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Kelvin Droegemeier, PhD, was confirmed as director of the White House Office of Science and Technology Policy on January 2, filling a vacancy left by John Holdren, PhD, who departed in 2017. Previously, Droegemeier was a professor of meteorology and vice president of research at the University of Oklahoma in Norman. He also co-founded and directed the National Science Foundation (NSF) Science and Technology Center for the Analysis and Prediction of Storms and the NSF Engineering Research Center for Collaborative Adaptive Sensing of the Atmosphere. His research has focused on severe thunderstorms and tornadoes.

José Baselga, MD, PhD, began his role as executive vice president of Research and Development Oncology at Astra Zeneca in January. Most recently, Baselga was physician-in-chief and chief medical officer at Memorial Sloan Kettering Cancer Center in New York, NY. He has also served as associate director of Massachusetts General Hospital Cancer Center in Boston, MA, president of the American Association for Cancer Research, and editor-in-chief of *Cancer Discovery*. Baselga has studied and helped develop molecularly targeted agents for breast cancer.


Jacqualyn Fouse

Jacqualyn Fouse, PhD, became chief executive officer of Agios on February 1, replacing David Schenkein, now the company's executive chairman. Most recently, Fouse was executive chairman of the biopharmaceutical startup Dermavant. Before that, she spent 8 years at Celgene: She joined the company as chief financial officer, moved on to become president of global hematology, and later advanced to president and chief operating officer.

BCL2/MDM2 Inhibitor Combo Effective in AML

The BCL2 inhibitor venetoclax (Venclexta; AbbVie) plus the MDM2 inhibitor idasanutlin (Roche) may be an effective therapy for relapsed/refractory acute myeloid leukemia (AML). In a phase Ib trial, 35.9% of patients treated with the combination responded, according to results presented at the 2018 American Society of Hematology Annual Meeting in San Diego, CA, in December.

Previous research established that venetoclax monotherapy has modest activity in AML (Cancer Discov 2016;6:1106–17). However, the drug is more effective when combined with other therapies: It was recently approved in combination with azacitidine, decitabine, or low-dose cytarabine as a first-line therapy for patients age 75 and older, or those who can't tolerate intensive chemotherapy. Now, Naval Daver, MD, of The University of Texas MD Anderson Cancer Center in Houston, and his colleagues are investigating another combination: venetoclax plus idasanutlin.

Venetoclax inhibits the antiapoptotic protein BCL2 in cancer cells, but the cells can become resistant to it by increasing production of other antiapoptotic proteins, such as MCL1. Idasanutlin inhibits MDM2, which results in MCL1 degradation via p53 activation. In a preclinical study of the combination, "blocking BCL2 with the venetoclax prevented the emergence of MCL1 as an escape mechanism, resulting in profound apoptosis and cell death," Daver says (Cancer Cell 2017;32:748–60).

At the meeting, Daver reported results from 39 patients age 60 and older with relapsed/refractory AML who were ineligible for chemotherapy or allogeneic stem cell transplant. Overall, 14 patients treated with the combination exhibited an antileukemic response (complete and partial remissions plus morphologic leukemia-free states), including 11 of 24 treated at doses being considered for the phase II expansion (600 mg venetoclax plus 150 mg or 200 mg of idasanutlin). Six of nine patients with a high ratio of BCL2:BCLxL or BCL2:MCL1 responded, compared with one of 10 patients with a low ratio. Further, responses appeared to be higher in patients who had *IDH* or *RUNX1* mutations. Low-grade diarrhea was the most common side effect, occurring in nearly everyone.

"The response rates, especially without using chemotherapy, and with both drugs being oral, well-tolerated, and outpatient, were quite encouraging," Daver says, adding that older patients with relapsed/refractory disease ineligible for chemotherapy, such as those in the trial, have limited treatment options.

Gabriel Mannis, MD, of the Helen Diller Family Comprehensive Cancer Center at the University of California, San Francisco, who was not involved in the trial, notes that complete remission rates—which were only 23.1% overall, and 33.3% at the recommended phase II doses—are encouraging, but leave room for improvement. He is more intrigued by the preliminary biomarker analysis.

"Potentially, there are ways that we could pick patients who would be more likely to respond to this combination," he says. "I think that by increasing the patient numbers, exploring further the responses based on both BCL2 family protein expression and mutational profile, this [drug] could certainly find a role in the relapsed/refractory setting."

For Eunice Wang, MD, of Roswell Park Comprehensive Cancer Center in Buffalo, NY, who also had no connection to the research, the trial reflects the general enthusiasm for venetoclax and the shift away from chemotherapy in AML treatment.

"We are into the era of targeted therapies for AML, and now that these targeted therapies have become standard of care, the next step is to figure out which combinations of targeted therapies for which specific molecular, biological subsets of AML will result in the best outcomes," she says.

–*Catherine Caruso* ■

Personalized Medicine Applied to AML

Clinicians may be closer to applying personalized medicine to the treatment of acute myeloid leukemia (AML), according to findings from the

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At the ASH meeting, Amy Burd, PhD, reported that sequencing and the assignment of patients to one of several treatment arms of the Beat AML Master Trial could be completed within a week.

ongoing Beat AML Master Trial. In this study, newly diagnosed patients are genomically sequenced, and the results are used to quickly assign first-line therapies.

