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Walter Alexander

Venetoclax (ABT-199/GDC-0199) Monotherapy Induces Deep Remissions, Including Complete Remission and Undetectable MRD, in Ultra-High-Risk Relapsed/Refractory Chronic Lymphocytic Leukemia With 17p Deletion: Results of the Pivotal International Phase 2 Study

• Stephan Stilgenbauer, MD, PhD, University of Ulm, Ulm, Germany

The prognosis is very poor for patients with del(17p) chronic lymphocytic leukemia (CLL), and treatment options are limited. Front-line chemoimmunotherapy progression-free survival (PFS) rates have historically been less than 12 months in this population. By binding to and inhibiting overexpressed B-cell lymphoma 2 (BCL-2), venetoclax, an orally bioavailable, selective BCL-2 inhibitor, induces apoptosis independent of the p53 suppressor gene.

In a phase 1 study, the high overall response rate (ORR) with venetoclax of 79% in patients with relapsed/refractory CLL included those with del(17p). Dr. Stilgenbauer’s pivotal phase 2, single-arm, multicenter study evaluated venetoclax monotherapy in 107 patients (median age 67 years, 65% male). Administration of full-dose venetoclax causes rapid tumor destruction with risk of tumor lysis syndrome (TLS). Therefore, investigators ramped up venetoclax doses weekly from 20 mg to the final 400-mg dose, with additional prophylaxis against TLS.

ORR, the primary outcome measure, was 79.4% (95% confidence interval [CI], 70.5–86.6) by independent review committee. Deep responses included complete response (CR) or CR with incomplete bone marrow recovery in 7.5%, and nodular partial responses in 2.8%. No response was reported in 20.6%. By investigator assessment, 26.2% had stable disease and 22.4% had progressive disease. Of 45 patients tested, 18 achieved minimal residual disease (MRD) negativity in peripheral blood.

In all 11 deep responders (CR, CR with incomplete bone marrow recovery, or nodal partial response), the response was maintained at 12 months, according to the independent review committee. Response was maintained, as well, in 82.6% of those with partial responses and in 94.4% of those who were MRD-negative in peripheral blood/bone marrow. MRD negativity was observed in more than 20% of responders. Lymphocytes returned to the normal range (less than 4 x 10^9/L) in 83 of 87 patients who had lymphocytosis at baseline, with a median time to normalization of 22 days. Among 96 evaluable patients for nodal size, 89 had a 50% or greater reduction in size from baseline (based on largest target lesion diameter). Also, of 45 patients tested, 18 achieved MRD negativity in peripheral blood.

Treatment-emergent adverse events were common (96%) and 76% of patients had grade 3–4 events, with neutropenia most frequent (43% overall; 40% grade 3–4). “Neutropenia was manageable with dose interruptions/reductions, G-CSF, and/or antibiotics,” Dr. Stilgenbauer said. Grade 3–4 anemia and thrombocytopenia were reported in 18% and 15% of patients, respectively. Dr. Stilgenbauer observed that neutropenia and infection incidence were similar to that seen with frontline chemoimmunotherapies.

During the dose ramp-up period, laboratory TLS occurred in five patients. It was managed with dose interruptions of one day each, with no clinical TLS events.

“Venetoclax may be an attractive component to novel combinations or sequencing with other agents in the treatment of del(17p) CLL,” Dr. Stilgenbauer concluded.

Commenting from the audience at the late-breaking clinical trial session, Kanti Rai, MD, Chief of the Division of Hematology-Oncology at North Shore–Long Island Jewish Medical System, underscored that patients should know that with venetoclax treatment, they have to be hospitalized initially for safety. While clinical TLS was effectively eliminated by the dose ramp-up and prophylaxis, frequent monitoring is needed at the start. Dr. Stilgenbauer responded, noting that based on safety experience with more than 500 patients, the current TLS risk mitigation scheme demands hospitalization only for high-risk patients. Low- and medium-risk patients can be treated as outpatients, although allopurinol, hydration, and eight- and 24-hour labs are required. “Clearly this efficacy comes with a price. Vigilance is required.”

