliculitis, Gastroenteritis, Lung abscess, Lung opacity, Osteomyelitis, Otitis media, Parotitis, Perirectal abscess, Pneumonia, Rash pustular, Rhinitis, Sepsis, Septic shock, Sinusitis, Skin infection, Soft tissue infection, Upper respiratory tract infection, and Urinary tract infection.
[j] Upper respiratory tract infection includes Human rhinovirus test positive, Rhinitis, Rhinovirus infection, Sinusitis, Upper respiratory tract infection, and Viral upper respiratory tract infection. Also includes terms reported under investigation SOC. Upper respiratory tract infections may also be included under pathogen categories.
[k] Viral infection includes Adenovirus test positive, Coronavirus infection, Cytomegalovirus syndrome, Cytomegalovirus viremia, Enterovirus infection, Gastroenteritis viral, Herpes zoster, Herpes zoster disseminated, Influenza, Influenza like illness, Oral herpes, Parainfluenza virus infection, Rhinovirus infection, Urinary tract infection viral, and Viral upper respiratory tract infection.
[l] Pneumonia includes Atypical pneumonia, Lung abscess, Lung opacity, Pneumocystis jirovecii pneumonia, Pneumonia, and Pneumonia aspiration.
[m] Sepsis includes Bacteremia, Bacterial sepsis, Pseudomonal bacteremia, Sepsis, Septic shock, and Staphylococcal bacteremia.
[n] Musculoskeletal pain includes Arthralgia, Back pain, Bone pain, Joint stiffness, Muscle strain, Musculoskeletal chest pain, Musculoskeletal discomfort, Musculoskeletal pain, Musculoskeletal stiffness, Myalgia, Neck pain, Non-cardiac chest pain, and Pain in extremity.
[o] Encephalopathy includes Amnesia, Bradyphrenia, Confusional state, Depressed level of consciousness, Disturbance in attention, Encephalopathy, Immune effector cell-associated neurotoxicity syndrome, Lethargy, Memory impairment, Mental impairment, Mental status changes, Noninfective encephalitis, and Somnolence.
[p] Dizziness includes Dizziness, Presyncope, and Syncope.
[q] Motor dysfunction includes Motor dysfunction, Muscle spasms, Muscle tightness, Muscular weakness, and Myoclonus.
[r] Cough includes Cough, Productive cough, and Upper-airway cough syndrome.
[s] Dyspnea includes Acute respiratory failure, Dyspnea, Dyspnea exertional, Respiratory failure, and Tachypnea.
[t] Hematologic malignancy includes Myelodysplastic syndrome and Acute myeloid leukemia.
[u] Hypotension includes Hypotension, and Orthostatic hypotension.
[v] Hemorrhage includes Conjunctival hemorrhage, Contusion, Ecchymosis, Epistaxis, Eye contusion, Hematochezia, Hemoptysis, Infusion site hematoma, Oral contusion, Petechiae, Post procedural hemorrhage, Pulmonary hemorrhage, Retinal hemorrhage, and Subdural hematoma.

Other clinically important adverse reactions that occurred in less than 10% of patients treated with CARVYKTI include the following:

- *Cardiac disorders:* cardiac arrhythmias[a] (8%), chest pain[b] (7%)
- *Eye disorders:* diplopia (1%)
- *Gastrointestinal disorders:* dysphagia (1%)
- *Immune system disorders:* HLH (1%), hypersensitivity reaction (5%)
- *Infections and Infestations:* bacterial infections[c] (9%), urinary tract infection[d] (4.1%)
- *Injury, Poisoning and Procedural complications:* fall (3.1%)
- *Metabolism and Nutrition Disorders:* tumor lysis syndrome (1%)
- *Musculoskeletal and Connective tissue disorders:* posture abnormal (1%)
- *Nervous system disorders:* aphasia[e] (8%), ataxia[f] (8%), peripheral neuropathy[g] (7%), tremor (6%), parkinsonism (4.1%), micrographia (4.1%), dysgraphia (3.1%), reduced facial expression (3.1%), cranial nerve palsies (3.1%), bradykinesia (2.1%), paresis[h] (1%), cogwheel rigidity (1%), cerebrovascular accident (1%), seizure (1%), slow speech (1%), nystagmus (1%)
- *Psychiatric disorders:* delirium[i] (5%) depression[j] (4.1%), psychomotor retardation (1%)
- *Renal and urinary disorders:* renal failure[k] (7%)
- *Skin and subcutaneous tissues:* rash[l] (8%)
- *Vascular Disorders:* thrombosis[m] (5%)

[a] Cardiac arrhythmias includes atrial fibrillation, atrial flutter, supraventricular tachycardia, ventricular extrasystoles, ventricular tachycardia.
[b] Chest pain includes Angina pectoris, Chest discomfort, and Chest pain.
[c] Bacterial infection includes Abscess limb, Cholecystitis, Cholecystitis acute, Clostridium difficile colitis, Clostridium difficile infection, Enterocolitis bacterial, Osteomyelitis, Perirectal abscess, Soft tissue infection, Staphylococcal infection.
[d] Urinary tract infection includes Urinary tract infection, and Urinary tract infection viral.
[e] Aphasia includes Aphasia, Dysarthria, and Speech disorder.
[f] Ataxia includes Ataxia, Balance disorder, and Gait disturbance.
[g] Peripheral neuropathy includes Peripheral neuropathy, Peripheral motor neuropathy and Peripheral sensory neuropathy.
[h] Paresis includes Facial paralysis, and Peroneal nerve palsy.
[i] Delirium includes Agitation, Hallucination, Irritability, Personality change, and Restlessness.
[j] Depression includes Depression, and Flat affect.
[k] Renal failure includes Acute kidney injury, Blood creatinine increased, Chronic kidney disease, and Renal impairment.
[l] Rash includes Erythema, Rash, Rash maculo-papular, and Rash pustular.
[m] Thrombosis includes Deep vein thrombosis, and Device related thrombosis.

Laboratory Abnormalities

Table 4 presents the most common Grade 3 or 4 laboratory abnormalities based on laboratory data, occurring in at least 10% of patients.

**Table 4: Grade 3 or 4 laboratory abnormalities in at least 10% of patients treated with CARVYKTI in CARTITUDE-1 (N=97)**

| Laboratory Abnormality | Grade 3 or 4 (%) |
|---|---|
| Lymphopenia | 99 |
| Neutropenia | 98 |
| White blood cell decreased | 98 |
| Anemia | 72 |
| Thrombocytopenia | 63 |
| Aspartate aminotransferase increased | 21 |

Laboratory abnormalities graded using NCI Common Terminology Criteria for Adverse Events version 5.0.
Laboratory abnormalities are sorted by decreasing frequency in the Grade column.

Other clinically important Grade 3 or 4 laboratory abnormalities (based on laboratory data) that occurred in less than 10% of patients treated with CARVYKTI include the following: fibrinogen decreased, hypoalbuminemia, alanine aminotransferase increased, hyponatremia, hypocalcemia, gamma glutamyl transferase increased, alkaline phosphatase increased, hypokalemia, blood bilirubin increased.

**Immunogenicity**

The immunogenicity of CARVYKTI has been evaluated using a validated assay for the detection of binding antibodies against the extracellular portion of the anti-BCMA CAR pre-dose, and at multiple timepoints post-infusion. In CARTITUDE-1, 19 of 97 (19.6%) patients were positive for anti-product antibodies. In CARTITUDE-4, 39 of 186 patients (21%) were positive for anti-CAR antibodies.

There was no clear evidence that the observed anti-product antibodies impact CARVYKTI kinetics of initial expansion and persistence, efficacy, or safety.

**Postmarketing Experience**

Because adverse events to marketed products are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to product exposure.

The following adverse event has been identified during postmarketing use of CARVYKTI.

