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JANUARY 2020

Evidence-Based ONCOLOGY

Exclusive Coverage of the
2019 American Society of Hematology Annual Meeting

DECEMBER 7-10 | ORLANDO, FLORIDA

Daratumumab Plus Carfilzomib and Dexamethasone Extends PFS in Relapsed/Refractory Myeloma

Jason M. Broderick

ADDING DARATUMUMAB (DARZALEX) to carfilzomib (Kyprolis) and dexamethasone (Decadron)—together, KdD—reduced the risk of disease progression or death by 37% compared with carfilzomib and dexamethasone (Kd) in patients with relapsed/refractory multiple myeloma, according to findings from the phase 3 CANDOR trial (NCT03158688).

The median progression-free survival (PFS) was not yet reached with the addition of the anti-CD38 antibody daratumumab compared with 15.8 months with Kd alone (hazard ratio [HR], 0.63; 95% CI, 0.46-0.85; $P = .0014$). At a median follow-up of 17 months, the median overall survival (OS) had not yet been reached in either arm (HR, 0.75; 95% CI, 0.49-1.13; $P = .08$).

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Initial Higher-Dose Duvelisib Improves Responses in Relapsed/Refractory PTCL

Lynne Lederman, PhD

PATIENTS WITH RELAPSED/refractory peripheral T-cell lymphoma (PTCL) who received a higher initial dose of duvelisib (Copiktra) of 75 mg twice daily had a higher overall response rate (ORR) of 62% compared with 40% in those who received 25 mg twice daily, according to data from the dose-optimization phase of the PRIMO trial (NCT03372057).

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Daratumumab Plus Carfilzomib and Dexamethasone Extends PFS in Relapsed/Refractory Myeloma

(CONTINUED FROM COVER)

"Patients treated with KdD achieved deeper responses than patients treated with Kd, with a nearly 10-times higher MRD [minimal residual disease]–negative complete response (CR) rate at 12 months versus Kd-treated patients," said lead study author Saad Z. Usmani, MD, of the Levine Cancer Institute. "KdD should be considered as a novel, efficacious, and tolerable [immunomodulatory imide drug]-free treatment option for relapsed/refractory multiple myeloma," Usmani added.

The open-label phase 3 CANDOR trial randomized (2:1) 466 patients with relapsed/refractory multiple myeloma treated with 1 to 3 prior therapies to either KdD (n = 312) or Kd (n = 154). Prior treatment with anti-CD38 antibodies and carfilzomib was allowed, as long as the patient reached at least a partial response, did not relapse for at least 60 days from treatment discontinuation, and had at least a 6-month treatment-free interval at the time of initiating study therapy. Overall, 90% of patents had taken bortezomib (Velcade), and 42% of patients had prior lenalidomide (Revlimid). One-third (33%) of patients were lenalidomide-refractory.

All treatments were administered over 28-day cycles. Daratumumab 16 mg/kg was administered on days 1, 8, 15, and 22 of cycles 1 and 2, every 2 weeks during cycles 3 to 6, and every 4 weeks during cycle 7 and beyond. Usmani noted that for patient convenience, the initial dose of daratumumab was split into two 8-mg/kg doses and administered on cycle 1, day 1 and cycle 2, day 2.

Carfilzomib and dexamethasone were administered at the same dose and schedule in both arms. Patients received carfilzomib on days 1, 2, 8, 9, 15, and 16 of each cycle. For cycle 1 only, patients received a 20-mg/m^2 loading dose of carfilzomib on days 1 and 2; the proteasome inhibitor was given at a dose of 56 mg/m^2 for all subsequent treatments. Dexamethasone was administered at 40 mg on days 1, 8, 15, and 22 of each cycle. During weeks when patients received carfilzomib and/or daratumumab infusions, a split dose of 20 mg each of dexamethasone was administered.

The primary end point was PFS, with key secondary end points including overall response rate (ORR), MRD-negative status, CR rate at 12 months, OS, duration of response, and safety.

Among patients exposed to lenalidomide, the median PFS was not reached in the KdD arm compared with 12.1 months in the Kd arm (HR, 0.52; 95% CI, 0.34-0.80). In patients who were refractory to lenalidomide, the median PFS was not reached in the KdD arm compared with 11.1 months in the Kd arm (HR, 0.45; 95% CI, 0.28-0.74).

"The PFS benefit of KdD is maintained in both lenalidomide-exposed and -refractory patients," said Usmani.

The ORR was 84.3% with KdD compared with 74.7% with Kd (P = .0040). The rates of CR or better were 28.5% versus 10.4%, respectively. The median time to first response was 1 month in both treatment arms. Among patients receiving KdD, the MRD-negative rate at 12 months was 12.5% compared with 1.3% with Kd.

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The American Journal of Managed Care® ISSN 1088-0224 (print) & ISSN 1936-2692 (online) is published monthly by Managed Care & Healthcare Communications, LLC, 2 Clarke Drive, Suite 100, Cranbury, NJ 08512.

"Patients treated with KdD showed improved and deeper responses than with Kd alone," said Usmani.

The safety analysis included 308 patients in the KdD arm and 153 patients in the Kd arm.

The overall safety profile with the treatment regimens was similar to what has been previously reported with single-agent use of these agents. The median treatment duration was 70.1 weeks in the KdD arm and 40.3 weeks in the Kd arm.

The rates of grade 3 or higher adverse events (AEs) were 56.2% versus 45.8%, and the rates of serious AEs were 56.2% versus 45.8%, in the KdD and Kd arms, respectively. The discontinuation rates due to AEs were 22.4% versus 24.8%, respectively. In the KdD arm, 3.9% of patients had grade 3 or higher cardiac failure compared with 8.5% in the Kd arm. Cardiac failure led to carfilzomib discontinuation in 3.9% versus 4.6% of the 2 arms, respectively.

"Although KdD patients had higher rates of grade 3 or higher AEs, treatment discontinuations due to AEs were similar in both arms and the safety profile was tolerable," said Usmani.

There were 5 treatment-related deaths, all occurring in the KdD arm, 1 each from pneumonia, sepsis, septic shock, *Acinetobacter* infection, and cardiorespiratory arrest.

"Four of the [5 deaths] were related to infections, and we know from other randomized phase 3 relapsed/refractory trials, as well as frontline studies, that the incidence of infection tends to be higher in both daratumumab- as well as carfilzomib-based regimens, but we haven't [previously] seen a fatal AE signal. I think you have to keep in context the patient population and also the fact that there were no differences in overall survival," said Usmani.

"The attribution [of the deaths] was definitely associated with treatment as per the definition—it is [considered] a treatment-emergent AE even if the therapy has been discontinued and the event happens within 30 days after that. But it's certainly pointing more toward infections rather than any other worrisome signal," added Usmani. ◆

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Initial Higher-Dose Duvelisib Improves Responses in Relapsed/Refractory PTCL

(CONTINUED FROM COVER)

Duvelisib, a dual phosphoinositide-3 kinase (PI3K)-δ,γ inhibitor, showed activity in patients with relapsed/refractory PTCL and cutaneous T-cell lymphoma in small phase 1 studies and was granted fast-track designation by the FDA for the treatment of patients with PTCL who had received at least 1 prior therapy. The phase 2 trial was designed to determine an optimal regimen of duvelisib monotherapy in relapsed/refractory PTCL and to characterize the efficacy and tolerability of duvelisib in this disease.

"Early on we saw a strong signal of activity in patients with peripheral T-cell lymphoma with duvelisib in the phase 1 study," said Steven M. Horwitz, MD, a medical oncologist at Memorial Sloan Kettering Cancer Center, during his presentation.