Dr. Rai said further that the trial results revealing venetoclax as a “really believably effective treatment” were “most welcome news” for a “horrible part of the CLL population with 17p deletion.”

Preliminary Results of a Phase 2, Open-Label Study of Venetoclax (ABT-199/GDC-0199) Monotherapy in Patients With Chronic Lymphocytic Leukemia Relapsed After or Refractory to Ibrutinib or Idelalisib Therapy

• Jeffrey Jones, MD, Clinical Director, CLL Research Program, Ohio State University Medical Center, Columbus, Ohio

The prognosis is poor in patients who relapse or are treatment-refractory after B-cell receptor signaling antagonists...
such as ibrutinib and idelalisib, Dr. Jones said. Median overall survival (OS) after ibrutinib discontinuation, for example, ranges from three to 18 months following progression as Richter’s transformation or CLL, respectively. In preliminary results of Dr. Jones’ phase 2 trial (NCT02141282), response rates were high with venetoclax monotherapy, despite the fact that more than 50% of included CLL patients were relapsed/refractory and had received five or more prior lines of therapy. Six patients had received both ibrutinib and idelalisib.

Dr. Jones’ study evaluating venetoclax monotherapy was conducted among 54 patients with CLL who had relapsed or were refractory to either ibrutinib (n = 41) or idelalisib (n = 13). Patients received venetoclax in ascending doses starting at 20 mg and increasing to 400 mg. Patients with high tumor burden were hospitalized prior to dosing to facilitate tumor lysis syndrome (TLS) prophylaxis (uric acid reducers and hydration) and were monitored for at least 24 hours after each dosing-level increase.

Dr. Jones noted that at least a third of patients had one or more high-risk biological characteristics and a substantial fraction had bulky tumors. In the ibrutinib and idelalisib arms respectively, 80% and 85% of patients remain on treatment. Progressive disease has been reported in four patients in the prior ibrutinib group and in one patient in the prior idelalisib group. The majority of patients had resolution of B-symptoms at week 8. Among the 66% and 69% of patients in the ibrutinib and idelalisib arms, respectively, who had lymphocytosis at baseline, 81% and 79%, respectively, in the ibrutinib and idelalisib arms achieved normalization of absolute lymphocyte counts. Reductions in nodal mass of 50% or more were reported in 74% and 56%, respectively in the ibrutinib and idelalisib groups. The median time to 50% or greater reduction was 50 days in both groups.

In the ibrutinib arm at 24 weeks, CRs have been observed in 13% of patients, with partial responses in 48% and stable disease in 13%. In the idelalisib arm, partial responses have been seen in 50%, with stable disease in 25%. An assessment of best objective responses to week 36 reveals an ORR of 61% in the ibrutinib arm and 50% in the idelalisib arm.

“Venetoclax exhibited a tolerable safety profile,” Dr. Jones said. He noted that while grade 3–4 neutropenia was reported in 39% of patients, it had been present in 31% of them before they received their first venetoclax dose. Thrombocytopenia was reported in 24%. Lower-grade nausea occurred in a third of patients. Serious adverse events overall were observed in 41%, with febrile neutropenia (7%) and pneumonia (7%) most common. Incidence of laboratory TLS was low and was managed effectively.

“The take-home,” Dr. Jones concluded, “is that in a group of patients deemed to be at high risk for death from their disease, venetoclax has shown acceptable safety and a respectable response rate as high as 61%, including some complete remissions.”

### Eltrombopag Added to Standard Immunosuppression as First Treatment In Aplastic Anemia

**• Danielle M. Townsley, MD, Hematology Branch, National Heart, Lung, and Blood Institute, National Institutes of Health, Bethesda, Maryland**

Despite many efforts, overall hematologic response rates for patients with aplastic anemia have not improved over the last 30 years, Dr. Townsley said. Hematopoietic stem cell transplantation or immunosuppression with horse antithymocyte globulin and cyclosporine, the standard of care, produces overall hematologic response rates of 60% to 65%, with CRs in about 10%.

