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Blood 142 (2023) 6741–6742

The 65th ASH Annual Meeting Abstracts

ONLINE PUBLICATION ONLY

653.MULTIPLE MYELOMA: PROSPECTIVE THERAPEUTIC TRIALS

Multicenter Open Label Phase 3 Benefit Study of Isatuximab Plus Lenalidomide and Dexamethasone with/without Bortezomib in the Treatment of Newly Diagnosed Non-Frail Transplant Ineligible Multiple Myeloma Elderly Patients. IFM2020-05

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Background. The current standard of care for non-transplant eligible (NTE) newly diagnosed multiple myeloma (NDMM) is the combination of anti-CD38 immunotherapy daratumumab to lenalidomide-dexamethasone (DRd) on the basis of the Maia study (Facon et al. NEJM). This regimen has considerably improved the survival objectives for the study and the patients, PFS and OS. Interestingly, the MRD sustained 10-5 negative rate of DRd in MAIA is lower than 15%, alluding to the hypothesis that DRd may be immunogenic more than profoundly debulking in its main MOAs.
We and other have hypothesized that adding a proteasome inhibitor (PI) to antiCD38 IT +Rd combination would significantly increase the sustained MRD negativity rate and might improve even further survivals. Two phase 3 studies for registration investigate the role of adding antiCD38 IT to VRd (antiCD38VRd quadruplet-based combination versus VRd), questioning on the added value of antiCD38 to the old standard of care VRd. We believe it is of importance to study the added value of a PI to antiCD38 IT +Rd combination in comparison to antiCD38 IT +Rd (the optimal standard of care today in the NTE NDMM) to demonstrate the impact in debulking of the PI on top of the immunogenic effect with the study of the MRD negative rate. We therefore have conducted the present study of Isa-VRd compared to Isa-Rd (IFM2020-05/Benefit, (NCT04751877). Benefit has fully enrolled as of September 2022, and there has been no safety warnings from the safety committee with the prolonged use of bortezomib for 18 months on a weekly basis in combination to Isa-Rd.
Study Design and Methods. 270 NTE NDMM patients, aged [65-79] years old and non-frail, were randomized 1:1 and assigned to either the anti-CD38 mAb isatuximab + Rd (Isa-Rd) or isatuximab + VRd (Isa-VRd lite). Stratification across arms was done according to high-risk MM, age cutoff of 75 years and study centers. Patients receive isatuximab IV 10 mg/kg on days 1, 8, 15, and 22 of cycle 1, days 1 and 15 from cycle 2 to 12 and day 1 from cycle 13 onward, 28-day cycles. Lenalidomide and dexamethasone were given orally as approved. Bortezomib was administered weekly and subcutaneously on days 1, 8, 15 at 1.3 mg/m² from cycle 1 to 12 and on days 1, 15 from cycle 13 to 18, and then stopped. All patients will discontinue dexamethasone after cycle 12. Patients will then continue receiving Isa-Rd until progression in both arms.
The primary objective is to evaluate the MRD negativity rate at 10-5 at 18 months in both arms, sustained MRD being key secondary at [12-24] months. The study will be considered positive if the MRD negativity rate at 10-5 at 18 months is 30% in the Isa-VRd arm, and twice as much as Isa-Rd arm within the same time point. Key secondary objectives include the survival analysis (OS, PFS, EFS, TTNT), response rates, duration of response, and safety.
Conclusion. The study is estimated to read out March 2024, 18 months after the last patient enrolls.

Disclosures Hulin: *Bristol Myers Squibb:* Honoraria; *Janssen:* Honoraria; *Amgen:* Honoraria; *Sanofi:* Honoraria; *AbbVie:* Honoraria; *Pfizer:* Honoraria. **Perrot:** *Abbvie, Adaptive, Amgen, BMS, Janssen, Pfizer, Sanofi, Takeda:* Honoraria. **Manier:** *Amgen:* Honoraria; *Janssen:* Honoraria; *BMS:* Honoraria; *Abbvie, Amgen, Celgene/BMS, GlaxoSmithKline, Janssen, Novartis, Pfizer, Regeneron, Roche, Sanofi, Takeda:* Membership on an entity's Board of Directors or advisory committees. **Karlin:** *Amgen, Celgene, GSK, Janssen, Takeda:* Consultancy; *AbbVie, Amgen, Celgene, Janssen, Sanofi, Takeda:* Honoraria. **Macro:** *Janssen, Takeda:* Honoraria, Other: Travel/accommodation, Research Funding; *GSK, Sanofi:* Honoraria. **Vincent:** *BMS, Takeda:* Membership on an entity's Board of Directors or advisory committees, Other: Financing meeting participation; *Janssen:* Honoraria, Membership on an entity's Board of Directors or advisory committees, Other: Financing meeting participation; *Pfizer:* Other: Financing meeting participation. **Touzeau:** *Bristol Myers Squibb:* Honoraria, Membership on an entity's Board of Directors or advisory committees. **Moreau:** *janssen, celgene BMS, abbvie, sanofi, amgen, takeda, pfizer:* Honoraria, Other: advisory boards; *GSK:* Honoraria, Other: Advisory Board. **Leleu:** *Sanofi:* Honoraria; *GSK:* Honoraria; *Janssen:* Honoraria; *Takeda:* Honoraria; *AbbVie:* Honoraria; *Novartis:* Honoraria; *Harpoon Therapeutics:* Honoraria; *BMS/Celgene:* Honoraria; *Merck:* Honoraria; *Amgen:* Honoraria.

https://doi.org/10.1182/blood-2023-185699