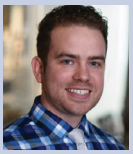
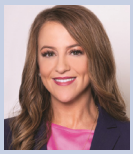
Hematologic Malignancies: ASCO20 Virtual Scientific Program Highlights for the Advanced Practitioner

Amy Pierre, MSN, ANP-BC, of Memorial Sloan Kettering Cancer Center, **P. Andrew Allred, MS, PA-C,** of Banner MD Anderson Cancer Center, and **Allyson Price, PA-C,** of MD Anderson Cancer Center, provide expert insights for advanced practitioners into the most talked-about abstracts on hematologic malignancies from the ASCO virtual meeting.

Abstract LBA3

Carfilzomib Triplet Fails to Improve Outcomes vs Standard Bortezomib-Based Regimen in Newly Diagnosed Myeloma

By Alice Goodman

Visit https://meetinglibrary.asco.org/record/186906/abstract to read the full abstracts and view author disclosures.

For newly treated patients with standard- and intermediate-risk multiple myeloma who are not slated for immediate autologous stem cell transplantation (ASCT), the triplet regimen of carfilzomib/lenalidomide/dexamethasone (KRd) failed to improve progression-free survival vs the current standard-of-care regimen of bortezomib/lenalidomide/dexamethasone (VRd). These results of the phase III ENDURANCE trial were presented at the Plenary Session of the ASCO20 Virtual Scientific Program.[1]

These results were somewhat surprising, as phase II studies suggested carfilzomib might outperform bortezomib. Once again, this is a reminder that phase II data do not always pan out in phase III trials.

"There was no improvement in progression-free survival by replacing bortezomib with carfilzomib in the current standard initial treatment of newly diagnosed patients with standard- or intermediate-risk myeloma, even though we observed a very good partial response rate with the carfilzomib combination," stated lead author Shaji K. Kumar, MD, of Mayo Clinic, Rochester, Minnesota. "Thus far, there is no difference in overall survival between the two regimens. Based on these data, VRd should remain the standard of care for initial therapy of newly diagnosed symptomatic multiple myeloma, where an early transplant is not planned, and should be considered the backbone for novel regimens as well as the control arm for clinical trials."

Dr. Kumar commented on toxicity: "The side-effect profiles of the two regimens were different, with a higher rate of peripheral neuropathy seen with VRd and higher rates of cardiac, pulmonary, and renal toxicities seen with KRd.

VRd has been the standard of care for newly diagnosed patients for several years. In a phase III trial, carfilzomib—a proteasome inhibitor like

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bortezomib—was superior to bortezomib in the relapsed setting, and a phase II trial suggested this might be the case in newly diagnosed patients, Dr. Kumar noted.

ENDURANCE Details

The ENDURANCE trial consisted of two parts. Part 1 evaluated induction therapy with VRd vs KRd in newly diagnosed patients with multiple myeloma. Part 2 randomly assigned patients from both arms again to two different duration of maintenance lenalidomide (every 4 weeks for 2 years or every 4 weeks until disease progression). During his presentation at ASCO20, Dr. Kumar reported results of part 1.

To be eligible for enrollment in ENDURANCE, patients had to have newly diagnosed symptomatic multiple myeloma with no intent for immediate upfront ASCT. Patients with high-risk features were excluded, with the exception of t(4;14), which some consider to be a high-risk feature. Patients had to have an Eastern Cooperative Oncology Group performance status of 0 or 1; they also had to have adequate hematologic parameters and no organ failure. Peripheral neuropathy, heart failure, and myocardial infarction were exclusion criteria.

At baseline, both arms were well balanced for disease characteristics. Nearly one-third of patients were 70 years of age or older, and almost 12% were black. Nearly 10% had t(4;14). "The percentage of black patients [who are at higher risk] was much higher than in typical phase III trials," Dr. Kumar noted.

Patients were randomly assigned 1:1, and 1,053 of them started treatment. Induction therapy with VRd was given every 3 weeks, for a total of 12 cycles, and KRd was given every 4 weeks, for a total of 9 cycles. Induction therapy was completed by 43% of those assigned to VRd vs 61.6% of the KRd group.

Progression-free survival was analyzed at the second interim analysis, when 79% of planned events had occurred from the time of induction randomization. At that time, the results were released for futility.

Key Findings

Progression-free survival was almost identical in the two arms. Median progression-free survival was 34.4 months with VRd vs 34.6 months with KRd, at a median estimated follow-up of 15 months. For patients aged 70 or older, median progression-free survival was 31.7 months and 28 months with KRd. When censored for ASCT or alternative therapy, median progression-free survival was almost identical: 31.7 months and 32.8 months, respectively.