The second-generation, small-molecule, oral, nonpeptide thrombopoietin receptor agonist eltrombopag received accelerated Food and Drug Administration (FDA) approval for chronic immune thrombocytopenia in 2008 and for refractory severe aplastic anemia in 2014. Research has shown that eltrombopag stimulation may expand the hematopoietic stem cell pool, and that it improves blood counts in about 40% of patients.

In Dr. Townsley’s presentation of results of a National Institutes of Health phase 2 trial among patients with treatment-naïve severe aplastic anemia, eltrombopag was associated with increases in CD34-positive cells, robust neutrophil and platelet recovery, and transfusion independence within one to two months.

Eighty-eight treatment-naïve patients with severe aplastic anemia were randomized 1:1:1 to standard immunosuppressive treatment plus one of three eltrombopag 150-mg regimens: 1) day 14 to six months; 2) day 14 to three months; 3) day 1 to six months. Complete remission at six months was the primary endpoint.

The CR rates for groups 1 to 3 were 33%, 36%, and 60%, respectively, with an overall rate of 30%. The respective overall hematologic response rates were 80%, 87%, and 95% (86% overall). Dr. Townsley noted that these rates compare favorably to historic rates of 12% and overall hematologic response rates of 63%.

In all patients, CD34-positive cells increased and neutrophil and platelet count recovery was robust. Median time to transfusion independence was 32 days for platelets and 42 days for red cells. After 47 days, white blood counts became adequate.

Few grade 3–4 adverse events were attributed to eltrombopag; two patients discontinued for severe cutaneous reactions and grade 2–3 transaminase and bilirubin elevations were reported in 10% of patients. No bone marrow fibrosis was observed. One death was attributed to thymoma with paraneoplastic encephalopathy. There were seven cases of clonal evolution.

Dr. Townsley concluded, “The rapid blood count improvement supports early use of eltrombopag and immunosuppressive therapy with newly diagnosed serious aplastic anemia.”

The moderator of the ASH press conference, Mark Crowther, MD, of McMaster University in Hamilton, Ontario, Canada, commented, “If I had this disease, I’d take this drug. Realistically, it’s a tremendously difficult disease to treat. The treatment options are somewhat complex to deliver, potentially
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toxic, and quite expensive. Eltrombopag is a very easy-to-use medication, and it will have a huge impact on careful care of patients who have this very severe illness.”

Long-Term Outcomes After Blinatumomab Treatment: Follow-Up of a Phase 2 Study in Patients With Minimal Residual Disease Positive B-Cell Precursor Acute Lymphoblastic Leukemia
• Nicola Gökbuget, MD, Department of Medicine II, Goethe University, Frankfurt, Germany

Blinatumomab is a bispecific T-cell engager (BiTE) antibody that directs cytotoxic T cells to CD19-positive target cells, leading to lysis in minimal residual disease (MRD)-positive acute lymphoblastic leukemia (ALL). It was tested in an open-label, multicenter, confirmatory phase 2 study (NCT01207388) in MRD-positive B-precursor ALL in 46 centers and 11 countries. MRD was defined as a level of 10^-3 or greater (molecular failure or molecular relapse) in an assay with a minimum sensitivity of 10^-4 in Dr. Gökbuget’s preplanned 18-month follow-up final analysis.

MRD assessment, which detects the presence of leukemic cells in bone marrow, is possible in more than 90% of ALL patients, Dr. Gökbuget said. Patients with persistent/recurrent MRD after first-line induction and consolidation have a higher risk of relapse and shorter survival than those with a complete MRD response (no detectable MRD with minimum sensitivity 0.01%). Dr. Gökbuget’s prior assessment of five trials showed that among patients who were MRD positive before stem cell transplantation, the relapse risk was 46% to 75%, compared with 6% to 20% in those who were MRD negative. “Nearly all patients with persistent or recurrent MRD relapse despite continued chemotherapy,” she said, “so MRD persistence indicates resistance to conventional chemotherapy.”

