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MORE IS MORE

Quadruplets have gained a foothold as standard in newly diagnosed multiple myeloma.

With expert opinions from:
Nisha Joseph, MD, Amrita Krishnan, MD, *and* **Timothy Schmidt, MD**

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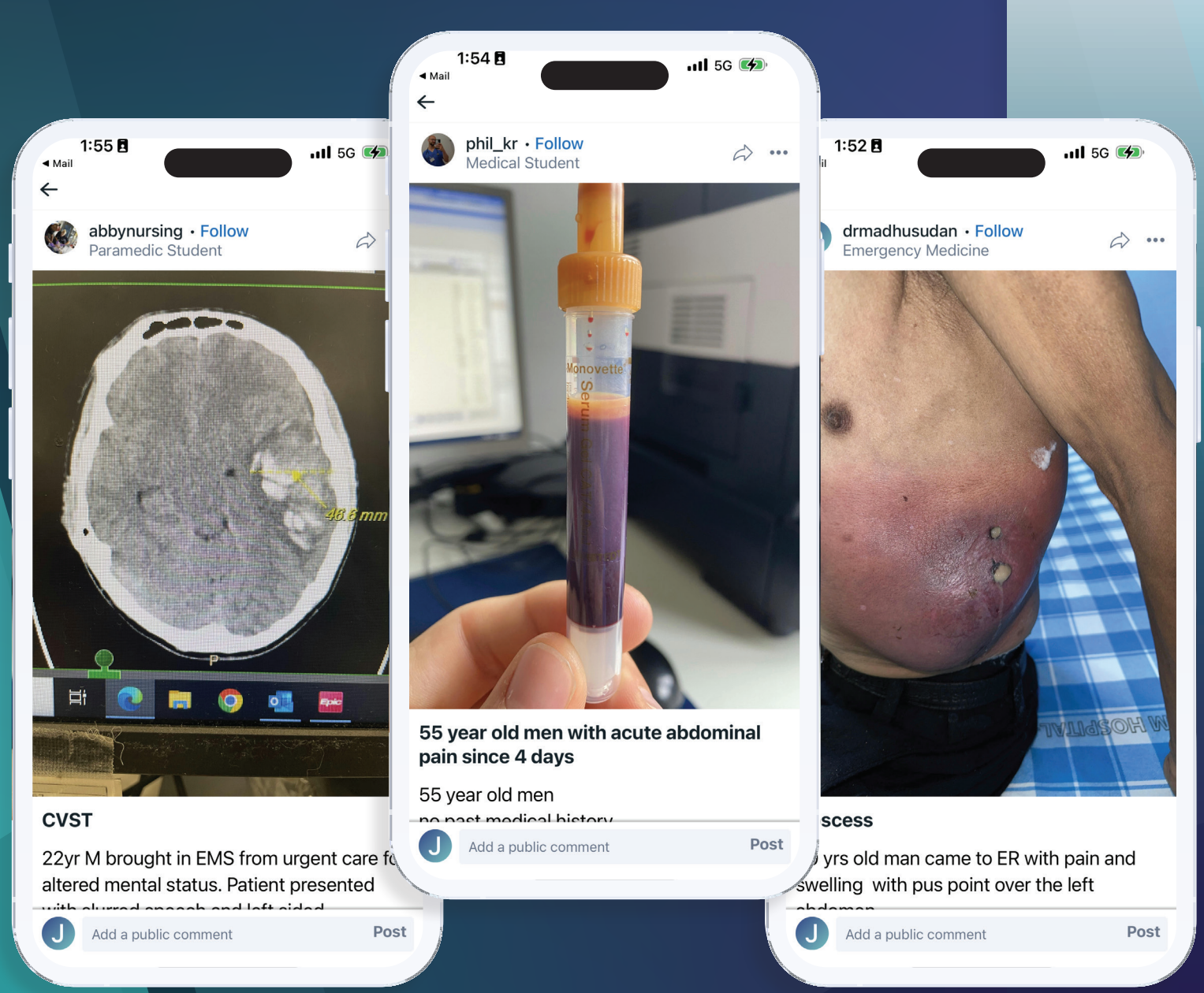

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March 7–9
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May 5–6
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May 23–25
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Get to Know

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

Craig Cole, MD

Craig Cole, MD, of the Karmanos Cancer Center, spoke with *Blood Cancers Today* about the family tragedies that made him an oncologist, his commitment to mitigating disparities for Black patients with myeloma, and the aquatic hobby most people would be surprised to learn.

*By **Melissa Badamo***

Where did you grow up, and when did you know you wanted to be a hematologist oncologist?
I grew up in Detroit, Michigan. I wasn't planning on being a clinician. I love astronomy and biology, so my life plan was to become an astrobiologist and go to Mars.

When I was in high school, my dad had metastatic colon cancer. He was on chemotherapy, which was rudimentary chemotherapy back in the 1980s. He was incredibly sick. He died when I was a junior in high school. In quick order, my grandfather had prostate cancer and died when I was a freshman in college at Michigan State. My grandmother, who was a retired licensed practical nurse, took care of both my dad and my grandfather. She said, "By the way, I've had colon cancer this whole time. I didn't get treated because I was taking care of your father and your grandfather. So now I'm going to go in for treatment." Of course, we were devastated.

Then, I went to Michigan State to study astrobiology. Everything was fine and dandy. I talked to her twice a week and she kept saying, "I'm fine, I'm fine." Halfway through my freshman year, she wanted me to take her to her oncology appointment. When I got to her house in Detroit, she was super sick. It took us half an hour to get her down the stairs because she was in so much pain.

When I was sitting in the office with her, the oncologist barges in and says, "Your cancer is worse, and we need to change chemotherapy." My grandmother wanted to go on hospice. Her doctor turned around, called her an idiot, and said it was a dumb decision. She said, "Why would you do something stupid like this? I'm not going to help you." She kept throwing insults at her, then walked out and slammed the door. I was in shock.

Getting her back in the car, my grandmother grabs my shoulder and says, "I think you can do a better job at being a doctor." I said, "I think you're right."

I went back to Michigan State and changed my major to physiology premed. That's how I wanted to be a clinician. I saw how rude doctors can be to their patients, and I saw how important patient empowerment is. My grandmother was empowered enough to tell her doctor, "No, I'm not going to go along with what you want to do." That became the two flags I carry to this day when I practice and what I teach about being a good physician. It's about listening to your patient and empowering your patient.

Were there any mentors who shaped your career path?
When I was a resident, I went to the American Society of Hematology (ASH) Annual Meeting & Exposition for the first time in 1999. The plenary session was on imatinib for chronic myeloid leukemia (CML).

I knew about CML and thought about doing transplant. I knew that the mortality of CML with transplant was 25%. I sat in the audience as they went through the history of CML. I said to myself, "Oh my goodness, this is the same old stuff. It's all known." Then, **Brian Druker, MD,** gets up and talks about imatinib having a response rate of 100%. I remember thinking, "This is the turning point in all of oncology."

Dr. Druker understood the science of CML. He designed a drug that fit the pathophysiology and had responses higher than any blood pressure medication, any cholesterol medication. There was no precedent for that in oncology, and he did it because he understood the science of the disease, not because he used some fancy chemotherapy regimen. I remember my dad, grandfather, and grandmother getting all this blunt chemotherapy, which had no science behind it.

I walked out of the plenary session saying, "I want to be a physician scientist. I want to do what he did and understand how the disease works and try to figure out a cure."

I also met **Robert Kyle, MD,** who did a lecture at the University of Michigan. He is the Brian Druker of myeloma. He really understands this disease and its history. He recommended that I work with **Ken Anderson, MD,** at the Dana-Farber Cancer Institute. So, I went to Dana-Farber for a year and worked in the lab with Ken Anderson and **Klaus Podar, MD, MSc, PhD,** to get an understanding of myeloma biology. I was there when lenalidomide and bortezomib came out. I was in the lab and at ground zero for a lot of that stuff, and that really hooked me.

Can you talk about your current clinical research?
My career took a couple of different turns. One of the biggest problems is how difficult it is to become a clinical trialist and do academics when you have tremendous medical debt.

After I finished my fellowship, I went to Gundersen Lutheran, where I could do research as a hematologist but still work at paying off my medical school debt. I worked there for five to six years. Then, I came back to the University of Michigan and continued to get scholarships and grants. I was full course clinical trials and myeloma therapeutics and doing early phase and middle phase clinical trials.

Then, I noticed something as I kept doing talks for patients with myeloma. The first slide was always patient demographics and how many people in the United States have myeloma. That instance is twice as much in people of African descent than in Caucasians. But when I looked out in the audience, everyone was White. I said, "Wait a minute. There's something wrong here. How is this disease twice as common in Blacks, but every audience I talk to is all White? I'm the only Black person in the room, and I don't have myeloma."

"In the next 10 years, I think that we will cure myeloma. The real challenge is that I don't consider a cure for the disease until everybody has access to that cure."

Then I got back to the University of Michigan, and I'm looking at the patients I have in clinic, and everyone's White. No Hispanics, no Asians, no Blacks. I started to look at the disparities in myeloma in the mid-2000s and 2010s. Between 2010 and 2017, the average number of Black people enrolled in myeloma

clinical trials was 5%, and the percentage of myeloma patients in the United States that are Black is 20%.