A subgroup analysis showed both regimens performed equally well in the majority of subgroups. However, there was a trend toward improved progression-free survival with KRd in patients with abnormal cytogenetics, whereas older patients seemed to do better with VRd.

Almost 85% of both treatment arms had an objective response. However, deeper responses were observed in KRd-treated patients. The rate of very good partial responses was higher with KRd (74% vs 65%, respectively, $P = .002$).

At the time of the presentation during ASCO20, 13.6% of patients in both arms had died, and overall survival seemed to be almost identical. Median overall survival has not yet been reached.

A similar percentage of patients in both treatment arms proceeded to ASCT: 28% in the VRd arm and 26.8% in the KRd arm. The median time to transplantation was 6.5 months and 8.5 months, respectively.

Adverse Events

The rate of grade 3 or higher treatment-related nonhematologic adverse events was 41% with VRd and 48% with KRd. The rates of peripheral neuropathy, fatigue, and diarrhea were higher in the VRd arm, whereas dyspnea, hypertension, heart failure, and acute kidney injury were more frequent in the KRd arm.

Significantly higher rates of cardiac, pulmonary, and renal toxicities were observed with KRd ($P < .001$), and a significantly higher rate of peripheral neuropathy was found with VRd ($P < .001$). The incidence of secondary primary cancers was about 3% in both arms.

Reference

1. Kumar SK, Jacobus SJ, Cohen AD, et al: Carfilzomib, lenalidomide, and dexamethasone (KRd) versus bortezomib, lenalidomide, and dexamethasone (VRd) for initial therapy of newly diagnosed multiple myeloma: Results of ENDURANCE (E1A11) phase III trial. ASCO20 Virtual Scientific Program. Abstract LBA3. Presented May 31, 2020.

The Advanced Practitioner Perspective

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As novel second-generation agents are developed for relapsed/refractory disease, it is always a question if the second-generation agents will outperform the first-generation class of medications in the frontline setting. The phase III ENDURANCE trial was designed to see if carfilzomib should replace bortezomib in combination with lenalidomide and dexamethasone for newly diagnosed multiple myeloma with standard risk cytogenetics, inclusive of t(4:14), which is typically characterized as an intermediate risk factor that can be mitigated with proteasome inhibitor therapy. Earlier phase II data from the NCT01402284 trial demonstrated that KRd was highly effective in the newly diagnosed setting and suggested greater efficacy than bortezomib-based therapy.

Given the phase II data, it was surprising to see the results from the phase III ENDURANCE trial that there was no difference in progression-free survival (PFS) or overall survival with KRd compared to VRd for newly diagnosed, standard-risk patients. Despite the higher rates of very good partial response achieved with the KRd arm compared with VRd, this did not translate to improved PFS or OS over VRd.

These results beg the following question: Which standard-risk myeloma patients benefit from KRd in the newly diagnosed setting? The ENDURANCE trial did demonstrate a clinically significant improvement with KRd for patients who had stage 3 disease and abnormal cytogenetics compared to VRd. In the VRd am, we saw a higher median PFS for patients over the age of 70 compared with those in this same age group with KRd. Given the results and reported toxicities from this trial, for myeloma patients with preexisting peripheral neuropathy and gastrointestinal issues or complex cytogenetics and higher-staged disease, KRd in the frontline setting would be an appropriate choice. For patients with preexisting cardiopulmonary and renal issues, or older age (greater than 70), VRd would an acceptable choice in the frontline setting. This emphasizes the fact that it is important to tailor treatment to the patient's individual characteristics and also potential adverse effects.

Implications for APs

As health-care providers, one fact we are certain of is that myeloma patients who continue on treatment have the best outcomes. In the ENDURANCE trial, 18% fewer patients completed the intended VRd induction regimen than KRd. The reasons for this could be toxicity, patients or their providers electing to proceed to stem cell transplant despite it not being the intended plan, or patient withdrawal or refusal. This highlights that optimizing the management of adverse events and communicating expectations is key for the advanced practitioner to allow patients to continue therapy for maximum efficacy.

As African Americans have the highest incidence of multiple myeloma compared to other ethnic groups, yet have poor representation in myeloma clinical trials, it was encouraging to see that nearly 12% of the patients in the ENDURANCE trial were African American. Enrollment in clinical trials can afford patients the opportunity to receive emerging novel agents that are being studied, and the underrepresentation of African Americans in myeloma clinical trials is a significant and preventable health-care disparity. As advanced practitioners, we must continue to communicate the importance of trial participation with minorities to continue to improve outcomes.

It will be interesting to see the additional conclusions from this trial, including the part 2 data revealing differences between maintenance dosing (continuous vs. fixed) and also results on minimal residual disease negativity rates and changes in gene mutation expression/clonal evolution, as this could shed more light on the inherent differences between these two highly efficacious induction regimens for newly diagnosed standard-risk multiple myeloma patients.