The usual next treatment step is allogeneic transplant. Patients may relapse, however, during preparation for stem cell transplant, and those with high MRD have higher post-transplant relapse rates. Achieving and maintaining molecular CR and avoiding hematologic relapse going into transplantation are therefore important treatment goals.

In the 18-month analysis, one-third of the included 116 patients (median age 45 years, range 18–76 years) were in their second or later remission. MRD responses were evaluated after the first cycle of treatment. Blinatumomab 15 mcg/m² per day was given by continuous intravenous (IV) infusion for four weeks, followed by a two-week break (one cycle). MRD responders in cycle 1 received up to three additional cycles or underwent hematopoietic stem cell transplant.

Eighty percent of patients achieved a complete MRD response. Among these, 67% were able to remain in continuous remission until transplant. OS was 36.5 months. OS was significantly more likely (P = 0.002) in those who achieved a complete MRD response, and duration of complete remission was longer (P = 0.049). Also, patients in their first remission at baseline had longer relapse-free survival (P = 0.004). Relapse-free survival after a median follow-up of 29.9 months was 54%. “Keeping in mind that in relapsed ALL the median survival is around six months, and that a third had prior relapses, this is very favorable,” Dr. Gökbuget said. Twelve percent of patients discontinued blinatumomab because of adverse events. Neurologic events, reported in 53% of patients, were grade 3 and 4 in 10% and 3%, respectively.

Dr. Gökbuget concluded, “Blinatumomab may contribute to prolonged relapse-free survival and OS in patients with MRD-positive ALL.”

Complete Molecular and Hematologic Response In Adult Patients With Relapsed/Refractory Philadelphia Chromosome-Positive B-Precurso r Acute Lymphoblastic Leukemia Following Treatment With Blinatumomab: Results From A Phase 2 Single-Arm, Multicenter Study (ALCANTARA)
• Giovanni Martinelli, MD, Institute of Hematology, S. Orsola-Malpighi University Hospital, Bologna, Italy

Philadelphia chromosome positivity (Ph+), the most common single cytogenetic abnormality in B-precursor ALL, occurs in 25% of adults (the frequency increases with age). This Ph+ ALL population has a historically poor prognosis, Dr. Martinelli said. Tyrosine kinase inhibitors (TKIs) added to first-line therapy have improved both response rates and the likelihood of achieving allogeneic hematopoietic stem cell transplants (HSCT). “Allogeneic hematopoietic stem cell transplant is probably the only curative way to long remission in these patients,” Dr. Martinelli added.

When HSCT is not an option, sequential use of chemotherapy with second- or third-generation TKIs is the dominant approach. Complete hematologic response rates with TKI monotherapy with nilotinib, dasatinib, or ponatinib have ranged from 33% to 41%, with one-year median OS of 3.3 to eight months. Dr. Martinelli pointed out that a significant proportion of TKI resistance is attributed to emergence of single and compound point mutations in BCR-ABL.

Blinatumomab redirects T cells to lyse the CD19-positive malignant and nonmalignant B cells expressed in virtually all B-lineage ALL cells. In Ph-negative relapsed and refractory ALL, the blinatumomab monotherapy combined rate of CR and complete remission with partial hematological recovery (CRh) was 43%. The ALCANTARA trial was conducted “to extend this initially very positive experience to the Ph+ population,” Dr. Martinelli said.

Patients included in the ALCANTARA trial had Ph+ B-precursor ALL that had relapsed or was refractory after at least one second- or third-generation TKI (and was intolerant of or refractory to imatinib). Patients (n = 45) received blinatumomab by continuous IV infusion (four weeks on, two weeks off) for up to five cycles (9 mcg per day on days 1–7 in cycle 1, and 28 mcg per day thereafter). The primary endpoint was CR/CRh during the first two cycles.