*Neoplasms:* T cell malignancies

## DRUG INTERACTIONS

HIV and the lentivirus used to make CARVYKTI have limited, short spans of identical genetic material (RNA). Therefore, some commercial HIV nucleic acid tests (NATs) may yield false-positive results in patients who have received CARVYKTI.

## USE IN SPECIFIC POPULATIONS

**Pregnancy**

Risk Summary

There are no available data on the use of CARVYKTI in pregnant women. No reproductive and developmental toxicity studies in animals have been conducted with CARVYKTI to assess whether it can cause fetal harm when administered to a pregnant woman. It is not known whether CARVYKTI has the potential to be transferred to the fetus and cause fetal toxicity. Based on the mechanism of action, if the transduced cells cross the placenta, they may cause fetal toxicity, including B-cell lymphocytopenia and hypogammaglobulinemia. Therefore, CARVYKTI is not recommended for women who are pregnant, or for women of childbearing potential not using contraception. Pregnant women should be advised that there may be risks to the fetus. Pregnancy after CARVYKTI therapy should be discussed with the treating physician.

In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2%-4% and 15%-20%, respectively.

**Lactation**

Risk Summary

There is no information regarding the presence of CARVYKTI in human milk, the effect on the breastfed infant, and the effects on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for CARVYKTI and any potential adverse effects on the breastfed infant from CARVYKTI or from the underlying maternal condition.

**Females and Males of Reproductive Potential**

Pregnancy Testing

Pregnancy status for females of child-bearing age should be verified prior to starting treatment with CARVYKTI.

Contraception

There are insufficient data to provide a recommendation concerning duration of contraception following treatment with CARVYKTI.

In clinical trials, female patients of childbearing potential were advised to practice a highly effective method of contraception and male patients with partners of childbearing potential or whose partners were pregnant were instructed to use a barrier method of contraception, until one year after the patient has received CARVYKTI infusion.

See the prescribing information for lymphodepleting chemotherapy for information on the need for contraception in patients who receive the lymphodepleting chemotherapy.

Infertility

There are no data on the effect of CARVYKTI on fertility.

**Pediatric Use**

Safety and effectiveness of CARVYKTI in pediatric patients have not been established.

**Geriatric Use**

Of the 97 patients in CARTITUDE-1 that received CARVYKTI, 28% were 65 to 75 years of age, and 8% were 75 years of age or older. CARTITUDE-1 did not include sufficient numbers of patients aged 65 and older to determine whether the effectiveness differs compared with that of younger patients. In 62 patients less than 65 years of age, all grade and Grade 3 and higher neurologic toxicities occurred in 19% (12/62) and 6% (4/62), respectively. Of the 35 patients ≥65 years of age, all grade and Grade 3 and higher neurologic toxicities occurred in 37% (13/35) and 20% (7/35), respectively.

Of the 188 patients in CARTITUDE-4 that received CARVYKTI, 38% were 65 to 75 years of age, and 2% were 75 years of age or older. In 112 patients less than 65 years of age, all grade and Grade 3 and higher neurologic toxicities occurred in 16% (18/112) and 3% (3/112) respectively. Of the 76 patients ≥65 years of age, all grade and Grade 3 and higher neurologic toxicities occurred in 34% (26/76) and 7% (5/76) respectively.

## REFERENCES

1 Lee DW, Santomasso BD, Locke FL, et al. ASTCT consensus grading for cytokine release syndrome and neurologic toxicity associated with immune effector cells. Biol Blood Marrow Transplant 2019; 25: 625-638.
2 National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) v 5.0; 2017.

## PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Medication Guide).

Inform patients of the risk of manufacturing failure [18%, (17/97 in the clinical study)]. In case of a manufacturing failure, a second manufacturing of CARVYKTI may be attempted. In addition, while the patient awaits the product, additional anticancer treatment (other than lymphodepletion) may be necessary and may increase the risk of adverse reactions during the pre-infusion period, which could delay or prevent the administration of CARVYKTI.

Advise patients that they will be monitored daily for the first 10 days following the infusion at a REMS-certified healthcare facility, and instruct patients to remain within proximity of a certified healthcare facility for at least 4 weeks following the infusion.

Prior to infusion, advise patients of the following risks and to seek immediate medical attention in the event of the following signs or symptoms:

**CARVYKTI®** (ciltacabtagene autoleucel)

Increased Early Mortality

Inform patients of the risk of early mortality. In a clinical study, treatment in the CARVYKTI arm was associated with a higher rate of death (14%) compared to the control arm (12%) in the first 10 months from randomization. This higher rate of death was observed before receiving CARVYKTI and after treatment with CARVYKTI. The reasons for death were progression of multiple myeloma and adverse events *[see Warnings and Precautions, Clinical Studies (14) in Full Prescribing Information]*.

Cytokine Release Syndrome (CRS)

Signs or symptoms of CRS, including fever, chills, fatigue, headache, tachycardia, hypotension, hypoxia, dizziness/lightheadedness or organ toxicities *[see Warnings and Precautions, Adverse Reactions]*.

Neurologic Toxicities

Signs or symptoms associated with neurologic events, some of which occur days, weeks or months following the infusion including *[see Warnings and Precautions, Adverse Reactions]:*

*ICANS:* e.g., aphasia, encephalopathy, depressed level of consciousness, seizures, delirium, dysgraphia
*Parkinsonism:* e.g., tremor, micrographia, bradykinesia, rigidity, shuffling gait, stooped posture, masked facies, apathy, flat affect, lethargy, somnolence
*Guillain Barré Syndrome:* e.g., motor weakness and polyradiculoneuritis
*Peripheral neuropathy:* e.g., peripheral motor and/or sensory nerve dysfunction
*Cranial Nerve Palsies:* e.g., facial paralysis, facial numbness

Prolonged and Recurrent Cytopenias

Signs or symptoms associated with bone marrow suppression including neutropenia, thrombocytopenia, anemia, or febrile neutropenia for several weeks or months. Signs or symptoms associated with bone marrow suppression may recur *[see Warnings and Precautions, Adverse Reactions]*.

Infections

Signs or symptoms associated with infection *[see Warnings and Precautions, Adverse Reactions]*.

Hypersensitivity Reactions

Signs or symptoms associated with hypersensitivity reactions including flushing, chest tightness, tachycardia, and difficulty breathing *[see Warnings and Precautions]*.

Secondary Malignancies

Secondary hematological malignancies, including myelodysplastic syndrome, acute myeloid leukemia, and T-cell malignancies have occurred *[see Boxed Warning, Warnings and Precautions, Adverse Reactions]*.

Advise patients of the need to:

- Have periodic monitoring of blood counts before and after CARVYKTI infusion *[see Warnings and Precautions]*.
- Contact Janssen Biotech, Inc. at 1-800-526-7736 if they are diagnosed with a secondary malignancy *[see Warnings and Precautions]*.
- Refrain from driving and engaging in hazardous occupations or activities, such as operating heavy or potentially dangerous machinery, for at least 8 weeks after treatment and in the event of any new onset of neurologic toxicities *[see Warnings and Precautions]*.
- Tell their physician about their treatment with CARVYKTI before receiving a live virus vaccine *[see Warnings and Precautions]*.

