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The 2020 BMT CTN Myeloma Intergroup Workshop on Immune Profiling and Minimal Residual Disease Testing in Multiple Myeloma

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Abstract

The fifth annual Blood and Marrow Transplant Clinical Trials Network (BMT CTN) Myeloma Intergroup Workshop on Immune Profiling and Minimal Residual Disease Testing in Multiple Myeloma was conducted as one of the American Society of Hematology Annual Meeting Scientific Workshops on Thursday December 3, 2020. This workshop focused on four main topics: 1) integrating MRD into clinical trial design and practice; 2) the molecular and immuno-biology of disease evolution and progression in myeloma; 3) adaptation of next generation sequencing, next generation flow cytometry and CyTOF techniques; and 4) chimeric antigen receptor T-cell and other cellular therapies for myeloma. In this report, we provide a summary of the workshop presentations and discuss future directions in the field.

Keywords

Minimal residual disease; immune profiling; multiple myeloma; endpoint; CAR T-cell; cellular therapy

Introduction:

Since 2016, the Blood and Marrow Transplant Clinical Trials Network (BMT CTN) Myeloma Intergroup has conducted an annual workshop focused on minimal residual disease (MRD) and immune profiling (IP) assessment in multiple myeloma (MM) which is held prior to the American Society of Hematology (ASH) annual meeting.[1–4] In 2019 and 2020, these workshops were formally associated with ASH as Scientific Workshops, with the 2020 workshop being conducted virtually due to the ongoing COVID-19 pandemic. The objectives of the 2020 workshop included discussing the latest scientific developments in plasma cell disorders (PCDs) with an emphasis on the immunology and molecular biology, presenting the most current clinical trial results with MRD and IP data, understanding regulatory issues regarding the use of novel endpoints in clinical trial design and drug approval, discussing novel strategies for MRD and IP testing and encouraging investigators and trainees from around the world to interact with experts in the field of PCDs.

MRD assessment of the bone marrow, most typically evaluated via either multiparametric flow cytometry (MFC) (also referred to as next generation flow (NGF)) or next generation sequencing (NGS), has been established as an important tool by which to evaluate depth of response to treatment in MM. In 2016, the International Myeloma Working Group (IMWG) published consensus guidelines for integrating MRD assessment into the response criteria.[5] These guidelines specified that if using MFC, then the Euro-Flow procedure[6] with a minimum sensitivity of 1×10^{-5} should be used, while if using NGS, then a

validated platform (e.g., the FDA-approved clonoSEQ assay (Adaptive Biotechnologies)) with a minimum sensitivity of 1×10^{-5} should be used. These guidelines moved depth of response beyond the traditional complete response (CR) or stringent complete response (sCR) categories, to include the following categories (all requiring fulfilment of CR criteria as well): flow MRD-negative, sequencing MRD-negative, imaging plus MRD-negative (flow or sequencing MRD as well as resolution of all areas of abnormal uptake on PET/CT) as well as sustained MRD-negative (MRD negativity in the marrow and by imaging confirmed a minimum of one year apart).[5] However, while the data are accumulating that achievement of MRD-negativity in MM is associated with superior progression free survival (PFS) or overall survival (OS) durations,[7–10] the field has not yet established that MRD-negativity can be used as a surrogate endpoint in clinical trials from a regulatory perspective or that MRD-response status should dictate treatment decisions. While most ongoing/planned clinical trials in MM are incorporating MRD assessment (at a minimum as an exploratory or secondary endpoint), the real-world use of MRD assessment is heterogeneous. The field is continuing to evolve, with new methodologies being developed (as discussed below) to evaluate not only bone marrow MRD but also peripheral blood MRD, as well as investigating connections between MRD status and immunophenotype[11–16] and MRD status in the context of novel cellular therapies.[17]

The 2020 workshop included 17 presentations as well as four live question and answer sessions (full agenda is shown in the Supplemental Material). In the present report we provide a comprehensive summary of the workshop, which focused on four main topics: integration of MRD into clinical trial design and practice, the molecular and immunological evolution of MM, novel detection methods, and chimeric antigen receptor (CAR) T-cell and other cellular therapies for MM.

Session 1: Integrating MRD into Clinical Trial Design and Clinical Practice:

Sarah Holstein (University of Nebraska Medical Center) discussed the results of the 2020 pre-workshop survey. This is the fourth pre-workshop survey conducted over the past five years with the goal of better understanding the real-world practices of MRD and IP testing in MM.[1, 3, 4] The 2020 survey was developed by the organizers of the workshop and distributed by BMT CTN to 228 individuals from 115 centers and 6 companies or regulatory agencies. Over time there has been a trend towards increasing utilization of MRD: 70% (28/40) in 2016, 67% (16/24) in 2018, 79% (45/57) in 2019 and 89% (51/57) in 2020. Of those who responded that they are not ordering MRD in 2020, reasons provided included barriers in access to proper technology, reimbursement and lack of practice guidelines. However, five out of the six respondents who indicated that they did not order MRD testing, do utilize advanced imaging as part of the response assessment before and/or after ASCT. Of those respondents who did report measuring MRD, 75% (38/51) use MFC, 61% (31/51) use NGS, 10% use MALDI-TOF (5/51), 53% (27/51) use PET/CT and 18% (9/51) use MRI. The majority of respondents reported that the sensitivity of the MRD assay used was either 10^{-5} (37%) or 10^{-6} (47%). Fifty-four percent of respondents are assessing MRD in patients who have achieved either very good partial response (VGPR) or CR while 39% reported ordering it only in patients who had achieved a CR. There continues to be heterogeneity with respect to when MRD is assessed, with 41% reporting assessing it after ASCT,

25% after stem cell collection, 43% at one-year post-ASCT, 37% on an annual basis and 10% on an every six month basis post-ASCT. The 2020 survey asked questions regarding how the MRD results were incorporated into practice. Fifty-six percent of respondents reported that the results triggered a change in surveillance while only 21% reported that the results triggered a change in treatment. Of those, one respondent reported completely discontinuing therapy in MRD-negative patients, five respondents reported de-intensifying therapy in MRD-negative patients, one respondent reported switching therapy in MRD-positive patients, two respondents reported intensifying therapy in MRD-positive patients and another noted that they discontinue treatment if there is sustained MRD negativity. Forty percent of respondents reported that the results are not used for clinical practice or are used inconsistently.

