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ORAL ABSTRACTS

653.MULTIPLE MYELOMA: PROSPECTIVE THERAPEUTIC TRIALS

GEM2017FIT Trial: Induction Therapy with Bortezomib-Melphalan and Prednisone (VMP) Followed By Lenalidomide and Dexamethasone (Rd) Versus Carfilzomib, Lenalidomide and Dexamethasone (KRd) Plus/Minus Daratumumab (D), 18 Cycles, Followed By Consolidation and Maintenance Therapy with Lenalidomide and Daratumumab: Phase III, Multicenter, Randomized Trial for Elderly Fit Newly Diagnosed Multiple Myeloma (NDMM) Patients Aged between 65 and 80 Years

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Background: In transplant-ineligible patients (pts) with NDMM, VMP and Rd have been standards of care. The Spanish Myeloma Group examined induction with VMP followed by Rd, and results were particularly striking for "fit" pts aged 65-

80 with a CR rate of 47% and an MRD negative rate (MRD(-)) of 20%. The median PFS was 34 months (m) and 4-years (yrs) OS rate was 70%.

Pts and study design: Based on this background, we consider VMP9-Rd9 as control arm and compared with KRd or D-KRd. Induction included 18 cycles, followed by 4 D-Rd consolidation cycles for the two first arms (to evaluate if anti CD38 consolidation might compensate its absence as induction). Subsequently, pts were stratified by MRD (positive and negative) to maintenance therapy with D-R vs observation.

Frailty was evaluated with Geriatric Assessment in Hematology (GAH scale) considering as fit those younger than 80 years and with a punctuation between 0 and 42.

VMP and Rd were given at conventional doses and in the K-based regimens, K was given at dose of 36mg/m ^{2} twice weekly during C1-2 and at 56 mg/m ^{2} weekly since C3. R was given at standard dose and D was planned as IV but switched to SC, both at the conventional dose and schedule.

The primary endpoint was to evaluate the MRD(-) rate (NGF 10 $^{-5}$) at the end of induction to compare both experimental arms, KRd and D-KRd to the control-one, VMP-Rd. A step-down testing procedure was applied, whereby inference for a test in the pre-defined hierarchy was dependent upon statistical significance having been achieved for the previous tests in the hierarchy. No formal adjustment for multiplicity of contrasts is required. Secondary endpoints referred to the induction phase included the serological responses, PFS and OS probabilities at 18 cycles and safety profile.

Results: 540 pts were screened and 78 were screening failures. 462 pts were randomized to VMP-Rd (154 pts), KRd (154 pts) and D-KRd (153 pts but one patient was not evaluable). Baseline characteristics of the pts were comparable in the three arms with a median age of 72 and around one third older than 75 years. Nearly one third of pts in the three arms had ISS 3 and 15% had extramedullary disease.

A total of 369 out of 461 pts have completed the 18 induction cycles (128 in VMP-Rd, 122 in KRd and 119 in D-KRd) and were evaluable for the primary endpoint. The MRD(-) rate at 10 $^{-5}$ was 32% for VMP-Rd, 69% for KRd ($p<0.0001$) and 79% for D-KRd ($p<0.0001$). At 10 $^{-6}$, the MRD(-) rate was also significantly superior for KRd (59%) and D-KRd (75%) in comparison with VMP-Rd (24%) (p values <0.0001).

The ORR at the end of induction was comparable in the three arms (87%, 89% and 89%, respectively) but the sCR/CR rate was significantly higher for KRd (59%) and D-KRd (61%) in comparison with VMP-Rd (40%) (p-values <0.0001).

At 18 m, the proportion of pts alive and progression-free was 79% for VMP-Rd and 87% for KRd and D-KRd, respectively. Only two pts who achieved MRD negativity have progressed thus far. The OS at 18 m in the VMP-Rd, KRd and D-KRd arms was 91%, 95% and 90%, respectively.

There were 48, 44 and 40 pts who early discontinued therapy in VMP-Rd, KRd and D-KRd, respectively, due to progressive disease (VMP-Rd: 23; KRd: 9;D-KRd: 6) or toxicity (VMP/Rd:8; KRd: 14; D-KRd: 6). Death occurred in 12 pts treated with D-KRd being infections the cause in 10 pts (Covid-19 in 3); 5 pts in the KRd arm (4 infections (Covid-19 in 1)) and 6 pts in VMP-Rd arm (infections in 4 pts).

Concerning hematological toxicity during induction, G3/4 neutropenia was higher in VMP-Rd (50%) than KRd (24%) ($p<0.0001$) and similar to D-KRd (47%). G3/4 thrombocytopenia was also higher in VMP-Rd (34%) than the other two arms (16% and 17%, $p<0.0001$)). G3/4 infections rate was comparable in the three arms (12% in VMP-Rd and 15%-16% in KRd and D-KRd). Cardiovascular G3/4 events were higher in KRd (11%) and D-KRd (14%) than in VMP-Rd (5%) ($p<0.0001$) being hypertension and cardiac failure the most frequent-ones.

Conclusions: The trial met its primary end point and the MRD(-) rates of 69% for KRd and 79% for D-KRd were significantly higher than VMP9-Rd9 (32%). Overall, the VMP-Rd arm had higher rates of neutropenia, while the D-KRd arm had higher rates of infections leading to death. The trial is ongoing to evaluate long term outcomes.

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