4756 High-Risk Multiple Myeloma in Benefit (IFM 2020-05) Phase 3 Randomized Study of Isatuximab (Isa) Plus Lenalidomide and Dexamethasone (Rd) with Bortezomib Versus Isard in Patients with Newly Diagnosed Transplant Ineligible Multiple Myeloma (NDMM TI)

Program: Oral and Poster Abstracts
Session: 654. Multiple Myeloma: Pharmacologic Therapies: Poster III
Hematology Disease Topics & Pathways:
Research, Clinical trials, Drug development, Plasma Cell Disorders, Clinical Research, Diseases, Treatment Considerations, Lymphoid Malignancies

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Abstract

Introduction:

Isa-VRd significantly increased the MRD negative rate at 10^{-5} (NGS) at 18 months compared to IsaRd (OR for MRD negativity 3.16, 95%CI 1.89-5.28, p<0.0001), the primary endpoint of BENEFIT study, including in high-risk (HR) NDMM TI. HR was initially defined using the IFM linear predictor (LP) cytogenetic score (HR if LP >1) according to Perrot et al in BENEFIT. The IMS has recently attempted to standardize the HR definition based on several genomic abnormalities alone [deletion 17p in more than 20% of sorted plasma cells, TP53 mutation, del(1p32)$^{del/del}$] or in combination [t(4;14) or t(14;16) or t(14;20) +gain/amp 1q or del(1p32)$^{del/wt}$, gain/amp 1q +del(1p32)$^{del/wt}$].We planned to investigate the efficacy of Isa-VRd over IsaRd in HR NDMM TI using the novel definition.

Methods:

BENEFIT is a prospective, multicenter, randomized, open-label, phase 3 study done at 68 IFM study sites in France. Patients were randomized 1:1 and stratified by age, centers and high-risk MM to receive Isa-VRd or IsaRd. Isa-VRd arm received V weekly for 12 months then day 1 and 15 up to 18 months; both arms received a classical IsaRd with d permanently discontinued at

12 months. At a median follow-up of 23.5 months, a total of 270 patients were enrolled with 135 assigned to either Isa-VRd or IsaRd arms, and received at least one dose of treatment. Data are presented in ITT. IMS new HR definition was defined based on targeted next generation sequencing of sorted plasma cells.

Results:

HR features characterized 32 (24%) patients and 24 (18%) across Isa-VRd or IsaRd arms using the IMS HR definition. Deletion 17p 10 (7%) and 7 (5%), TP53 mutation 6 (4%) and 5 (4%), del(1p32)$^{del/del}$ 1 (1%) and 0, t(4;14) or t(14;16) or t(14;20) +gain/amp 1q or del(1p32)$^{del/wt}$ 13 (10%) and 10 (7%), gain/amp 1q +del(1p32)$^{del/wt}$ 6 (4%) and 5 (4%), respectively across arms. Overall, the new IMS HR definition reclassified 30 (13%) NDMM TI patients in the HR category compared to the IFM LP score. Of note, the HR patients according to the IFM LP score were all considered HR by the new IMS definition.The 18-months MRD negativity rate at 10^{-5} was higher for Isa-VRd in high-risk NDMM TI with the IMS HR definition, 18 (56%) and 6 (25%) across arms, [odds ratio (OR) for MRD negativity in Isa-VRD group compared to IsaRd group was 3.86 (95%CI, 1.2 to 12.3)]. Similar data were observed at 10^{-6} at 18 months, 16 (50%) and 6 (25%) across arms [OR 3.00 (95%CI, 0,95 to 9.52)]. Higher MRD negativity rates were also observed at 12 months at both 10^{-5} and 10^{-6} and in patients with a response ≥ CR and MRD negative status in Isa-VRd in HR NDMM TI.The 18-month MRD negativity rate at 10^{-5} was higher for Isa-VRd also in NON high-risk NDMM TI (IMS HR definition) [OR 3.00 (95%CI, 1.7 to 5.3)], as well as at 10^{-6} [OR 2.61 (95%CI, 1.3 to 5.0)] and at 12 months at both 10^{-5} and 10^{-6} thresholds and in patients with a response ≥ CR and MRD negative status. Although no statistically significant interaction was detected across HR and NON HR, the greater benefit of IsaVRD vs. IsaRd for MRD negativity was systematically higher for HR patients, regardless of the timepoints (12 months, 18 months), MRD thresholds (10-5 or 10-6) and MRD negativity definition (≥CR or not)

Conclusions:

The results from the BENEFIT study demonstrated meaningful benefit of the quadruplet-based Isa-VRd regimen compared to IsaRd in all NDMM TI patients. Of importance, the benefit of the Isa-VRd regimen was greater in HR compared to NON HR NDMM TI patients. This data supports Isa-VRd as a new SOC for NDMM TI aged of 65 to 79 patients over the current triplet-based SOC DRd, particularly for HR NDMM TI.

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