Carfilzomib does not improve outcomes in newly diagnosed myeloma compared to bortezomib

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The combination of carfilzomib, lenalidomide, and dexamethasone (KRd) did not show superior efficacy in patients with newly diagnosed myeloma absent a high-risk disease prognosis, compared with the standard of care—bortezomib, lenalidomide, and dexamethasone (VRd). Data from a planned interim analysis for efficacy and toxicity for the ENDURANCE (E1A11) randomized phase three trial will be presented in the plenary session of the American Society of Clinical Oncology (ASCO) annual meeting to occur virtually from May 29-31 (Abstract LBA3). The data safety monitoring committee for the trial recommended the release of the interim data based on futility.

The ECOG-ACRIN Cancer Research Group designed and conducted the ENDURANCE trial with funding from the National Cancer Institute, part of the National Institutes of Health.

"There was no improvement in progression-free survival by replacing bortezomib with carfilzomib in the current standard initial treatment of patients with newly diagnosed standard- or intermediate-risk myeloma, even though we observed a higher very good partial response rate with the carfilzomib combination," said lead investigator Shaji K. Kumar, MD (Mayo Clinic). "We observed more severe cardiac, pulmonary, and renal toxicities with carfilzomib, while neuropathy was more common among those receiving bortezomib."

The combination of bortezomib, lenalidomide, and dexamethasone (VRd) is the current standard initial therapy in patients with newly diagnosed multiple myeloma. Carfilzomib (Kyprolis, Amgen) is a next-generation proteasome inhibitor. It is used to treat patients with relapsed or refractory multiple myeloma who have received one to three previous treatments for multiple myeloma. Carfilzomib is FDA-approved for use in combination with dexamethasone or with lenalidomide plus dexamethasone.

In the ENDURANCE trial, patients with newly diagnosed multiple myeloma were randomized to receive VRd or KRd (1:1) for 36 weeks (induction) and stratified based on intent for transplant at disease progression. Upon completion of induction treatment, patients were randomized a second time to receive indefinite lenalidomide maintenance versus two years (1:1). Currently, following standard treatment, patients often receive lenalidomide as maintenance therapy until disease progression. However, the ideal duration of maintenance is presently unknown and will be addressed as part of this trial.

Among the key eligibility criteria for the ENDURANCE trial was no intent for immediate autologous stem cell transplantation (ASCT) or ineligible for ASCT. Patients with a high-risk disease prognosis as defined by genetics [t(14;16), t(14;20) or deletion 17p on FISH; high-risk GEP70 signature] or clinically (serum LDH >2xULN; plasma cell leukemia) were not enrolled.

The ENDURANCE study enrolled 1087 patients between December 2013 and February 2019 at 272 centers in the US. The median age was 65 years. As of the planned second interim analysis (data cut-off January 7, 2020), there were 298 progression-free survival (PFS) events (75% of 399 events at full information). Median PFS (95% CI) was 34.4 (30.1 to NE) months for VRd compared with 34.6 (28.8 to 37.8) months for KRd; the PFS treatment hazard ratio (HR=KRd/VRd) in a stratified analysis was 1.04 (95%CI, 0.83 to 1.31); P=0.742.

Grade 3 or higher treatment-related non-hematologic toxicity rates were 41% for VRd and 48% for KRd; P=0.024. Very good partial response
rates were higher on the KRD arm (74% versus 65%); P=0.002. At 29 months of follow-up, the three-year OS probability (95% CI) is 0.84 (0.80 to 0.88) for VRd and 0.86 (0.82 to 0.89) for KRd.

Dr. Kumar continued: "The ENDURANCE study highlights the importance of using data from phase three trials to drive clinical practice. Although phase two trial data suggested a better outcome with KRd, compared to historical data with VRd, this has not borne out in the phase three ENDURANCE trial. It also raises concern for toxicities, which need to be carefully monitored for."

The following cooperative research groups in the NCI's National Clinical Trials Network all collaborated in the trial: Alliance for Clinical Trials in Oncology, ECOG-ACRIN Cancer Research Group, NRG Oncology, and SWOG.

"This trial represents another success for the National Clinical Trials Network. We found that a regimen that was very promising in small phase two studies was not better than the current standard, but in fact, was associated with more side effects. To me, it reemphasizes the importance of randomized controlled trials in oncology," said ECOG-ACRIN Myeloma Committee Chair S. Vincent Rajkumar, MD (Mayo Clinic).

Dr. Kumar concluded: "Based on this analysis, VRd should remain the standard of care for standard and intermediate-risk newly diagnosed multiple myeloma patients who are ineligible or will defer transplant, and it should be the backbone for adding newer therapies for those patients."

Provided by ECOG-ACRIN Cancer Research Group


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