The primary end point for the dose-optimization phase is investigator-assessed ORR, and for the dose-expansion phase, it is ORR by blinded independent review committee (IRC). The dose-optimization phase enrolled 33 patients with relapsed/refractory PTCL who had received at least 2 cycles of 1 prior therapy that did not include a PI3K inhibitor. Patients received duvelisib twice daily at 25 mg (cohort 1, n = 20) or 75 mg (cohort 2, n = 13). At the start of therapy, patients had a median time of 1.5 years from initial diagnosis and a median of 2 prior therapies.

Patients were evaluable if they completed 1 cycle of duvelisib and had at least 1 efficacy assessment. Response was assessed in the evaluable and overall populations. All patients in cohort 2 and 13 of 20 patients in cohort 1 completed 1 cycle of therapy. Seven patients in cohort 1 discontinued therapy early because of disease progression and/or toxicity.

Pharmacokinetic (PK) analysis demonstrated a dose-related increase in exposure, with about a 2-fold increase in the steady-state exposure of duvelisib at the 75- versus 25-mg twice-daily dose. No differences were observed in pharmacodynamic markers (pAKT in monocytes and B cells) at the 25- and 75-mg dose levels.

Responses were observed in both cohorts. In the modified intent-to-treat population (mITT) who had received at least 1 dose of the study drug, ORR was 54% by investigator assessment and 62% by IRC assessment in the 75-mg cohort; ORR for the 25-mg group was 35% by investigator assessment and 40% by IRC assessment.

There were 4 patients with complete responses (CRs) in the 75-mg cohort and 5 patients with CRs in the 25-mg cohort. Four patients in the 25-mg cohort had stable disease at the end of cycle 1 and received an escalated dose of 50 mg of duvelisib twice a day. Of the 4 patients, responses were seen in 2 patients as determined by investigator assessment; these 4 patients were also assessed by IRC, with 3 patients identified as responders. There was no correlation between drug exposure and efficacy in a preliminary analysis.

There were no unexpected toxicities. All patients experienced treatment-emergent adverse events (TEAEs); serious TEAEs occurred in 75% of patients in the 25-mg cohort and 69% of patients in the 75-mg cohort. Serious adverse events (AEs) included colitis, pyrexia, disease progression, sepsis, pneumonia, hyponatremia, dyspnea, pneumonitis, and respiratory failure. There were 5 fatal AEs in the 25-mg cohort and 1 in the 75-mg cohort. Discontinuations because of AEs occurred in 30% of patients in the 25-mg cohort and 8% of patients in the 75-mg cohort. Grade 4 low CD4 counts (<50 cells/mm^3) were associated with early discontinuation of duvelisib.

"One of the questions was, 'Is there an optimal dose for the T-cell lymphoma, and is that dose different from the FDA-approved dose?'" said Horwitz. "The short conclusion is that for these aggressive diseases, starting with the high dose is better, probably due to more reliable early PK to control aggressive disease and reduce the risk of early progression."

The expansion phase of the PRIMO trial will investigate duvelisib starting at 75 mg twice daily for 2 cycles to achieve rapid tumor response, followed by 25 mg twice daily to maintain long-term disease control and mitigate the potential for later-onset toxicity, with a target enrollment of 100 patients.

"Of course, when we have a targeted agent [like duvelisib], if we can understand the use, our long-term goal is to move these into combination therapies where we can have the greatest impact on what happens to patients," Horwitz concluded. ◆

REFERENCE

Horwitz SM, Mehta-Shah N, Pro B, et al. Dose optimization of duvelisib in patients with relapsed or refractory peripheral T-cell lymphoma from the phase 2 Primo trial: selection of regimen for the dose-expansion phase. Presented at: 61st American Society of Hematology Annual Meeting and Exposition; December 7-10, 2019; Orlando, FL. Abstract 1567.

Lenalidomide Plus Obinutuzumab Achieves 100% Overall Response Rate in Rituximab-Refractory Indolent Non-Hodgkin Lymphoma

Gina Columbus

THE COMBINATION OF LENALIDOMIDE (REVLIMID) and obinutuzumab (Gazyva) elicited a 100% overall response rate (ORR) in patients with relapsed indolent non-Hodgkin lymphoma (NHL) that was refractory to rituximab (Rituxan), according to findings from a single-arm, phase 1/2 trial.

Specifically, in a subgroup of patients with marginal zone lymphoma (MZL) and small lymphocytic lymphoma (SLL), results showed that the ORR was 88%, which included a complete response (CR)/CR unconfirmed (CRu) rate of 44%, a partial response (PR) rate of 44%, and a 25% rate of stable disease (SD). In patients with follicular lymphoma, the ORR was 100%, with a 75% CR/CRu rate, and a 25% PR rate. No cases of progressive disease (PD) were observed in either group.

"The combination of lenalidomide and obinutuzumab is very active with high response rates in [patients with] relapsed low-grade lymphoma, and, importantly, we saw very high responses in 3 subsets of patients: those who are rituximab refractory, those who had progressed within 2 years, and those who are in their third line of therapy," lead study author Nathan Fowler, MD, professor of medicine,

Department of Lymphoma and Myeloma, Division of Cancer Medicine at The University of Texas MD Anderson Cancer Center, said in a presentation. "The toxicity profile was very similar to what we reported in several trials with lenalidomide/rituximab."

Treatment options for patients with relapsed indolent NHL are often linked with short remissions or intolerable adverse events (AEs). Preclinical data have demonstrated that lenalidomide in additsion to a CD20-directed monoclonal antibody increases antibody-dependent cellular cytotoxicity (ADCC). While lenalidomide plus rituximab is highly active in patients with treatment-naive and relapsed indolent NHL, obinutuzumab is said to have enhanced affinity for the FcγRIIIa reception, which leads to improved ADCC and is also active in rituximab-refractory NHL, thus demonstrating rationale for this trial, according to Fowler.

In the phase 1/2 trial, investigators evaluated the combination of lenalidomide and obinutuzumab in 66 patients with grade 1 to 3a follicular lymphoma (n = 57), SLL (n = 5), or MZL (n = 4). Patients could not have had transformation of disease and must have received at least 1 prior therapy to be eligible for enrollment.

Treatment was given in a 3 + 3 study design with 3 dose levels of lenalidomide at 10 mg, 15 mg, or 20 mg on days 2 through 22 in 28-day cycles; if patients were responding at the end of 6 cycles, they were given the option to stop therapy. Otherwise, they received lenalidomide for up to 12 cycles. Obinutuzumab was given weekly at 1000 mg in cycle 1, followed by monthly doses for up to 6 cycles. After this, obinutuzumab was switched to a maintenance schedule and administered every 2 months for up to 30 months. If patients progressed after 1 year of lenalidomide/obinutuzumab, treatment was discontinued.

The median age of participants was 64 years (range, 36-81), and 35 (53%) patients were men. Fourteen (23%), 31 (47%), and 17 (26%) patients had 1, 2, or 3 or more prior lines of therapy, respectively. Sixteen (24%) patients were refractory to rituximab, 50 (76%) received a prior chemotherapy backbone, and 3 (5%) were previously treated with lenalidomide and rituximab. The coprimary end points of the trial were maximum tolerated dose (MTD) and ORR; secondary end points included PR and CR rates, progression-free survival (PFS), overall survival (OS), and effect on tumor and immune microenvironment.

In the phase 1 portion of the trial, the recommended dose for lenalidomide when in combination with obinutuzumab was determined to be 20 mg. No dose-limiting toxicities were observed. The median time to response, evaluated by Cheson criteria, was 3 months, and all patients were evaluable for response; 23 patients remain on therapy. Moreover, in patients who were refractory to rituximab, the ORR with the combination was 100% with a 63% CR rate; 6 PRs were reported in this subgroup, and no patients had SD. For patients who received 3 or more prior lines of therapy, the ORR was 97%, the CR rate was 68%, and the PR rate was 29%; 1 (3%) patient had SD. Patients who had disease progression within 2 years achieved a 96% ORR, which comprised a 66% CR rate, 30% PR rate, and 4% SD rate. No cases of PD were reported in any of these 3 stratified groups. "You see a trend that, regardless of these different populations, the ORR and CR rates were actually fairly similar," Fowler commented.