Manufactured/Marketed by:
Janssen Biotech, Inc.
Horsham, PA 19044, USA
U.S. License Number 1864

Marketed by:
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Somerset, NJ 08873, USA

For patent information: www.janssenpatents.com


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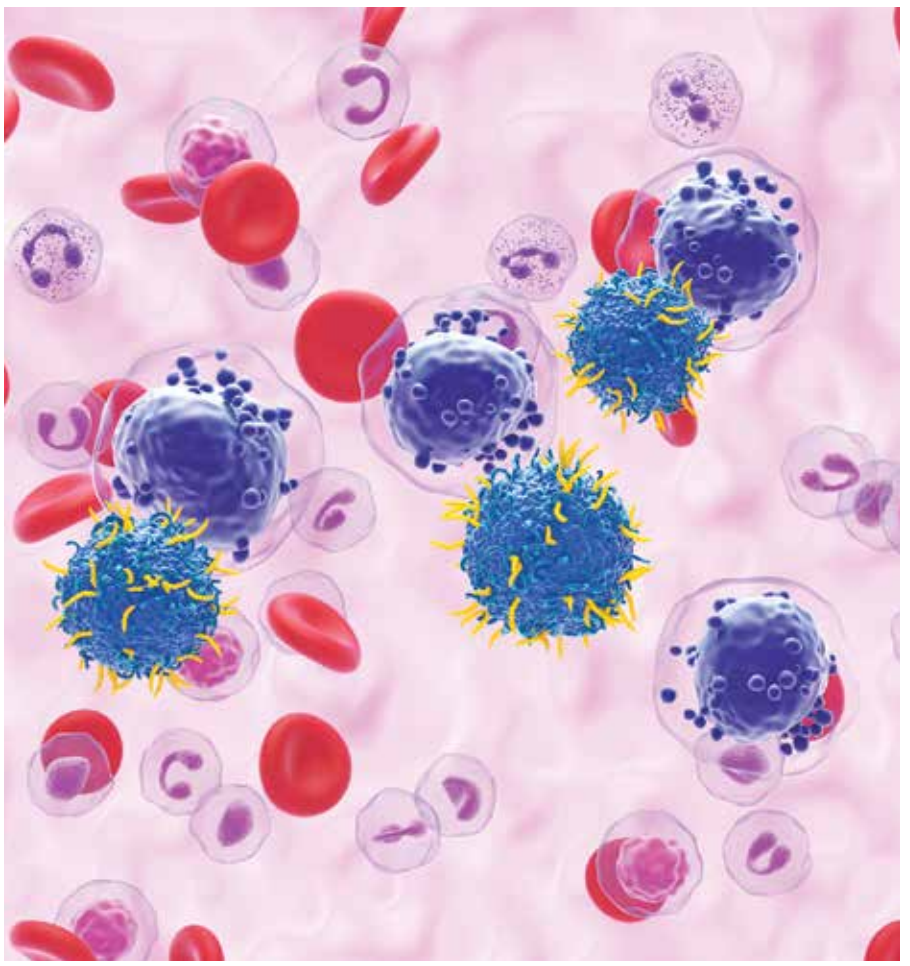

## Oral Hypomethylating Regimen Under FDA Review for Newly Diagnosed AML

*By **Melissa Badamo***

The FDA has accepted a Supplemental New Drug Application (sNDA) for decitabine and cedazuridine (INQOVI) plus venetoclax for the treatment of adult patients with newly diagnosed acute myeloid leukemia (AML) who are ineligible for intensive induction chemotherapy. The FDA is expected to make a decision by February 25, 2026.[1]

The sNDA is supported by the phase 2b portion of the ASCERTAIN-V trial presented at the European Hematology Association 2025 Congress. Among 101 adult patients who received decitabine-cedazuridine plus venetoclax, 46.5% (95% CI, 36.5%–56.7%) achieved complete remission (CR), and 63.4% (95% CI, 53.2%–72.7%) achieved CR/CR with incomplete hematologic recovery. The median time to CR was 2.4 months.[2]

In terms of safety, 98.0% of patients experienced grade 3 or higher adverse events, most commonly febrile neutropenia (49.5%), anemia (38.6%), and neutropenia (35.6%). The 30-day mortality rate was 3.0%, and the 60-day mortality rate was 9.9%.[2]

Decitabine-cedazuridine is currently indicated in the US to treat adult patients with myelodysplastic syndromes and chronic myelomonocytic leukemia.[1]

"We have an unwavering dedication to developing innovative new cancer treatments, and the FDA's acceptance of our sNDA for INQOVI in combination with venetoclax highlights the need for novel approaches in AML," said **Harold Keer, MD, PhD,** chief medical officer of Taiho Oncology, in a press release.[1] "If approved for patients with AML who are not eligible to undergo intensive induction chemotherapy, INQOVI in combination with venetoclax would offer the first all-oral alternative to current therapies."

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1. PR Newswire. Accessed July 11, 2025. https://www.prnewswire.com/news-releases/taiho-oncology-and-taiho-pharmaceutical-announce-us-fda-acceptance-of-supplemental-new-drug-application-for-inqovi-in-combination-with-venetoclax-to-treat-patients-with-acute-myeloid-leukemia-302501545.html
2. Roboz G, et al. European Hematology Association 2025 Congress. Abstract S135

## FDA, Biotech Company Hash Out Criteria for Primary Vitreoretinal Lymphoma Agent's NDA Resubmission

*By **Andrew Moreno***

Biotechnology company Aldeyra Therapeutics, Inc, is developing the investigational drug candidate ADX-2191 as a possible treatment for primary vitreoretinal lymphoma (PVRL), retinitis pigmentosa, and other rare retinal diseases. In a press release, the company announced it has received a Special Protocol Assessment Agreement Letter from the FDA for this agent in PVRL management.

ADX-2191 is a novel intravitreal injection formulation of methotrexate. At this time, no therapies for PVRL are approved by the FDA, but intravitreal injection of compounded methotrexate has been the current standard of care.

"ADX-2191, a novel, vitreous-compatible formulation of methotrexate that is specifically designed for intraocular injection, potentially allows for a reduced injection volume relative to compounding," explained Aldeyra president and chief executive officer **Todd C. Brady, MD, PhD,** in the statement announcing the FDA's grant of the Agreement Letter.

This agent previously received Orphan Drug Designation from the FDA for treatment of PVRL and retinitis pigmentosa. In March 2023, the FDA accepted a literature-based New Drug Application (NDA) for Priority Review, submitted by Aldeyra for therapeutic use of the agent in PVRL. In June of that year, the FDA issued Aldeyra a Complete Response Letter, informing the company that evidence for the agent's efficacy in the available literature was insufficient.

In the Response Letter, the FDA informed Aldeyra that properly executed, controlled clinical trials would be required for the approval of ADX-2191. The FDA has since reached agreement with the company that the NDA for this agent will be acceptable for resubmission with a single clinical trial backed by literature references.

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Business Wire. Accessed July 14, 2025. https://www.businesswire.com/news/home/20250626651175/en/Aldeyra-Therapeutics-Receives-Special-Protocol-Assessment-Agreement-Letter-from-the-U.S.-Food-and-Drug-Administration-for-ADX-2191-for-the-Treatment-of-Primary-Vitreoretinal-Lymphom

# News Roundup

*The latest news and updates in hematologic oncology research*

## Leukemia & Lymphoma Society Rebrands to 'Blood Cancer United'

*By **Melissa Badamo***

The Leukemia & Lymphoma Society (LLS) has changed its name to Blood Cancer United to expand its reach to all patients with blood cancers, according to a press release from the nonprofit organization.[1]

The name change took effect on August 28, ahead of Blood Cancer Awareness Month in September. It now reflects all 100+ types of blood cancers beyond leukemia and lymphoma, including myeloma, myelodysplastic syndromes, and myeloproliferative neoplasms.

"The word 'united' is transformational and inviting," said **E. Anders Kolb, MD,** President and CEO of LLS, in the press release. "I believe in the power of bringing together patients, families, scientists, volunteers, donors, business leaders, and health systems under a shared purpose. Blood Cancer United reflects who we are today and who we aspire to be—a unifying force advancing progress for every person impacted by blood cancer."[1]

The organization's rebrand stems from community feedback and will further support its mission to fund blood cancer research, provide education and patient services, and advocate for policies that increase access to quality healthcare. Recently, the organization invested $5 million in research to increase clinical trial access and participation, particularly among underrepresented groups, to advance treatment options and improve patient outcomes.[2]

"We are at a pivotal moment—not only for our organization, but for our community—when funding for cancer research and access to treatment and care are at risk," said Dr. Kolb.[1] "Patients and researchers are telling us they're worried about the impact these changes will have for anyone dealing with blood cancer, so there's no better time for a resource that helps us reach more of the patients who need us."