I kept advocating and saying, "We need to do something about this." It didn't get much traction up until the past six to seven years. I began to take this three-pronged approach: (1) Make my colleagues in myeloma research aware of these disparities. (2) Push to enroll equally on clinical trials to make myeloma patients—especially Black myeloma patients—aware of these disparities. (3) Outreach to the community and to communities of color to make them aware of the disease itself.

There's so much data showing how people of color are diagnosed late and treated late. They have more disease complications because of the delays in diagnosis between people of color and Caucasians in the United States.

I still put patients on clinical trials, but my career has come full circle. It started with my grandmother and patient empowerment. It's currently back to where it started to empower patients—especially patients of different socioeconomic status, patients of color, and patients of different age groups—to be enrolled in clinical trials and to be empowered to talk to their doctors to get the best available therapy for myeloma. My career is still in myeloma therapeutics, but a large part of my life is dedicated to trying to eliminate these disparities in care.

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

In the next 10 years, I think that we will cure myeloma. There are anecdotal reports of patients having long-term remissions with myeloma. The technology we have with bispecifics, chimeric antigen receptor T-cell therapy, T-cell engagement, and novel therapeutics will cure the disease for some patients.

The real challenge is that I don't consider a cure for the disease until everybody has access to that cure. It doesn't make any sense that you cure myeloma for the richest people in the United States that have access to the drugs. You cure maybe 2-5% of the population when you only have that treatment accessible to the wealthy and to the patients who are most well connected to an academic center. The people I worry about not getting cured are the people in the inner cities, the people in rural populations, the elderly, the poor, the uninsured, and the people in countries that still don't have access to a lot of these drugs.

"When people talk about unmet needs in myeloma, they generally talk about high-risk myeloma and cytogenetically mutated myeloma. Nobody talks about the people who we don't enroll in clinical trials. That is the true unmet need."

When people talk about unmet needs in myeloma, they generally talk about high-risk myeloma and cytogenetically mutated myeloma. Nobody talks about the people who we don't enroll in clinical trials. That is the true unmet need. The elderly, the people of color, and the people in countries around the world that don't have access to these drugs.

Do you have any hobbies outside of work that most people would be surprised to learn?

I collect Star Wars stuff. Everybody knows about my Star Wars obsession, but a lot of people don't know I have a 150-gallon saltwater reef fish tank. There's a serpent starfish in the tank that's about 14 years old. He's huge, and I have to feed him crab meat by hand.

I also play guitar. That's my own gig I do at home. I have a 12-string acoustic guitar, and I play classic rock stuff.

FEATURES

In Focus

Blood Cancers Today *takes an in-depth look at hot topics in hematologic oncology*

MORE IS MORE

Quadruplets have gained a foothold as standard in newly diagnosed multiple myeloma.

By Leah Lawrence

Blood Cancers Today **recently spoke with several clinicians familiar with the use of quadruplet regimens to find out more about how the new approach is changing the treatment landscape.**

Historical research on the treatment of newly diagnosed multiple myeloma (MM) has shown that "more tends to be better," according to **Nisha Joseph, MD,** associate professor in the Department of Hematology and Medical Oncology at Emory University School of Medicine.

"If we hit myeloma cells from different angles using different mechanisms of action," Dr. Joseph said, "it often results in a better depth of response."

This approach initially started with the use of doublets—typically immunomodulatory drugs—in combination with a steroid. The approach evolved to triplet regimens, which added proteasome inhibitors (PIs) to the mix.

In 2024, the National Comprehensive Cancer Network Clinical Practice Guidelines for MM included a quadruplet regimen—adding an anti-CD38 monoclonal antibody—as a category 1 recommendation and a preferred first-line option for patients with transplant-eligible or transplant-ineligible newly diagnosed MM.[1]

Building on Therapy

"MM is a clonally heterogenic type of disease," explained **Amrita Krishnan, MD,** director of the Judy and Bernard Briskin Multiple Myeloma Center at City of Hope, Duarte, California. "The thought process is that if you use different drugs, you may be able to target different clones with varying sensitivity to each class of agent."

"In addition to their varying targets, the other reason these classes of drugs seem to work well

together is that they have non-overlapping toxicities … for the most part," Dr. Krishnan said.

One of the first trials to tackle the question of quadruplet regimens was the phase II GRIFFIN trial. GRIFFIN tested consolidation with lenalidomide, bortezomib, and dexamethasone (RVd) with or without daratumumab followed by maintenance with lenalidomide with or without daratumumab in transplant-eligible newly diagnosed MM.[2] At the end of post-transplant consolidation, stringent complete response rate favored daratumumab (42.4% vs 32.0%; *P*=.068), and with a longer median follow-up of about 22 months, it was significantly better with daratumumab (62.6% vs 45.4%; *P*=.0177). Measurable residual disease (MRD) negativity was also significantly improved.

These data were further confirmed by results from two phase III trials. The CASSIOPEIA trial, which tested bortezomib, thalidomide, and dexamethasone (VTd) with or without daratumumab before and after transplantation, showed improved depth of response and progression-free survival (PFS) with daratumumab.[3]

Most recently, the PERSEUS trial comparing VRd with or without subcutaneous daratumumab in transplant-eligible patients again confirmed the significant PFS benefit of adding daratumumab.[4] These results led to the July 2024 FDA approval of the drug combination for transplant-eligible patients.

Uptake in Transplant-Eligible Population

"Following PERSEUS, I think a quadruplet regimen with RVd and an anti-CD-38 monoclonal antibody should be the standard of care for transplant-eligible patients," Dr. Joseph said. "We have been using daratumumab-RVd since 2018."

In fact, Dr. Joseph and colleagues recently published data from 326 patients at their institution who received induction therapy with daratumumab plus RVd with intent to transplant. The data showed a PFS benefit favoring the quadruplet regimens among standard- and high-risk patients; the 2-year PFS was 93% with daratumumab/RVd compared with 82% for RVd alone (*P*<.001). The 2-year overall survival was 94% with daratumumab/RVd compared with 91% without (*P*<.034). There was also improved depth of response favoring the addition of daratumumab.[5]

"Clinical trial populations aren't always representative of the real world," Dr. Joseph said. "Here we are seeing the benefit translate to a real-world setting; for that reason, we think it is the standard of care in this population, and we have been using it for a long time."

Timothy Schmidt, MD, assistant professor of Hematology, Medical Oncology and Palliative Care at University of Wisconsin School of Medicine and Public Health, agreed that the use of quadruplet regimens in the transplant-eligible population is being broadly adopted, at least across the US.

"My vantage point as a myeloma specialist at an academic center may be different from other regions," Dr. Schmidt said. "Here in the Midwest, I think perhaps there was a bit of a later uptake of quadruplet regimens compared to what was seen on the coasts, but over the last two to three years, there has been increasing utilization of quadruplet regimens in academic centers as well as in the community."

Transplant-Ineligible Population

Transplant-ineligible patients are typically those who are older, frail, have poor performance status, or have high comorbidity burdens.[6] However, there are now multiple phase III trials supporting the use of quadruplet regimens in this population as well.

Results of GEM2017FIT, presented at the 65th American Society of Hematology (ASH) Annual Meeting & Exposition, compared two experimental consolidation arms—carfilzomib, lenalidomide, and dexamethasone (KRd) with and without daratumumab—against bortezomib-melphalan and prednisone (VMP) followed by lenalidomide and dexamethasone (Rd) in transplant-ineligible patients. MRD negativity was highest in the daratumumab-KRd arm at 79%.[7]

The phase III CEPHEUS trial showed that daratumumab-VRd significantly improved MRD negativity, PFS, and complete response rate compared with VRd alone in patients "for whom transplant was not planned as initial therapy."[8]

"If we hit myeloma cells from different angles using different mechanisms of action, it often results in a better depth of response." *—Nisha Joseph, MD*

Finally, the international IMROZ trial randomly assigned 446 patients 3:2 to VRd with or without isatuximab. The estimated 5-year PFS was 63.2% with isatuximab-VRd, compared with 45.2% with VRd alone, a 40% reduction in the risk for progression or death with the quadruplet regimen (98.5% CI, 0.41-0.88; *P*<.001). Significantly more patients assigned to receive isatuximab achieved MRD negativity as well (55.5% vs 40.9%; *P*=.003).[9]

"The biggest difference between the regimens in these trials is the percentage of patients achieving not just a very good partial response but a complete response and MRD negativity," Dr. Schmidt said. "We are seeing significantly higher rates in the groups of patients treated with a quadruplet regimen."

Dr. Schmidt acknowledged that these studies can be hard to interpret as a group because of differences in ongoing use of one drug versus two drugs, as well as other differences; but overall, they indicate that patients treated with quadruplet regimens have not just better depth of response but also durability of response manifested as PFS.

Unlike the uptake of quadruplet regimens in transplant-eligible patients, the uptake in the transplant-ineligible population is more complicated, Dr. Krishnan and the others said.

"The uptake in the nontransplant–eligible population is likely still not over 50%," Dr. Krishnan said. "Use of quadruplet regimens in the transplant-ineligible population is a more nuanced discussion that has to be based on a geriatric assessment and a risk-benefit discussion with the patient."

