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POSTER ABSTRACTS

652.MULTIPLE MYELOMA: CLINICAL AND EPIDEMIOLOGICAL

Early Peripheral Blood Minimal Residual Disease Status By NGS in Patients with Newly Diagnosed Multiple Myeloma (MM) on a Phase 2 Trial Receiving Elotuzumab, Carfilzomib, Lenalidomide, and Dexamethasone (Elo-KRd)

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Background: Assaying for minimal residual disease (MRD) in the peripheral blood (PB) of patients with multiple myeloma (MM) could solve issues of patchy and extramedullary disease leading to false-negative MRD tests based on bone marrow (BM) only assessments. However, PB testing is challenging due to limited circulating myeloma cells and/or paraprotein. Further, early PB assessments for MRD by paraprotein are unreliable due to the extended half-lives of immunoglobulins. In this analysis, we investigated the concordance and prognostic significance of early MRD status after 4 cycles of treatment with Elo-KRd by next generation sequencing (NGS) in both the BM and PB and by International Myeloma Working Group (IMWG) response criteria.

Methods: All patients received 12 cycles of Elo-KRd in 28-day cycles without intent for stem cell transplant: Elo per standard dosing; K 56/70 mg/m ^{2} (highest tolerated) days 1, 8 and 15 (20 mg/m ^{2} on day 1 of cycle 1) ; R 25 mg days 1-21; and dexamethasone 40 mg days 1, 8, 15, 22. An MRD-adapted design was used to determine the duration of carfilzomib as previously reported (Derman et al. *JAMA Oncology* 2022). MRD by NGS in BM (sensitivity threshold 10 $^{-6}$,clonoSEQ, Adaptive Biotechnologies) was performed at multiple timepoints per protocol. PB mononuclear cells were evaluated for MRD using the same assay; any quantifiable signal was considered positive in PB. Conventional response was assessed per IMWG response criteria. Paired IMWG response and MRD status in the PB and BM were assessed for concordance and prognostic significance at the end of cycle 4 (C4). The Kaplan-Meier method was used to assess progression free survival (PFS) based on a landmark assessment at C4.

Results:

A total of 46 patients initiated treatment with Elo-KRd; patient baseline characteristics were reported previously (Derman et al. *JAMA Oncology* 2022). With a median follow-up of 39 months, estimated 4-year PFS was 75%.

Of the 42 patients in response at C4, 39 (93%) achieved >VGPR, and 13 (31%) reached >CR. When stratified by >CR vs <CR at C4, there was no difference in PFS (HR 1.4, 95% CI 0.3-6.9, p=0.7).

BM MRD status at C4 was available for 34 patients: 11 (32%) patients were BM MRD(-)and 23 (68%) were MRD(+). Matched PB MRD samples at C4 were available for 31 patients; 22 (69%) patients were PB MRD(-) using the best available threshold based on sample input (16 at 10 $^{-6}$, 6 at 10 $^{-5}$). Of the 9 (31%) patients with PB MRD(+), 6 (67%) had at least one high-risk cytogenetic abnormality (del17p in n=4, +1q in n=2, t(4;14) in n=1). Extramedullary disease relapse was a manifestation of progression in 4 (44%) patients.

BM MRD(-) at C4 was associated with superior PFS (HR not estimable, p=0.04; **Figure 1A**). No patient with MRD(-) BM after C4 had disease progression. PB MRD(+) at C4 was also associated with inferior PFS (HR 21, 95% CI 2.3-184, p=0.002; **Figure 1B**).

In comparing BM and PB MRD status, 8/9 (89%) patients with PB MRD(+) at C4 had BM MRD(+), and 14/22 (61%) patients with BM MRD(+) at C4 had PB MRD(-). 3/9 (33%) patients with PB MRD(+) at C4 were in >CR; 16/22 (73%) patients with PB MRD(-) at C4 were in a PR/VGPR. With progression serving as the reference standard, PB MRD(+) carried a sensitivity of 71%, a specificity of 83%, a positive predictive value of 56%, and a negative predictive value of 91%.

There were 19 matched BM MRD(+)/PB MRD(+) samples across all timepoints; Pearson's correlation coefficient of detected cells per million between BM and PB MRD was r=0.93. BM MRD detected aberrant cells at higher concentrations, with a median log difference of 1.38 compared to PB MRD (range 0.07-3).

Conclusions: MRD by NGS in the PB was less sensitive compared to the same assessment in the BM by 1-2 logs; however, PB MRD status following 4 cycles of induction therapy was strongly prognostic given its association with PFS. PB MRD status early in treatment may represent a leading indicator of early response and/or a marker of high-risk disease features, and validation of these findings may help to eventually guide intensification of therapy.