At a median follow-up of 17.7 months, the median projected 2-year PFS rate in all evaluable patients was 73% (95% CI, 58-83). When broken down by disease state, the projected 2-year PFS rate in patients with follicular lymphoma was 74% and 65% in those with MZL/SLL. For those who received at least 2 prior lines of therapy, the median projected 2-year PFS rate was 64%. The rates differed slightly for patients who received 6 or fewer cycles versus greater than 6 cycles of combination therapy, at 72% versus 78%, respectively. The projected 2-year OS rate in all evaluable patients was 94% (95% CI, 77-98).

Regarding safety, grade 3/4 hematologic adverse events (AEs) included anemia (2%), neutropenia (21%), and thrombocytopenia (11%). Most nonhematologic AEs that occurred in more than 10% of patients were grade 1/2; grade 3 or higher AEs that occurred in more than 1 patient were cardiac disorders, cough, fatigue, infection, pain, and rash. Specifically, grade 3/4 rash was reported in approximately 6% of patients, and 2 patients developed grade 4 sepsis.

"Grade 3/4 infections were seen in approximately 13% to 14% of patients; fatigue was the most common [AE], although most of the patients' [events were] grade 1/2," said Fowler. "We also saw rash as we would expect from a drug like lenalidomide and occasionally constipation and diarrhea, although very few of these were grade 3/4."

Prophylactic growth factor was not allowed, but it was permitted if patients developed neutropenia at any time during the trial (n = 14). Five secondary malignancies were reported, 4 of which occurred in 1 patient, Fowler added. Fowler noted in his presentation that correlative studies are ongoing to predict patients who are at risk of early relapse with the combination. Furthermore, larger randomized studies are needed to determine if this regimen is superior to lenalidomide combined with rituximab, he concluded.◆

REFERENCE

Fowler NH, Nastoupil LJ, Chin C, et al. A phase I/II study of lenalidomide plus obinutuzumab in relapsed indolent lymphoma. Presented at: 61st American Society of Hematology Annual Meeting and Exposition; December 7-10, 2019; Orlando, FL. Abstract 348.

The Resistance-Targeting BTK Inhibitor ARQ 531 Is Active Across B-Cell Malignancies

THE INVESTIGATIONAL BRUTON tyrosine kinase (BTK) inhibitor ARQ 531 demonstrated safety and clinical activity across a range of B-cell malignancies, a preliminary clinical trial showed.

Overall, 14 of 47 patients had partial responses (PRs) with ARQ 531, which targets the *BTK* C481S mutation associated with resistance to ibrutinib (Imbruvica). An additional 10 patients had stable disease associated with tumor reduction of as much as 48%. Responses were observed in patients with chronic lymphocytic leukemia (CLL), Richter transformation (RT), diffuse large B-cell lymphoma (DLBCL), and follicular lymphoma (FL).

Across a range of doses as high as 75 mg once daily, no dose-limiting toxicity occurred, and treatment with ARQ 531 was associated with a low frequency of toxicities. No atrial fibrillation or bleeding occurred, Jennifer Woyach, MD, an associate professor at The Ohio State University Comprehensive Cancer Center—James, said at the 2019 American Society of Hematology (ASH) Annual Meeting.

"You can definitely see that responses are very good," Woyach noted in an interview. "This and other studies of other agents in this class have confirmed the efficacy of this class of drugs, the reversible BTK inhibitors."

"For this study, 2 things really are striking," continued Woyach. "One is that 89% of patients with [*BTK* C481S–mutated CLL] who were treated at the recommended phase 2, 65-mg dose responded. [Further], half of the people with Richter's transformation responded, and Richter's is a very unmet need in CLL, very difficult to treat. Seeing that kind of activity early on is really encouraging."

Despite major advances in the treatment of B-cell malignancies cases, primary and secondary resistance continue to emerge, as well as the association with poor outcomes and limited available treatment optionsWoyach said 80% to 85% of patients who progress on BTK inhibitor therapy do so because of the emergence of the *BTK* C481S mutation.

ARQ 531 is an orally available, reversible, dual inhibitor of wild-type and C481S-mutant *BTK*. The drug has demonstrated superiority over ibrutinib in mouse models of CLL and DLBCL, and targets ibrutinib-resistant CLL, RT, and other B-cell malignancies, Woyach and colleagues noted in a poster presentation.

During the presentations, results of a phase 1 dose-escalation trial involving patients with relapsed or refractory B-cell malignancies were discussed. The objectives were to evaluate the safety, pharmacology, and anticancer activity of ARQ 531 in patients with *BTK* C481S resistance mutations.

Forty-seven patients enrolled in the study had a median age of 65, and men accounted for 85% of the total. The cohort comprised 29 patients with CLL/small lymphocytic lymphoma and 18 with B-cell non-Hodgkin lymphomas: 9 with RT, 3 with DLBCL, 4 with FL, and 1 each with mantle cell lymphoma and Waldenstrom macroglobulinemia (WM), respectively. Patients had received a median of 4 (range, 1-12) prior systemic regimens.

Investigators evaluated ARQ 531 doses ranging from, at most, 30 mg once daily to 75 mg once daily. The 13 patients who received the recommended phase 2 dose consisted of 5 patients with CLL, 7 with RT, and 1 with WM.

Eight of 9 patients with high-risk relapsed/refractory CLL achieved PRs with the 65-mg dose. Three of 6 patients with RT treated with the 65-mg dose also had PRs. The remaining 3 responses all occurred at ARQ 531 doses ≥45 mg. Three additional patients with RT were able to proceed with chimeric antigen receptor (CAR) T-cell therapy.

The 1 dose-limiting toxicity in the trial (grade 3 generalized rash) occurred in a patient with CLL treated with the 65-mg dose. The most common adverse events (AEs; all patients/grades) were: hypertension (34%), back pain (32%), nausea (30%), fatigue (30%), rash (28%), constipation (28%), peripheral edema (26%), pyrexia (26%), headache (26%), diarrhea (23%), upper respiratory tract infection (23%), and cough (23%). The most common grade 3 or higher AEs included decreased neutrophil count (19%) and decreased platelets, anemia, and hypertension (13% each).

Drug-related AEs were uncommon. Grade 3 or higher drug-related AEs consisted of 6 (13%) cases of decreased neutrophil count, 2 (4%) cases of decreased platelets, and 1 (2%) case of rash.

With respect to pharmacokinetics, the 65-mg dose of ARQ 531 achieved a steady-state mean C_{min} exceeding 1 µM and plasma half-life of 56 hours. At the recommended phase 2 dose, ARQ 531 drives complete BTK inhibition.

Woyach et al reported that ongoing clinical development of ARQ 531 includes phase 2 studies in relapsed/refractory CLL, RT, and multiple B-cell malignancies. Plans for trials of combination therapy and earlier lines of therapy are in development. ◆

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Woyach J, Stephens DM, Flinn IW, et al. Final results of phase 1, dose escalation study evaluating ARQ 531 in patients with relapsed or refractory B-cell lymphoid malignancies. Presented at: 61st American Society of Hematology Annual Meeting and Exposition; December 7-10, 2019; Orlando, FL. Abstract 4298.

Acalabrutinib Alone or in Combination Improves PFS in Frontline CLL

Gina Columbus

ACALABRUTINIB (CALQUENCE) AS A SINGLE AGENT or in combination with obinutuzumab (Gazyva) led to a statistically significant improvement in progression-free survival (PFS) compared with obinutuzumab plus chlorambucil in treatment-naive patients with chronic lymphocytic leukemia (CLL), according to results from the phase 3 ELEVATE-TN trial (NCT02475681).