The organization aims to "enable patients with blood cancers to gain more than one million years of life" by 2040.

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1. Leukemia & Lymphoma Society. Accessed August 1, 2025. https://www.lls.org/news/lls-unveils-name-change-reach-all-blood-cancer-patients
2. Leukemia & Lymphoma Society. Accessed August 1, 2025. https://www.lls.org/news/lls-invests-nearly-5-million-research-committed-increasing-clinical-trial-access-participation


## BCL-2 Inhibitor Development Continues Amid Mixed Phase 3 Outcomes in RRMM

*By **Nichole Tucker***

Shaji Kumar, MD

In clinical trials, multiple BCL-2 inhibitors are being developed to potentially treat patients with relapsed or refractory multiple myeloma (RRMM). Recently, the first-generation BCL-2 inhibitor venetoclax demonstrated less favorable overall survival (OS) compared with placebo plus bortezomib and dexamethasone, signaling that the future of BCL-2 inhibitors in RRMM might lie with next-generation agents.

Results come from the final analysis of the phase 3 BELLINI study by **Shaji Kumar, MD,** of the Mayo Clinic in Rochester, Minnesota, and colleagues. The study included 291 patients with RRMM who were treated in one of 90 centers across 16 countries. The patients were randomly assigned according to a 2:1 ratio to receive either venetoclax (n=194) or placebo (n=94).

At a median follow-up of 45.6 months (interquartile range, 43.6-48.3 months), median OS was not reached in the venetoclax group (95% CI, 44.4-not estimable [NE]) or in the placebo group (95% CI, 44.0-NE); the hazard ratio (HR) was 1.19 (95% CI, 0.80-1.77; *P*=0.39). However, the median progression-free survival was 23.4 months (95% CI, 16.2-26.4) with venetoclax compared with 11.4 months (95% CI, 9.5-14.6) with placebo (HR, 0.58; 95% CI, 0.43-0.78; *P*=0.00026).

Thrombocytopenia and neutropenia were the most common grade 3 and 4 adverse events, having occurred in 26% versus 40% and 30% versus 8% of the venetoclax and placebo groups, respectively. Four deaths resulted from treatment-related adverse events.

"The increased mortality was primarily among patients without the t(11;14) translocation and/or no elevated BCL-2, especially among those with high-risk cytogenetic abnormalities. The results suggest that BCL-2 inhibitors have a major role to play in the treatment of myeloma patients with t(11;14) and those with increased expression of BCL-2, though for the latter group, we do not have an assay we can use in the clinic yet," Dr. Kumar told *Blood Cancers Today*.

Dr. Kumar also pointed out, "Venetoclax combinations are effective in patients with relapsed myeloma who have t(11;14), and those patients should be on infectious disease prophylaxis if this option is chosen, and patients should be carefully monitored."

### Reference


Kumar S, et al. *Lancet Haematol.* 2025 Jun 27:S2352-3026(25)00139-5. doi:10.1016/S2352-3026(25)00139-5

# Incidental Follicular Lymphoma Diagnosis Associated With Earlier-Stage Disease

*By* ***Melissa Badamo***

Compared with patients who have lymphoma-related symptoms, patients who have an incidental, asymptomatic diagnosis of follicular lymphoma (FL) are more likely to have early-stage disease and more favorable disease characteristics. However, no association was found between diagnosis type and survival outcomes.

**Suheil Albert Atallah-Yunes, MD,** of the Mayo Clinic, and colleagues reported their results in *Blood Cancer Journal,* investigating the role of multi-cancer early detection tests (MCEDs) on patient outcomes.

"Multi-cancer early detection tests have shown promise in identifying lymphomas, including FL, at early stages through blood-based assays," Dr. Atallah-Yunes told *Blood Cancers Today.* "Our study may serve as a surrogate for what MCEDs might detect."

To compare disease characteristics and outcomes among patients diagnosed incidentally versus symptomatically, the researchers reviewed 908 patients with newly diagnosed FL enrolled in the Molecular Epidemiology Resource from 2002 to 2015. A total of 259 patients (28.5%) were diagnosed incidentally without symptoms, and 649 patients (71.5%) had lymphoma-related symptoms.

Patients with an incidental diagnosis were more likely to have stage I or II disease (43.2% vs 30.6%, respectively; $P = 0.0003$), normal lactate dehydrogenase levels (87.2% vs 80.8%, respectively; $P = 0.03$), and lower Follicular Lymphoma International Prognostic Index (FLIPI) scores (49.8% vs 42.2%, respectively; $P = 0.1$) compared with those with a symptomatic diagnosis.

However, the rates of event-free survival (hazard ratio [HR], 1.01; 95% CI, 0.80-1.27; $P = 0.93$), overall survival (HR, 0.93; 95% CI, 0.68-1.28; $P = 0.66$), and lymphoma-specific survival were comparable between the two groups.

"In FL, early detection doesn't automatically translate into improved outcomes under current treatment paradigms, as a watch-and-wait strategy remains appropriate for many patients," Dr. Atallah-Yunes told *Blood Cancers Today.*

Patients in the incidental group received less immunochemotherapy and were more likely to be observed compared with the symptomatic group, the researchers noted.

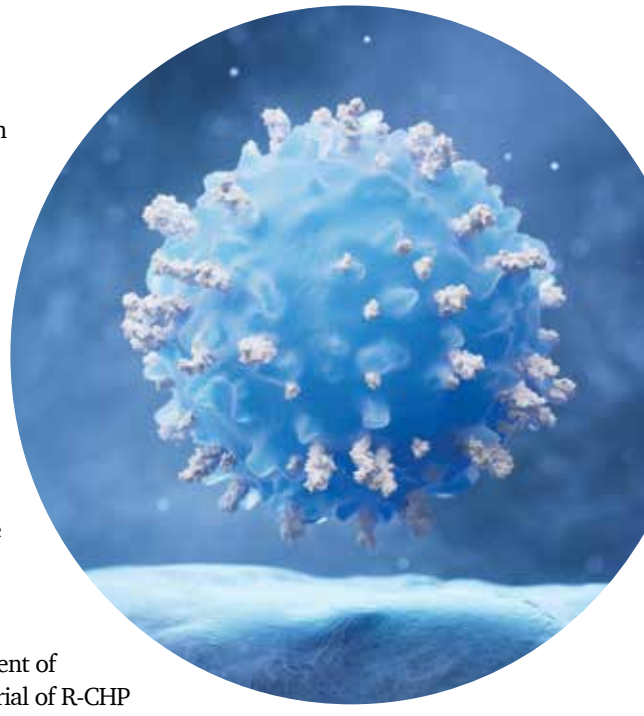
"The real question is whether detecting FL at a preclinical molecular stage, earlier than our incidentally diagnosed group, would lead to different results and outcomes than those observed in our study. That remains unanswered, and future studies must weigh the benefits of earlier detection against risks of overtreatment, patient psychosocial factors, and healthcare costs," Dr. Atallah-Yunes added. "The ultimate value of MCEDs in FL will depend on whether early intervention can meaningfully improve outcomes. Until such data emerge, clinical decision-making must continue to balance early identification with the principles of patient-centered care."

**Reference**

Atallah-Yunes SA, et al. *Blood Cancer J.* 2025;15(1):116. doi:10.1038/s41408-025-01322-9

# Glofitamab Shows Staying Power When Paired With R-CHOP or Pola-R-CHP in LBCL

*By* ***Sara Karlovitch***



Glofitamab produced high rates of durable responses when combined with R-CHOP or Pola-R-CHP in younger patients with high-burden, high-risk large B-cell lymphoma (LBCL), according to results from the phase 2 COALITION study.