Dr. Joseph agreed that quadruplet regimens are not yet the standard for all patients who are transplant ineligible, particularly not in community practices.

"I have gotten a lot of questions about it, but it is not yet routine," Dr. Joseph said. "People are doing it in select patients, but not for everybody."

Dr. Joseph has also discussed the use of a daratumumab-RVd "light" approach with community oncologists. This approach involves reducing the dose of the drugs to make the regimen more tolerable. This could mean reducing the dose of lenalidomide or bortezomib to only once a week or reducing the dose of steroid.

More Drugs, More Toxicities

Dose reduction may be necessary for some patients because there is always the concern that adding more drugs will result in more toxicity, Dr. Schmidt said.

"Myeloma is a disease that primarily affects older patients—with a median age at diagnosis of 70—and that could prove to be difficult from a tolerability standpoint," he said.

It was for this reason that quadruplet regimens were first tested in the transplant-eligible population.

"What we found was that the addition of the anti-CD38 monoclonal antibody to the backbone treatment didn't result in much more toxicity," Dr. Schmidt said. "Patients didn't feel that different, and, in fact, when studies reported on quality of life, it had improved."

A meta-analysis of quadruplet regimens in the treatment of newly diagnosed MM found "light to no difference" in the rate of serious adverse events and a "slight increase" in the rates of grade 3 or 4 infections (relative risk, 1.22; 95% CI, 1.07-1.39) with quadruplet compared with triplet regimens. Quadruplets also appeared to be associated with increased risk for grade 3 to 4 neutropenia (risk ratio [RR], 1.81; 95% CI, 1.42-2.31) and grade 3 to 4 thrombocytopenia (RR, 1.30; 95% CI, 1.07-1.58). The authors also noted that "additional studies may be needed particularly among frail older adults."[10]

"Daratumumab is an injection, so there may be injection site reactions," Dr. Joseph said. "There is also a slightly increased rate of infections with daratumumab, but otherwise, the toxicities we see with the quadruplet tend to be more associated with the other agents in the regimen."

In fact, if clinicians were going to limit treatment to a triplet regimen for some patients, one question that has been asked is whether the drug class to be eliminated should be the PI and not the newcomer anti-CD38 monoclonal antibody.

Bortezomib is associated with a higher risk for falls, Dr. Schmidt said, which can be devastating for older patients. An alternative PI, carfilzomib, carries an increased risk for cardiovascular side effects.

The phase III BENEFIT trial was designed to examine the question of eliminating the PI. The trial randomly assigned 270 transplant-ineligible patients to treatment with isatuximab lenalidomide and dexamethasone with (Isa-VRd) and without (Isa-Rd) weekly bortezomib.[11] The primary endpoint of MRD negativity at 18 months was reported in 26% of patients assigned Isa-Rd compared with 53% assigned the quadruplet.

"In BENEFIT, the arm with bortezomib had more neuropathy, which was not a surprise," Dr. Krishnan said. "That was, in part, why they used weekly bortezomib."

Nuances

As with any clinical research, there are nuances to interpreting the data from the trials examining use of quadruplet regimens.

For example, in the IMROZ trial, Black patients were underrepresented, the trial only enrolled patients aged up to 80 years, and the majority of patients had an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1.[9] The CEPHEUS trial allowed only patients with a frailty score of 0 or 1 as classified by the International Myeloma Working Group (IMWG) frailty scale.[12]

Exclusion of older adults or frail patients means that use of quadruplet regimens in these populations is left to the discretion of the clinician. The IMWG frailty score is recommended to assess whether a patient is fit or frail, but Dr. Joseph said it is not often used in clinical practice.

"We often use clinical gestalt or experience," Dr. Joseph said. "We discuss functional status, if the patient can climb stairs, can walk a couple of miles, if their comorbidities are managed, if they have a history of heart disease."

There has also been some research looking into whether transplant is still necessary for transplant-eligible patients who achieve deep and durable responses to therapy.

"If you ask this question to 10 MM specialists who are also transplanters, you will get a variety of answers," Dr. Schmidt said.

"We have been asking this question for 20 years with the introduction of each new class of drugs," he said. "The studies have been done over and over again, and the answer remains the same, even with the addition of new drugs, if you incorporate autotransplant you are going to have a better PFS, better rates of MRD negativity, and depth of response."

However, Dr. Schmidt admitted that the field may be closer to the point at which the use of transplant could be more tailored, when studies could look at deferring transplant for patients with standard-risk disease who achieve MRD negativity after initial therapy.

Another question being asked is whether the use of chimeric antigen receptor (CAR) T-cell therapy will replace stem cell transplant. The answer is still unknown, according to Dr. Joseph. In the ongoing phase III EMagine/CARTITUDE-6 trial, daratumumab-VRd followed by ciltacabtagene autoleucel (cilta-cel) followed by lenalidomide will be compared with daratumumab-VRd followed by autotransplant, daratumumab-VRd, and lenalidomide in the treatment of newly diagnosed MM.[13]

In addition to these nuances, there are also inherent challenges associated with administering (or receiving) a quadruplet regimen.

"One challenge might include logistics of adding more drugs," Dr. Schmidt said. "That said, adding the anti-CD38 antibody doesn't add any extra visits really, maybe one or two over the course of the first six months."

When quadruplets were first incorporated into treatment algorithms, Dr. Joseph noted that insurance coverage could sometimes be a challenge.

"Now though, I see about 30 to 40 new patients with MM per year, and I can think of one or two examples where insurance came back with questions," Dr. Schmidt said. "It is becoming more of a nonfactor, especially as more long-term data back up their use."

Finally, although cost is something that clinicians don't consider when making day-to-day decisions in the clinic, it can't be entirely ignored.

In a piece published before the widespread use of these regimens, **Vincent Rajkumar, MD,** wrote that the addition of daratumumab would create quadruplet regimens "that could cost in excess of $300,000 to $500,000 per year."[14]

A more recent study looking at data from GRIFFIN and CASSIOPEIA estimated that first-line daratumumab used with RVd or VTd was cost-effective for transplant-eligible MM when considering improved outcomes.[15] However, the long-awaited availability of a generic form of lenalidomide has not turned out to be the cost-saving event anticipated because the generic form is "volume-limited" until 2026.[16]

"There is no question that by adding drugs we are increasing the cost of care," Dr. Schmidt said. "We need to find ways to reduce those costs either by limiting how long patients are treated or bringing down the cost of drugs by other measures."

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Regulatory Actions

Recent therapy approvals, updates, and clinical trial results in the field of hematologic oncology

FDA Approves First Menin Inhibitor for Relapsed, Refractory Acute Leukemia With KMT2A Translocation

*By **Melissa Badamo***

Revumenib (Revuforj®) was approved by the US Food and Drug Administration (FDA) as the first menin inhibitor to treat adult and pediatric patients with relapsed or refractory acute leukemia with a *KMT2A* translocation, according to a press release from Syndax, the manufacturer of the drug. Revumenib will be available for order in the United States beginning November 2024.

The approval is based on results of the phase I/II AUGMENT-101 trial, where revumenib achieved a complete remission (CR) plus CR with partial hematologic recovery (CRh) rate (CR+CRh) of 21% (95% CI, 13.8-30.3%); a median duration of CR+CRh of 6.4 months (95% CI, 2.7-not estimable); and a median time to CR or CRh of 1.9 months (0.9-5.6 months). Twenty-three percent of patients proceeded to hematopoietic stem cell transplantation following treatment.

Due to adverse events (AEs), 10% of patients had dose reductions and 12% discontinued treatment. Common AEs included hemorrhage, nausea, musculoskeletal pain, infection, febrile neutropenia, diarrhea, and differentiation syndrome.

"FDA approval of the first menin inhibitor is a major breakthrough for patients with [relapsed or refractory] acute leukemia with a *KMT2A* translocation, a genetic alteration associated with a very poor prognosis," **Ghayas C. Issa, MD,** an Associate Professor of Leukemia at The University of Texas MD Anderson Cancer Center and study investigator, said in the press release.

He concluded, "The significant clinical benefit and robust efficacy seen with [revumenib] represents a substantial improvement over what has been historically observed in these patients with previously available therapies and has the potential to be an important new treatment option for patients."

Reference: Syndax Announces FDA Approval of Revuforj® (revumenib), the First and Only Menin Inhibitor to Treat Adult and Pediatric Patients with Relapsed or Refractory Acute Leukemia with a KMT2A Translocation. November 15, 2024. Accessed December 19, 2024. https://ir.syndax.com/news-releases/news-release-details/syndax-announces-fda-approval-revuforjr-revumenib-first-and-only

Obe-cel Receives FDA Approval for Relapsed, Refractory B-ALL

*By **Melissa Badamo***

Obecabtagene autoleucel (obe-cel) received FDA approval for the treatment of adults with relapsed or refractory B-cell acute lymphoblastic leukemia (B-ALL), according to a press release from Autolus Therapeutics, the manufacturer of the chimeric antigen receptor T-cell therapy.

The approval is based on results of the FELIX trial, which evaluated the safety and efficacy of obe-cel. In 65 efficacy-evaluable patients, 51% achieved complete remission (CR) at any time and 12% achieved CR with incomplete hematologic recovery at any time. Forty-two percent achieved CR at three months, and the median duration of remission was 14.1 months.