Routine use of IP has been variable across the surveys. In 2016, 35% (14/40) responded that they assessed immune reconstitution before and/or after ASCT. In 2017, 30% (7/23) responded yes, 53% (30/57) in 2019 and 41% (23/56) in 2020. Of those who reported assessing immune reconstitution in 2020, the majority assessed immunoglobulin levels (91%), while 56% reported using peripheral blood flow cytometry, 17% bone marrow flow cytometry and 35% measured vaccine titers. Six respondents reported that the immune reconstitution results triggered a change in surveillance while 7 respondents reported that the results triggered a change in treatment. The majority of respondents (84%) do not utilize Hevylite assessment.

In aggregate these survey results indicate that there is increasing real-world utilization of MRD assessment but heterogeneity remains with respect to modality, sensitivity, timing, frequency as well as whether the results are actually used to guide treatment decisions. Use of IP assessment remains variable, with most respondents not routinely performing comprehensive immune profiling. The Roswell Park group recently reported that serological response to vaccinations after ASCT correlates with PFS and OS,[18] and thus if future studies confirm these findings, more routine monitoring of vaccine titers may occur.

Nicole Gormley from the FDA discussed regulatory considerations surrounding novel endpoints and biomarker-driven clinical trials in myeloma. Factors that are considered when evaluating regulatory submissions include whether the MRD assessment (i.e., sample, timing, threshold) is a clinically valid biomarker for the proposed context (i.e., for the specific disease, the disease status, the type of therapy) as well as whether the MRD assay is analytically valid for the range of results that are important to the trial (https://www.fda.gov/media/134605/download). This information must be included as part of the IND clinical trial submission, as well as information regarding the specific test method (instruments, reagents, specimen handling), how the test method was validated analytically for each specimen type, and a summary of the test's performance including accuracy, precision, specificity and sensitivity. For clinical trials using MRD assays that are not FDA approved, it is also critical that the informed consent documents indicate that the MRD assay is investigational. She also discussed the different ways that biomarkers can be used in clinical trial designs. One approach is the enrichment design, in which subjects are assessed for eligibility based on the biomarker assay. If subjects test negative then they are not included in the study, while positive subjects are randomized to different treatment strategies.[19, 20]

The advantages of this approach include a straightforward study design and the potential for a small sample size if the effect size is large. However, disadvantages include needing to screen a large number of patients if the prevalence of the biomarker in the population is low as well as not gaining any information about the biomarker-negative population. This approach is best used when there is very convincing data that treatment benefits are limited to the biomarker-positive subpopulation. Another approach is the stratified design in which patients are stratified based on biomarker result and then both groups (positive and negative) are randomized to treatment.[19, 20] The advantages of this approach include providing information about both the biomarker-positive and −negative populations while the disadvantages include that it may require more patients. This approach can be used when there are data that suggest that the treatment benefits are more likely to be effective in the biomarker-positive population but an effect cannot be ruled out in the biomarker-negative population. There are various statistical approaches for this type of stratification, including sequential testing of the various populations in different orders (e.g., testing the biomarker-positive population and then the biomarker-negative population or first testing the overall population and then testing the biomarker-positive population) with the goal of limiting the type I error rate. It is recommended that the trial design and the statistical considerations be discussed with the FDA when considering using these types of designs. She also noted a number of additional challenges with biomarker-driven studies. The development of the assay may lag behind the development of the therapeutic such that it may be challenging to decide whether the therapeutic should be developed for the biomarker-positive population, the biomarker-negative population or the overall unselected population. The assay may need further refinement to increase its analytical performance such that early in development it might be hard to interpret due to high false positive or negative rates. If the biomarker is a continuous variable there may be uncertainty early in the development as to what the appropriate cut-off is that will result in a clinically meaningful selection of patients. An additional consideration for biomarker-driven trial designs is inclusion of interim analyses for futility, particularly in the biomarker-negative populations to limit potential exposure to ineffective therapies. Finally, she discussed the distinctions between a companion diagnostic and a complementary diagnostic. The former is a medical device that provides information that is essential for the safe and effective use of a corresponding drug/biologic product while the latter provides information to aid risk-benefit decisions for individual patients related to the use of a specific drug/biologic product and is not essential for that product’s safe and effective use. Thus there are multiple regulatory considerations when using biomarkers in clinical trials, but there is the potential to help expedite drug development and ultimately improve outcomes for patients. Currently the general recommendation from the FDA is to include MRD as a key secondary endpoint with adequate statistical analysis as further development is needed before it could be used for regulatory decisions.

Pierre Démolis from the European Medicines Agency (EMA) provided the EMA perspective of integrating MRD into clinical trial design and practice. He noted that the process to develop guidelines on the use of MRD as a clinical endpoint in MM studies began in early 2018 and has thus far been a slow process. There are multiple points of agreement: MRD negativity is an important prognostic marker; outcomes for patients achieving MRD negativity are superior to simply achieving a CR; and it has the potential to be used as

an early decision basis to speed approvals when it is not optimal to await PFS or OS outcomes. However, demonstration of predictivity should come from several comparative trials, not from patients' records (not at the patient-level) and for that the differences in MRD negativity between arms as well as the differences in PFS/OS outcomes must be studied as part of the surrogacy evaluations. He noted there are a number of "tricky issues" at stake. These include timing of MRD assessment (e.g., at time of CR, before ASCT, during maintenance, etc.), whether depth or duration of response matters, whether MRD predicts outcomes independent of therapies, and whether the same level of evidence is needed for both early and late stages of MM. Questions remain as to how to determine surrogacy and whether thresholds could be used. There are also issues related to regulatory agencies evaluating a product based on MRD outcomes but then also needing to take into account the toxicity profiles of the therapy. All of these issues are under ongoing discussion within the EMA including through the Scientific Advice Working Party, the Oncology Working Party and the Committee for Medicinal Products for Human Use.