The open-label, multicenter study was conducted at over 15 centers across Australia and led by **Adrian Minson, MBBS, PhD,** of the Peter McCallum Cancer Center. It was published in the *Journal of Clinical Oncology.*

The trial included patients aged 18 to 65 with high-risk LBCL who were either untreated or received one cycle of R-CHOP. Patients with International Prognostic Index (IPI) greater than or equal to 3, NCCN-IPI greater than or equal to 4, or the presence of double-hit (DH) lymphoma characterized by *MYC* and *BCL2* and/or *BCL6* rearrangements using fluorescent in situ hybridization (FISH) were classified as high risk. Patients with transformed indolent lymphoma (tiNHL), excluding Richter's syndrome, were eligible if they had not received a regimen including anthracycline. The study excluded patients with central nervous system involvement by lymphoma.

The primary objective of the study was the safety of the treatment, along with the deliverability of the protocol treatments. Secondary end points included objective response rates (ORR), complete response (CR) rates, progression-free survival (PFS), and overall survival (OS).

Of the 81 patients recruited from July 2021 to July 2023, 80 (median age, 58) were deemed eligible to participate. The data cutoff date was August 15, 2024. After one cycle of R-CHOP, patients were assigned to arm A or arm B. Patients in arm A received an additional five 21-day cycles of R-CHOP with glofitamab. Patients in arm B received Pola-R-CHP and glofitamab on the same schedule. Each arm received two cycles of glofitamab monotherapy at the conclusion of combination therapy.

The ORR was 100%, and the complete metabolic response was 98%. The 12-month PFS was 92% overall, 90% in arm A and 95% in arm B. The 12-month OS was 97% overall and 98% in both arms. The 24-month PFS was 86% across the board. The 24-month OS was 92% overall in arm A and 91% in arm B.

Ninety-nine percent of patients experienced at least one adverse effect (AE). Peripheral neuropathy was the most observed AE, occurring in 44% of the study population overall. Febrile neutropenia occurred in 15% of arm B. Grade 3 or higher was observed in 58% of patients. One grade 5 AE was observed in each arm.

"This is a very strong endorsement of the ongoing randomized clinical trial of R-CHP with glofitamab versus R-CHP (SKYGLO) that is currently running globally and continues to recruit in multiple centers across the US. It suggests the potential of this regimen to have positive outcomes in that clinical trial," study author **Michael J. Dickinson, MBBS, DMSc,** of Peter MacCallum Cancer Center, told *Blood Cancers Today.*

**Reference**

Adrian M, et al. *JCO.* 0, JCO-25-00481. doi:10.1200/JCO-25-00481

Highlights From the **2025 PAN PACIFIC LEUKEMIA CONFERENCE JULY 15–18, 2025, IN LAHAINA, HAWAII.**

# Treatment Advances in Double-Refractory CLL Signal a Shift in Outlook

*By* ***Katie Kosko***

Novel therapies have led to more options for patients with double-refractory chronic lymphocytic leukemia (CLL), a historically challenging population to treat.

Two pivotal clinical trials have helped reshape the treatment landscape for this disease with additional exciting therapies under investigation, which **Susan O'Brien, MD,** of the University of California, Irvine, discussed during a presentation at the Pan Pacific Leukemia Conference held July 15-18, 2025, in Lahaina, Hawaii.

Susan O'Brien, MD

The lecture, "Double-Refractory CLL: An Emerging Clinical Challenge," described how agents, such as pirtobrutinib, lisocabtagene maraleucel (liso-cel), epcoritamab, and BGB-16673, are being explored and used in the treatment of CLL.

### *Given the Green Light*

"We now have two FDA-approved agents (pirtobrutinib and liso-cel) for the treatment of refractory patients with CLL, and there are other agents, which look very promising, that are on the horizon," Dr. O'Brien said in an interview with *Blood Cancers Today*.

Pirtobrutinib, a highly selective, noncovalent (reversible) Bruton's tyrosine kinase inhibitor (BTKi), was approved in December 2023 for adult patients with CLL or small lymphocytic lymphoma (SLL) who received at least two prior lines of therapy, including a BTKi and a B-cell lymphoma 2 (BCL2) inhibitor. The accelerated approval was based on findings from the BRUIN CLL-321 study.

In the BRUIN CLL-321 study, previously treated patients with CLL or SLL were randomized to receive pirtobrutinib monotherapy (n=119) or investigators' choice of idelalisib plus rituximab (IdelaR; n=82) or bendamustine plus rituximab (BR; n=37). Investigators observed a median progression-free survival of 14 months with pirtobrutinib compared with 8.7 months with IdelaR or BR. Moreover, adverse events of interest with pirtobrutinib were comparable to those seen in the phase 1/2 BRUIN study, Dr. O'Brien explained.

In March 2024, the FDA granted another accelerated approval to liso-cel, a CD19-targeted chimeric antigen receptor (CAR) T-cell therapy.

The phase 1/2 TRANSCEND CLL 004 trial evaluated the CAR T-cell therapy in patients with CLL or SLL who experienced disease progression after treatment with a BTKi and venetoclax. A single dose of liso-cel resulted in a 20% complete response rate and durable remission in patients with double-refractory CLL, O'Brien said. Any-grade cytokine release syndrome (CRS) was seen in 85% of patients, and 45% of patients experienced neurologic events. More than half of the study population had prolonged cytopenias. However, all toxicities were manageable.

### *Bispecifics and Beyond*

Dr. O'Brien shared encouraging early findings from studies evaluating a bispecific antibody and a chimeric degradation activating compound (CDAC) degrader.

Epcoritamab, already FDA approved for other hematologic malignancies, is a bispecific antibody that targets CD3 on T cells and CD20 on CLL cells. The EPCORE CLL-1 study has shown clinical promise. Preliminary data determined that the agent could produce high response rates with undetectable measurable residual disease in patients with highly refractory CLL, Dr. O'Brien emphasized. Although CRS rates were high, they were mainly grade 1 or 2, with 8% experiencing grade 3 CRS.

BGB-16673, a CDAC degrader, was the final investigational agent discussed by Dr. O'Brien. She highlighted updated safety and efficacy findings from the ongoing phase 1 CaDAnCe-101 trial of 66 patients with highly refractory disease who received a median of four prior lines of therapy.

Investigators observed an overall response rate of 94% in patients who were given a 200-mg dose, taken once daily (n=16). Furthermore, toxicity was minimal, Dr. O'Brien said. The most common treatment-emergent adverse events included fatigue (37%) and contusions (30%).

Together, the approved therapies and those in the pipeline offer renewed hope for patients with double-refractory CLL.

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4. Danilov A, et al. *Blood.* 2024;144(suppl 1):883. https://doi.org/10.1182/blood-2024-199708
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# Dr. Julie Vose on Time-Limited Therapy and Other Strategy Shifts in CLL

*By **Nichole Tucker** & **Melissa Badamo***

Julie Vose, MD

**Julie Vose, MD,** chief of the Division of Oncology and Hematology at the University of Nebraska Medical Center, joined *Blood Cancers Today* to discuss the main takeaways from the chronic lymphocytic leukemia (CLL) session at the 2025 Pan Pacific Leukemia Conference from July 15 to 18 in Lahaina, Hawaii.

Dr. Vose outlined the most significant shifts in CLL treatment, including time-limited therapy, the challenges of managing Richter's transformation, and how she makes individualized treatment decisions for patients with CLL based on age and mutation status.

**Given the rapid evolution of targeted therapies, what are the biggest factors influencing choice of first-line treatment for young versus older patients with CLL?**

The biggest influencers are the genetics of the CLL. Do they have a *TP53* mutation? Do they have unmutated disease? Of course, there's the overall wishes for the patient as far as being on long term oral medication versus time-limited therapy. Thankfully, most patients don't have to use chemotherapy anymore. It's more a question of immunotherapy with different oral medications, including BTK [Bruton's tyrosine kinase] inhibitors and BCL2 [B-cell lymphoma 2] inhibitors. It's more about working with the patient to understand their needs and reviewing their insurance to ensure they can be covered for whatever treatment we recommend. It's a lot of personalized care.