CR and CRh rates were 31% and 4%, respectively, and the complete MRD response rate was 88%. Four of the 16 patients (25%) with blinatumomab-induced remission went on to HSCT. One died within 100 days post-transplant. Response rates were independent of mutational status, including the presence of T315I mutations, and were equivalent in patients younger
than 55 years of age and those 55 or older. Median OS was 7.1 months (95% CI, 5.6 months—not estimable), and relapse-free survival was 6.7 months among responders.

Adverse events were consistent with prior blinatumomab experience in this population. They led to discontinuations in 7% of patients, with febrile neutropenia (27%) and thrombocytopenia (22%) most common.

Dr. Martinelli concluded, “In this poor prognostic Ph+ patient population, we observed a median overall survival of 7.1 months.” A high percentage of responders (88%), he added, achieved complete MRD responses.

### Treatment With Anti-CD19 BITE Blinatumomab

#### In Adult Patients With Relapsed/Refractory B-Precurso R Acute Lymphoblastic Leukemia

Post-Allogeneic Hematopoietic Stem Cell Transplantation

- Anthony Selwyn Stein, MD, Gehr Leukemia Center, City of Hope Medical Center, Duarte, California

In patients whose ALL relapses after allogeneic hematopoietic stem cell transplantation, outcomes are poor, with median one-year OS in two studies at 17% and 30%, and two-year median OS at 1% and 16%, respectively.2,3

In a large, confirmatory, open-label, single-arm, multicenter phase 2 study of patients with ALL, the overall response rate was 43%. The aim of the present analysis was to characterize a subset of these patients who, before treatment with blinatumomab, had relapsed or refractory ALL and prior allogeneic HSCT. All 189 patients in the trial had Philadelphia chromosome-negative B-precursor ALL.

Relapse-free survival (RFS), OS, and incidence of adverse events were the outcomes of interest in the 64 patients (median age 32 years, 43% male) with post-stem cell transplant relapse treated subsequently with blinatumomab. The median time to relapse after transplant or after salvage therapy was six months. After transplant (before treatment with blinatumomab), 69% of patients had required salvage therapy.

CR or CRh was reported in 45% of patients (95% CI, 33–58), with 76% of these achieving CR/CRh in the first cycle. Blast-free hypoplastic/aplastic bone marrow was found in 6% of patients, and 19% did not respond to therapy. Among the 18 patients who achieved CRs in the first two cycles of blinatumomab, 16 (89%) had MRD responses, and 15 (83%) had complete MRD responses.

After a median follow-up of 12.4 months, median RFS was 7.4 months (95% CI, 5.0–10.1). After median follow-up of 16.6 months, median OS was 8.5 months (95% CI, 4.2–11.2).

“Fatal adverse events occurred only in patients with uncontrolled leukemia,” Dr. Stein commented, noting that they had occurred in eight patients (five infections, one disease progression, one hemorrhage, and one respiratory failure). None among these had achieved CR/CRh. Graft versus host disease, mostly mild or moderate, was reported in 11% of patients. Overall, adverse event rates for post-transplant relapse patients were consistent (45% versus 43%) with those in the larger population. Similarly, Dr. Stein concluded, rates of median RFS and OS in this population were similar to those found in the overall study population.

“The addition of other immunotherapies to blinatumomab may be considered for future investigations in this population to improve the response rate and duration of response,” Dr. Stein said.

### Carfilzomib and Dexamethasone Versus Bortezomib and Dexamethasone in Patients With Relapsed Multiple Myeloma: Results of The Phase 3 Study ENDEAVOR (NCT01568866)

#### According to Age Subgroup

- Antonio Palumbo, MD, Professor of Hematology, University of Torino, Torino, Italy

Improvements in PFS for relapsed multiple myeloma patients receiving carfilzomib and dexamethasone compared with bortezomib and dexamethasone in prior presentations of ENDEAVOR results were statistically and clinically significant (median 18.7 versus 9.4 months; hazard ratio [HR], 0.53; 95% CI, 0.44–0.65; P < 0.001). Carfilzomib is a selective proteasome inhibitor that is approved in the U.S. and abroad for treatment of relapsed and refractory multiple myeloma.