Disclosure: Ms. Pierre has served on advisory boards for Karyopharm and Amgen. She has also served as a consultant for Celgene.

Abstract 8507

Elotuzumab Fails to Add Benefit in Newly Diagnosed High-Risk Myeloma

By Caroline Helwick

Visit https://meetinglibrary.asco.org/record/186157/abstract to read the full abstract and view author disclosures.

The addition of elotuzumab to a standard three-drug induction regimen did not improve outcomes in patients with high-risk multiple myeloma enrolled in the randomized phase II SWOG S1211 trial, according to findings reported during the ASCO20 Virtual Scientific Program by Saad Zafar Usmani, MD, FACP, of Levine Cancer Institute/Atrium Health, Charlotte, North Carolina.[1]

"In the first randomized high-risk multiple myeloma study reported to date, the addition of elotuzumab to lenalidomide/bortezomib/dexamethasone [RVd] induction and maintenance did not improve patient outcomes," Dr. Usmani reported.

The S1211 trial randomly assigned 134 patients with newly diagnosed high-risk myeloma to RVd with or without elotuzumab at 10 mg/kg on days 1, 8, and 15. Induction consisted of eight 21-day cycles. Maintenance continued indefinitely with all RVd drugs given at lower doses and elotuzumab still administered at 10 mg/kg. The primary endpoint was progression-free survival.

The study hypothesized that the addition of elotuzumab could overcome high-risk features. High risk was defined by a poor-risk score on gene-expression profiling, one or more cytogenetic abnormalities, primary plasma cell leukemia, or elevated levels of serum lactate dehydrogenase (two times higher than the institutional upper limit of normal).

No Improvement in Progression-Free or Overall Survival

After 53 months' median follow-up, the addition of elotuzumab did not increase progression-free or overall survival. Median progression-free survival was 34 months with RVd and 31 months with RVd plus elotuzumab (P = .449). Median overall survival was not reached with RVd and was 68 months with RVd/elotuzumab (P = .239). "The median progression-free survival and overall survival seen in both arms of the study exceeded the original statistical assumptions," Dr. Usmani pointed out.

Response rates were also not significantly different: 88% with RVd and 83% with RVd/elotuzumab. The elotuzumab arm experienced more grade > 3 infections (16% vs 8%) and more peripheral neuropathy (13% vs 8%).

"This was the first randomized study evaluating the role of a monoclonal antibody in high-risk multiple myeloma. Although no benefit was found for elotuzumab, the study does support the role of a proteasome inhibitor plus immunomodulatory agent as maintenance therapy in this patient population," Dr. Usmani said. "The data will serve as a benchmark for future randomized, high-risk myeloma trials."

Reference

1. Usmani SZ, Ailawadhi S, Sexton R, et al: Primary analysis of the randomized phase II trial of bortezomib, lenalidomide, dexamethasone with/without elotuzumab for newly diagnosed, high-risk multiple myeloma (SWOG-1211). ASCO20 Virtual Scientific Program. Abstract 8507.

The Advanced Practitioner Perspective

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Multiple myeloma patients with high-risk features represent approximately 10% to 15% of patients at diagnosis. High-risk multiple myeloma was characterized in this trial as a poor risk score on gene-expression profiling, one or more cytogenetic abnormalities (t(14; 16), t(14; 20), del(17p) or amplification 1q21), primary plasma cell leukemia, or elevated levels of serum lactate dehydrogenase. These abnormalities can lead to poorer outcomes compared with those patients with standard risk multiple myeloma. Given this, finding a tailored therapy for high-risk multiple myeloma patients is crucial to help overcome these poor prognostic features. Elotuzumab, an anti-SLAMF7 monoclonal antibody, has a novel mechanism of action compared to other myeloma therapeutics and demonstrates synergy with lenalidomide and dexamethasone by enhancing cell-medi-

ated cytotoxicity of natural killer (NK) cells. The progressive decline in NK cell immunity as myeloma advances plays a key role in myeloma progression. Therefore, use of elotuzumab in combination with bortezomib, lenalidomide, and dexamethasone earlier in the disease trajectory, such as during induction and maintenance therapy, may prove advantageous in enhancing NK cell activity and possibly overcoming the earlier risk of relapse seen with high-risk multiple myeloma.

Surprisingly, the randomized phase II SWOG S1211 trial demonstrated that the addition of elotuzumab to a standard three-drug induction regimen of VRd or in maintenance therapy with VRd did not improve outcomes in patients with high-risk multiple myeloma. Other quadruplets with different mechanisms of action are being increasingly studied in the frontline setting in multiple myeloma and have been proven to demonstrate higher overall response rates compared to their triplet control arms. Unfortunately, this quadruplet regimen of Elo-VRd did not improve overall response rates compared to the triplet VRd.