**How do you see treatment sequencing strategies changing as more patients become double refractory to some of the current standards of care?**

The minority of patients so far have become double refractory, but as time goes on, that may change. Currently, for double refractory patients, we would check the genetics for the CLL and see if they've changed from the original ones. CAR [chimeric antigen receptor] T-cell therapy is an opportunity for those patients, as well as bispecific antibodies.

I think there will be a lot more new developments as more of those patients become double refractory. It's not a huge problem right now, but I can see down the line where that may be, and we'll need other alternatives.

**Richter's transformation remains a significant challenge. What promising approaches or clinical trials are on the horizon that may change the way you manage this?**

Richter's transformation is still an unmet medical need. Typically, we would treat those patients like a de novo diffuse large B-cell lymphoma, possibly with CLL-directed therapy depending on the situation. If it's a younger patient, we can get them into remission, then an allogeneic transplant could still be an option for those patients.

**Which biomarkers or patient characteristics are proving most valuable in guiding individualized treatment in CLL?**

It would be FISH [fluorescence in situ hybridization] testing to see if they have a *TP53* mutation, plus the *TP53* mutation itself, as well as the immunoglobulin heavy chain gene rearrangement. The latter only needs to be checked once and the patient never changes, but the CLL FISH does need to be checked with each subsequent progression or as time has gone on, when they need treatment to make sure it hasn't changed.

**Looking 5 years ahead, what do you anticipate will be the biggest shifts in CLL therapy? What hurdles need to be addressed to get there?**

Using time-limited therapy in appropriate patients is a big shift. I also think checking for minimal residual disease or ctDNA may be a big shift in trying to utilize that strategy or other strategies to see if we can limit the therapy for patients. Nobody wants to be on therapy long-term if they can help it, certainly from the toxicity profile and cost profile. If we can figure out ways for more people to access time-limited therapy, whether that involves extending the duration or adding an agent. That's one of the big goals we should have.

**What is your main takeaway from the CLL session at the Pan Pacific Leukemia Conference?**

The biggest takeaway is that we need to individualize care, and considering the genetic profile of CLL, as well as the patient's wishes, is crucial. These patients typically live for a very long time, and we need to make sure that we plan for the long term and that we're not causing more side effects without helping the patients. We must always balance side effects, the cost of the agent, and the treatment of the disease.

# Time-Limited, Targeted, Tailored: The Future of Frontline CLL Treatment

*By **Nichole Tucker***

Selecting the right frontline therapy for chronic lymphocytic leukemia (CLL) is less a fixed formula and more a shifting landscape, where age is just one landmark among many on the path to personalized care.

This topic commenced the CLL session at the Pan Pacific Leukemia Conference, during which **Nitin Jain, MD,** professor of medicine in the Department of Leukemia at The University of Texas MD Anderson Cancer Center, gave a presentation on optimal treatment for older patients. His presentation followed one by **R. Gregory Bociek, MD, MSc,** professor, UNMC Division of Oncology & Hematology Non-Hodgkin Lymphoma, Hodgkin Disease, Chronic Lymphocytic Leukemia, who presented on optimal treatment for young patients with CLL.

Nitin Jain, MD

Following his presentation, Dr. Jain sat for an interview with *Blood Cancers Today* to unpack the details of his presentation and discuss the evolving practice of treating older patients with CLL in the upfront setting.

**The optimal upfront treatment for CLL is a moving target. What is the most recent information you can share on deciding which treatment to give?**

For patients with CLL, the treatment has remarkably changed in the last decade or so. These days, we're only using targeted therapies such as BTK [Bruton's tyrosine kinase] inhibitors, PCL2 inhibitors, and CD20 antibodies. We have completely moved away from chemoimmunotherapy. In the discussion at the

meeting, one of the points was which therapies to select for patients with CLL. We are increasingly deciding therapies based on not just the age of the patient, but more importantly, their comorbidities, and genomic risk for the CLL, including things like *IGHV* and deletion 17p mutation.

We also focus on organ function; for example, if they have kidney problems or they have heart issues, atrial fibrillation, and anticoagulation. All these therapies we have for CLL are quite effective, and it comes down to a discussion with the patient about their preferences because there's a big difference in strategy with CLL. Some therapies are given orally once daily for a long time. The recommendation would be to take it forever, and other strategies are a bit more involved. These would likely involve two drugs or three drugs, but those therapies are generally given for 1 to 2 years. So, it depends on the intent of the patient as well as how much time they want to spend in the hospital, including monitoring visits and travel to the center for therapy.

The good thing is that all the therapies, whether you talk about a BTK inhibitor alone, whether you talk about BTK plus BCL2, or BTK/BCL2 plus CD20 antibodies, all these are very effective therapies for patients with CLL.

**What are the key differences in treatment of older patients and younger patients in the upfront setting?**

The age distinction is merging in the context of CLL because, in some sense, older versus younger patients was more relevant when we were treating with chemotherapy. With chemotherapy, you don't want to give intensive chemotherapy to older patients 65 years and up. But now that we're using more targeted therapies, which are non-chemotherapies, I think this distinction between younger and older patients has become less clear, where the same therapies are being used across the board.

Some of the doublet and triplet therapies, which are more involved because they involve frequent visits to the hospital, have some more side effects like neutropenia. That is something which may be more desirable or more appropriate for patients on the younger side. When I say younger side, I mean less than 70 to 75 years of age. On the flip side, patients who are certainly in the older category, above 80 years old, may be okay with just taking a pill every day or twice a day, such as with a BTK inhibitor, and not to be bothered by frequent visits to the clinic for tumor lysis monitoring and whatnot.

So, this distinction of younger versus older patients is kind of merging a bit. But yes, there are a few differences, especially with older patients above 75 years old, where you could rely more on continuous BTK inhibitor therapy if that's what the patient desires versus two or three drugs together for a time-limited approach.

**What were the key points from your presentation at the 2025 Pan Pacific Leukemia Conference?**

The key points from my presentation are that the frontline therapy of CLL is continuing to evolve and that we are increasingly using time-limited approaches for patients with CLL. Again, those will be approaches generally limited to maybe patients who are less than 75 to 80 years of age, but age is just one criterion. You have to look at the patient overall, their performance status, cardiac functions, and comorbidities.

We had some recent clinical trial data from the European Hematology Association Congress from a trial called FLAIR, which was done for patients in their 60s, so not very old patients in the context of CLL. Nonetheless, that trial showed that if you use two drugs together, namely ibrutinib plus venetoclax for 2 to 6 years of therapy, that led to better progression-free and overall survival compared to one drug, namely ibrutinib, given continuously.

That and other trials are making a point that there is something to be said about using time-limited approaches if a patient can tolerate it. I would say most patients with CLL can tolerate it unless they have a single cardiac comorbidity or renal dysfunction.

**What are the main clinical trials or real-world studies helping to guide your treatment choices today?**

In the context of CLL, several randomized clinical trials in the frontline setting have been conducted and reported. One of the main ones, more recently, was the FLAIR trial, which I mentioned, which showed that a combination of ibrutinib plus venetoclax was superior to the ibrutinib monotherapy.

There are other clinical trials in the field. For example, we have a trial called the GLOW trial, which showed that a combination of ibrutinib plus venetoclax was better in terms of both progression-free and overall survival compared to a historical control, chlorambucil plus obinutuzumab.

Then, there are several other ongoing trials, such as the CLL13 and CLL14 trials, and some trials with continuous BTK inhibitors with ibrutinib, acalabrutinib, and zanubrutinib, all of which have been reported in the last 5 years or so. All these trials have come to the conclusion that certainly we should move away from chemotherapy, and we should be doing targeted therapy for our patients.

There are several ongoing randomized clinical trials that have not yet been reported, but we're expecting some data in the next 1 to 2 years. I think these trials will further help streamline or identify the right mix of treatment regimens for patients with CLL.