At a median follow-up of 28.3 months, the combination of the Bruton tyrosine kinase (BTK) inhibitor with obinutuzumab led to a 90% reduction in the risk of disease progression or death compared with obinutuzumab/chlorambucil (hazard ratio [HR], 0.10; 95% CI, 0.06-0.17; *P* <.0001). When used as a monotherapy, acalabrutinib also showed a statistically significant benefit in PFS (HR, 0.20; 95% CI, 0.13-0.30; *P* <.0001).

"Acalabrutinib has demonstrated efficacy and a consistent safety profile in treatment-naive and relapsed/refractory patients and is now an approved treatment option for patients with CLL," said lead study author Jeff P. Sharman, MD, director of research at Willamette Valley Cancer Institute and medical director of hematology research for The US Oncology Network, in a presentation.

Obinutuzumab combined with chlorambucil was a standard frontline option for patients with CLL prior to the introduction of the BTK inhibitor ibrutinib (Imbruvica). In November 2019, the FDA granted approval to acalabrutinib for the treatment of patients with CLL or small lymphocytic lymphoma, partly based on data from the ELEVATE-TN trial, as well as the ASCEND trial (NCT02970318), which evaluated the BTK inhibitor compared with either rituximab (Rituxan) or idelalisib (Zydelig) in previously treated patients with CLL.

"Acalabrutinib is a more selective BTK inhibitor, with less off-target kinase inhibition in vitro compared with ibrutinib and a favorable safety profile, prompting this evaluation as a frontline therapy with or without obinutuzumab," Sharman said.

In the randomized, multicenter, open-label, phase 3 ELEVATE-TN (ACE-CL-007) trial, investigators evaluated the safety and efficacy of acalabrutinib alone or in combination with obinutuzumab versus chlorambucil/obinutuzumab in 535 treatment-naive patients with CLL. Patients were randomized 1:1:1 into 3 arms: chlorambucil plus obinutuzumab (n = 177), 100 mg of acalabrutinib twice daily in combination with obinutuzumab until disease progression or unacceptable toxicity (n = 179), or single-agent acalabrutinib at 100 mg twice daily until disease progression or unacceptable toxicity (n = 179). Patients were stratified by 17p deletion status, Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 1 or 2, and geographic region. Crossover from the obinutuzumab/chlorambucil arm was permitted after independent review committee (IRC)–confirmed disease progression; therefore, these patients were not included in the PFS data that were presented.

Baseline characteristics were similar across the 3 treatment arms. The median patient age for the trial was 70.5 years, 63% of patients had an unmutated *IGHV*, 47% had Rai stage III or IV disease, 18% had 11q deletion, and 14% had 17p deletion or *TP53* mutation. Most patients (93.6%) had an ECOG performance status between 0 and 1. High-risk features were evenly distributed.

The treatment discontinuation rates were 20.7%, 20.1%, and 18.1% in the acalabrutinib/obinutuzumab, acalabrutinib-alone, and obinutuzumab/chlorambucil arms, respectively. The most common reason patients discontinued treatment was due to adverse events (AEs), which occurred in 11.2%, 8.9%, and 14.1% of patients, respectively. Two deaths were reported in the acalabrutinib combination arm, 3 deaths in the single-agent acalabrutinib arm, and 1 death in the chemoimmunotherapy group. The median duration of treatment in the acalabrutinib arms was 27.7 months and 5.6 months in the chlorambucil/obinutuzumab arm; 79.3% of patients were still continuing on treatment.

The primary end point was PFS in the acalabrutinib/obinutuzumab arm compared with the chlorambucil/obinutuzumab arm, as assessed by IRC. Secondary end points included IRC-assessed PFS in the acalabrutinib-alone arm versus chlorambucil/obinutuzumab, as well as objective response rate (ORR), time to next treatment, overall survival (OS), and safety.

Results by IRC assessment showed that the median PFS was not reached with either acalabrutinib arm, compared with 22.6 months (95% CI, 20.2-27.6) with

chlorambucil/obinutuzumab. The 2-year PFS rates were 93%, 87%, and 47% for acalabrutinib/obinutuzumab, single-agent acalabrutinib, and chemoimmunotherapy, respectively.

Although the trial was not powered or designed to compare the PFS outcomes between the 2 acalabrutinib arms, Sharman noted that an exploratory post hoc analysis showed that acalabrutinib plus obinutuzumab was superior to acalabrutinib alone (HR, 0.49; 95% CI, 0.26-0.95).

The IRC-assessed PFS benefit with the acalabrutinib regimens was found to be consistent across prespecified subgroups, irrespective of high-risk disease characteristics.

"In contrast with several recent studies, treatment with the combination of acalabrutinib/obinutuzumab yielded an overall PFS benefit compared with the control in both unmutated and mutated *IGHV* subgroups," Sharman explained.

OS favored both the acalabrutinib/obinutuzumab arm (HR, 0.47; 95% CI, 0.21-1.06; $P = .0577$) and the single-agent acalabrutinib arm (HR, 0.60; 95% CI, 0.28-1.27; $P = .1556$); however, this benefit was not found to be statistically significant. The estimated 2-year OS rates were 95%, 95%, and 92% with acalabrutinib/obinutuzumab, acalabrutinib alone, and chemoimmunotherapy, respectively.

Thirty-one percent of patients who were randomized to chemoimmunotherapy experienced disease progression, and 82% of this subgroup crossed over to receive the BTK inhibitor alone.

"Despite crossover for disease progression in the obinutuzumab/chlorambucil arm, fewer deaths were seen with acalabrutinib/obinutuzumab and acalabrutinib monotherapy, though longer follow-up is needed to detect a difference in OS," Sharman said.

Additionally, the IRC-assessed ORR was 93.9% (95% CI, 89.3-96.5) with acalabrutinib/obinutuzumab and 78.5% (95% CI, 71.6-89.9) with chemoimmunotherapy ($P < .0001$), a difference that was found to be statistically significant. The acalabrutinib combination ORR comprised a 13% complete response (CR) rate and an 81% partial response (PR) rate; 2% of patients achieved stable disease (SD).

In the single-agent acalabrutinib arm, the ORR was 85.5% (95% CI, 79.6-89.9), with a 1% CR rate, an 85% PR rate, and a 5% SD rate; compared with the chlorambucil/obinutuzumab ORR, this difference was not found to be statistically significant, according to Sharman. The obinutuzumab/chlorambucil arm consisted of a 5% CR rate, 74% PR rate, and a 9% SD rate.

Due to the study design in which continuous BTK inhibitor therapy was compared with fixed-duration chemoimmunotherapy, Sharman noted that there was an imbalance of reporting AEs that occurred within 30 days of the last dose, with a longer reporting period in the BTK inhibitor–containing arms.

Regarding safety, no new or unexpected patterns were observed. At least 1 all-grade AE was observed in all 3 arms; more serious AEs were observed with acalabrutinib/obinutuzumab (38.8%) compared with acalabrutinib alone (31.8%) or obinutuzumab/chlorambucil (21.9%). The rates of grade 3 or higher AEs were 70.2%, 49.7%, and 69.8%, respectively. Twelve grade 5 AEs were observed in the chemoimmunotherapy arm, 7 in the acalabrutinib monotherapy arm, and 5 in the acalabrutinib combination arm; these were observed from the entire treatment-emergent and nontreatment-emergent period.