Grade 3 cytokine release syndrome occurred in 3% of patients; there were no Grade 4 or 5 events. Grade 3 or higher immune effector cell-associated neurotoxicity syndrome occurred in 7% of patients.

"Adult ALL is an extremely aggressive cancer, and there is a high unmet medical need that exists in the treatment of patients with this disease once they relapse, where historically they suffer from poor outcomes," **Elias Jabbour, MD,** a Professor in the Department of Leukemia at The University of Texas MD Anderson Cancer Center and lead investigator of the FELIX study, said in the press release. "This milestone approval, based on the demonstrated clinical benefit of [obe-cel], brings new hope for adult patients with relapsed or refractory B-ALL."

Reference: Autolus Therapeutics Announces FDA Approval of AUCATZYL® (obecabtagene autoleucel – obe-cel) for adults with relapsed/refractory B-cell acute lymphoblastic leukemia (r/r B-ALL). November 8, 2024. Accessed November 21, 2024. https://autolus.gcs-web.com/news-releases/news-release-details/autolus-therapeutics-announces-fda-approval-aucatzylr

Remestemcel-L Now an FDA Approved Treatment for Pediatric SR-aGVHD

*By **Nichole Tucker***

The FDA has granted approval for remestemcel-L-rknd (Ryoncil) for the treatment of pediatric patients aged two months and older with steroid-refractory acute graft versus host disease (SR-aGVHD).[1]

Approval was granted by the FDA on the basis of findings from the phase III MSB-GVHD001 clinical trial (NCT02336230), in which remestemcel-L showed robust efficacy along with tolerable safety.

The study included 54 pediatric patients with SR-aGVHD who had undergone allogeneic hematopoietic stem cell transplantation and whose disease was grade B to D. The patients received remestemcel-L at 2×10^6 cells/kg twice weekly for four weeks.

The overall response rate observed was 70% (95% CI, 56.4-82.0) at day 28, and the complete response rate was 30% (95% CI, 18.0-43.6). Partial responses to remestemcel-L were observed in 41% of patients (95% CI, 27.6-55.0). In terms of response durability, the time from response at day 28 to events of disease progression, new systemic therapy for aGVHD, or death of any cause was 54 days (range, 7–159+ days).[1,2]

The overall survival rate was 74.1% at day 100 and 68.5% at day 180. Furthermore, the study showed that response was predictive of improvement in overall survival (OS). Survival was determined to be significantly improved among patients who responded to therapy by day 28 (86.8% OS rate) compared with those who did not respond by day 100 (47.1% OS rate; $P = .0001$). The same was shown through day 180 with a 78.9% OS among responders versus 43.8% among nonresponders ($P = .0003$).[2]

In terms of safety, the most common nonlaboratory adverse reactions were viral infectious disorders, bacterial infectious disorders, infection with an unspecified pathogen, pyrexia, hemorrhage, edema, abdominal pain, and hypertension. These adverse reactions were seen in 20% or more of patients treated with remestemcel-L.[1]

Based on study data and the priority review of the biologic license application for remestemcel-L, the FDA-recommended dose is 2×10^6 mesenchymal stromal cells /kg body weight per intravenous infusion. Remestemcel-L is to be administered twice a week for four consecutive weeks for a total of eight infusions. Infusions must be administered three days apart and may be continued based on response at 28 days after the initial infusion.

References

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2. Kurtzberg J, Abdel-Azim H, Carpenter P, et al. A phase 3, single-arm, prospective study of remestemcel-l, ex vivo culture-expanded adult human mesenchymal stromal cells for the treatment of pediatric patients who failed to respond to steroid treatment for acute graft-versus-host disease. Biol Blood Marrow Transplant. 2020;26(5):845-854. doi: 10.1016/j.bbmt.2020.01.018

FDA Grants Fast Track Designation to LYT-200 for AML

*By **Melissa Badamo***

LYT-200 has received Fast Track designation from the FDA for the treatment of AML, according to a press release from PureTech, the developer of the drug.

This designation is expected to streamline the development and accelerate the assessment of LYT-200, a first-in-class anti-galectin-9 monoclonal antibody.[1] LYT-200 previously received Orphan Drug designation in March 2024.

A phase I trial of LYT-200 monotherapy and in combination with venetoclax and hypomethylating agents for patients with AML and high-risk myelodysplastic syndromes was presented at the 66th American Society of Hematology Annual Meeting & Exposition by **Amir Fathi, MD,** of Massachusetts General Hospital.

Clinical benefit with LYT-200 was observed in 100% of patients in the single-agent cohort and 88% of patients in the combination cohort. No dose-limiting toxicities were observed at doses ranging from 2 mg/kg to 16 mg/kg in the single-agent cohort and from 4 mg/kg to 12 mg/kg in the combination cohort.[2]

"LYT-200 is an intriguing novel agent, targeting galectin 9, and in this way harnessing the power of the immune system in attacking malignancy," Dr. Fathi told *Blood Cancers Today*. "Based on early results from clinical study, it appears that there is some promising activity in patients with myeloid malignancies. This should be studied further and rigorously to identify the patients who may benefit."

A second phase I/II trial is evaluating the drug in advanced and metastatic solid tumors.

References

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2. Fathi AT, Filipovic A, Maher K, et al. A phase I dose escalation and expansion trial of Lyt-200 (a first-in-class anti-galectin-9 antibody) alone and in combination with venetoclax/HMA in relapsed/refractory AML/MDS. Abstract #1499. Presented at the 66th American Society of Hematology Annual Meeting & Exposition; December 7-10, 2024; San Diego, California.

FDA Speeds Up Develop of Relmacabtagene Autoleucel for Relapsed, Refractory LBCL

*By **Nichole Tucker***

The FDA has granted breakthrough therapy designation (BTD) for relmacabtagene autoleucel (relma-cel) injection (Carteyva), a second-line treatment intended for adult patients with relapsed or refractory large B-cell lymphoma (LBCL). Relma-cel is an anti-CD19 chimeric antigen receptor (CAR) T-cell product.[1]

"These results appear excellent and this CAR T cell construct, tested and manufactured in China, offers another potential option for patients with LBCL," **Leo I. Gordon, MD,** Abby and John Friend Professor of Cancer Research, professor in Medicine, co-director, Hematologic Malignancies Program, Division of Hematology/Oncology, Northwestern University Feinberg School of Medicine, told *Blood Cancers Today*.

Relma-cel has induced an overall response rate (ORR) of 84% in patients being treated in the JWCAR029-216 clinical trial (NCT06093841), which is the basis for the FDA BTD. With a phase II, open-label, single-arm, multicenter design, in JWCAR029-216, investigators are exploring the efficacy and safety of relma-cel with ORR at three months as the primary endpoint. The secondary endpoints of the study include duration of response (DOR), time to response, progression-free survival (PFS), overall survival (OS), frequency of adverse events, and pharmacokinetic outcomes.

JWCAR029-216 follows the phase II RELIANCE study conducted in China, which led to the National Medical Products Administration approval of relma-cel in China for patients with relapsed or refractory follicular lymphoma. Two-year follow-up results showed a high 2-year OS rate and a manageable safety profile.[1,2]

Prior Research

Fifty-nine patients in the RELIANCE study were administered a single infusion of 100×10^6 or 150×10^6 CAR+ T cells. At a median follow-up of 24 months (95% CI, 4.86 to not assessed [NA]), the median PFS was 7.0 months (95% CI, 4.76-24.15), and the median DOR was 20.3 months (95% CI, 4.86-NA). The median OS was NA (95% CI, NA-NA). At the 2-year mark, the PFS rate was 38.3%, the DOR rate was 38.1%, and the OS rate was 69.0%.[2]

Treatment-emergent adverse events (TEAEs) were reported in 91.5% of patients. The most common grade ≥3 TEAEs observed in the study were neutropenia (42.4%) and leukopenia (22%). After 90 days of treatment, the most common grade ≥3 AEs reported were lymphocytopeni (3.4%), neutropenia (3.4%), and leukopenia (1.7%). In addition, 28.8% of patients died in the study; 20.3% died as a result of disease progression.

"To date there are no significant efficacy differences among the CAR-T products that are FDA approved, and we will have to see if this offers any major differences compared with existing CAR-T constructs. Costs and manufacturing time will likely help to inform choices among physicians and investigators," said Dr. Gordon.

