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ORAL ABSTRACTS

652.MULTIPLE MYELOMA: CLINICAL AND EPIDEMIOLOGICAL

Genomic Profiling to Interpret the Outcomes of Early Intervention for High-Risk Smoldering Myeloma

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Introduction

Early intervention for High-Risk Smoldering Multiple Myeloma (HR-SMM) achieves deeper and more prolonged responses compared to Newly Diagnosed (ND) MM. Various clinical risk models estimate the risk of SMM progression to MM but there is significant discordance between them (Hill et al., JAMA Onc. 2021). It is unclear if beneficial outcomes of interventional studies in HR-SMM are due to treatment of less complex, susceptible disease or inaccuracy in clinical definition of cases entered.

Methods

To gain greater biologic insight into treatment outcomes, we performed the first whole genome sequencing (WGS) analysis of treated HR-SMM for 27 patients treated with carfilzomib, lenalidomide, and dexamethasone (KRd) and R maintenance (NCT01572480, presented in parallel). We pooled genomic features from 27 patients with HR-SMM treated with Elotuzumab (Elo)R+/-d; (E-PRISM). Genomic features were compared to those of 701 patients with NDMM from CoMMpass (NCT01454297).

Results

After a median follow-up of 52.8 months, median PFS was not reached with KRd/R. After 8 cycles of KRd, 19 (70.3%) achieved minimal residual disease (MRD) negativity (LOD 10^{-5}). At data cutoff, June 13, 2023, 14 patients (51.9%) achieved sustained MRD-negativity, 6 patients (22.2%) lost an initial MRD-negative response and 5 patients clinically progressed (18.5%). Overall, there was discordance between risk models: 3 patients (11.1%) were HR by Mayo2008 criteria, 14 (51.9%) by Mayo 20/2/20, 18 (66.7%) by PETHEMA, and 21 (77.8%) by Rajkumar/Landgren/Mateos criteria (Rajkumar et al., Blood. 2015). Eighteen (66.7%) met criteria for 2 or more scores. The estimated 5-year risk of progression ranged 4.8 to 82.1% (Pangea, median 18.6%).

We compared the pooled HR-SMM to NDMM from CoMMpass. The frequency of HR translocations was similar (t(4;14), t(14;16), t(14;20); $p>0.05$). Consistent with the early disease stage of SMM, mutations of NRAS were lower in SMM ($p = <0.001$) as were events at the *MYC* locus (8q24; $p <0.001$) and gains of 1q ($p = 0.039$). Next, tumor suppressor genes (TSG) were interrogated together with copy number loss at their loci. Consistent with their late onset in tumor evolution, aberrations at key TSG were less common in HR-SMM ($p < 0.05$): *CDKN2C*, *CYLD*, *TENT5C*, *FUBP1*, *MAX*, *NCOR1*, *NF1*, *NFKBIA*, *PRDM1*, *RB1*, *RPL5*,and *TRAF3* ($p < 0.05$). In a genome-corrected comparison, APOBEC (SBS2+SBS13) mutational signatures

were diminished in KRd WGS compared to 60 Dara-KRd-treated NDMM (Maura et al., ASH. 2021; 48% vs 87%, $p < 0.001$) and in E-PRISM vs CoMMpass (15% vs 45%, $p = 0.001$).

We next related genomic features associated with HR-SMM to treatment outcomes. Patients treated with KRd/R had yearly MRD testing and gain1q, *MYC* dysregulation via loss of *MAX*, and t(4:14) were all associated with failure to sustain MRD-negativity. Across pooled HR-SMM, inactivation of *CYLD*, *CREBBP*, *MAX*, and *HIST1H2BK*; t(4;14), APOBEC expression, loss at select GISTIC peaks (**Fig 1A)** and chromothripsis all were associated with HR-SMM progression in the face of triplet therapy ($p<0.05$). Presence of any one or more of these features was associated with progression ($p = 0.005$; **Fig1B**). Conversely, no clinical risk score was able to discern those with this molecular high risk.