Earlier studies with elotuzumab have established the increased risk of infections with this agent, and this was confirmed in the SWOG S1211 trial. However, what was surprising to see was the 5% increased risk of peripheral neuropathy with the addition of elotuzumab, as this agent typically is not associated with peripheral neuropathy.

This was the first major trial designed to address the disparate gap in outcomes we see for high-risk multiple myeloma patients. Despite the lack of benefit seen with the addition of elotuzumab to VRd, the study did prove that the addition of a proteasome inhibitor to lenalidomide in the maintenance setting can be beneficial for high-risk multiple myeloma patients, as the median overall survival was not reached with the RVd maintenance group, which is impressive in this patient population.

Implications for APs

As advanced practitioners in oncology, we strive to achieve optimal outcomes for our patients, particularly those at high risk. This trial incorporated the toughest myeloma patients to treat and was able to exceed the original statistical assumptions for median overall survival with continuous maintenance therapy with VRd. As advanced practitioners, we can feel confident in educating our patients with high-risk multiple myeloma that augmenting their lenalidomide maintenance therapy could potentially allow improved overall survival outcomes for this at-risk group of patients.

Disclosure: Ms. Pierre has served on advisory boards for Karyopharm and Amgen. She has also served as a consultant for Celgene.

Abstracts 8503, 8504, and 8505

Clinical Trials of Chimeric Antigen Receptor T-Cell Therapies for Relapsed/Refractory Multiple Myeloma

By P. Andrew Allred

Visit https://meetinglibrary.asco.org/record/186139/abstract, https://meetinglibrary.asco.org/record/186159/abstract, and https://meetinglibrary.asco.org/record/186155/abstract to read the full abstracts and view disclosures.

During the virtually held American Society of Clinical Oncology (ASCO) Annual Meeting in May 2020, exciting data were shared on B-cell maturation antigen (BCMA)-targeted chimeric antigen receptor (CAR) T-cell therapies in the treatment of relapsed/refractory multiple myeloma (RRMM) from the KarMMa, EVOLVE, and CARTITUDE studies.

Idecabtagene Vicleucel (ide-cel; bb2121), a BCMA-Targeted CAR T-Cell Therapy, in Patients With RRMM: Initial KarMMa Results

The BCMA-targeted CAR T-cell therapy idecabtagene vicleucel (ide-cel) is currently being researched in the phase II KarMMa study. Initial data from this ongoing clinical trial were reported in Abstract 8503. Munshi and colleagues stated this therapy "showed promising tolerability and efficacy in RRMM patients in the phase I CRB-401 study." Relapsed/refractory multiple myeloma patients were defined as those who pro-

gressed through three or more prior regimens that included immunomodulatory agents, proteasome inhibitors, and anti-CD38 antibodies. A total of 140 patients were enrolled in the study, and 128 received ide-cel following lymphodepletion with fludarabine and cyclophosphamide. Nearly 90% of patients received bridging therapy while CAR T-cells were being manufactured.

The median follow-up was 11.3 months. The overall response rate was 73%, and median progression-free survival was 8.6 months. There was a positive correlation between dose and overall response rate/progression-free survival. Overall response rate was 50% among older and high-risk patients. The most common toxicities were cytopenias at a rate of 97% and cytokine release syndrome (CRS) at a rate of 84%. Most CRS was either grade 1 or 2; however, five patients had grade 3, one patient experienced grade 4, and one patient expired from cytokine release syndrome. Neurotoxicity was not seen infrequently, with 18% of patients developing the side effect, but only three patients experienced grade 3 toxicity. Researchers concluded that "Ide-cel demonstrated deep, durable responses in heavily pretreated RRMM [patients]. Efficacy and safety reflected prior reports and support a favorable ide-cel clinical benefit-risk profile across the target dose range."

Orvacabtagene Autoleucel (orva-cel), a BCMA-Directed CAR T-Cell Therapy for Patients With RRMM: Update of the Phase I/II EVOLVE Study

Updated data from the phase I/II EVOLVE study reported in Abstract 8504 by Mailankody and colleagues demonstrate the safety and efficacy of orvacabtagene autoleucel (orva-cel), another BCMA-directed CAR-T cell therapy, for heavily pretreated RRMM patients. Orva-cel is unique in that it has a fully human binder. Fifty-one RRMM patients who progressed through at least three lines of therapy, including a proteasome inhibitor, immunomodulatory drug, and anti-CD38 monoclonal antibody, were given fludarabine and cyclophosphamide lymphodepleting therapy and then infused with orva-cel. These patients had a median time from diagnosis of 7 years and a median of six prior regimens. Just over 60% of patients received bridging therapy.