References

1. Receipt of breakthrough therapy designation for Carteyva® in China as second-line treatment in relapsed or refractory adult large B-cell lymphoma. JW Therapeutics. News release. January 10, 2025. Accessed January 10, 2025. https://www.jwtherapeutics.com/en/media/press-release/20250110/

2. Ying Z, Song Y, Yang H, et al. Two-year follow-up result of RELIANCE study, a multicenter phase 2 trial of relmacabtagene autoleucel in Chinese patients with relapsed/refractory large B-cell lymphoma. *J Clin Oncol.* 2022;40:16(suppl 7529). 1200/JCO.2022.40.16_suppl.752

FDA Approves Acalabrutinib With Bendamustine and Rituximab for Frontline MCL

*By **Melissa Badamo***

The FDA has approved acalabrutinib with bendamustine and rituximab for the treatment of mantle cell lymphoma (MCL) in the frontline setting for adult patients ineligible for hematopoietic stem cell transplantation.[1]

Acalabrutinib was previously granted priority review in October 2024 based on results from the phase III ECHO trial, in which acalabrutinib combined with bendamustine and rituximab reduced the risk of disease progression or death by 27% compared with standard-of-care chemoimmunotherapy (hazard ratio, 0.73; 95% CI, 0.57-0.94; P=.016). The median progression-free survival (PFS) was 66.4 months for the acalabrutinib combination and 49.6 months for standard-of-care chemoimmunotherapy. Overall survival also showed a favorable trend with acalabrutinib.[2]

Additional efficacy and safety results of the ECHO trial were presented at the 66th American Society of Hematology Annual Meeting & Exposition by Martin Dreyling, MD, of Klinikum der Universitaet Munchen in Germany. Data showed that acalabrutinib plus bendamustine and rituximab significantly improved PFS compared with placebo plus bendamustine and rituximab for patients with high-risk characteristics.[3]

Among those with measurable residual disease (MRD) positivity at the end of induction, 37.5% in the acalabrutinib combination arm and 20% in the placebo arm had achieved MRD negativity during maintenance. Similar rates of treatment-emergent adverse events were reported in each arm.[3]

References

1. FDA approves acalabrutinib with bendamustine and rituximab for previously untreated mantle cell lymphoma. US Food and Drug Administration. January 16, 2025. Accessed January 17, 2025. https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-acalabrutinib-bendamustine-and-rituximab-previously-untreated-mantle-cell-lymphoma

2. Calquence plus chemoimmunotherapy reduced the risk of disease progression or death by 27% vs. standard of care in patients with untreated mantle cell lymphoma in ECHO Phase III trial. AstraZeneca. June 16, 2024. Accessed January 10, 2025. https://www.astrazeneca.com/media-centre/press-releases/2024/calquence-plus-chemoimmunotherapy-reduced-the-risk-of-disease-progression-or-death-by-27-percent.html

News Roundup

The latest news and updates in hematologic oncology research

NCCN Awards Grants to Three Research Projects for CLL, SLL

*By **Melissa Badamo***

The National Comprehensive Cancer Network (NCCN) Oncology Research Program (ORP) has awarded quality improvement research grants to advance care for patients with chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL). The ORP will oversee the following three research projects funded by AstraZeneca:

1. The CLL/SLL Care Road Map: Accessible, Flexible, and Interactive Web Enabled Resources for High Quality Treatment Decisions led by **Larry Cripe, MD,** of the Indiana University Melvin and Bren Simon Comprehensive Cancer Center.
2. Improving The Detection of Other Cancers in Patients with Chronic Lymphocytic Leukemia Using Multicancer Early Detection Testing led by **Alessandra Ferrajoli, MD,** of The University of Texas MD Anderson Cancer Center.
3. Predictors of Health-Related Quality of Life in Adults with Chronic Lymphocytic Leukemia or Small Lymphocytic Lymphoma led by **Sara Tinsley-Vance, PhD, APRN,** of Moffitt Cancer Center.

These projects aim to improve patient quality of life, address treatment disparities, and increase access to care.

"There is clear and growing evidence that patients with CLL are a group of cancer patients at a remarkably high risk to develop solid and hematological cancers and that when OCs [other cancers] develop in patients with CLL, they have a more aggressive clinical course," Dr. Ferrajoli told *Blood Cancers Today*. "Currently, there are no programs that systematically screen patients with CLL for the presence of OCs. We will be offering the multicancer early detection (MCED) Galleri test to patients with CLL."

MCED testing is a novel, noninvasive screening tool with the ability to detect up to 50 different types of cancers through blood samples, Dr. Ferrajoli explained.

"If the test reveals a possible cancer, additional testing will be performed to determine its presence or not and to obtain a biopsy," she added. "The goals of this proposal are to identify OCs in patients with CLL in a timely fashion, improve their curability rates, and ultimately reduce the number of deaths due to OCs in patients with CLL."

The three proposals were peer reviewed by a scientific review committee of oncologists and experts in the field of hematologic malignancies across 33 NCCN Member Institutions.

"We congratulate these researchers and look forward to seeing their contributions make a tangible difference in future care for CLL/SLL patients," said **Crystal S. Denlinger, MD,** Chief Executive Officer of NCCN, in a press release.

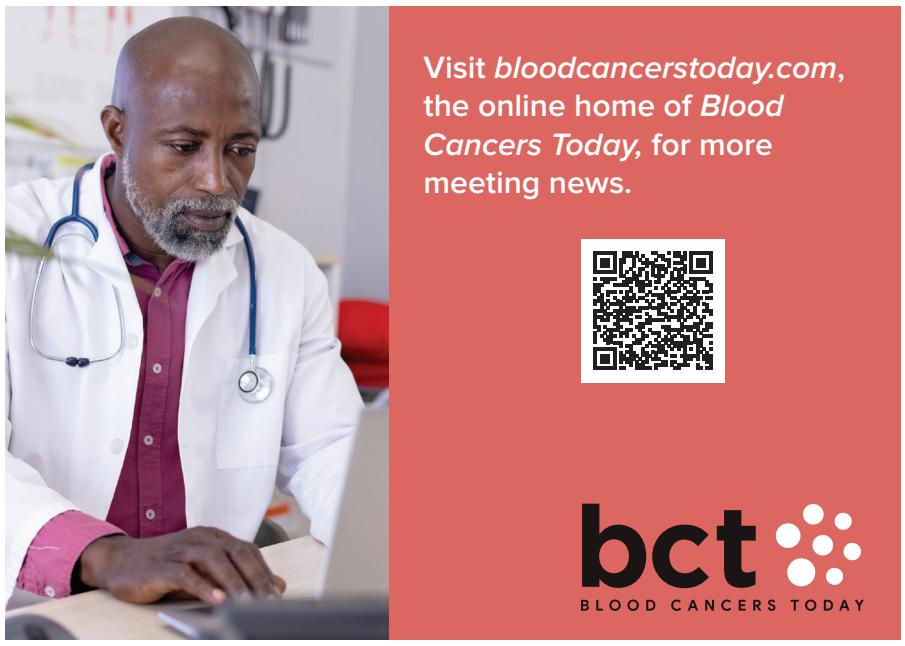
Reference

NCCN awards grants to improve care for patients with chronic lymphocytic leukemia/small lymphocytic lymphoma. NCCN News. December 4, 2024. Accessed January 2, 2025. https://www.nccn.org/home/news/newsdetails?NewsId=4864

FDA, HHS Work on Recommendations Regarding Inclusion of Tissue Biopsies in Clinical Trials

*By **Andrew Moreno***

The FDA has issued a new draft guidance with the goal of ultimately producing recommendations regarding inclusion within clinical trials of tissue biopsies collected from trial participants. The FDA announced this new guidance in a news release.



Working in conjunction with the US Department of Health and Human Services' (HHS) Office for Human Research Protections, the FDA's Oncology Center of Excellence, Office of the Chief Medical Officer, Center for Drug Evaluation and Research, Center for Devices and Radiological Health, and Center for Biologics Evaluation and Research composed the guidance. It is titled "Considerations for Including Tissue Biopsies in Clinical Trials: Guidance for Industry, Investigators, Institutions, and IRBs."

"This new draft guidance builds on the agency's ongoing efforts to enhance clinical trials by providing recommendations to improve participant safety and further clinical research," commented **Richard Pazdur, MD,** director of the Oncology Center of Excellence and acting director of the Office of Oncologic Diseases at the Center for Drug Evaluation and Research.

The guidance is directed toward an audience of clinical investigators, institutional review boards, and researchers in industry. It pertains to clinical trials evaluating investigational medical products or trials conducted in association with the HHS.

Issues encompassed by the new guidance include whether biopsies should be mandatory or optional and the information to include when obtaining informed consent from trial participants. It addresses considerations for both adult and pediatric trials, especially risks and benefits related to collecting biopsy specimens from children.

Reference

FDA issues draft guidance on including tissue biopsies in clinical trials. FDA news release. FDA. January 6, 2025. Accessed January 9, 2025.

Highlights From the **66TH AMERICAN SOCIETY OF HEMATOLOGY ANNUAL MEETING & EXPOSITION**

Venetoclax Plus Obinutuzumab Superior to FCR-BR in Patients With CLL

*By **Melissa Badamo***

Venetoclax plus obinutuzumab demonstrates superior safety and efficacy compared with fludarabine-cyclophosphamide-rituximab (FCR) and bendamustine-rituximab (BR) in patients with untreated chronic lymphocytic leukemia (CLL).

Jeff P. Sharman, MD

The results were derived from the international, open-label, randomized, phase III CRISTALLO study presented at the 66th American Society of Hematology Annual Meeting & Exposition by **Jeff P. Sharman, MD,** of Willamette Valley Cancer Institute.

Adult patients without del(17p) or *TP53* mutations were randomized 1:1 to receive either six cycles of venetoclax plus obinutuzumab plus six cycles of venetoclax (n=80) or six cycles of FCR-BR (n=86). A five-week ramp-up period of oral daily venetoclax was initiated on cycle 1 day 22, and 400 mg was administered from cycle 3 day 1 onward. Intravenous obinutuzumab was administered for six cycles on cycle 1 days 1, 2, 8, and 15 and on day 1 of the remaining cycles. The median follow-up was 32 months.