The most common all-grade AEs (≥15%) in the acalabrutinib/obinutuzumab and single-agent acalabrutinib arms were headache (39.9% vs 36.9%, respectively), diarrhea (38.8% vs 34.6%), neutropenia (31.5% vs 10.6%), fatigue (28.1% vs 18.4%), contusion (23.6% vs 15.1%), arthralgia (21.9% vs 15.6%), cough (21.9% vs 18.4%), upper respiratory tract infection (21.3 vs 18.4%), nausea (20.2% vs 22.3%), and dizziness (18.0% vs 11.7%). Grade 3 or higher neutropenia was highest with obinutuzumab/chlorambucil (41.4%) versus acalabrutinib/obinutuzumab (29.8%) and acalabrutinib alone (9.5%).

The most common (≥2%) serious AEs with acalabrutinib/obinutuzumab, acalabrutinib alone, and obinutuzumab/chlorambucil were pneumonia (6.7% vs 2.8% vs 1.8%, respectively), infusion-related event (2.2% vs 0% vs 1.2%), anemia (1.7% vs 2.2% vs 0%), febrile neutropenia (1.7% vs 1.1% vs 4.1%), and tumor lysis syndrome (0.6% vs 0% vs 4.7%). These events were consistent with the previously established safety profile of this class of agents, Sharman said.

Specific AEs were of clinical interest for acalabrutinib. Any-grade atrial fibrillation was observed in 6 (3.4%) patients receiving acalabrutinib/obinutuzumab, 1 of which was at least grade 3. Seven cases of atrial fibrillation were observed in the acalabrutinib-only arm. Hypertension, bleeding, infections, and second primary malignancies, excluding nonmelanoma skin cancer, were also AEs of interest with the BTK inhibitor. ◆

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Carfilzomib Treatment Frequency, Maintenance Regimens, and Minimal Residual Disease in Multiple Myeloma

Hayley Fahey

CARFILZOMIB HAS BEEN SHOWN to offer unique benefits when used in combination with other agents in patients with multiple myeloma (MM). Results from the CANDOR trial, for example, showed a 37% reduced risk of disease progression or death with the addition of daratumumab to carfilzomib plus dexamethasone compared with carfilzomib plus dexamethasone in patients with relapsed or refractory MM (RRMM).[1] Beyond the CANDOR data, the clinical profile of carfilzomib continues to take shape, as evidenced by findings from several other studies investigating the agent in different patient populations. This article reviews a selection of these studies.

Once-Weekly Versus Twice-Weekly Carfilzomib

To better understand the impact of treatment frequency on efficacy, investigators conducted a systematic review of the safety and efficacy of twice-weekly carfilzomib-based therapies in RRMM, in accordance with the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) criteria. Through in-depth searches of PubMed, EMBASE, AdisInsight, and www.clinicaltrials.gov, investigators identified the most recent clinical trials that have tested the clinical efficacy and safety of carfilzomib in this patient population.[2]

Investigators evaluated once-weekly carfilzomib in 406 patients across 4 trials, compared with twice-weekly carfilzomib in 1869 patients across 16 trials. All studies that were included reported patient responses based on International Myeloma Working Group response criteria. There were reports of high-risk cytogenetics in 15% (n = 60) of patients in the once-weekly dosing population and 17% (n = 317) in the twice-weekly dosing group. Of all patients evaluated, patients had between 1 and 8 prior lines of therapy in the once-weekly cohort and between 1 and 20 in the twice-weekly cohort. Patients receiving once-weekly carfilzomib achieved a higher cumulative overall response rate compared with patients receiving the twice-weekly regimen (70.4% [n = 286] vs 48.0% [n = 896], respectively), as well as a better complete response (CR; 11.5% [n = 47] vs 5.2% [n = 99]). Very good partial response was achieved in 30% (n = 123) of patients in the once-weekly group versus 21% (n = 389) of patients in the twice-weekly group, with partial response rates of 28.5% (n = 116) and 22% (n = 412), respectively.[2]

Both groups achieved similar minimal response rates (5% in the once-weekly group vs 8% in the twice-weekly group); however, fewer patients who were taking carfilzomib once weekly experienced disease progression compared with the twice-weekly dosing group (5.6% [n= 23] vs 15.6% [n= 293], respectively). Patients in the twice-weekly group were found to have a higher rate of stable disease than those in the once-weekly group (20.0% vs 12.3%, respectively). The phase 1 data from most clinical trials analyzing once-weekly dosing did not have mature survival data; however, median progression-free survival (PFS) was found to range from 1 day to 12.6 months in patients taking carfilzomib once weekly and 3.7 to 44.4 months in the twice-weekly cohort.[2]

Toxicity profiles were similar between the dosing groups. The most prevalent hematologic adverse events (AEs) among patients in both groups were anemia and thrombocytopenia. Fatigue, nausea, and infections were the most common nonhematologic AEs in both groups. Hypertension was the most common cardiac AE and contributed to 50% (n = 7) and 64% (n = 40) of all grade 3 cardiac AEs in the once-weekly and twice-weekly groups, respectively. Grade 3 or higher cardiac AEs were documented in 3.4% and 3.3% of patients in the once- and twice-weekly dosing cohorts, respectively.[2]

In addition to these findings indicating superior or at least similar response rates for once-weekly dosing compared with twice-weekly dosing, there may also be a financial and convenience benefit for patients using the once-weekly option. Nevertheless, the investigators noted that more research is needed to confirm the ideal treatment frequency with carfilzomib.[2]

Maintenance Therapy in Elderly Patients

Carfilzomib has also been explored as maintenance therapy. The multicenter, phase 1 IFM 2012-03 study evaluated carfilzomib maintenance therapy in elderly patients with newly diagnosed MM who previously received the combination of carfilzomib, melphalan, and prednisone.[3]

Investigators recruited 30 patients, with a median age of 75 years, and Revised International Staging System stage II or III MM. Eleven percent of patients were high-risk

cytogenetic. Carfilzomib maintenance therapy was given every 2 weeks for 13 cycles at 36 mg/m^2. Among 22 patients who started therapy, 16 (73%) completed treatment. Four participants experienced disease progression, and 2 patients discontinued treatment due to AEs (renal amyloidosis, sensory neuropathy), while on maintenance therapy. The CR following maintenance therapy completion (50%) was comparable to the CR following the previous combination regimen (46.7%). Three patients (14%) showed an improvement in treatment response during maintenance therapy.[3]

Investigators noted that carfilzomib monotherapy can be administered to elderly patients with newly diagnosed MM who are older than 75 years of age as a safe maintenance therapy for 1 year. They also suggested that carfilzomib, because of its deep response rate, could be considered an alternative to lenalidomide as a maintenance therapy. However, because of the small patient population of the study, more data are needed to confirm the results.[3]

Minimal Residual Disease

With the development of new methods to measure the effects of minimal residual disease (MRD) in MM, clinicians increasingly may classify response based on MRD levels. In one study, investigators used multiparameter flow cytometry to analyze patient responses to carfilzomib plus lenalidomide and dexamethasone (together, KRd) and compare survival outcomes among the different cohorts, defined by MRD categorization.[4]

The EuroFlow next-generation flow method was used to evaluate patients with RRMM who received KRd therapy at 4 centers from September 2016 to October 2018. After multiple cycles of KRd therapy, investigators evaluated MRD levels using bone marrow cells with lower limit detection set at 1 x 10^{-5}. Fluorescence in situ hybridization (FISH) was used to detect the incidence of high-risk cytogenetics (del17p, t[4;14], t[14;16]) in bone marrow cells.[4]

