770 Isatuximab, Bortezomib, Lenalidomide, and Dexamethasone (Isa-VRd) in Patients with Newly Diagnosed Multiple Myeloma (NDMM): Analyses of Minimal Residual Disease (MRD) Negativity Dynamics in the Phase 3 Imroz Study

Program: Oral and Poster Abstracts
Type: Oral
Session: 654. Multiple Myeloma: Pharmacologic Therapies: Refining the Evidence: Randomized Trials in Multiple Myeloma
Hematology Disease Topics & Pathways:
Research, Clinical trials, Clinical Research, Measurable Residual Disease

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Abstract

Introduction:

In the global Phase 3 IMROZ study (NCT03319667), transplant-ineligible patients (pts) with NDMM demonstrated significantly improved progression-free survival (PFS) with Isa-VRd

followed by Isa-Rd compared with VRd followed by Rd, along with deep and sustained responses. Pts in the Isa-VRd arm demonstrated a significantly higher overall MRD-negative (MRD-neg) complete response (CR) rate at 10^{-5} sensitivity threshold vs the VRd arm (56% vs 41%; *p*=0.003), as well as higher rates of MRD-neg (58% vs 44%) and almost double the rate of sustained MRD-neg (sustMRD-neg) for ≥12 months (47% vs 24%) at any point during the study in the ITT population. The median time to MRD-neg was half as long with Isa-VRd (14.7 months) vs VRd (32.8 months). Here we report further analyses from IMROZ on the dynamics of MRD-neg.

Methods:

In the open-label IMROZ trial, 446 pts were randomized 3:2 to receive Isa-VRd (n=265) in the initiation phase followed by maintenance with Isa-Rd vs VRd (n=181) followed by Rd in pts ≤80 years of age. Pts received Isa (10 mg/kg IV) in the Isa-VRd arm and bortezomib (1.3 mg/m^2 SC), lenalidomide (25 mg PO), and dexamethasone (20 mg IV/PO) in both arms. The primary endpoint was PFS. Key secondary endpoints included MRD-neg CR rates assessed by clonoSEQ® next-generation sequencing (NGS) at 10^{-5} sensitivity threshold in bone marrow aspirates obtained at baseline, and during the initiation (month 6) and maintenance (months 12, 18, 24 and 36) phases from pts with a very good partial response or better. Exploratory analyses included assessments at 10^{-6} sensitivity threshold and using next-generation flow (NGF).

Results:

MRD dynamics were measured by NGS using 1610 MRD assessments done over 5 years. Of the 306 patients who had an initial MRD assessment during initiation, 50.0% vs 41.1% were MRD-neg in Isa-VRd vs VRd, respectively. MRD-neg deepened over time with an MRD-neg rate of 68.6% and 50.8% for Isa-VRd vs VRd, respectively by month 36. Consistent with the previously published observations of sustMRD-neg for ≥12 months, sustMRD-neg rates at ≥24 and ≥36 months were higher with Isa-VRd than VRd (36.0% vs 13.3% and 25.7% vs 7.2%, respectively); similar observations of sustMRD-neg rates were seen at 10^{-6} sensitivity threshold. Looking at MRD status during maintenance at month 12, 18, 24 and 36 revealed that a higher proportion of Isa-VRd vs VRd pts converted from MRD positivity during initiation to MRD-neg during maintenance, and this positive-to-negative conversion rate increased over the maintenance period (month 12: 20.8% vs 16.3%; month 18: 22.7% vs 18.8%; month 24: 35.0% vs 18.0%; month 36: 47.2% vs 32.3%, respectively). Correlation of MRD status change and of time to first MRD-neg status with PFS benefit will be presented.

In addition, key subgroup analyses by MRD-neg status at 10^{-5} and 10^{-6} demonstrated a benefit and a shorter median time to MRD-neg with Isa-VRd vs VRd. Good concordance was shown between NGS and NGF for MRD-neg (10^{-5}) pts (70.4%) and MRD-neg CR pts (75.9%).

Conclusions:

Isa-VRd followed by Isa-Rd led to greater depth of response of MRD-neg over time, with higher rates of MRD-neg at both the end of initiation and during maintenance compared with the control arm. Results from these analyses continue to demonstrate higher rates of sustMRD-neg over time at 10^{-5} and 10^{-6} sensitivity thresholds, and more pts retained MRD-neg status through maintenance phase. More pts had positive-to-negative conversions with Isa-VRd vs VRd, with conversion events increasing over the maintenance period. These data support the

benefit of Isa in addition to VRd as initiation therapy, as well as the addition of Isa to Rd during maintenance in transplant-ineligible pts with NDMM.