The safety and tolerability of the therapy were demonstrated with only two patients experiencing dose-limiting toxicities, which included neutropenia and a neurological event. Only 2% of patients experienced CRS of grade 3 or greater, and 4% of patients experienced neurological events of grade 3 or higher. The efficacy was demonstrated with a 91% objective response rate and a 39% complete response/stringent complete response rate. The authors concluded that "Orva-cel at [higher doses] demonstrated manageable safety and compelling efficacy in heavily pretreated patients with relapsed refractory multiple myeloma."

Update of CARTITUDE-1: A Phase Ib/II Study of JNJ-4528, a BCMA-Directed CAR T-Cell Therapy in RRMM

In Abstract 8505, Berdeja and colleagues reported new data from the phase Ib/II clinical trial, CARTITUDE, which also studied a BCMA-directed CAR-T cell therapy, JNJ-68284528 (JNJ-4528), in RRMM patients. Study subjects were required to have a diagnosis of multiple myeloma, measurable disease, demonstrated refractoriness to a proteasome inhibitor and immunomodulatory drug, and received an anti-CD38 antibody. JNJ-4528 was administered after the patient had received 3 days of lymphodepletion with cyclophosphamide and fludarabine.

The median follow-up time was 9 months. All patients developed neutropenia, 93% experienced CRS, and 93% had thrombocytopenia. Of those experiencing CRS, 25 patients experienced grade 1/2, one experienced grade 3, and one expired at day 99 from prolonged cytokine release syndrome. Only four patients experienced treatment-related neurotoxicity, one of which was grade 3.

Astonishingly, this BCMA-targeting CAR-T cell therapy demonstrated a 100% overall response rate, with 76% of patients achieving a complete response and 21% a very good partial response. Sixteen of the study subjects were evaluable 6 months post therapy for minimal residual disease (which is highly sensitive testing that can detect a single myeloma cell out of 100,000 to 1,000,000 cells), and all had undetectable disease. The researchers concluded that "JNJ-4528 treatment led to responses in

all [patients]. These responses were early, deep, and durable at a low dose of CAR-T cells with 26/29 (90%) [of patients] progression free at median 9-[months] follow-up. [Cytokine release syndrome] was manageable in most patients, supporting outpatient dosing." ●

The Advanced Practitioner Perspective

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Multiple myeloma is a blood cancer of plasma cells that is treatable, but almost always relapses or becomes refractory to treatment. Current therapies for multiple myeloma include chemotherapy, proteasome inhibitors, immunomodulatory drugs, anti-CD38 monoclonal antibodies, steroids, and autologous hematopoietic stem cell transplantation among others. Novel drug classes, newer generations of agents, and varying combinations of therapies have resulted in better progression-free and overall survival for multiple myeloma. However, a cure is still elusive for nearly all patients. In the words of Sumit Madan, MD, Director of the Myeloma Program at Banner MD Anderson Cancer Center, "If a cure for myeloma is to be found, it will require more than the current approved therapies. We need new classes of drugs with novel mechanisms and their combinations to cure myeloma."

For this reason, the early successes of B-cell maturation antigen (BCMA)-targeted chimeric antigen receptor (CAR) T-cell clinical trials in relapsed/refractory multiple myeloma are tremendously exciting. Particularly compelling is the 100% overall response and 76% complete response rates of JNJ-4528 in multiple myeloma that has relapsed after or is refractory to immunomodulatory drugs and proteasome inhibitors. Arguably more impressive is the 91% objective response and 39% complete response rates of orvacabtagene autoleucel in relapsed/refractory multiple myeloma patients who had received a median of six prior regimes. These efficacy data coupled with strong safety data bring new hope to patients and providers dealing with relapsed/refractory multiple myeloma, which is notoriously difficult to treat.

Implications for APs

Advanced practitioners working in hematology/oncology regularly are asked about upcoming and cutting-edge therapies, especially by patients newly diagnosed with cancer. It is important to note that CAR T-cell therapies at the time of this writing are only U.S. Food & Drug Administration (FDA) approved in two populations: 1) adults with certain relapsed or refractory B-cell lymphomas and 2) children or young adults with relapsed or refractory acute lymphoblastic leukemia. However, further FDA approval for CAR-T cell therapy in mantle cell lymphoma is rumored to be expected by the end of 2020. Should the KarMMa, EVOLVE, and CARTITUDE studies continue to demonstrate high levels of safety and efficacy, FDA approval of BCMA-targeted CAR T-cell therapies in relapsed/refractory multiple myeloma is all but certain in the next few years.

Disclosure: Mr. Allred has no conflicts of interest to disclose.

Abstract 7500

Ivosidenib Plus Venetoclax With or Without Azacitidine for *IDH1*-Mutated AML

By The ASCO Post Staff

Visit https://meetinglibrary.asco.org/record/185312/abstract to read the full abstracts and view author disclosures.

