

Notes from Charlotte Plasma Cell Disorders (PCD) meeting Aug 9-11, 2019
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This was the inaugural meeting of PCD, organized primarily by Dr Saad Usmani, myeloma specialist at Levine Cancer Institute in Charlotte, NC. The audience consisted of about 100 attendees, mostly doctors as well as 6 patient advocates. And we heard from a who's who of the Myeloma community such as: Drs R Kyle, S Kumar, and A Dispenzieri from Mayo; Drs K Anderson, N Munshi, and I Ghobrial of Dana Farber; International Drs. M-V Mateos (Spain) and P Sonneveld (Netherlands), and our host Drs S Usmani and P Voorhees (Levine) plus many more.

Most of the slides can be found and downloaded from the link at:

<https://www.charlotteahc.org/continuing-professional-development/handouts/57702.pdf>. And you find Dr. Sagar Lonial's missing slides

at <https://www.dropbox.com/s/c7zk1wgu7swcke/Lonial%20Slides.pdf?dl=0>

Hopefully they'll remain in place but if at any time they become unavailable, you can email me. I believe the conference was also recorded so perhaps that recording will become available.

In the meantime, I've listed below some key takeaways and quotes that follow the agenda (see slides):

- 1) As you're aware, there are trials for high-risk Smoldering Myeloma (SMM) pts and the question comes up about earlier treatment for SMM or even MGUS, a pre-cursor to SMM and MM. Dr Kyle, considered the "father of MM", said "10% of MGUS pts will develop MM whereas 90% will die of heart disease, stroke or something else." Instead of telling his MGUS patients they have a 1% risk of developing active myeloma each year, he tells them they have a 99% chance of not progressing to myeloma within the next year.
- 2) We've heard that the risk for MGUS progressing to MM is 1% per year. A finer analysis examined 3 low risk factors for MGUS: m-spike < 1.5; IgG, and normal Free Light Chain ratio and the risk of progressing to MM over 20 years is only 2%. If you have risk factors: 1 of these => 10%; 2 => 18%; and all 3=> 27%.
- 3) Dr. I Ghobrial examined the genomics of MM as a means of early detection. She noted "We need to change the concept of waiting to treat MM. We do screening for breast cancer patient via mammograms. We look for polyps before they become colon cancer. Why don't we do blood tests to look for an early diagnosis of blood cancers, [noting that] a blood test is certainly much easier for patients than a mammogram." She also showed a slide correlating patient clinical responses with their high-risk factors and noted that there wasn't always a correlation. She asked the audience to consider all persons are at potentially high risk for development of myeloma (African Americans, first degree relatives of known myeloma patients) to sign up for Dana Farber's PROMISE study. Find it online at <https://www.enroll.promisestudy.org/>. She, and many other speakers, emphasized that we need better biomarkers to predict progression.