Dr. Palumbo’s analysis examined whether the carfilzomib benefit extended to a specific high-risk population. “As a second-generation proteasome inhibitor, with carfilzomib we have higher efficacy compared to bortezomib. The question was whether this activity with low toxicity held true in the very elderly population,” Dr. Palumbo said. Age stratification in the ENDEAVOR trial was as follows: younger than 65 years: carfilzomib plus dexamethasone, n = 223; bortezomib plus dexamethasone, n = 210; 65–74 years: carfilzomib plus dexamethasone, n = 164; bortezomib plus dexamethasone, n = 189; 75 years or older: carfilzomib plus dexamethasone, n = 77; bortezomib plus dexamethasone, n = 66).

Among patients younger than 65 years, for the primary endpoint of PFS, the median was not estimable in the carfilzomib-plus-dexamethasone group and was 9.5 months in the bortezomib-plus-dexamethasone group (HR, 0.581; CI, 0.436–0.774). Among patients 65–74 years, median PFS was 15.6 months in the carfilzomib group and 9.5 months in the bortezomib group (HR, 0.528; CI, 0.382–0.728). In the group 75 years or older, median PFS was 18.7 months in the carfilzomib group and 8.9 months in the bortezomib group (HR, 0.383; CI, 0.227–0.647).

Rates of grade 2 or higher peripheral neuropathy in the carfilzomib and bortezomib groups were 5.8% and 26.9%, respectively, in patients younger than 65 years; 8% and 33.9% in patients 65–74, and 2.6% and 43.1% in patients 75 years or older. Rates were low but higher in the carfilzomib group than in the bortezomib group for grade 3 hypertension (carfilzomib, 7.4% to 11.7%; bortezomib, 2.2% to 3.1%), dyspnea (carfilzomib, 3.6% to 7.8%; bortezomib, 1.4% to 3.3%), cardiac failure (carfilzomib, 0.9% to 3.9%; bortezomib, 0.5% to 1.5%), and renal failure (carfilzomib, 1.3% to 1.8%; bortezomib, 0 to 1.1%).

Dr. Palumbo’s analysis revealed further benefits in older patients for carfilzomib versus bortezomib. In the 75-or-older group, the rate of treatment discontinuations for adverse events was higher in the bortezomib arm than in the carfilzomib arm (35% versus 26%). Rates were similar in the two younger
age groups. Also, the rate of grade 2 or higher peripheral neuropathy was much higher in the bortezomib arm (43.1% versus 2.6%). Furthermore, for PFS there was a trend toward greater improvement in the carfilzomib arm for the 75-or-older age group.

While noting that the perfect carfilzomib dose for this population has yet to be defined, he said, “I’m 100% sure of the 36-mg/m² dose and 70% sure for the 56-mg/m² dose.”

“The take-home,” Dr. Palumbo continued, “is that we have a second-generation proteasome inhibitor that is more potent and better tolerated than bortezomib in the elderly.”

**Efficacy and Safety of Carfilzomib and Dexamethasone Versus Bortezomib and Dexamethasone in Patients With Relapsed Multiple Myeloma Based on Cytogenetic Risk Status: Subgroup Analysis From the Phase 3 Study ENDEAVOR (NCT01568866)**

- Meletios A. Dimopoulos, MD, National and Kapodistrian University of Athens, School of Medicine, Athens, Greece

Beyond the significant reductions in the risk of progression or death with carfilzomib versus bortezomib shown in the phase 3 ENDEAVOR trial among patients with relapsed or refractory multiple myeloma (HR, 0.53, 95% CI, 0.44–0.65; P < 0.0001), carfilzomib has demonstrated single-agent activity in a particularly difficult-to-treat subpopulation within the relapsed/refractory group. That subset includes patients with high-risk cytogenetic abnormalities such as t(4;14) and del(17p), both associated in this population with poor survival.