Francesca Gay (University of Torino) provided updates from the FORTE clinical trial with an emphasis on the MRD data that was presented at ASH 2020.[21–23] The FORTE trial is a randomized phase II study of 474 newly diagnosed transplant-eligible MM patients with three treatment arms for the first randomization: KCd (carfilzomib, cyclophosphamide, dexamethasone) induction followed by ASCT and KCd consolidation; KRd (carfilzomib, lenalidomide, dexamethasone) induction followed by ASCT and KRd consolidation; KRd induction/consolidation without ASCT (KRd12). There is a second randomization at time of maintenance to lenalidomide (R) alone vs carfilzomib + lenalidomide (KR). MRD was assessed by MFC after induction (optional), pre-maintenance in those achieving VGPR or better, and every six months during maintenance until PD. MRD was also assessed by NGS at the pre-maintenance time point in those achieving ≥ CR as well as every six months during maintenance until PD. While the rates of MRD negativity after consolidation were similar between the two KRd arms (and superior to the KCd arm),[24] the rate of sustained MRD negativity (defined as MRD negativity at two time points, one year apart using MFC with a sensitivity of 10^{-5}) was significantly higher in the KRd/ASCT arm (68%) compared to KRd12 (54%, p=0.02) or KCd/ASCT (45%, p<0.001).[22] This corresponded to superior PFS for the KRd/ASCT arm compared to the other two arms (3-yr PFS of 78% vs 66% (KRd12) vs 58% (KCd/ASCT)).[21] The 3-yr OS was 90% in the KRd/ASCT and KRd12 arms compared to 83% in the KCd/ASCT arm.[21] During the maintenance phase, a significantly higher proportion of patients (46% vs 32%, p=0.04) in the KR arm converted from MRD positive to MRD negative (MFC, 10^{-5}), which was associated with superior PFS (30-month PFS 81% (KR) vs 68% (R), p=0.026). Data were presented showing PFS outcomes by MRD status (using either MFC or NGS at 10^{-5}) and maintenance arm, with the best outcomes observed in the MRD-negative KR subgroup and the worst outcomes in the MRD-positive R subgroup. The outcomes for the MRD-negative R and the MRD-positive KR subgroups were very similar. There was strong concordance between the two techniques used to assess MRD. The prognostic impact of MRD-negativity on PFS was observed across multiple subgroups, including age, ISS, standard and high risk FISH, R-ISS and LDH. Benefit of achieving MRD negativity was also observed in patients with circulating plasma cells at baseline. Overall these data highlight the importance of not only assessing MRD

negativity at discrete time points, but assessing sustained MRD negativity in the context of correlation with PFS outcomes.

Session 2: Molecular and Immunobiology of Disease Evolution and Progression in Multiple Myeloma:

This session focused on recent translational studies interrogating the molecular and immunological landscape of PCDs. Niccolò Bolli (University of Milan) discussed the molecular and genomic evolution of MM. He noted that currently the field's view of PCDs is that we do not treat patients with MGUS, consider treating patients with smoldering MM (SMM) and treat patients with MM. However, should we be treating a disease that is biologically aggressive independent of the disease burden and before evident clinical sequelae? Are we able to distinguish indolent vs aggressive disease and if so, should we be treating based on that classification and not the historical diagnosis? In work presented at ASH 2020, whole genome sequencing was performed on CD138-positive bone marrow mononuclear cells from MGUS and SMM patients and compared with samples from patients with MM.[25] These studies revealed that patients with non-progressive MGUS/SMM had a distinct genomic profile which lacked most of the key genomic MM hallmarks compared to the progressive patients whose disease already had many of the genomic drivers associated with MM.[25] Previous work investigating modes of evolution of SMM showed two routes to MM: one characterized by continuous evolution during which subclones are gained and lost, generally starting indolently and taking years to become aggressive vs the static progression mode which is genomically aggressive from the start and only needs to accumulate to a large enough burden to meet criteria for MM.[26] It is postulated that the latter represents a category of SMM which should be treated as active MM from time of diagnosis. Additional groups have reported that incorporation of genetic features can improve prognostication of SMM.[27, 28] Thus it is posited that future classification of PCDs will no longer include SMM and instead include indolent (asymptomatic) gammopathy vs aggressive (symptomatic) MM which would be determined using genomic data or other criteria.[29]

Irene Ghobrial (Dana-Farber Cancer Institute) discussed the immune microenvironment in MM. She noted that the microenvironment is critical for the growth of tumor cells, contributing to the progression/evolution from MGUS to MM. Single cell RNA sequencing (scRNA seq) analysis of healthy, MGUS, SMM and MM plasma cells and immune cells revealed that there are detectable changes in the composition of the immune cells even at the MGUS stage.[30] During the evolution to MM there is memory CD8+ T-cell depletion as well as transcriptional changes involved with the IFN-α response leading to immune escape.[30] Studies using 10x Genomics analysis of the BM microenvironment are also revealing compositional changes in the immune cells across the PCD spectrum. These immune alterations are heterogeneous but differences are observed between healthy controls and MGUS samples. Differences in NK cells across the disease spectrum have also been described.[31, 32] Further T-cell characterization shows loss of memory CD4 cytotoxic T-cells during progression along with increasing Tregs. These changes might have therapeutic implications if they could be reversed. Previous work in a mouse model showed that if Tregs

are depleted this can prevent MM progression.[33] Their group has also found an enhanced interferon response in multiple cell subtypes, including NK cells, CD14+ monocytes and CD16+ monocytes. Single cell RNA (scRNA) studies in the CD14+ monocytes revealed increases in MHC II mRNA levels. However, cytometry by time of flight (CyTOF) studies showed lower levels of these molecules as a consequence of regulation of surface trafficking, thus highlighting the importance of validating discoveries based on RNA data at the protein level. Ultimately the hope is that understanding the compositional changes in the immune microenvironment in patients with PCDs will lead to therapeutic interventions that can prevent progression to active MM.

