Addition of Isatuximab to Lenalidomide, Bortezomib and Dexamethasone As Induction Therapy for Newly-Diagnosed, Transplant-Eligible Multiple Myeloma Patients: The Phase III GMMG-HD7 Trial

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Background:

In newly-diagnosed multiple myeloma (NDMM), lenalidomide/bortezomib/dexamethasone (RVd) is one of the most widely used combination regimens. Anti-CD38 monoclonal antibodies (CD38-moAb) increase efficacy when added to standard-of-care regimens. Here we present the first primary endpoint of the randomized, open-label, multicenter, phase III GMMG-HD7 trial, comparing RVd without (arm IA) or with the CD38-moAb isatuximab (Isa, arm IB) with regard to the rate of minimal residual disease (MRD) negativity after induction therapy in patients with transplant-eligible NDMM.

Patients and Methods:

Patients with transplant-eligible NDMM at 67 sites in Germany were equally randomized to receive three 42-day cycles of RVd (lenalidomide 25 mg/d p.o., d1-14 and d22-35; bortezomib 1.3 mg/m 2 s.c. d1, 4, 8, 11, 22, 25, 29, 32; dexamethasone 20 mg/d d1-2, 4-5, 8-9, 11-12, 15, 22-23, 25-26, 29-30, 32-33) in both arms. Isa was added to arm IB only (10 mg/kg i.v., cycle 1: d 1, 8, 15, 22, 29; cycles 2-3: d 1, 15, 29). Randomization for induction was stratified according to revised International Staging System (R-ISS). Primary endpoint of the trial was MRD negativity assessed by next-generation flow (NGF, cut off 1x10 -5) after induction. Secondary endpoints included rates of complete response (CR) after induction and safety. Data cut-off for the present analysis was April 2021.

Results:

Between 10/2018 and 09/2020, 662 patients were included in the trial. 660 patients were eligible for intention-to-treat analysis and 658 patients started induction (RVd: 329/328 and Isa-RVd: 331/330). Median age was 58 (range 26-70) years and baseline characteristics were well balanced between treatment arms. On induction, 35 (10.6%) and 18 (5.4%) patients discontinued treatment in the RVd vs. Isa-RVd arms (p=0.02). Among these, 8 (2.4%, RVd) vs. 7 (2.1%, Isa-RVd) patients discontinued induction due to adverse events (AE). 293 (89.1%) vs. 312 (94.3%) patients in the RVd vs. Isa-RVd arms continued further study treatment after induction.

MRD negativity rates after induction were 35.6% vs. 50.1% (odds ratio [OR]=1.83, 95% confidence interval [95% CI]: 1.34-2.51, p<0.001) for RVd vs. Isa-RVd, respectively. On multivariate analyses including treatment arm, R-ISS, performance status, renal impairment, age and sex, treatment with

Isa-RVd (vs. RVd) remained the only significant predictor for increased MRD negativity after induction (OR=1.82, 95% CI: 1.33-2.49, p<0.001). While the rates of CR after induction did not yet differ between the RVd vs. Isa-RVd arms (21.6% vs. 24.2%, p=0.46), the rate of very good partial response or better (≥VGPR) was significantly higher in the Isa-RVd arm (60.5% vs. 77.3%, p<0.001). The rates of progressive disease were 4.0% (RVd) vs. 1.5% (Isa-RVd).

At least one AE (grade ≥3) on induction occurred in 61.3% (RVd) and 63.6% (Isa-RVd) of patients (p=0.57). Most common AE (grade ≥3) by system organ class (SOC) for RVd vs. Isa-RVd were: "investigations": 23.5% vs. 23.9% (p=0.93), "blood and lymphatic system disorders": 16.8% vs. 25.8% (p=0.006), "infections and infestations": 10.4% vs. 13.0% (p=0.33) and "nervous system disorders": 10.1% vs. 8.5% (p=0.50). Rates of serious AE (SAE, any grade) on induction were similar between RVd and Isa-RVd (36.3% vs. 34.8%, p=0.75). Eight (RVd) and four (Isa-RVd) patients died during induction.

Conclusions:

The GMMG-HD7 trial met its primary endpoint. To the best of our knowledge this is the first phase III trial to demonstrate superiority of MRD negativity rates after induction by adding a CD38-moAb to RVd. There were no increased rates of SAE or early discontinuation in patients treated with Isa-RVd compared to RVd. The trial is ongoing, including analyses post autologous transplantation, which is followed by a second randomization to compare the efficacy of the addition of Isa to lenalidomide maintenance.