Combination therapy with the isocitrate dehydrogenase 1 (IDH1) inhibitor ivosenidib plus the BCL2 inhibitor venetoclax with or without hypomethylating agent azacitidine showed activity in patients with *IDH1*-mutated acute myeloid leukemia (AML) in a phase Ib/II trial. The results of the study—presented by Lachowiez et al during the Hematologic Malignancies Oral Abstract Session of the ASCO20 Virtual Scientific Program (Abstract 7500)—may support a novel course of action for patients with AML harboring an *IDH1* mutation—a group who have historically had few treatment options.

Mutations in the *IDH1* gene lead to myeloid differentiation arrest and subsequent induction of leukemia. Ivosidenib, as an IDH1 inhibitor, is a well-tolerated oral therapy that aims to interrupt this leukemogenic process.

The combination of venetoclax and azacitidine was previously established to be well tolerated and effective against newly diagnosed AML, and ivosidenib is approved as a single agent for relapsed *IDH1*-mutated AML. This trial sought to evaluate the safety, tolerability, and response rate of adding ivosidenib to either venetoclax alone as an oral doublet, or to the combination of azacitidine/venetoclax to treat this subset of patients with AML and a specific genetic mutation.

"This trial is the manifestation of remarkable basic and translational work that is resulting in improved clinical outcomes for patients," said lead author Curtis Lachowiez, MD, hematology fellow at The University of Texas MD Anderson Cancer Center, in an institutional statement. "The triplet combination may ultimately result in a new, effective therapeutic regimen. As the median age at AML diagnosis is 68, these findings are particularly important for older [patients with] AML who may not be fit enough to receive the aggressive cytotoxic chemotherapy regimens historically used to treat AML."

Study Methods and Findings

Patients with AML or high-risk myelodysplastic syndrome were assigned one of three treatment cohorts: ivosidenib plus venetoclax at 400 mg, ivosidenib plus venetoclax at 800 mg, or ivosidenib plus venetoclax at 400 mg plus azacitidine.

Across all treatment groups, the composite complete remission rate was 78% overall and 100% for treatment-naive patients. Half of the patients who achieved complete remission also were negative for minimal residual disease.

The median time to best response was 2 months. Of the 18 evaluable patients, 9 remain enrolled in the study, and 3 proceeded to receive a stem cell transplant following complete remission.

"To our knowledge, azacitidine plus venetoclax and azacitidine plus ivosidenib 'doublets' are effective but not curative for newly diagnosed [patients with] *IDH1*-mutated AML, and patients still ultimately relapse. This triplet combination trial aims to determine whether this regimen leads to deeper responses and even curative therapy in some patients," said Courtney DiNardo, MD, Associate Professor of Leukemia at MD Anderson and the study's senior author. "Additionally, this trial evaluates the oral ivosidenib plus venetoclax doublet for the first time, and we hope patients will benefit from this outpatient regimen."

Based on a patient's molecular profile, their care team may be able to decide on options like closer monitoring or earlier transition to transplant for high-risk patients. Further, as in the case of patients with molecular mutations associated with favorable responses, the care team may be able to prescribe tailored therapeutic combinations, leading to durable remissions and potential cures.

"This study is exciting because it displays that we are able to tailor therapy for...patients based on their molecular profile," said Dr. Lachowiez. "While some mutations have traditionally been associated with poor outcomes, we can now identify certain subgroups of patients with genetic mutations who are more likely to respond to a specific therapy, and then we can design a treatment and follow-up plan to best suit them."

Study accrual is continuing, and the research team is conducting additional follow-up to elucidate biomarkers and potential duration of response. ●

The Advanced Practitioner Perspective

Allyson Price, PA-C
MD Anderson Cancer Center

This study is of interest because it gives this specific patient population another treatment option. With increased genomic profiling and the utilization of tailored treatment, we are able to target *IDH1* mutation while introducing a BCL2 inhibitor (assisting with apoptosis) with or without a hypomethylating agent. *IDH1* is present in approximately 7% to 14% of AML patients. While ivosidenib is FDA approved for relapsed AML as monotherapy, the use of combination therapy in this study demonstrates successful composite complete remission (CRc: $CR+CR_i+CR_h$) rates at 78% overall. This is also an important decision as AML patients with *IDH1* mutations can harbor other

mutations such as *NPM1* or *RAS*. The combination therapy also seems to be tolerable with dose adjustments or prolonged cycles secondary to myelosuppression.