Conclusion

In patients treated on 2 parallel clinical trials for HR-SMM, we found a uniform and relative genomic simplicity. Moreover, non-progressors appear genomically similar to patients with non-progressive/stable MGUS and SMM under observation (Oben et al., Nat Comm 2021). However, within clinical HR-SMM, a set of high-risk genomic features portends progression despite intervention. These results suggest that clinical risk scores do not effectively discriminate between genomically indolent and aggressive disease. Though possible that results reflect treatment before the acquisition of key drivers, prior data suggest that many of these high-risk features are not acquired within the 5 years preceding clinical diagnosis of MM (Bolli et al., Nat Comm. 2018; Bustoros et al., J Clin Onc. 2020). Altogether, these results support the use of genomics to contextualize the advantage of early intervention in SMM (i.e., to avoid overtreatment of non-progressors and to better identify cases likely to progress without therapy).

Fig1A: Heatmap of High-Risk Features in Patients treated with KRD/R and EPRISM. **Fig1B:** Kaplan-Meier curve for time to progression by presence of HR features for KRD/R.

Disclosures Diamond: *Sanofi:* Honoraria; *MJH Cure:* Honoraria; *Janssen:* Honoraria. **Kazandjian:** *Aptitude Health:* Consultancy, Honoraria; *MMRF:* Ended employment in the past 24 months, Honoraria; *MJH Life Sciences:* Current Employment, Honoraria; *Curio Science:* Ended employment in the past 24 months, Honoraria; *Bridger Consulting Group:* Consultancy, Honoraria; *Karyopharm Therapeutics:* Current Employment, Speakers Bureau; *Bristol Myer Squibb:* Consultancy, Honoraria; *Plexus Communications:* Ended employment in the past 24 months, Honoraria; *Sanofi:* Consultancy, Honoraria; *Arcellx:* Consultancy, Current Employment, Honoraria; *Aperture Medical Technology, LLC:* Consultancy, Honoraria; *Alphasights:* Consultancy, Honoraria. **Usmani:** *Sanofi:* Membership on an entity's Board of Directors or advisory committees, Research Funding; *SkylineDX:* Membership on an entity's Board of Directors or advisory committees, Research Funding; *Takeda:* Membership on an entity's Board of Directors or advisory committees, Research Funding; *Moderna:* Membership on an entity's Board of Directors or advisory committees; *SecuraBio:* Membership on an entity's Board of Directors or advisory committees; *Novartis:* Membership on an entity's Board of Directors or advisory committees; *Oncopeptides:* Membership on an entity's Board of Directors or advisory committees; *Seattle Genetics:* Membership on an entity's Board of Directors or advisory committees, Research Funding; *TeneoBio:* Membership on an entity's Board of Directors or advisory committees; *Array Biopharma:* Research Funding; *Merck:* Research Funding; *Pharmacyclics:* Research Funding; *K36 Therapeutics:* Membership on an entity's Board of Directors or advisory committees; *Janssen:* Membership on an entity's Board of Directors or advisory committees, Research Funding; *GSK:* Membership on an entity's Board of Directors or advisory committees, Research Funding; *Gilead Sciences:* Membership on an entity's Board of Directors or advisory committees, Research Funding; *Genentech:* Membership on an entity's Board of Directors or advisory committees; *EdoPharma:* Membership on an entity's Board of Directors or advisory committees; *Celgene:* Membership on an entity's Board of Directors or advisory committees, Research Funding; *Bristol Meyer Squibb:* Membership on an entity's Board of Directors or advisory committees, Research Funding; *Amgen:* Membership on an entity's Board of Directors or advisory committees, Research Funding; *Abbvie:* Membership on an entity's Board of Directors or advisory committees, Research Funding. **Davies:** *Amgen:* Membership on an entity's Board of Directors or advisory committees; *Regeneron:* Membership on an entity's Board of Directors or advisory committees; *BMS / Celgene:* Membership on an entity's Board of Directors or advisory committees; *pfizer:* Membership on an entity's Board of Directors or advisory committees; *sanofi:* Membership on an entity's Board of Directors or advisory committees; *Janssen:* Membership on an entity's Board of Directors or advisory committees; *Takeda:* Membership on an entity's Board of Directors or advisory committees. **Getz:** *Scorpion Therapeutics:* Consultancy, Current equity holder in publicly-traded company, Other: Founder; *IBM:* Research Funding; *Pharmacyclics:* Research Funding; *SignatureAnalyzer GPU:* Patents & Royalties; *MSMuTect:* Patents & Royalties; *MSMutSig:* Patents & Royalties; *MSIDetect:* Patents & Royalties; *POLYSOLVER:* Patents & Royalties. **Ghobrial:** *Adaptive:* Honoraria; *10x Genomics:* Honoraria; *Menarini Silicon Biosystems:* Consultancy, Honoraria; *Novartis:* Consultancy, Honoraria, Research Funding; *Amgen:* Consultancy; *Regeneron:* Consultancy, Honoraria; *Sanofi:* Consultancy, Honoraria; *Pfizer:* Consultancy, Honoraria; *GlaxoSmithKline:* Consultancy, Honoraria; *The Binding Site:* Consultancy; *Janssen:* Consultancy, Honoraria; *Bristol-Myers Squibb:* Consultancy, Honoraria; *Takeda:* Consultancy, Honoraria; *Janssen:* Consultancy, Honoraria; *Aptitude Health:* Consultancy; *Vor Biopharma:* Ended employment in the past 24 months, Honoraria, Speakers Bureau; *AbbVie:* Consultancy, Honoraria; *Huron Consulting:* Consultancy; *Window Therapeutics:* Consultancy; *Oncopeptides:* Consultancy; *Disc Medicine:* Other: Spouse is Chief Medical Officer and holds equity in the company. **Landgren:** *Merck:* Consultancy, Honoraria, Membership on an entity's Board of Directors or advisory committees, Other: Membership on independent data monitoring committees; *Amgen:* Consultancy, Honoraria, Membership on an entity's Board of Directors or advisory committees, Other: Membership on independent data monitoring committees; *Takeda:* Consultancy, Honoraria, Membership on an entity's Board of Directors or advisory committees, Other: Membership on independent data monitoring committees; *Janssen:* Consultancy,