Twenty-one patients were selected, with a median age of 66 years at KRd initiation (range, 30-83) and a median of 3 (range, 1-6) prior treatments, including bortezomib (n = 12), lenalidomide (n = 19), and autologous stem cell transplantation (n = 12). High-risk chromosomal abnormalities were present in 4 patients, including del17p and t(14;16). The proportion of patients who achieved a complete or partial response was significantly higher in patients after KRd treatment compared with previous therapies. Responses before KRd treatment included 2 stringent CRs, 7 very good partial responses, 6 partial responses, 3 cases of stable disease, and 3 cases of progressive disease; after KRd treatment, responses improved in 19 (90%) patients and were consistent in 2 (10%) patients who had a partial response. MRD negativity was accomplished in 12 of 16 (75%) patients during therapy and 15 of 21 (71%) patients after therapy; all 4 patients with high-risk cytogenetics achieved MRD negativity.[4]

The range of treatment lines following KRd therapy was 0 to 5 (median, 1). Two-year PFS and 2-year overall survival from KRd initiation was achieved in 100% of patients who were MRD positive. Among patients who were MRD negative, 2-year PFS and 2-year overall survival from KRd initiation was reached in 92% and 100% of patients, respectively. Median follow-up was 1.8 years. There was 1 case of a patient who was MRD negative who was not high-risk cytogenetic and experienced extramedullary relapse at 1.4 years following the last KRd cycle. Investigators found that KRd elicited a deep response in RRMM patients, who all eventually achieved a high PFS. They noted that further imaging studies may be needed postremission in patients who experienced extramedullary plasmacytomas, even with accomplished flow MRD negativity.[4]

MRD negativity is also the subject of another study evaluating patients with newly diagnosed MM. Sharing preliminary findings from an ongoing phase 2 study, investigators evaluated 2 patient groups (N = 82) based on Simon's optimal 2-stage design, with one group (n = 41) receiving weekly dosing of carfilzomib 56 mg/m^2 with lenalidomide and dexamethasone in combination with daratumumab (wKRd-D), and the other parallel group (n = 41) receiving biweekly (twice a week) dosing of carfilzomib 36 mg/m^2 with lenalidomide and dexamethasone plus daratumumab (bKRd-D). The primary end point was to achieve an MRD negativity rate of up to 80%.[5]

Physically fit patients were recommended to undergo stem cell collection following 4 to 6 cycles of therapy. Bone marrow–based MRD assays were used to assess treatment response (1 myeloma cell in 100,000 bone marrow cells [10^{-5}]) using 10-color single-tube flow cytometry and Invivoscribe IGHV sequencing. Targeted DNA sequencing for FISH-Seq and somatic mutational characteristics were used to analyze baseline bone marrow samples.[5]

Currently, the first stage of the cohort receiving KRd-D weekly has been entirely enrolled (N = 28), with 13 more patients expected to complete enrollment in the second stage shortly. A total of 29 patients have currently met the criteria (14 men, 15 women). The median age is 59 years, and 12 (41%) patients have a high-risk FISH/single nucleotide polymorphism signature of 1 or more of the following: 1q+, t(4;14), t(14;16), t(14;20), and 17p–. As of December 2019, 28 patients have completed at least 1 cycle of wKRd-D, and 10 have completed therapy (median number of cycles, 6). Seven of these 10 patients have been shown to be MRD negative. Among patients receiving weekly dosing who were eligible to be evaluated for the MRD primary

end point, 15 of 18 (83%) patients showed MRD negativity. There have been no reports of major clinical toxicities with wKRd-D compared with bKRd-D. Results from the biweekly dosing group and weekly dosing group were comparable, with similar safety and efficacy profiles, but significant reductions in the number of infusions (51 vs 27, respectively) led investigators to conclude that wKRd-D may be an appealing option for patients with newly diagnosed MM.[5]

Conclusions

These additional analyses provide insights into using carfilzomib in different patient groups with MM, as well as decreasing the rate of MRD. With further research in these areas in larger patient populations, the use of carfilzomib could continue to expand across the MM treatment spectrum. ◆

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Enasidenib Plus Azacitidine Significantly Improves Responses in Newly Diagnosed *IDH2*-Mutated AML

Wayne Kuznar

ENASIDENIB (IDHIFA), AN ORAL, SMALL MOLECULE inhibitor of mutant isocitrate dehydrogenase (NADP(+)) 2, mitochondrial (*IDH2)* proteins, significantly improves complete remission and overall response when combined with azacitidine (Vidaza) compared with azacitidine alone in patients with newly diagnosed acute myeloid leukemia (AML) with *IDH2* mutations, according to data from an interim phase 2 trial.[1]

Results from the ongoing AG221-AML-005 trial (NCT02677922) revealed that at a median follow-up of 14 months, median event-free survival (EFS) was 17.2 months in patients randomized to receive the combination of enasidenib and azacitidine compared with 10.8 months in those who were given azacitidine alone (hazard ratio [HR], 0.59; 95% CI, 0.30-1.17; $P = .1278$), said Courtney D. DiNardo, MD, an assistant professor in the Department of Leukemia, Division of Cancer Medicine at The University of Texas MD Anderson Cancer Center.

No significant difference in overall survival (OS) was observed between the 2 groups, but 21% of patients in the azacitidine-alone arm received subsequent treatment with enasidenib monotherapy after discontinuation, noted DiNardo.

IDH2 mutations occur in around 8% to 19% of patients with AML[2]; they are often considered to be founder mutations with stability over the course of therapy. "It is now well recognized that *IDH2* mutations can be acquired at the time of progression, of transformation [of] myelodysplastic syndrome, or even more commonly, myeloproliferative neoplasms," she said.[3] *IDH2* mutations lead to the accumulation of 2-hydroxyglutarate (HG), an oncometabolite that competitively inhibits alpha-ketoglutarate, which is a key required substrate for many dioxygenase reactions.

Enasidenib, already approved by the FDA for use in adults with *IDH2*-mutant relapsed/refractory AML, indirectly reduces DNA methylation by suppressing 2-HG, thereby

restoring function to alpha-ketoglutarate–dependent ten-eleven translocation family enzymes, among other substrates.

In a large phase 1/2 study, enasidenib monotherapy led to an overall response rate (ORR) of 30.8% in patients with newly diagnosed AML and a complete response (CR) rate of 18%.[4] In vitro, the combination of enasidenib and azacitidine enhanced single-agent effects on releasing differentiation block and reduced leukemic stem/progenitor cell populations.[5] Tolerability and efficacy data from the phase 1b dose-finding portion of the current study supported further testing of the combination, according to DiNardo.

The phase 2 portion of the trial enrolled 101 patients with newly diagnosed *IDH2*-mutant AML who were ineligible to receive intensive chemotherapy. Participants were randomized 2:1 to receive either enasidenib plus azacitidine or azacitidine alone in repeated 28-day cycles. All patients received subcutaneous azacitidine at 75 mg/m^2/d for the first 7 days of each treatment cycle; patients who were randomized to the combination also received continuous enasidenib at 100 mg once daily.

The median age of the study population was 75 years (range, 62-85). About one-fourth of patients enrolled in the trial had secondary AML. At baseline, about one-fourth of patients had an *IDH2*-R140 mutation, and about one-fourth had an *IDH2*-R172 mutation. Forty-five patients in the combination arm and 18 in the azacitidine monotherapy arm had comutations. The most common co-occurring mutations were *DNA (cytosine-5)-methyltransferase 3A, ASXL1*, and *runt-related transcription factor 1*. "[There was] a notable underrepresentation of patients with either *FMS-like tyrosine kinase 3 internal tandem duplication* or *nucleophosmin* compared with expectations," said DiNardo. Eighty percent of patients had intermediate-risk cytogenetics in the combination arm.

At the time of data cutoff, August 19, 2019, 94% of patients in the azacitidine-alone arm and 69% in the combination arm had discontinued therapy. The most common reason for discontinuation in both arms was disease progression: 52% in the azacitidine-alone arm and 31% in the combination arm. Discontinuation due to adverse events (AEs) was rare in both arms, at 6%.