Maximilian Merz (Roswell Park Comprehensive Cancer Center) discussed the use of single cell sequencing to evaluate intraclonal myeloma heterogeneity. He noted that scRNA seq analysis is one of the fastest developing techniques but while there are now multiple commercial kits available, the bottleneck can be the downstream analysis. Several groups have shown the feasibility of scRNA analysis in MM.[30, 34] His group is conducting a study in which paired biopsies from bone marrow and osteolytic lesions are analyzed to determine whether there are differences in the myeloma cells, the surrounding microenvironment and whether there are longitudinal changes during therapy.[35] The plasma cell compartment is subjected to scRNA-seq and whole exome sequencing (WES) while the non-plasma cell compartment is subjected to NGF and bulk T-cell receptor sequencing. The scRNA-seq occurs same day to eliminate any transcriptional changes that happen during the freezing process. More than 70,000 cells are isolated from each location and thus far 10 patients have been enrolled (7 newly diagnosed MM, 3 relapsed/refractory MM). His group has compared the gene expression data from the scRNAseq and variant allele frequencies and found significant correlations between the plasma cells from the bone marrow and from those isolated from the lytic lesions for all patients. Of note, in one patient with relapsed/refractory MM and extramedullary disease, significant differences based on location were found. These studies are enabling dissection of the spatial heterogeneity of the disease at single cell resolution and allowing identification of longitudinal transcriptional changes in plasma cells in response to therapy.

Leif Bergsagel (Mayo Clinic, Scottsdale) discussed the role of the gut microbiota in shaping the evolution of MM. Clues that the gut microbiota might influence MM disease biology were obtained from studies utilizing the Vk*MYC transgenic mice that spontaneously develop monoclonal gammopathy that eventually progresses to MM. It was noted that the rate of progression to MM in this model was different in mice housed in a pathogen-free vivarium in Italy compared to mice bred in Arizona.[36] While the incidence of monoclonal gammopathy remained constant, the progression to MM differed. In studies using the transplantable MM cell line Vk12598 it was found that if recipient mice were pretreated with antibiotics, engraftment of the myeloma cells was significantly delayed and survival significantly prolonged.[36] Analysis of the fecal microbiota from the mice that more rapidly progressed led to identification of Prevotella, which was absent in the mice from Italy. Subsequently, studies with the Vk12598 transplantation model in which mice were administered Prevotella via oral gavage, showed that these mice had faster engraftment and shorter survival than the vehicle control animals.[36] This work led to the hypothesis that the presence of bacteria such as segmented filamentous bacteria or Prevotella which

are associated with high levels of Th17[37], contribute to progression.[36] In this model, the Th17 cells which are stimulated by the bacteria in the gut then home to the bone marrow where they can stimulate MM cells through IL-17 as well as stimulate eosinophils which secrete IL-6 and promote MM progression.[36] It is noted that SMM patients that progressed to MM more quickly (in this case, used a 3-yr cut-off) had higher levels of IL-17 in the bone marrow than those who progressed more slowly. The gut microbiome has also been implicated in the post-ASCT setting in MM. Work by Pianko et al., identified butyrate-producing microbiota as being associated with achievement of MRD-negativity at the three-month post-ASCT time-point.[38] These bacteria have been associated with decreased Th17 cell production. Potentially related to the gut microbiome story is a study that was conducted in asymptomatic MM patients in which they received the IL1-Ra agent Anakinra for 6 months.[39] This study demonstrated that a decrease in CRP was associated with prolonged progression to MM.[39] Thus in aggregate these studies suggest that the gut microbiome and inflammatory microenvironment are linked to MM progression. It is possible that modulation of the microbiome (e.g., with probiotics, antibiotics, fecal transplant, diet) with or without anti-inflammatory agents (e.g., anti-IL1β, IL1-RA, anti-IL6, anti-IL17) could delay or prevent progression to MM.

Session 3: Adaptation of Next Generation Sequencing, Next Generation Flow Cytometry, and CyTOF: diverse ways of detection.

This session focused on the use of novel techniques to assess MRD in MM. Bruno Paiva (Clinica Universidad de Navarra) discussed issues related to the use of flow cytometry in measuring MRD and IP in MM. As has been reported now in multiple studies, there is a difference in PFS in patients achieving MRD-negativity vs MRD-positivity. In a recent analysis of the PETHEMA/GEM2012MENOS65 trial, achievement of MRD-negativity (as assessed by NGF with median limit of detection 2.9×10^{-6}), was associated with significant reduction in risk of progression or death and overcame poor prognostic features at diagnosis, including high-risk cytogenetics.[40] He advocated for the use of NGF in assessing MRD status as this technique allows for evaluation of sample quality (e.g., assessment of hemodilution) as well as simultaneous immune profiling of the tumor microenvironment. As an example, in a subset of patients from the PETHEMA/GEM2012MENOS65 study, immune monitoring studies were performed using 17-color NGF as well as combined scRNA/TCR sequencing. These studies revealed that patients with higher CD27−/+ T-cell ratios have prolonged PFS irrespective of MRD status and that this parameter was a surrogate for how many clonotypic T-cells were present in the bone marrow.[41] A future is envisioned in which this type of analysis is routinely performed, allowing prediction of outcomes of patients exposed to specific therapies based on the MRD level, immune composition, patient demographics, staging, cytogenetics and prior therapies.