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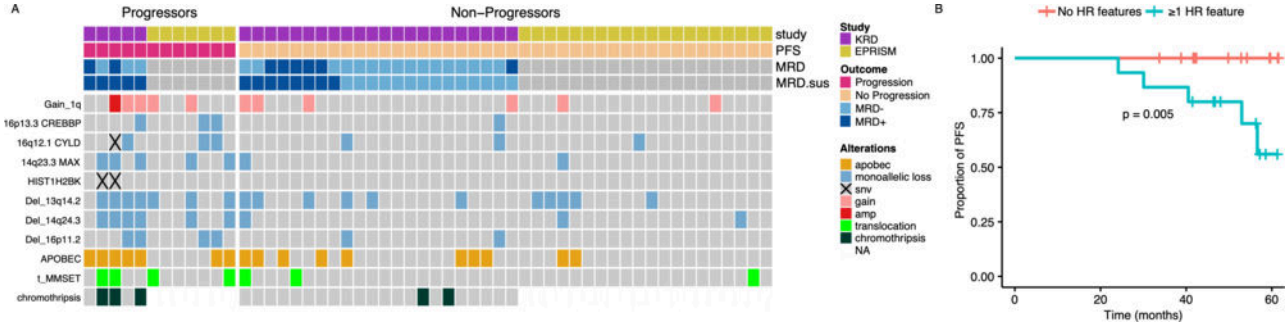

Figure 1

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