**What advice do you have for your peers on approaching upfront CLL treatment in patients who are elderly and possibly frail?**

I think this is a group of patients where you will have to first look at what other comorbidities they have besides being frail. For example, you probably will not be thinking of doublets and triplets for patients with certain comorbidities. You may be thinking of just monotherapies because they are frail. In that context, a BTK inhibitor monotherapy such as acalabrutinib or zanubrutinib given continuously, daily, may be an appropriate strategy.

However, if a patient has single cardiac comorbidities, they have atrial fibrillation, and is on anticoagulation, one could argue that maybe a venetoclax-based therapy such as venetoclax plus obinutuzumab may be a safer approach. Similarly, for patients who are frail and on the older side, there are occasional patients where the goal is just for some count control and some symptom control, even as drugs such as single-agent rituximab or single-agent obinutuzumab could be considered.

Most patients these days are receiving an appropriate single-agent BTK inhibitor if they're older and frail, and these second-generation BTK inhibitors are very well tolerated.

**What are some unanswered questions you hope to see clarified in future studies?**

There are several unanswered questions. One, we still believe the treatments have been fantastic. The question for time-neutral approaches has been how long to continue treatment.

Most trials have looked at 1 year of therapy. Now, some ongoing trials are looking at what is called MRD [measurable residual disease]-guided therapy, where you look at the response by MRD at 1 year and 2 years, and depending on that, you can extend treatment. That remains an unanswered question.

The second is whether you need a doublet versus a triplet, especially in younger patients. Which patient groups should we rely on doublets or triplets? That is still evolving, and for patients who have 17P deletion or *TP53* mutation, which are high-risk patients, the recommendation for them will be to use a single-agent BTK inhibitor. However, could you use doublets and triplets in a time-limited approach for these patients, allowing the option of retreatment if they were to progress down the line? Again, some trials are looking into this now.

## Calendar

**October 10-11**
**National Comprehensive Cancer Network (NCCN) Annual Congress: Hematologic Malignancies**
San Diego, CA

**October 17-21**
**2025 European Society for Medical Oncology (ESMO) Congress**
Berlin, Germany

**November 5-9**
**Society for Immunotherapy of Cancer (SITC) 40th Annual Meeting**
National Harbor, MD

**December 6-9**
**67th American Society of Hematology (ASH) Annual Meeting and Exposition**
Orlando, FL

# Editor's Picks

Blood Cancers Today *works with contributors to highlight recent practice-changing articles in different specialties. This month,* ***Matthew Davids, MD,*** *professor of medicine at the Icahn School of Medicine at Mount Sinai, highlights recent research in chronic lymphocytic leukemia in honor of World CLL Day on September 1.*

*Visit bloodcancerstoday.com to stay up to date on the latest news in each area of hematologic oncology.*

Matthew Davids, MD

## CHRONIC LYMPHOCYTIC LEUKEMIA

## Pirtobrutinib Outperforms Investigators' Choice Treatment in Relapsed or Refractory CLL and SLL

*By* ***Melissa Badamo***

Pirtobrutinib improved progression-free survival (PFS) compared with idelalisib plus rituximab or bendamustine plus rituximab in patients with chronic lymphocytic leukemia (CLL) or small lymphocytic leukemia (SLL) pretreated with a covalent Bruton's tyrosine kinase inhibitor, according to the BRUIN CLL-321 trial.

The phase 3, global, open-label, multicenter, randomized study, led by **Jeff Sharman, MD,** of the Willamette Valley Cancer Institute and Research Center, was published in the *Journal of Clinical Oncology*.

A total of 238 patients were randomly assigned 1:1 to receive pirtobrutinib (n=119) at 200 mg once daily or investigator's choice of idelalisib and rituximab (n=82) or bendamustine and rituximab (n=37). Patients had a median of three prior lines of treatment, which the researchers stratified by del(17p) status and prior venetoclax treatment. The median follow-up was 17.2 months (95% CI, 9.7-23).

Pirtobrutinib demonstrated a superior PFS of 14 months, compared with 8.7 months with investigator's choice treatment (hazard ratio [HR], 0.58; 95% CI, 0.38- 0.89; *P*=0.011). The study team replicated the PFS benefit across various subgroups, including patients with a *TP53* mutation or del(17p), unmutated *IGHV*, and those with a complex karyotype. Pirtobrutinib improved PFS regardless of whether patients received prior venetoclax treatment.

Patients in the pirtobrutinib group also had longer event-free survival (14.1 months vs 7.6 months, respectively) and time to next treatment or death (TTNT; 24 months vs 10.9 months, respectively) compared with the investigator's choice groups. However, the 18-month overall survival (OS) rate was comparable among the pirtobrutinib and investigator's choice groups, at 73.4% and 70.8%, respectively. The authors noted that the high crossover rate (76%) confounded their OS assessment.

Most patients experienced any grade treatment-emergent adverse events (TEAEs), specifically 93.1% in the pirtobrutinib group and 98.2% in the investigator's choice groups. Grade 3 or higher TEAEs occurred in 57.7% and 73.4% of patients, respectively. The most common TEAEs were pneumonia, anemia, and neutropenia with pirtobrutinib and diarrhea, pyrexia, fatigue, and nausea with investigator's choice. Fewer patients receiving pirtobrutinib discontinued treatment due to AEs compared with those receiving investigator's choice (17.2% vs 34.9%, respectively).

"This study demonstrated a significant, clinically meaningful improvement in PFS and a more favorable safety profile with pirtobrutinib versus IdelaR/BR [idelalisib plus rituximab or bendamustine plus rituximab] in patients with CLL/SLL," Dr. Sharman and colleagues concluded.

**Why I chose this research:**

*"This trial is significant because it represents the first phase 3 study in CLL to focus exclusively on a post–covalent BTKi–treated population. The trial met its primary end point, as the noncovalent BTKi pirtobrutinib, which currently has an accelerated approval in double exposed CLL, was found to be superior to the control arm of idelalisib plus rituximab or bendamustine plus rituximab with respect to PFS. The excellent safety profile of pirtobrutinib is also one of the major takeaways from the study for me. This work supports a broader use of pirtobrutinib in patients with relapsed CLL and seems likely to lead to full regulatory approval of the drug in this setting."*

## SEQUOIA's 5-Year Outcomes Reinforce Zanubrutinib as Preferred Frontline Therapy for Untreated CLL/SLL

*By* ***Lauren Evoy Davis***

High-risk patients with chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL) experienced a benefit in progression-free survival (PFS) when treated with zanubrutinib compared with bendamustine plus rituximab (BR), according to a 5-year review of the SEQUOIA trial.

The findings were published in the *Journal of Clinical Oncology* and presented at the 2025 American Society of Clinical Oncology (ASCO) Annual Meeting in Chicago. Zanubrutinib is an oral Bruton's tyrosine kinase (BTK) inhibitor, which targets the BTK protein and interferes with B-cell signaling pathways.

This phase 3, open-label trial enrolled 479 patients across North America, Europe, and the Asia-Pacific region. Researchers randomly assigned 241 patients without the 17p deletion to receive zanubrutinib 160 mg orally twice daily in 28-day cycles until disease progression occurred or patients could not tolerate adverse effects. The other arm (n=238) received BR intravenously for six cycles. Both groups had similar demographic characteristics in age range and sex. Sixty-four patients in the zanubrutinib arm and 56 in the BR arm were aged 75 years or older. About half of each group had an unmutated immunoglobulin heavy-chain variable region gene *(IGHV)*, which can affect survival time and prognosis.

The most common adverse event was infection of any grade, experienced by 79.6% of patients in the zanubrutinib arm and 65.6% in the BR arm. Approximately half (52.1%) of patients in the zanubrutinib arm experienced bleeding, although this group had less neutropenia (17.1% vs 56.8%), which is critical in reducing the risk of or mitigating infection. Only 13.2% in the BR arm experienced bleeding. Second primary malignancies occurred in both groups (zanubrutinib, 23.8%; BR, 15%), with skin cancer being the most common (zanubrutinib, 12.9%; BR, 8.8%).