Of note, patients during cycle 1 need to remain in the vicinity of the institution administering the therapy. The patient will need to be monitored at minimum once weekly for pancytopenia, transfusion needs, and adverse events. After cycle 1, the patient is required to return biweekly for cycle 2 and then monthly for cycles 3 to 12. If the patient has a sustained remission (determined per bone marrow), then the patient can have the medications shipped to a local oncologist and return to the treating facility every 3 months. The patient is required to return a medication diary to the research team for increased compliance and monitoring. For cohort 1 and 2, this is appealing for patients because it eliminates either IV or subcutaneous chemotherapy. Advanced practitioners will have to be a vital part of compliance and ensure that the patient is taking both medications daily and as directed.

During the COVID-19 pandemic, this study has not seen a decline in participant enrollment. We have been able to safely monitor adverse events with the assistance and communication between local oncologist and academic centers. The research team has maintained documentation of any deviations and requests labs per trial requirements. We have also utilized telemedicine/virtual visits to assist in the safety monitoring of this trial. We have been able to ship medications to patients. Further follow-up and accrual of patients is ongoing and needed to better define duration and response rates. We need to continue to assess allelic burden of *IDH1* and biomarker response.

Disclosure: Ms. Price has no conflicts of interest to disclose.

Abstract 7506

Mikkael A. Sekeres, MD, on MDS, CMML, or AML: Pevonedistat and Azacitidine

By The ASCO Post Staff

Visit https://meetinglibrary.asco.org/record/185314/abstract to read the full abstracts and view author disclosures.

Mikkael A. Sekeres, MD, of the Cleveland Clinic, discusses data from a phase II study of pevonedistat plus azacitidine vs azacitidine alone in patients with higher-risk myelodysplastic syndromes, chronic myelomonocytic leukemia, or low-blast acute myeloid leukemia (Abstract 7506). Below is a transcript of an interview with Dr. Sekeres that has been edited for length.

Commentary by Mikkael A. Sekeres, MD

In the phase II study of pevonedistat and azacitidine vs. azacitidine alone in patients with higher risk myelodysplastic syndrome, chronic myelomonocytic leukemia, or low-blast count acute myeloid leukemia, we looked at the experimental agent pevonedistat, which inhibits NEDD8-activating enzyme, also known as a neddylation inhibitor. By doing this, it affects DNA replication as a cell cycle inhibitor and affects NF-κB signaling, leading to cell apoptosis and cancer cell death.

In this study, we randomized 120 patients to receive pevonedistat and azacitidine vs. azacitidine alone. We followed these patients for a primary endpoint of overall survival (OS), with event-free survival (EFS) and response rate as the secondary endpoints. The median age of patients enrolled on this study was approximately 72 years. 67 of these patients had higher-risk myelodysplastic syndromes (prognostic risk category based on the IPSS-R: very high = >6 points, high = >4.5–6 points), 17 had chronic myelomonocytic leukemia, and 36 had low-blast acute myeloid leukemia.

Interestingly, adverse events were similar between the two arms. We had anticipated we would see increased rates of adverse events for the combination. In fact, we didn't, including similar rates of suppression of blood counts and febrile neutropenia.

There was an improvement for patients who received pevonedistat and azacitidine with a median EFS of 21 months vs. 16.6 months for azacitidine, with a trend towards significance.

This study was not powered to look at differences in OS. However, there was an improvement in the median OS for those patients who received pevonedistat and azacitidine at 22 months vs. 19 months for azacitidine that was not significantly different.

Focusing on the group of patients with higher-risk myelodysplastic syndrome, there was a significant improvement in median EFS for those who received pevonedistat and azacitidine at 20 months vs. 14.8 months for those who received azacitidine. There was a numerical improvement in OS for those who got the combination at a median of 24 months vs. 19 months for those who received azacitidine.

When we focus specifically on the population of patients who had low blast count acute myeloid leukemia, there was a trend towards significant improvement in median OS for those who got the combination at a median of 23.6 months vs. 16 months for those who received azacitidine monotherapy.

Our conclusion from this study is that there was an improvement for patients who received azacitidine and pevonedistat vs. azacitidine alone. And this was likely in part due to the tolerability of the combination. Patients could receive the combination of drugs for a long enough period of time to enjoy their improvements in EFS, and in some, in OS. ●

The Advanced Practitioner Perspective

Allyson Price, PA-C
MD Anderson Cancer Center

This abstract highlights the use of pevonedistat, a small-molecule inhibitor of the NEDD8-activating enzyme that controls the degradation of many proteins that play vital roles in cell-cycle progression and DNA damage. It has shown promising clinical activity, specifically in EFS of high-risk MDS/CMML and low-blast AML.

Patients enrolled in this study were naive to hypomethylating agents and were randomized 1:1 with pevonedistat + azacitidine vs. azacitidine monotherapy. Pevonedistat is given IV for ~60 minutes on days 1, 3, and 5. The combination is noted to have a similar side effect profile to azacitidine and is well tolerated. In addition, patients were not noted to have an increase in neutropenic fevers, which is important in treatment decision-making and continuation of care.