The researchers reported undetectable measurable residual disease (uMRD) in peripheral blood, defined as less than one CLL cell in 10,000 leukocytes, less than 10^{-4}, using next-generation sequencing. More patients treated with venetoclax plus obinutuzumab achieved uMRD at month 15 than patients treated with FCR-BR (81.3% vs 54.7%, respectively; 95% CI, 12.3-40.9; *P*=.0004). The uMRD rates in peripheral blood at end of treatment (EOT) were also higher with venetoclax plus obinutuzumab versus FCR-BR (81.3% vs 60.5%, respectively; 95% CI, 6.7-34.9; *P*=.0053), a trend also seen with uMRD rates in bone marrow at EOT (70.0% vs 38.4%, respectively; 95% CI, 16.6-46.7; *P*<.0001).

Progression-free survival (PFS) was immature at the data cutoff, but fewer patients treated with venetoclax plus obinutuzumab had disease progression or died. The two-year PFS rates were 95.7% for venetoclax plus obinutuzumab and 90.4% for FCR-BR.

Common treatment-related adverse events (AEs) in both cohorts included infusion-related reaction, COVID-19 infection, thrombocytopenia, diarrhea, and nausea. The rate of AEs was 97.4% for patients treated with venetoclax plus obinutuzumab and 89.4% for patients treated with FCR-BR. Patients treated with venetoclax plus obinutuzumab had a lower rate of discontinuation due to AEs (6.5% vs 15.3%, respectively).

"At the primary analysis, VenO [venetoclax plus obinutuzumab] demonstrated superiority over FCR-BR in driving deep molecular remissions; uMRD rate at Month 15 in PB [peripheral blood] was significantly higher in pts treated with VenO versus FCR-BR," the researchers concluded. "There was a numerical but non-significant PFS benefit at this immature timepoint. No new safety signals were identified with VenO."

Reference

Sharman JP, Laurenti L, Ferrant E, et al. CRISTALLO: results from a phase III trial of venetoclax–obinutuzumab versus fludarabine, cyclophosphamide and rituximab or bendamustine–rituximab in patients with untreated chronic lymphocytic leukemia without del(17p) or *TP53* mutations. Abstract #3237. Presented at the 66th American Society of Hematology Annual Meeting & Exposition; December 7-10, 2024; San Diego, California.

Liso-cel Versus Mosunetuzumab in Follicular Lymphoma: Cost, Clinical Outcomes, Time Toxicity

*By **Melissa Badamo***

Although lisocabtagene maraleucel (liso-cel) has a higher total cost than mosunetuzumab, it provides increased survival and reduced time toxicity, travel distance, and productivity loss for patients with third-line or later follicular lymphoma (3L+ FL), according to a study presented at the 66th American Society of Hematology Annual Meeting & Exposition by **Saurabh Dahiya, MD,** of Stanford University School of Medicine.

Saurabh Dahiya, MD

To estimate patient survival and progression-free survival (PFS), the researchers created a health economic model using parametric techniques in Microsoft Excel. Time toxicity, clinical outcomes, and economic outcomes were estimated over three timespans: 1–5 years, 10 years, and lifetime. Five years was used as the base case.

Patients received either one administration of liso-cel or eight infusions of mosunetuzumab. Patients treated with liso-cel also received leukapheresis, bridging therapy, and lymphodepletion, which contributed to pretreatment costs. Indirect costs included travel costs for outpatient visits or hospitalizations, as well as lost wages. Productivity loss accounted for eight hours of productive time loss while receiving care. Time toxicity (time spent receiving medical care) accounted for every occurrence of patient outpatient visits, laboratory tests, and other health care resource utilization (HCRU).

Over a period of five years, patients treated with liso-cel had a higher median PFS than those treated with mosunetuzumab (51 months vs 18 months, respectively). The cost per median PFS month was lower with liso-cel than mosunetuzumab ($11,650 vs $18,180, respectively). However, due to the high costs of liso-cel, patients treated with the chimeric antigen receptor T-cell therapy incurred an extra $265,226.

Due to more infusion visits and disease progression, the time toxicity for patients treated with mosunetuzumab was 44 days longer than for those treated with liso-cel. The researchers noted that "As the time horizon increased, this differential widened due to worse disease progression."

Patients treated with mosunetuzumab had an increased HCRU, including an additional 1,148 hours in productivity loss, $3,126 in lost wages, 246 more miles traveled, and an extra $1,323 in transportation costs.

"The increase in PFS with liso-cel versus mosunetuzumab translates to less downstream HCRU," the researchers concluded. "Further, as liso-cel only requires a single administration, it provides reduced time toxicity, travel distance, and productivity loss, which improve the quality of life of patients and their caregivers."

Reference

Dahiya S, Saunders AC, Kumar J, et al. "Cost consequence and time toxicity model for the treatment of third-line or later (3L+) follicular lymphoma (FL) using advanced therapies: a comparison of lisocabtagene maraleucel (liso-cel) with mosunetuzumab." Abstract #3651. Presented at the 66th American Society of Hematology Annual Meeting & Exposition; December 7-10, 2024; San Diego, California.

Early Study Looks at Combining HMA with Immunotherapy-Based Regimens in MDS

*By **Leah Lawrence***

A phase II trial exploring immunotherapy-based hypomethylating agent (HMA) combinations for patients with previously untreated myelodysplastic syndromes (MDS) showed that "there are unique cytogenic and molecular predictors of response and survival" associated with the approaches.

Ian M. Bouligny, MD

Ian M. Bouligny, MD, of the University of Texas MD Anderson Cancer Center, and colleagues presented their findings in a poster at the 66th American Society of Hematology Annual Meeting & Exposition.

Their study enrolled 66 patients with previously untreated disease. Patients received azacitidine with either ipilimumab (azo-ipi; 33 patients), nivolumab (aza-nivo; 20 patients), or both (aza-ipi-nivo; 13 patients). The primary efficacy outcome was overall response defined as complete response (CR), CR with limited count recovery (CL_L), or hematologic improvement (HI).

The overall response rate was 26.7% for aza-ipi, 55% for aza-nivo, and 53.8% for aza-ipi-nivo. CR was achieved by 6.7%, 40.0%, and 23.1% of patients assigned the regimens, respectively. There was no significant difference between the treatment regimens.

There was also no difference in event-free survival (EFS) or overall survival (OS) between the regimens. Median OS was 22.7 months for aza-ipi, 14.3 months for aza-nivo, and 11.8 months for aza-ipi-nivo. However, a landmark analysis showed that aza-ipi was associated with superior OS, compared with aza-ipi, for patients with IPSS-R intermediate-risk disease (P=.049).

Among patients who went on to transplant, the OS for those who received either of the doublet regimens was 49.6 months compared with 13.7 months for those who received triplet therapy (P=.008). OS was also significantly better among patients who did not experience pneumonitis compared with those who experienced grade 2 or worse pneumonitis (22.7 vs 7.4 months; P=.025).

The researchers concluded that "the doublet combinations appeared to be well tolerated" while "the triplet combination was associated with more frequent high-grade toxicity."

Reference:

Bouligny IM, Montalban-Bravo G, Sasaki K, et al. A phase II trial of azacitidine with ipilimumab, nivolumab, or ipilimumab and nivolumab in previously untreated myelodysplastic syndrome. Abstract #4601. Presented at the 66th American Society of Hematology Annual Meeting & Exposition; December 7-10, 2024; San Diego, California.

First-in-Human Phase I Study Results Presented: Trispecific CAR T-Cell Therapy

*By **Andrew Moreno***

A first-in-human phase I study has evaluated trispecific chimeric antigen receptor (CAR) T-cell therapy for targeting CD19, CD20, or CD22. This therapy is safe and viable for production, according to findings presented at the 66th American Society of Hematology Annual Meeting & Exposition in San Diego, California by **Evandro Bezerra, MD,** of the Ohio State University, Columbus.

Evandro Bezerra, MD

"Despite lack of persistence of cells beyond day 30, durable remissions have been observed. Remissions have been observed in [mantle cell lymphoma (MCL)], [follicular lymphoma (FL)], [diffuse large B-cell lymphoma (DLBCL)] and [B-cell acute lymphoblastic leukemia (B-ALL)]," wrote Dr. Bezerra and colleagues.

For the study, successful manufacture of a trispecific CAR T-cell product was achieved for 15 of 16 patients, with a median transduction efficiency of 26%, median fold expansion of five, and median time to manufacturing of seven days.

Among 15 patients, complete response (CR) was achieved in six, two of whom by day 30 and four by day 90.

Of nine patients with non-Hodgkin lymphoma (NHL), five achieved CR, three of whom have maintained CR beyond one year following treatment.

CR was observed in patients with B-ALL, DLBCL, FL, and MCL, while there were no responses in patients with Richter's transformation. One patient with B-ALL had achieved response after disease progression following commercial anti-CD19 CAR T-cell therapy. In patients with chronic lymphocytic leukemia (CLL) and B-cell prolymphocytic leukemia (B-PLL) stable disease was observed at day 30.

In three patients who had disease relapse, biopsy was performed to evaluate CD19, CD20, or CD22 expression before and after the trispecific CAR T-cell therapy.