Dr. Dimopoulos conducted an analysis of the 21% of patients with high-risk cytogenetics (t(4;14), t(14;16), or del(17p)) among the 464 enrolled in ENDEAVOR receiving carfilzomib and the 24% of the 465 receiving bortezomib who had high-risk cytogenetics.

Disease progression or death in the overall ENDEAVOR population was 37% and 52% in the carfilzomib-plus-dexamethasone and bortezomib-plus-dexamethasone groups, respectively, after a median follow-up of 11.2 months. Median PFS was 18.7 and 9.4 months in the carfilzomib and bortezomib groups, respectively (P < 0.0001).

The carfilzomib benefit persisted in high-risk patients, with median PFS at 8.8 months for carfilzomib and six months for bortezomib (HR, 0.646; 95% CI, 0.433–0.921). Median PFS and ORR were worse for patients with del(17p) than for t(4;14). For standard-risk patients, while median PFS was not estimable, it was 10.2 months in the bortezomib group (HR, 0.439; 95% CI, 0.333–0.578).

The carfilzomib benefit was observed in ORR, as well, at 72.2% and 58.4%, respectively. Rates in standard-risk patients were 79.2% for carfilzomib and 66% for bortezomib-containing regimens.

Dr. Dimopoulos summarized the findings, saying that carfilzomib response rates were higher, responses were deeper, and responses had a longer duration across cytogenetic subgroups.

“As expected, median progression-free survival was lower compared with the overall population. However, patients treated with carfilzomib had a clinically meaningful improvement in progression-free survival compared with bortezomib with high- or standard-risk cytogenetics,” he concluded.

**Impact of Prior Treatment on Patients With Relapsed Multiple Myeloma Treated With Carfilzomib and Dexamethasone Versus Bortezomib and Dexamethasone in a Subgroup Analysis of the Phase 3 ENDEAVOR Study (NCT01568866)**

- Philippe Moreau, MD, University of Nantes, Nantes, France

A prespecified analysis of the impact of prior treatment on outcomes in the multiple myeloma ENDEAVOR trial justifies confidence that even patients with several lines of prior therapy can receive the advantages of carfilzomib plus dexamethasone versus bortezomib and dexamethasone.

In the ENDEAVOR trial, 929 adult patients with relapsed multiple myeloma previously treated with one to three lines of therapy were randomized 1:1 to IV carfilzomib along with oral dexamethasone versus IV or subcutaneous bortezomib and oral dexamethasone. Cycles were repeated until disease progression or unacceptable toxicity. PFS was the primary endpoint. Results were published online in *The Lancet Oncology* to coincide with Dr. Moreau’s ASH presentation. Treatment outcomes were stratified according to the number and types of prior therapies.

Looking at subpopulations according to the number of prior therapies, Dr. Moreau said that in those who had received one line of prior therapy, disease progression or death occurred in 70 (30.2%) and 109 (47%) among patients receiving carfilzomib and bortezomib, respectively. Clinically meaningful improvements in PFS for carfilzomib compared with bortezomib were evident regardless of the number of prior lines of therapy. Median PFS was improved by more than a year with carfilzomib (22.2 months; 95% CI, 17.7 to not estimable [NE]) versus bortezomib (10.1 months; 95% CI, 8.8–12.7) (HR, 0.45; 95% CI, 0.33–0.61). In those who had received two or more prior lines of therapy, disease progression and death occurred in 101 (43.5%) and 134 (57.5%) in patients receiving carfilzomib and bortezomib, respectively, with median PFS of 14.9 months (95% CI, 10.2 to NE) and 8.4 months (95% CI, 6.5–10.2) (HR, 0.60; 95% CI, 0.47–0.78), respectively.