Clinical trial registration: NCT03319667. **Funding:** Sanofi.

Disclosures: Orlowski: *Bristol Myers Squibb, CARsgen Therapeutics, Exelixis Inc, Heidelberg Pharma, Janssen Biotech Inc, Sanofi, Takeda Pharmaceuticals USA Inc; Laboratory Research Funding: Asylia Therapeutics Inc, BioTheryX Inc, Heidelberg Pharma:* Research Funding; *AbbVie Inc, Adaptive Biotechnologies Corporation, Asylia Therapeutics Inc, BioTheryX Inc, Bristol Myers Squibb, Karyopharm Therapeutics, Meridian Therapeutics, Monte Rosa Therapeutics, Nanjing IASO Biotherapeutics, Neoleukin Therapeutics, Oncopeptides, Pf:* Membership on an entity's Board of Directors or advisory committees; *DEM BioPharma, Inc., Karyopharm Therapeutics, Lytica Therapeutics, Meridian Therapeutics, Monte Rosa Therapeutics, Myeloma 360, Nanjing IASO Biotherapeutics, Neoleukin Corporation, Oncopeptides AB, Pfizer, Inc., Regeneron Pharmaceuticals, Inc., Sporos Bio:* Membership on an entity's Board of Directors or advisory committees; *Asylia Therapeutics Inc.:* Current equity holder in private company, Patents & Royalties; *BioTheryX:* Membership on an entity's Board of Directors or advisory committees, Research Funding; *Bristol-Myers Squibb Pharmaceuticals:* Membership on an entity's Board of Directors or advisory committees; *Sanofi, Takeda Pharmaceuticals:* Membership on an entity's Board of Directors or advisory committees, Research Funding. **Dimopoulos:** *AMGEN:* Honoraria, Membership on an entity's Board of Directors or advisory committees; *SANOFI:* Honoraria; *REGENERON:* Honoraria; *MENARINI:* Honoraria; *TAKEDA:* Honoraria; *GSK:* Honoraria; *BMS:* Honoraria; *JANSSEN:* Honoraria; *BEIGENE:* Honoraria; *SWIXX:* Honoraria; *ASTRA ZENECA:* Honoraria. **Leleu:** *Kite, A Gilead Company:* Consultancy, Honoraria. **Hajek:** *Takeda:* Consultancy, Honoraria, Research Funding; *Janssen:* Consultancy, Honoraria, Research Funding; *Amgen:* Consultancy, Honoraria, Research Funding; *Celgene:* Consultancy, Honoraria, Research Funding; *AbbVie:* Consultancy; *BMS:* Consultancy, Honoraria, Research Funding; *PharmaMar:* Consultancy, Honoraria; *Novartis:* Consultancy, Research Funding. **Špička:** *Charles University and General University Hospital in Prague, Czech republic:* Current Employment; *BMS:* Honoraria; *Amgen:* Honoraria, Membership on an entity's Board of Directors or advisory committees; *Janssen-Cilag:* Honoraria; *Takeda:* Honoraria, Membership on an entity's Board of Directors or advisory committees; *Sanofi:* Honoraria, Membership on an entity's Board of Directors or advisory committees; *GSK:* Honoraria; *Johnson and Johnson:* Membership on an entity's Board of Directors or advisory committees; *Novartis:* Membership on an entity's Board of Directors or advisory committees. **Romejko-Jarosinska:** *AstraZeneca, Gilead, Roche, Janssen, Celgene, Sanofi, Takeda:* Honoraria, Speakers Bureau; *Gilead, Roche, Takeda:* Other: Support for attending meetings and/or travel; *Swixx:* Other: Participation on a Data Safety Monitoring Board or advisory board. **Besemer:** *Oncopeptides:* Honoraria; *GlaxoSmithKline:* Honoraria; *Janssen:* Honoraria; *Takeda:* Honoraria; *AMGEN:* Honoraria; *Pfizer:* Honoraria. **Goldschmidt:** *Adaptive Biotechnologies:* Membership on an entity's Board of Directors or advisory committees; *Amgen:* Honoraria, Membership on an entity's Board of Directors or advisory committees, Other: Support for attending meetings and/or travel; grants and/or provision of Investigational Medicinal Product, Research Funding; *Bristol Myers Squibb:* Honoraria, Membership on an entity's Board of Directors or advisory committees, Other: Support for attending meetings and/or travel, Research Funding; *Karyopharm:* Research Funding; *Incyte Corporation:* Research Funding; *Janssen:* Honoraria, Membership on an entity's

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