- 4) Dr. M V Mateos and others are conducting both “preventative” (increase time to progress to MM) and “curative” (high dose therapy to cure future MM) clinical trials for High Risk SMM patients. Preventative trials have already shown a PFS benefit. She reminded attendees that “Early treatment does not induce more resistant relapses.” Her thinking is certainly in line with that of Dr. Ghobrial.
- 5) Dr. S Usmani asked “Who are High-Risk Pts in 2019?” and answered: 1) Del 17p >55%; 2) Some t(4;14); 3) Multiple intermediate factors; 4) TP53 gene mutations; 5) Other mutations? 6) ISS3 + 1q gain; 7) Poor responders; and 8) Early relapses. He explained that not all 17-P deletions are the same. Some patients have lost just one copy (mono-allele) and some have lost both copies (bi-allele). He suggested that IMWG needs to revise criteria of HR factors.
- 6) Dr. J Hillengass (Roswell Park, Buffalo) when discussing bone imaging techniques “If you can do something more than a skeletal survey xray, please do. You shouldn’t have to wait for half your bone being destroyed.” “Furthermore Bone and Bone Marrow imaging are not the same thing. Imaging options from least to most effective: Bone (xrays but CT is better), Bone Marrow (CT but MRI is better), and Functional Information (MRI, PET/CT). Dr Hillengass also said “Every patient deserves an optimistic oncologist.” He also said that marrow biopsies can vary greatly “depending on where you put your needle in”, and demonstrated it with an interesting slide of an affected pelvis.
- 7) Dr. S Kumar when discussing treatment options: “Why is age an important issue when considering treatment? Co-morbidities, frailty, altered drug metabolism, limited social support, financial issues, and limited independence/mobility.”
- 8) Dr. P Hari (Medical College of Wisconsin) indicated that there are only 4 institutions that perform most of the allo transplants for myeloma (about 150-200 per year): MCW, Memorial Sloan Kettering, City of Hope (LA), and The Hutch (Seattle). Further most are “mini” allos but some are not so “mini” starting with 140mg/m² of Melphalan (200mg/m² is standard high-dose auto transplant).
- 9) Dr. S Atrash (Levine) discussed Plasma Cell Leukemia (PCL), classically defined by having 20% circulating plasma cells but agreed with others that having any circulating plasma cells might be considered PCL. Further, PCL should be consider the “highest of HR MM” and be part of clinical trials focusing on HRMM pts. However, the majority of PCL pts die within 3 years. During Q&A discussion Dr. Voorhees said the name Plasma Cell Leukemia is unfortunate and should be changed. PCL is the highest possible risk myeloma; it is not leukemia.
- 10) Dr. N Munshi reminded attendees “It doesn’t matter how you get to MRD-, which generally results in better PFS and OS than MRD+. Plus confirming MRD- 6-12 mos later is very important for longer PFS/OS.” There are still too many open questions regarding using MRD status to inform treatment decisions, though hopefully this will change with time.

- 11) Other plasma cell disorders Amyloidosis, Waldenstrom's, and POEMS were all discussed. See slides for further information.
- 12) Dr. S Lonial (Emory, Atlanta) when asked about giving a second transplant (SCT) upon relapse said "I believe at least 4 years remission from a first SCT and maintenance should be a minimum length of time when considering a second SCT."
- 13) Dr. Lonial also noted that the median PFS for the regimen of Dara-Pom-dex at first relapse has not yet been reached at 41 mos! However, if Dara has already been used up front, consider Elo-Pom-dex.
- 14) Dr. P Voorhees provided a "Blue Ribbon" PABST approach to therapy decisions for previously treated MM: P-Past medical history; A-Adverse events; B-Biochemical vs clinical relapse/progression; S-Standard vs High-risk disease biology; and T-Treatment history.
- 15) Dr C Rodriguez (Wake Forest) reminded attendees not to forget about alkylating agents: Melphalan, Cytosin, Melflufen, Bendomustine, Tenostamustine, Evofosfamide, and more.
- 16) Dr. K Anderson spoke about future immunotherapies and made several comments and observations during his talk and the conference:
 - "Maybe it would be better to block pathways rather than targeting mutations."
 - "In Dr Kumar's recent HR SMM trial comparing Rev-only to no treatment, the incidence of secondary cancers was 11.4% to 3.4%."
 - "Vaccines can work because they increase T-cell response as a result of reducing T-reg. So perhaps pts will get a vaccine shot every so often to increase the effective T-cell memory."
 - "When we treat the tumor, we're only treating half the problem, the microenvironment being the other part. But that will change. In the future, prognostic staging will include an analysis of the microenvironment (T-cells, monocytes, natural killer cells) as well as the MM cell."
 - Isatuximab [CD38 mAb like Daratumumab] has a direct killing effect unlike Dara. I expect it to receive FDA approval within the next few months. [However, we don't know if Isa will work in Dara-refractory pts or vice-versa.]
 - Iberdomide, a new generation IMiD of Cereblon modulator, might overcome resistance to Rev and Pom.
 - Dana Farber is looking at combining IMiDs with BiTEs.

That's my summary of this excellent conference. In fact, I would venture to guess (and hope) that this conference will be held annually.