The ORR was 71% in the combination arm (95% CI, 58-81) and 42% in the azacitidine-alone arm (95% CI, 26-61; $P = .0064$); the CR rates were 53% (95% CI, 41-65) versus 12% (95% CI, 3-28; $P = .0001$), respectively. Time to first response was about 2 months in each arm, and the time to CR was 5.5 months (range, 0.7-19.5) with enasidenib/azacitidine and 3.7 months (range, 3.0-4.1) with azacitidine alone. In patients who responded, the median duration of response was 24.1 months (range, 11.1-not reached) with combination enasidenib/azacitidine and 12.1 months (range, 2.8-14.6) with azacitidine alone.

"Responses were observed in patients with Ras pathway comutations, which have been associated with resistance to enasidenib monotherapy," DiNardo said.

The median number of treatment cycles received was 10 in the combination arm and 6 in the azacitidine-only arm. The most common treatment-emergent adverse events (TEAEs) with enasidenib/azacitidine and azacitidine alone were thrombocytopenia (62% and 44%, respectively), nausea (69% and 38%), anemia (53% and 44%), and vomiting (49% and 47%). Grade 3 or higher AEs were similar between arms, with the exception of isocitrate dehydrogenase differentiation syndrome (IDH-DS). In the combination arm, IDH-DS occurred in 18% of patients at a median of 28.5 days. The median time to IDH-DS resolution was 11.5 days.

The 60-day mortality rates were 7% in the combination arm and 3% in the azacitidine-only arm. Most deaths were related to progression of disease. Two deaths were considered likely or possibly due to IDH-DS.

The historical median OS with azacitidine alone is about 10 months, noted DiNardo. In this study, the median OS in either arm was 22 months. In patients treated with the combination who achieved a CR, the median OS was not reached, with an estimated 1-year OS greater than 90%.

"We saw deep reductions in 2-HG concentrations with the combination, which is indicative of on-target activity," DiNardo said. "The combination led to impressive reductions in the IDH2 variant allele frequency." ◆

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Triplet Regimen Induces High Rate of Complete Response in Relapsed/Refractory Follicular Lymphoma

THE COMBINATION OF POLATUZUMAB VEDOTIN (POLIVY), obinutuzumab (Gazyva), and lenalidomide (Revlimid) induced a high rate of durable responses in patients with relapsed/refractory follicular lymphoma, according to new findings.

Catherine Diefenbach, MD, director of the Clinical Lymphoma Program at NYU Langone Health's Perlmutter Cancer Center, reported responses by both the Lugano 2014 criteria and the modified Lugano 2014 criteria. By the original Lugano criteria, 83% of patients had investigator-assessed objective responses, with 76% by independent review. Complete response (CR) rates were 74% and 72%, respectively. The 12-month progression-free survival (PFS) rate was 83%. By the modified criteria, the investigator-assessed response rate was 83%, decreasing to 76% by independent review. CR rates were 61% and 63%, respectively.

"Our study of the novel triplet combination demonstrates a safety profile consistent with the known profiles of the individual drugs," Diefenbach said. "The first report of the full efficacy population showed high complete response rates at the end of induction therapy in a heavily pretreated and refractory population, which compares favorably with currently available therapies for relapsed and refractory follicular lymphoma."

A subgroup analysis showed an objective response rate (ORR) of 55% and a CR rate of 45% in patients whose disease progressed within 24 months during first-line therapy, and an ORR of 83% and CR of 80% in patients who had no progression after 24 months. Patients with Follicular Lymphoma International Prognostic Index (FLIPI) low-risk (0-2) disease had an 85% ORR, including CR in 75% of patients, compared with an ORR of 70% in the FLIPI high-risk subgroup. All responses in the FLIPI high-risk cohort were CRs.

Additional response analyses showed an ORR of 68% for patients who were refractory to their last line of therapy and 86% for those who were not refractory. ORR was 77% for those who underwent 1 or 2 prior lines of therapy versus 75% for patients who underwent 3 or more lines of therapy. "These compelling findings support further investigation in a larger patient population as this novel triplet combination has a potential place as therapy for patients with relapsed and refractory follicular lymphoma," Diefenbach said.

After a median follow-up of 15.1 months, the data remain immature for calculating the median PFS, she added. The trial design included a dose-escalation phase that identified the recommended phase 2 dosing of 1.4 mg/kg polatuzumab vedotin, 20 mg lenalidomide, and 1000 mg obinutuzumab. Induction consisted of day 1 dosing of polatuzumab vedotin for six 28-day cycles, obinutuzumab on day 1 of the first cycle and then days 1, 8, and 15 on cycles 2 through 6, and lenalidomide on days 1 to 21 of each cycle.

Patients who attained an objective response or stable disease continued treatment with obinutuzumab for a maximum of 24 months and lenalidomide for 12 months. After excluding 10 patients who did not receive the recommended phase 2 dosing, 46 patients remained for the efficacy analysis, 39 of whom completed the induction phase.

The median age was 62 years, and men accounted for 59% of the total population. Diefenbach reported that 88% of patients had Ann Arbor stage III/IV disease, 16% had bulky disease, 43% had bone marrow involvement, and 55% had ≥3 FLIPI.

Patients had received a median of 3 prior lines of therapy: 59% were refractory to the last prior therapy, 71% were refractory to any anti-CD20 therapy, and 25% had disease progression within 24 months on first-line therapy.

Thirty-one (55%) patients experienced grade 3/4 neutropenia. The second most common adverse event (AE) was thrombocytopenia (27%), infections (20%), anemia (14%), and febrile neutropenia (11%). AEs of special interest included tumor flare in 4 patients and myelodysplastic syndrome and lung malignancy in 1 patient each. Seventy-seven percent of patients had AEs leading to dose interruption, 34% required dose reduction, and 30% discontinued because of AEs.

In June 2019, the FDA approved polatuzumab vedotin in combination with bendamustine (Bendeka) and rituximab (Rituxan) for the treatment of adults with relapsed/refractory diffuse large B-cell lymphoma who had received at least 2 prior therapies. ◆

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Patients With B-Cell Malignancies Experience Stable Disease on Vecabrutinib Therapy

Wayne Kuznar

VECABRUTINIB, A REVERSIBLE, noncovalent Bruton tyrosine kinase (BTK) inhibitor, exhibited evidence of clinical activity in adults with B-cell malignancies without producing any grade at least 3 drug-related adverse events (AEs), according to new data.

Among 29 patients who were previously exposed to ibrutinib (Imbruvica) and subsequently treated with vecabrutinib as part of a phase 1b/2 dose-escalation trial, there have been no patients with an objectively defined response, but 7 patients did experience stable disease.[1] Three of 5 patients whose doses were increased and moved to cohort 5 (300 mg twice daily) experienced stable disease, 2 of whom remain on treatment.

"We anticipate that with higher doses, we may start to see responses, as we are starting to see a potential signal at the doses that we're at right now," John Allan, MD, assistant professor of medicine at Weill Cornell Medicine in New York City, said in an interview. "The longest patient on study is approaching about a year and has been through all of the dose cohorts and has been escalated…so we see some signs of stability of disease, and in some of the more recent patients at higher dose levels, we've had close to partial responses, and they remain on study."

Mutations in BTK cysteine residue C481, which is required for covalent bond formation, occurs in most patients with chronic lymphocytic leukemia who have relapsed while on covalent BTK inhibition. Vecabrutinib, a noncovalent inhibitor of wild-type and *C481S*-mutated BTK, binds to the BTK domain independent of C481, which suggests that it might have activity in both covalent BTK inhibitor–relapsed and –naive disease, said Allan.

"The class in general is felt to be able to potentially overcome BTK mutations, which are the major reason for covalent-bound BTK inhibitor resistance, and therefore these agents have improved pharmacokinetics that might be able to regain efficacy in these BTK-mutated–resistant patients to covalent-bound inhibitors," said Allan.