Preliminary results were presented by Amy Burd, PhD, of the Leukemia & Lymphoma Society, during the 2018 American Society of Hematology Annual Meeting in San Diego, CA, in December. Burd noted that AML is not only one of the most common and most lethal adult leukemias, with an overall survival rate of 25%, but also highly heterogeneous, with numerous distinct genetic subtypes driven by different combinations of mutations. Increasing evidence that this disease may respond to targeted therapies prompted the question, "Could we improve outcomes by matching patients to the appropriate therapies?"

To find out, Burd and colleagues launched Beat AML, a large umbrella trial, in 2016. "The guiding principle is to move quickly and use the best science available, to try to identify patients where we'll see significant effects," explained study co-leader Brian Druker, MD, director of the Knight Cancer Institute at Oregon Health & Science University in Portland. "The goal is to sequence the patient's leukemia, turn that around within 7 days, and then assign the treatment based on the genomics," via an algorithm developed within the trial.

Burd highlighted the first 285 patients enrolled in the trial, all of whom were at least 60 years old and not previously treated for AML. Of these, 273 patients were assigned to therapies within 7 days, with 146 then going on to be treated in one of 11 study arms; the remaining patients either declined treatment or were assigned to therapies outside this study. She noted that Beat AML's commitment from Cambridge, MA–based Foundation Medicine to prioritize sequencing tumor samples from this trial is one factor contributing to the quick turnaround time.

Preliminary data from two Beat AML study arms were presented: According to a phase II trial, the IDH2 inhibitor enasidenib (Idhifa; Celgene), which is FDA-approved for patients with relapsed/refractory *IDH2*-mutant AML, is also active as a first-line therapy, eliciting an overall response rate of 44.4%. Meanwhile, a phase Ib trial established safety and dosing for the investigational anti-CD33 therapy BI 836858 (Boehringer Ingelheim) combined with azacitidine for patients with a DNA hypermethylation signature, and those without any mutations in leukemia-associated genes. This combination is now being tested in a phase II trial.

"The advantage of this [approach] is that you're really tailoring therapies to individual patients" based on the genomic landscape of their tumors, which is especially important as more targeted therapies become available, said Monica Guzman, PhD, of Weill Cornell Medicine in New York, NY, who is not involved in the research. "I think it's a great example of what personalized medicine should look like."

Joseph Mikhael, MD, of the International Myeloma Foundation, who is also not connected to the trial, noted that it addresses one of the biggest challenges of implementing personalized medicine in aggressive diseases like AML: how long it often takes to perform genomic sequencing and analyze results. "To be able to obtain [genomic data] early is so fundamental," he said, adding that the Beat AML Trial demonstrates how "we can come up with those answers more quickly."
–*Catherine Caruso* ■

BiTE Therapy Active in Multiple Myeloma

AMG 420 (Amgen), a bispecific T-cell engager (BiTE), may be safe and effective for patients with relapsed/refractory multiple myeloma, according to preliminary results presented at the 2018 American Society of Hematology Annual Meeting in San Diego, CA, in December. In a phase I trial, the drug elicited responses in a high percentage of patients and was associated with relatively manageable side effects.

AMG 420 consists of light chains derived from two antibodies: One targets B-cell maturation antigen (BCMA) on multiple myeloma cells and the other binds to CD3 on T cells. "The idea is that the bispecific will engage with the myeloma cells and bring in T cells" that then kill the cancer cells, says Max Topp, MD, of the University Hospital of Würzburg in Germany, who presented the results. Topp notes that blinatumomab (Blincyto; Amgen), a BiTE targeting CD19 on acute lymphoblastic leukemia cells, is already approved.

To investigate AMG 420, Topp and his colleagues tested the drug at doses from 6.5 to 800 µg/day in 42 patients with multiple myeloma who had received a median of four prior therapies. Overall, 13 patients (31%) responded to the drug, with seven complete responses and six partial remissions; seven out of 10 patients (70%) treated at 400 µg/day exhibited a response. Sixteen patients (38%) developed cytokine release syndrome, with most cases classified as grade 1, and 12 patients (29%) developed infections related to treatment, with nine cases classified as grade 3 or higher.

"I do definitely see this as a potential emerging option for fourth- and fifth-line patients," Topp says. He adds that because AMG 420 is an off-the-shelf therapy, patients can be treated right away, whereas those treated with personalized BCMA-targeting CAR T-cell therapies such as bb2121 (Bluebird Bio) and JCARH125 (Celgene) must have their T cells extracted, modified, and reinfused. Researchers plan to start a phase II trial of AMG 420 at 400 µg/day later this year.

"What we saw from AMG 420 was the first evidence that using a bispecific, or BiTE-based, approach would have efficacy in myeloma—it's proof of principle to me that this kind of approach can work," says Sagar Lonial, MD, of the Winship Cancer Institute at Emory University School of Medicine in Atlanta, GA, who was not involved in the trial.

Suzanne Lentzsch, MD, PhD, of Columbia University Medical Center