"In one patient, CD20 positivity changed to CD20 dim expression upon relapse. In another patient, CD20 negative status changed to CD20 + after CAR-T," Dr. Bezerra and colleagues noted.

Regarding safety events, cytokine release syndrome (CRS) occurred in three patients; two experienced grade 1, one experienced grade 2, and all required tocilizumab. One patient experienced grade 1 immune effector cell-associated neurotoxicity syndrome (ICANS). There were no occurrences of hemophagocytic lymphohistiocytosis observed and no patients required steroids.

Among the patients who achieved CR, pleomorphic sarcoma manifested in one and prostate cancer in another, both malignancies deemed unrelated to the treatment. Mortality due to intracranial hemorrhage occurred on day 32 in one patient with persistent B-ALL.

Reference

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Reaching for the Holy Grail in Myelofibrosis With Imetelstat Combinations

By **Blood Cancers Today** ***Staff Writers***

In an exclusive interview with *Blood Cancers Today* (BCT) at the 66th American Society of Hematology (ASH) Annual Meeting & Exposition, **John Mascarenhas, MD,** of the Icahn School of Medicine at Mount Sinai, spoke about the development of the human telomerase inhibitor imetelstat for the treatment of myelofibrosis (MF). He shared updates about imetelstat as an investigational monotherapy and as a combination therapy with Janus kinase (JAK) inhibitors, including data from the IMproveMF study, which was presented at ASH.

BCT: Could you tell us about the rationale of the IMproveMF study and the unmet need that may be addressed by this trial?

John Mascarenhas, MD

"The rationale of the trial is based on the cumulative evidence that targeting telomerase, which is an enzyme that's constitutively activated in CD34-positive cells of patients with MF, is a potential disease-modifying approach to MF," explained Dr. Mascarenhas. Imetelstat is an approved drug for patients with transfusion-dependent lower-risk myelodysplastic syndromes, and there is evidence that it has the potential to reduce clonal markers of the disease.

"We have all of this preclinical data, a lot of it generated from work that Dr. Ron Hoffman has done here at Mount Sinai, indicating that imetelstat is an anticlonal stem cell–directed therapy. Dr. Ayalew Teferry was the first pioneer to test imetelstat in patients with MF as a single agent in the relapsed or refractory setting, demonstrating pretty profound responses in the bone marrow and promising histopathologic and molecular responses."[1]

Consequently, Dr. Mascarenhas and colleagues designed a larger, randomized, phase II multicenter study in the relapsed and refractory setting. In this trial, imetelstat was associated with spleen volume reductions and a modest degree of symptom improvement. "The results were comparable to symptom improvement with second-line JAK inhibitors," clarified Dr. Mascarenhas. "However, most notable and most impactful was the survival that we saw in the 9.4 mg/kg dose arm. We observed a median overall survival of almost 30 months, compared with about 19 or 20 months in the 4.7 mg/kg arm.[2] This compares favorably to multiple independent reports showing that patients with MF who failed on JAK inhibitors have a median survival somewhere between 12 and 15 months."

Dr. Mascarenhas further explained that the responses appeared to be correlated with on-target activity: modulation of hTERT [human telomerase reverse transcriptase] RNA expression levels, telomerase activity, and markers of disease biology, such as driver mutation and bone marrow fibrosis grade. "All this data suggested that the drug was anticlonal, which endorsed the randomized, phase III study. In this trial, imetelstat will be compared with the best available therapy, excluding a JAK inhibitor, in patients with MF who have progressed on a JAK inhibitor."[3]

"At this point, I think it's natural to ask some questions with regard to the application of imetelstat in MF," Dr. Mascarenhas continued. "Do we wait for patients to fail on ruxolitinib? Should we add imetelstat earlier on?" A number of years ago, Dr. Hoffman's group presented a preclinical abstract at ASH that provided the rationale for combining the two agents, ruxolitinib and imetelstat, in targeting these MF CD34 cells.[4]

"This is pretty much the holy grail," according to Dr. Mascarenhas. "Based on these findings we decided to do a phase lb study. We dose escalated imetelstat, starting at a dose of 4.7 mg/kg, and went up in several dose cohorts to 9.4 mg/kg, every four weeks. Imetelstat is intravenously administrated in this group of patients with MF that had been on a stable dose of ruxolitinib for at least four weeks. It was the investigators' decision whether patients showed a suboptimal response in terms of anemia, spleen reduction, or symptom burden. Subsequently, imetelstat was added to the treatment regimen of these suboptimally responding patients."

The data, which are being presented at ASH 2024,[5] show that the combination is well tolerated. "We didn't see any dose-limiting toxicities in the 17 enrolled patients," said Dr. Mascarenhas. "We did see some myelosuppression, anemia, and neutropenia, as was expected. Fortunately, these were manageable and reversible cases. Moreover, we did not see grade 3 or 4 thrombocytopenia." Dr. Mascarenhas mentioned that musculoskeletal pain of the extremities was a notable, but not necessarily concerning, toxicity.

"Furthermore, we did not observe a lot of dose modifications or discontinuations due to toxicity, which is the primary aim of a phase I study," Dr. Mascarenhas continued. "Since we never hit a dose-limiting toxicity, the recommended phase II dose for the expansion going forward is going to be 9.4 mg/kg, intravenously administered, every four weeks." Dr. Mascarenhas said there are preliminary efficacy data as well. "We will show some data with regard to spleen response, symptom reduction, and driver mutation response, but we do not have a lot of efficacy data yet."

BCT: What are the next steps? Are you trying to identify which patients may respond well to the combination?

"It is not likely that we'll identify the subset of patients for whom this combination is ideal," responded Dr. Mascarenhas. "The question was, can we combine ruxolitinib and imetelstat safely? The answer is yes. If we continue on this road, we will probably have results in 2026 in terms of a readout for the randomized, phase III study and as a single agent with a survival endpoint. We should think about how to generate data with respect to earlier use of this combination therapy. One cohort that we are intending to do is an upfront cohort. That would be the next step. Thus, JAK inhibitor–naive patients would receive ruxolitinib and imetelstat in the first-line setting. This approach has been tested with different agents, such as pelabresib, navitoclax, and selinexor. The idea is to not wait for patients to have more advanced disease but to try and get synergy of combination therapies up front."

BCT: Can you say something about the pharmacokinetic properties of this combination therapy?

"We looked at the pharmacokinetic profiles of imetelstat and ruxolitinib to ensure that one drug wasn't interfering with the metabolism of the other drug," answered Dr. Mascarenhas. "Fortunately, we did not see such an interference pattern. For imetelstat, we observed a dose-dependent C_{max} [maximum concentration] that was reached in approximately two hours after the start of infusion, and it mimicked what was seen in the monotherapy setting. So, it was not affected by ruxolitinib. Conversely, we noticed the dose-dependent C_{max} and clearance that you would expect to see for ruxolitinib monotherapy. Thus, there were no concerning drug-drug interactions."

BCT: What is the take home message for your colleagues?

"The current phase I study showed that the combination of ruxolitinib and imetelstat is well tolerated in patients with MF," concluded Dr. Mascarenhas. "The recommended phase II dose of imetelstat will be 9.4 mg/kg, intravenously administered, every four weeks, in combination with ruxolitinib. With reassuring pharmacokinetic profiles and early signs of clinical activity, I look forward to the further development of this combination in MF."

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Editor's Picks

In each issue of Blood Cancers Today, *we will take a closer look at a particular topic in hematologic malignancies. This month, Executive Editor* ***Elias Jabbour, MD,*** *Professor of Medicine in the Department of Leukemia at the University of Texas MD Anderson Center, highlights recent research in acute myeloid leukemia.*

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

Elias Jabbour, MD

ACUTE MYELOID LEUKEMIA

All-Oral SAVE Regimen Achieves High Rates of Remission in Relapsed or Refractory AML

By ***Nichole Tucker***

The addition of the menin-KMT2A inhibitor revumenib to decitabine and cedazuridine (ASTX727) and venetoclax (SAVE) for older and unfit patients with relapsed or refractory acute myeloid leukemia (AML) demonstrated strong efficacy and favorable safety in a phase I/II, investigator-initiated trial presented at the 66th American Society of Hematology Annual Meeting & Exposition.

Of the 26 patients included in the study, 12 were treated during phase I and 14 were treated during phase II at the recommended phase II dose of 163 mg once daily. The study population had a median age of 35 years (range, 12–79 years) and included five patients younger than 18.

Eleven patients (42%) had *KMT2Ar* AML, 10 (38%) had *NPM1mt* disease, five (20%) had NUP98r disease, and four (15%) had extramedullary disease. The population had received a median of three prior lines of therapy including venetoclax (65%), hematopoietic stem cell transplantation (HSCT; 42%), and menin inhibition (.08%).

Treatment with the SAVE regimen led to an overall response rate of 88% and a complete response (CR) or CR with partial hematologic recovery of 58%, a CR rate of 46%, and CR with partial hematologic recovery (CRh) of 12%. Some patients (12%) treated with the combination of revumenib, venetoclax, and ASTX727 achieved a CR with incomplete platelet recovery or a partial response (4%). Fifteen percent of patients reached a morphologic leukemia-free state.