Of the 29 patients enrolled so far, 23 have chronic lymphocytic leukemia (CLL). As part of phase 1b of the study, they were treated in an open-label fashion using a modified 3 + 3 design, starting at 25 mg twice daily (cohort 1). Dose escalation has progressed to 400 mg (cohort 6), with no dose-limiting toxicities (DLTs). Cohort 7 will receive vecabrutinib at 500 mg twice daily and is planned before a phase 2 study in CLL/small lymphocytic leukemia (SLL) commences.

Patients must have received at least 2 prior regimens and progressed on therapy with a covalent BTK inhibitor. Patients continue to receive vecabrutinib until time of progression or intolerable toxicity. The safety period for assessment of DLT is cycle 1 (4 weeks).

Three patients received treatment in cohort 1, 10 in cohort 2 (50 mg twice daily), 7 in cohort 3 (100 mg twice daily), 4 in cohort 4 (200 mg twice daily), and 5 in cohort 5 (300 mg twice daily). In addition to the 23 patients with CLL, 2 had mantle cell lymphoma, 3 had Waldenstrom macroglobulinemia, and 1 had marginal zone lymphoma. The median number of prior regimens is 4.

At screening, among the 23 patients with CLL, 78% had mutated or deleted *TP53*, 61% had *BTK C481* mutations, 13% had phospholipase C gamma 2 mutations, and 57% had del(17p).

There were 10 serious AEs in 7 patients, none of which were considered drug related. These included cellulitis, intestinal perforation, pleural effusion, pain in extremity, lymphocytosis, deep vein thrombosis, hematuria, myelitis, and sepsis. The most common treatment-emergent AEs (TEAEs) of any grade were anemia (35%), headache (28%), and night sweats (24%). Headache and nausea (10% each) were the 2 most common drug-related TEAEs. To date, no drug-related grade 3 or 4 TEAEs have been observed at dose levels >50 mg.

Of the 7 patients with stable disease, 4 had *BTK C481S* mutations and 3 had *BTK C481* wild-type disease. All other patients in cohorts 1 to 5 had disease progression at or before the first response assessment and discontinued treatment, except for 1 patient who withdrew consent. The pharmacokinetic profile of vecabrutinib showed sustained exposure over the dosing interval. Exposure and median steady-state trough concentrations continue to increase with increasing vecabrutinib dosing.

Phase 2 of the study will focus on patients with BTK inhibitor–resistant, mutationally defined CLL/SLL and those with prior BTK inhibitor intolerance. ◆

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Ibrutinib May Thwart PFS Decline in Relapsed/Refractory Mantle Cell Lymphoma

IN PATIENTS WITH RELAPSED/REFRACTORY mantle cell lymphoma (MCL), treatment with ibrutinib (Imbruvica) might mitigate a historical trend toward decreased progression-free survival (PFS) with succeeding lines of therapy, according to long-term follow-up data from a prospective trial.

"This pooled analysis of ibrutinib in relapsed/refractory MCL with extended follow-up to 7.5 years indicates a late plateau in the PFS curve with a notable number of patients experiencing remissions greater than 5 years," Simon Rule, MD, of University of Plymouth Peninsula Medical School in England, and colleagues concluded in a poster presentation. "Patients with only 1 prior line of therapy and those achieving a complete response continued to have the best outcomes with ibrutinib."

Investigators reported updated pooled data from 3 clinical trials, SPARK (MCL2001; NCT01599949), RAY (MCL3001; NCT01646021), and PCYC-1104-CA (NCT01236391), of ibrutinib in relapsed/refractory MCL. All patients enrolled (N = 370) in the 3 trials received ibrutinib 560 mg once daily until disease progression or development of unacceptable toxicities. Patients who continued to benefit at the end of the study could enroll in a long-term access study.

The median PFS was 12.5 months (range, 9.8-16.6) with ibrutinib compared with an estimated 10.9 months with patients' most recent prior regimens. More than half of the patients had a longer PFS with ibrutinib than with their prior regimen, and 27% had a PFS of at least 1 year longer than the prior regimens' estimated PFS.[1]

Patient age and number of prior lines of therapy did not significantly affect PFS with ibrutinib, although patients with a single prior line of therapy had the best PFS, along with those who attained a complete remission. "Ibrutinib represents a significant advance in MCL and should be considered standard of care in second line, regardless of a patient's initial response to frontline therapy," the authors added.

The study originated with the recognition that PFS in MCL declines with each successive line of chemoimmunotherapy, regardless of patient age.[2] Additionally, patients who progress within 24 months of frontline treatment have a shorter PFS and overall survival (OS) than those who progress later.[3] As a result, second-line therapies that reverse or mitigate the historical trends would fulfill an unmet need, the authors noted. Ibrutinib has an approved indication for relapsed/refractory MCL, and Rule and colleagues previously reported improved outcomes with earlier use of ibrutinib.[4]

Investigators defined PFS with the most recent prior regimen as the time from first dose of the regimen to the first dose of ibrutinib. They further defined disease progression on frontline therapy as occurring within 24 months (progression of disease [POD]24) or later (POD≥24).

"Ibrutinib represents a significant advance in MCL and should be considered standard of care in second line, regardless of a patient's initial response to frontline therapy."

The study population comprised 99 patients with one prior line of therapy and 271 with more than 1 line (median, 2). Investigators reported that 44% of the patients with 1 prior line of therapy were at least 70 years of age, 26% had a high-risk simplified MCL International Prognostic Index (MIPI) score, 6% had blastoid variant, and 43% had POD24.

Median exposure to ibrutinib for all patients was 11.1 months. Almost a third of patients continued treatment for at least 2 years, and half of that group remained on treatment for 4 years or more. With follow-up for as long as 92 months (median, 41), 11.9% of patients discontinued ibrutinib because of adverse events (AEs). The estimated 5-year OS for the entire cohort was 41%.

The objective response rate was 69.7%, including a complete response (CR) rate of 27.6%. The subgroup with 1 prior line of therapy had a response rate of 77.8%, including CRs in 37.4%, a median PFS of 25.4 months, and median OS of 61.6 months. Patients who attained CR had a median

response duration of 65.6 months. The responses were durable, regardless of the number of prior lines of therapy.

In the subgroup with known blastoid and/or *TP53*-mutated disease (n = 61), a third had a longer PFS with ibrutinib versus the prior regimen. The median duration of PFS was 5.4 months in the blastoid group and 4.0 months in patients with *TP53*-mutated disease. Among the 27% of patients whose PFS with ibrutinib was at least 1 year longer than with their prior regimen, 66% attained CR, compared with 14% of patients who did not have at least a 1-year improvement in median PFS.

Patients whose PFS was longer with ibrutinib compared with the prior regimen were less likely to have high-risk MIPI (38.8% vs 61.2%), bulky disease (44.4% vs 55.6%), blastoid variant (37.2% vs 62.8%), and *TP53*-mutated disease (20.0% vs 80.0%). In the subgroup of patients who received ibrutinib second line, PFS and response duration were longer with POD≥24 versus POD24. PFS with second-line ibrutinib was similar to the estimated PFS with a patient's frontline regimen, regardless of age. Median PFS for patients with POD24 was similar with ibrutinib and frontline therapy but was 15 months longer with ibrutinib for patients with POD≥24.

With additional follow-up, no late unexpected toxicity emerged in patients treated with ibrutinib. The most common grade 3 or higher treatment-emergent AEs were neutropenia (17%), pneumonia (13.5%), and thrombocytopenia (12.4%). The most frequently reported serious AEs were pneumonia (13.2%), atrial fibrillation (5.7%), and dyspnea (4.3%). Secondary malignancies occurred in 11.4% of patients, primarily nonmelanoma skin cancer. ◆

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NOTES

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