Disclosures Derman: *BMS:* Other: independent reviewer for clinical trial; *Janssen:* Consultancy; *COTA Healthcare:* Consultancy. **Simmons:** *Adaptive Biotechnologies:* Current Employment, Current equity holder in publicly-traded company. **Zonder:** *Janssen, Prothena, Regeneron:* Consultancy; *Takeda, Telios:* Other: Consultancy which has ended within the past 24 months; *Bristol-Myers Squibb/Celgene:* Research Funding. **Grinblatt:** *Celgene:* Consultancy; *Astellas:* Consultancy; *MorphoSys:* Consultancy; *Abbvie:* Consultancy. **Anderson:** *AbbVie:* Consultancy, Honoraria, Membership on an entity's Board of Directors or advisory committees; *Janssen:* Consultancy, Honoraria, Membership on an entity's Board of Directors or advisory committees, Research Funding; *Celgene:* Consultancy, Honoraria, Membership on an entity's Board of Directors or advisory committees, Research Funding; *Bristol Myers Squibb:* Consultancy, Honoraria, Membership on an entity's Board of Directors or advisory committees, Research Funding; *Amgen:* Consultancy, Honoraria, Membership on an entity's Board of Directors or advisory committees; *GlaxoSmithKline:* Consultancy, Honoraria, Membership on an entity's Board of Directors or advisory committees; *Beigene:* Consultancy, Honoraria, Membership on an entity's Board of Directors or advisory committees; *Cellectar:* Consultancy, Honoraria, Membership on an entity's Board of Directors or advisory committees; *Sanofi:* Consultancy, Honoraria, Membership on an entity's Board of Directors or advisory committees; *Prothena:* Consultancy, Honoraria, Membership on an entity's Board of Directors or advisory committees. **Gurbuxani:** *UpToDate:* Patents & Royalties: Royalties for contributions to various topics; *Jazz Pharmaceuticals:* Consultancy; *AbbVie:* Consultancy. **Jacob:** *Adaptive Biotechnologies:* Current Employment, Current equity holder in publicly-traded company. **Jakubowiak:** *BMS:* Consultancy, Honoraria, Membership on an entity's Board of Directors or advisory committees; *Janssen:* Consultancy, Honoraria, Membership on an entity's Board of Directors or advisory committees; *Amgen:* Consultancy, Honoraria, Membership on an entity's Board of Directors or advisory committees; *Sanofi-Aventi:* Consultancy, Honoraria, Membership on an entity's Board of Directors or advisory committees; *GSK:* Consultancy, Honoraria, Membership on an entity's Board of Directors or advisory committees; *Abbvie:* Consultancy, Honoraria, Membership on an entity's Board of Directors or advisory committees.

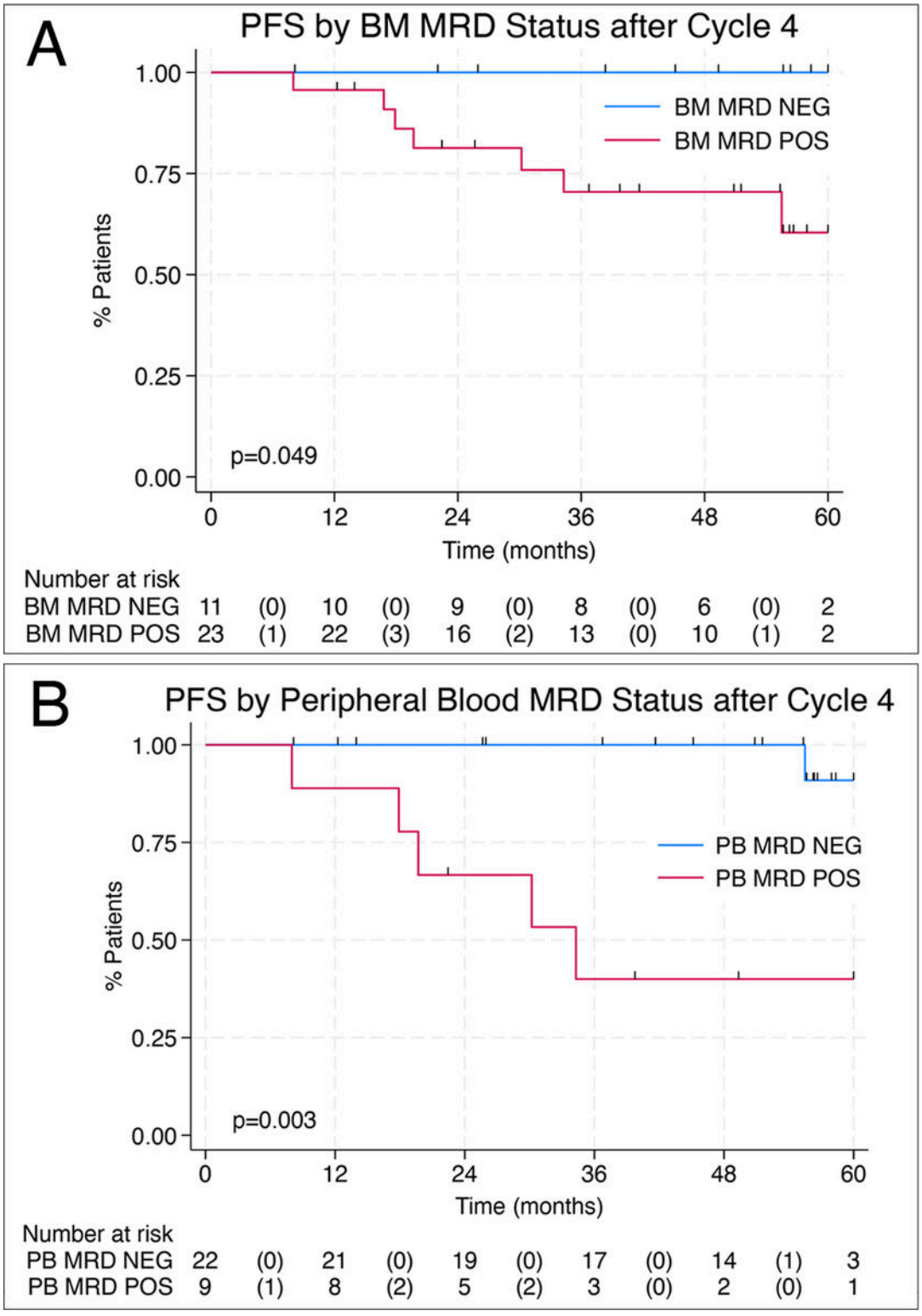

Figure 1

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