Efficacy assessed by flow cytometry showed a 93% measurable residual disease (MRD)–negative rate among patients who had a CR or CRh and 74% among other responders. Patients with *NUP98r* disease had the lowest MRD-negative rate.

At a median follow-up of 6.6 months, the six-month relapse-free survival rate shown with the revumenib combination was 59% (95% CI, 26-81). The study population also had an overall survival rate of 74% (95% CI, 39-83). The median duration of response was not reached at the time of data cutoff. Two of the 12 patients who underwent HSCT maintenance after treatment with the SAVE combination completed treatment and remain in remission.

Safety findings show that no early mortality occurred among those treated with revumenib, venetoclax, and ASTX727. The most common treatment-emergent adverse events (TEAEs) of any grade included QT prolongation (58%), elevation in aspartate aminotransferase/alanine aminotransferase (54%), febrile neutropenia (46%), hyperphosphatemia (46%), and nausea (42%). In terms of high-grade toxicity (grade ≥ 3), TEAEs observed were febrile neutropenia (46%) and lung infection (42%). Investigators also reported grade ≥ 3 treatment-related AEs including thrombocytopenia (12%), neutropenia (8%), QT prolongation (8%), and differentiation syndrome (4%).

Why I chose this research:

"The all-oral combination of revumenib (SNDX-5613) with decitabine/cedazuridine (ASTX727) and venetoclax (SAVE) results in an objective response rate of 82% (CR-CRh 58%; CR 46%) in patients with relapsed or refractory AML with KMT2Ar, NPM1mt or NUP98r. Thirteen patients (39%) proceeded to allogeneic stem cell transplantation with 12-month duration of response and survival of 65% and 51%, respectively."

Reference

Issa G, Cuglievan B, Daver N, et al. Phase I/II study of the all-oral combination of revumenib (SNDX-5613) with decitabine/cedazuridine (ASTX727) and venetoclax (SAVE) in R/R AML. Abstract #216. Presented at the 66th American Society of Hematology Annual Meeting & Exposition; December 7-10, 2024; San Diego, California.

Enhanced AML Remission With Cladribine Alternating Therapy

By **Blood Cancers Today** ***Staff Writers***

The combination of cladribine, low-dose cytarabine, and venetoclax alternating with azacitidine and venetoclax (AZA-VEN) achieved high rates of composite complete remission (CRc) and favorable overall survival (OS) in patients with acute myeloid leukemia (AML). Patients undergoing hematopoietic stem cell transplantation and of particular genomic backgrounds had significantly improved survival, highlighting the effectiveness of the regimen for diverse risk groups.

In a single-center, single-arm, prospective phase II clinical trial, cladribine in combination with low-dose cytarabine and venetoclax (CLAD-LDAC-VEN) was investigated in an alternating schedule with azacytidine and venetoclax.[2] The trial included patients (n=141) with untreated nonacute promyelocytic leukemia AML who were at least 50 years old or younger and ineligible for standard induction chemotherapy. Previous data showed promising 24-month OS and complete remission with CRc,[1] and the researchers aimed to extend the follow-up period and include a larger cohort for further analysis.

Why I chose this research:

*"Cladribine-low-dose cytarabine-venetoclax alternating with azacitidine plus venetoclax produces an excellent CR/CRi rate of 85% (CR 73%) with high rates of MRD negativity (78%) , translating into favorable long term OS (two-year 62%) and EFS (two-year EFS 55%) in patients aged ≥ 60 years or those unfit for intensive chemotherapy. Benefit was seen across most genomically defined subgroups, including those with favorable mutations (*NPM1 *or* DDX4*) where the two-year OS rate is 85.1%."*

The CRc for the CLAD-LDAC-VEN alternating with AZA-VEN was 85%, with a measurable residual disease negativity rate of 78%. The two-year OS was 61.6%, which was consistent with the smaller study,[1] and the four-year OS was 52.3%. Event-free survival at two and four years was 54.5% and 50.3%, respectively. Patients receiving stem cell treatment (n=62) had significantly improved OS at two and four years compared with patients not receiving stem cell treatment (n=63; $P<.001$).

The investigators also created a predictive model to identify patient characteristics that determine OS. Using Cox regression and random force model to select prognostic variables, patients were stratified into four OS categories. The top category, which included patients with *NPM1* or *DDX41* mutations, had a median OS of 60 months. The worst category, which included patients with a complex karyotype or a *TP53* mutation, had a median OS of seven months.

"Of note, patients with *K* or *NRAS* mutations treated with CLAD-LDAC-VEN showed an improved survival of 21 months, which compares favorably with historical data when these patients are treated with standard HMA-VEN where the expected survival is about 12 months," the researchers wrote.

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HemOnc Happenings

Reporting on recent announcements, awards, and appointments in the hematology/oncology sphere

ASH Announces Honorific Awards at 66th Annual Meeting

By Melissa Badamo

The American Society of Hematology (ASH) recognized exemplary hematologist oncologists at the Announcement of Awards Ceremonies on Sunday, December 8, and Tuesday, December 10, 2024 at the 66th Annual Meeting & Exposition in San Diego. Both sessions were moderated by **Mohandas Narla, DSc,** President of ASH and a distinguished scientist at the New York Blood Center.

"On the final day of the meeting, it's appropriate to reflect on the outstanding and inspiring research presented at this meeting, from the bench to the bedside, discoveries that resulted in new treatments and improved the lives of patients with blood disorders," Dr. Narla said in his introduction.

Wallace H. Coulter Award for Lifetime Achievement in Hematology

Éliane Gluckman, MD, PhD, Professor Emeritus of Hematology at the University of Paris, received the Wallace H. Coulter Award for a lifetime of achievement in cord blood transplantation. According to ASH, Dr. Gluckman performed the world's first human umbilical cord blood transplant in 1988, demonstrating that cord blood can be used as a successful source of stem cells for patients requiring hematopoietic stem cell transplantation. She also served as Medical Director of the Bone Marrow Transplant Service and Head of the Department of Hematology at the Saint-Louis Hospital, leading cord blood research.

Éliane Gluckman, MD, PhD

"I am deeply honored and humbled to receive the prestigious Wallace Coulter award," Dr. Gluckman said. "It underlines not only my personal achievement, but also the progress we are making towards greater representation of women in the field."

ASH Mentor Awards

Two ASH Mentor Awards were presented, one to **Stephen Nimer, MD,** for his community-focused mentorship to more than 100 hematology trainees and one to **Charles Schiffer, MD,** for leading, challenging, and training clinical investigators whose research has advanced leukemia research and patient outcomes.

Stephen Nimer, MD

Specializing in myeloid leukemia and myelodysplastic syndromes, Dr. Nimer currently serves as Director of the Sylvester Comprehensive Cancer Center. His research interests include the transcriptional regulation of hematopoiesis, according to his faculty profile.

Charles Schiffer, MD

Dr. Schiffer, a retired hematologist and medical oncologist at the Karmanos Cancer Institute, has expertise in platelet transfusion therapy and adult leukemia treatment.

"The mentor award was established to recognize hematologists who have excelled in mentoring trainees and colleagues," Dr. Narla said. Upon receiving their awards, the two recipients provided advice for younger trainees in the field of hematology oncology.

"Get to know those in your field—as many as you can and profoundly as you can. They are your peers and will be your lifelong friends," Dr. Nimer advised. "Some last words of advice: never give up what makes you who you are and what brings you joy. What joy you have all given me."

"Woody Allen is credited with the statement, 'Half of life is showing up,'" Dr. Schiffer said. "That has been my message to younger people who work with me. I felt it was my obligation to give them good places to show up and demonstrate their intellect, curiosity, and zeal. I can't imagine a better time in medicine than showing up. The opportunities scientifically and clinically are extraordinary."

ASH Award for Leadership in Promoting Diversity

James George, MD, George Lynn Cross Research Professor at the University of Oklahoma and former President of ASH in 2005, received the ASH Award for Leadership in Promoting Diversity. Dr. George is credited for leading a more diverse hematology workforce and supporting the ASH Minority Medical Student Award Program, which has supported more than 300 research opportunities for students who are underrepresented in medicine.

James George, MD

"I'm honored to receive this diversity award. Diversity is at the heart of ASH," Dr. George said. "From ASH's beginning 60 years ago, it had laboratory research for the principal activity and was led by White men who were leaders of their own groups. The new programs that were developed at the beginning of the century expanded the research to include clinical research and patient care. They were developed not just by men, but principally by women in addition to men. They were developed by people of all color and all races. This was the beginning of the new ASH. The ASH of our generation."

William Dameshek Prize

Ami Bhatt, MD, PhD, Professor of Medicine at Stanford University, received the William Dameshek Prize for her outstanding contributions to the field of hematology. The award is named after the late William Dameshek, former president of ASH and original editor of *Blood*.

Ami Bhatt, MD, PhD

Dr. Bhatt pioneered genomic approaches to studying the microbiome and has explored the microbiome in connection with strategies for graft-versus-host disease prophylaxis.

"The Dameshek Prize recognizes our work in studying the microbiome, revealing how these tiny and truly incredible organisms evolve, adapt, and profoundly impact transplant outcomes," said Dr. Bhatt. "This prize isn't just a recognition of prior accomplishments, but an invitation to keep exploring."

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