Daratumumab in the Emerging Landscape of Functional High-risk Multiple Myeloma

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The evolution of increasingly effective first line therapies (1L) for newly diagnosed multiple myeloma (NDMM) has mandated a continuous upgrading of consensus criteria to define responses. The accepted gold standard and a recognised valid endpoint for clinical trials is now the achievement of measurable residual disease (MRD) negativity. However, before the era of highly effective therapies it was recognised that the duration of first remission was the most powerful predictor of overall survival (OS). This concept in the MRD era still holds true with available evidence questioning the notion that the attainment of MRD negativity is a robust biomarker of survival in patients with truly high-risk disease. Initial studies identifying sub-optimal depth or duration of response to 1L led to the concept of functional high-risk (FHR) NDMM. The definition of FHR has evolved with a recent EMN consensus defining FHR as progressive disease (PD) within 18 months of commencing 1L in the absence of any IMS-IMWG consensus genomic staging (CGS) high-risk criteria. Surprisingly, limited data shows that only about 1 in 3 patients demonstrating PD within 18 months of IL meet CGS high-risk criteria. Moreover, multiple data-sets concur in demonstrating that in the context of VRd induction the FHR rate is approximately 20%, being mindful that this incorporates a minority of patients with CGS high-risk features. The role of CD38 targeting therapies in the context of FHR remains unclear. A pooled post hoc analysis of the pivotal POLLUX and CASTOR trials demonstrated that patients enrolled on those trials after only one prior line of therapy and with PD within 24 months clearly benefited from the addition of daratumumab when compared to the standard of care comparator treatment but the adverse impact of earlier progression was not entirely overcome. Subsequently, a number of retrospective meta-analyses have consistently shown superior outcomes in both high-risk and lenalidomide refractory disease with the use of CD38 targeted therapy. The implication being that subsets of FHR patients within these cohorts are similarly experiencing outcome benefit. Finally, the recently reported PERSEUS trial showed that NDMM patients receiving D-VRd induction and ASCT had a rate of PD within 18 months of 3%, however, the comparator VRd cohort showed similarly low rates of early PD of around 7% in stark contrast to real-world rates of approximately 20%. The true impact of quad-based induction approaches on FHR will only be fully defined with their accumulative use over time in real-world patients.