At around the 5-year mark (61.2 months), 77 patients in the zanubrutinib arm dropped out either due to disease progression or intolerance to adverse effects. Neither group reached median overall survival. After 5 years, approximately 85.8% of patients treated with zanubrutinib and 85.0% of those treated with BR were still alive.

Zanubrutinib appears to be a favorable treatment for patients with CLL and SLL who have not been previously treated for hematologic malignancies, the authors concluded. Larger studies will further inform the efficacy and safety of this treatment option.

**Why I chose this research:**

*"This paper represents an important update of the SEQUOIA study, a phase 3 trial randomizing previously untreated patients with CLL and without deletion 17p to continuous treatment with zanubrutinib or a 6-month course of bendamustine and rituximab. A prior report showed a positive outcome with superior PFS of zanubrutinib in the study, but the follow-up at that time was only just over 2 years. This new report has a median follow-up of more than 5 years, and remarkably, the median PFS has not been reached with zanubrutinib. No new safety signals have emerged with longer-term use of the drug. Overall, this study provides confidence that continuous zanubrutinib is an excellent initial therapy for patients with CLL."*

# Acalabrutinib-Venetoclax Combination Prolonged PFS for Patients With Untreated CLL

*By **Lauren Evoy Davis***

Investigators in the AMPLIFY trial evaluated whether a new first-line treatment is more effective than the standard of care for patients with chronic lymphocytic leukemia (CLL).

AMPLIFY is a phase 3, open-label trial that included patients from 133 hospitals in 27 countries who had an Eastern Cooperative Oncology Group (ECOG) performance score of 0 to 2 and did not have the 17p deletion or *TP53* mutation. The investigators randomly assigned patients in a 1:1:1 ratio to receive acalabrutinib-venetoclax (A-V), acalabrutinib-venetoclax-obinutuzumab (A-V-O), or chemoimmunotherapy with investigator's choice of fludarabine-cyclophosphamide-rituximab or bendamustine-rituximab. The treatments were given in 28-day cycles.

Of the 867 patients in the study, 291 received A-V, 286 received A-V-O, and 290 received chemoimmunotherapy (143 received fludarabine-cyclophosphamide-rituximab and 147 received bendamustine-rituximab). The median age of patients was 61 years, and 64.5% of patients were male. Of the total study population, 58.6% had an unmutated immunoglobulin heavy-chain variable region gene *(IGHV)*.

The primary end point was progression-free survival (PFS). The researchers concluded that the A-V combination with or without obinutuzumab significantly prolonged PFS more than chemoimmunotherapy. At 36 months, the PFS was 76.5%, 83.1%, and 66.5% for the A-V group, the A-V-O group, and the chemoimmunotherapy group, respectively. Overall survival (OS) at 36 months was 94.1%, 87.7%, and 85.9% for the A-V, A-V-O, and chemoimmunotherapy groups, respectively.

An independent blinded committee evaluated safety and efficacy by testing blood and bone marrow throughout the trial. Adverse effects included neutropenia, which occurred in 32.3%, 46.1%, and 43.2% of the A-V, A-V-O, and chemoimmunotherapy groups, respectively. Some patients had side effects that caused them to stop taking acalabrutinib, about 7.6% in the A-V group and 13.7% in the A-V-O group. Side effects also led to lowering the dose of at least one study drug in 14.1% of patients in the A-V group, 20.8% in the A-V-O group, and 11.2% in the chemoimmunotherapy group. This trial occurred during the COVID-19 pandemic, and 56 deaths were due to the virus: 10 in the A-V group, 25 in the A-V-O group, and 21 in the chemoimmunotherapy group.

Chemoimmunotherapy was once the standard of care for CLL. This study highlights a shift toward targeted, time-limited regimens in modern CLL therapy.

**Why I chose this research:**

*"This phase 2, investigator-initiated trial evaluated the acalabrutinib-venetoclax-obinutuzumab triplet as initial therapy for a broad population of patients with CLL. The study was enriched for patients with high genetic risk disease, defined by* TP53 *aberration, which comprised nearly two-thirds of the study population. This MRD-guided regimen of 15 to 24 cycles for most patients led to high rates of undetectable MRD in the bone marrow, with relatively modest toxicity. The 4-year PFS of 70% in patients with the* TP53 *aberration makes this a particularly appealing regimen to consider for patients with high-risk disease who desire time-limited therapy. This study led to an NCCN listing as a frontline therapy option for that population."*

# Vinay Prasad Resigns from FDA Following Recent Controversies

*By **Melissa Badamo***

**Vinay Prasad, MD, MPH,** has stepped down as director of the FDA's Center for Biologic Evaluation and Research (CBER), less than 3 months after he was appointed in May 2025 by FDA Commissioner **Martin Makary, MD, MPH.** Dr. Prasad, a hematologist-oncologist, was also named as the agency's chief medical and scientific officer in June.

Anonymous sources told *The Associated Press* that his departure was driven by several recent controversies.[1] Dr. Prasad faced backlash from right-wing journalist and activist Laura Loomer, who described Dr. Prasad as a "progressive leftist saboteur undermining President Trump's FDA" in a July 20 article.[2] Loomer wrote that Dr. Prasad's policy views—including his support for single-payer healthcare—oppose the beliefs and priorities of the Trump Administration, and urged for his removal from the FDA.[2]


Vinay Prasad, MD, MPH

"Dr. Prasad did not want to be a distraction to the great work of the FDA in the Trump administration and has decided to return to California and spend more time with his family," a spokesperson from the Department of Health and Human Services said in a statement to STAT News.[3] "We thank him for his service and the many important reforms he was able to achieve in his time at FDA."

Dr. Prasad also faced controversy in regard to safety concerns around Sarepta Therapeutics' gene therapy for Duchenne muscular dystrophy.[1] On July 25, the FDA requested and received voluntary suspension of distribution of the gene therapy after the death of an 8-year-old boy. A subsequent investigation determined that the death was unrelated to the gene therapy.[4,5]

In his role as CBER director, Dr. Prasad oversaw the "FDA's work regulating biological products for human use under federal laws," according to the agency's website. The CBER is responsible for ensuring that biological products are safe, effective, and available to patients, while informing the public about their safe and appropriate use.[6]

Before his FDA appointment, Dr. Prasad served as professor in the Department of Epidemiology and Biostatistics at the University of California at San Francisco (UCSF). He completed a fellowship in cancer prevention at the National Cancer Institute and a fellowship in oncology at the National Institutes of Health. His research has focused on medical evidence, clinical decision-making, health policy, and cancer drug pricing, according to his faculty profile at UCSF.[7]

"He did a tremendous amount of implementation of new policies in the time he was at the FDA," Dr. Makary told CNBC in response to Dr. Prasad's departure.[8] "I think the guy's a genius. He's published 550 peer-reviewed studies in his career…he gave us some of his time. He's got family in California; the commute was brutal. When he saw some of these smear pieces, he didn't want to be a distraction."

Dr. Prasad also raised criticism during the COVID-19 pandemic for his alleged "anti-vax" views, a label he denied during an FDA Direct conversation with Dr. Makary,[9] *Blood Cancers Today* previously reported. Rather, he considers whether clinical evidence supports vaccination and described himself as "a longstanding believer in evidence-based medicine" during a CBER Town Hall meeting on May 20, where he outlined the FDA's evidence-based strategy for COVID vaccination.[10]

Dr. Prasad announced that based on prior immunologic end points, the FDA will consider approval for patients 65 and older and for those at severe risk for COVID-19. In addition, the FDA asks companies to conduct a randomized trial testing their product against a placebo in patients aged 50 to 64.[10]

"These data are vital to inform an updated risk-benefit analysis that's fit for 2025," he said during the meeting.[10]

Drs. Prasad and Makary have not responded to *Blood Cancers Today's* request for comment.

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