David Foureau (Levine Cancer Institute) discussed the use of mass spectrometry (MS) as a potential measure of MRD, reporting on the results of a study in which 10-marker NGF MRD testing (bone marrow aspirate) was compared with MS-based MRD testing (peripheral blood) in order to compare sensitivity and concordance rates. The MS protocol involves an immuno purification step (to assess IgG, IgA, IgM, total light chains and

free light chains) followed by matrix-associated laser desorption/ionization (MALDI)-MS or liquid chromatograph (LC)-MS to detect the monoclonal protein. A diagnostic sample is required to define the original monoclonal protein for the MS method. Twenty-eight matched bone marrow aspirate and serum (collected within 2 weeks of each other) specimens were analyzed. In six patients with kappa free light chain disease (as defined by serum immunofixation electrophoresis (SIFE)), the MALDI-MS method could also identify a heavy chain. In addition, MALDI-MS could detect therapeutic antibodies (e.g., daratumumab) as well as glycosylated monoclonal proteins. Concordance rates between the two methods were compared at three levels of sensitivity (for NGF; 10^{-4},10^{-5}, 10^{-6}) and were found to be in the 60–70% range. This is comparable to previously reported rates from other groups.[42, 43] However, in this cohort none of the samples were negative by LC-MS, thus it is unclear whether this technique has higher sensitivity or lower specificity. Several examples were discussed where a patient was negative for MRD by NGF (10^{-6}) but positive by MALDI-MS or LC-MS. However, another example was discussed where there was discordance between NGF (10^{-6}) and MALDI-MS at a one-year post-ASCT time point because the glycosylated monoclonal protein identified at diagnosis became unglycosylated at the later time point (thus MALDI-MS was reported as negative) while NGF could still detect residual clonal cells. Thus MS-MRD may be more sensitive than NGF in some patients (perhaps because it is not dependent on marrow involvement), but NGF can detect residual disease independent of monoclonal protein glycosylation.

Martin Kaiser (Institute of Cancer Research) discussed MRD assessment in the context of myeloma genetics and clinical trial design. He noted that many planned/ongoing studies are assessing MRD at a fixed time point and then making treatment decisions based on the results (e.g., escalation, continuation, de-escalation). However, the question is raised as to whether this type of approach adequately addresses different disease biologies. He noted a study evaluating high-risk MM using gene expression profiling and cytogenetic information in which an ultra-high risk subgroup was identified which has a higher proliferative capacity than the other high risk groups and had early relapse.[44] This is of note because if studies are designed evaluating high-risk MM but there is a significant number of patients progressing during induction before the MRD-driven treatment decision point is reached, then only a fraction of patients would benefit from treatment escalation if they are MRD-positive. It is also important to note that there have been examples of false negative MRD results in patients with ultra-risk disease where whole body diffusion weighted MRI can detect residual disease. In this context, the UK has designed clinical trials which combine both MRD-adapted approaches and risk-adapted approaches. For example, in the UK-MRA Myeloma XV study, patients with ultra-high risk disease do not undergo MRD-adapted treatment while those without ultra-high risk disease have treatment which is dictated by MRD status post-ASCT. Thus while MRD-negativity is desirable for all risk groups, it is important that MRD-adapted therapy consider disease heterogeneity.

Nizar Bahlis (University of Calgary) discussed single cell immune profiling in myeloma. Previously reported studies using single cell profiling have provided detailed views and insight into immune cell populations, clonal heterogeneity, and tumor ecosystem temporal-spatial dynamics.[45–48] Epigenetic analysis at the single cell level in conjunction with transcriptome analysis using projectory inference can better define the origin and trajectory

of these key immune cells. In an analysis of MM patients treated with daratumumab +/− pomalidomide, it was determined that daratumumab- and immunomodulatory drug (IMiD)-sensitive patients have different immunomes than resistant patients, with bone marrow enrichment of CD8+C27+TEM cells noted in the sensitive patients.[49] In contrast, resistant patients had an enrichment in exhausted T cells with high expression of the checkpoint inhibitors LAG3 and TIGIT, granzyme B and, at the transcriptional level, high expression of TBX21 and lack of TCF7. In addition to this T cell deregulation, the dendritic cells were largely immature, lacking class II MHC molecules and the ratio of dendritic cells to Tregs was significantly higher in sensitive patients vs resistant. These data suggest that the immature dendritic cells in resistant patients results in ineffective priming of CD4 helper T cells which leads to a dysfunctional cytotoxic T cell response, and that the chronic stimulation results in exhausted T cells. They have also characterized the mononuclear cells in patients receiving B-cell maturation antigen (BCMA) CAR T-cell therapy as well as BCMA bispecific T-cell directing therapy. In an patient that failed to respond to a bispecific agent, cellular indexing of transcriptomes and epitopes (CITE)-seq profiling revealed that the CD8 T-cells were mostly CD45RA-positive, lacked selectin and CD28 and had high expression of senescence and exhaustion markers.[50] A model arises where sensitive patients have an immunity phenotype (reminiscent of MGUS) whereas resistant patients have a tolerance phenotype (reminiscent of symptomatic MM).[30, 51] It is hypothesized that the expansion of terminally exhausted T cells with upregulation of checkpoint inhibitors and enrichment of immature tolerogenic dendritic cells mediate resistance to immune-based interventions. It is hoped that further single cell studies at the level of the transcriptome, proteo-metabolome and epigenome will eventually allow for therapeutic interventions that can reverse tolerance.

