LBA4 **Plenary Session**

Lenalidomide, bortezomib, and dexamethasone (RVd) ± autologous stem cell transplantation (ASCT) and R maintenance to progression for newly diagnosed multiple myeloma (NDMM): The phase 3 DETERMINATION trial.

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Background: Optimal use of triplet/quadruplet induction, ASCT, and R-based maintenance in patients (pts) with NDMM who are eligible for transplant continues to evolve. The IFM 2009 trial, which used R maintenance for 1 year (y), showed progression-free survival (PFS; median, 35.0 vs. 47.3 months [mos]) but no overall survival benefit (OS; 60 vs. 62% at 8 y; median follow-up, 89.8 mos) with RVd + ASCT vs. RVd alone in the setting of multiple effective options at relapse, including ASCT at first relapse in 77% of pts (Attal M et al, *N Engl J Med* 2017; Perrot A et al, ASH 2020). We report primary data from our US DETERMINATION trial, which used R maintenance until progression. **Methods:** Pts with NDMM aged 18-65 y were randomly assigned to receive 3 RVd cycles, stem cell mobilization, and then 5 more RVd cycles (Arm A) or IV melphalan 200 mg/m^2 + ASCT and 2 RVd cycles (Arm B). Each 21-d RVd cycle comprised PO R 25 mg (d 1-14), IV/SC bortezomib 1.3 mg/m^2 (d 1, 4, 8, 11), and PO dexamethasone 20/10 mg (cycles 1-3/≥ 4; d 1, 2, 4, 5, 8, 9, 11, 12). Both arms received R 10-15 mg/d maintenance until progression or intolerance. The primary endpoint was PFS (90% power to detect PFS hazard ratio [HR] of 1.43 [Arm A vs. B] with $\alpha = 0.05$ on stratified two-sided log-rank test; full information: 329 events in 720 pts). Data cut-off was Dec 10, 2021. **Results:** 357 and 365 pts were randomly assigned to Arms A and B, respectively; median age was 57 and 55 y, 14% and 13% had ISS stage III MM, and 18% each had high-risk cytogenetics [t(4;14), t(14;16), del17p]. In the respective arms, 291 and 290 pts received R maintenance for a median duration of 36 and 41 mos. After median follow-up of 76 mos and 328 events, median PFS was 46.2 vs. 67.6 mos in Arm A vs. B (HR 1.53; 95% CI, 1.23–1.91; p < .0001). Best responses in pts assessed to date were 52 vs. 62% ≥ CR (p = .006), 79 vs. 83% ≥ VGPR and 94 vs. 96% ≥ PR; in 251 evaluable pts, rate of MRD negativity (10^{-5}) was 37.3 vs. 52.1% (p = .021) within 1 y of maintenance. 63 vs. 53% of pts have received subsequent treatment; of Arm A, 22% had ASCT as first non-protocol therapy. With 90 vs. 88 pts having died in Arm A vs. B, 4-y OS was 84% (95% CI, 80–88%) vs. 85% (95% CI, 81–88%); HR 1.10 (95% CI, 0.81–1.47; p = .274). Grade ≥ 3 related adverse events were less common in Arm A vs. B (78 vs. 94%; hematologic: 61 vs. 90%, p < .0001); 10 vs. 11% had secondary malignancies (ALL, 7 vs. 3 pts, p = .22; AML/MDS, 0 vs. 10 pts, p = .002). Difference in mean change from baseline in EORTC QLQ-C30 global health status score was < 10 points throughout treatment except at RVd cycle 5 vs. post-ASCT (compliance rate, 75% vs. 55%; mean change +3.0 vs. –11.1; p < .0001). Whole-genome sequencing, additional QOL, and correlative analyses are ongoing. **Conclusions:** RVd ± ASCT and R maintenance to progression resulted in the longest median PFS reported for each approach, and a highly significant 21.4-mo gain in median PFS benefit using RVd + ASCT. No OS advantage has been observed to date. Clinical trial information: NCT01208662. Research Sponsor: Support for this study was provided by grants #U10HL069294 and #U24HL138660 to the Blood and Marrow Transplant Clinical Trials Network from the National Heart, Lung, and Blood Institute and the National Cancer Institute, Other Foundation, Pharmaceutical/Biotech Company.