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POSTER ABSTRACTS

652.MULTIPLE MYELOMA: CLINICAL AND EPIDEMIOLOGICAL

Comprehensive Genomic Characterization of Response and Resistance to Daratumumab-Based Quadruplet Induction in Newly Diagnosed Multiple Myeloma Patients

Kylee H Maclachlan, PhDBSc,FRACP,FRCPA[1], Carlyn Rose Tan, MD[2], Tala Shekarkhand, MS[1], Colin Rueda[1], Edith Serrano[3], David Nemirovsky, MS[4], Andriy Derkach, PhD[4], Andrew McPherson, PhD[5], Benjamin Diamond, MD[6], Bachisio Ziccheddu[6], Eileen Boyle, MBChB, PhD[7], Hani Hassoun, MD[1], Sham Mailankody, MBBS[1], Urvi A Shah, MD[1], Malin Hultcrantz, MDPhD[1], Sergio A. Giralt, MD FACP[8], David Chung, MDPhD[8], Heather Landau, MD[8], Oscar Boutros Lahoud[8], Michael Scordo[8], Gunjan L. Shah[9], Yanming Zhang, MD[10], Robert Cimera[11], Maria E. Arcila, MD[12], Ahmet Dogan, MD PhD[13], Alexander Lesokhin, MD[1], Gareth J. Morgan, MD, PhD[14], Ola Landgren, MD[6], Francesco Maura, MD[6], Neha Korde, MD[1], Saad Z Usmani, MD[2]

[1] Myeloma Service, Department of Medicine, Memorial Sloan Kettering Cancer Center, New York, NY
[2] Myeloma Service, Division of Hematologic Oncology, Department of Medicine, Memorial Sloan Kettering Cancer Center, New York, NY
[3] Memorial Sloan Kettering Cancer Center, New York, NY
[4] Department of Biostatistics and Epidemiology, Memorial Sloan Kettering Cancer Center, New York, NY
[5] Computational Oncology, Memorial Sloan Kettering Cancer Center, New York, NY
[6] Sylvester Comprehensive Cancer Center, Myeloma Division, University of Miami, Miami, FL
[7] Department of Hematology, UCL Cancer Institute, London, United Kingdom
[8] Adult Bone Marrow Transplant Service, Department of Medicine, Memorial Sloan Kettering Cancer Center, New York, NY
[9] Adult Bone Marrow Transplant Service, Division of Hematologic Oncology, Memorial Sloan Kettering Cancer Center, New York, NY
[10] Cytogenetics Laboratory, Department of Pathology, Memorial Sloan Kettering Cancer Center, New York, NY
[11] Cytogenetics Laboratory, Department of Pathology, Memorial Sloan Kettering Cancer Center, New York City, NY
[12] Department of Pathology, Memorial Sloan Kettering Cancer Center, New York, NY
[13] Department of Pathology and Laboratory Medicine, Hematopathology Service, Memorial Sloan Kettering Cancer Center, New York, NY
[14] Perlmutter Cancer Center, Multiple Myeloma Research Program, NYU Grossman School of Medicine, NYU Langone Health, New York, NY

Introduction: Current prognostic scores for newly diagnosed multiple myeloma (NDMM) rely on measures of tumor bulk and limited genomic information. A recent artificial-intelligence-based model suggested that individualized prognostication and prediction of response to specific therapies may be improved by more comprehensive genomic assessment (IRMMa, Maura et al Blood 2022). The 20 significant genomic contributors included APOBEC mutational activity, gain/amp1q, *TP53* aberration, and loss of any of *CDKN2C*, *RPL5*, *FUBP1*, *RB1*, *RASA2*, 10q23 or 12p13. The highest impact on progression-free (PFS) and overall survival (OS) came from copy number (CN) signature profiles suggesting the structural variant chromothripsis (Maclachlan et al Nat Comm 2021).
We have previously demonstrated that CN features consistent with chromothripsis can be detected in targeted sequencing data, potentially increasing clinical application (Maclachlan el at Blood 2020). One limitation of the recently presented IRMMa model was an absence of patients prescribed daratumumab-based quadruplet induction, (dara-quads; daratumumab, lenalidomide, dexamethasone with carfilzomib [DKRd] or bortezomib [DVRd]).
Methods: We applied comprehensive genomic assessment to a cohort of 234 NDMM patients from Memorial Sloan Kettering Cancer Center initiated on dara-quad induction prior to May 2023. Genomic data included FISH (n=215), SNP-array (n=127), targeted sequencing (MSK-IMPACT-Heme, n=78) and whole genome sequencing (WGS, n=45). A further 80 samples are undergoing MSK-IMPACT-Heme (n=25) and WGS (n=55) currently.

Results: Among 234 patients analyzed, 86 patients received DKRd and 148 DVRd. Overall median follow-up was 1.4 years (y); 4.2y with DKRd (IQR 1.9-4.7, max 5.7) and 1y with DVRd (IQR 0.5-1.4, max 3.4). 25 patients progressed following DKRd and 20 following DVRd, with 9 progressing during induction chemotherapy.

ISS stage did not predict for PFS or OS, either in the whole cohort, or in individual regimens. The inclusion of genomic assessment improved prognostication; while R-ISS, high-risk cytogenetics as per R-ISS, and R2-ISS each improved PFS prediction ($p<0.01$), consideration of every feature assessable by FISH (including del1p, amp1q, t(14;20), *MYC*-translocations) further increased discrimination ($p=0.009$). Assessing as per the Master study (Costa JCO 2022), 2+ co-occurring high-risk features predicted for shorter PFS when compared with 1 or 0 risk factors ($p=0.002$). Within the 9 who progressed during induction, 4 were ISS III, 6 had a risk factor evident via FISH, and 4 had multiple high-risk features, while 4 had no risk factors by standard methods.

Using comprehensive genomic assessment (SNP-array, MSK-IMPACT-Heme and WGS) allowed for the assessment of additional genomic features in those with adequate follow up (predominantly DKRd). Del1p22.1 (*RPL5*) was strongly predictive of shorter PFS ($p<0.0001$), as were del22q12.1 (*XBP1*, $p=0.02$) and high APOBEC-mutational activity ($p=0.01$). Additional features demonstrated a trend to significance, including del1p12 (*TENT5C*, $p=0.06$) and the complex structural variant chromothripsis.

Parallel performance of MSK-IMPACT-Heme and WGS on the same samples allowed demonstration that CN signatures detected by targeted sequencing were accurate indications of complex chromothripsis events. The expanded WGS cohort will further define sensitivity and specificity of this detection.

Discussion: In the context of highly effective dara-quad induction, ISS stage did not predict for either PFS or OS. Limited cytogenetic assessment improved prognostication, while advanced genomic assessment was highly discriminatory. The current study provides the rationale for more comprehensive genomic assessment in patients receiving dara-quads in order to refine prognostication and consider novel treatment approaches for high-risk patients. We are significantly expanding our cohort of WGS in dara-quad-treated patients, formalizing the accuracy for CN signature detection of chromothripsis from targeted sequencing data, allowing application in routine clinical practice.

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