Session 4: CAR-T and other Cellular Therapy for Multiple Myeloma:

This session focused on novel cellular therapies for myeloma, including NK cells, allogeneic CAR T-cells and autologous CAR T-cells. Michael O'Dwyer (National University of Ireland) discussed the potential for NK cells to serve as an allogeneic cell source. NK cells are dysfunctional in MM[52], and while certain therapies (e.g., IMiDs) can improve NK cell function they may not completely reverse it. In addition, treatment with anti-CD38 monoclonal antibodies (mAbs) can lead to prolonged depletion of NK cells. Therefore allogeneic NK cell therapy may be an attractive alternative which allows for off-the-shelf therapy. The potential sources for the NK cells include umbilical cord blood, healthy donors, NK cell-derived cell lines or stem cells. Following enrichment and/or differentiation, along with T-cell depletion, NK cells undergo extensive expansion prior to infusion or cryopreservation. These expanded NK cells can be genetically modified or alternatively, progenitors, such as induced pluripotent stem cells, can be genetically engineered prior to subsequent differentiation into mature NK cells. Promising preliminary data have emerged from clinical trials, including the trial conducted by Shah et al., supporting the safety and potential efficacy of allogeneic NK cells in MM.[53] In addition, it is noted that allogeneic NK cells can be combined with mAbs and NK-engaging molecules to further enhance their targeting and cytotoxicity. There are many ways that NK cells can be engineered to optimize their function, cytotoxicity, persistence and homing.[54] Using gene editing

(e.g., with CRISPR/Cas9) it is now possible to routinely knock out inhibitory receptors in primary NK cells with high efficiency improving their function.[55] Another example includes knocking out CD38 to avoid fratricide when targeting CD38.[56] This modification has been shown to not only enhance antibody-dependent cellular cytotoxicity (ADCC) in the presence of anti-CD38 antibodies but also to enhance the metabolic profile of NK cells.[56] NK cells can also be engineered to express CARs along with a potent form of TRAIL to maximize apoptosis via the death receptor pathway and minimize antigen escape (ONK Therapeutics). Overall, engineered NK cells may have several advantages over the autologous CAR T-cell approach.[54] The engineered NK cells are allogeneic, frozen, off-the shelf, dependent on innate killing and independent of antigen. While historically NK cells have been more difficult to engineer, recent advances have overcome many of the limitations. Thus far, NK cell therapy has not been associated with CRS or neurotoxicity and therefore have the potential for outpatient administration. It was noted that encouraging responses were reported in a CD19 B cell malignancy trial involving CAR NK cell therapy.[57] The persistence of NK cells may be a limitation as traditionally, allogeneic NK cells have not been detected beyond approximately two weeks. However, with engineering, persistence can be much longer and in the work by Liu et al, they were able to detect the presence of the construct via PCR in the peripheral blood after a year.[57] Whether the duration of NK cell persistence needs to be the same as CAR T-cell persistence remains to be determined.[57] While engineered NK cell therapy is first being tested in the relapsed/refractory MM setting, it does have the potential to be moved to the frontline setting, possibly for patients with high risk cytogenetics or persistent MRD-positivity. Indeed, given their potential to efficiently target clonogenic MM cells,[58] NK cells may be particularly effective in eradication of MRD.

Carrie Brownstein (Cellectis Inc) discussed allogeneic CAR T-cell therapy. She noted that allogeneic cells offer several potential advantages over autologous cells—they can be readily available, may be produced more reliably and on a greater scale. The use of allogeneic cells avoids the manufacturing delays and/or failures sometimes associated with an autologous product. Other potential advantages of using allogeneic cells include the use of healthy donor T cells which may confer better clinical activity, enhanced standardization as well as the opportunity for re-dosing. Finally, there may be an advantage from a cost-effectiveness perspective if multiple doses can be produced from one donor. Cellectis is focusing on the production of allogeneic products using the TALEN® gene-editing tool. The manufacturing process starts with healthy donor leukopaks that are transduced with a lentivector and gene edited by TALEN. The CAR T-cells are then amplified, purified and frozen. She discussed the UCARTCS1A product which recognizes MM cells via the anti-CS1 CAR. Potential advantages of the CS1 CAR product include lymphocyte CS1 expression, which could result in extended lymphodepletion and enhanced CAR T-cell persistence. The TALEN gene editing tool allows for an engineered product that lacks CS1 (to avoid fratricide) as well as the T-cell receptor (to avoid graft-vs-host disease) to improve the yield of CD8+ cells, creating a less differentiated T-cell phenotype and resulting in higher *in vitro* anti-tumor activity. This product also expresses a CD20 mimotope (RQR8) that serves as a safety switch responsive to rituximab treatment. What remains to be determined is how long the allogeneic CAR T-cells need to persist in order to confer a durable remission. As CS1 is expressed on lymphocytes in addition to MM cells, finding the optimal window

of UCARTCS1A expression and persistence that will induce MRD negativity without long-term lymphopenia is critical. The first-in-human study (MELANI-01) is evaluating the safety and tolerability of the UCARTCS1A product in triple-class refractory MM patients. The study was placed on clinical hold in July 2020 after a subject experienced a fatal cardiac arrest. In November 2020 the FDA lifted the clinical hold and the study is currently ongoing.

Marcela Maus (Massachusetts General Hospital) discussed the approach her research group is taking in developing novel autologous CAR T-cell therapies. She noted that current anti-BCMA CAR T-cell therapies are not curative and that this may be because they contain non-human sequences that can be rejected or there is loss of BCMA expression on the target cell. APRIL (a proliferation-inducing ligand) is produced by myeloid cells within the bone marrow microenvironment and promotes survival of MM cells via binding to BCMA and TACI (transmembrane activator and calcium modulator and cyclophilin ligand interactor). Soluble APRIL forms a trimer which can then interact with BCMA and TACI. Her group is designing CARs that use a fully human trimeric APRIL that can bind to two different antigens on the plasma cell simultaneously. They have evaluated both a monomeric APRIL fused to the CAR backbone as well as a trimeric APRIL CAR (TriPRIL).[59] The truncated monomeric APRIL had very weak binding to BCMA and negligible binding to TACI. However, the TriPRIL CAR, which is composed of the APRIL domains connected via linker domains, has enhanced binding to both BCMA and TACI.[59] Evaluation of TriPRIL in *in vitro* studies revealed enhanced functionality (measured via single cell cytokine analysis) compared with the monomeric APRIL CAR or a BCMA CAR. TriPRIL was demonstrated to lyse primary MM cells.[59] Finally, in xenograft studies they were able to demonstrate activity of the TriPRIL CAR T cells *in vivo* in both BCMA-positive and BCMA-negative MM models.[59] Efforts are now underway to move this novel cellular therapy to the clinic. A GMP vector has been made and the investigators are in the process of scaling up manufacturing using the CliniMACS Prodigy ® system. A phase I trial is expected to begin enrolling in 2021. Notably, the study will include patients who have previously received BCMA-directed therapy.

