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Improving Outcomes for Patients With High-Risk Myeloma Via Prospective Trial Evidence: The Myeloma UK nine OPTIMUM Trial

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INTRODUCTION

Outcomes for patients with molecular high-risk (HR) multiple myeloma (MM) are poor with traditional approaches. Recent trials have demonstrated that novel combination therapies such as daratumumab/lenalidomide/dexamethasone improve outcome for HR disease at relapse, but access to these novel combination therapies remains limited in many public health care systems. Innovative clinical trials with robust and inclusive molecular testing strategies are needed to generate evidence for stratified therapy for HRMM in standard care. We reported that genetic double-hit, i.e. presence of two or more HR genetic lesions, predicts poor outcome in MM (Shah V, Leukemia 2017). Gene expression profiling (GEP) with the EMC92/SKY92 signature (SkylineDx) identifies patients with short survival (Kuiper R, Leukemia 2012). We present here updated data on an integrated genetic and GEP molecular risk stratification strategy, which will be used in the Myeloma UK (MUK) nine OPTIMUM trial to generate evidence for improved treatment of HRMM.

METHODS AND RESULTS

We present updated survival analyses (data cut-off July 2016) for 336 representative patients from the transplant-eligible cohort of the UK NCRI Myeloma XI trial (median follow-up 42 months). For all patients a complete dataset for adverse genetic lesions del(1p32), gain(1q21), del(17p), adverse translocations was generated using MLPA and qRT-PCR (Shah V, Leukemia 2017). All tumors were GEP risk profiled using the SKY92 MMprofiler on an Affymetrix DX2 platform. 32% of MM tumors carried at least one HR genetic lesion, and 22% carried a double-hit. Double-hit was associated with a hazard ratio of 2.1 for progression-free survival (PFS) ($P < 0.0001$; median 18.1 vs. 33.6 months without double-hit) and 3.1 for OS ($P < 0.0001$; median 38.3 mo. vs. not reached). SKY92 HR status was present in 25% of tumors with a hazard ratio of 2.9 for PFS ($P < 0.0001$; median 15.8 vs. 33.6 mo. in SKY92 standard risk) and 3.9 for OS ($P < 0.0001$; median 36.7 mo. vs. not reached). Ten percent of tumors carried both double-hit and SKY92, 15% only SKY92 and 12% only double-hit, suggesting that, although overlapping, each method is capable of identifying HR patients that are not detected by the other method. 36% were characterised by either double-hit or SKY92 with a hazard ratio of 2.6 for PFS (median 18.1 vs. 37.0 months) and 3.9 for OS (median 43.6 vs. not reached). Overall adequacy of risk prediction using C-statistics demonstrated an inferred C-value for 48 months OS of 0.67 (0.61-0.72) for the combined genetic and GEP risk approach, which was an improvement to either classifier alone. Patients fulfilling either double-hit or GEP or both HR criteria at diagnosis will be treated in the OPTIMUM trial.

The phase IIb MUKnine OPTIMUM trial investigates innovative combination therapy with Daratumumab, Cyclophosphamide, Velcade, Lenalidomide, Dexamethasone

(DCVRd) induction followed by high dose melphalan + ASCT augmented by Velcade, intensified consolidation (DVR) and maintenance (DR) in patients with molecular high risk status as above. Its design follows recommendations for trials in rare cancers (Bogaerts J, Eur J Canc 2015), using a Bayesian strategy to compare outcomes with DCVRd against near-concurrent control data from the Myeloma XI trial, as reported above. The primary endpoint is PFS, with interim futility analyses of PFS and Minimal Residual Disease (MRD) negativity in OPTIMUM patients vs. Myeloma XI HR patients defined by the same molecular criteria. OPTIMUM is designed to detect an increase in PFS of 25% compared to Myeloma XI control data and, based on Bayesian modelling, up to 620 newly diagnosed patients will be molecularly screened for HR disease and up to 105 patients with HR status will be treated on the OPTIMUM trial. All other patients will be treated according to UK standard and data will be collected as for the HR group. Secondary endpoints include response, PFS2 and OS. Exploratory research accompanying the trial is planned to include longitudinal MRD dynamics and diffusion-weighted MRI imaging.

CONCLUSION

The UK Myeloma Research Alliance (MRA) MUKNine OPTIMUM study is one of the first trials in MM designed to provide comparative evidence for stratified treatment of patients with molecular high-risk MM. The trial has regulatory approval and is scheduled to start Q3 2017 in 22 hospitals of the Myeloma UK Clinical Trial Network.