The average age of patients enrolled was in the 70s, and an ECOG between 0 to 2 was accepted. This highlights an older patient population, which we often have difficulty treating. Since there is no cure for MDS/CMML, clinical trial enrollment with low side effect profile, tolerability, logistics, and overall improvement in EFS/OS are important in our treatment plan. It will be interesting to look at other parameters of this study, including transfusion dependency and duration of OS.

Disclosure: Ms. Price has no conflicts of interest to disclose.

Abstract 7508

Farhad Ravandi-Kashani, MD, on Acute Myeloid Leukemia: AMG 330 in Patients With Relapsed or Refractory Disease

By The ASCO Post Staff

Visit https://meetinglibrary.asco.org/record/185299/abstract to read the full abstract and view author disclosures.

Farhad Ravandi-Kashani, MD, of MD Anderson Cancer Center, discusses updates from a phase I dose-escalation study of AMG 330, a bispecific T-cell engager molecule. It showed early evidence of an acceptable safety profile, drug tolerability, and antileukemic activity, supporting further dose escalation in patients with acute myeloid leukemia. A transcript of the commentary by Dr. Ravandi-Kashani follows.

Commentary by Farhad Ravandi-Kashani, MD

AMG 330 is a canonical bispecific T-cell engager (BiTE) molecule. It targets CD3 on the surface of

T cells and CD33 on the surface of AML blasts. CD33 is a well-established target on AML blasts and is expressed on the majority of AML blasts and not the hematopoietic stem cells and not outside the hematopoietic system.

AMG 330 brings T cells into close proximity of CD33-expressing AML blasts and results in activation of T cells, leading to the killing of AML cells by T cells. This was a phase I dose escalation study. The initial 5 cohorts were single-patient cohorts, and the subsequent cohorts were using a classic 3+3 dose escalation design.

The expected toxicity of BiTE molecules is cytokine release syndrome. A number of strategies were employed to try to mitigate this. First, by using dexamethasone steroid prophylaxis prior to step-up doses, and also by stepping up the dosing schedule where lower doses were given initially, and then higher doses were given in the next step of dose escalation, which allowed an eventually higher-target dose to be achieved with acceptable toxicity.

60 patients were enrolled in this study, all with confirmed diagnoses of AML in relapse. A majority of patients had heavy pretreatment with multiple prior regimens, with at least half of patients having 4 or more prior therapies.

There were 8 responses, including 3 CRs, 4 CRis, and 1 morphological leukemia-free state. The latter cohorts of the study were associated with a higher response rate, where there was a 21% CR/CRi in the last three cohorts of the study.

There were a number of potential correlations explaining response. For example, higher disease burden was associated with a lower likelihood of response, as well as a higher likelihood of developing cytokine release syndrome. Also, release of cytokines such as IL-6, as expected, was associated with a higher likelihood of developing cytokine release syndrome.

Overall, this study showed that this molecule is relatively safe without any significant toxicity beyond the expected cytokine release syndrome, which can be managed with medication strategies (steroid prophylaxis, tocilizumab, as well as a step-up dosing schedule).

There were responses, and these responses were more likely to occur where a higher-target dose of AMG 330 was achieved. ●

The Advanced Practitioner Perspective

Allyson Price, PA-C
MD Anderson Cancer Center

This abstract highlights a patient population that is difficult to treat in the relapsed/refractory period. Many patients on this trial were heavily pretreated prior to enrollment. Antibodies are increasingly used in treating hematologic malignancies. AMG 330 is a BiTE molecule that targets CD3 on T cells and CD33 on myeloblasts, allowing the T cells to target these CD33+ cells, activate T cells, and lead to apoptosis. Primary endpoints for this phase I trial were incidence of adverse events and dose-limiting toxicities.

Logistical Considerations

Unfortunately, AMG 330 is a continuous infusion via pump that patients carry for 2 to 4 weeks. Patients can be apprehensive about this. They are required to remain inpatient during dose escalations, which presents its own issues, especially with no-visitor policies during the pandemic. Patients require frequent lab reviews, physical examinations, and EKGs per protocol. They need to be monitored for cytokine release syndrome (CRS), and prophylaxis for CRS is not definitively defined. CRS typically occurs within the first 24 hours of administration, and there is a correlation between disease burden and CRS severity. This is a phase I study and further information regarding safety profile, tolerability, and overall response rate is still needed.

As is the case for most phase I trials, logistics may be a potential issue for enrollment. As advanced practitioners, we need to ensure patients understand the requirements for cycle 1 and beyond, including testing, repeat bone marrows, and ability to stay at the treating facility. This patient population is complex and options are limited; we look forward to adding the potential of more antibody therapies to the treatment landscape in relapsed/refractory AML.

Disclosure: Ms. Price has no conflicts of interest to disclose.