MultipleMyelomaHub

Relapsed/refractory patients

ASH 2017 | Genomic predictors of response to carfilzomib in RRMM patients in the ENDEAVOR trial

Devona Williams | Dec 19, 2017

The MM Hub is pleased to share exciting findings from the 59th American Society of Hematology (ASH) Annual Meeting in Atlanta, Georgia. On Monday 11 December, the evening oral abstract session took place for Myeloma: Therapy, excluding Transplantation Studies in Relapsed and Refractory Multiple Myeloma. In this session, Dr. Robert J. Pelham of Amgen presented data based on Abstract 839: *Genomic Predictors of Progression-Free Survival Among Patients with Relapsed or Refractory Multiple Myeloma Treated with Carfilzomib and Dexamethasone (Kd56) or Bortezomib and Dexamethasone (Vd) in the Phase 3 Endeavor Trial*. The MM summary here is based both on updated data presented at the ASH session and may differ from that in the pre-published abstract.

The goal of this study was to identify potential gene expression signatures to stratify patients who will experience enhanced benefit from Kd56 or Vd therapy in RRMM. The study used whole transcriptome RNA sequencing testing of 13 genes at baseline levels of CD138+ expression from baseline bone marrow (BM) aspirates of patients in the ENDEAVOR trial.

The ENDEAVOR trial compared carfilzomib with bortezomib in patients with relapsed or refractory multiple myeloma (RRMM). Carfilzomib showed improvement in progression-free survival (PFS), overall response rate (ORR) and complete response (CR). See previous MM Hub article with details of the ENDEAVOR trial set up, and additional MM Hub articles with data from a secondary analysis, the OS data and analysis via cytogenetic risk status.

Least Absolute Shrinkage and Selection Operator (LASSO) was the regression analysis method used as an assessment of prediction for the genomic testing, in addition to Cox proportional hazards model. LASSO performs regularization and variable selection analysis. There were 13 genes measured for benefit with carfilzomib therapy. Among the genes in the classifier, several have previously been implicated to confer resistance to proteasome inhibitors, including *CLIP4, IGHD, and SH3RF3*. The genes in the classifier were as follows: *ACOXL, ITPRIPL2, UGT3A2, IGHD, TCF7, FRK, SHROOM3, COCH, SH3RF3, CLIP4, RNASE6, CLEC2B, NAP1L5*.

Key Findings:

- ENDEAVOR trial; n = 929 patients (pts)
- PFS: Kd56 = 18.7 months vs Vd = 9.4 months HR 0.53 (0.44,0.65) p = 0.0001
- ORR; Kd56 = 77% vs Vd = 63%
- CR: Kd56 = 13% vs Vd = 6%
- N = 303 patients in biomarker study: n = 155 Kd56, n = 148 Vd
- Median age = 65 years old

- Median PFS in biomarker substudy cohort = 18.7 months
- Median PFS in Kd56 patients predicted to have enhanced benefit was not reached
- 70% reduction in risk of progression in Kd56 *vs* Vd pts (HR = 0.30 (0.19, 0.44) p = 2.2×10^{-8}
- Carfilzomib patients with enhanced response signature (ERS+) had improved PFS *vs* those without enhanced response signature (ERS-) Kd56 patients
- 69% of ENDEAVOR patients profiled had ERS+ to Kd56

This study identified a set of genes which may be used to identify and stratify RRMM patients who may achieve enhanced benefit from Kd56 therapy. This was a retrospective study of the ENDEAVOR trial, and therefore these results require validation in further prospective studies. Nevertheless, the study holds exciting prospects for enhanced treatment strategies using this stratification model.

References

1. Pelham RJ. *et al*. Genomic Predictors of Progression-Free Survival Among Patients with Relapsed or Refractory Multiple Myeloma Treated with Carfilzomib and Dexamethasone or Bortezomib and Dexamethasone in the Phase 3 Endeavor Trial. Abstract #839. 59th American Society of Hematology (ASH) Annual Meeting 2017, Atlanta, GA.