J. Joseph Melenhorst (University of Pennsylvania) discussed IP studies being conducted in both responders and non-responders to CAR T-cell therapy in a variety of hematological malignancies. He noted that while in acute lymphoblastic leukemia (ALL) the responses to CD19 CAR T-cell therapy are quite high,[60] the responses (using the same CAR) are much lower in chronic lymphocytic leukemia (CLL).[61] In a study evaluating CTL019-treated CLL patients, it was found that responders to this therapy had higher CD27 and lower CD45RO levels in the peripheral blood T-cells that were used in manufacturing.[62] This CD27+CD45RO− biomarker was found to have 89% specificity and 80% sensitivity in the discovery cohort and 100% specificity/sensitivity in the validation cohort for identifying CR patients.[62] More recently his group has been performing fate mapping studies of CD19 CAR T-cells. Two patients with CLL treated with CTL019 in July 2010 have been found to have persistent CAR T-cells, 7–10 years after infusion, and remain in remission. Using a 40-marker CyTOF panel, the cells can be used to interrogate T-cell differentiation, activation, exhaustion and the anti-CAR19 idiotype mAb. This analysis showed multiple different clusters separated by CD4 and CD8 expression which varied in dominance over time. Over time, the CD4+ CAR T-cells gradually dominated the CAR T-cell repertoire

in both patients, suggesting a role for these cells in sustained remissions. The pattern and tempo of the clonal evolution differed between the two patients, but in both patients at later time points there was an oligoclonal repertoire suggesting that the remission is being sustained by a few persisting clones. Studies are ongoing to evaluate the hypothesis that the integration site potentially disrupts endogenous genes and thereby affects the potency of the CAR T-cells. Studies are also underway to identify clusters enriched in responding and non-responding patients to determine whether the CLL biomarker profile can be validated in other malignancies such as MM. Previously published work from this group revealed the impact that prior therapies have on the percent of T-cells with the CD8+CD27+CD45RO− phenotype, with higher levels post-induction but then lower levels in the relapsed/refractory setting.[63] Finally, it was noted that the species of CAR used may have an impact on the re-expansion of the cells as four patients who had previously been treated with a murine BCMA CAR T-cell and relapsed subsequently responded to a fully human BCMA CAR.[64]

Sandy Wong (University of California San Francisco) discussed the clinical laboratory predictors of durable response to CAR T-cell therapy. She noted that the traditional IMWG criteria rely on clearance of monoclonal protein, but because of the half-life of antibodies, this can lag behind cell killing. CAR T-cell treatment can induce dramatic early responses. Therefore the question is raised whether there are other markers which could be used to evaluate an early response that is also associated with PFS. She presented an analysis of 54 patients treated at her institution on five different industry-sponsored BCMA CAR T-cell trials. An analysis of PFS by IMWG response in this cohort showed no statistically significant difference between those patients achieving partial response/VGPR and those achieving a CR. However, normalization of the involved free light chain (FLC) at either day 15 or day 30 was associated with improved PFS. Achievement of MRD negativity (10^{-6}) by NGS at month 1 or month 3 was associated with improved PFS as was achievement of MRD negativity (10^{-5}) or PET/CT negativity. In this cohort, the occurrence of CRS and neurotoxicity was not associated with PFS. Larger prospective studies are needed to determine whether normalization of FLC at day 15 or MRD-negativity at 1 month could be validated as predictors of durable response to CAR T-cell therapy in MM.

Future directions:

The role for MRD assessment in determining clinical trial design, regulatory evaluation and real-world treatment decisions is continuing to evolve. While it is most likely that initial establishment of MRD as a surrogate endpoint will be based on MFC/NGF assessment of bone marrow aspirate samples, much uncertainty remains as to the optimal timing of MRD assessment as well as the optimal definition of sustained MRD. The FORTE study is a prime example of the importance of not forming conclusions regarding relative efficacy of different treatments based on one MRD assessment point alone. As noted above, while the MRD negativity results for the two KRd arms were similar post-consolidation, it is the rate of sustained MRD negativity which is now correlating with PFS outcomes, demonstrating superiority of KRd/ASCT over KRd12. Thus the evaluation of multiple time points is likely critical. The potential to move beyond marrow-based assessments is significant, as this would allow more frequent assessments in a non-invasive manner and can capture evidence of disease that is outside of the marrow. The role of MS-based monitoring of residual

monoclonal proteins is continuing to evolve but appears poised to become an important complement to marrow-based MRD assays.

As noted by Dr. Gormley, there are a number of challenges as well as potential benefits of using biomarker-driven trial designs. One key point made by Dr. Kaiser is that disease biology also needs to be accounted for, and that studies utilizing MRD status to determine treatment path may exclude patients with aggressive MM that progress prior to ever reaching the MRD-guided time point. Thus design of clinical trials incorporating MRD assessment in MM require substantial input from disease specialists, statisticians and regulatory agencies. The results from the 2020 pre-workshop survey again revealed heterogeneity in real-world use of MRD assessment. Until there are data demonstrating that the results of MRD testing can actually be used to change treatment practices (with resulting improvement in long-term outcomes), it is likely that practitioners will continue to make either anecdotally-driven treatment decisions (e.g., treatment was stopped in a patient with MRD-negativity and they are doing fine, therefore that should form the basis of routine practice) or they will collect the MRD data for use in future retrospective studies. The latter approach may prove helpful, as there remains an absence of high quality data supporting the use of MRD-adapted treatment approaches.