The PFS benefit, Dr. Moreau underscored, persisted regardless of prior exposure to bortezomib or lenalidomide, with median PFS in patients previously receiving bortezomib at 15.6 months for carfilzomib and 8.1 months for bortezomib (HR, 0.56; 95% CI, 0.44–0.73). For those without prior bortezomib exposure, median PFS had not yet been reached for carfilzomib and was 11.2 months for bortezomib (HR, 0.48; 95% CI, 0.36–0.66). In patients previously treated with lenalidomide, the median PFS for carfilzomib and bortezomib was 12.9 months and 7.3 months, respectively (HR, 0.69; 95% CI, 0.52–0.92); for those not previously receiving lenalidomide, the respective values were 22.2 months and 10.2 months (HR, 0.43; 95% CI, 0.32–0.56).
In patients receiving two or more prior lines of therapy, grade 3 or greater adverse events (AEs) were reported in 177 (76.6%) and 160 (69.9%) of carfilzomib and bortezomib patients, respectively. For those with one prior line of therapy, 162 (69.8%) and 145 (63.9%) grade 3 or higher AEs were reported, respectively.

While hypertension, dyspnea, and cardiac failure were more prevalent in those receiving carfilzomib, peripheral neuropathy was less prevalent with carfilzomib treatment. AE-related discontinuations or death were similar in frequency between all four subgroups.

Dr. Moreau concluded, “Carfilzomib had a favorable benefit–risk profile in relapsed multiple myeloma, irrespective of prior treatment. Carfilzomib should be considered in patients who have progressed on lenalidomide maintenance.”

**Nonadherence to 6-Mercaptopurine (6MP) therapy in childhood ALL can have very significant consequences. In Dr. Landier’s C0G AALL03N1 study, electronically measured 6MP adherence rates lower than 95% were associated with a 3.7-fold increased risk of relapse.**

**Durable remissions in childhood ALL require about two years of maintenance chemotherapy with daily oral 6MP. Accurate assessment of 6MP intake, Dr. Landier said, is crucial to ensure timely intervention for nonadherent patients. Use of self-reporting is attractive because it is convenient and inexpensive. The accuracy of self-reporting and parent-reporting of 6MP adherence during ALL maintenance, however, is unknown. The aim of Dr. Landier’s study was to identify predictors of overreporting of prescribed 6MP through a comparison of self-reported 6MP intake to electronically monitored reporting.**

Dr. Landier’s prospective, six-month study enrolled 416 individuals 21 years of age or younger (median age, 6 years; range, 2 to 20 years; 66.6% male) with an ALL diagnosis who were in the maintenance phase of 6MP treatment. All were in their first remission. Treatment intake for each patient was measured electronically and via self-report (under 12 years by parent, 12 years or older by child). With the electronic monitoring (MEMS), 6MP was dispensed in a bottle with TrackCap, a microprocessor chip that records the date and time of each bottle opening. Data were downloaded at the end of the study period and compared with a self-report questionnaire. At the end of each of four months, the child or parent reported the number of days that 6MP had been taken during the preceding month.

Based on the comparison, patients were identified as “perfect reporters,” “overreporters,” or “others.” The influence of sociodemographic and clinical factors was addressed through multivariate logistic regression. Only 12% of patients were identified as perfect reporters; 23.6% were overreporters, and 64.4% were considered “others.”

For each increasing year of age, the risk of overreporting increased by 7%, Dr. Landier said. Racial factor analysis showed that Hispanic children and parents were 2.4 times more likely to overreport, Asians were 3.1 times more likely to overreport, and African-Americans were 5.3 times more likely to overreport compared with non-Hispanic white children and parents. Children whose father did not attend college were 2.1 times more likely to overreport.

Summarizing, Dr. Landier said that subjective overreporting of 6MP intake during maintenance therapy is common, with about a quarter of children and parents overreporting. Also, overreporting is more likely in patients who are nonadherent to 6MP, older, of a minority race, and from households with lower paternal education.

An intervention study, Dr. Landier said, is looking at ways to improve adherence, and is comparing education, education with text messaging, a reminder system, and direct parental supervision.

### REFERENCES

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