The exploration of the MM immune microenvironment is becoming more sophisticated with multiple groups now evaluating the immunome at the cellular level. As discussed in this workshop, different signatures have been identified in different disease contexts and it is likely that while there may be some unifying themes (e.g., association with T-cell exhaustion/senescence phenotypes and PCD progression and/or resistance), some of these phenotypes will be specific to discrete disease states and/or therapies. A more consistent incorporation of comprehensive IP studies in all prospective MM therapeutic intervention trials would provide a wealth of information. This would require not only consensus within the field regarding optimal IP techniques (e.g., MFC vs CyTOF vs scRNAseq vs other) but also commitment from sponsors to pay for these correlative studies. In the long run this could prove cost-effective if phenotypes are identified that may predict for sensitivity (or resistance) to high-cost therapies such as cellular or T-cell engaging therapies as well as expensive multi-agent combination therapies. Another layer of complexity is the role of the gut microbiome in modulating PCD progression, responsiveness to therapies and toxicities. While most recent studies have focused on the role of the gut microbiome in the hematopoietic stem cell transplant setting,[65–67] there is emerging work exploring the association between the microbiome and CAR T-cell therapy.[68, 69] Thus with the development of not only autologous CAR T-cell but also allogeneic CAR T-cell and NK cell therapy for MM, there is significant opportunity to perform comprehensive IP and microbiome studies to better understand treatment efficacy and toxicity. The long-term effects of autologous CAR T-cell therapy are still being discovered[70] and it remains to be determined whether NK cell[71] or allogeneic CAR T-cell therapies will have distinct short-term and/or long-term toxicities. Finally, the use of simpler, more readily available assessments of immune reconstitution such as seroconversion following vaccine administration post-ASCT (particularly in the COVID-19 pandemic era) should also be considered.[18]

The continued progress being made in dissecting the genetic and immunological underpinnings of PCDs should ultimately lead to therapeutic interventions that may delay/prevent progression of PCDs as well as new therapeutic strategies for the management of MM. In addition, identification and incorporation of novel biomarkers into clinical trial designs should enable precision medicine-based approaches for MM. Progress is continuing to be made in establishing MRD as a surrogate endpoint, with the hope that this could accelerate drug approval timelines. However, surrogacy has not yet been established and many questions remain regarding the requisite duration of response, depth of response and timing of response. Ultimately the development of evidence-based guidelines for the use of MRD and IP in real-world practice will depend on continued collaborative efforts amongst researchers, industry sponsors and regulatory agencies.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Conflict of Interest:

SAH: has served on advisory boards for Genentech, GlaxoSmithKline, Oncopeptides, Sanofi, Takeda; has served as a consultant for Celgene, Sorrento; has received research funding from Oncopeptides.

NB: has received honoraria from Janssen, Celgene, Amgen, Takeda, AbbVie, GlaxoSmithKline, Sanofi, Genentech and Karyopharm; has served as a consultant/advisor for Janssen, Celgene, Amgen, Takeda, AbbVie, GlaxoSmithKline, Karyopharm, and Genentech

PLB: has served as a consultant for Bristol-Myers Squibb, Janssen, Amgen and Novartis

MB: has served on speaker bureaus for Amgen, Bristol-Myers Squibb, Takeda; has served as a consultant for Sanofi Genzyme; has received research funding from Celgene, Bristol-Myers Squibb, Cerecor, Cellularity, Janssen, MedImmune, Takeda, Prothena

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CB: is a full-time employee of Cellectis, Inc.

PD: has nothing to disclose

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IMG: has served as a consultant or advisor for GlaxoSmithKline, Sanofi, Janssen, Takeda, Karyopharm, AbbVie, GNS, Cellectar, Adaptive, Bristol-Myers Squibb, Oncopeptides.

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MK: has served as a consultant for Amgen, Bristol-Myers Squibb/Celgene, GlaxoSmithKline, Janssen, Karyopharm, Seattle Genetics, Takeda; has received honoraria from Bristol-Myers Squibb/Celgene, Janssen, Takeda; has received travel/educational support from Bristol-Myers Squibb/Celgene, Janssen, Takeda; has received research support to institution from Bristol-Myers Squibb/Celgene

MVM: is an inventor on patents related to adoptive cell therapies held by Massachusetts General Hospital and University of Pennsylvnia (some licensed to Novartis). She holds equity in Ichnos, TCR2 and Century Therapeutics, and has served as a consultant for Adaptimmune, Agenus, Allogene, Arcellx, Astellas, AstraZeneca, Atara, Bayer, BMS, Cabaletta Bio (SAB), Cellectis (SAB), CRISPR therapeutics, In8bio (SAB), Innovakine, Intellia, GlaxoSmithKline, Kite Pharma, Micromedicine, Novartis, TCR2 (SAB), Tmunity, Torque, and WindMIL (SAB). She is on the Board of Directors for Ichnos Science.

JJM: has received research funding from IASO Biotherapeutics and Kite Pharma, a Gilead company. He has served as speaker for Novartis and Johnson & Johnson and consults for Simcere of America, Shanghai Unicar Therapy, Janssen Research & Development, LLC, Poseida, Allogene, and IASO Biotherapeutics. He is on the Medical and Scientific Advisory Board of IASO Biotherapeutics. He holds patents related to CAR T cell manufacturing and biomarkers.

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Highlights

- Comprehensive summary of the 2020 BMT CTN Myeloma Intergroup MRD/IP workshop
- Real world use of MRD testing is limited by lack of evidence-based guidelines
- Challenges exist in establishing MRD as a surrogate endpoint
- Molecular and IP studies reveal insight into disease biology and treatment response
- Cellular therapy is evolving beyond autologous BCMA CAR T-cells